STUDIES ON MACROCYCLIC ACETYLENIC COMPOUNDS

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SUMMARY

Section I

In an attempt to synthesise compounds related to the as yet unknown 1,6-didehydro-[10]-annulene, intermolecular Castro type coupling of the cuprous salts of 1-(o-iodophenyl)-2-propyn-1-ol and derivatives was investigated. Intermolecular coupling of derivatives suggested by model reactions was either unsuccessful, however, or gave a complex mixture, the nature of which could not be clarified. The synthesis of 'half-cyclised' compounds, formally only one stage away from the desired ten membered ring system was achieved, however, and some new examples of the Castro reaction, including some anomalies and failures, were discovered.

Section II

Intermolecular Castro-type coupling of the cuprous salt of m-iodophenylacetylene was found to give a complex mixture, the major component of which was shown to be the 'cyclic pentamer' derived from five molecules of the cuprous salt. Evidence was obtained for the presence of similar cyclic compounds of lower and higher molecular weight. A series of compounds resulting from mixed oxidative and Castro-type coupling was also isolated from the reaction product.

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SECTION I

INTRODUCTION

In 1865, Kekulé suggested that benzene, which had been known for some time to be closely related to the naturally occurring, carbon rich 'aromatic' compounds, was best described by the cyclohexatriene structure.[1] He later modified this to a 'dynamic' structure,[2] involving continuous interchange between two 'Kekulé' forms, and this picture of a symmetrical benzene molecule became generally accepted.[3] An interpretation of the special stability of benzene in electronic terms was first given in 1925 by Armit and Robinson,[4] with the idea of an 'aromatic sextet' of electrons.

The real basis, however, for much of the recent interest in aromatic compounds, and in particular, higher homologues of benzene, lies in the suggestion of Hückel,[5] on the basis of molecular orbital theory, that fully conjugated monocyclic polyolefins should be aromatic, if they contain $(4n + 2)\,\pi$ electrons and are planar. Perhaps surprisingly, this postulate did not arouse any immediate interest on the part of organic chemists until Dewar,[6] in 1945, suggested that both stipitatic acid and colchicine contained a seven membered aromatic ring related to the cycloheptatrienyl (tropylium) cation, which contains six π-electrons and had been predicted by Hückel to be a stable system. Considerable speculation[7] on the synthesis and possible properties of higher homologues of benzene occurred in the following ten to fifteen years, and after the tropylium cation had been synthesised in 1954 by Doering and Knox,[8] the first homologue of benzene comprising a monocyclic fully conjugated polyene (or annulene) containing $(4n + 2)\pi$ electrons, [18]-annulene (1), was synthesised in 1959 by Sondheimer and Wolovsky.[9]

Since then, great interest has been shown in both the synthesis and theoretical aspects, not only of the annulenes themselves, but of various related compounds. For example, many 'dehydroannulenes' have been synthesised by Sondheimer and his group, in which double bonds have been replaced by triple bonds or cumulene type systems, and in which Hückel's rule can be applied to the 'out of plane' π electrons. In addition, in some polycyclic systems, the peripheral electrons can be considered as a monocyclic system, with the cross-links as only minor perturbations, and several systems of this type have been synthesised. Evidence from all these types of compound supports the validity of the Hückel (4n + 2) rule, up to at least 18 π electron systems. Several recent reviews[10] and a monograph[11] have appeared, summarising the present state of knowledge.

If we consider the annulenes, however, it can immediately be seen that certain factors arise which are not present in the case of benzene. In the smallest member after benzene of the (4n + 2) series, [10]-annulene, the possible planar configurations required by Hückel for aromaticity involve serious interaction of two internal hydrogens (2), considerable angle strain (3), or in a third form (4), a combination of both types of strain. Similar, though not so congested, hydrogen interactions occur in higher members of the series, and for this reason Mislow,[7a] in 1952, considered that [30]-annulene (5) would be the first member which could attain planarity. Baker[7b] considered Mislow's view unduly pessimistic, on the grounds that complete planarity is not always necessary even in benzenoid aromatic compounds, and suggested that the smallest cyclopolyene which would exhibit aromatic properties would probably be [18]-annulene (1). Theoretical objections also exist to the simple Hückel rule. Longuet-Higgins and Salem[12] have stated that above a certain, undefined ring size, bond alternation will occur and any special properties will be lost. Recent calculations by Dewar and Gleicher[13] suggest that this may occur between [22]- and [26]-annulene.

Another difficulty occurs when we consider how any special 'aromatic' properties might be observed. The word 'aromatic', as applied to chemical compounds, has always been rather loosely defined.[14] Thus there has always been a conflict between whether 'aromatic' should describe compounds with benzene like structure, or benzene like properties, such as relative stability and tendency to undergo substitution reactions.[15] Typical benzenoid properties, however, such as the tendency to undergo substitution reactions, are far from satisfactory as a criterion of aromaticity. These properties are connected with the excited state of the molecule and are known to vary widely in compounds such as furan, benzene and resorcinol, for example, which are all generally accepted as aromatic. On the basis of chemical behaviour, indeed, [14]- and [18]-annulene appeared to behave very much like polyenes and indeed resembled the 4n annulenes in reactivity.[16]

A more useful concept in discussing aromaticity is π electron delocalisation. For this to be effective, the molecule must be approximately planar, and it results in the equivalence, or near equivalence, of all the carbon-carbon bonds. Delocalisation of the π electrons also has a marked effect on the nuclear magnetic resonance spectrum, in that in an aromatic molecule, an induced diamagnetic ring current is set up in an applied magnetic field, with the result that protons on the outside of the ring are deshielded, or move to lower field values, whereas those inside the ring are shielded and move to higher field values.[17] Elvidge and Jackman[18] have in fact defined an aromatic compound as one which will sustain an induced (diamagnetic) ring current. In some cases (e.g. [14]-annulene[10c,19]), because of the rapid interchange of the inner and outer protons, the nuclear magnetic resonance spectrum must be observed at low temperature for this effect to be noticed.

It was originally thought that the 4n annulenes would be olefinic in character, rather like cyclooctatetraene, and that the nuclear magnetic resonance spectra would show only olefinic absorption. This appeared to be the case[20] until in 1966, work was published on the low temperature nuclear magnetic resonance spectra of [16]-annulene by Schroder and Oth,[21] and of [24]-annulene by Calder and Sondheimer,[22] which showed that these compounds exhibit an 'anti-aromatic' spectrum, in which the lower protons absorb at low field and the outer protons at high field. This has been attributed to the existence of paramagnetic ring currents in the molecule and discussions of their theoretical basis have appeared by Longuet-Higgins,[23] Pople and Untch,[24] and Baer, Kuhn and Regel.[25] The existence of this effect was suggested to Pople and Untch[24] by the very high shielding ($\tau = 5{\cdot}58$) of the protons in 1,5,9-tridehydro-[12]-annulene (6),[26] and similar, though not very large effects had in fact been noticed earlier, though not explained in these terms, for example in the tetradehydro-[24]-annulene (7) synthesised by Sondheimer and Wolovsky in 1962.[27] In this molecule the inner protons appear at $\tau = 1{\cdot}60$ and the outer protons in a complex band at $\tau = 4{\cdot}40 - 5{\cdot}02$. It should be noted that although the idea of diamagnetic and paramagnetic ring currents is generally accepted, their existence has been vigorously denied by Musher.[28] At the moment, however, his views would appear to be very much in the minority.

Using the above criteria, nuclear magnetic resonance spectra, planarity and bond lengths, the 4n and (4n + 2) annulenes so far prepared can be clearly distinguished.[10c] [14]- and [18]-Annulene possess aromatic spectra whereas [16]- and [24]-annulene have the 'anti-aromatic' type. (The case of [10]-annulene will be discussed later, [12]- and [22]-annulene have not yet been prepared and [20]- and [30]-annulene have not yet been thoroughly examined). X-ray crystallography has shown that [14]-annulene does not exhibit bond alternation,[29] that [16]-annulene has alternate cis and trans double bonds and deviates considerably from planarity,[30] and that [18]-annulene is almost planar with approximately equal bond lengths.[31]

As was mentioned earlier, many dehydroannulenes have been synthesised, mainly by Sondheimer and co-workers.[10] These were first predicted to be of interest by Sworski,[32] and have the advantage over simple annulenes that internal hydrogen interactions are greatly reduced. Of the two types, those which formally contain simple triple bonds [e.g. (8) and (9)] are more numerous, but two interesting examples exist where, to obtain a Kekulé structure, two double bonds and a single bond must be replaced by a cumulene type unit. Sondheimer's group have found that the remarkably stable 1,8-didehydro-[14]-annulene[33] is a planar and symmetrical compound with a typical aromatic nuclear magnetic resonance spectrum. The compound is best represented by the symmetrical structure (10) rather than the Kekulé forms, (11) and (12). 1,8-Didehydro-[14]-annulene undergoes electrophilic substitution and is much more stable and more obviously 'aromatic' than [14]-annulene itself. A similar tetramethyltetradehydro-[18]-annulene (13) has now been synthesised by Japanese workers,[34] and though rather unstable, it exhibits an aromatic nuclear magnetic resonance spectrum similar to (10).

In general, the (4n + 2) dehydroannulenes show aromatic spectra, and some have been shown to be planar, whereas the 4n compounds show 'anti-aromatic' spectra. The lowest members of the series are the dehydro-[12]-annulenes (6)[26] and (14).[26b,35] The largest dehydroannulenes so far examined by nuclear magnetic resonance are 26 and 30 π electron compounds.[10c,36] Results so far, in particular with a tridehydro-[26]-annulene,[36] the spectrum of which has been examined at -60°, suggest that bond alternation[12,13] may be occurring.

Unfavourable steric interactions can also be overcome by the replacement of hydrogens by bridging atoms of various kinds. This has been particularly effective in the case of [10]-annulene, where the strongest interactions occur. The work of Vogel[37] on bridged compounds such as 1,6-methano-[10]-annulene (15) has shown that these compounds are undoubtedly aromatic.

1,6-Methano-[10]-annulene (15) can be regarded as a valence tautomer of the dihydronaphthalene derivative (16), which has a 'double norcaradiene' structure and would be expected to be unstable relative to (15). The synthesis[38] of (15) was therefore approached by a synthetic scheme formally leading to the valence tautomer (16). Naphthalene was reduced to 1,4,5,8-tetrahydronaphthalene (17), and dichlorocarbene was selectively added to the tetrasubstituted double bond to give (18).

Reductive elimination of the chlorine, followed by bromination and dehydrobromination, led via (19) and (20) to 1,6-methano-[10]-annulene (15) rather than the valence tautomer (16).

A similar approach was used in the synthesis of the 11,11-dihalogeno-1,6-methano-[10]-annulenes[39] (21), (22) and (23), although in good yield only in the case of the difluoro compound (21). Recently, however, an improvement in the synthesis of the dichloro compound (22) has been described by Nelson and Untch,[40] resulting in an overall yield of (22) from the dichlorocarbene adduct (18) of 50%. The same authors also describe a three-step synthesis of 1,6-methano-[10]-annulene (15) itself from naphthalene, involving carbene addition to the tetrahydronaphthalene (17) to give (19) in 50% yield, followed by dichlorodicyanobenzoquinone (DDQ) oxidation to the bridged [10]-annulene (15) in 90% yield.[40] Similar systems bridged by a hetero atom [(24)[41] and

(25)[42]] have also been synthesised as have the ionic species (26)[43] and (27).[44]

These bridged 10 π electron systems all possess aromatic properties, in particular exhibiting a nuclear magnetic resonance spectrum with the protons on the ten membered ring at low field, and the bridge protons at high field. The case of 1,6-methano-[10]-annulene (15) has been particularly extensively studied. The nuclear magnetic resonance spectrum shows an A_2B_2 system centred at 2·9 τ, corresponding to the eight protons of the ten membered ring, and a singlet at 10·5 τ for the two methylene protons. These chemical shifts are notably different from those in the model compound 9,10-ethano-9,10-dihydronaphthalene (28)[45] which exhibits a similar spectrum but with chemical shifts of 4·5 and 7·45 τ. 1,6-Methano-[10]-annulene also undergoes electrophilic substitution reactions,[37] mainly in the 2-position, and X-ray crystallographic analysis[46] of the 2-carboxylic acid has shown that the C_{10} perimeter is in fact even closer to planarity than would be inferred from models, and that the bond lengths all come into the range of 1·38 to 1·42 Å. This range is even narrower than in the case of naphthalene (1·36 - 1·42 Å). The above evidence, and also the ultraviolet spectrum and the lack of polyene type reactivity, shows conclusively that 1,6-methano-[10]-annulene can be considered an 'aromatic' compound.

In addition to their intrinsic theoretical interest, 1,6-bridged [10]-annulenes have other properties of interest to the organic chemist. The 11,11-dihalogeno-1,6-methano-[10]-annulenes [(21), (22) and (23)] have been used as carbene transfer reagents,[39] and with an excess of cyclohexene give high yields of the 7,7-dihalogenonorcarane (29). In addition, the carbene addition to cis- or trans-2-butene appears to be stereospecific. 1,6-Methano-[10]-annulene (15) has been converted into benzocyclopropene (30) by gas phase pyrolysis of the Diels-Alder adduct (31) obtained at elevated temperatures with acetylene dicarboxylic ester or dicyanoacetylene.[47] Pyrolysis of the Diels-Alder adducts of several other 11-substituted 1,6-methano-[10]-annulenes failed to produce any substituted benzocyclopropenes but in the case of the 11,11-difluoro compound (21), pyrolysis of the Diels-Alder adduct (32) proceeds successfully, producing 1,1-difluorobenzocyclopropene (33).[48]

This approach to the problem of internal hydrogen interactions in the annulenes has been extended by Vogel to the synthesis of some doubly bridged [14]-annulenes.[49-52] It is clear, however, that in these doubly bridged compounds, two geometrical isomers can exist, with the bridges either syn (34) or anti (35) to one another. Examination of models[49a] shows that only the syn compound can be approximately planar and can therefore be expected to be aromatic, and this has been borne out by the examples so far synthesised. Thus syn-1,6;8,13-bisoxido-[14]-annulene (34a),[49] 1,6;8,13-propano-[14]-annulene (36),[50] and syn-1,6-methano-8,13-oxido-annulene (34b)[51] exhibit 'aromatic' nuclear magnetic resonance spectra whereas anti-1,6;8,13-dimethano[14]-annulene (35a)[52] appears to have localised double bonds.

Another remarkably stable aromatic system, the trans-15,16-dimethyldihydropyrene system (37) which is effectively a bridged [14]-annulene has been synthesised by Boekelheide and co-workers.[53] The methyl groups in (37) are inside the cavity of the π -electron cloud of the 14 membered ring and appear at very high field (14·25 τ), whereas the peripheral protons appear at 1·33 - 2·02 τ. Further evidence for the aromaticity of (37) comes from its chemical properties, and from the X-ray crystallographic analysis[54] of the 2,7-diacetoxy compound (38) which shows that the molecule is almost planar with approximately equal bond lengths. Compound (37) can be converted to its valence tautomer (39) by visible light, but (39) rapidly reverts to the dihydropyrene form (37) in the dark. In contrast, the metacyclophane derivatives (40a)[55] and (40b),[56] do not isomerise to the corresponding cis-15,16-dihydropyrenes (41a) and (41b) although the protonated form (42) of the epoxide (40a) appears to be present to some extent in solution in strong acids.

The work of Badger and co-workers has been directed towards the synthesis of [18]-annulenes bridged by heteroatoms (43).[57] It has been established, on the basis of ultraviolet and nuclear magnetic resonance spectra, that the trioxide (43a) and dioxide-monosulphide (43b) are aromatic. In contrast, the mono-oxide-disulphide (43c) and the trisulphide (43d) behave as five membered heterocyclic rings joined by ethylene groups, as does the monoepimino-disulphide (43e).

This difference in behaviour has been attributed to the larger size of sulphur as compared to oxygen, which results in a non-planar system, but it may also arise partially from the relative resonance energies of the heterocycles, furan, pyrrole and thiophen, and of the macrocyclic 18 π electron system.[58] A recent synthesis by Elix[59] of annulene polyoxides, via the chloroaldehyde (44) has produced not only [18]-, but also [24]-, [30]-, and [36]-annulene polyoxides. It is of interest that the [24]-annulene tetroxide (2 isomers) shows an 'anti-aromatic' nuclear magnetic resonance spectrum, whereas the [30]- and [36]-annulene polyoxides show absorption similar to acyclic vinylfurans. The spectrum of [30]-annulene pentoxide shows very little change over the range -60 to +100°, indicating that bond alternation[12,13] is occurring.

18 π Electron systems with nitrogen in the ring as well as in bridges occur in some naturally occurring

compounds such as porphine (45) which has been shown to possess an 'aromatic' nuclear magnetic resonance spectrum.[60] Johnson and co-workers have recently synthesised, not only some oxygen and sulphur compounds related to porphins and porphyrins, and which appear to contain a delocalised 18 π electron system, but also two similar compounds (46)[61] and (47),[62] which are the first examples of [22]-annulene derivatives. Both of these macrocycles exhibit 'aromatic' nuclear magnetic resonance spectra, showing that bond alternation[12,13] is not occurring. This is in agreement with the suggestion of Dewar and Gleicher[13] that [22]-annulene itself will be aromatic, but that bond alternation will occur in [26]-annulene. As mentioned earlier, the evidence so far from [26]- and [30]-annulene derivatives[10c,36,59] suggests that the latter part of this prediction may also be correct.

Among other recent advances in the chemistry of annulenes and related compounds has been the synthesis of the dianion (48) of [16]-annulene by Oth, Anthoine and Gilles.[63] This 18 π electron system (48) is much more stable than [16]-annulene itself, and in fact appears to have greater resonance energy than [18]-annulene. The hexadehydro-[18]-annulene (49) has been synthesised by Okamura and Sondheimer,[64] and although the compound is rather unstable, the nuclear magnetic resonance spectrum indicates the presence of a diamagnetic ring current. The protons in (49) appear as a singlet at $\tau = 3{\cdot}0$, in contrast to those in the related 1,5,9-tridehydro-[12]-annulene (6),[26] which appear at $\tau = 5{\cdot}58$, and to the olefinic protons in the acyclic model compound (50), which appear at $\tau = 4{\cdot}11$.[64]

Considerable interest has been shown in the study by nuclear magnetic resonance spectroscopy of the interconversion of both equivalent and non equivalent conformers of the annulenes and dehydroannulenes. Sondheimer and co-workers have studied the transfer of hydrogens from internal to external positions in [18]-annulene,[65] and also the effect of replacing one hydrogen atom by a bulky substituent such as a nitro or an acetyl group.[66] The synthesis of these monosubstituted [18]-annulenes,[66] using specially mild conditions, shows that [18]-annulene can also be regarded to some extent as 'aromatic' on the basis of the older and rather unsatisfactory definition of aromaticity in terms of chemical reactivity. The synthesis of [16]-annulene and four dehydro-[16]-annulenes has been redescribed by Sondheimer and co-workers,[67] and the nuclear magnetic resonance spectrum of three of the dehydro compounds has been examined.[68] These compounds show interesting conformational effects including the interconversion in solution of non equivalent conformers. The existence in solution of two non equivalent conformers of [16]-annulene has been demonstrated by Oth and Gilles.[69]

These authors have also proposed a new system of nomenclature for the various possible conformers of annulenes, based on the arrangement of cis and trans double bonds and using the binary number system.[69] On this basis the more stable isomer (51) of [16]-annulene is described as [16]-85-annulene and the less stable (52) as [16]-91-annulene.[69] Studies on mono-substituted [16]-annulenes have shown that in these compounds, the equilibrium is displaced towards the [16]-91-annulene form.[70] The nuclear magnetic resonance spectra of several annulenes and dehydroannulenes have been used by Calder and Garrat to calculate the energy barrier for interconversion of the inner and outer hydrogens.[71]

The generic name 'annulenones' has been proposed[72] for the macrocyclic conjugated ketones homologous with cyclopropenone, cyclopentadienone and tropone, and the first two annulenone derivatives containing a ring larger than the seven membered one have recently been synthesised. These two 'dehydroannulenones', (53)[72] and (54),[73] contain a (4n + 1) membered ring and are therefore related to the unstable cyclopentadienone system and would not be expected to be aromatic.[72] In fact (54) is a very unstable compound, and in the nuclear magnetic resonance spectrum the two inner protons appear as a double doublet centred at $\tau = -0{\cdot}31$ and the outer protons absorb at $\tau = 3{\cdot}88 - 4{\cdot}95$, indicating the presence of a paramagnetic ring current. The spectrum of (53) is less informative as no protons are bound directly to the conjugated ring. The pentatridecafulvalene derivative (55) was obtained from (53) by reaction with cyclopentadiene in the presence of sodium methoxide.[74] The synthesis of annulenones, or their derivatives, containing a (4n + 3) membered ring would obviously be of great interest as these compounds might be expected to be similar to tropone in properties. Recent theoretical, nuclear magnetic resonance, and dipole moment studies, however, suggest that the resonance energy of the tropone and tropolone systems has been greatly exaggerated in the past, and that these systems, as neutral species at least, are best considered as normal polyenones.[75]

Although the work of Vogel[37] on bridged [10]-annulenes, described above, has shown that a planar delocalised [10]-annulene system can be obtained, and although azulene (56) can be regarded as a slightly perturbed [10]-annulene,[76] these systems owe their aromaticity to the replacement of internal hydrogens by bridging atoms or by a single bond. In the parent [10]-annulene, the gain in resonance energy will be offset by the unfavourable steric factors present in the planar forms (2), (3), and (4). The mono-trans configuration (4) probably represents the best compromise between the extremes of angle strain in the all-cis configuration (3) and of unfavourable hydrogen interactions in the di-trans configuration (2).

The existence of the aromatic, apparently planar, all-cis cyclononatetraenyl anion (57),[77] however, suggests that a large amount of the strain in the all-cis configuration (3), might possibly be offset by the gain in resonance energy derived from the formation of a planar aromatic system. It seems probable, however, that [10]-annulene, whether in configuration (2), (3), or (4), will be less stable than [14]-annulene, and all the evidence to date is in agreement with this view. Although evidence has been produced for the existence of [10]-annulenes as reaction intermediates, or at low temperatures, and some derivatives formally containing a monocyclic [10]-annulene have been synthesised, the parent compound has not yet been isolated.

A number of unsuccessful attempts to synthesise [10]-annulene and its derivatives have been reported.[78] Among recent examples is the synthesis by Mulligan and Sondheimer[79] of the diketo form (58) of 1,6-dihydroxy-[10]-

annulene. This compound, however, shows no tendency to enolise to the [10]-annulene form (59), and attempts to convert it to the corresponding 1,6-diacetoxy- or 1,6-dichloro- [10]-annulenes have not so far been successful. 1,6-Dichloro - 2,7-dihydro-[10]-annulene (60) has been synthesised by Grohmann and Sondheimer,[80] but isolable [10]-annulenes or derivatives have not been obtained from it. Dehydrochlorination of (60) gives the triene-yne (61) and naphthalene, and it is possible that the naphthalene arises from an intermediate diene - diyne (62), while treatment with butyl lithium gives a dark red colour, which may also be due to a [10]-annulene derivative.

The mono-trans form (4) of [10]-annulene has been suggested by Masamune and co-workers[81] as an intermediate in the thermolysis of the bicyclotetraene (63) to trans - 9,10-dihydronaphthalene (64), and a similar fluorochloro-[10]-annulene (65) has been suggested by Schröder and Martini[82] to be involved in the pyrolysis of the fluorochlorotetraene (66) to the 1-halogeno-naphthalene (67). In both of these examples, the mono-trans-[10]-annulene (4) is the form predicted by the Woodward-Hoffmann rules,[83] assuming a concerted rearrangement of the bicyclotetraenes (63) and (66).

In 1967, van Tamelen and Burkoth[84] produced good evidence for the existence of [10]-annulene itself [either configuration (2) or (3) being predicted by the Woodward-Hoffmann rules] in the low temperature photolysis of trans-9,10-dihydronaphthalene (64). After photolysis at -190°, cis-9,10-dihydronaphthalene (68) could be detected only after allowing the product to warm to room temperature. Direct diimide reduction of the photolysis product at as low a temperature as possible, gave a 40% yield of cyclodecane, indicating the monocyclic nature of the initial photolysis product.

In 1969, however, Masamune and Seidner[85] also produced evidence for the production of [10]-annulene in low temperature photolysis reactions, but were completely unable to reproduce the results of van Tamelen and Burkoth. Masamune and Seidner found that only the cis form (68) of 9,10-dihydronaphthalene (which had been stated by van Tamelen and Burkoth to show no promise as a precursor of [10]-annulene) produced [10]-annulene in low temperature photolysis, and that [10]-annulene was produced in reasonable yield only at temperatures of -70° to -50° under the conditions used. In addition they found diimide to be a rather ineffective reducing agent at low temperatures. The Woodward-Hoffmann rules[83] predict that a concerted opening of cis-9,10-dihydronaphthalene will produce the mono-trans-[10]-annulene (4), and Masamune and Seidner have observed a temperature dependent signal, centred at $\tau = 4{\cdot}16$ (-40°), in the low temperature nuclear magnetic resonance spectrum of the photolysis product which they attribute to (4). In addition, a sharp temperature independent singlet at $\tau = 4{\cdot}34$ is attributed to the all-cis form (3), formed from (4) photolytically. These τ values, in addition to the thermal instability of the [10]-annulenes produced, are strong evidence for the non-planarity and lack of aromatic stability of these forms of [10]-annulene. Hydrogenation at -70° over a rhodium catalyst gave cyclodecane in a yield of 80% based on the calculated amount of [10]-annulene.

Thus although good evidence is available for the existence of polyene-like [10]-annulenes, the situation is somewhat confused by the lack of agreement between the two groups of workers.

In addition to the all-cis cyclononatetraenyl anion (57) mentioned above, other 10 π electron aromatic anions have been obtained. The cyclo-octatetraenyl dianion (69) has been known since 1960, when it was synthesised by Katz,[86] and more recently an analogous heterocyclic dianion (70) derived from the azocine system (71) has been characterised by Paquette and co-workers.[87]

The chemical shifts of the protons in these anions are close to those to be expected from the competing deshielding effect of the aromatic diamagnetic ring current, and the shielding effect arising from the negative charge on the ring. In the pentalene dianion (72), the extent of the agreement depends on the method used to calculate the charge densities on the various atoms, but the dianion does appear to be aromatic.[88] The monohomocyclooctatetraenyl dianion (73) also seems to show an appreciable ring current.[89] Very recently the trans, cis, cis, cis- form of the cyclononatetraenyl anion has been synthesised.[90] The method used was essentially identical to that used by Katz and Garrat in the synthesis of the all-cis anion (57) except that the reaction temperature was lowered to -40°. Treatment of (74) with potassium in tetrahydrofuran at -40° gives the mono-trans anion (76) [contaminated with only about 4% of the all-cis anion (57)], presumably by the conrotatory, orbital symmetry allowed,[83] opening of the cyclopropyl anion in the intermediate (75). The nuclear magnetic resonance spectrum of the mono-trans anion (76) shows a doublet centred at $\tau = 2{\cdot}73$ (2 H) and absorption at $\tau = 3{\cdot}0 - 3{\cdot}6$ (6 H), corresponding to the outer protons, and a triplet centred at $\tau = 13{\cdot}52$ (1 H) corresponding to the inner proton, whereas the all-cis form (57) shows only a singlet at $\tau = 2{\cdot}87$. The mono-trans anion (76) can be kept for days at -40° in a closed vessel but is converted to the all-cis form at room temperature.

The dipolar structure (77) related to the cyclononatetraenyl anion can be considered as a form contributing to the stability of the recently synthesised 10,10-bis(dimethylamino)nonafulvene (78).[91] Spectroscopic evidence suggests that temperature and solvent dependent conformational equilibria are set up, and the all-cis representation (78) is therefore arbitrary. The synthesis of diazocyclononatetraene (79), in which the ionic form (80) might be expected to play a large part, has been claimed, but the compound has not been obtained in a pure state, and the evidence for its structure is based mainly on infra-red spectroscopy.[92]

Two neutral, heterocyclic, 10 π electron systems homologous with furan and N-carbethoxypyrrole have recently been synthesised. N-carbethoxyl-1-azacyclonona-2,4,6,8-tetraene (N-carbethoxyazonin) (81),[93] and 1-oxacyclonona-2,4,6,8-tetraene (oxonin) (82)[94] were obtained from the photolysis at 0^{o} of the corresponding cyclo-octatetraene derivatives (83) and (84) using benzophenone as sensitizer, the products being separated by low temperature chromatography. As predicted by orbital symmetry considerations,[83,95] the all-cis forms are obtained. Both (81) and (82) are non-planar and polyenic in character, as evidenced by their nuclear magnetic resonance spectra, and by their fairly rapid rearrangement to (85) and (86) respectively at room temperature. In both cases, the products of thermal rearrangement have the cis configuration, in agreement with orbital symmetry considerations,[83,95] the assignment of the trans configuration (87) in the original description[94a] of the oxonin synthesis being a result of inconsistencies in the published literature.[94b] It thus appears that in both of these 10π electron systems (81) and (82) that the resonance energy which results from delocalisation of the π electrons in a planar arrangement is not sufficient to overcome the angle strain involved. Both (81) and (82), in fact, appear to be similar to the all-cis cyclononatetraene system (88) which has recently been synthesised independently by four groups of workers[96] by the careful protonation at low temperatures of the all-cis cyclononatetraenyl anion (57). This cyclononatetraene also undergoes a fairly rapid thermal rearrangement at room temperature resulting in cis-8,9-dihydroindene (89). The lack of aromaticity of the oxonin and azonin systems is not particularly surprising, in view of the rather low resonance energy of the homologous furan and pyrrole systems.[97] The greater 'aromaticity' of thiophen suggests that the analogous 10 π electron sulphur compound thionin (90) should be more promising as a potentially aromatic system, but the properties of the system will again depend on the balance between angle strain and resonance stabilisation. The thionin derivative, 4,5: 6,7-dibenzothionin (91) has been synthesised, as has 4,5: 6,7 dibenzoxonin (92), and these compounds have also been shown to exist in buckled non-planar configurations.[98] It remains possible, however, that thionin itself will be an aromatic system, as benzannelation will almost certainly decrease the likelihood of π electron delocalisation in the 9-membered ring, since some of the contributing structures would involve disruption of the extremely stable benzenoid sextet.

Benzannelation has in fact been used widely in the synthesis of annulenes, despite the fact that the annelated annulene produced is a rather poor model for the parent system. It has the advantage that the overall stability of the system is generally increased and the synthesis simplified. In addition the properties of these annelated annulenes, such as their spectra, conformational properties and transannular interactions are themselves of great interest. Benzannelation was used in the synthesis of the first macrocyclic annulene derivatives,[99] and in recent years a number of very interesting benzannelated and naphth-annelated [10]-annulenes, and also a related system containing an 11-membered ring, have been synthesised.

The mono-trans-tribenzo-[10]-annulene (93) has been synthesised by Grohmann and Sondheimer[100] in 15% yield by a Wittig reaction[101] between the di-ylid (94) and o-phthalaldehyde (95). Although spectral evidence indicates that the 10-membered ring is not a planar delocalised system,

(93) is reasonably stable, probably because the symmetry allowed,[83] disrotatory thermal rearrangement would lead to the o-xylylene derivative (96) in which one of the benzenoid sextets has been disrupted. Heating of (93) at 190° for 5 minutes, however, produces 9,10-dihydro-1,2:3,4-dibenzanthracene (97), probably via (96) as an intermediate. A recent attempt by Bindra and Elix to synthesise the heterocyclic compound (98) analogous to (93) gave only compounds of the type (99).[102]

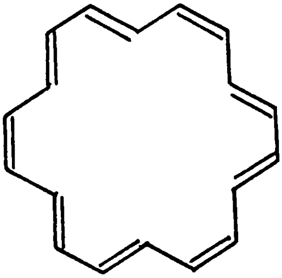
The Wittig reaction between a di-ylid and a dialdehyde has been used in the synthesis of a number of other medium sized unsaturated rings. Among these has been the synthesis by Bindra, Elix and Sargent of the di-trans-dibenzofuro-[10]-annulene (100).[103] As in the case of [14]-annulene,[10c] the internal hydrogen interactions result in the existence of two isomers (100a) and (100b). These isomers are separable, and the less stable is converted to the more stable on standing. The dibenzofuro-[10]-

annulene (100), however, should perhaps not be regarded as a true annelated [10]-annulene because of the low bond order of the bridging C-C bond in the furan ring. This low bond order may also account for the reasonable stability, and the fragmentation rather than transannular rearrangement of (100) at high temperatures, as an electrocyclic reaction is unlikely if one of the 'double' bonds involved has very little double bond character. On prolonged refluxing with dimethyl fumarate in benzene, the dibenzofuro-[10]-annulene (100) undergoes a Diels Alder reaction to give the authentic di-trans-dibenzo-[10]-annulene (101),[103] annelated by only two aromatic nuclei. Only one isomer of (101) could be isolated. In the case of (101), concerted rearrangement is possible, and after two weeks at 0°, 50% conversion to (103) had taken place, probably via the intermediate (102) expected on orbital symmetry grounds, followed by auto-oxidation to (103). In both (100) and (101), the nuclear magnetic resonance spectrum indicates the olefinic nature and lack of planarity of the system.

A dinaphth-[10]-annulene has been obtained by Mitchell and Sondheimer, though in only 2% yield, again by a Wittig reaction, and probably exists in the non-planar, di-cis configuration (104).[104] This compound is reasonably stable at -15° but at room temperature or above undergoes transannular isomerisation to dihydrozethrene (105) which is then oxidised in the presence of air to zethrene (106), both of these compounds being isolable under suitable conditions. It is noteworthy that no Kekulé forms of (104), which involve a fully conjugated 10-membered ring, can be drawn. The related compound (107), containing an 11-membered ring, has also been synthesised by a Wittig reaction, in a yield of 58%, and has been found to have the mono-trans configuration.[105]

The dihydropyrene valence isomers (39), (40a) and (40b) discussed earlier can also be regarded as benzannelated

[10]-annulenes although, as in the case of the dinaphth-[10]-annulene (104), no Kekulé structures involving a fully conjugated 10-membered ring can be drawn. Once again, there is no evidence that these compounds contain a delocalised [10]-annulene system.



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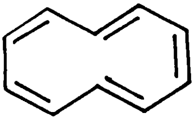

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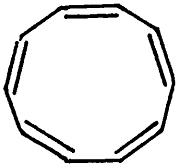

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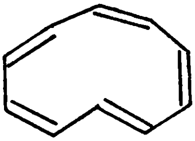

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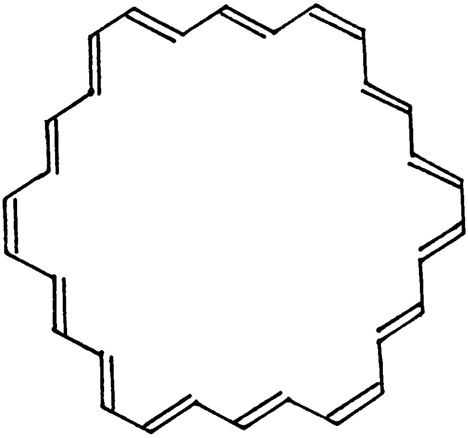

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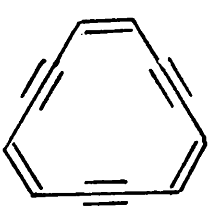

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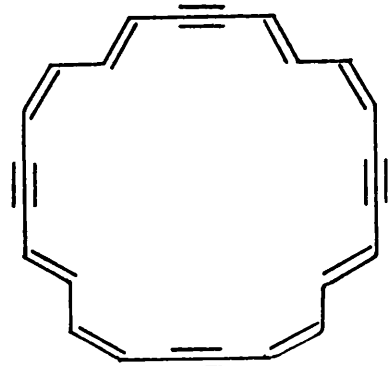

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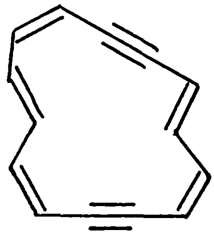

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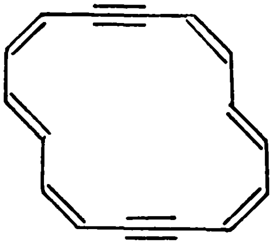

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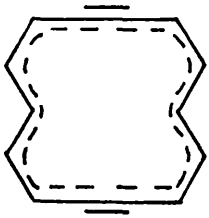

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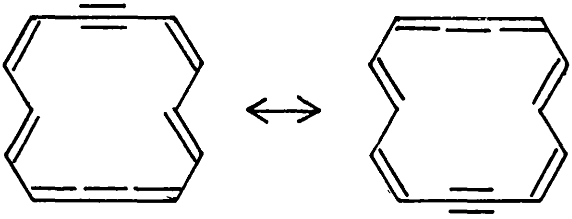

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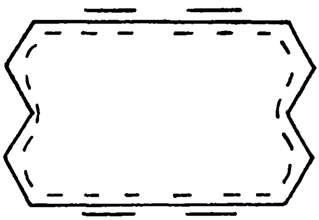

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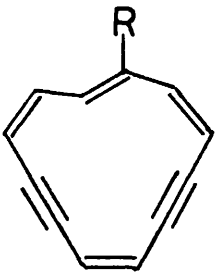

R = H or Br

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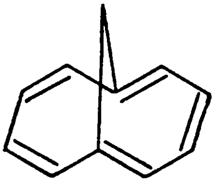

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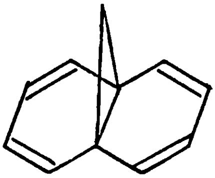

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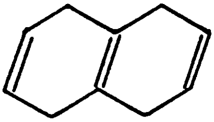

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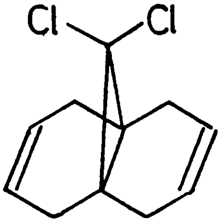

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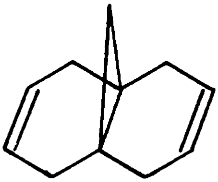

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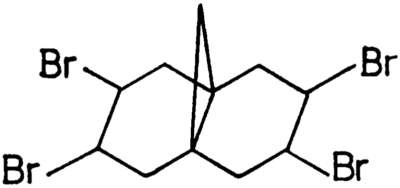

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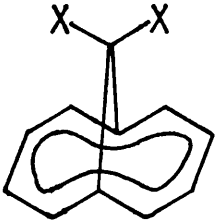
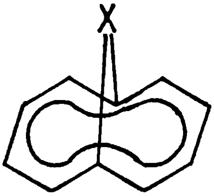


21 X = F

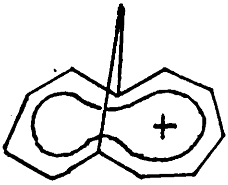
22 X = Cl

23 X = Br



24 X = O

25 X = NH



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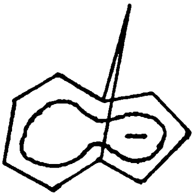

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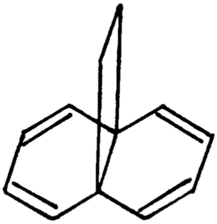

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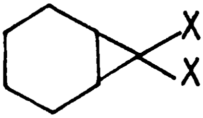

X = F, Cl or Br

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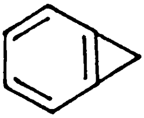

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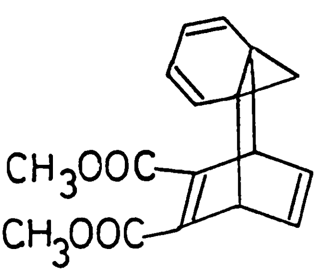

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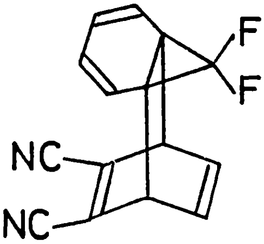

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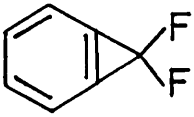

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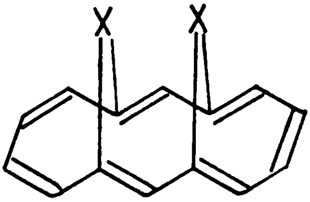
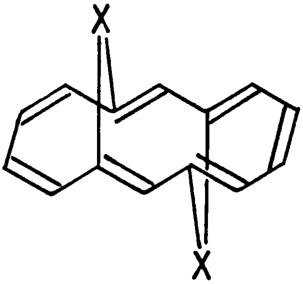


34 a ; X = O
b ; X = CH_2



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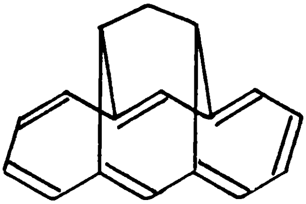

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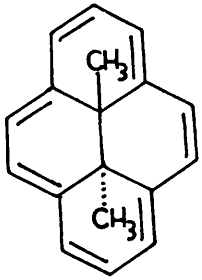

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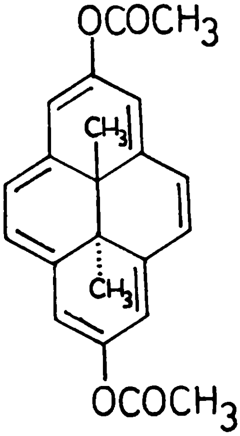

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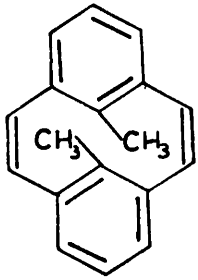

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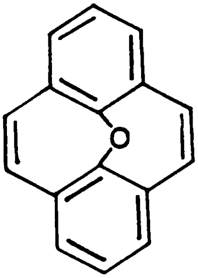

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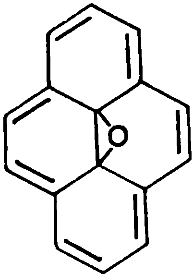

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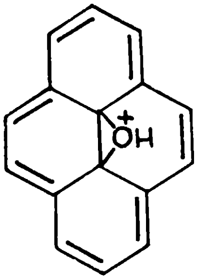

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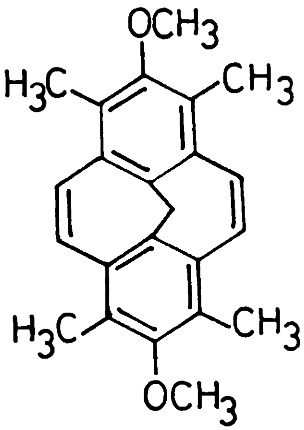

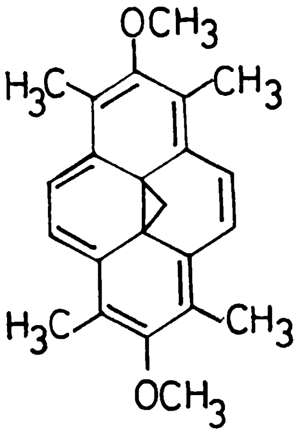

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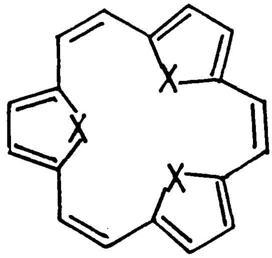
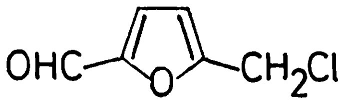


43

a; X = O,O,O
b; X = O,O,S
c; X = O,S,S
d; X = S,S,S
e; X = NH,S,S



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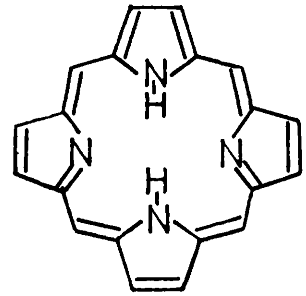

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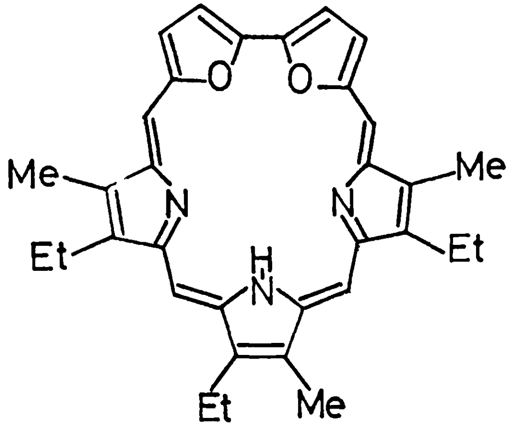

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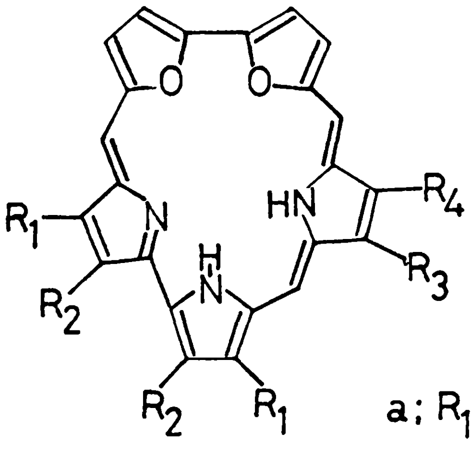

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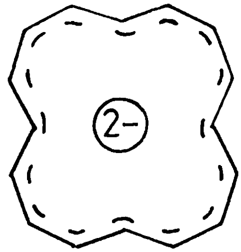
a; $R_1=R_3=R_4=Me \quad R_2=H$

b; $R_1=R_3=Me \quad R_2=R_4=Et$



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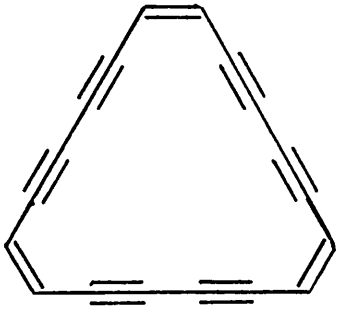

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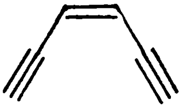

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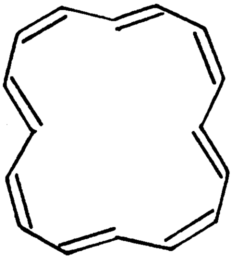

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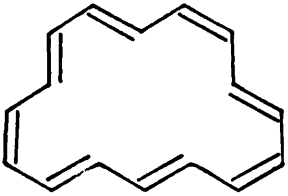

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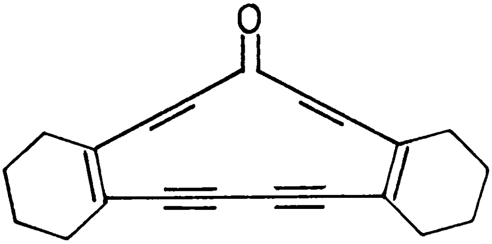

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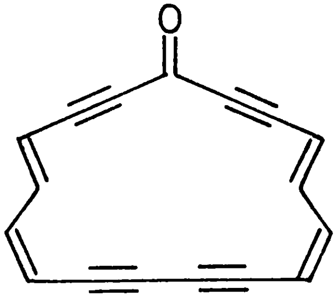

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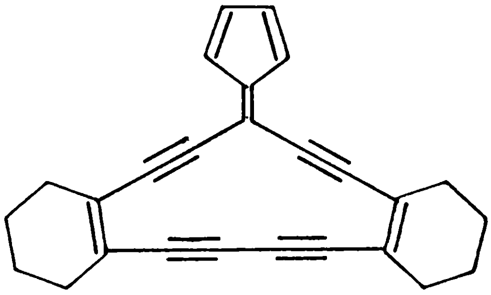

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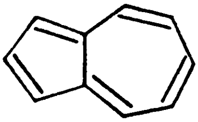

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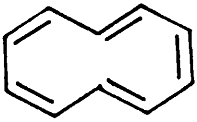

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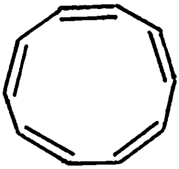

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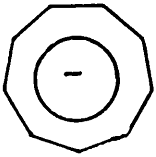

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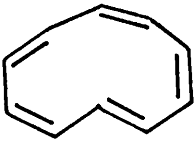

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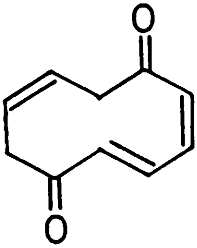

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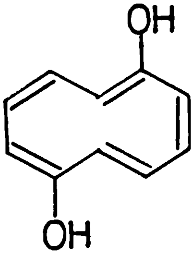

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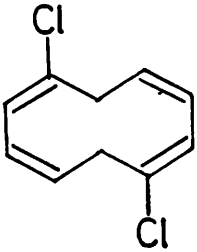

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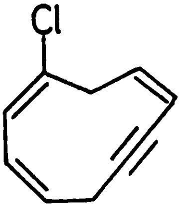

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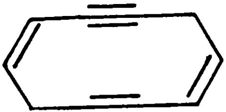

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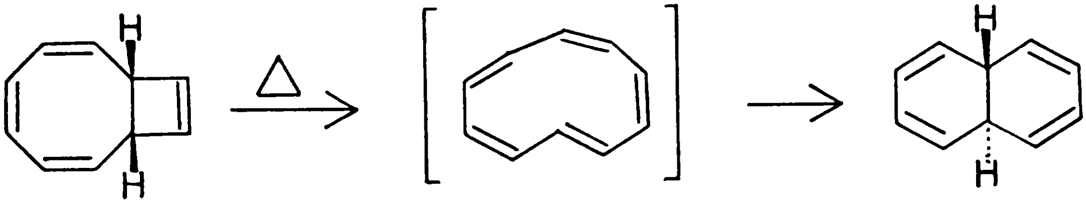

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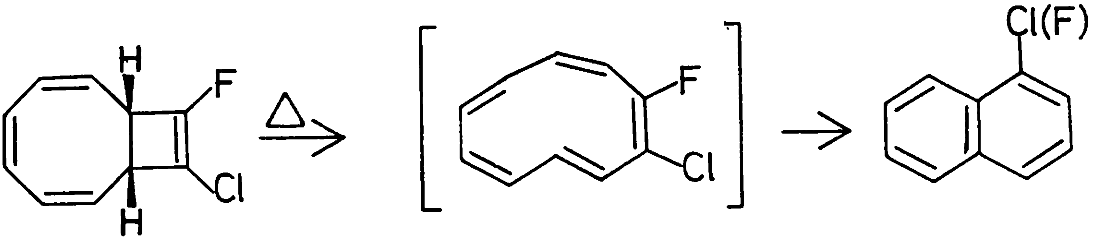

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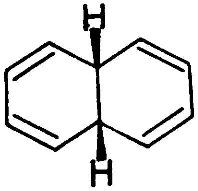

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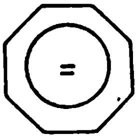

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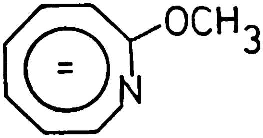

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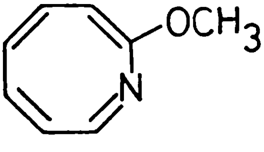

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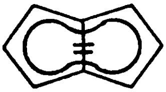

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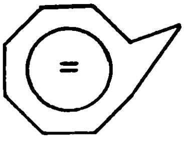

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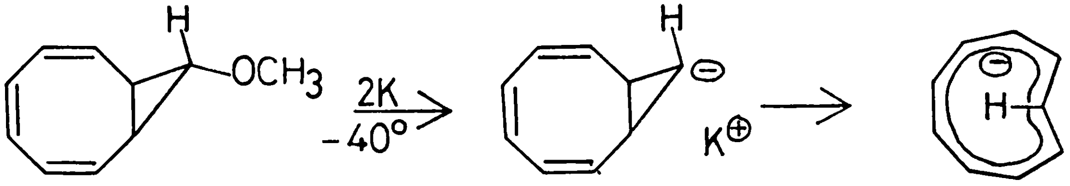

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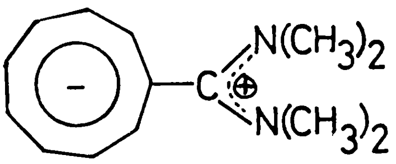

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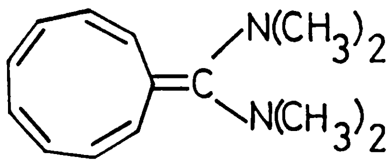

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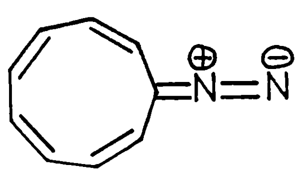

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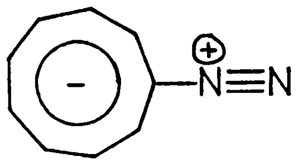

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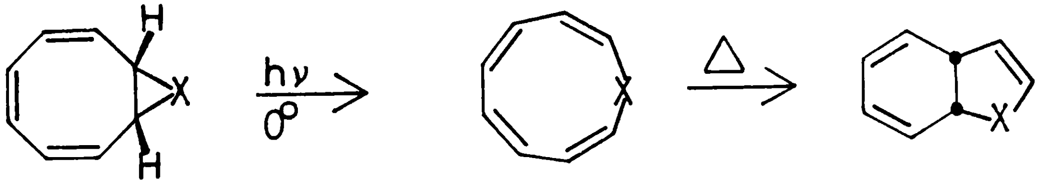


83 X = NCO_2Et

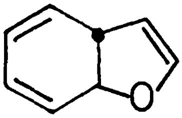
84 X = O

81 X = NCO_2Et

82 X = O

85 X = NCO_2Et

86 X = O



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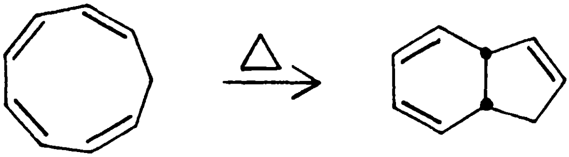

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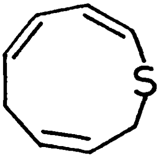

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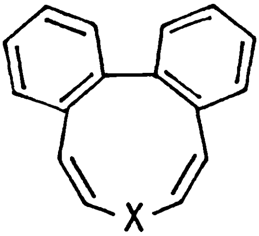
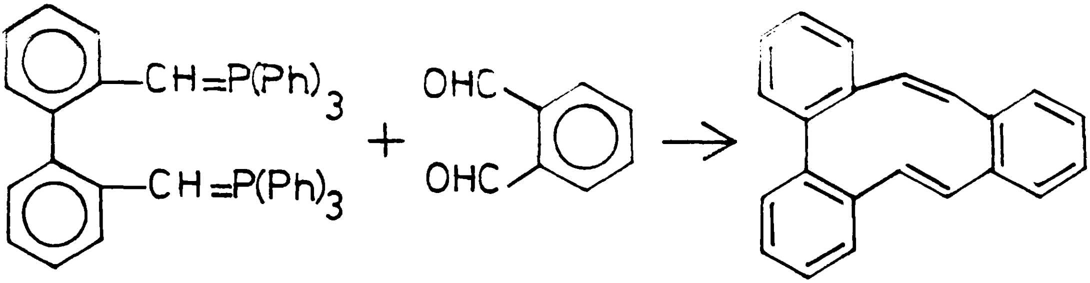


91 X=S

92 X=O



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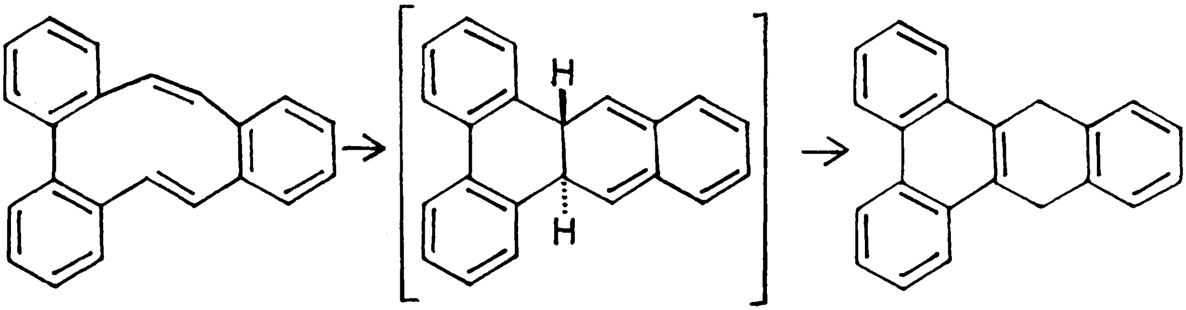

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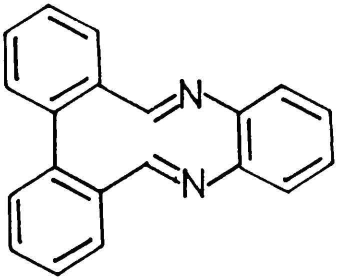

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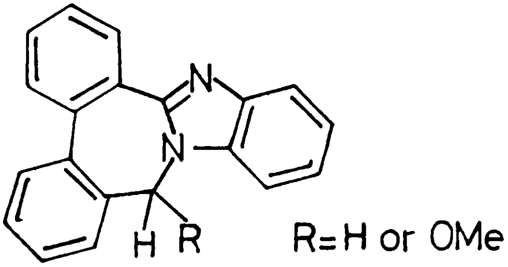

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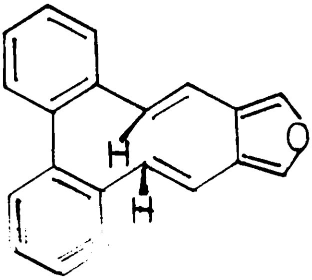

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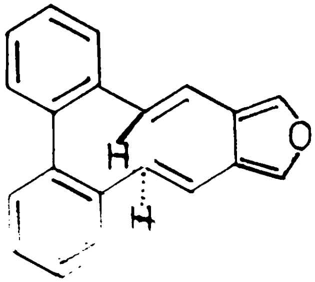

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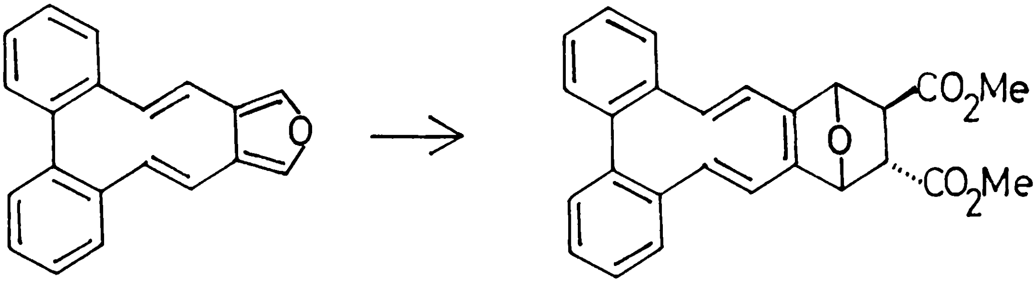

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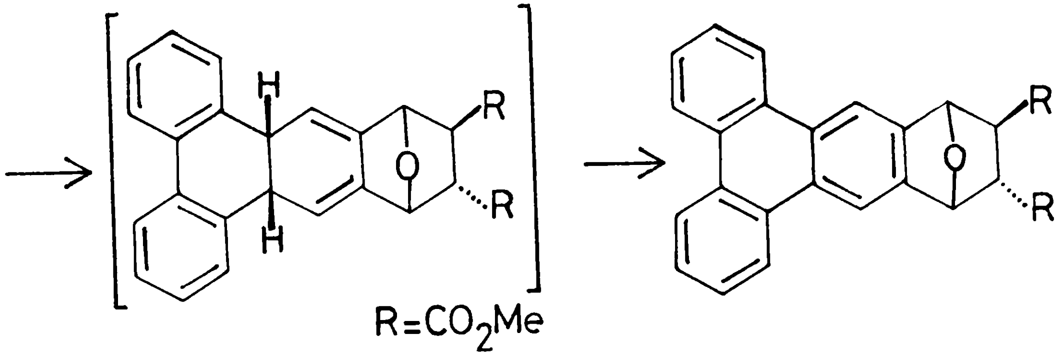

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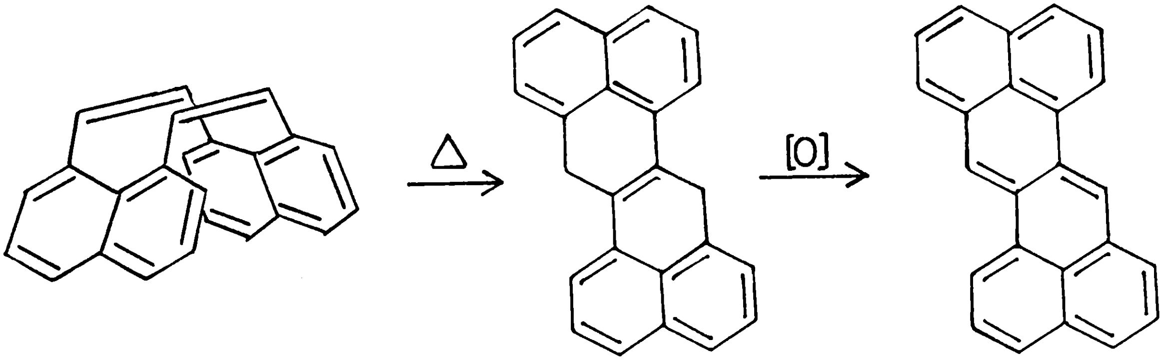

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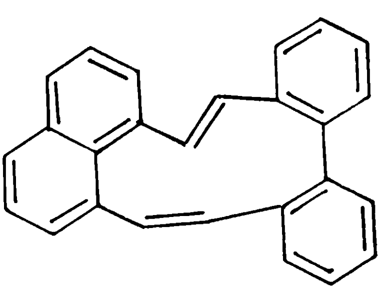

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DISCUSSION

1,6-Didehydro-[10]-annulene (108), first discussed theoretically by Sworski[32] in 1948, represents a further example of a planar, delocalised 10 π-electron system. Sworski considered this compound in terms of resonance hybrids involving the two structures (109) and (110), without any reference to the Huckel (4n + 2) rule,[5] but it is clear that (108) is a [10]-annulene derivative analogous to the very stable 1,8-didehydro-[14]-annulene (10)[33] described by Sondheimer and co-workers in 1962, and to the more recently synthesised and less stable tetramethyltetradehydro-[18]-annulene (13).[34] Like all the dehydroannulenes, 1,6-didehydro-[10]-annulene (108) has the advantage over the parent annulene that unfavourable internal hydrogen interactions are greatly reduced, in this case being completely eliminated, and like (10) and (13), it has normal bond angles. In addition the known aromaticity of (10) and (13), and in particular the great stability of (10), provide further impetus to the search for the ten membered ring homologue, 1,6-didehydro-[10]-annulene (108). In contrast to (10) and (13), however, (108) may well be destabilised by interference between the 'in plane' π-electrons, as a result of the proximity of the triple bonds. At the start of this project, neither 1,6-didehydro-[10]-annulene (108) nor any derivatives had been synthesised and it was decided to attempt initially the synthesis of the dibenzo-diol (111), which might then be capable of oxidation to the 'quinone' type compound (112) or possibly of dehydroxylation to the 1,6-didehydro-[10]-annulene derivative (113). The properties of these systems, in particular relating to possible transannular reactions arising from the proximity of the triple bonds, would obviously be of interest.

Various examples existed in the literature at the start of this project of cyclic compounds with closely juxtaposed triple bonds, but the extent of the resulting destabilisation appeared to vary considerably. For example, cyclotetradeca-1,3,8,10-tetrayne,[106] which exists in the chair form (114), is less stable than analogous open chain compounds and analogous cyclic compounds (115) containing a larger number of methylene groups, and decomposes explosively at about 115°. The transannular interaction between the triple bonds also has a marked effect on the ultraviolet spectrum which exhibits a bathochromic shift similar to that observed in the lower members of the paracyclophane series (116).[107] 1,6-Dioxacyclodeca-3,8-diyne (117)[108] decomposes rather rapidly before its melting point of 170-172°, but the corresponding dithia compound (118)[109] is considerably more stable (possibly because of the greater size of sulphur as compared to oxygen), melting at 200° (with decomposition) and being sublimable at 100° at a pressure of 0·1 mm. Also known at the start of this project was the dark green azulene homologue (119).[110] Although (119) exhibits an apparently 'aromatic' nuclear magnetic resonance spectrum, and is reversibly extracted from organic solvents by strong acids, possibly by formation of the delocalised cation (120), it is an extremely unstable substance in the solid state. During the course of this work, continuing interest has been shown in the interaction of triple bonds in both cyclic and acyclic systems by various groups of workers and the synthesis of some compounds related to 1,6-didehydro-[10]-annulene (108) has been described.

Among recent work in this field has been the attempted synthesis[111,112] of a dinaphthannelated derivative (121) of 1,6-didehydro-[10]-annulene (108). It has been found by Staab, Nissen and Ipaktschi[111] that the Castro-type[113] coupling reaction of the cuprous derivative (122) of 1-ethynyl-8-iodonaphthalene in refluxing pyridine gives a 50% yield of zethrene (106). It is probable that the diyne (121) is the initially formed product but that it rapidly undergoes transannular isomerization to zethrene.

An alternative approach using 1,8-diiodonaphthalene (123) and the bis-cuprous derivative (124) of 1,8-diethynylnaphthalene gives only a trace of zethrene.[111,112] Evidence that the diyne (121), if formed, would be an extremely unstable compound, is available from work on other 1,8-diacetylenic naphthalenes. Oxidative coupling of 1,8-diethynylnaphthalene (125), which itself undergoes transannular reactions,[111] gives a very low yield of the 'cyclic dimer' (126), a dinaphthannelated tetradehydro-[14]-annulene.[114] Compound (126) is extremely unstable, and all attempts to obtain it in the solid state, or even in concentrated solution, resulted in its decomposition. The main evidence for its structure was derived from the ultraviolet spectrum, the lack of terminal acetylene units, and from its hydrogenation products (127), (128) and (129).

The chemistry of acyclic 1,8-diacetylenic naphthalenes, in particular 1,8-bis(phenylethynyl)naphthalene (130), has been extensively investigated by several groups of workers.[115,116,117] Interaction between the triple bonds occurs readily, compound (130), for example, being converted to 7-phenylbenzo[k]fluoranthene (131) in high yield by either thermal or photochemical means. Although interaction between triple bonds is known in other situations, for example, in o-bis(phenylethynyl)benzene (132)[117,118,119] and in 2,2'-diacetylenic biphenyls (133),[117,120,121] only in the 1,8-diacetylenic naphthalene derivatives are the acetylenic units forced to be approximately parallel to one another at such a short distance.[122] This 'peri' interaction in 1,8-disubstituted naphthalenes of a wide variety of types is of course well known[125] and arises not only from the relative geometry of the C_1, C_8 and C_9 atoms but also from the comparative lack of flexibility of the naphthalene nucleus. Two recent examples related to the diacetylenic compounds discussed above are those of 1,8-distyrylnaphthalene (134) which can be converted photochemically and thermally to (135) and (136) respectively,[124] and 1,8-bis(4'-vinylstyryl)naphthalene (137) which on irradiation rather surprisingly gives the 17-membered ring system (138).[125]

It would thus appear that the instability of the dinaphthannelated dehydroannulenes (121) and (126) is attributable, in part at least, to the rigid geometry of the naphthalene nucleus. The acetylenic units are either held rigidly in close proximity or must be considerably bent and thus strained if the distance between them is to be increased. Further evidence for this is that cyclotetradeca-1,3,8,10-tetrayne (114),[106] although destabilised to some extent by the proximity of the triple bonds, is much more stable than (126). It is thus possible that the parent 1,6-didehydro-[10]-annulene (108), the dibenzo-diol (111) which was the initial object of this work, and the related compounds (112) and (113), may be more stable than the dinaphthannelated derivative (121) on account of their greater flexibility. An interesting recent case where flexibility seems to confer stability is provided by the cyclic diacetylene (139)[126] synthesised by treatment of bi(2-bromophenyl)acetylene with butyl lithium at -40°. Compound (139) is remarkably stable, having a melting point of 221-222°, despite the fact that with 'normal' bond angles, the triple bonds would approach to a distance of only 2 Å from one another. The very low absorption wavelength in the ultraviolet spectrum suggests that this unfavourable interaction is partly relieved by twisting of the aromatic rings.

As was discussed above, the initial object of this work was the synthesis of the dibenzo-diol (111) and the study of its conversion to the 'quinone' type compound (112) and possibly to (113). A simple route to (111) appeared to be the intermolecular Castro-type coupling[113] of the cuprous derivative (141) of 1-(o-iodophenyl)-2-propyne-1-ol (140), which seemed readily preparable by the reaction of o-iodobenzaldehyde (142) with either acetylenemonomagnesium bromide[127] or lithium or sodium acetylide.[128]

The readily available o-iodobenzoic acid (143) seemed an obvious starting material for the aldehyde, but the literature method[129] of reduction of the anilide of (143) looked unpromising for large scale application. The method of McFadyen and Stevens[130] via the hydrazide and benzenesulphonylhydrazide was therefore investigated but gave unpromising results at the last stage. It was then decided to investigate the synthesis of the aldehyde by reduction of methyl o-iodobenzoate (144) to o-iodobenzyl alcohol (145) with lithium aluminium hydride, followed by oxidation of (145) to the aldehyde (142). This route had been used satisfactorily in these laboratories by Campbell[131] but was known not to be completely reliable.[132] Although lithium aluminium hydride reduction of the ester (144)[131,133] and of the corresponding acid chloride[133] had been reported to proceed in high yield, it was found by Campbell[132] that the yield of o-iodobenzyl alcohol from the ester was sometimes greatly reduced by the replacement of iodine by hydrogen to give benzyl alcohol in fairly high yield. In the present work, this was indeed found to be the case, but eventually it was found that by cooling the ethereal solution of the ester to -70° and using an inverse addition of lithium aluminium hydride that pure o-iodobenzyl alcohol could be obtained in a yield of more than 70%.

Difficulties had also been encountered in the oxidation of (145) to o-iodobenzaldehyde with manganese dioxide in refluxing benzene,[134] and other oxidising agents were therefore investigated. Ceric ammonium nitrate[135] in aqueous acetic acid was found to produce a good yield of the crude aldehyde, but the product, which was contaminated with small amounts of starting material and by-products, proved rather difficult to purify on a large scale. The use of nickel peroxide[136] was briefly investigated but the product was again found to be contaminated with starting material. Eventually manganese dioxide was found to be satisfactory, giving yields of over 80% of essentially pure o-iodobenzaldehyde, but the optimum conditions for the reaction were found to vary considerably with the batch of manganese dioxide used.

For the synthesis of 1-(o-iodophenyl)-2-propyn-1-ol (140), the use of the alkali metal derivatives[128] of acetylene in liquid ammonia was first investigated, on account of their greater ease of manipulation. It was found, however, that even using a large excess of the acetylide, complete conversion to the acetylenic carbinol could not be achieved. Essentially pure material could be obtained, however, by recycling the crude product twice more with sodium acetylide. A trial run using benzaldehyde and a similar excess of sodium acetylide gave the expected phenylethynylcarbinol (146) in high yield and free from starting material. This apparent difference in reactivity may be due to the steric effect of the ortho iodine substituent, or possibly to the formation of the aldehyde ammonia (147) stabilised by hydrogen bonding.

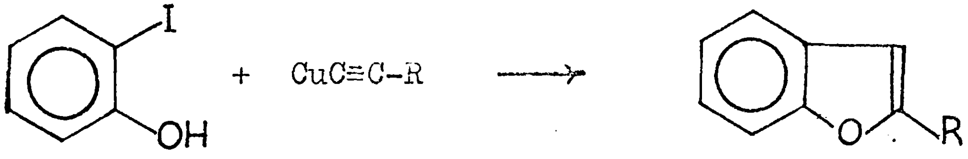
The reaction of o-iodobenzaldehyde with acetylenemonomagnesium bromide,[127] however, was found to proceed very satisfactorily, giving high yields of the required alcohol (140).

While these reactions were being carried out, it was decided to investigate the coupling reaction of the cuprous derivative (148) of phenylethynylcarbinol (146) with iodobenzene as a model for later work using the corresponding ortho iodo compound (140), since Castro-type coupling reactions had not previously been carried out using this type of benzylic, acetylenic alcohol. This coupling reaction, which was independently reported in 1963 by Castro and Stephens,[113] and by Sladkov, Ukhin and Korshak,[137] involves basically the reaction of an aryl iodide with the cuprous derivative of a monosubstituted acetylene to give a disubstituted acetylene as shown below.

$$\text{R-C}\equiv\text{CCu} + \text{I-Ar} \longrightarrow \text{R-C}\equiv\text{C-Ar}.$$

Shortly afterwards its application to the introduction of acetylenic units into the thiophen and furan systems was described by Curtis and co-workers.[138] The reaction has since been widely used both in the synthesis of acyclic compounds, such as the bis(phenylethynyl) derivatives of benzene, naphthalene and biphenyl described above, and in the synthesis and attempted synthesis of cyclic compounds (see above, and also Section II).

The analogous reaction of cuprous acetylides with vinyl iodides[139] and polyfluorylalkyl halides[139,140] has also been described and occurs under similar conditions. At higher temperatures the reaction of cuprous acetylides with benzylic halides can be brought about,[141] and allylic halides also react under various conditions.[137,141,142] The extension of the coupling reaction to the synthesis of monosubstituted acetylenes by the use of an easily removable substituent attached to the acetylene unit has also been described.[143,144] When aryl iodides bearing an ortho nucleophilic substituent are used, cyclisation generally takes place,[113,145,146] o-iodophenol (149), for example, giving the substituted benzofuran (150).



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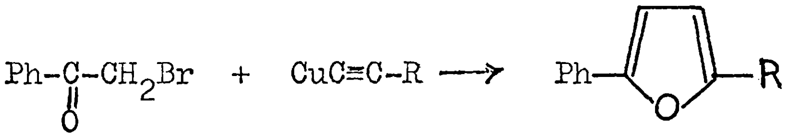
The reaction of phenacyl bromides (151) with cuprous acetylides can also be brought about and results in cyclisation to substituted furans (152).[141]



151 152

In cases where cyclisation is possible, the precise course of the reaction depends to some extent on the solvent, and a very recent paper by Castro and co-workers[147] describes some rather anomalous results, including a wide variation in the course of the reaction depending on the solvent and on whether homogeneous or heterogeneous conditions are employed. Some new examples of the reaction where the aryl iodide carries an ortho substituent have been investigated in the course of this work. The coupling reaction has been used widely with di-iodo compounds to give diacetylenes, but the reaction of the bis-cuprous derivative (124) of 1,8-diethynylnaphthalene gave only a trace of 1,8-bis(phenylethynyl)naphthalene (130), possibly because of the insolubility of the bis-cuprous derivative in the solvent pyridine.[112] A short review of the Castro coupling reaction and related reactions of acetylenic and halogen compounds has appeared.[148]

The Castro reaction is normally carried out using preformed cuprous acetylides in refluxing pyridine, and under a nitrogen atmosphere to prevent oxidative coupling[149] of the cuprous acetylide to a diacetylene. Other solvents have also been used satisfactorily,[113] but dimethylformamide has been found by Castro and co-workers to be more favourable to cyclisation in some cases where this is possible.[145,147] Mitchell[112] has found the lowest temperature at which the reaction between cuprous phenylacetylide and iodobenzene proceeds satisfactorily to be about 85°. In the case of 1,8-diiodonaphthalene (123), however, the reaction with cuprous phenylacetylide has been found by Schechter and co-workers[116] to proceed at room temperature to give a high yield of 1,8-bis(phenylethynyl)naphthalene (130). It is interesting that when a similar reaction between cuprous phenylacetylide and 1,5-diiodonaphthalene was attempted[116] at room temperature, not only did no Castro-type coupling take place, but a large amount of oxidative coupling to diphenyldiacetylene occurred despite stringent measures taken to exclude oxygen.

Although phenylethynylcarbinol (146) had not previously been used as the acetylenic component in the Castro reaction, acetylenes carrying a wide variety of functional groups had been used successfully, particularly by Curtis and co-workers,[138] and it was expected that (146) would behave similarly. The cuprous salt (148) was therefore prepared from ammoniacal cuprous chloride[150] in the usual way,[151] and appeared to be reasonably stable in the solid state, the alcohol (146) being recovered almost pure by hydrolysis of a sample of the cuprous salt which had been allowed to stand for 3 months. On attempted reaction with iodobenzene in refluxing pyridine, however, none of the expected 1,3-diphenyl-2-propyn-1-ol (153)[152] could be detected in the reaction product, which consisted mainly of benzaldehyde and unreacted iodobenzene. Examination of the behaviour of the cuprous salt (148) alone in refluxing pyridine showed that it underwent decomposition giving benzaldehyde as the main product. Phenylethynylcarbinol (146) itself could be recovered unchanged from either refluxing pyridine or refluxing pyridine containing cuprous iodide. When (146) was heated in pyridine, however, with an approximately equimolar amount of cuprous phenylacetylide, no (146) could be recovered, benzaldehyde (and phenylacetylene) being the main products. This latter reaction presumably occurs by way of interchange of copper between the two acetylenes, resulting in the existence of the cuprous salt (148) of phenylethynylcarbinol (146) in solution. The failure of cuprous iodide to behave similarly is not surprising as 'in situ' generation of the cuprous derivative in this way was found to be unsuccessful, a mixture of phenylacetylene, iodobenzene and cuprous iodide in pyridine failing completely to give any detectable quantity of diphenylacetylene after 40 hours reflux under nitrogen. Similarly Castro and co-workers have found[145] that 'in situ' generation of cuprous acetylides for the Castro reaction by the use of cuprous iodide and N-ethylpiperidine in dimethylformamide is not very successful except in special cases. The cuprous salt (141) of 1-(o-iodophenyl)-2-propyn-1-ol (140) was found to behave similarly to (148), giving o-iodobenzaldehyde very readily on only brief heating in pyridine. In fact, on preparation of (141) by the method of Bohlmann[153] (see p. 60), the combined ethanol and ether washings of the cuprous salt were found to contain o-iodobenzaldehyde, as well as unreacted (140), indicating that decomposition to the aldehyde can occur very readily indeed. The precise reason for this formation of aldehyde is not clear, particularly since the cuprous salts of propargyl alcohol and 3-phenyl-propyne react normally,[138] but is clearly connected with the stereochemical arrangement of the cuprous salt in solution and its interaction with the various possible ligands, including solvent.

Obviously the point of attack in this 'retro-Grignard' reaction is the hydrogen of the free hydroxyl group. Attention was therefore turned to methods of protecting the hydroxyl function in phenylethynylcarbinol (146), and to this end the corresponding acetate (154) and tetrahydropyranyl ether (155) were prepared by standard methods. The acetate was prepared by treatment of (146) with acetic anhydride in pyridine and the tetrahydropyranyl ether by treatment of (146) with a small excess of dihydropyran, using a trace of phosphorus oxychloride as catalyst.[154] The tetrahydropyranyl ether (155) appeared to undergo some hydrolysis back to (146) on distillation and the crude reaction product was therefore used for preparation of the cuprous salt. Confirmation of the structure of (155) was provided by hydrolysis to (146) with methanol containing a trace of p-toluenesulphonic acid and by acetolysis[155] to (154) on refluxing in acetic anhydride.

At first some difficulty was experienced in converting the acetate (154) and tetrahydropyranyl ether (155) to their cuprous salts (156) and (157). When the normal method[151] involving ammoniacal cuprous chloride[150] was used, the cuprous salt appeared to form but very rapidly dissolve or decompose in the aqueous ammonia medium. Similar difficulties were described at about the same time by Curtis and co-workers,[138c] who found that using a method similar to the standard one mentioned above, the cuprous salt of 3,3-diethoxypropyne proved difficult to isolate. This difficulty was overcome[138c] by using a modified technique in which cuprous chloride was dissolved in aqueous ammonium hydroxide solution and the solution made alkaline with sodium acetate pentahydrate. About the same time, however, another method was described by Bohlmann and co-workers,[153] and in the present work, this method was frequently used on account of its simplicity. The method involves addition of a large volume of aqueous sodium bicarbonate solution to a solution of the acetylene and cuprous iodide in dimethyl sulphoxide. The cuprous salt is generally obtained in high yield, although in the present work, cases were noticed where a large amount of the free acetylene could be recovered. Using this method, the cuprous salts of the acetate (154) and of the tetrahydropyranyl ether (155) were prepared in good yield.

The cuprous salt of the acetate (154), however, completely failed to undergo Castro coupling with iodobenzene.

A vigorous reaction appeared to occur when the cuprous salt was added to warm pyridine containing iodobenzene, and examination of the product after refluxing under nitrogen showed no identifiable compounds. The reason for this is not clear, but again is probably connected with the stereochemical arrangement of the cuprous salt in solution. When the cuprous salt of the tetrahydropyranyl ether (155) was used, however, the Castro reaction proceeded in good yield to give 1,3-diphenyl-1-(2'-tetrahydropyranyloxy)-2-propyne (158). For comparison purposes, 1,3-diphenyl-2-propyn-1-ol (153)[152] was prepared by the reaction of either sodium phenylacetylide or phenylacetylene magnesium bromide with benzaldehyde, and converted in the usual way to the tetrahydropyranyl ether (158).

The removal of the tetrahydropyranyl protecting group from (158) was found to present some difficulty. Although tetrahydropyranyl ethers are normally easily hydrolysed by dilute mineral acid,[154] and some even by magnesium sulphate,[156] (158) prepared by the Castro reaction was found to survive work-up with dilute sulphuric acid without any detectable amount of hydrolysis to the alcohol (153). Because of this, and the failure of preliminary attempts at hydrolysis using similar aqueous acid conditions, the frequently used method of transacetalisation with methanol containing a trace of p-toluenesulphonic acid was tried. Although this method was successful with the tetrahydropyranyl ether (155) of phenylethynylcarbinol (146), in the case of (158), either the methyl ether (159) or a mixture of (159) and the desired 1,3-diphenyl-2-propyn-1-ol (153) was obtained. Treatment with methanol containing aqueous hydrochloric acid similarly gave a mixture of the methyl ether (159) and the alcohol (153), and treatment with ethanol containing a trace of p-toluenesulphonic acid also gave a second product, presumably the ethyl ether, as well as the alcohol (153). The methyl ether (159) probably results from initial cleavage of the tetrahydropyranyl ether to the alcohol (153), in accordance with the generally accepted mechanism[157] for acetal hydrolysis, involving carbonyl carbon-oxygen cleavage, followed by methanolysis of (153) to the methyl ether. This is further suggested by the fact that treatment of the alcohol (153) itself with either methanol containing a trace of p-toluenesulphonic acid, or methanol and aqueous hydrochloric acid, gave a mixture of alcohol (153) and methyl ether (159). It was then fortunately found that treatment of the tetrahydropyranyl ether (158) directly with Jones reagent,[158] led by hydrolysis and oxidation to 1,3-diphenyl-2-propyn-1-one (160)[159] in good yield. The use of acetone and aqueous sulphuric acid (i.e., Jones conditions but without chromium trioxide) gave hydrolysis to the alcohol (153) in good yield, but a little tetrahydropyranyl ether remained even after prolonged treatment.

Partly because of the unexpected difficulties encountered in hydrolysis of the tetrahydropyranyl ether

(158), the use of the cuprous salt (162) of phenyl ethynyl ketone (161) was also investigated. Phenyl ethynyl ketone[158] (161), prepared from phenyl ethynyl carbinol (146) by Jones oxidation,[158] was converted to its red cuprous salt (162) by the method of Bohlmann[153] in excellent yield. Rather surprisingly, since the free ketone (161) decomposes rapidly in pyridine, the cuprous salt (162) reacted smoothly with iodobenzene in refluxing pyridine to give 1,3-diphenyl-2-propyn-1-one (160),[159] identical to a sample prepared by Jones oxidation of the alcohol (153). Thus the formation of the cuprous salt effectively protects (161) from attack by pyridine, in addition to enabling it to undergo Castro-type coupling with iodobenzene.

Two satisfactory models were thus now available for application to the projected synthesis of the ten membered ring cyclic compounds (111) and (112), and 1-(o-iodophenyl)-2-propyn-1-ol (140) was therefore converted to its tetrahydropyranyl ether (163) in the usual way, and to 1-(o-iodophenyl)-2-propyn-1-one (164) by Jones oxidation. The n.m.r. spectrum of (163) showed clearly the presence of the expected two diastereoisomers [as did the spectra of the tetrahydropyranyl ethers (158) and (165)]. Separation of the diastereoisomers of (163) was achieved by preparative thin layer chromatography and the n.m.r. spectrum of each was examined. The chemical shift differences were generally small ($\not> 0 \cdot 5\ \tau$) except in the case of the C_2 and C_6 protons of the tetrahydropyranyl ring. In the less polar isomer, the C_2 proton appeared at $\tau \doteq 4 \cdot 76$ as a broadened triplet, and the two C_6 protons as a multiplet at $\tau = 5 \cdot 9 - 6 \cdot 67$. In the more polar isomer the C_2 proton was at $\tau = 5 \cdot 32$ (broadened triplet) and the C_6 protons appeared as separate multiplets at $\tau = 5 \cdot 7 - 6 \cdot 2$ and $\tau = 6 \cdot 2 - 6 \cdot 67$. The mixture of isomers was generally used for further reactions.

The cuprous salt of 1-(o-iodophenyl)-2-propyn-1-one

(164) was prepared in good yield by the method of Bohlmann,[153] and appeared from hydrolysis results to be reasonably stable in the solid state. On attempted intermolecular Castro-type coupling in refluxing pyridine, however, the reaction product appeared to consist almost entirely of tarry, polar material. The u.v. spectrum showed no characteristic peaks and the i.r. spectrum showed rather broad carbonyl absorption at 1705 cm^{-1}. The few extremely faint spots observed on t.l.c. were no stronger than the very minor spots observed with completely successful reactions of this type. It was then found that even after 20 minutes at room temperature, a stirred mixture of the cuprous salt of (164) in pyridine under nitrogen had turned dark, and that after work-up under either acid or neutral conditions, no starting ketone (164) could be recovered. The product was again a tarry material similar to that described above. The use of dimethyl sulphoxide as solvent, at an intermediate

temperature (85°), gave very similar results. The failure of this reaction is again difficult to rationalise, but may be connected with the proximity of the interacting copper and iodine atoms to the carbonyl group of the ketone.

The preparation of the cuprous salt of the tetrahydropyranyl ether (163) was now carried out, again by the method of Bohlmann.[153] It was found that conversion to the cuprous salt was rather low, the free tetrahydropyranyl ether being recovered in yields of 50-60% and the cuprous salt being contaminated with precipitated cuprous iodide. Hydrolysis of the cuprous salt back to the free tetrahydropyranyl ether indicated that it was about 50% pure, but since the contaminant, cuprous iodide, is produced under coupling conditions, the cuprous salt obtained in this way could be used for the Castro reaction without any difficulties. The i.r. spectrum of the cuprous salt was practically identical to that of the free tetrahydropyranyl ether, apart from the lack of terminal acetylenic absorption, but the position of the triple bond stretching frequency[160] could not be definitely observed.

The Castro-type coupling of the cuprous salt of the tetrahydropyranyl ether (163) was now investigated in the hope of obtaining the di-tetrahydropyranyl derivative (166) of the dibenzo-diol (111). It was found that the reaction product was complex, thin layer chromatography (t.l.c.) showing at least six spots and considerable streaking. The ultraviolet (u.v.) spectrum, however, showed a sharp peak at 274 mμ of intensity almost equal to the rather broader absorption at 230 mμ. Attempted isolation by preparative t.l.c. of the substance responsible for this ultraviolet absorption failed, although very small amounts of material showing absorption in the same region were recovered. The infra-red (i.r.) spectrum of the crude product was not examined after every run, the crude product being treated directly in some cases with various reagents in preliminary attempts to convert the tetrahydropyranyl ether functional group to a more stable group. In those cases examined, the i.r. spectra were not identical, in one case (dilute acid work up) some free acetylene and considerable tetrahydropyranyl ether absorption being present, but in another (neutral work up) strong absorption at 1720 cm^{-1} being observed.

Among the observations made on treatment of the crude product with various reagents was that treatment with Jones reagent[158] gave more than negligible amounts of acetylenic ketone (easily identified from the very strong $\nu C\equiv C$ band in the i.r. spectrum) only when some free acetylenic material was observed in the crude coupling product. This does not prove the absence of the cyclic diyne (166) which might well rearrange on treatment with Jones reagent, but it suggests that very little coupling to cyclic products derived from three or more molecules of (163) had taken place, as these products would almost certainly give some acetylenic ketone. Some absorption at $\sim$ 1800 and 1720 cm^{-1} was noted. Treatment of the crude product with methanol containing a trace of p-toluenesulphonic acid gave a product which again showed sharp u.v. absorption at 274 mμ and which showed hydroxyl but no tetrahydropyranyl ether absorption in the i.r. spectrum, indicating that hydrolysis had probably taken place successfully. Material with this u.v. absorption (and other material absorbing strongly in the same region) could be recovered after preparative t.l.c., but the substances thus isolated seemed to be mixtures by t.l.c.

If the cyclic diyne (166) had been formed, it might possibly have undergone rearrangement similar to that observed in the related cases[111,112,114-117] discussed earlier (p. 43-45), and the use of lower reaction temperatures in an attempt to prevent this was therefore examined briefly. When the reaction was carried out at room temperature, oxidative coupling[149] to (167) appeared to take place, the ether soluble product having i.r. and t.l.c. properties practically identical to those of a sample of (167) prepared by treatment of (163) with cupric acetate in pyridine and methanol.[161] When the reaction was carried out at 85°, the product was less complex than that obtained at reflux temperature. T.l.c. suggested, however, that some of the product was again derived from oxidative coupling. The u.v. spectrum showed some absorption at ca. 275 mμ and the i.r. spectrum showed strong tetrahydropyranyl ether type absorption.

Although a detailed investigation of the course of this coupling reaction, including particularly the effect of lowering the temperature, and the use of high dilution techniques and better methods of separation, would obviously have been of interest, lack of time precluded further work on this approach. Concurrently with the work described above, however, an alternative approach via the half-cyclised compound (168) was investigated; intramolecular Castro coupling of the cuprous salt of the di(tetrahydropyranyl ether) (168) might be expected to be a better method of obtaining the cyclic diyne (166) than intermolecular coupling of the cuprous salt of (163), since side reactions and polymerisation should be less likely, particularly under high dilution conditions.

The fact that the cuprous salt of (163), unlike that of the ketone (164), appeared to be reasonably stable in pyridine suggested that if it were treated with an excess of an aromatic iodide, self-coupling of the cuprous salt should be suppressed, and normal coupling between the cuprous salt and the iodide should take place. Thus if the cuprous salt of (163) were treated with an excess of the free tetrahydropyranyl ether (163), the half-cyclised compound (168) should be obtained. To test this hypothesis, the cuprous salt of (163) was first treated in refluxing pyridine with the more readily available o-iodobenzaldehyde (which had been shown to react normally with cuprous phenylacetylide, see p. 78). The reaction product showed only one major spot on t.l.c. in addition to unreacted o-iodobenzaldehyde. This product was isolated by preparative t.l.c. in about 46% yield (from the cuprous salt) and was shown by i.r., nuclear magnetic resonance (n.m.r.) and mass spectrometry to be the aldehyde-tetrahydropyranyl ether (165). The reaction between the tetrahydropyranyl ether (163) and the cuprous salt of (163) was then carried out in the same way and gave only one major product, which was isolated by preparative t.l.c. in about 35% yield. The i.r., n.m.r., and u.v. spectra of this product strongly suggested that it was in fact the desired di(tetrahydropyranyl ether) (168). Attempted distillation of this viscous oily product resulted in its decomposition, however, and a mass spectrum could not be obtained from the crude material, but its structure was proved by conversion to the dione (169) with Jones reagent.

The dione (169) was a yellow crystalline solid whose structure was supported by i.r., u.v., n.m.r., and mass spectroscopic evidence. The i.r. spectrum[162] of (169) was particularly interesting, the $\nu C{\equiv}C$ absorption of the two triple bonds appearing at 2230 cm^{-1} (disubstituted) and 2120 cm^{-1} (monosubstituted),and two carbonyl peaks being observed at 1655 and 1630 cm^{-1}. The cuprous salt of the di(tetrahydropyranyl ether) (168) was prepared and subjected to a preliminary intramolecular Castro-type coupling reaction in pyridine. The product, after removal of the pyridine by azeotroping with benzene, was again a rather complex mixture by t.l.c. but the u.v. spectrum showed a strong sharp peak at 274 mμ, and was essentially identical to the spectrum of the product of intermolecular coupling of the cuprous salt of (163). It thus appears that the cuprous salt of (168) is indeed formed as an intermediate in the intermolecular Castro coupling reaction of the cuprous salt of (163). Lack of time, however, prevented further investigation of the behaviour of the cuprous salts of (163) and (168).

Although no definite characterisation of the products of these coupling reactions was achieved, some conclusions can be drawn from the data available. The cuprous salt of (163) appears to give the cuprous salt of (168) which then undergoes further reaction, possibly normal Castro coupling, to give a final product with the strong u.v. absorption observed. This u.v. absorption cannot be accounted for by unstrained open chain or macrocyclic coupled products, and although the proximity of the triple bonds in the cyclic diyne (166) might result in a shift to longer wavelength, it is unlikely that (166) could give rise to a peak of such intensity. Assuming the compound responsible for this spectrum to be the diyne (166) or a derived compound of similar molecular weight, and that it constituted all of the reaction product, an approximate extinction coefficient (ε) of 5,000 was calculated. Since it is unlikely that the compound responsible is present to a very large extent in the complex reaction product, the true ε value must be considerably greater than 5,000, an ε value which is very unlikely for the diyne (166). It seems more likely that the compound responsible is an aromatic compound derived from transannular cyclisation of (166). Considering only the formation of six-membered rings, although other transannular cyclisations are possible, the initial products could be the diradicals (170) and (171) which might then rearrange and/or pick up hydrogen to give polycyclic compounds such as (172) to (177). Of these the tetracene derivative (174) must be ruled out from the lack of u.v. absorption in the 400 mμ region,[163] and the dihydro compounds (172) and (175) would probably not give rise to such strong absorption. From comparison with known compounds,[163] the chrysene derivative (177) seems the most likely of the remaining structures, but the spectrum obtained is not totally characteristic of a substituted chrysene, and for this reason, in addition to the qualifications mentioned above, the assignment of structure (177) to the compound responsible for this u.v. spectrum must obviously remain very tentative. It seems not unlikely, however, despite the lack of definite evidence, that the cyclic diyne (166) is formed and that it then undergoes rearrangement to some polycyclic aromatic compound or compounds.

Towards the end of this work directed towards the synthesis of the diyne (166), the synthesis of the related compound (178) was described by Whitlock and Reed.[164] The diol (178) was obtained by treatment of 2,2'-diformyldiphenylacetylene (180) with acetylenedimagnesium bromide, and was characterised chiefly as its diacetate (179). The diacetate (179) appears to be a reasonably stable compound, although a mass spectrum could not be obtained. However, the conditions under which the diol (178) was synthesised (in tetrahydrofuran at -5°) were much milder than those required for the Castro reaction, and it is possible that (166) and the corresponding diol (111) might also be reasonably stable at room temperature. It is interesting that the u.v. spectrum of (178) is similar to that of a normal diphenylacetylene, but with less fine structure. Among the observations made by Whitlock and Reed was that on solvolysis in acetic acid containing sulphuric acid, the diacetate (179) gave in good yield the polycyclic diacetate (181). They suggest, somewhat tentatively, that the fully conjugated didehydro-[10]-annulene derivative (182) is an intermediate in this solvolysis.

During the course of this work, a number of model Castro-type coupling reactions were carried out using iodobenzenes carrying ortho substituents. It was found that o-iodobenzaldehyde (142) and methyl o-iodobenzoate (144) reacted normally with cuprous phenylacetylide to give the substituted tolanes (183) and (184) respectively, and that (144) also reacted normally with the cuprous salt (162) of phenyl ethynyl ketone to give the acetylenic keto-ester (186). 2-Hydroxymethyldiphenylacetylene (185) was also prepared from o-iodobenzyl alcohol (145) and cuprous phenylacetylide as described by Castro and co-workers[145] and converted to the aldehyde (183) by oxidation with Jones reagent, and the structure of the carbomethoxytolane (184) was further confirmed by reduction to (185) with lithium aluminium hydride. When the reaction between o-iodobenzyl alcohol (145) and cuprous phenylacetylide was worked up with dilute sulphuric acid, the product appeared from its spectral properties to be 1-benzylidenedihydroisobenzofuran (187) which was obtained by Castro and co-workers[147] by a neutral reaction work up when the time of reaction was greatly prolonged.

EXPERIMENTAL: GENERAL TECHNIQUES

Melting points were taken on a Kofler block, and are uncorrected; boiling points are uncorrected. Evaporations and solvent removals were carried out under reduced pressure on a rotary evaporator unless otherwise stated. Analytical thin layer chromatography (t.l.c.) was carried out on plates prepared with Kieselgel G (Merck Chemical Co.) except where otherwise indicated, and with Kieselgel HF_{254} in certain cases. Plates were examined under u.v. light (Kieselgel HF_{254}) and by spraying with iodine and ceric ammonium sulphate solution. Preparative t.l.c. was carried out with 0·5 mm. thick, 20 x 20 mm. plates of Kieselgel G or HF_{254}.

Infrared (i.r.) spectra were taken as liquid films or nujol mulls on a Unicam SP.200 spectrophotometer and as KBr discs on a Perkin-Elmer 257 spectrophotometer. Ultraviolet (u.v.) spectra were recorded on Unicam SP.800 and SP.800A spectrophotometers. Nuclear magnetic resonance (n.m.r.) spectra were recorded on Perkin-Elmer R10 (60 Megacycles) or Varian T60 (60 Megacycles) spectrometers using deuterochloroform as solvent and tetramethylsilane as internal standard, except where otherwise indicated. A Varian HA100 (100 Megacycles) instrument was used in one case. Mass spectra were generally taken on an A.E.I.-G.E.C. - M.S.12 mass spectrometer. A few, including a high resolution spectrum, were recorded on an A.E.I.-G.E.C. - M.S.9 instrument.

Petrol refers to light petroleum fraction, b.p. 60--80°, unless otherwise stated. Dry pyridine for Castro coupling reactions was distilled from barium oxide and stored over potassium hydroxide pellets. Nitrogen (for Castro reactions) was purified by passing through Fieser's solution[165] and blue silica gel. Jones reagent[158] (345 ml.) was prepared from chromium trioxide (87·5 g.), water (250 ml.) and concentrated sulphuric acid (74 ml.). Cuprous phenylacetylide was prepared using excess ammonical cuprous chloride[150] by the method of Jacobs[151] and dried on the rotary evaporator at 30-40° for 15 minutes.

Warning: Although cuprous acetylides have been handled safely by many workers, they should be regarded as potentially explosive substances and handled with care, especially when dry.

EXPERIMENTAL

Cuprous derivative (148) of phenylethynylcarbinol (146).

Ammoniacal cuprous chloride was prepared in the usual way[150] from cupric sulphate pentahydrate (9 g.). A solution of phenylethynylcarbinol (3·18 g.) in a little ethanol was added, the mixture stoppered and shaken thoroughly, and the yellow precipitate filtered off and washed five times each with water, ethanol and ether. Drying in a vacuum desiccator gave the cuprous derivative (2·8 g., 60%) as a yellow solid.

It was noticed that the cuprous derivative darkened slowly on standing and after 3 months was a brownish orange colour and exhibited a faint odour not unlike benzaldehyde or phenyl ethynyl ketone. Hydrolysis of a small sample in the usual way (p.172) gave a product which was shown by i.r. and t.l.c. (20% ethyl acetate/petrol) to be still mainly phenylethynylcarbinol, but containing small amounts of impurities (although no detectable amounts of benzaldehyde or phenyl ethynyl ketone).

Attempted Castro-type coupling of the cuprous derivative (148) with iodobenzene.

Iodobenzene (1·15 g.) and the cuprous derivative (148) (1 g.) of phenylethynylcarbinol were added to dry pyridine (80 ml.) and the mixture was heated under reflux in a nitrogen atmosphere for 6½ hours. After being allowed to cool, the reaction mixture was poured into an excess of dilute sulphuric acid and ice, extracted with ether, dried (magnesium sulphate) and filtered. After evaporation of the solvent, a little pyridine still appeared to be present, and this was removed by azeotroping with benzene. The crude product (~0·82 g., but both products rather volatile) appeared from its i.r. spectrum (liquid film) to consist of a mixture of benzaldehyde and iodobenzene. T.l.c. (20% ethyl acetate/petrol) also showed that iodobenzene and benzaldehyde were the main constituents of the mixture.

Behaviour of the cuprous derivative (148) under Castro-type conditions.

Dry pyridine (50 ml.) was purged with nitrogen for

1 hour, the cuprous derivative (0·6 g.) of phenylethynylcarbinol was added, and the mixture heated under reflux in a nitrogen atmosphere for 7 hours. The reaction mixture, which became black shortly after heating was commenced, was allowed to cool, was filtered to remove a black solid, and was poured into an excess of dilute H_2SO_4 and ice and extracted twice with ether. The combined ethereal extracts were washed with dilute sulphuric acid and brine, dried (magnesium sulphate) and filtered. Evaporation of the solvent gave the crude product ($\sim$ 60 mg., 18%) which showed one major spot on t.l.c. (20% ethyl acetate/petrol) of identical R_F value and staining properties to benzaldehyde. The i.r. spectrum (liquid film) was very similar to that of an authentic sample of benzaldehyde. The yield of benzaldehyde would have been higher but for the earlier removal of a considerable portion of the reaction mixture. The volatility of the product is probably also partly responsible for the low yield.

Stability of phenylethynylcarbinol (146) under Castro-type conditions.

Phenylethynylcarbinol (146) (1·19 g.) was dissolved in dry pyridine (50 ml.) and the solution was heated under reflux in a nitrogen atmosphere for 6½ hours. The reaction mixture was allowed to cool, was poured into an excess of dilute sulphuric acid and ice, and was extracted twice with ether. The combined ethereal extracts were washed with dilute sulphuric acid and brine, dried (magnesium sulphate) and filtered. Evaporation of the solvent gave unchanged phenylethynylcarbinol (146) (1 g., 84%) as an oil. The i.r. spectrum (liquid film) was practically identical to that of the starting material, and t.l.c. (20% ethyl acetate/petrol) showed only one spot, of identical R_F value to (146).

Reaction of phenylethynylcarbinol (146) and cuprous phenylacetylide under Castro-type conditions.

Phenylethynylcarbinol (146) (130 mg.) was dissolved in dry pyridine (10 ml.) and the solution was purged with nitrogen for 10 minutes. Cuprous phenylacetylide (164 mg.) (p. 81) was added and the mixture was heated under reflux in a nitrogen atmosphere for 2 hours. It was noticed that the reaction mixture turned dark just before boiling commenced and stayed a similar colour to the end of the reaction. After being allowed to cool, the reaction mixture was poured into an excess of dilute sulphuric acid and ice and extracted three times with ether. The combined ethereal extracts were filtered to remove insoluble material (of darker colour than in normal coupling reactions), washed with dilute sulphuric acid, sodium bicarbonate solution and brine, dried (anh. sodium sulphate) and filtered. Evaporation of the solvent gave a dark oil (~150 mg., but major products both rather volatile) which was shown by i.r. and t.l.c. (20% ethyl acetate/petrol) to consist mainly of benzaldehyde and phenylacetylene.

Attempted reaction of (146) and cuprous iodide under Castro-type conditions.

Phenylethynylcarbinol (146) (132 mg.) was dissolved in dry pyridine (10 ml.) and the solution was purged with nitrogen for 10 minutes. Cuprous iodide (192 mg.) was added and the solution was heated under reflux in a nitrogen atmosphere for 2 hours. The reaction was worked up as in the above experiment to give practically unchanged (146) (123 mg. 93%), as a dark oil. T.l.c. (20% ethyl acetate/petrol) showed essentially one spot, of identical R_F value to (146), and the i.r. spectrum (liquid film) was also practically identical to that of starting material.

1-Acetoxy-1-phenyl-2-propyne (154).

A solution of phenylethynylcarbinol (4·32 g.) in acetic anhydride (10 ml.) and dry pyridine (5 ml.) was stoppered and allowed to stand at room temperature for 24 hours, before pouring into water (~ 20 ml.) and extracting with ether (2 x 75 ml.). The combined ethereal extracts were washed with dilute sulphuric acid and sodium carbonate solution, dried (magnesium sulphate) and filtered. Evaporation of the solvent gave the crude acetate (6·25 g.), distillation of 6·1 g. of which gave, after a small forerun, 1-acetoxy-1-phenyl-2-propyne (154) (4·76 g., 86%), b.p. 117-118·5°/12 mm., (lit.,[166] 124°/18 mm.), one spot on t.l.c. (20% ethyl acetate/petrol). The i.r. spectrum (liquid film) was devoid of absorption in the hydroxyl region, and showed strong absorption at ~1740 cm^{-1} (ν C=O). The n.m.r. spectrum showed peaks at $\tau = 2·6$ (5H, multiplet, aromatic protons); $\tau = 3·57$ (1H, doublet, J = 2-3 cps., benzylic proton); $\tau = 7·37$ (1H, doublet, J = 2-3 cps., acetylenic proton); $\tau = 7·9$ (3H, singlet, methyl protons).

<u>Cuprous derivative (156) of 1-acetoxy-1-phenyl-2-propyne (154)</u>.

Cuprous iodide (2·25 g., ~3% excess) was dissolved in 30ml. dimethylsulphoxide in a nitrogen atmosphere and 1-acetoxy-1-phenyl-2-propyne (154) (2 g.) was added. To the solution was added rapidly, with stirring, sodium bicarbonate solution (280 ml.). The yellow precipitate was filtered off, washed five times with water, twice with ethanol (washings strongly yellow coloured) and five times with ether, and was then dried on the rotary evaporator at 40-45° for $1^3/4$ hours to give the cuprous derivative (2·41 g., 89%) as a yellow solid.

Attempted Castro-type coupling of the cuprous salt (156) with iodobenzene.

Dry pyridine (50 ml.) was heated under reflux in a nitrogen atmosphere, and refluxing was then stopped. Iodobenzene (1·72 g.) was added, followed by the cuprous salt (156) (2·015 g.) of 1-acetoxy-1-phenyl-2-propyne. Addition of the cuprous salt caused a rather vigorous reaction and the mixture immediately turned dark. The mixture was heated under reflux in a nitrogen atmosphere for 7 hours, was allowed to cool, and was poured into an excess of dilute sulphuric acid and ice before extracting thoroughly with ether. The insoluble material obtained was greenish blue in colour unlike that obtained in normal coupling reactions. The ethereal extract was washed with water, sodium bicarbonate solution and water, dried (anh. sodium sulphate) and filtered. Evaporation of the solvent gave a dark oil (1·05 g.), the i.r. spectrum (liquid film) of which suggested that it was largely iodobenzene. T.l.c. (20% ethyl acetate/petrol) showed a major spot of R_F 0·3 (in addition to iodobenzene) but preparative t.l.c. of 90 mg. (Kieselgel G, 0·5 mm., 20% ethyl acetate/petrol) gave only a very small amount of a dark oil, the i.r. spectrum of which was devoid of carbonyl absorption but showed broad absorption at 3450 cm^{-1} and 1240 cm^{-1}.

1-Phenyl-1-(2'-tetrahydropyranyloxy)-2-propyne (155).

Phenylethynylcarbinol (146) (4·47 g.) and dihydropyran (3·03 g., ~7% excess, redistilled, b.p. 85-86°) were stirred until homogeneous, and phosphorus oxychloride (1 drop) was added. The mixture soon became warm and was cooled under the tap for a short time before stoppering and stirring at room temperature for 3 hours. The reaction mixture was diluted with ether, washed with dilute potassium hydroxide solution and brine, dried (anh. sodium sulphate) and filtered. Evaporation of the solvent and excess dihydropyran gave the crude tetrahydropyranyl ether (7·26 g., 99%) as a clear yellow oil, essentially one spot on t.l.c. (20% ethyl acetate/petrol). The i.r. spectrum (liquid film), which was devoid of absorption in the hydroxyl region, showed absorption at 3340 cm^{-1} (strong, $\nu \equiv C-H$) and 2150 cm^{-1} (weak, ν $C \equiv C$), at 2900 cm^{-1} and 2980 cm^{-1} (ν C-H) and in the ν C-O region at $\sim$990-1200 cm^{-1}. Attempted distillation of the product caused some formation of the starting phenylethynylcarbinol and the crude product was therefore used without purification. Hydrolysis to phenylethynylcarbinol (146) and acetolysis to 1-acetoxy-1-phenyl-2-propyne (154) were carried out as described below.

Hydrolysis of 1-phenyl-1-(2'-tetrahydropyranyloxy)-2-propyne (155).

The tetrahydropyranyl ether (155) (379 mg.) was heated under reflux in dry methanol (10 ml.) with a trace of p-toluenesulphonic acid for 3 hours. The reaction mixture was poured into water (50 ml.) and extracted three times with ether. The combined ethereal extracts were washed with saturated sodium carbonate solution, water and brine, dried (anh. sodium sulphate) and filtered. Evaporation of the solvent gave the crude product (294 mg.) as an oil. T.l.c. (20% ethyl acetate) showed essentially one spot, of identical R_F value to phenylethynylcarbinol. The i.r. spectrum (liquid film), after evaporation of some volatile material, probably 2-methoxytetrahydropyran, was practically identical to that of phenylethynylcarbinol (146).

<u>Acetolysis of 1-phenyl-1-(2'-tetrahydropyranyloxy)-2-propyne (155)</u>

The tetrahydropyranyl ether (155) (259 mg.) was heated under reflux in acetic anhydride (5 ml.) for 24 hours. The reaction mixture was treated with methanol to remove acetic anhydride, and the solvent was evaporated. The residue was taken up in ether, washed with 50% sodium carbonate solution and brine, dried (anh. sodium sulphate) and filtered. Evaporation of the solvent gave the crude acetate (plus by-products) (260 mg.) as a brownish oil. Preparative t.l.c. (Kieselgel G, 0.5 mm., 20% ethyl acetate/petrol) of the crude product (56 mg.) gave 1-acetoxy-1-phenyl-2-propyne (154) (21 mg., 47%) as a clear oil, identical to an authentic sample in t.l.c. behaviour and i.r. and n.m.r. spectra.

Cuprous derivative (157) of 1-phenyl-1-(2'-tetrahydropyranyloxy)-2-propyne (155).

Cuprous iodide (2·6 g., ~ 10% excess) was stirred in dimethyl sulphoxide (32 ml.) under a nitrogen atmosphere till solution was complete. The tetrahydropyranyl ether (155) (2·7 g.) was added, and to the resulting yellow solution was added rapidly with stirring, sodium bicarbonate solution (280 ml.). After a few minutes stirring (under nitrogen), the yellow precipitate was filtered off, washed eight times with water, five times each with ethanol and ether, and dried on the rotary evaporator at 35-45° for 35 minutes to give the cuprous derivative (2·72 g., 78%) as a light yellow solid.

1,3-Diphenyl-1-(2'-tetrahydropyranyloxy)-2-propyne (158)

(a) From Castro coupling reaction of the cuprous salt (157) with iodobenzene.

Dry pyridine (100 ml.) was heated under reflux in a nitrogen atmosphere for ½ hour and then allowed to cool for 10 minutes. Iodobenzene (2·04 g.) and the cuprous derivative (157) (2·63g) of 1- phenyl-1-(2'-tetrahydropyranyloxy)-2-propyne (155) were added, and the mixture was heated under reflux in a nitrogen atmosphere for 10 hours. After being allowed to cool, the reaction mixture was poured into an excess of dilute sulphuric acid and ice, and extracted three times with ether. The combined ethereal extracts were washed with dilute sulphuric acid and saturated sodium carbonate solution, dried (anh. sodium sulphate) and filtered. Evaporation of the solvent gave the crude product (2·27 g., 83%, still containing some iodobenzene) as a dark oil which partly solidified on standing. The i.r. spectrum (liquid film) was free of terminal acetylenic absorption, and apart from some peaks corresponding to iodobenzene, was identical to that of an authentic sample of 1,3-diphenyl-1-(2'-tetrahydropyranyloxy)-2-propyne (158) prepared from the corresponding alcohol (153) as described below. T.l.c. (20% ethyl acetate/petrol) showed essentially one spot, of identical R_F value to (158).

(b) From the alcohol (153) and dihydropyran.

1,3-Diphenyl-2-propyn-1-ol (153) (1·8 g.) was stirred with dihydropyran (0·9 g., ~ 25% excess, redistilled, b.p. 85-87°) and phosphorus oxychloride (1 drop) was added. The mixture soon became warm and was cooled under the tap for a short time before stoppering and stirring at room temperature for 1 hour. The crude product, which had partly solidified, was dissolved in ether (~100 ml.), which was then washed with dilute potassium hydroxide solution and brine, dried (anh. sodium sulphate) and filtered. Evaporation of the solvent (and excess dihydropyran) gave the crude tetrahydropyranyl ether (158) (2·6 g., ~ quant.) as an oil which soon became semi-solid. T.l.c. (20% ethyl acetate/petrol) showed essentially one spot. The i.r. spectrum was devoid of absorption in the hydroxyl region, and showed absorption at 2900 and 2980 cm^{-1} (ν C-H), at ~ 2250 cm^{-1} (weak, ν C≡C) and in the ν C-O region at ~ 970-1200 $cm.^{-1}$. The n.m.r. spectrum showed clearly the presence of two diastereomers (see also p.120), the benzylic proton appearing as two singlets at 4·27 and 4·37 τ.

1,3-Diphenyl-2-propyn-1-ol (153).

(a) Phenylacetylene magnesium bromide/benzaldehyde method.

An ethereal solution of ethyl magnesium bromide was prepared under nitrogen from magnesium (3·4 g.), ethyl bromide (18 g.) and sodium dried ether (80 ml.) and the solution was cooled in an ice bath. A solution of phenylacetylene (13·2 g., redistilled, b.p. 142-144^{o}) in sodium dried ether (20 ml.) was added and the mixture was heated under reflux in a nitrogen atmosphere for 5 hours and then cooled in an ice/salt bath. A solution of benzaldehyde (10·4 g., redistilled) in sodium dried ether (20 ml.) was added over 5 minutes and the mixture was stirred at room temperature for 20 minutes. Saturated aqueous ammonium chloride solution was carefully added, followed by dilute hydrochloric acid. The ethereal layer was extracted with ether, and the combined ethereal extracts were washed with sodium bicarbonate solution and brine, dried (anh. sodium sulphate) and filtered. Evaporation of the solvent gave the crude product (23·3 g.) as an orange oil. Unreacted phenylacetylene was removed by distillation at the water pump and the residue was distilled at the oil pump to give, after a small forerun, 1,3-diphenyl-2-propyn-1-ol (153) (14·7 g., 72%), b.p. 176-182°/~2 mm. (lit.,[152] 180°/5 mm.). T.l.c. (20% ethyl acetate/petrol) showed essentially one spot, but traces of impurity were definitely present. The i.r. spectrum (liquid film) showed strong absorption at ~3500 cm^{-1} (broad, ν O-H) and weak absorption at 2250 cm^{-1} (ν C≡C), and in the n.m.r. spectrum the following peaks were observed: τ = 2·27-2·9 (10H, multiplet, aromatic protons); τ = 4·36 (1H, singlet, carbinyl proton); τ = 7·58 (1H, broad singlet, disappears on D_2O exchange, hydroxyl proton).

(b) Sodium phenylacetylide/benzaldehyde method.

A suspension of sodamide in liquid ammonia was prepared in the usual way[128] from sodium (1·4 g., 61 m.moles) in liquid ammonia (120 ml.) using a small amount of ferric nitrate as catalyst. A soda lime drying tube was attached, the suspension was stirred for 3 hours, and more liquid ammonia was added to make good losses by evaporation. A solution of phenylacetylene (6 g., 59 m.moles, redistilled, b.p. 140-141°) in sodium dried ether (25 ml.) was added over 5 minutes, followed after 30 minutes stirring by a solution of benzaldehyde (4 g., 38 m.moles, redistilled) in sodium dried ether (15 ml.), and the mixture was stirred for 8 hours. Solid ammonium chloride (8 g.) was added carefully, followed by ether, and the mixture was stirred overnight. The ethereal solution was poured off, the residue dissolved in water and extracted with ether, and the combined ethereal extracts were washed with dilute sulphuric acid, saturated sodium bicarbonate solution and brine, dried (anh. sodium sulphate) and filtered.

Evaporation of the solvent gave the crude product (8 g.) as an oil. Distillation at the water pump removed relatively volatile material (mainly unreacted phenylacetylene and benzaldehyde) and the residue was distilled at the oil pump to give 1,3-diphenyl-2-propyn-1-ol (153) (3·05 g., 15 m.moles, 39%), b.p. 144-148°/0·7 mm. (lit.,[152] 180°/5 mm.). The i.r. spectrum (liquid film) was identical to that of the material prepared by the Grignard method and t.l.c. (20% ethyl acetate/petrol) again showed essentially one spot (of identical R_F value to the Grignard product) with traces of impurity.

Hydrolysis (and oxidation) of the tetrahydropyranyl ether (158).

(a) Methanol/p-toluenesulphonic acid

Treatment of (158) with dry methanol and p-toluenesulphonic acid in the usual way (p. 91) led to the formation of a second compound (in high yield) in addition to the desired alcohol. This second compound, which on one run was practically the sole product, appeared to be 1,3-diphenyl-1-methoxy-2-propyne (159) from comparison of its i.r. and t.l.c. properties with that of a sample prepared from the alcohol (153) itself by similar treatment with methanol/p-toluenesulphonic acid and purified by preparative t.l.c. The i.r. spectrum showed a sharp peak at 2840 cm^{-1} (ν C-H, O-CH_3) and the n.m.r. (sample prepared from alcohol) showed singlets at $\tau = 4{\cdot}7$ (1H) and $\tau = 6{\cdot}51$ (3H) in addition to the aromatic multiplet at $\tau = 2{\cdot}33 - 2{\cdot}8$.

Treatment of (158) with methanol and aqueous hydrochloric acid at room temperature led to a similar mixture, and heating with dry ethanol and p-toluenesulphonic acid also gave a second product.

(b) Jones reagent.

The tetrahydropyranyl ether (158) (126 mg.) was dissolved in acetone (~1 ml.) and stirred in an ice bath. Jones reagent (p. 81) (0·6 ml.) was added and the mixture was stirred at room temperature for 75 minutes before diluting with water and extracting twice with ether. The combined ethereal extracts were washed with saturated sodium bicarbonate solution and brine, dried (anh. sodium sulphate) and filtered.

Evaporation of the solvent gave 1,3-diphenyl-2-propyne-1-one (160) (66 mg., 75%), identical to an authentic sample (p.105) by i.r. and t.l.c.

(c) Acetone/sulphuric acid.

The tetrahydropyranyl ether (158) (140 mg.) was dissolved in acetone (2·5 ml.) and sulphuric acid (0·8 ml., 75% by volume) was added. After stirring at room temperature for 6 hours, the mixture was diluted with water and worked up as in the Jones oxidation above to give the crude product (97 mg.) as an oil. T.l.c. and i.r. suggested that the product was mainly the desired alcohol (153) but contained a little starting material (158). The composition of the mixture seemed to be very similar to that obtained when the reaction was stopped after 1½ hours. Preparative t.l.c. of 52 mg. (Kieselgel G, 0·5 mm., 20% ethyl acetate/petrol) gave 1,3-diphenyl-2-propyn-1-ol (153) (27 mg., 51%) and unreacted tetrahydropyranyl ether (158) (6 mg., 8%), both products having the expected i.r. and t.l.c. properties.

Phenyl ethynyl ketone (161).

Phenylethynylcarbinol (146) (6·74 g.) was dissolved in acetone (10 ml.) and stirred in an ice/salt bath under a nitrogen atmosphere. Jones reagent (p. 81) (13·5 ml.) was added over 50 minutes, the bath temperature being maintained at -10° to 0°, and the mixture was stirred for 1 hour at 0-10° (bath temperature) and for ½ hour at room temperature. T.l.c. (20% ethyl acetate/petrol) showed that a little starting material (146) was still present, and Jones reagent (1 ml.) was added as above and stirring continued for ½ hour at room temperature. The mixture was diluted with water (∿150 ml.) and extracted three times with ether. The combined ethereal extracts were washed with saturated sodium bicarbonate solution and water, dried (anh. sodium sulphate) and filtered. Evaporation of the solvent gave the crude ketone (6·3 g., 95%). Crystallisation from aqueous methanol with ice/salt bath cooling (followed by drying in a desiccator over silica gel) gave phenyl ethynyl ketone (5·12 g., 77%) as very pale yellow needles, m.p. 48-49·5° (lit.,[158] 50-51°), one spot on t.l.c. (20% ethyl acetate/petrol). The i.r. spectrum (melted film) showed the expected absorption at ~3300 cm^{-1} (ν C-H, medium), 2120 cm^{-1} (ν C≡C, strong) and ~1650 cm^{-1} (ν C=0, strong, broad or doublet). In the n.m.r. spectrum the following peaks were observed τ = 1·65-1·83 and τ = 2·25-2·48 (2H multiplets, aromatic protons); τ = 6·56 (1H, singlet, acetylenic proton).

Cuprous derivative (162) of phenyl ethynyl ketone (161).

Cuprous iodide (1·3 g., ~10% excess) was dissolved in dimethyl sulphoxide (16 ml.) under a nitrogen atmosphere and phenyl ethynyl ketone (0·81 g.) was added. To the resulting red solution was added rapidly with stirring, sodium bicarbonate solution (150 ml.). The red precipitate was filtered off, washed five times each with water, ethanol and ether, and dried on the rotary evaporator at 30-40° for 2 hours to give the cuprous derivative (1·24 g., >100%, probably contains cuprous iodide) as a red solid. Hydrolysis of the cuprous derivative (57 mg.) in the usual way (p.172) gave phenyl ethynyl ketone

(28 mg., 73%), essentially pure by t.l.c., i.r., and u.v., showing that the cuprous derivative obtained was at least 73% pure.

1,3-Diphenyl-2-propyne-1-one (160).

(a) Castro-type coupling reaction.

Dry pyridine (125 ml.) was purged with nitrogen for 1½ hours and iodobenzene (3·39 g.) and the cuprous derivative (3·26 g.) of phenyl ethynyl ketone were added. The mixture was heated under reflux in a nitrogen atmosphere for 5 hours (the cuprous derivative dissolving almost completely after 2 hours), and after being allowed to cool was poured into and excess of dilute sulphuric acid and ice and extracted three times with ether. The combined ethereal extracts were washed with dilute sulphuric acid, saturated sodium bicarbonate solution and brine, dried (anh. sodium sulphate) and filtered. Evaporation of the solvent gave the crude ketone (160) (3·14 g.) as a dark oil. Distillation of 2·74 g. gave 1,3-diphenyl-2-propyn-1-one (160) (1·46 g., 48%) as a light coloured liquid, b.p. 130-136°/0.04 mm. (lit.,[167] 136-139°/3 mm.) (excess iodobenzene being collected in the cold trap of the oil pump). The distilled product was identical by t.l.c., i.r., and n.m.r. to a sample of (160) prepared by Jones oxidation of the corresponding alcohol (153) as described below.

(b) Jones oxidation of 1,3-diphenyl-2-propyn-1-ol (153).

A solution of the alcohol (153) [1·06 g., already partially oxidised atmospherically to the ketone (160)] in acetone (1·5 ml.) was cooled in an ice bath. Jones reagent (p. 81) (1·5 ml.) was added dropwise and the mixture was stirred at room temperature for 30 minutes before diluting with water and extracting three times with ether. The combined ethereal extracts were washed with water, saturated sodium bicarbonate solution and brine, dried (anh. sodium sulphate) and filtered. Evaporation of the solvent gave the crude ketone (160) (980 mg., 93%) as an oil which could not be solidified on cooling. Crystallisation from aqueous ethanol gave 1,3-diphenyl-2-propyn-1-one (160) (535 mg., 51%) as off-white crystals, m.p. 45·5 - 47·5° (lit.,[159] 49°), essentiall one spot on t.l.c. (20% ethyl acetate/petrol). The i.r. spectrum (melted film) showed strong absorption at 2230 cm^{-1} (ν C≡C) and 1640 cm^{-1} (ν C=O) and the n.m.r. spectrum showed only the expected aromatic protons as multiplets at τ = 1·68 - 1·85 (2H) and 2·21-2·64 (8H).

Methyl o-iodobenzoate (144).

o-Iodobenzoic acid (20 g.) was heated in methanol (40 ml.) till solution was almost complete. Concentrated sulphuric acid (3 ml.) was then added carefully and the solution was heated under reflux for 2½ hours. The reaction mixture was allowed to cool, poured into water (150 ml.) and extracted thoroughly with ether. The combined ethereal extracts were washed with water, sodium carbonate solution and brine, dried (anh. sodium sulphate) and filtered. (Acidification of the sodium carbonate washings gave unchanged acid (1·86g., 9·3%)]. Evaporation of the solvent gave methyl o-iodobenzoate (18·5 g., 87·5%) as an almost colourless oil. T.l.c. (20% ethyl acetate/petrol) showed only one spot, and the i.r.

spectrum (liquid film) was identical to that of an authentic sample. The ester (144) was normally used without further purification, but after one run, the product was distilled, giving a 75% yield of methyl o-iodobenzoate, b.p. 139-141°/ 12 mm. (lit.,[168] 145-146°/16 mm.).

o-Iodobenzyl alcohol (145).

A solution of methyl o-iodobenzoate (18·5 g.) in sodium dried ether (175 ml.) was cooled to -70° in an acetone/dry ice bath. To the stirred solution was added a suspension of lithium aluminium hydride (3 g.) in sodium dried ether (75 ml.) over 40 minutes. The suspension was stirred at -70° for 40 minutes, removed from the dry ice bath and the various complexes destroyed by the careful addition of a saturated solution of sodium sulphate over 30 minutes. The ether was decanted off, the solid thoroughly extracted with ether, and the combined ethereal solutions were dried (anh. sodium sulphate) and filtered. Evaporation of the solvent gave the crude alcohol (14·9 g.). T.l.c. (20% ethyl acetate/petrol) showed a small amount of benzyl alcohol (R_F 0·3) in addition to the required alcohol (R_F 0·4). Crystallisation from boiling water gave o-iodobenzyl alcohol (11·86 g., 72%) as white needles, m.p. 88-90° (lit.,[168] 89·5-90°). T.l.c. now showed only one spot and the i.r. spectrum (liquid film) was identical to that of an authentic sample.

o-Iodobenzaldehyde (142).

(a) Ceric ammonium nitrate method.

The use of ceric ammonium nitrate in ~ 4% excess[135] failed to give complete conversion to the aldehyde. The use of 10-25% excess of the reagent was therefore investigated but again failed to give pure aldehyde. A typical experiment was as follows. A solution of ceric ammonium nitrate (25g., 45·6 m.moles) in 50% aqueous acetic acid (90 ml.) was added to o-iodobenzyl alcohol (145) (4·21 g., 18 m.moles). The deep red solution was warmed on the steam bath for a few minutes till the colour changed to pale yellow, and was allowed to cool. The ether extract of the reaction mixture was washed with 1·5M potassium hydroxide solution and brine, dried (magnesium sulphate) and filtered, and the solvent was evaporated to give the crude aldehyde (3·35 g., 80%). T.l.c. and i.r. suggested that o-iodobenzaldehyde was the main product, but three minor spots, one of which was due to starting material, were observed on t.l.c. (20% ethyl acetate/petrol).

(b) Nickel peroxide method.

o-Iodobenzyl alcohol (0·5 g.) was dissolved in dry benzene (4 ml.), nickel peroxide (0·74 g.) was added and the mixture was stirred and heated under reflux for 1 hour. The solid was filtered off and washed with benzene and the benzene solutions combined. T.l.c. (20% ethyl acetate/petrol) and i.r. spectroscopy showed that considerable starting material remained in addition to the aldehyde (142).

(c) Manganese dioxide method.

Manganese dioxide (30 g.) was stirred and heated in refluxing sodium dried benzene (200 ml.) for 1 hour with constant water separation. o-Iodobenzyl alcohol (7·5 g.) was added and heating under reflux was continued for a further 4 hours. The reaction mixture was allowed to cool, was filtered under suction, the manganese dioxide being washed eight times with benzene, and the combined benzene extracts were filtered through glass paper to give a clear solution. After evaporation of the solvent, the product was dissolved in ether, dried (anh. sodium sulphate) and filtered, and the solvent was evaporated to give o-iodobenzaldehyde (6 g., 81%) as an oil which solidified on chilling to a pale yellow solid, m.p. 33-36° (lit.,[168] 37°). T.l.c. (20% ethyl acetate/petrol) showed only one spot (R_F 0·7) and the i.r. spectrum (melted film) was practically identical to that of an authentic sample. (A very small band at 1640 cm^{-1} may be due to an impurity). The crude product was generally used without further purification.

On another run using the same quantities as above but a different batch of manganese dioxide, t.l.c. of a small sample extracted from the reaction mixture after 6 hours showed that some starting material remained. Manganese dioxide (30 g.) and sodium dried benzene (50 ml.) were added and refluxing was continued for a further 2½ hours. Only after addition of a further 10 g. of manganese dioxide and heating under reflux for a further 2½ hours, was the starting material essentially removed. Work up as above gave the crude aldehyde (7·4 g., 99%). Distillation gave, after a small forerun, o-iodobenzaldehyde (6·4 g., 89%), b.p. 128-131°/16 mm. (lit.,[129] 129°/14 mm.), which on standing gave a solid, m.p. 31-35° (lit.,[168] 37°). T.l.c. showed essentially one spot and the i.r. spectrum was identical to that of the crude product described above.

<u>1-(o-Iodophenyl)-2-propyn-1-ol (140)</u>.

(a) <u>Alkali metal acetylide method</u>.

A suspension of lithium amide in liquid ammonia was prepared in the usual way[128] from lithium (0·95 g., 137 m.moles) in liquid ammonia (120 ml.), using a small amount of ferric nitrate as catalyst, in a 250 ml. three-necked flask equipped with a dry ice condenser, a soda lime drying tube, and a magnetic stirrer. Cylinder acetylene (purified by passage through an acetone/dry ice trap, concentrated sulphuric acid, and solid potassium hydroxide) was passed in rapidly for 2-3 hours. For safety reasons, a mercury valve and empty wash bottles were also placed in the acetylene train. The passage of acetylene was slowed, a solution of o-iodobenzaldehyde (0·73 g., 3·15 m.moles) in sodium dried ether (6 ml.) was added, and the mixture was stirred for 3 hours. The acetylene flow was stopped, solid ammonium chloride (20 g.) was added carefully, followed by ether, and the ammonia was allowed to evaporate overnight. The ethereal solution was poured off, the solid extracted with ether, and the combined ethereal solutions were washed with dilute sulphuric acid (washings rather cloudy), saturated sodium carbonate solution and brine, dried (anh. sodium sulphate) and filtered. Evaporation of the solvent gave the crude product (776 mg.) as an oil. T.l.c.

(20% ethyl acetate/petrol) showed two spots, corresponding to (140) (R_F 0·5) and the starting material (R_F 0·8). The i.r. spectrum (liquid film) showed the presence of a fairly small amount of starting material (ν C=O at 1685 cm^{-1}) in addition to the required acetylenic carbinol (140). Preparative t.l.c. [Kieselgel G, 0·5 mm. (2 plates), 20% ethyl acetate/petrol] of 135 mg. gave 1-(o-iodophenyl)-2-propyn-1-ol (140) (68 mg., 48%), essentially identical by i.r., n.m.r., and t.l.c. to an authentic sample prepared by method (b) as described below.

The use of longer reaction times and the employment of a greater proportion of ether in the reaction mixture gave results very similar to those described above. An experiment using a ten-fold excess of lithium apparently resulted in less conversion to the carbinol (140). Sodium acetylide, even when employed in large excess and for longer reaction times, similarly failed to give complete conversion to (140). Recycling of the crude product [from o-iodobenzaldehyde

(2·3 g.), sodium (1·86 g.) and liquid ammonia (150 ml.)], however, twice more with excess sodium acetylide gave an oil (1·8 g.) which appeared from i.r. and t.l.c. evidence to be free of starting material. Distillation (of 1·355 g.) gave the carbinol (140) (0·88 g., 46%) as a clear liquid, b.p. 98-100°/0·2 mm., identical by i.r. and t.l.c. to an authentic sample (see below).

A trial run using benzaldehyde (1·56 g.), sodium (1·7 g., ~ five fold excess) and liquid ammonia (120 ml.) gave a crude yield of phenyl ethynyl carbinol (146) (pure by i.r. and t.l.c.) of 95%.

(b) Acetylenemonomagnesium bromide method.[127]

A solution of ethylmagnesium bromide in tetrahydrofuran was prepared under nitrogen from magnesium (5 g.), ethyl bromide (22 ml.) and dry tetrahydrofuran (125 ml., distilled from lithium aluminium hydride) in a 250 ml. three-necked flask. The Grignard solution was filtered under nitrogen, using more dry tetrahydrofuran (50 ml.), into a 250 ml.

pressure equilibrated dropping funnel, which was then stoppered at both ends. Meanwhile, dry tetrahydrofuran (100 ml.) in a 500 ml. three-necked flask was saturated for 40 minutes with cylinder acetylene (purified as described on p. 112 and with the same precautions). The acetylene flow was maintained from this point until the end of the reaction, and to this solution was added over 30 minutes with stirring, the Grignard solution prepared above, nitrogen flow through the dropping funnel also being used. After a further 30 minutes stirring, a solution of o-iodobenzaldehyde (4·54 g.) in dry tetrahydrofuran (40 ml.) was added (over 10 minutes), the mixture was stirred for 30 minutes, the flow of acetylene was stopped, and an excess of saturated aqueous ammonium chloride solution was carefully added. The tetrahydrofuran solution was filtered off, the residue extracted with ether, and the ether and tetrahydrofuran solutions were combined and the solvent evaporated. The residue was taken up in ether, dried (anh. sodium sulphate) and filtered. Evaporation of the solvent gave the crude carbinol (140) (5·14 g., ~ quant.), essentially one spot on t.l.c. (20% ethyl acetate/petrol).

Distillation gave, after a small forerun, 1-(o-iodophenyl)-2-propyn-1-ol (140), (4·45 g., 88%) as a clear liquid, b.p. 98-100°/0·15 mm., essentially one spot on t.l.c. The i.r. spectrum (liquid film) showed a sharp peak at 3340 cm^{-1} ($\nu \equiv C-H$) with a broad shoulder at ~3350-3600 cm^{-1} (ν O-H), and also weak absorption at 2150 cm^{-1} (ν $C \equiv C$). In the n.m.r. spectrum the following peaks were observed: $\tau = 2{\cdot}02 - 2{\cdot}3$ (2H, multiplet) and $\tau = 2{\cdot}42 - 3{\cdot}14$ (2H, multiplet) (aromatic protons); $\tau = 4{\cdot}34$ [1H, doublet (J = 6 cps.) of doublets (J = 2-3 cps.), collapsing to a doublet (J = 2-3 cps.) on D_2O exchange, carbinyl proton]; $\tau = 7{\cdot}35$ [1H, doublet (J = 2-3 cps.), acetylenic proton]; $\tau = 7{\cdot}48$ [1H, doublet (J = 6 cps.), disappearing on D_2O exchange, hydroxyl proton]. A small sample was purified for analysis by preparative t.l.c. (Kieselgel G, 0·5 mm., 20% ethyl acetate/petrol) and microdistillation, b.p. 90-100°(block)/0·03 mm. (Found: C, 41·88; H, 2·87. Required for C_9H_7IO: C, 41·89; H, 2·74%).

Cuprous derivative of 1-(o-iodophenyl)-2-propyn-1-ol (140).

Cuprous iodide (200 mg., 3% excess) was dissolved in dimethyl sulphoxide (2·5 ml.) in a nitrogen atmosphere and (140) (263 mg.) in dimethyl sulphoxide (1·5 ml.) was added. To the resulting solution was added rapidly with stirring, saturated sodium bicarbonate solution (40 ml.). The yellow precipitate was filtered off and washed five times each with water, ethanol and ether (washings all rather slow) and allowed to dry in air to give the cuprous derivative (183 mg., 56% if pure) as a yellow solid. The ethanol and ether washings of the cuprous derivative were combined and the solvent evaporated to give an oil (48 mg.) which appeared from t.l.c. (20% ethyl acetate/petrol) to consist of a mixture of (140) and o-iodobenzaldehyde.

Hydrolysis of the cuprous salt (29 mg.) in the usual way (p. 172) with dilute hydrochloric acid gave an oil (14 mg., 60%) which appeared from i.r. and t.l.c. to be almost pure (140).

Attempted intermolecular Castro coupling of the cuprous salt of (140).

Dry pyridine (6 ml.) was purged with nitrogen for 15 minutes and the cuprous salt of (140) (88 mg.) was added. The cuprous salt quickly dissolved without heating and a small aliquot of the reaction mixture was extracted. The pyridine was removed from this extracted sample by azeotroping with benzene, and the residue extracted with ether. The ether extract was shown by i.r. and t.l.c. to contain essentially pure o-iodobenzaldehyde. The ether insoluble material was hydrolysed in the usual way (p. 172) with dilute hydrochloric acid but practically no 1-(o-iodophenyl)-2-propyn-1-ol (140) could be detected.

1-(o-Iodophenyl)-1-(2'-tetrahydropyranyloxy)-2-propyne (163).

1-(o-Iodophenyl)-2-propyn-1-ol (140) (655 mg.) was stirred with dihydropyran (290 mg., 36% excess, redistilled, b.p. 85-86°) and phosphorus oxychloride (1 drop) was added. The mixture soon became warm and was cooled under the tap for a short time before stoppering and stirring at room temperature for 2 hours. The reaction mixture was diluted with ether, washed with dilute potassium hydroxide solution and brine, dried (anh. sodium sulphate) and filtered. Evaporation of the solvent and excess dihydropyran gave the crude tetrahydropyranyl ether (163) (875 mg., ~ quant.) as a clear yellow oil, essentially one spot [or two very close spots (diastereomers)] on t.l.c. (20% ethyl acetate/petrol). The i.r. spectrum was identical to that of a sample purified by preparative t.l.c. and microdistillation (see below) and the crude product was generally used without further purification. Preparative t.l.c. of 70 mg. (Kieselgel G, 0·5 mm., 20% ethyl acetate/petrol) gave the tetrahydropyranyl ether (163) (54 mg.), pure by t.l.c. A small sample was microdistilled, b.p. 100-140^o (block)/0·6 mm. (Found: C, 50·02; H, 4·59. Required for $C_{14}H_{15}IO_2$: C, 49·14; H, 4·42%). The mass spectrum showed peaks at $^m/e = 342$ (M^+) and $^m/e = 215$ ($M^+ - I$). The i.r. spectrum (liquid film) was devoid of hydroxylic absorption and showed absorption at 3340 cm^{-1} (strong, $\nu \equiv$C-H) and 2150 cm^{-1}

(weak, ν C≡C). The absorption in the C-H and C-O regions was very similar to that in the model compounds (155) and (158) (p. 90 and 95).

The n.m.r. spectrum (of material purified by preparative t.l.c.) showed clearly the presence of the expected two diastereomers. The benzylic proton appeared as two overlapping doublets (J = 2-3 cps.) at 4·32 and 4·36 τ and the acetylenic proton as two overlapping doublets (J = 2-3 cps.) at 7·41 and 7·46 τ. The benzylic proton collapsed to two singlets on irradiation at 7·43 τ and conversely the acetylenic proton appeared as two singlets on irradiation at 4·34 τ. The proton at position 2 in the tetrahydropyran ring appeared as two broadened triplets at 4·76 and 5·32 τ. Separation of the diastereomers was achieved by preparative t.l.c. (Kieselgel G, 0·5 mm, run twice in 10% ethyl acetate/petrol). The i.r. spectra (liquid film) of the two diastereomers showed slight differences, mainly in the ν C-O region. In the n.m.r. spectrum of the less polar diastereomer the benzylic proton appeared as a doublet (J = 2-3 cps.) at τ = 4·32, the acetylenic proton as a doublet (J = 2-3 cps.) at $\tau = 7{\cdot}46$ and the C_2 proton of the tetrahydropyran ring as a broadened triplet at $\tau = 4{\cdot}76$. For the more polar isomer the respective τ values were 4·36, 7·41 and 5·32. Differences were also observed for the C_6 protons (multiplets) of the tetrahydropyran ring.

Hydrolysis and oxidation of (163) with Jones reagent.

The tetrahydropyranyl ether (163) (11 mg.) was dissolved in acetone (1 ml.), Jones reagent (p.81) (0·1 ml.) was added, and the mixture was stirred for 100 minutes before diluting with water and extracting twice with ether. The combined ethereal extracts were washed with sodium bicarbonate solution and brine, dried (anh. sodium sulphate) and filtered. Evaporation of the solvent gave 1-(o-iodophenyl)-2-propyn-1-one (164) (6 mg., 70%) essentially pure by i.r. and t.l.c. comparison with an authentic sample (p.122).

1-(o-Iodophenyl)-2-propyn-1-one (164).

A solution of 1-(o-iodophenyl)-2-propyn-1-ol (140) (1·6 g.) in acetone (2 ml.) was stirred in an ice bath. Jones reagent (p. 81) (2·1 ml.) was added dropwise over 10 minutes and the mixture was stirred at room temperature for 2 hours before diluting with water and extracting three times with ether. The combined ethereal extracts were washed with water, saturated sodium bicarbonate solution and brine, dried (sodium sulphate) and filtered. Evaporation of the solvent gave the crude ketone (1·4 g., 88%) as a yellow oil which quickly solidified. T.l.c. (20% ethyl acetate/petrol) showed essentially one spot (R_F 0·6) with traces at R_F 0·4 (starting material) and R_F 0·8. Preparative t.l.c. (Kieselgel G, 0·5 mm., 20% ethyl acetate/petrol) gave the ketone (164), one spot on t.l.c. The i.r. spectrum (melted film) showed strong absorption at 3320 cm^{-1} (ν ≡C-H), 2120 cm^{-1} (ν C≡C) and 1660 cm^{-1} (ν C=O) with a shoulder at 1640 cm^{-1}. The u.v. spectrum (ethanol) had $\lambda_{max.}$ 221 (sh) (log ε 4·07), 230 (4·08), 269 (3·79), 277 (sh) (3·75) and 320 (3·35) mμ. The n.m.r. spectrum showed the following peaks: τ = 1·65-1·98 [2H, aromatic protons, probably overlapping doublets (J = ~7 c.p.s.) of doublets (J = 2-3 c.p.s.)]; τ = 2·27-2·9 (2H, multiplet, aromatic protons); τ = 6·52 (1H, singlet, acetylenic proton). Microdistillation gave 1-(o-iodophenyl)-2-propyn-1-one (164), b.p. $<100^\circ$ (block)/0·02 mm., quickly solidifying to yellow needles, m.p. 43-44·5°. (Found: C, 42·68; H, 2·06. Required for C_9H_5IO: C, 42·22; H, 1·97%). Alternatively purification could be carried out by column chromatography (1·27 g. of crude product) on silica (50 g.), using petrol (2 x 150 ml.) and then 5% benzene/petrol as eluent. The ketone (164) (785 mg.), pure by t.l.c., was obtained, but the i.r. spectrum showed traces of aliphatic C-H absorption resulting from petrol residues. This absorption was not completely removed, even after evacuation on the oil pump, but the product was sufficiently pure for preparation of the cuprous salt.

Cuprous derivative of 1-(o-iodophenyl)-2-propyn-1-one (164).

Cuprous iodide (475 mg., 10% excess) was dissolved under nitrogen in dimethyl sulphoxide (6 ml.) and a solution of the ketone (164) (580 mg.) in dimethyl sulphoxide (4 ml.) was added. The resulting orange solution was stirred vigorously under nitrogen and sodium bicarbonate solution (100 ml.) was added quickly. The orange precipitate was filtered off and washed with water, ethanol and ether, and dried on the rotary evaporator at 40-50° for ½ hour to give the cuprous salt (662 mg., ~93%) as an orange solid, which was then kept under nitrogen at 0°.

Hydrolysis after two weeks at room temperature of the cuprous salt (29 mg.) in the usual way (p.172) gave the crude ketone (164) (20 mg., 86%) as an oil which quickly solidified. T.l.c. (20% ethyl acetate/petrol) showed a faint spot (R_F 0·5) in addition to the ketone (164) (R_F 0·4). The i.r. spectrum was practically identical to that of (164).

Attempted intermolecular Castro coupling of the cuprous salt of (164).

(a) In refluxing pyridine.

Dry pyridine (10 ml.) was purged with nitrogen for 10 minutes, the cuprous salt of 1-(o-iodophenyl)-2-propyn-1-one (164) (90 mg.) was added and the mixture, which very quickly became dark, was refluxed under nitrogen for 1 hour. The reaction mixture was allowed to cool, poured into excess dilute hydrochloric acid and water and extracted three times with ether, some ether insoluble material being separately dissolved in chloroform. The combined ethereal extracts were washed with dilute hydrochloric acid, sodium bicarbonate solution and brine, dried (sodium sulphate) and filtered. T.l.c. (20% ethyl acetate/petrol) showed practically no product other than polar material at the origin and a few extremely faint fluorescent spots. (The chloroform extract similarly showed no identifiable products). The i.r. spectrum of the crude product (tarry film or nujol mull) showed fairly strong but rather broad absorption at 2950, 1705, 1600, 1580, 1280 and 760 cm^{-1}. The u.v. spectrum showed gradually increasing absorption with shortening wavelength, with peaks at 240 mμ and 280-290 mμ (plateau).

The use of dilute sulphuric acid in place of dilute hydrochloric, and the removal of pyridine under reduced pressure gave very similar results, tarry materials being isolated with very similar t.l.c., i.r., and u.v. properties to the above.

(b) In pyridine at room temperature.

Dry pyridine (6 ml.) was purged with nitrogen for 30 minutes, the cuprous salt of (164) (34 mg.) was added and the mixture was stirred under nitrogen at room temperature for 20 mins. The cuprous salt dissolved completely in this time and the solution became dark in colour. The pyridine was removed on the rotary evaporator, the residue first extracted with ether (A) and then with dilute hydrochloric acid and ether (B) as on p.172 . T.l.c. of solutions A and B showed no starting ketone (164), considerable polar material at the origin, some very faint non polar spots and one faint fluorescent spot. The i.r. and u.v. spectra were very similar to those described in (a) above.

(c) In dimethyl sulphoxide at 85°.

The cuprous salt of (164) (63 mg.) was added to dimethyl sulphoxide (5 ml., purged with nitrogen for 10 mins.) and the mixture was stirred under nitrogen ~85° for 30 mins., the cuprous salt dissolving and the mixture darkening after ~ 5 minutes. The mixture was allowed to cool, was diluted with ether, was washed thoroughly with water and concentrated. T.l.c. and i.r. properties were essentially identical to those above, and the u.v. spectrum showed broad absorption at 240 and 300 mμ. The weight of the ether extract was 8 mg.

Cuprous salt of 1-(o-iodophenyl)-1-(2'-tetrahydropyranyloxy)-2-propyne(163).

The tetrahydropyranyl ether (163) (1·035 g.) was dissolved under nitrogen in dimethyl sulphoxide (12 ml.), cuprous iodide (0·725 g., 25% excess) was added, and the mixture was stirred under nitrogen till solution was complete. Sodium bicarbonate solution (150 ml.) was added rapidly to the stirred solution and stirring under nitrogen was continued for 5 minutes. The rather oily yellow precipitate was washed five times with water, stirred thoroughly with ethanol, washed five times with ethanol, and after partially drying by suction was allowed to dry in air to give the cuprous salt of (163) (825 mg., contains excess cuprous iodide). The yield of cuprous salt, assuming ~50% purity (see below) was therefore ~33%. The ethanol washings were combined, the solvent was evaporated, and the residue was taken up in ether, washed with water, dried (sodium sulphate) and filtered. Evaporation of the solvent gave unchanged tetrahydropyranyl ether (163) (595 mg., 57·5%), essentially pure by i.r. and t.l.c. The cuprous salt of (163) was soluble in chloroform and apparently slightly soluble in ether, being found in the ether washings if the product was washed in ether. The i.r. spectrum (nujol mull) was free of absorption at 3340 cm^{-1} (ν ≡C-H) but was otherwise very similar to that of the free tetrahydropyranyl ether. The ν C≡C absorption could not be definitely observed.

Hydrolysis of the cuprous salt (24 mg.) in the usual way (p.172) with dilute hydrochloric acid gave the tetrahydropyranyl ether (163) (10 mg., 50%) as an oil, essentially pure by i.r. and t.l.c.

Attempted intermolecular Castro coupling of the cuprous salt of (163).

(a) In refluxing pyridine

A typical experiment was as follows. Dry pyridine (10 ml.) was purged with nitrogen for 15 minutes, the cuprous salt of the tetrahydropyranyl ether (163) (427 mg., ~50% pure) was added, and the mixture was refluxed under nitrogen for 4 hours before adding to excess dilute hydrochloric acid and ice and extracting thoroughly with ether. (A large amount of insoluble material was filtered off at this stage, but the amount appeared to be less on more dilute runs). The ether extract was washed with dilute hydrochloric acid and saturated sodium bicarbonate solution and dried (sodium sulphate). Before complete removal of the solvent to give a dark tarry oil (75 mg.) (complex mixture by t.l.c.), the u.v. spectrum (ethanol) of an aliquot of the concentrated solution was run, and had λ_{max} 230 and 274 mμ with shoulders at 264, 293 and 307 mμ. The approximate optical density was measured and the extinction coefficient is discussed on p.75. The i.r. spectrum (film) was not identical in the cases examined (p.69).

Small samples of the crude product were treated with either excess Jones reagent[158] in acetone (2 ml.) (20 mins. at 0°) or with methanol (5 ml.) containing a trace of p-toluenesulphonic acid (PTSA) (1 hour reflux) and the reactions were worked up in the usual way (see e.g., p.102 and 91). The results are discussed on p.69-70. Separation of the products of the coupling reaction and of the methanol/PTSA reaction was briefly investigated using preparative t.l.c. (Kieselgel G, 0·5 mm., 20% ethyl acetate/petrol) (see p. 68 and 70).

(b) In pyridine at room temperature

Dry pyridine (5 ml.) was purged with nitrogen for 5 minutes, the cuprous salt of (163) (35 mg.) was added and the mixture was stirred under nitrogen for 24 hours at room temperature before removal of the pyridine by azeotroping with benzene. The crude product was extracted with ether and the ether extract filtered and evaporated to give an oil (8 mg.), essentially one spot on t.l.c. (20% ethyl acetate/petrol) of identical R_F value and staining properties to a sample of the oxidatively coupled product (167) prepared as described on p.132, though apparently containing a trace of unreacted (163). The i.r. spectrum (liquid film) showed only a trace of terminal acetylene absorption at 3340 cm^{-1} and was otherwise practically identical to that of a sample of (167). The u.v. spectrum (ethanol) showed weak absorption at 250 and 264 mμ, identical to that observed for (167).

(c) In pyridine at 85°.

Dry pyridine (5 ml.) was purged with nitrogen for 10 minutes, the cuprous salt of (163) (33 mg.) was added and the solution was stirred under nitrogen in an oil bath maintained at ~85° for 2½ hours. The pyridine was removed by azeotroping five times with benzene, the residue ether extracted and the ether evaporated to give an oil (11 mg.). T.l.c. (20% ethyl acetate/petrol) suggested that the product contained the oxidatively coupled compound (167) and at least one or two more polar compounds, but the mixture was less complex than that obtained in refluxing pyridine. The i.r. spectrum (liquid film) showed only a little carbonyl absorption and no free acetylene absorption, but characteristic tetrahydropyranyl ether absorption at 975-1200 cm^{-1}. The u.v. spectrum (ethanol) showed a rather small peak at ca. 275 mμ but overall the absorption increased with shortening wavelength with additional shoulders at 231, 244 and 257 mμ. Re-examination of the t.l.c. of this product, and that of a repeat reaction in which the pyridine was purged with nitrogen at 85° before addition of the cuprous salt, suggested that the amount of oxidatively coupled product (167) might be rather low, but lack of time prevented further investigation of the nature of the reaction product.

Oxidative coupling of the tetrahydropyranyl ether (163).

1-(o-Iodophenyl)-1-(2'-tetrahydropyranyloxy)-2-propyne (163) was dissolved in pyridine/methanol (50:50) (3 ml.), cupric acetate (68 mg.) was added and the mixture was heated under reflux for 1 hour before removal of the solvent by azeotroping with benzene. The residue was extracted thoroughly with ether, and the ether extract filtered and the solvent evaporated to give a yellow oil (39 mg.). T.l.c. (20% ethyl acetate/petrol) showed essentially one spot, running closely behind a small amount of unreacted (163). Preparative t.l.c. (Kieselgel G, 0·5 mm., 20% ethyl acetate/petrol) gave the oxidatively coupled product (167) (24·5 mg., 63%). The i.r. spectrum (liquid film) was devoid of terminal acetylenic absorption at 3340 cm^{-1}, but showed characteristic tetrahydropyranyl ether absorption at 975-1200 cm^{-1} (νC-O) and 2980 and 2900 cm^{-1} (νC-H). The n.m.r. spectrum showed the following peaks: τ = 2·08-3·17 (8H, multiplet, aromatic protons); τ = 4·27 and 4·32 ($\sim$3:1 ratio) (2H, singlets, benzylic protons); τ = 4·83 and 5·33 (2H, broadened triplets, C_2 protons of ether rings); τ = 5·7-6·7 (4H, multiplet,

C_6 protons of ether rings); $\tau = 8{\cdot}33$ (12H, envelope, ring methylene protons).

3-o-Formylphenyl-1-o-iodophenyl-1-(2'-tetrahydropyranyloxy)-2-propyne (165).

A solution of o-iodobenzaldehyde (212 mg.) in dry pyridine (15 ml.) was purged with nitrogen for 10 minutes and the cuprous salt of 1-(o-iodophenyl)-1-(2'-tetrahydropyranyloxy)-2-propyne (163) (95 mg., ~50% pure) was added. The mixture was refluxed under nitrogen for 4½ hours, allowed to cool, poured into excess dilute hydrochloric acid and ice and extracted thoroughly with ether. The ether extract was washed with dilute hydrochloric acid, sodium bicarbonate solution and brine, dried (anh. sodium sulphate) and filtered, and the solvent evaporated. Preparative t.l.c. (Kieselgel G, 0·5 mm., 3 plates, 20% ethyl acetate/petrol) of the crude product (224 mg. dark oil, two major spots on t.l.c.) gave, in addition to o-iodobenzaldehyde (157 mg.), the coupling product (165) (24 mg., 46% based on cuprous salt) as a yellow oil, essentially one spot on t.l.c. The i.r. spectrum (liquid film) was devoid of terminal acetylene absorption, showed strong absorption at 2980 and 2900 cm^{-1} (νC-H) and at 1695 cm^{-1} (νC=O), and characteristic absorption in the νC-O region at $\sim$990-1200 cm^{-1}. The n.m.r. spectrum showed the following peaks, indicating the presence of two diastereomers: τ = -0·5, -0·47 (1H, singlets, aldehyde proton); τ = 2·01-3·1 (8H, multiplet, aromatic protons); τ = 4·07, 4·1 (1H, singlets, benzylic proton); τ = 4·7, 5·25 (1H, broad singlets, C_2 proton on ether ring); τ = 5·8-6·6 (2H, multiplet, C_6 protons on ether ring); τ = 8·27 (6H, envelope, ring methylene protons). Microdistillation of (165), b.p. 120-150° (block)/ 0·4 mm., caused decomposition, the distilled material showing 2 clean spots on t.l.c. (20% ethyl acetate/petrol), R_F 0·3 and R_F 0·6 (165). The mass spectrum of undistilled (165) showed peaks at m/e = ca. 446 (M^+) and ca. 319 (M^+ - I). ($C_{21}H_{19}O_3I$ requires M.W. 446).

The di(tetrahydropyranyl ether) (168).

A solution of 1-(o-iodophenyl)-1-(2'-tetrahydropyranyloxy)-2-propyne (163) (433 mg.) in dry pyridine (25 ml.) was purged with nitrogen for 10 minutes, the cuprous salt of (163) (276 mg., ~50% pure) was added, and the mixture was refluxed under nitrogen for 4 hours. The pyridine was removed by azeotroping with benzene six times, the residue was extracted thoroughly with ether, and the ether extract filtered and the solvent evaporated to give an oil (500 mg.), two major spots on t.l.c. (20% ethyl acetate/petrol). Preparative t.l.c. (Kieselgel G, 0·5 mm., 8 plates, 20% ethyl acetate/petrol) gave, in addition to unchanged (163) (304 mg.), the coupling product (168) (64 mg., 34% based on cuprous salt), essentially one spot on t.l.c. The i.r. spectrum showed medium absorption at 3340 cm^{-1} (ν≡C-H) and very weak, though reproducible, absorption at 2250 cm^{-1} (ν R-C≡C-R) and 2140 cm^{-1} (ν R-C≡C-H), as well as characteristic tetrahydropyranyl ether absorption at 2980 and 2900 cm^{-1} (νC-H) and 990-1200 cm^{-1} (νC-O). The u.v. spectrum (ethanol) had λ_{max} 233, 247 and 257 mμ. The n.m.r. spectrum, complicated by the number of diastereomers present, showed the following peaks: τ = 2·03-3·17 (8H, multiplet, aromatic protons); τ = 4·1 (apparent doublet) and τ = 4·3 (apparent triplet) (ratio ca. 5:1) (2H total, benzylic protons); τ 4·67, τ = 4·83 (broad singlets) and τ = 5·07-5·5 (multiplet) (integrals ca. equal) (2H totals, C_2 protons on ether rings); τ = 5·7-6·8 (4H, multiplet, C_6 protons on ether rings); τ = 7·4-7·6 (1H, multiplet, acetylenic proton); τ = 8·3 (12H, envelope, ring methylene protons). Attempted distillation at 0·8 mm. pressure caused decomposition and a mass spectrum of the crude product could not be obtained but further confirmation of the structure of (168) was obtained from conversion of (168) to (169) with Jones reagent.

Cuprous salt of the di(tetrahydropyranyl ether) (168) and attempted intramolecular Castro coupling.

The di(tetrahydropyranyl ether) (168) (17 mg.) was dissolved in dimethyl sulphoxide (0·5 ml.) under nitrogen, cuprous iodide (16 mg.) was added and the mixture stirred till solution was complete. Aqueous sodium bicarbonate solution (8 ml.) was added and the yellowish precipitated cuprous salt was stirred under nitrogen for 5 minutes before washing five times with water and ethanol and then three time with a very small volume of ether.

The cuprous salt was not weighed but was dissolved directly in dry pyridine (5 ml.) and the solution was purged with nitrogen for 5 minutes before refluxing under nitrogen for 2 hours. The pyridine was removed by azeotroping four times with benzene. T.l.c. (20% ethyl acetate/petrol) showed the product to be a complex mixture but the u.v. spectrum (ethanol) showed a sharp peak at 274 mμ of approximately equal intensity to the broader absorption at 225-230 mμ.

Hydrolysis and oxidation of the di(tetrahydropyranyl ether) (168) with Jones reagent.

A solution of (168) (64 mg.) in acetone (3 ml.) was stirred in an ice bath. Jones reagent (p. 81) (0·7 ml.) was added dropwise. The mixture was stirred at 0° for 30 minutes and then at room temperature for 1 hour before diluting with water and extracting thoroughly with ether. The ether extract was washed with sodium bicarbonate solution and brine, dried (sodium sulphate) and filtered. Evaporation of the solvent gave the crude dione (169) (24 mg., 54%), essentially one spot on t.l.c. (20% ethyl acetate/petrol), as a crystalline solid. The n.m.r. spectrum of the crude product showed a complex multiplet at $\tau = 1{\cdot}3-3{\cdot}0$ (ca. 8H, aromatic protons) and a singlet at $6{\cdot}5\ \tau$ (1H, acetylenic proton). Part of the product was crystallised from ether/ 40-60° petrol to give the dione (169) as yellow needles, m.p. 121-123° (dec.), one spot on t.l.c. The i.r. spectrum (nujol mull) showed peaks at 3250 (ν ≡C-H), 2230 (ν R-C≡C-R), 2120 (ν R-C≡CH), 1655 (ν C=O) and 1630 (ν C=O) cm^{-1}. The u.v. spectrum (ethanol) had λ_{max} 230 (log ε 4·49), 262 (4·29), 300 sh. (4·09) and 325 (4·13) mμ. The mass spectrum (of material purified by preparative t.l.c.) showed peaks at m/e = 384 (M^+) and 257 (M^+-I). ($C_{18}H_9O_2I$ requires M.W. 384).

<u>Castro-type coupling of o-iodobenzyl alcohol (145) and cuprous phenylacetylide</u>.

Dry pyridine (10 ml.) was purged with nitrogen for 10 minutes and cuprous phenylacetylide (p. 81) (153 mg.) was added, followed after a few minutes' reflux by o-iodobenzyl alcohol (145)(200 mg.). The mixture was heated under reflux in a nitrogen atmosphere for 6 hours, the pyridine was removed on the rotary evaporator and the crude product (~375 mg., almost completely chloroform soluble) was extracted with hot petrol. The petrol extract, which showed two major spots (R_F 0·3 and 0·6) on t.l.c. (20% ethyl acetate/petrol), was concentrated and crystallised to give 2-hydroxymethyldiphenylacetylene (185) (55 mg., 31%) as white needles, m.p. 68-70° (lit.,[145] 69-71°, 71-71·5° after further recrystallisation), one spot (R_F 0·3) on t.l.c. The i.r. spectrum (nujol mull) showed typical hydroxyl absorption at ~3200-3400 cm^{-1} and the u.v. spectrum (ethanol)had λ_{max} 268 mμ (log ε 4·24), 275 (shoulder) (4·28), 283 (4·39), 291·5 (4·24) and 301 (4·28). In the n.m.r. spectrum (carbon tetrachloride as solvent) the following peaks were observed: $\tau = 2{\cdot}4-2{\cdot}9$ (9H, multiplet, aromatic protons); $\tau = 5{\cdot}22$ (2H, singlet, carbinyl protons); $\tau = 7{\cdot}79$ (1H, broad singlet, disappears on D_2O exchange, hydroxyl proton).

When the reaction was worked up with dilute sulphuric acid (see e.g. p. 104) the main product appeared to be 1-benzylidenedihydroisobenzofuran (187) from comparison of its spectral properties with those described by Castro and co-workers.[147] Moreover, this product seemed from t.l.c.

i.r. and u.v. evidence to be the second component in the crude product obtained from neutral work up (see above). When dilute hydrochloric acid was used, a more complex product was obtained, t.l.c. showing two major spots, and the i.r. spectrum (film) showing strong absorption at 1760 cm^{-1}.

2-Formyldiphenylacetylene (183).

(a) Castro-type coupling reaction.

Dry pyridine (5 ml.) was purged with nitrogen for 10 minutes, cuprous phenylacetylide (p. 81) (77 mg.) was added and the mixture was refluxed under nitrogen for a few minutes. o-Iodobenzaldehyde (96 mg.) was added and refluxing under nitrogen was continued for 4½ hours. The reaction mixture was allowed to cool, was poured into an excess of ice-cold dilute sulphuric acid and was extracted three times with ether. The combined ethereal extracts were filtered, washed with dilute sulphuric acid, saturated sodium bicarbonate solution and brine, dried (anh. sodium sulphate) and filtered, and the solvent was evaporated. Preparative t.l.c.

(Kieselgel G, 0·5 mm., 2 plates, 20% ethyl acetate/petrol) of the crude product (86 mg. oil, t.l.c. essentially one spot) gave 2-formyldiphenylacetylene (183) (48 mg., 56%) as a clear oil. The i.r. spectrum (liquid film) showed absorption at 2760 and 2860 cm^{-1} (medium, ν C--H, aldehyde), 2250 cm^{-1} (medium, ν C≡C) and 1690 cm^{-1} (strong, ν C=O). The n.m.r. spectrum showed the following peaks: τ = -0·7 (1H, singlet, aldehyde proton); τ = 1·9-2·18 (1H, multiplet, aromatic proton); τ = 2·25-2·74 (8H, multiplet, aromatic protons). A small sample was microdistilled, b.p. 130-140° (block)/ 0·7 mm. (Found: C, 87·12; H, 4·99. Required for $C_{15}H_{10}O$: C, 87·35; H, 4·89%).

(b) Jones oxidation of the alcohol (185).

A solution of 2-hydroxymethyldiphenylacetylene (185) (10 mg.) in acetone (0·5 ml.) was stirred in an ice bath. Jones reagent (p.81) (0·03 ml.) was added and the mixture was stirred at 0° for 20 minutes before diluting with water and extracting twice with ether. The combined ethereal extracts were washed with saturated sodium bicarbonate solution and brine, dried (anh. sodium sulphate) and filtered Evaporation of the solvent gave 2-formyldiphenylacetylene (183) (6 mg., 61%) as an oil, one spot on t.l.c. (20% ethyl acetate/petrol), identical by t.l.c., i.r. and u.v. to a sample prepared by method (a) above.

2-Carbomethoxydiphenylacetylene (184).

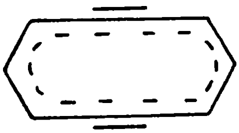
Methyl o-iodobenzoate (144) (79 mg.) was dissolved in dry pyridine (5 ml.), the solution was purged with nitrogen for 15 minutes, and cuprous phenylacetylide (p.81) (55 mg.) was added. The mixture was heated under reflux in a nitrogen atmosphere for 6½ hours, allowed to cool, poured into excess dilute hydrochloric acid and ice, and extracted thoroughly with ether. The ether extract was washed with dilute hydrochloric acid, sodium bicarbonate solution and brine, dried (anh. sodium sulphate) and filtered, and the solvent was evaporated. Preparative t.l.c. (Kieselgel G, 0·5 mm., 20% ethyl acetate/petrol) of the crude product (72 mg. oil, t.l.c. essentially one spot) gave 2-carbomethoxydiphenylacetylene (184) (53 mg., 75%) as a clear oil. The i.r. spectrum (liquid film) showed absorption at 2240 cm^{-1} (weak, ν C≡C), 1720 cm^{-1} (ν C=O) and 1250 and 1290 cm^{-1} (ν C–O). The n.m.r. spectrum exhibited the following peaks: τ = 1·95–2·17 (1H, multiplet, aromatic proton). τ = 2·28–2·87 (8H, multiplet, aromatic protons); τ = 6·07 (3H, singlet, methyl protons). A small sample was microdistilled, b.p. 120–150° (block)/ 0·8 mm. (Found: C, 81·24; H, 5·08. Required for $C_{16}H_{12}O_2$: C, 81·34; H, 5·12%). The mass spectrum showed peaks at m/e = 236 (M^+), 221 ($M^+ - CH_3$) and 177 ($M^+ - CO_2CH_3$). The u.v. spectrum (ethanol) had λ_{max} 218 (shoulder) (log ε 4·68), 236 (4·59), 273 (4·55), 280 (4·59), 288 (4·64) and 308 (4·46) mμ.

Reduction of (184) with lithium aluminium hydride.

2-Carbomethoxydiphenylacetylene (184) (24 mg.) was dissolved in sodium dried ether (5 ml.), excess lithium aluminium hydride was added and the mixture was stirred at room temperature for 40 minutes. Saturated sodium sulphate solution was carefully added, the product was extracted with ether, and the ether extract dried (sodium sulphate) and filtered and the solvent evaporated. Preparative t.l.c. (Kieselgel G, 0·5 mm., 20% ethyl acetate/petrol) of the crude product (24 mg. oil, t.l.c. one major spot) gave 2-hydroxymethyldiphenylacetylene (185) (13 mg., 61%) as a white crystalline solid. Crystallisation from petrol gave white needles, m.p. 64-68° (lit.,[145] 69-71°) identical with an authentic sample by i.r., u.v., and t.l.c. comparison.

<u>3-(o-Carbomethoxyphenyl)-1-phenyl-2-propyn-1-one (186)</u>.

A solution of methyl o-iodobenzoate (47 mg.) in dry pyridine (5 ml.) was purged with nitrogen for 5 minutes and the cuprous salt (162) (40 mg.) of phenyl ethynyl ketone was added. The mixture was refluxed under nitrogen for 3 hours, allowed to cool, poured into excess dilute hydrochloric acid and ice, and extracted thoroughly with ether. The ether extract was washed with dilute hydrochloric acid, sodium bicarbonate solution and brine, dried (sodium sulphate) and filtered, and the solvent evaporated. Preparative t.l.c. (Kieselgel G, 0·5 mm., 20% ethyl acetate/petrol) of the crude product (45 mg. oil, t.l.c. essentially one spot) gave the coupling product (186) (20 mg., 42%) as a low melting solid (t.l.c. pure). The i.r. spectrum (melt) showed strong absorption at 2240 cm^{-1} (ν C≡C) and at 1720 and 1640 cm^{-1} (ν C=O). The n.m.r. spectrum showed the following peaks: τ = 1·57-1·8 (2H), τ = 1·86-2·05 (1H) and τ = 2·17-2·7 (6H) (multiplets, aromatic protons); τ = 6·03 (3H, singlet, methyl protons). A small sample was microdistilled to give a clear oil, b.p. 120-150^{o} (block)/0·3 mm., which was solidified to a crystalline solid, m.p. 66-70^{o}. The mass spectrum showed peaks at m/e = 264 (M^+), 249 (M^+ - CH_3) and 205 (M^+ - CO_2CH_3). ($C_{17}H_{12}O_3$ requires M.W. 264). The u.v. spectrum (ethanol) had λ_{max} 240 (sh.) (log ε 4·11), 273 (4·14), 288 (4·15) and 310 (sh.) (4·08) mμ.



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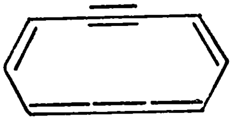

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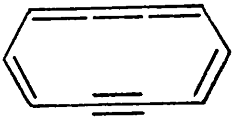

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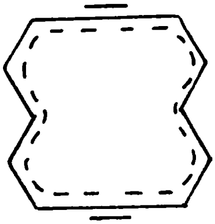

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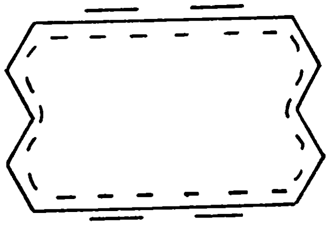

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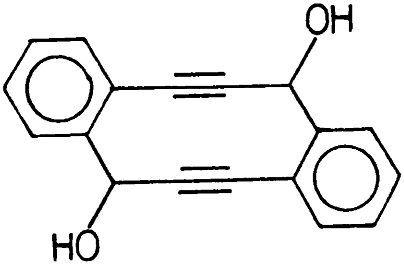

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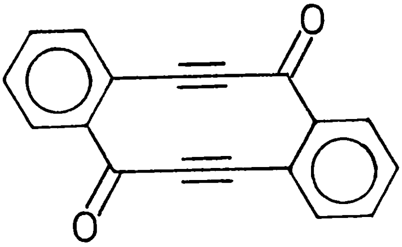

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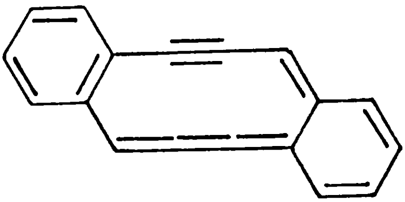

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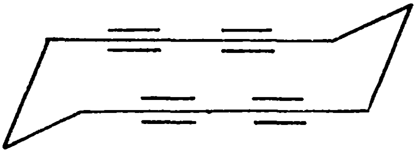

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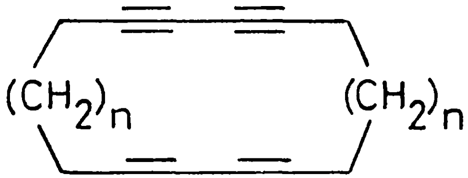

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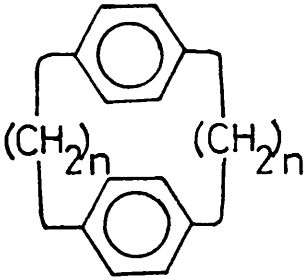

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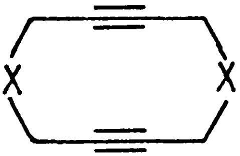

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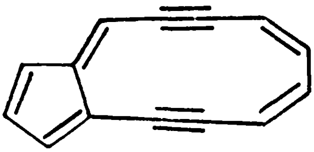

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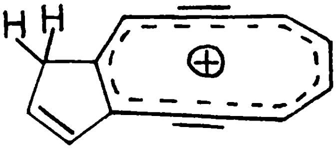

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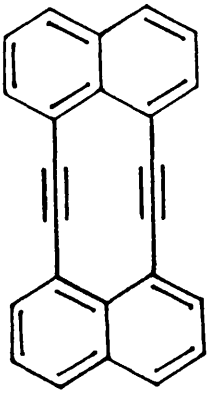

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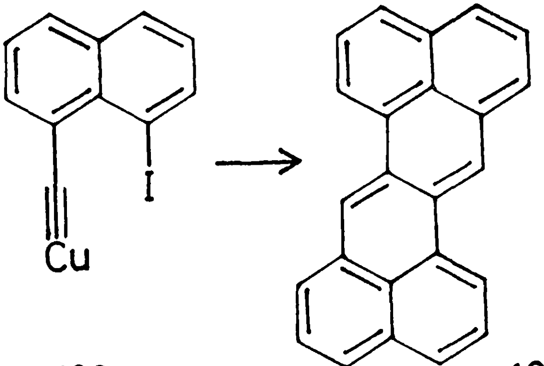

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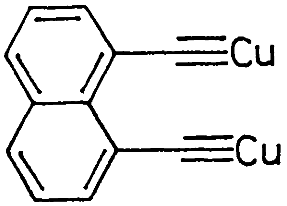

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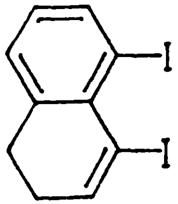

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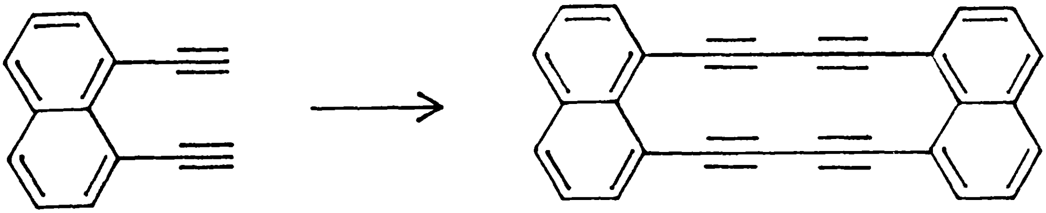

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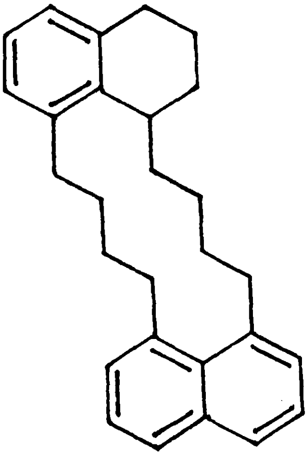

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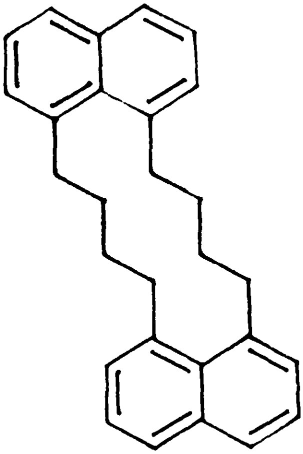

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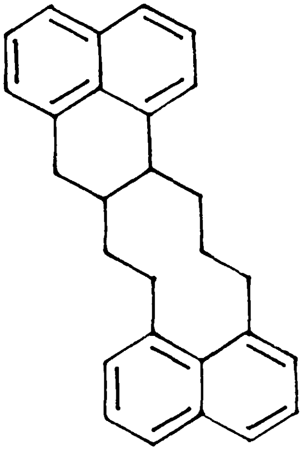

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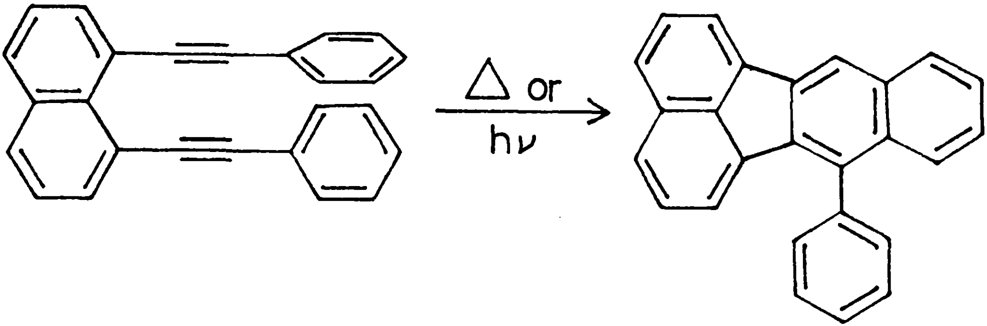

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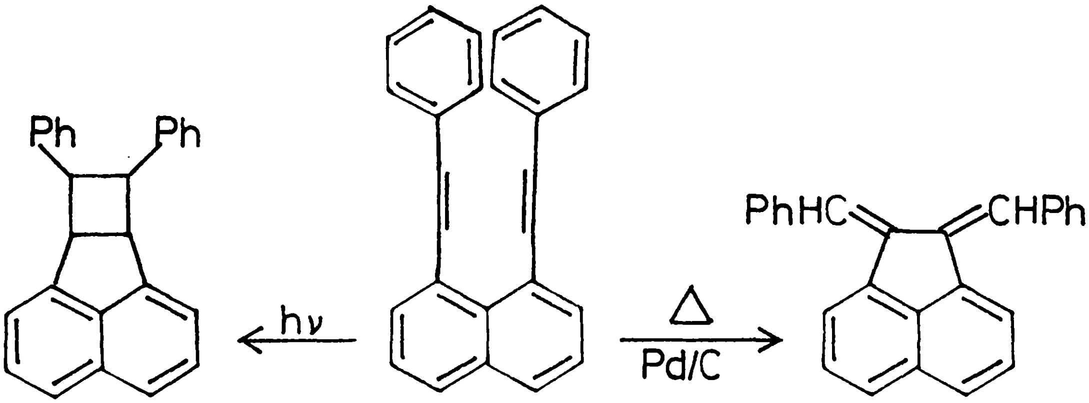

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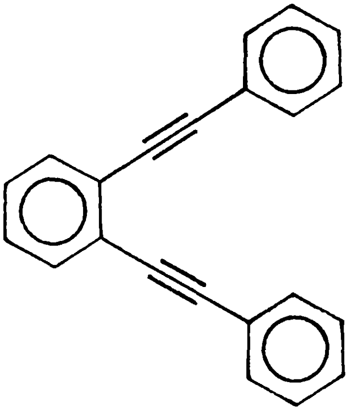

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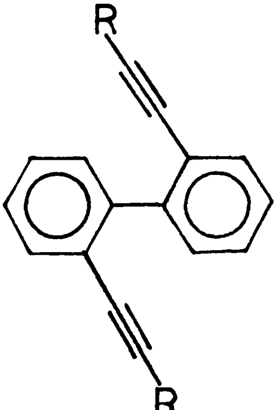

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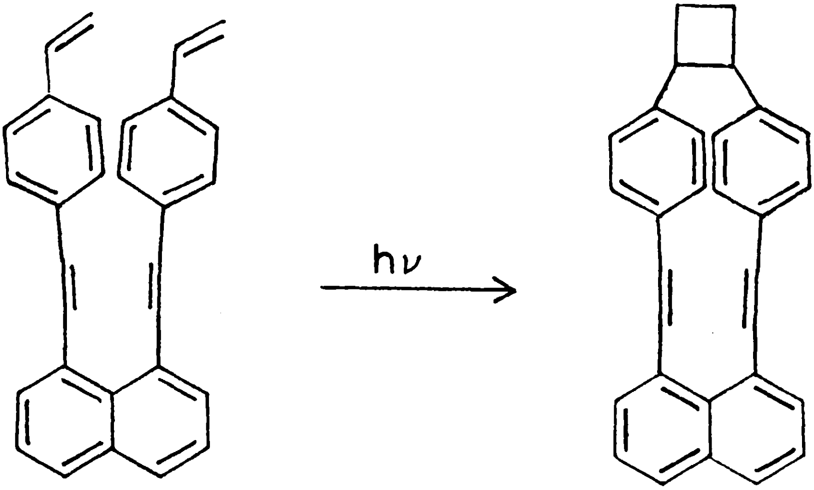

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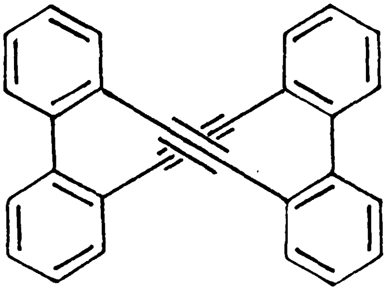

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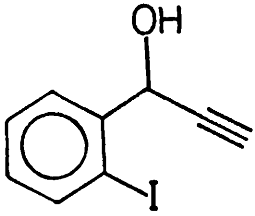

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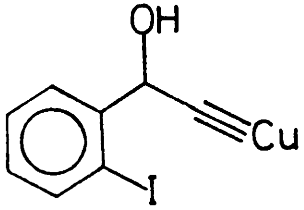

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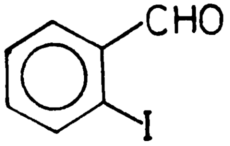

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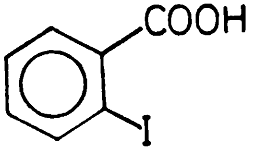

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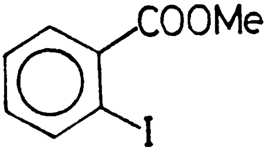

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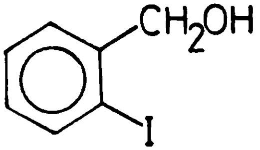

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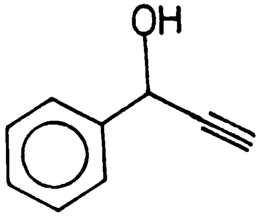

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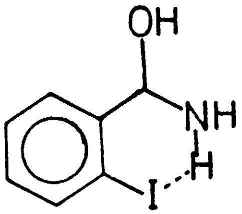

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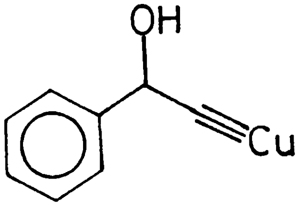

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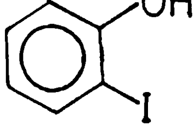

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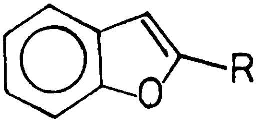

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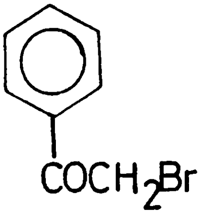

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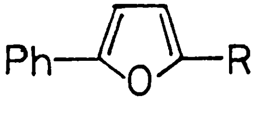

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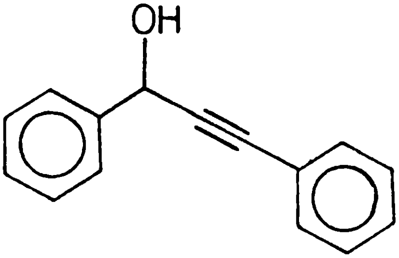

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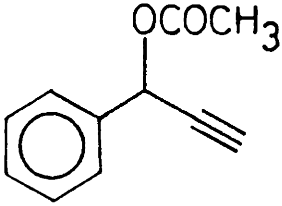

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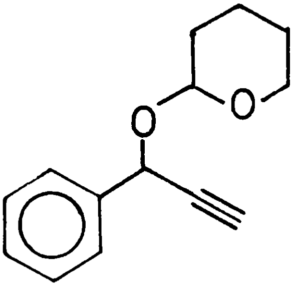

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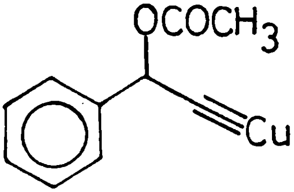

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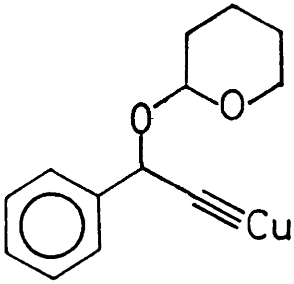

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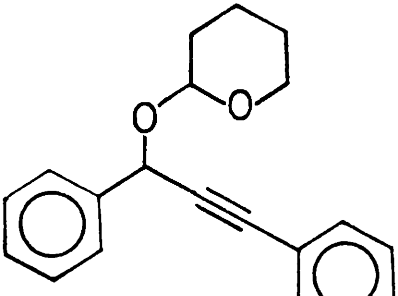

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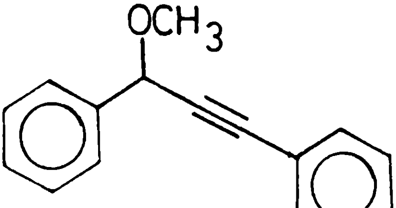

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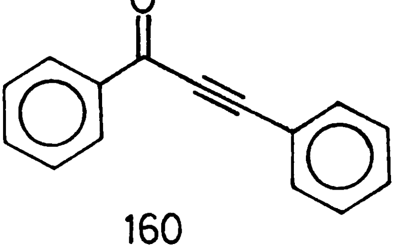

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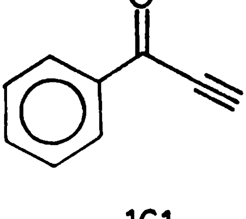

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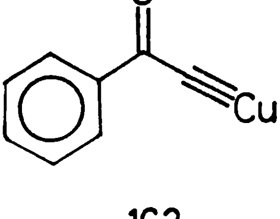

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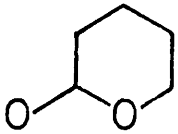

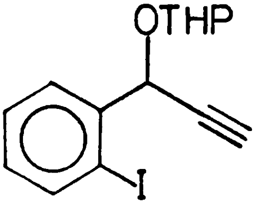

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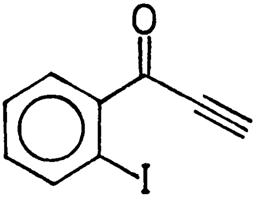

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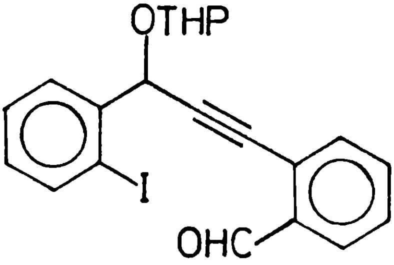

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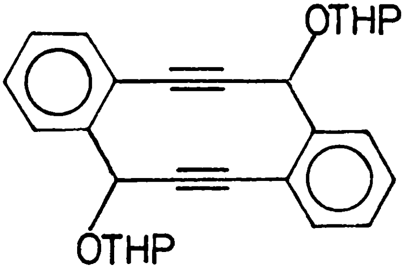

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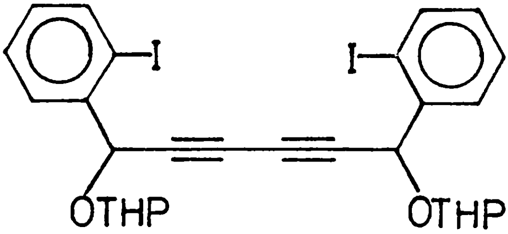

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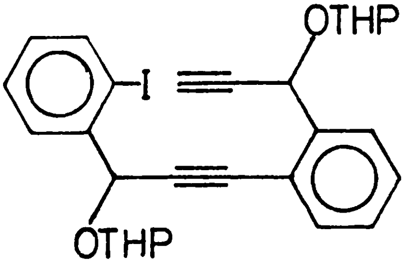

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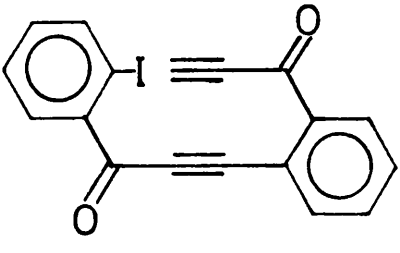

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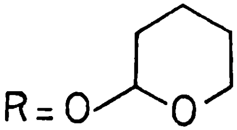

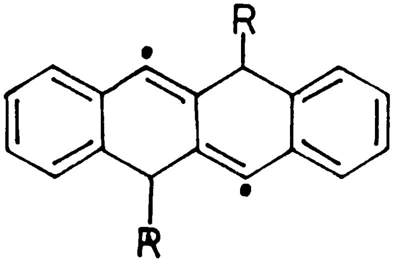

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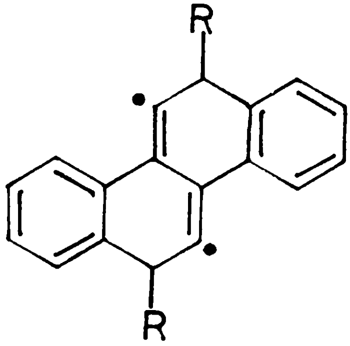

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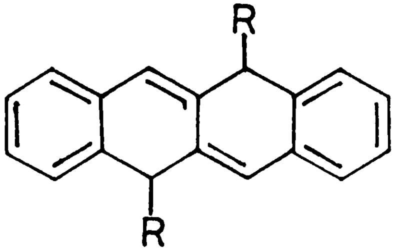

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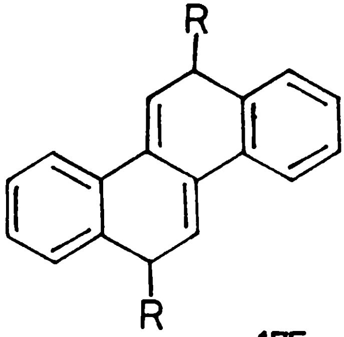

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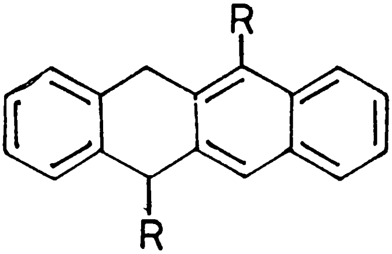

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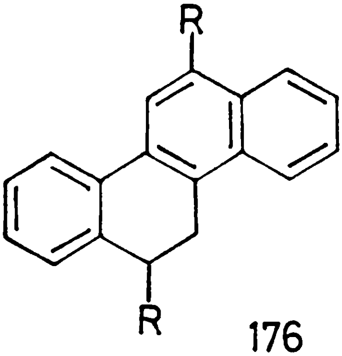

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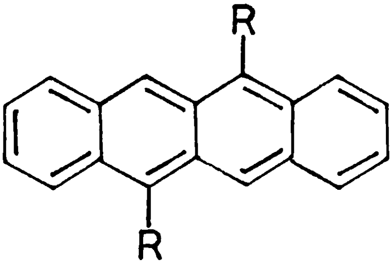

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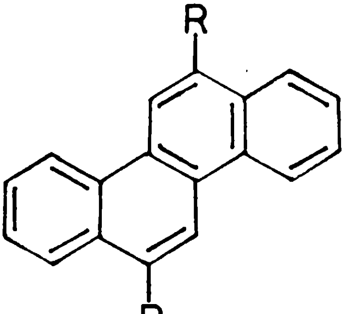

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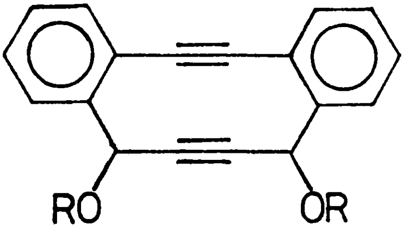
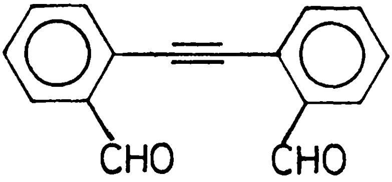


178 R = H

179 R = $COCH_3$



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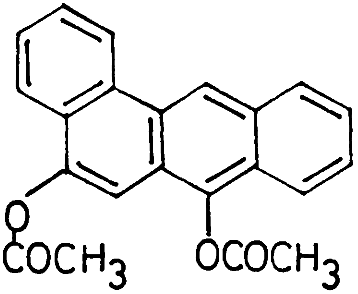

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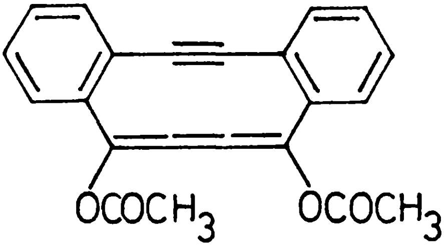

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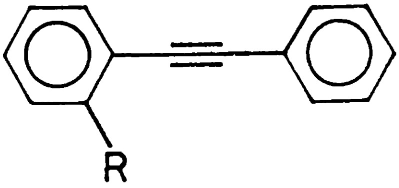
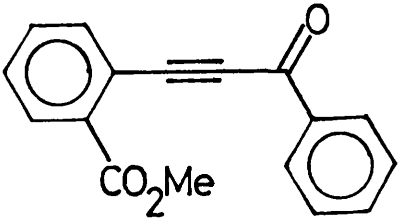


183 R = CHO

184 R = CO_2Me

185 R CH_2OH



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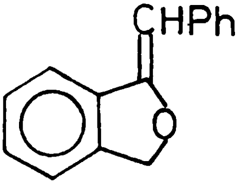

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SECTION II

INTRODUCTION and DISCUSSION

In recent years, considerable interest has been shown in this department in the synthesis and study of macrocyclic acetylenic compounds. This interest was stimulated by the discovery by Eglinton and Galbraith[161] of a modification of the well-known Glaser oxidative coupling[149] of terminal acetylenes to diacetylenes. By the use of this method,[161] employing cupric acetate in pyridine and methanol, intramolecular coupling of certain α,ω-diacetylenes to macrocyclic diacetylenes was achieved,[161] whereas the normal method,[149] involving an aqueous cuprous chloride-ammonium chloride solution and an oxygen atmosphere, gave unsatisfactory results. The cupric acetate technique, the normal Glaser technique, and a modification[169] of the normal Glaser technique, have all been used in the classic work of Sondheimer and co-workers on the synthesis of a large number of macrocyclic polyacetylenes and their conversion to fully conjugated macrocyclic polyolefins or 'annulenes'[10] (see (Section I). Among the macrocyclic compounds synthesised in this department was the highly strained tetra-acetylene (190) which was obtained from oxidative coupling of o-diethynylbenzene (188)[170] or from the half-cyclised hydrocarbon (189).[171] More recently the strainless macrocyclic compound (191) has been synthesised[172] by Castro-type coupling[113] of the cuprous salt of o-iodophenylacetylene. A synthesis of (191) by a longer route has been reported by Staab and Graf.[173] Despite the fact that it is formally a tribenzo-tridehydro-[12]-annulene, (191) is a highly stable compound.

As a natural extension of the synthesis of (191) by intermolecular Castro-type coupling, it was decided to investigate the Castro-type coupling of the cuprous salt (192) of m-iodophenylacetylene, which should lead to the production of macrocyclic compounds of higher molecular weight. The most likely product seemed to be the completely strain-free macrocycle (193), resulting from coupling of six molecules of the cuprous salt (192), although it seemed likely that larger and smaller macrocycles might also be obtained.

The compound (193) contains a 30-membered ring and is therefore formally related to [30]-annulene. The existence of a ring current[17,18] throughout the 30-membered ring of (193) is unlikely, however, on account of the fact that no Kekulé structures can be drawn which incorporate a fully conjugated macrocyclic ring. It is probable also that bond alternation will occur in [30]-annulene and related compounds.[12,13] Calculations by Ege and Fischer[174] suggest that the related hexa-m-phenylene system (194) [and also the triphenanthrene type system (195)] should behave as isolated benzene rings and this has been borne out by the synthetic work of Staab and co-workers.[175] The properties of (193) would therefore be of interest as an extension of the work on m-phenylenes.

The starting point in the synthesis of m-iodophenylacetylene was m-iodobenzoic acid,which was converted to its acid chloride and then via the diethyl acylmalonate (196) to m-iodoacetophenone by the method of Walker and Hauser.[176] Treatment of m-iodoacetophenone with phosphorus pentachloride gave a crude chlorination product, probably a mixture of the dichloride (197) and the vinyl chloride (198),[177] which was then dehydrochlorinated to m-iodophenylacetylene. It was found, in agreement with the work of Bott, Eaborn and Walton[178] on similar halogenophenylacetylenes that potassium hydroxide in ethanol was an effective dehydrochlorinating agent. The use of sodamide in liquid ammonia gave an apparently polymeric product containing terminal acetylene units, but little or no m-iodophenylacetylene. The product (from potassium hydroxide-ethanol dehydrochlorination) was difficult to purify by distillation and the m-iodophenylacetylene was therefore isolated via the cuprous salt.[151]

Castro-type coupling of the cuprous salt of m-iodophenylacetylene was now carried out in refluxing pyridine. Thin layer chromatography (t.l.c.) of the crude product, using 20% benzene/petrol as solvent, showed it to be a complex mixture of at least ten compounds(numbered I → X in order of increasing polarity below), but the infra-red (i.r.) and ultraviolet (u.v.) spectra suggested that Castro-type coupling had taken place successfully. The i.r. spectrum showed only typical aromatic absorption; the u.v. spectrum showed characteristic diphenylacetylene (tolane) type absorption at 271, 286 and 304 mμ (i.e. at slightly longer wavelengths than tolane itself) and a little absorption at 333-334 mμ, later shown to be of the diaryldiacetylene type.

Although the product was a complex mixture, the separation of the compounds on analytical t.l.c. seemed reasonable, particularly when multiple running of the plates was used. Preparative t.l.c. employing 10-20% benzene/petrol mixtures as solvent was therefore investigated. It was soon found, however, that although separation of compounds I → IV was straightforward, and although V and VI could also be obtained in a fairly pure state, compounds VII → X were extremely difficult to separate from VI and from one another. The reason for this is probably the decreasing solubility in petrol with increasing molecular weight of compounds I → X, which results in streaking and overlapping on t.l.c. except when very small quantities of material are used. Column chromatography of the crude product on alumina using the solvent systems described by Jenny[179] for the separation of the macrocyclic metacyclophanes (199) [i.e., petrol and petrol/ethyl acetate (200:1)] gave very similar results. Sublimation of a mixture consisting mainly of VI, VIII and IX at 250-270°/0·02-0·5 mm. over a period of 20 hours gave reasonable separation of these compounds, but the method seemed unpromising for application on even a moderately large scale.

The use of carbon tetrachloride (in which the reaction products appeared to be moderately soluble) as an alternative non-polar solvent to petrol was then investigated. Carbon tetrachloride/petrol (70:30) was found to be greatly superior to the previous solvent systems employed for preparative t.l.c., except that the separation between compounds VIII and IX was rather poor; for this reason benzene/petrol mixtures were frequently used for analytical t.l.c. The separation of compounds VI → X by column chromatography was also greatly improved by the use of carbon tetrachloride/petrol mixtures as solvent, and under these conditions, the separation of VIII and IX was almost complete. Separation of the products on a fairly large scale was therefore carried out by chromatography on alumina followed by preparative t.l.c. (using Kieselgel HF_{254}), in both cases employing carbon tetrachloride/petrol mixtures extensively. The compounds thus obtained are described below. For comparison purposes, m-bis(phenylethynyl) benzene (200)[145] was prepared by the Castro reaction between m-diiodobenzene and cuprous phenylacetylide. The synthesis of (200) in this way had already been described by Castro and co-workers,[145] but very little information on the spectral properties of the compound had been given.

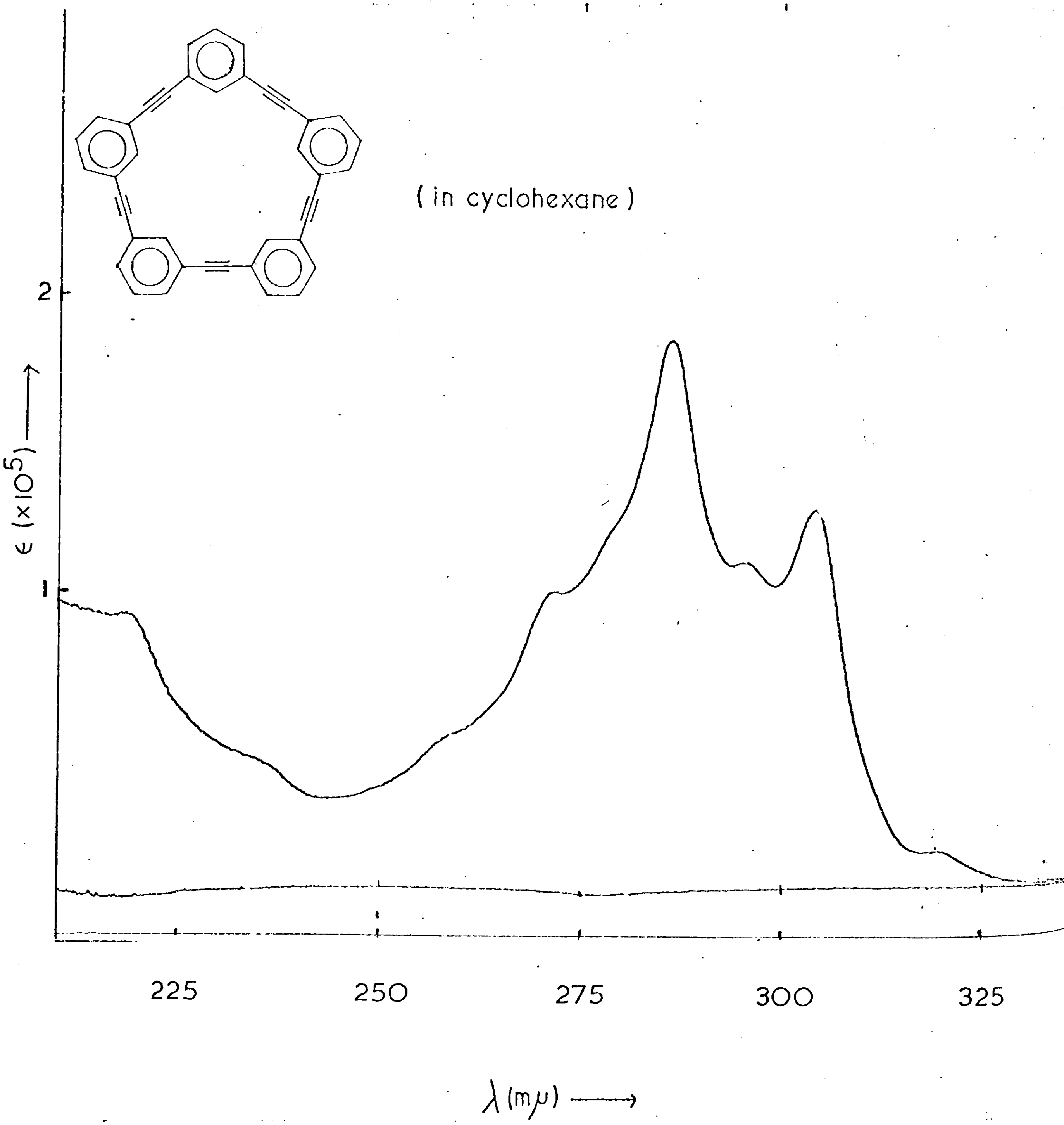
Compound I, eluted with petrol, appeared from its spectroscopic properties, in particular the mass spectrum (parent peak at m/e = 454) and the characteristic diaryldiacetylene type u.v. spectrum (λ_{max} at 293, 312 and 334 mμ) to be 3,3'-diiododiphenyldiacetylene (201). This was confirmed by comparison with an authentic sample of (201), synthesised by oxidative coupling[149] of m-iodophenylacetylene by the cupric acetate-pyridine-methanol method.[161] The formation of (201) under Castro-type conditions is obviously the result of a small amount of oxidative coupling of the cuprous salt taking place as a side reaction (see e.g. p. 55).

The presence of (201) in the reaction mixture would be expected to lead to a series of uncyclised compounds of general structure (202) by Castro coupling of the cuprous salt (192) of m-iodophenylacetylene with (201). Compounds II and III, eluted with petrol, and compound IV and possibly compound V, eluted with 50% carbon tetrachloride/petrol, seem to be uncyclised products of this type. The mass spectra of II, III and IV had parent peaks at m/e = ca. 554, 654 and 754 respectively, suggesting the structures (202a), (202b) and (202c) respectively, the existence of isomers being possible in the cases of III and IV. The pattern of the major peaks in the mass spectra of II, III and IV, mainly attributable to doubly charged ions and loss of iodine, was very similar to that observed with (201). The u.v. spectra of II, III and IV, taken in conjunction with the mass spectra, provide further strong evidence for these structures.

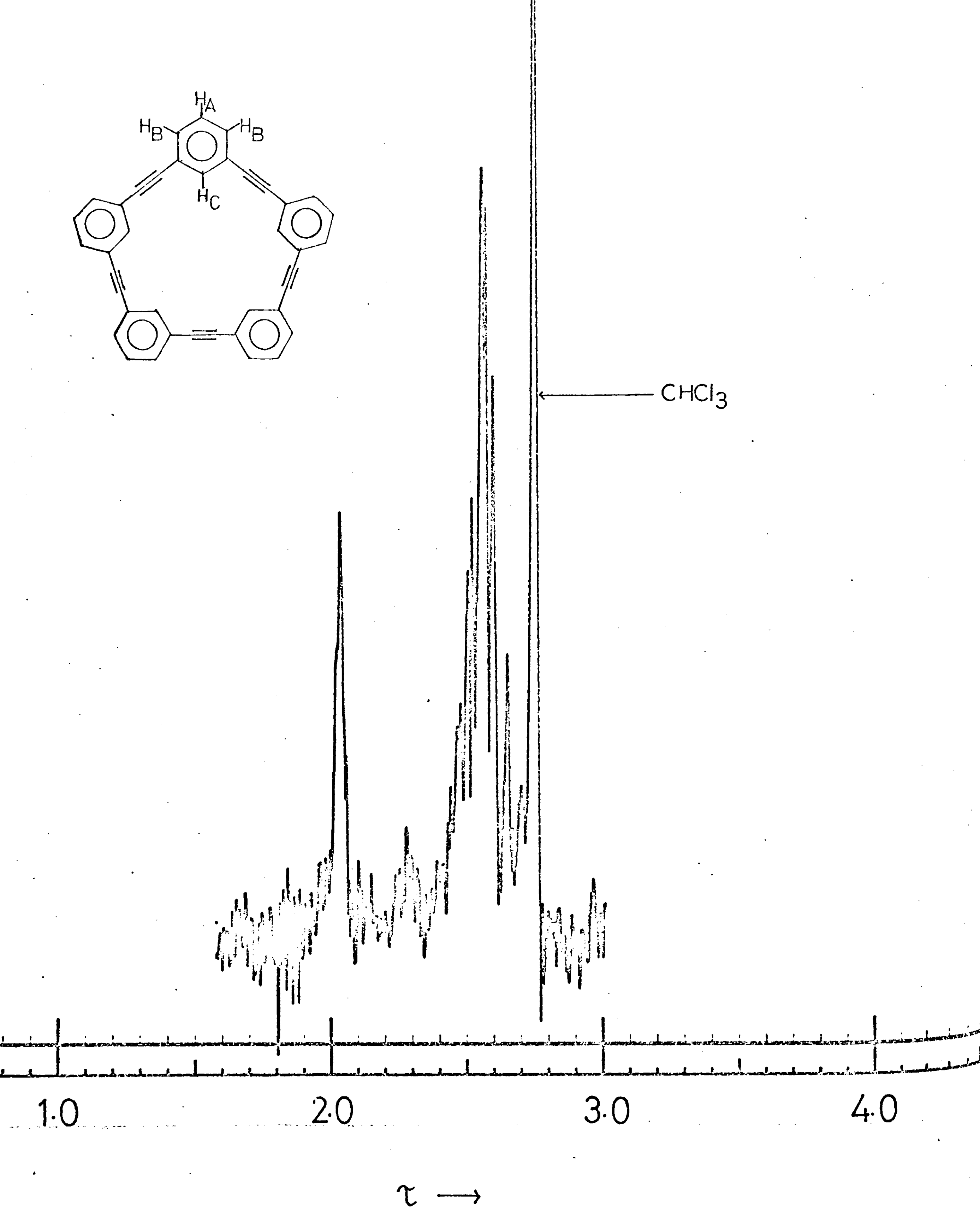
Assuming that there is little interaction between the tolane and diaryldiyne type chromophores in compounds of the general type (202), as seems probable from the tolane type spectra of m-bis(phenylethynyl)benzene (200) and the cyclic compounds described below, the u.v. spectra of II, III and IV can be completely rationalised in terms of the superimposition of increasing amounts of tolane type absorption on a diaryldiyne spectrum. The u.v. peak of longest wavelength occurs for diaryldiynes at ca. 330 mμ ($\varepsilon \sim 30,000$) whereas tolanes generally show very little absorption above 325 mμ and have maximum absorbance at ca. 280 mμ ($\varepsilon \sim 30,000$). 3,3'-diiododiphenyldiacetylene (201) and compounds II → IV (and V) all show a diaryldiyne peak at 333-334 mμ, and using the fact that for (201) the ε value at 287 mμ is about 48% of the ε value at 334 mμ, the contributions to the total absorption of II → IV at 286 mμ from the tolane and diaryldiyne chromophores can be calculated. The results obtained are shown in the table opposite and are in good agreement with the known ε values of the two chromophores. The extinction coefficients quoted are rather approximate, but as is shown in the graph, the ratio of tolane to diaryldiyne type absorption is in every case in very close agreement with that expected from the proposed structures.

Although the extinction coefficient of compound V is rather low (possibly because of its low solubility in cyclohexane), the ratio of tolane to diaryldiyne absorption (see p.154a) suggests that it is of the same type as compounds II → IV, and has structure (202d), M.W. 854. The mass spectrum, however, not only failed to show any peaks in this region, which could be explained by the involatility of (202d), but in fact gave a very simple spectrum with peaks essentially only at $m/e = 400$ and 200. Although no other evidence is available, this mass spectrum alone strongly suggests the presence of the rather strained 'cyclic tetramer' (203), (M.W. 400) derived from Castro coupling of four molecules of the cuprous salt. This characteristically simple type of spectrum, showing essentially only the singly and doubly charged molecular ions, was also obtained from the cyclic tribenzotriyne (191),[172,173] from the 'cyclic pentamer' (204) (see below) and from m-bis(phenylethynyl)benzene (200). This apparent conflict between the u.v. and mass spectra suggests either that 'V' is a mixture of the involatile (202d) with a trace of the more volatile (203), or, less likely, that 'V' contains a large proportion of (203) but that (203) has an anomalous u.v. spectrum arising from the strain in the molecule.

Compound VI, which appeared to be the major product, was eluted next (with 50% carbon tetrachloride/petrol) and was shown to be the 'cyclic pentamer' (204), M.W. 500. Purification was carried out by preparative t.l.c. followed by crystallisation from benzene/petrol to give (204) as small lustrous white plates which did not melt but gradually darkened on heating in a sealed tube to 500°. The mass spectrum, like those of the cyclic tribenzotriyne (191)[172,173] and m-bis(phenylethynyl)benzene (200), was extremely simple, the main peaks being at $m/e = 500$ (M^{+}) and $m/e = 250$ (M^{2+}) and a small peak also being observed at $m/e = 166{\cdot}7$ (M^{3+}).


(in cyclohexane)
2
1
ε (×10⁵) ⟶
225
250
275
300
325
λ (mμ) ⟶

A high resolution mass spectrum confirmed that these peaks were attributable to a $C_{40}H_{20}$ hydrocarbon. The structure (204) was also confirmed by the other spectroscopic data obtained. The i.r. spectrum was typical of an aromatic hydrocarbon. The u.v. spectrum (see opp.) [cyclohexane, λ_{max} 286 mμ (ε = 185,000)] was of the characteristic tolane (281 mμ, ε = 30,000) type, but as in the case of m-bis(phenylethynyl)benzene (200) (283·5 mμ, ε = 66,000), showed less distinct fine structure. Unlike (200), however, and unlike compounds VIII and IX which also had tolane type spectra, (204) also showed a small peak at 319 mμ (ε = 13,000). It is possible that the presence of this small peak is a result of strain in the macrocyclic ring of (204), but the amount of strain present would appear from Dreiding models and from the high stability of the compound to be rather small. As can be seen from the data above, the wavelength of maximum absorption exhibits a slight bathochromic shift on going from tolane to (200) and from (200) to (204). The maximum extinction coefficients of (200) and (204), however, are not significantly


H_A
H_B
H_B
H_C
CHCl3
1.0
2.0
3.0
4.0
τ →

different from those obtained by simple addition of either two or five tolane type chromophores.

The n.m.r. spectrum of (204),(see opp.) measured in deuterochloroform at 100 Mc/s., showed a broadened singlet, possibly a poorly resolved triplet, at $\tau = 2{\cdot}03$, (H_C) and a multiplet at $\tau = 2{\cdot}55$ (H_A and H_B), in a ratio of approximately 1:3. This pattern is compatible with the expected AB_2X system, and the chemical shifts are close to those observed by Jenny with the hexabenzo-all-trans-hexaene (205)[180] for which the corresponding values were $\tau = 2{\cdot}08$ (H_C), $\tau = 2{\cdot}46$ (H_B) and $\tau = 2{\cdot}61$ (H_A). Similar, though even greater, deshielding of the H_C proton was observed in the m-phenylene type compounds [e.g. (194)] synthesised by Staab and co-workers.[175] Further confirmation of the structure (204) for compound VI was obtained by hydrogenating a small sample over palladium/charcoal. The product showed one major spot on t.l.c., of identical R_F value to a sample of [2.2.2.2.2]metacyclophane (199a)[179] kindly provided by Professor W. Jenny. The hydrogenation product was purified by preparative t.l.c. and the mass spectrum was found to be identical to that of (199a).

The remaining compounds were not fully characterised. Compound VII appeared to be a very minor constituent of the mixture and was not isolated in a pure state. Compounds VIII and IX were purified by repeated preparative t.l.c. and both were found to have characteristic tolane type u.v. spectra (λ_{max} 286 mμ) with no trace of diaryldiyne absorption. As in the case of compound VI (204), the fine structure was not very distinct, but in contrast to the case of (204) there was no peak at 319 mμ. It is thus possible that VIII and IX are higher homologues of (204), but mass spectra of VIII and IX (and also X) could not be obtained on either M.S.9 or M.S.12 instruments, presumably because of the involatility of the substances. Mass spectra run earlier, however, on samples which apparently were mixtures (though almost pure by t.l.c.) had shown that a compound of molecular weight 600 was present in addition to (204), M.W. 500, and that it gave rise to a similar type of spectrum to (204). A high resolution spectrum[181] showed that this peak was attributable to a

$C_{48}H_{24}$ hydrocarbon which must be the 'cyclic hexamer' (193). A small peak at m/e = 700 was also observed which could indicate the presence of the corresponding 'heptamer'. Since these peaks were obtained only with mixtures, however, the firm assignment of structures to VIII and IX cannot be made. The maximum u.v. extinction coefficient of both VIII and IX was calculated to be ca. 185,000 assuming a molecular weight of 600 and ca. 215,000 assuming a molecular weight of 700. Hydrogenation of VIII on a very small scale gave a mixture of two compounds (by t.l.c.) neither of which corresponded to a sample of [2.2.2.2.2.2.]metacyclophane (199b)[179] provided by Professor W. Jenny, but this preliminary result cannot be taken as conclusive evidence that VIII is not the 'cyclic hexamer' (193).

To summarise, therefore, the major product of the intermolecular Castro type coupling of the cuprous salt (192) of m-iodophenylacetylene has been shown to be the 'cyclic pentamer' (204). Evidence was also obtained for the presence in the complex reaction product of the cyclic 'tetramer' (203) and 'hexamer' (193) and possibly the cyclic 'heptamer'. A series of uncyclised compounds resulting from mixed Castro and oxidative type coupling was also isolated from the mixture.

Work was also commenced on a second project directed towards the synthesis of the macrocyclic tetraacetylenic-tetraketone (208) containing an 18-membered ring, by oxidative coupling of m-bis(1-hydroxy-2-propynyl)benzene (206) to the 'dimer' (207) followed by oxidation to (208).

The starting material in the synthesis of the diacetylenic diol (206) was isophthalic acid, which was converted to isophthalaldehyde by formation of the dimethyl ester, reduction of the diester to isophthalyl alcohol with lithium aluminium hydride, and oxidation of the diol to the dialdehyde. The use of aqueous ceric ammonium nitrate solution[135a] was found to be a particularly simple and effective method of carrying out this oxidation. Isophthalaldehyde was converted to the diacetylenic diol (206) by treatment with either excess sodium acetylide[128] or acetylenemonomagnesium bromide.[127] The latter reagent gave almost complete conversion to (206), whereas with excess sodium acetylide, although (206) was the major product, rather more aldehyde containing material was present in the product. The diol (206) (presumably a mixture of diastereoisomers) was purified by preparative t.l.c. and microdistillation and gave a satisfactory n.m.r. spectrum, but good analytical figures could not be obtained. Its structure was confirmed by oxidation to the dione (209) with Jones reagent. Satisfactory i.r., u.v., n.m.r. and mass spectra were obtained for (209).

Only very preliminary experiments on the oxidative coupling of the diol (206) were carried out. The model compound, phenylethynylcarbinol (146) had frequently been oxidatively coupled to 1,6-diphenyl-2,4-hexadiyne-1,6-diol (210)[182] by the normal Glaser type method using cuprous chloride and ammonium chloride.[149] It was found, however, that the simpler method of Eglinton and Galbraith[161] could also be used, very successfully, provided the reaction time (under the concentrated conditions used) was limited to about

10 minutes. Oxidative coupling of the diol (206) under these conditions not surprisingly gave a rather complex mixture (by t.l.c.) The u.v. spectrum showed small peaks at 246 and 261 mμ (ratio of ε's, 1·4:1) in addition to the much stronger end absorption below 220 mμ. This pattern is essentially identical to that of (210) but could of course be due to either cyclised or uncyclised products.

EXPERIMENTAL *

m-Iodobenzoyl chloride

Crude thionyl chloride (100 ml.) was purified by distillation from quinoline (40 ml.) and then from linseed oil (40 ml.), the material of boiling point 75-76° then being used as described below.

m-Iodobenzoic acid (24.5 g.) and thionyl chloride (40 ml.) were heated under reflux for 2 hours in a 100 ml. flask, the reflux condenser being fitted with a calcium chloride drying tube. Excess thionyl chloride was then distilled off at 75-90° and the product was transferred with benzene to a 50 ml. flask. Benzene and any thionyl remaining were removed by distillation at the water pump and the residue was then distilled to give, after a small forerun, m-iodobenzoyl chloride (23 g., 87·5%), b.p. 145·5-148·5°/16 mm. (lit.,[168] 159-160°/23 mm.). The i.r. spectrum (liquid film) showed typical aromatic acid chloride carbonyl absorption at 1750 cm^{-1} and 1790 cm^{-1}.

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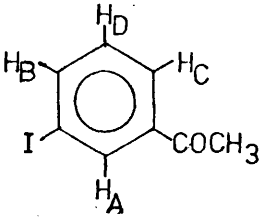
* For general techniques employed, see p.80.

m-Iodoacetophenone

Magnesium (2·31 g.) was placed in a 250 ml. three-necked flask fitted with a dropping funnel and a reflux condenser protected by a drying tube, and absolute ethanol (2·15 ml.) and carbon tetrachloride (0·22 ml.) were added. The reaction, which started fairly quickly on scratching with a glass rod, was allowed to proceed for a few minutes until it was well under way, and sodium dried ether (32·5 ml.) was then added cautiously. The resulting mixture was placed on a steam bath, and a solution of diethyl malonate [(15·2g.), redistilled, b.p. 196-197° (lit.,[168] 198·9)] in absolute ethanol (9 ml.) and sodium dried ether (11 ml.) was added at such a rate that rapid refluxing was maintained, heat being applied when necessary. The mixture was heated under reflux for 3 hours, by which time the magnesium had almost completely dissolved. A solution of m-iodobenzyl chloride (23 g.) in sodium dried ether (50 ml.) was then added with vigorous stirring (magnetic) and the mixture was refluxed for ½ hour. The reaction mixture was cooled, acidified with dilute sulphuric acid, the ether layer separated, and the aqueous layer extracted twice with ether. The ethereal solutions were combined, washed with brine, dried over anhydrous sodium sulphate and filtered, and the solvent was evaporated to give the crude diethyl acylmalonate (34·4 g., quant.) as an oil. The i.r. spectrum (liquid film) showed the expected carbonyl absorption at $\sim$1690 cm^{-1} and 1720-1750 cm^{-1}, and t.l.c. (20% ethyl acetate/petrol) showed a major component of R_F 0·3 with traces of R_F 0·4 and R_F 0·5.

To the crude diethyl acylmalonate was added a solution of glacial acetic acid (26 ml.), water (17·5 ml.) and concentrated sulphuric acid (3·25 ml.) and the mixture was heated under reflux for 5 hours; it was then chilled in an ice bath, made alkaline with 20% aqueous sodium hydroxide solution, and extracted three times with ether. The combined ethereal extracts were washed with water and brine, dried over anhydrous sodium sulphate and filtered, and the solvent was evaporated to give crude ketone (18·5., 87%) as a yellow oil. Distillation gave, after a small forerun containing some diethyl malonate, m-iodoacetophenone (14 g., 66%), b.p. 151-154°/16 mm. (lit.,[168] 117°/4 mm.). T.l.c. (20% ethyl acetate/petrol) showed essentially one spot (R_F 0·6) with a trace of impurity (R_F 0·75). The i.r. spectrum (liquid film) was practically identical to that of an authentic sample,[183] and in the n.m.r. spectrum the following peaks were observed:-



τ = 1·73 [H_A, triplet (J=1-2 cps.)];

τ = 2·1 [H_B and H_C, doublet (J=7 cps.) of doublets (J=1-2cps.)];

τ = 2·72 [H_D, triplet (J=7 cps.)];

τ = 7·45 [3H, singlet, methyl protons].

Reaction of m-iodoacetophenone with phosphorus pentachloride

N.B. It was found that phosphorus pentachloride, once exposed, must be kept in a desiccator until used, if satisfactory results are to be obtained.

Phosphorus pentachloride (6·42 g., i.e. ~25% excess) was placed in a 10 ml. Quickfit conical flask and cooled in an ice bath. m-Iodoacetophenone (5·8 g.) was added, a silica gel drying tube was fitted, and the mixture was stirred for 16 hours at room temperature. The mixture was then carefully poured into water (~70 ml.), cooled in ice, and extracted three times with ether. The combined ethereal extracts were washed with water, sodium bicarbonate solution and brine, dried over anhydrous sodium sulphate and filtered, and the solvent was evaporated to give the crude product (5·97 g.) as a clear oil. The i.r. spectrum showed only a trace of carbonyl absorption at 1690 cm^{-1}, and t.l.c. (20% ethyl acetate/petrol) showed essentially one spot (R_F 0·8) with minor spots of R_F 0·5 (ketone) and R_F 0·7 (probably impurity in ketone).

Attempted dehydrochlorination with sodamide in liquid ammonia

A suspension of sodamide in liquid ammonia was prepared in the usual way[128] from sodium (3 g.) in liquid ammonia (200 ml.), using a small amount of ferric nitrate as catalyst. A solution of the crude chlorination product (3·2 g.) [from m-iodoacetophenone (2·98 g.)] in sodium dried ether (50 ml.) was added, and the mixture was stirred for four hours. Solid ammonium chloride (15 g.) was carefully added, followed by ether (200 ml.), and the mixture was stirred overnight to allow the ammonia to evaporate. The ether layer was poured off, the solid extracted with ether, and the combined ether layers were washed with dilute sulphuric acid, sodium bicarbonate solution and water, before drying over magnesium sulphate and filtering. Evaporation of the solvent gave an oil (0·9 g.), the t.l.c. of which was complex. The i.r. spectrum showed strong absorption at 3340 cm.$^{-1}$ (ν $\equiv$C-H) and weak absorption at 2150 cm.$^{-1}$ (ν C$\equiv$C), but comparison with an authentic sample of m-iodophenylacetylene (see below) showed that very little, if any, of this material was present. Treatment with an excess of ammoniacal cuprous chloride[150] in the usual way[151] gave a brown solid (600 mg.) but hydrolysis (see below) of a portion of this cuprous derivative back to the free acetylene gave a product which was shown by t.l.c. to be a mixture of several compounds.

Dehydrochlorination with potassium hydroxide/ethanol and isolation of m-iodophenylacetylene via the cuprous derivative.

(a) Concentrated conditions

The crude chlorination product (3·2 g.) [from m-iodoacetophenone (2·98 g.)] was heated under reflux in absolute ethanol (7 ml.) with potassium hydroxide (2·52 g.) for 25 hours. The reaction mixture was poured into water (70 ml.) and extracted three times with ether. The combined ethereal extracts were washed thoroughly with water, dried over magnesium sulphate and filtered. The solvent was evaporated to give an oil, the i.r. spectrum (liquid film) of which showed only a small amount of acetylenic absorption at 3350 cm.$^{-1}$ (ν ≡C-H).

Treatment of the crude dehydrochlorination product with ammoniacal cuprous chloride[150] [from cupric sulphate pentahydrate (3 g.)] in the usual way[151] gave cuprous m-iodophenylacetylide (370 mg., 10·5% based on m-iodoacetophenone) as a yellow solid. Hydrolysis (see below) of

37 mg. of this solid gave m-iodophenylacetylene as an oil, the i.r. spectrum (liquid film) of which was practically identical to that of an authentic sample prepared later (see below). T.l.c. (petrol) showed essentially one spot.

(b) Dilute conditions

Potassium hydroxide (7·7 g.) was heated under reflux in absolute ethanol (100 ml.) till solution was almost complete. A solution of the crude chlorination product (5·97 g.) [from m-iodoacetophenone (5·8 g.)] in absolute ethanol (50 ml.) was added, and the mixture was heated under reflux for 24 hours. About 120 ml. of ethanol was distilled off and the residue was diluted with water (150 ml.) and extracted three times with ether. The combined ethereal extracts were washed with water and brine, dried over anhydrous sodium sulphate and filtered. Evaporation of the solvent gave an oil (4·68 g.), the i.r. spectrum (liquid film) of which showed fairly strong absorption at 3350 cm.$^{-1}$ (ν ≡C-H).

Ammoniacal cuprous chloride was prepared in the usual way,[150] using 9 g. of cupric sulphate pentahydrate. The crude dehydrochlorination product (4·68g.) was added in a small volume of ethanol, and the mixture was stoppered and shaken thoroughly. The yellow precipitate was filtered off and washed successively five times each with water, ethanol and anhydrous ether. The yellow solid was allowed to dry in air for a short time and was then placed on the rotary evaporator for 20 minutes at 40°, during which time no decrease in weight occurred. The weight of cuprous m-iodophenylacetylide was 2·35 g. (34·3% based on m-iodophenone).

Cuprous m-iodophenylacetylide (288 mg.) was shaken with dilute hydrochloric acid and ether in a separating funnel till the solid had almost completely dissolved. The ether layer was separated, the aqueous layer was extracted twice with ether, and the combined ethereal extracts were washed with water, sodium bicarbonate solution and brine, dried over anhydrous sodium sulphate and filtered. The solvent was evaporated to give crude m-iodophenylacetylene (211 mg., 93·5% based on cuprous derivative) (almost pure by i.r. and t.l.c.). Preparative t.l.c. (Kieselgel HF_{254}, 0·5 mm., petrol) followed by microdistillation gave m-iodophenylacetylene as a clear liquid, b.p. 45-50^{o} (block temperature)/0·5 mm. (Found: C, 42·23; H, 2·26. Required for C_8H_5I: C, 42·2; H, 2·2%). The mass spectrum showed peaks at $^{m}/e = 228$ (M^+) and $^{m}/e = 101$ ($M^+ - I$). The i.r. spectrum showed strong absorption at 3350 cm.$^{-1}$ ($\nu \equiv C-H$) and very weak absorption at 2130 cm.$^{-1}$ (ν $C\equiv C$) as well as normal aromatic type absorption. In the n.m.r. spectrum the following peaks were observed: $\tau = 2{\cdot}1 - 3{\cdot}1$ (4H, multiplet, aromatic protons); $\tau = 6{\cdot}9$ (1H, singlet, acetylenic proton).

Castro-type coupling reaction of cuprous m-iodophenylacetylide.

Dry pyridine (300 ml.) was heated under reflux in a nitrogen atmosphere for 1 hour. Cuprous m-iodophenylacetylide (1·96 g.) was added and the mixture heated under reflux in a nitrogen atmosphere for 20 hours. Pyridine (200 ml.) was distilled off under nitrogen, and the residue was allowed to cool before being poured into an excess of dilute sulphuric acid and ice, and being extracted three times with benzene. A fairly large volume of insoluble material was obtained and this was filtered off and then extracted with benzene, and the combined benzene extracts were washed with dilute sulphuric acid, water and brine, dried over anhydrous sodium sulphate and filtered. The solvent was evaporated to give a light yellow solid (584 mg.). T.l.c. (Kieselgel HF_{254}, 20% benzene/petrol, run 3x) showed a complex mixture of at least ten compounds, numbered I → X below in order of increasing polarity. The i.r. spectrum (nujol mull) of the mixture was devoid of terminal acetylene absorption but showed characteristic aromatic absorption at 1595 (ν C=C), 905, 800 and 695 (δ C-H) cm^{-1}. The u.v. spectrum (cyclohexane) showed strong peaks at 271, 286 and 304 mμ and a smaller peak at 333 mμ. Separation of the components was carried out as follows. (For a discussion of other attempted methods of separation and the reasons for the choice of the method below, see p.150).

The crude product (335 mg., preadsorbed on alumina (1 g., Woelm, Grade I, neutral) was chromatographed on alumina (150 g., Woelm, Grade II, neutral, made up in petrol), the following fractions being taken, and their contents being examined by t.l.c. [Kieselgel HF$_{254}$, 20% benzene/petrol, run 1x (compounds I → IV) or 3x (IV → X); 25% benzene/petrol, 3x (X → XI)].

Fractions	Solvent	Weight (mg.)	Compounds	Structures
1	Petrol(250 ml.)	-	-	-
2	"	10	I	(201)
4-6	"	15.5	II	(202a)
9-10	50% Petrol/CCl_4 (100 ml.)	14·5	III	(202b)
11	"		III + IV	
12-15	"	15·5	IV	(202c)
16-18	"		IV + V	
19	50% Petrol/CCl_4 (250 ml.)	5	V	probably (203) + (202d)
20-21	"		V + VI	
22-25	"	33	VI	(204)
26-34	"	31	VI + IX	
35-46	"	25	VI + VIII + IX	
47-68	"	43	VIII	
69-74	CCl_4/Petrol(2:1) (250 ml.)	18	mainly at origin	
75-82	CCl_4 (100 ml.)	19	"	
83-95	"	14	X	
96-105	CCl_4 (250 ml.)	17	X + XI	
106-113	"	9	XI	

<u>Notes</u>: Frs. 22-46 probably contained traces of V, and frs. 53-74 traces of VII. From fr. 47 onwards, considerable material at the origin was noted on t.l.c. Compound VII appeared to be a very minor constituent and was not isolated, whereas small amounts of compound XI, not observed in the crude product, were isolated. Further purification and characterisation of the

reaction products were carried out as described below. The melting points obtained for compounds I — V were rather wide. This may be the result of poor crystalline form, of traces of involatile solvent residues, or in the cases of III — V, of the presence of isomers of the same gross structure.

Compound I, which was shown to be 3,3'-diiododiphenyldiacetylene (201), was obtained from fraction 2 as a white crystalline solid, rapidly turning yellow (10 mg., 0·7%). Crystallisation from ether/petrol gave a microcrystalline solid, m.p. 124-127° (but considerable softening and partial melting from ca. 110°), whose i.r., u.v. (quantitative) and mass spectra were essentially identical to those of an authentic sample of (201) (p.185). T.l.c. (20% benzene/petrol) showed one spot, of identical R_F value to (201).

Compound II. (15·5 mg., 1·2 %), obtained from fractions 4 - 6 as a white crystalline solid, rapidly turning yellow, was purified by preparative t.l.c. (Kieselgel HF_{254}, 0·5 mm., 25% benzene/petrol) and was then crystallised from ether/

petrol to give a microcrystalline solid, m.p. 124-128° (partial melting by ~122°). The structure (202a) was assigned on the basis of the following spectral evidence. The i.r. spectrum (KBr disc) showed typical aromatic absorption at 3040 cm^{-1} (ν C-H), 1580, 1540 and 1470 cm^{-1} (ν C=C) and 895, 880, 870, 785, 775, 670 and 650 cm^{-1} (δ C-H). The u.v. spectrum (cyclohexane) had λ_{max} 223 sh. (ε 42,000), 233 (43,000), 242 sh. (41,000), 261 sh. (33000), 266 (35,000), 288 (38,000), 292 sh. (37,000), 303 (33,000), 311 (35,000), 323 (13,000) and 334 (28,000) mμ. The mass spectrum showed peaks at m/e = ca. 554 (M^+), ca. 427 (M^+ - I), 300 (M^+ - 2I), 277 (M^{2+}), 213·5 (M^{2+} - I) and 150 (M^{2+} - 2I). ($C_{24}H_{12}I_2$ requires M.W. 554).

<u>Compound III</u> [from fractions 9 - 10, 14·5 mg., 1·3 % (minimum)] was obtained as white crystals, which fairly quickly became yellow. Purification by preparative t.l.c. (Kieselgel HF_{254}, 0·5 mm., 25% benzene/petrol, considerable streaking observed) followed by crystallisation twice from ether, after filtration through a little alumina (Grade V),

gave a white microcrystalline solid, m.p. 156-168° (mostly melted by 160°). The structure (202b) was assigned on the basis of the following spectral evidence. The i.r. spectrum KBr disc) showed typical aromatic absorption at 905, 890, 785 and 680 cm^{-1} (δ C-H). The absorption in the 1500-1600 cm^{-1} region was poorly resolved. The u.v. spectrum (cyclohexane) had λ_{max} 223 sh. (ε 61,000), 232 (62,000), 242 (62,000), 271 (65,000), 279 sh. (67,000), 287 (79,000), 293 sh. (72,000), 304 (69,000), 323 (19,000), and 334 (38,000) mμ. The mass spectrum showed peaks at m/e = ca. 654 (M^+), ca. 527 (M^+ -I), 400 (M^+ - 2I), 327 (M^{2+}), 263·5 (very small, M^{2+} - I) and 200 (M^{2+} - 2I). ($C_{32}H_{16}I_2$ requires M.W. 654).

<u>Compound IV</u> was obtained from fractions 12-15 (15·5 mg., 1·5 % minimum) as white crystals, becoming yellow fairly quickly. Crystallisation from benzene/petrol gave a microcrystalline solid, m.p. 168-175°. The structure (202c) was assigned on the basis of the following spectral evidence. The i.r. spectrum (KBr disc) showed typical aromatic

absorption at 3020-3060 cm^{-1} (ν C-H), at 1600, 1580, 1570, 1560 (trace), 1550-1540, 1480 and 1470 cm^{-1} (ν C=C) and at 905, 890, 850 (weak), 790, 780, 760 (weak), 710 (weak), 680 and 655 (weak) cm^{-1} (δ C-H). The u.v. spectrum (cyclohexane) had λ_{max} 223 (ε 59,000), 233 (59,000), 243 (59,000), 271 (72,000), 287 (92,000), 304 (81,000) and 334 (32,000) mμ. The mass spectrum showed peaks at m/e = ca, 754 (M^+), ca. 627 (M^+ - I), ca. 500 (M^+ - 2I), 377 (M^{2+}), 313·5 (M^{2+} -I) and 250 (M^{2+} - 2I). ($C_{40}H_{20}I_2$ requires M.W. 754).

Compound V (5 mg.) was obtained from fraction 19. Purification by preparative t.l.c. (Kieselgel HF_{254}, 0·5 mm., 25% benzene/petrol, run 2x) was attempted, but streaking was so great that some V could be recovered from the origin. The use of carbon tetrachloride/petrol (70:30) (run 2x) was much more satisfactory and V was therefore purified in this way. Careful examination of the t.l.c. properties of 'V' suggested that it might contain two closely running compounds, but the apparent difference in R_F values was too small to allow separation. Crystallisation of V from chloroform/petrol gave off-white micro-crystals, m.p. ~ 180-200°. The possible structures for 'V' are discussed on p.155. The u.v. spectrum (cyclohexane) [ε values assuming structure (202d)] had λ_{max} 222 (ε 36,000), 234 (35,000), 243 (35,000), 271 (49,000), 287 (65,000), 304 (55,000) and 334 (17,000) mμ. The mass spectrum showed peaks essentially only at m/e = 400 and m/e = 200.

Compound VI, which was shown to be the 'cyclic pentamer' (204), was a major component of fractions 21, 22-25 (33 mg., almost pure, ~ 5%) and 26-34 (31 mg., VI + IX) and was also present in fractions 20 and 35-46. Purification (material from fractions 22-34) was carried out by repeated preparative t.l.c. [Kieselgel HF_{254}, 0·5 mm., carbon tetrachloride/petrol (70:30), run 3x], frequently using less than 5 mg. of material to avoid streaking, until the material was completely t.l.c. pure (examination using Kieselgel HF_{254}, solvent as on prep. t.l.c. or 20% benzene/petrol, run 3x). Crystallisation of the material thus obtained (32 mg.) from benzene/petrol gave VI, (204), as small lustrous white plates, which did not melt on heating in a sealed tube to 500° but from about 260° slowly darkened. Sublimation at 250-270°/0·5 mm. could be carried out, however, with little decomposition. The i.r. spectrum (KBr disc), which was simpler than that of the uncyclised compounds (202a-c), showed characteristic aromatic type absorption at 3020-3080 cm^{-1} (weak, ν C-H), at 1600 (strong), 1570 (weak) and 1485 (s.) cm^{-1} (ν C=C) and at 895 (medium), 790 (s.), 755 (m.) and 680 (s.) cm^{-1} (δ C-H). A number of weak peaks were also present, including one at 2210 cm^{-1} (ν C≡C). The u.v. spectrum (p.157a) (cyclohexane) had λ_{max} 219 (ε93,000), 271 (101,000), 286 (185,000), 295 (110,000), 304 (128,000) and 319 (13,000) mμ. The mass spectrum showed peaks essentially only at m/e = 500 (M^+) and m/e = 250 (M^{2+}), and a very small peak was also observed at m/e = 166·7 (M^{3+}). A high resolution mass spectrum gave a value of m/e = 500·1573 for the parent peak. ($C_{40}H_{20}$ requires M.W. 500·1565). The n.m.r. spectrum (p.158a) (100 Mc./s., deuterochloroform as solvent) showed the following peaks (ratio approximately 1:3): τ = 2·03, broadened singlet, possibly poorly resolved triplet (H_C); $\tau = 2{\cdot}55$, multiplet (H_A and H_B).

Hydrogenation of VI (~1·5 mg.) for 20 minutes over 10 % palladium/charcoal in ethyl acetate gave a product which was essentially one spot on t.l.c. [Kieselgel HF_{254}, CCl_4/petrol (70:30), run 2x], of identical R_F value to [2.2.2.2.2]metacyclophane[179] (199a). The mass spectrum of the hydrogenation product [purified by prep. t.l.c., Kieselgel HF_{254}, 0·2 mm., CCl_4/petrol (80:20), run 2x] was identical to that of a sample of (199a).

Compound VIII (from frs. 47-68) and compound IX (from frs. 26-34) were obtained in small amounts (ca. 5 mg. each) by repeated preparative t.l.c. [Kieselgel HF_{254}, 0·5 mm., CCl_4/petrol (70:30), run 3x, using very small amounts (< 5 mg.) on the plates] and were crystallised from benzene/petrol to give white crystals (needle-like in the case of IX). The u.v. spectra (cyclohexane) were very similar to that of VI but were without a small peak at 319 mμ (see p.160). Mass spectra could not be obtained for VIII and IX but in the mass spectra of some mixtures, peaks were observed at m/e = 500 (VI), 600 (high resolution[181] gave m/e = 600·18737: $C_{48}H_{24}$ requires 600·18774) and at 700 (smaller). The peaks at m/e = 600 and 700 were observed at a source temperature of ca. 300°, whereas at a temperature of ca. 200°, the spectrum corresponded to that of VI. Hydrogenation of VIII (~0·5 mg.) for 20 minutes over 10% palladium/charcoal in ethyl acetate gave a mixture of two products by t.l.c. [Kieselgel HF_{254}, 30% benzene/petrol, run 2x] of R_F 0·35 and R_F 0·45 (faint) neither of which corresponded to a sample of [2.2.2.2.2.2.]-metacyclophane[179] (R_F 0·4).

Compound X, isolated in very small amounts in a fashion similar to VIII and IX, likewise did not yield a mass spectrum and was not further investigated.

3,3'-Diiododiphenyldiacetylene (201).

Cupric acetate (400 mg.) was partially dissolved in pyridine (2 ml.) and methanol (2 ml.) by heating under reflux and a solution of m-iodophenylacetylene (192 mg.) in pyridine (1·5 ml.) and methanol (1·5 ml.) was added. The mixture was refluxed for 20 minutes, cooled, poured into ice-cold dilute sulphuric acid and extracted thoroughly with ether. The ether extract was washed with dilute sulphuric acid, sodium bicarbonate solution and brine, dried (anh. sodium sulphate) and filtered. Evaporation of the solvent gave a yellow solid (187 mg.), m.p. ~122-129°, one spot on t.l.c. (20% benzene/ petrol). Crystallisation from petrol after animal charcoal treatment gave the diacetylene (201) (118 mg., 61%) as a yellowish microcrystalline solid, m.p. 125-129°. Recrystallisation of a small sample from aqueous ethanol gave whitish plates, m.p. 124-128°, and microdistillation (block temp. 180°/0·1 mm.) gave a sample of m.p. 127-130°. (Found: C, 43·63; H, 2·11. Required for $C_{16}H_8I_2$. C, 42·3; H, 1·78%). The i.r. spectrum (KBr disc) showed typical aromatic absorption at 1580 and 1550 cm^{-1} (ν C=C) and at 805, 790, 680 and

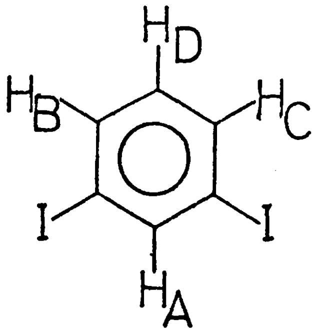
655 cm^{-1} (δ C-H) but no ν C≡C absorption. The n.m.r. spectrum showed a complex multiplet at 2·08-3·08 τ. The u.v. spectrum (cyclohexane) had λ_{max} 231 (ε 58,000), 264·5 (30,000), 275 (18,000), 293·5 (24,500), 312·5 (34,000), 324 (16,000) and 334 (34,500) mμ. The mass spectrum had base peak m/e = 454 (M^+), major fragments at m/e = 327 (M^+ - I), 200 (M^+ - 2I) and 100 (M^{2+} - 2I) and smaller peaks at 227 (M^{2+}) and 163·5 (very weak) (M^{2+} - I).

m-Bis(phenylethynyl)benzene (200).

Dry pyridine (50 ml.) was purged with nitrogen for 30 minutes and m-diiodobenzene (1·26 g.) and cuprous phenylacetylide (p. 81) (1·4 g.) were added. The mixture was refluxed under nitrogen for 16 hours, allowed to cool, poured into excess dilute sulphuric acid and ice and extracted three times with ether. The combined ethereal extracts were filtered, washed with dilute sulphuric acid, sodium bicarbonate solution and brine, dried (anh. sodium sulphate) and filtered. Evaporation of the solvent gave a light coloured solid (1·13 g.), one major spot on t.l.c. (petrol). Treatment of the crude product with a little animal charcoal and crystallisation twice from petrol gave m-bis(phenylethynyl)benzene (480 mg., 45%) as white needles, m.p. 112-113° (lit.,[145] 114-115°), one spot on t.l.c. (petrol). The i.r. spectrum (KBr disc) showed extremely weak absorption at 2210 cm^{-1} (ν C≡C) and typical aromatic absorption at 3000-3100 cm^{-1} (w) (ν C-H), 1600 (m), 1575 (w) and 1495 (m) cm^{-1} (ν C=C), and 805, 755 and 690 cm^{-1} (δ C-H, all strong). Medium peaks were also observed at 1445, 1070, 1025, 915 and 905 cm^{-1}. The u.v. spectrum (cyclohexane) had λ_{max} 218 (43,000), 223 (38,000), 268·5 (ε 47,000), 276 (51,000), 283·5 (66,000), 291·5 (48,000) and 301 (56,000) mμ. The n.m.r. spectrum showed only the expected aromatic multiplet at 2·2-2·9 τ (one proton as a multiplet at 2·2-2·3 τ). The mass spectrum had its base peak at m/e = 278 (M^+), its second strongest at 139 (M^{2+}) and a trace at 92·7 (M^{3+}).

m-Diiodobenzene.

A solution of m-phenylenediamine (8·23 g.) in concentrated hydrochloric acid (500 ml.) and water (500 ml.) was stirred in an ice/salt bath till the temperature fell to 0°. A solution of sodium nitrite (11·3 g.) in water (30 ml.) was added at such a rate that the temperature was maintained at 0-3°. A solution of potassium iodide (80 g.) in water (150 ml.) was then added at such a rate that the temperature remained below 5° (mainly at ~2°). The mixture was stirred at room temperature for 40 minutes, heated to boiling on an isomantle (~ 25 mins.), boiled for 2-3 mins., allowed to cool and extracted three times with ether. The combined ethereal extracts were filtered, washed with dilute hydrochloric acid, dilute sodium hydroxide solution and brine, dried (anh. sodium sulphate) and filtered. Evaporation of the solvent gave a dark oil (18·08 g.), the i.r. spectrum (liquid film) of which showed a fairly strong peak at 2130 cm^{-1} in addition to the expected aromatic absorption. Distillation (of 17·65 g.) gave, after a small forerun, m-diiodobenzene (8·54 g., 35%), b.p. 153-156°/21 mm. (lit.,[168] 285°/760 mm.), as a dark oil which quickly solidified. The i.r. spectrum (melt) still showed some absorption at 2130 cm^{-1}. Crystallisation of the distillate (6·65 g.) from ethanol/ether, using chilling in acetone/dry ice and rapid filtration, followed by similar recrystallisation of the mother liquors twice more, gave m-diiodobenzene (4·46 g., 23·5%), m.p. 33-34° [lit.,[168], 40° (36·5)], as lustrous off-white plates. The i.r. spectrum (melt) showed only typical aromatic absorption and t.l.c. (petrol) showed only one spot. In the n.m.r. spectrum the following peaks were observed: $\tau = 1{\cdot}95$ [H_A, triplet (J = 2 cps.)]; $\tau = 2{\cdot}35$ [H_B and H_C, doublet (J = 8 cps.) of doublets (J = 2 cps.)]; $\tau = 3{\cdot}18$ [H_D, triplet (J = 8 cps.)].



Dimethyl isophthalate.

Isophthalic acid (50 g.) was heated with methanol (500 ml.) till partially dissolved, concentrated sulphuric acid (25 ml.) was added carefully, and the mixture was heated under reflux for 3 hours. Excess methanol (~ 400 ml.) was removed by distillation and the residue was diluted with water and extracted thoroughly with ether. The ether extract was washed with sodium carbonate solution and brine, dried (anh. sodium sulphate) and filtered. Evaporation of the solvent gave dimethyl isophthalate (53·5 g., 91%) as a white crystalline solid, m.p. 66-68° (lit.,[168] 68°), one spot on t.l.c. (50% ethyl acetate/petrol). The i.r. spectrum (nujol mull) showed typical carbonyl absorption at 1720 cm^{-1}.

Isophthalyl alcohol.

A solution of dimethyl isophthalate (23·2 g.) in sodium dried ether (200 ml.) was added dropwise to a stirred suspension of lithium aluminium hydride (10 g.) in sodium dried ether (300 ml.). After stirring for 3 hours at room temperature, the various complexes were destroyed by the careful addition of saturated aqueous sodium sulphate solution. The ether solution was decanted, and the residue extracted with ether and dried (anh. sodium sulphate). The residue was then dissolved in dilute hydrochloric acid and extracted again with ether. This ether extract was washed with sodium bicarbonate solution and brine, dried (anh. sodium sulphate) and combined with the first extract. Evaporation of the solvent gave the crude diol (13·75 g., 83%) as an oil, essentially one spot on t.l.c. (50% ethyl acetate/petrol). Crystallisation from benzene (using seeding) gave isophthalyl alcohol (12·25 g., 74%) as white needles, m.p. 53·5-55·5° [lit.,[168] 57(46-7)°], one spot on t.l.c. The i.r. spectrum (nujol mull) was devoid of carbonyl absorption and showed broad absorption at ~3200-3400 cm^{-1} (ν O-H).

Isophthalaldehyde.

To a stirred solution of isophthalyl alcohol (10·5 g., 76 m.moles) in water (320 ml.)was added a solution of ceric ammonium nitrate (176 g., 321 m.moles) in water (320 ml.). The resulting solution was heated on a steam bath with occasional shaking till the colour changed from deep red to light yellow, allowed to cool and extracted thoroughly with ether. The ether extract was washed with sodium bicarbonate solution and brine, dried (anh. sodium sulphate) and filtered. Evaporation of the solvent gave the crude product (9·15 g., 90%), m.p. 87-90°, essentially one spot on t.l.c. (40% ethyl acetate/petrol). Crystallisation from water gave isophthalaldehyde (7·4 g., 70·5%) as white needles, m.p. 88-90·5° (lit.,[168] 89-90°). The i.r. spectrum (nujol mull) showed typical carbonyl absorption at 1690 cm^{-1}.

Treatment of isophthalyl alcohol (0·51 g.) with manganese dioxide(7 g.) in refluxing benzene for 9 hours, followed by stirring at room temperature for 20 hours, gave (after work up similar to that on p.110), crude isophthalaldehyde (135 mg., 27%), almost pure by i.r. and t.l.c.

m-Bis(1-hydroxy-2-propynyl)benzene (206).

A solution of ethylmagnesium bromide in tetrahydrofuran was prepared under nitrogen from magnesium (4 g.), ethyl bromide (17 ml.) and dry tetrahydrofuran (100 ml., distilled from lithium aluminium hydride). Using the method described on p.114, the Grignard solution (under nitrogen) was added over 20 minutes, with a little external cooling when necessary, to dry tetrahydrofuran (70 ml.) which had been saturated with acetylene for 50 minutes. After 20 minutes' stirring with passage of acetylene, isophthalaldehyde (1·35 g.) in dry tetrahydrofuran (25 ml.) was added (over 5 mins.) and the mixture was stirred for 45 minutes with passage of acetylene before working up as on p.115 to give the crude product as a viscous oil (1·9 g.), essentially one spot on t.l.c. (40% ethyl acetate/petrol). Distillation (b.p. 130-134°/0·05 mm.) proved rather difficult because of the viscosity of the product, and a sample of the crude product (51 mg.) was purified by preparative t.l.c. (Kieselgel G, 0·5 mm. 40% ethyl acetate/petrol) to give diol (206), presumably a mixture of diastereoisomers, (32 mg.,65 %) as a colourless oil. The i.r. spectrum (liquid film) showed strong absorption at 3340 cm^{-1} (ν ≡C-H) with a shoulder at 3350-3700 cm^{-1} (ν O-H) and rather weak absorption at 2140 cm^{-1} (ν C≡C). The n.m.r. spectrum showed the following peaks: τ = 2·33 (1H, broadened singlet) and τ = 2·54 (3H, finely split doublet with small side bands at τ=2·43 and 2·61) (aromatic protons); τ = 4·59 [2H, doublet (J = 2-3 cps.), carbinyl protons]; τ = 6·97 (2H, broad singlet, disappearing on D_2O exchange, hydroxyl protons); τ = 7·37 [2H, doublet (J = 2-3 cps.), acetylenic protons].

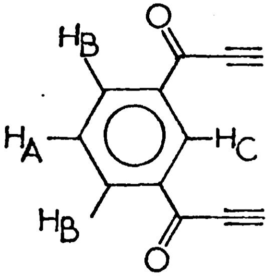
The diol (206) could also be obtained from isophthalaldehyde by treatment with sodium acetylide[128] in liquid ammonia (method as on p.111). Using a tenfold excess of sodium acetylide, only partial conversion to the diol (206) was achieved, some of the half-reacted aldehyde-acetylenic carbinol being present in the mixture (from i.r. and t.l.c.) as well as a little isophthalaldehyde apparently. With a twentyfive-fold excess of sodium acetylide, however, almost complete conversions to the diol (206) was achieved.

m-Bis(1-keto-2-propynyl)benzene (209)

A solution of m-bis(1-hydroxy-2-propynyl)benzene (468 mg., crude product of Grignard reaction above) in acetone (3 ml.) was stirred in an ice bath and Jones reagent (p.81) (1·4 ml.) was added. The mixture was stirred at room temperature for 30 mins. before diluting with water and extracting thoroughly with ether. The ether extract was washed with water, saturated sodium bicarbonate solution and brine, dried (sodium sulphate) and filtered. Evaporation of the solvent gave the crude dione (209) (400 mg.) as a light yellow solid, essentially one spot on t.l.c. (40% ethyl acetate/petrol). The dione was purified by preparative t.l.c. (Kieselgel G., 0·5 mm., 20-40% ethyl acetate/petrol) to give a microcrystalline solid, m.p. 108-113° (with decomposition). The dione (209) seemed reasonably stable in the solid state, but rapidly developed a red colour either in solution, or on standing on a preparative t.l.c. plate for less than 1 minute. Attempted crystallisation from aqueous ethanol appeared to result in decomposition, and sublimation at 70-90°/0·01 mm. gave a red coloured material which appeared, however, to be fairly pure (209) from t.l.c. The i.r. spectrum (nujol mull) of (209) (purified by prep. t.l.c.) showed strong absorption at 2130 cm^{-1} (ν C≡C) and 1650 cm^{-1} (ν C=O) and medium absorption at 3270 cm^{-1} (ν ≡C-H). The u.v. spectrum (ethanol) had λ_{max} 230 sh. (log ε 4·23), 251 (4·31), 297 sh (3·23) and 307 (3·11) mμ. The n.m.r. spectrum showed the following peaks:

τ = 1·15 [1H, poorly resolved triplet (J = ~2 cps.), H_C];

τ = 1·65 [2H, doublet (J = 8 cps.) of doublets (J = 2 cps.), H_B];



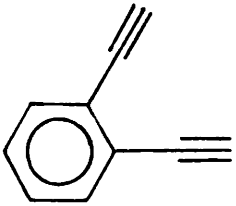
$\tau = 2{\cdot}37$ [1H, triplet (J = 8 cps.), H_A]; $\tau = 6{\cdot}45$ (2H, singlet, acetylenic protons). The mass spectrum had parent peak at m/e = 182 (M^+) ($C_{12}H_6O_2$ requires M.W. 182).

Oxidative coupling of phenylethynylcarbinol (146) using cupric acetate-pyridine-methanol.[161]

Cupric acetate (5·88g., 30 m.moles) was heated under reflux with pyridine (25 ml.) and methanol (20 ml.) to give a partial solution. A solution of phenylethynylcarbinol (2·65 g., 20 m.moles) in methanol (5 ml.) was added and the mixture was refluxed for 5 minutes, cooled immediately under the tap, poured into excess dilute sulphuric acid and ice, and extracted thoroughly with ether. The ether extract was washed with dilute sulphuric acid and saturated sodium bicarbonate solution, dried (sodium sulphate) and filtered. Evaporation of the solvent gave a red oil (2·59 g., quant.) which quickly solidified. Crystallisation from benzene gave the oxidatively coupled product 1,6-diphenyl-2,4-hexadiyne-1,6-diol [2·1 g., 79%, one spot on t.l.c. (40% ethyl acetate/petrol)], presumably a mixture of diastereoisomers, The melting point as expected was over a range (85-134°). [Lit. values vary for the m.p. range of diastereoisomeric mixtures. M.pts. of separated isomers, 134° (D/L pair) and 113° [184]]. The i.r., u.v., n.m.r. [peaks at $\tau = 2{\cdot}6$ (10H, multiplet), $\tau = 4{\cdot}5$ (2H, singlet) and $\tau = 7{\cdot}45$ (2H, broad singlet, disappearing on D_2O exchange] and mass spectra of the product confirmed that it was 1,6-diphenyl-2,4-hexadiyne-1,6-diol. When the reaction time was prolonged to 1½ hours, the product was a complex mixture (by t.l.c.) containing very little of the oxidatively coupled product.

Oxidative coupling of m-bis(1-hydroxy-2-propynyl)benzene (206).

Cupric acetate (0·6 g.) was heated under reflux in 50% pyridine/methanol (2 ml.) to give a partial solution. The diol (143 mg., crude Grignard product) was added in 50% pyridine/methanol (2 ml.) and the mixture was refluxed for 10 minutes, cooled immediately, poured into excess ice-cold dilute sulphuric acid and extracted thoroughly with ether. The ether extract was washed and dried as in the above experiment to give a viscous oil (25 mg.) which solidified on scratching. T.l.c. (80% ethyl acetate/petrol) showed a complex mixture, mainly two groups of closely running compounds, R_F 0·4 and R_F 0·5. The u.v. spectrum (ethanol) showed small peaks at 246 and 261 mμ in addition to strong end absorption.



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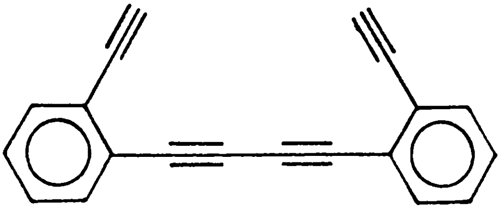

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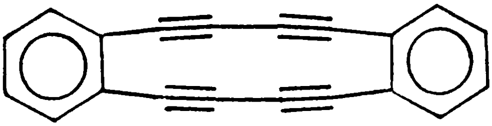

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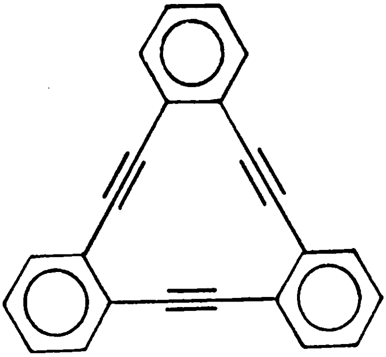

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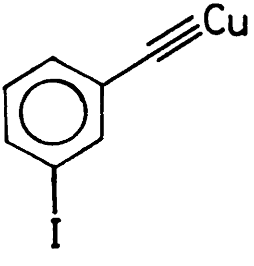

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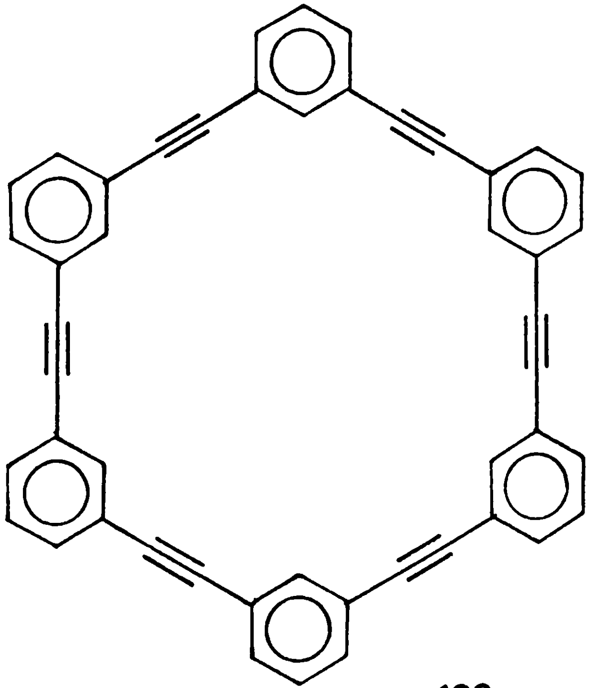

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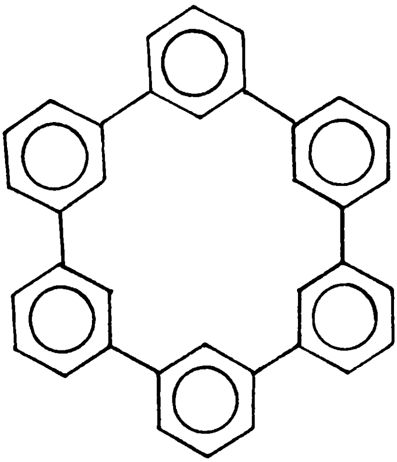

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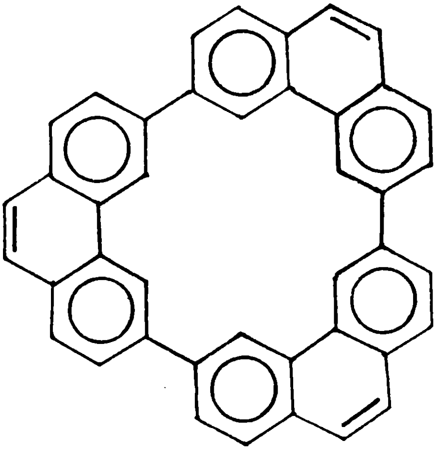

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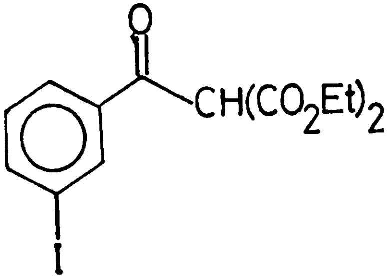

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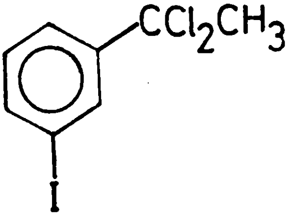

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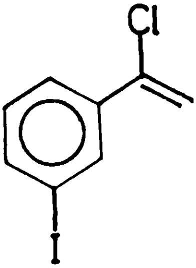

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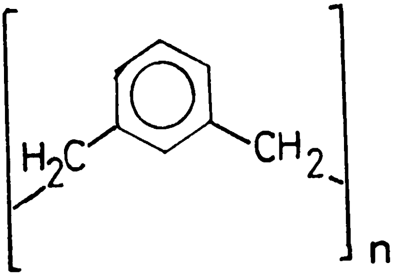
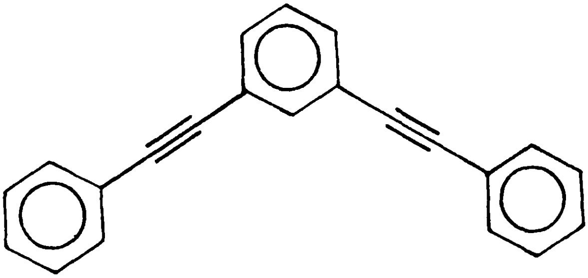


199 ($n = 2,3,4,5,6,8$)

199a $n = 5$



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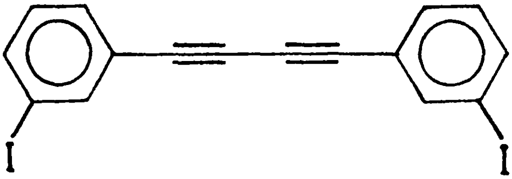

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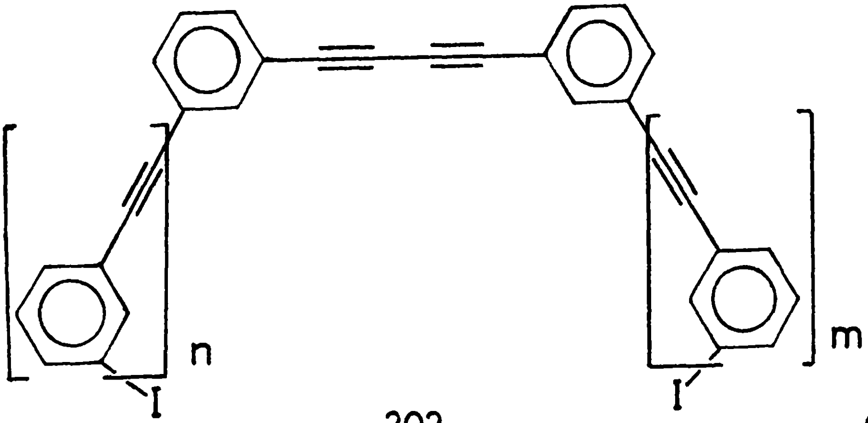


202

a ; n = 1, m = 0

b; n = 1, m = 1

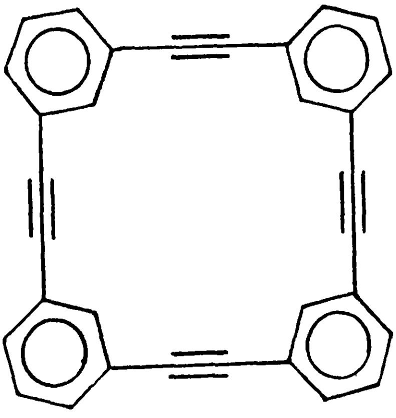
or n = 2, m = 0

c; n = 2, m = 1

or n = 3, m = 0

d; n = 2, m = 2

or n = 3, m = 1 or n = 4, m = 0



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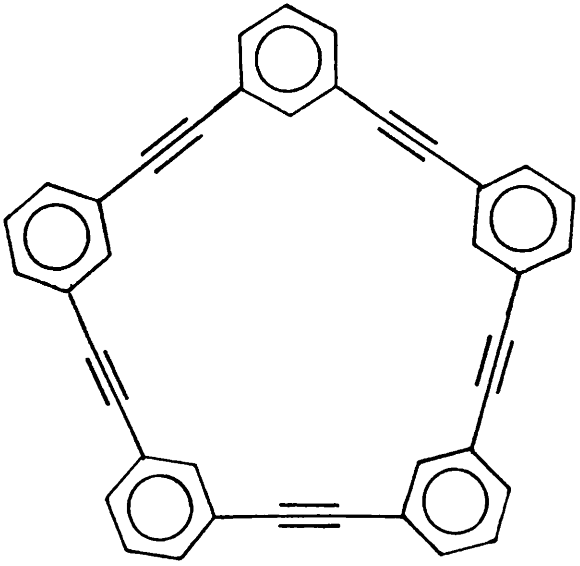

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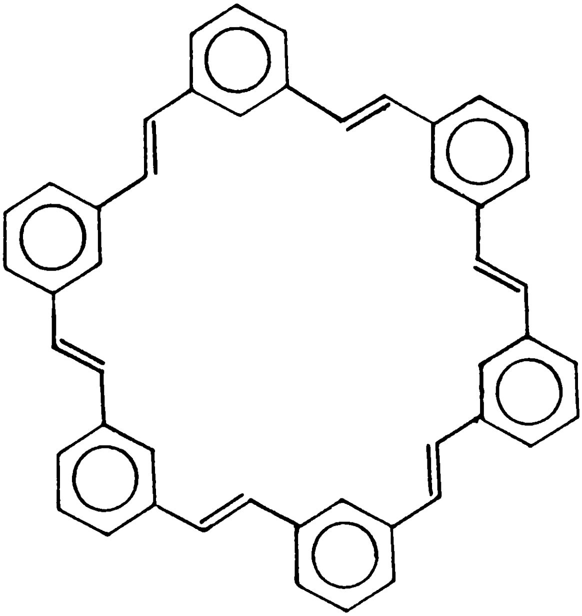

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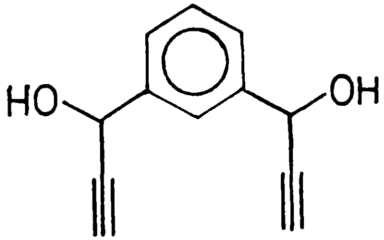

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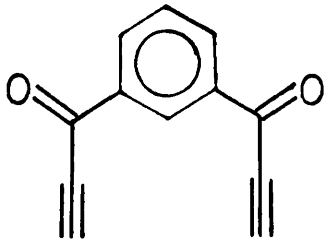

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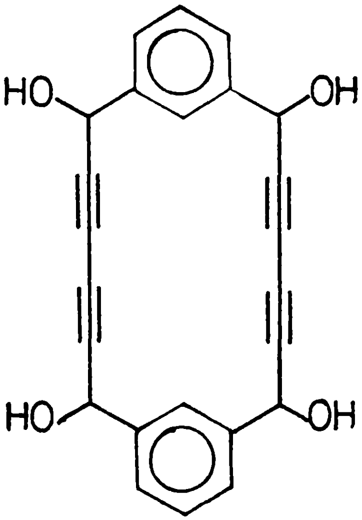

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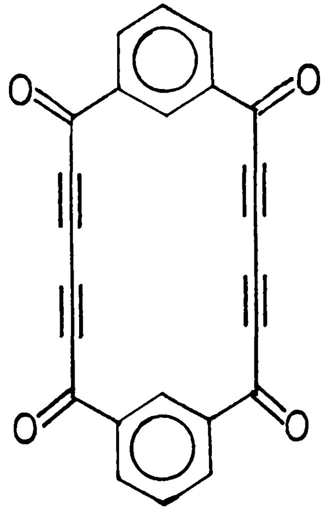

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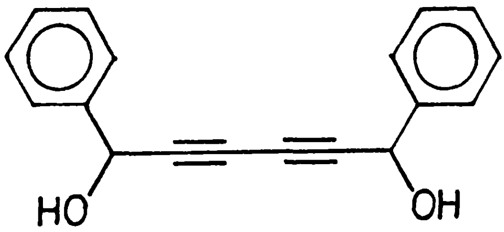

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