A

THESIS

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THE

ACTION OF AMINES

ON

SEMICARBAZONES

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FOREWORD

The principal work described under the title of this thesis might be sub-divided as follows:-

(1). The preparation of inactive and active α-phenylethylamine for use in (2).

(2). The preparation of δ-substituted semicarbazides, the most important of which was an active form of δ-α-phenylethylsemicarbazide (hydrochloride).

(3). Derivatives and decomposition products of δ-substituted semicarbazides.

(4). The action of δ-substituted semicarbazides on benzoin whereby a number of geometrical isomerides were obtained, and a resolution of benzoin was effected.

A number of problems closely related to the above have been investigated.

Halogenation in ultra-violet light, a subject accepted by the University of Glasgow as part-title of the author's intended work for the degree of Doctor of Philosophy, is described in the last chapter.

CHAPTER I

α-PHENYLETHYLAMINE:

Preparation, Resolution and Salts.

The synthesis and resolution of amines forms one of the most interesting fields of organic chemistry. Many examples of this work have been recorded, but in few, if any, is the result so easily attainable as in the case of α-phenylethylamine, the optical enantiomorphs of which have proved effective in the following resolutions :- Mandelic acid, atrolactinic acid and α-phenylethylglycollic acid (J.prakt.chem.1911,84.731); dichlorsuccinic acids (Svensk.Kem.Tidskrift.24.105); keto-lactone of benzophenone tetracarboxylic acid (J.C.S. 1920.117.1407). In the last resolution the commoner alkaloids had failed, and the author (William Hobson Mills) expresses the opinion that α-phenylethylamine might also prove useful for other compounds not resolvable by alkaloids.

The present investigation forms part of the work on the preparation of an optically active semicarbazide (δ-α- phenylethyl-semicarbazide) from d-α-phenylethylamine and acetone semicarbazone (J. C. S. 1922, 121, 866). See also p. 41.

$C_6H_5CH(CH_3)NH_2 + NH_2CONHN{:}C(CH_3)_2 = C_6H_5CH(CH_3)NHCONHN{:}C(CH_3)_2 + NH_3$

The above acetone derivative on hydrolysis with 5% hydrochloric acid yields d-δ-α-phenylethylsemicarbazide hydrochloride ($[\alpha]_D^{12} = +66{\cdot}0°$) which combines readily in the usual manner with aldehydes and ketones, and it is hoped to effect with its aid the resolution of some aldehydes or ketones containing an asymmetric carbon atom. For resolution of benzoin see p.185.

The methods of preparing and resolving α-phenylethylamine were investigated, and as the amine was prepared in large quantities the opportunity was taken to study in detail the methods already recommended in the literature, and in these considerable improvement has been effected.

α-phenylethylamine is usually prepared from acetophenone , the oxime of which yields the amine on reduction.

$C_6H_5{\cdot}C(;NOH)CH_3 + H_2 = C_6H_5CH(CH_3){\cdot}NH_2 + H_2O.$

The oxime was prepared by Janny's method (Ber. 1882. 15. 2781) which consists in heating for 8 hours in aqueous alcoholic solution, hydroxylamine hydrochloride (1 mol.) acetophenone (1 mol.) and rather less than 1 mol of potassium hydroxide. Owing to the union of hydroxylamine with the ketone, the acidity of the solution gradually increases. By neutralising (with alkali), at intervals, this acidity which would otherwise retard the completion of oxime formation, it was found that the duration of heating could be shortened, and a solid product invariably secured on pouring the reaction mixture into water. It was also found that acetophenone oxime ($B.P.^{760}$ 246° – with decomposition) distils unchanged at 156° under 20 mms. pressure. This is the best method of purifying samples which do not solidify, since owing to its low melting point (59°) the presence of foreign bodies (generally acetophenone) often makes crystallisation ineffective.

The reduction of the oxime by Goldschmidt's method, i.e. with sodium amalgam in alcoholic solution—acetic acid being added at intervals, has been described by Tafel (Ber. 1886. 19. 2929) and by Hunter and Kipping (J. C. S. 1903. 83. 1147). The method was found effective but requires very large quantities of amalgam. Kann and Tafel (Ber. 1884. 27. 2306) state that the amine is very easily obtained by reducing the oxime with sodium in absolute alcohol, but no details are given. This process was studied and a method and apparatus devised which gave excellent results and which seem adaptable to many 'sodium-alcohol' reductions.

α-phenylethylamine has a considerable vapour pressure in alcohol and in ether, and when the amine is recovered by distillation from these solvents much of it is carried over with their vapours. In the method worked out the amine carried over by ether in the final distillation was recovered from the ether distillate by passing in carbon dioxide, and the carbamate formed filtered off. The properties of the carbamate are described; it can be used directly for the resolution.

Loven (Ber. 1896. 29. 2313) effected a partial resolution of the amine by fractional crystallisation of the salts formed with d-tartaric acid. The d-amine hydrogen d-tartrate salt containing 1½ H_2O separated first and on decomposition with alkali gave amine of rotation + 0·75°. From the mother liquor the anhydrous salt of the l-amine separated and this gave base of rotation - 8·5°.

Pope and Harvey (J. C. S. 1899. 75. 1160) obtained partially racemic salts of the amine with d-camphor sulphonic acid. Hunter and Kipping (loc. cit.) state there is no doubt that fractional crystallisation of the salt formed with d-brom-camphor sulphonic acid affords a means of resolution, though partially racemic salts were obtained; they obtained l-base having $[\alpha]_D$ -25° and its hydrochloride having $[\alpha]_D$ -3·7°.

Marckwald and Meth. (Ber. 1905. 38. 801) obtained the d-amine ($[\alpha]_D$ + 39·66°) and l-amine ($[\alpha]_D$ -39·51°) by fractional crystallisation of the amide formed with active quinic acid.

Loven (J. prakt. Chem. 1905, ii, 72, 307) combined the inactive base with l-malic acid, and obtained the d-amine l-malate as large prisms soluble in 18·1 parts of water at 10°, which yielded the d-base having $[\alpha]^{15}_D$ 40·27°. l-α-phenylethylamine l-malate is highly soluble in water and crystallises only from a viscid syrup. The base, obtained from the mother-liquor of the d-amine salt, on combination with d-tartaric acid yielded l-base hydrogen d-tartrate. Loven's method was employed in the present investigation and details of the method of crystallisation for obtaining the best yield of d-amine, are given.

Pope and Read (J.C.S. 1909, 95, 172.) combined d-oxymethylene camphor with α-phenylethylamine, and obtained two isomeric condensation products melting at 145-148° and 112-114·5° respectively. These products (which strongly resisted hydrolysis) on decomposition by bromine yielded the hydrobromides of the active forms of the base (J.C.S.1913,105,444).

Tafel(Ber.1886,19,1929) prepared the hydrochloride (M.P.155°) of the racemic amine, by treating an ethereal solution of the base with an alcoholic solution of hydrochloric acid. Marckwald and Meth.(loc.cit.) for the hydrochloride of the l-base give M.P.171°, and specific rotation - 3·5°, while Hunter and Kipping give - 3·7° for the latter constant. It seemed of sufficient interest to examine the hydrochloride of the d-base since this salt has not been previously mentioned in the literature; it was prepared by mixing an ethereal solution of d-base with a like solution of hydrochloric acid. Its rotation was examined at different temperatures, and was found to increase with increase of concentration, and to decrease with rise of temperature.

Tafel (Ber. 1886. 19. 1929.) prepared the sulphate of the inactive base [$(C_8 H_{11} N)_2 . H_2SO_4$, M.P. 170°] by treating an alcoholic solution of the base with a like solution of sulphuric acid. A similar method was followed (p. 29) in preparing this salt of the d-base, which melted with decomposition at 262°. For the sulphate of the d-base, Marckwald and Meth. give M.P. 272°. The specific rotation of the salt was found to increase both with concentration and with temperature, the influence of the latter factor on the hydrochloride and sulphate being in marked contrast.

It was thought that the malic acid used in the resolution could be recovered similarly to the preparation of malic acid from mountain ash berries, by a process in which calcium malate is converted into the much-more soluble calcium acid malate, which on treatment with lead acetate gives lead malate, and this on decomposition with sulphuretted hydrogen yields malic acid. In this so much difficulty was encountered that it was decided to investigate the whole process for the preparation of malic acid (Hagen, Annalen 1841. 38. 257. and Lennsen, Ber. 1870. 3 966). (c.f. Thorpes Dictionary of Applied Chemistry, Vol. 3, p. 380.) Samples of pure calcium malate, calcium acid malate, and lead malate were prepared, and converted in the order given, into malic acid.

For the conversion of calcium malate into calcium acid malate, dilute nitric acid (1 : 10) as recommended by Hagen and Lennsen gave a syrupy solution from which the acid-salt did not crystallise readily; 1 part of 60% acid to 10 of water, however was satisfactory, a 92% yield being obtained.

The acid malate was recrystallised from water not heated above 60°; its solubility at 18° is 1·8 gms. per 100 gms. water.

To convert calcium acid malate into lead malate, aqueous solutions of lead acetate (2½ mols)[$Ca(C_4H_5O_5)_2\ 6H_2O + 2Pb(CH_3COO)_2\ 3H_2O \rightarrow 2\ C_4H_4O_5.Pb.3H_2O$] and calcium acid malate (1 mol.) saturated at room temperature were mixed at 50°. A higher temperature was avoided because calcium acid malate decomposes at 60° into malic acid and normal calcium malate, and the latter then appears in the precipitate along with the lead malate, unlike which it is not readily decomposed by hydrogen sulphide. Under these conditions the lead malate was obtained in a crystalline form readily decomposed by passing hydrogen sulphide through its aqueous suspension, and a 75% yield of malic acid was obtained.

All processes for the isolation of natural malic acid make use of calcium malate and calcium hydrogen malate, but for the remainder of the process there are alternative methods. Broeksmit (Pharm. Weeklad 42, 637) decomposes lead malate with the theoretical amount of sulphuric acid; Warren

(J. Amer. Chem. Soc. 1911, 33:1205) treats calcium hydrogen malate with the theoretical quantity of oxalic acid, while Hartzen (Arch. Pharm, [3], VI, 110) in order to separate lead malate from lead salts of other organic acids likely to be associated with it, found that dissolving it in dilute acetic acid at 50-70°, and cooling to 40-30°, gave pure crystals.

EXPERIMENTAL.

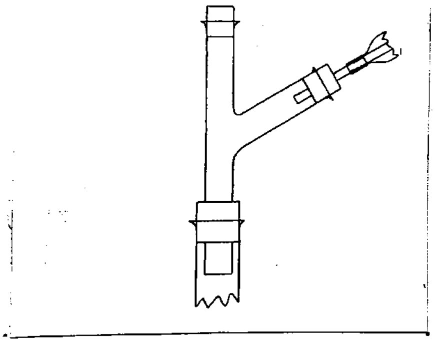
ACETOPHENONE OXIME.

To 50 gms. (1 mol.) of hydroxylamine hydrochloride dissolved in 100 ccs. of water and contained in a flask, 30 gms. (less than 1 mol) of potassium hydroxide dissolved in 50 ccs. of water, were added. 80 gms. (slightly less than 1 mol.) of acetophenone were then added, and the mixture heated in a reflux apparatus on a boiling water bath. Alcohol in small quantities at a time was run down the condenser until the boiling solution just became clear. After an hour, heating was stopped, the solution cooled, and a drop tested on litmus paper; it should be acid owing to the absorption of hydroxylamine by the ketone. Caustic potash solution was then carefully added until the solution was neutral. The condenser was again attached and boiling continued for about 30 minutes, at the end of which time the solution was tested, and if acid, was cooled and neutralised with caustic potash.

After about 10 minutes further heating, the solution was once more tested with litmus and a few drops of it mixed with ice water. If neutral, and if the test sample solidified quickly in water, the reaction was complete, and the contents of the flask were poured into 1000 ccs. of water containing lumps of ice. (If the test sample does not solidify, further heating and perhaps neutralisation are necessary). The water should be vigorously stirred during the addition to cause the separation of the oxime in small lumps and flakes. The product was filtered off, and washed with water, pressed on a porous plate to dry, and recrystallised from petroleum ether. Yield 89% theoretical (80 gms.). B.P.^{760} 246° (with decomposition); B.P.^{20} 156-157° (without decomposition). The best way to purify a sample which does not solidify on pouring into water, is to distil at 20 mms. pressure.

α- PHENYLETHYLAMINE.

50 gms. acetophenone oxime and 100 ccs. absolute alcohol were placed in a litre round bottomed flask having a long neck. The flask was fitted with a cork carrying an addition tube (see fig.), the sloping limb of which was attached to a long reflux condenser, while the vertical limb was closed with a cork. Pieces of bright sodium (about 50 gms.) of a size that easily slip down the addition tube, were placed in a bottle containing benzene. The flask was heated on a water bath until the alcohol boiled. pieces of sodium



(one at a time) were introduced through the vertical limb of the addition tube, the cork in which was momentarily withdrawn; a piece of drawn out glass rod served to transfer the sodium, from which adherent benzene need not be removed. The reaction was vigorous with the first pieces of sodium, but later became moderate, and the sodium melted to a ball which remained largely, and at times completely immersed in the liquid. When the reaction became sluggish or when a white coating appeared on the sodium, more alcohol (about 100 ccs. at a time) was added. The contents of the flask were kept actively boiling throughout the operation. Altogether about 500 ccs. absolute alcohol and 40 gms. sodium were required to effect complete reduction, which was proved when a sample (about 2 ccs.), mixed with water (2 vols.) and conc. hydrochloric acid (1 vol.), and boiled for a minute, did not reduce hot Fehling's solution. When reduction was complete and the sodium all dissolved, the flask was cooled, and 200 ccs. water added to decompose the ethoxide. A sloping condenser was then attached and heating continued on a water bath until distillation slackened. A further 200 ccs. water were then added, and heating continued on a sand bath, until all the alcohol had passed over, and a thermometer inserted in the neck of the flask registered 96°. The contents of the flask, consisting of a layer of amine and a layer of caustic soda, were cooled and poured into a separating funnel. A little ether was used to complete the transference of the amine. The total distillate, containing alcohol, water and α-phenylethylamine, was made strongly acid with hydrochloric acid and evaporated to small bulk, after which the residual aqueous solution of amine hydrochloride was added to the contents of the separating funnel where the excess of caustic soda liberated the base. After some time the lower layer of caustic soda was run off; the upper layer of amine was agitated with 20 ccs. ·720 ether, and the final traces of caustic soda separated. The ethereal solution along with ethereal washings were dried over anhydrous sodium sulphate and distilled. At first ether containing some amine passed over - this portion of distillate, which was alkaline to litmus, was kept separate for recovery as carbamate. The temperature then rose rapidly to 186-187°, at which the amine distilled; the condenser which should be long, was only half-filled with water at this stage. Owing to the avidity of the amine for carbon dioxide it should be collected in a flask having a soda-lime side tube. Yield 90% theoretical; dry carbon dioxide passed into the dry ethereal distillate, caused precipitation of a quantity of carbamate which increased the yield to 95%.

For the recovery of the amine from the reduction liquor, a different method, involving neutralisation of the alkali with hydrochloric acid, and subsequent decomposition of the α-phenylethylamine hydrochloride with caustic soda, is given by Cumming, Hopper and Wheeler: 'Systemmatic Organic Chemistry' p. 361.

Mr. A.B. Crawford, of this College, has found the method and apparatus described above, excellent for the reduction of menthone oxime (private communication).

α-PHENYLETHYLAMINE CARBAMATE.

$C_6H_5 \cdot CH(CH_3) \cdot NHCOONH_3 \cdot CH(CH_3) \cdot C_6H_5$.

The carbamate is precipitated in theoretical yield when dry carbon dioxide is passed into an absolute ethereal solution of the amine. Traces of alcohol or water inhibit precipitation. Found: N = 10·0%; theory = 9·8%. M.P. 101–102° (with dissociation). It is insoluble in ether or petroleum ether, and is decomposed with liberation of carbon dioxide when treated with alcohol or carbon disulphide. The only method by which it was obtained crystalline (needles) was when the amine absorbed carbon dioxide from air.

α- PHENYLETHYLAMINE CARBONATE.

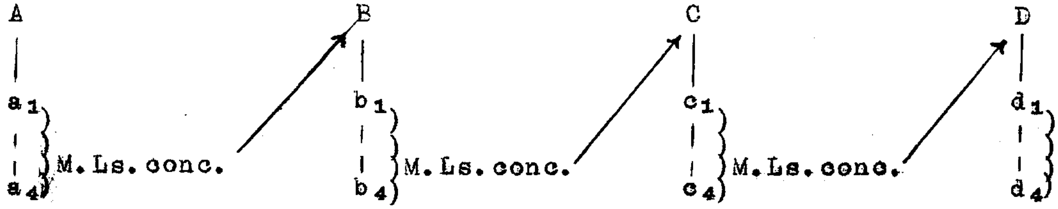
$[C_6H_5CH(CH_3)NH_3]_2\ CO_3$.

2 gms. of α-phenylethylamine carbamate were dissolved in 10 ccs. water on a steam bath. After slight cooling, the solution deposited a crop of long feathery needles, and further crops were obtained on standing. M.P. 94° (with decomposition). Found: N (by Kjeldahl method) =9·13 per cent; $C_{17}H_{24}O_3N_2$ requires N=9·21 per cent.

RESOLUTION OF α-PHENYLETHYLAMINE.

A mixture of 80 gms. of l-malic acid (commercial malic acid) and 320 gms. cold water, was placed in a bath of cold water, and without waiting for the acid to dissolve, 70 gms. (theory 72 gms.) of inactive α-phenylethylamine were added in a thin stream with constant stirring. The amine dissolves immediately and the acid disappears gradually, but before the latter has completely dissolved, the d-amine l-malate begins to separate and the mass becomes pasty. After stirring for a few minutes until the acid had all dissolved, a heavy crop separated, which was kept overnight, filtered off, and washed with 50 ccs. water. When dried in air the yield of the salt weighed 80 gms. (i.e.82% theory). The mother liquor (L) was kept apart for the recovery of the l-base.

The above operation was repeated in instalments; 537 gms. of the base gave 480 gms. of crude malate.



(M.Ls. = mother liquors).

The crude salt A(see diagram) was dissolved in rather more than twice its weight of water by heating not above 90°. The solution was filtered, cooled in ice water, and stirred in order to obtain small crystals which, after 30 minutes in the cooling medium, were filtered off, washed first with 100 ccs. water, and after draining well, with 50 ccs. alcohol. (The alcoholic washings contained a slight amount of colouring matter, and were kept apart.) Proceeding in this way, A was crystallised four times from water, and gave 160 gms. of pure d-amine l-malate. The aqueous mother liquors from the recrystallisation of A were concentrated (not above 90°) to one-half volume, and the crop B, which separated on cooling, was recrystallised 5 times from water, yielding 43 gms. of pure salt. Further procedure is indicated in diagram. C_5 and d_6 weighed 22 and 20 gms. Throughout the work, each crop was washed with water and with alcohol.

The mother liquors from D were considerably coloured, and on concentration did not give a sufficient amount of salt to justify further recovery; still since they contained a preponderance of d-amine [on decomposition they gave 80 gms.

amine having rotation + 1·7°] they were not mixed with the liquors L from which l-amine was recovered, because it is most important to have removed as much as possible of the dextro-isomer before proceeding to the isolation of the laevo-. The reason for this is obvious when it is recalled that Loven, on combining the inactive base with tartaric acid, found that the d-amine tartrate being the less soluble, separated first.

The pure malate dissolved in 8 times its weight of water was placed in a separating funnel and gradually treated with the theoretical amount + 10% excess of 50% caustic soda solution. On cooling, the mixture was shaken up with ether and allowed to stand overnight, when it was separated, and the ethereal layer dried over sodium sulphate. The ether was distilled off, and the residue distilled from a Claisen flask in a current of pure dry hydrogen whereby any carbamate present is dissociated at 101°, and the carbon dioxide swept away - also further absorption of CO_2 is prevented. A portion was collected directly in a polarimeter tube placed inside a Brühl's fractional distillation receiver. The amine distilled at 186°. Yield 131 gms. (50% theory, calculated on racemic amine). At 15°, $\alpha = +38{\cdot}78°$ and $[\alpha]^{15}_{D} = +40{\cdot}80°$.

As mentioned in theory (p.6.), the carbamate may be used for the above resolution, the theoretical quantity of the solid carbamate being gradually added to the aqueous solution of malic acid. Carbon dioxide is evolved and the crude d-amine l-malate separates quickly.

RESOLUTION - L-BASE.

The mother liquors L (p.21) were treated in a separating funnel with an excess of 50% sodium hydroxide solution. A coloured layer of amine separated on top; when mixed with ether and kept overnight the colour was largely discharged and evidently reabsorbed by the alkali. If, as recommended by Loven, the caustic soda had been run off first, and ether then added, a thick brown liquid would have separated, and this would have required to be run off from the colourless ethereal layer. [Attempts were made, without much success, to investigate this bye product formed during the recrystallisation of α-phenylethylamine malate; it is formed in moderate quantity when the mother liquors containing l-amine malate are concentrated to the syrupy stage; it is soluble in conc. alkali and less soluble in dilute alkali; when steam distilled in contact with alkali, α-phenylethylamine passes over.]

The ethereal layer of α-phenylethylamine was separated, dried over sodium sulphate and fractionated. The amine obtained gave a rotation of -27° in a 1 dem. tube. 250 gms. of d-tartaric acid were mixed with 1000 ccs. cold water and 200 gms. of this base added with cooling and stirring. The product attained the consistency of a stiff paste, and in 15 minutes crystals separated. After 12 hours these were filtered off and re-dissolved in water from which it was allowed to recrystallise until mixed crystals began to appear. The product was recrystallised 6 times from water, and a sample in the form of a 10% aqueous solution had then a rotation of + 1·10° at 15°. 223 gms. of crude tartrate gave 181 gms. of pure salt from which by decomposition with alkali in a manner similar to that for the d-amine malate, 50 gms. l-amine, having $\alpha = -38 \cdot 58°$ and $[\alpha]_D^{15°} = -40 \cdot 59°$, were obtained.

A comparison of the work of Kipping and Hunter (Chem. Soc. Trans. 1903, 1147), with the earlier work of Loven (Ber. 1896. 29. 2313) would indicate that d-bromcamphor sulphonic acid is a much better reagent than tartaric acid for isolating the l-base. The former workers, by combining the inactive amine with d-brom-camphor sulphonic acid, obtained from the more insoluble part of the salt, l-amine of rotation -25°. The latter worker, by combining the inactive amine with d-tartaric acid, found the salt of the d-amine to separate first, and from the mother liquors portion, he obtained l-amine of rotation - 8·5°. It appears to the author, therefore, that for the complete purification of samples of l-amine having already a high negative rotation, it would be better to combine them with d-brom-camphor sulphonic acid. The accessibility of tartaric acid however, favours Loven's method.

d-α- PHENYLETHYLAMINE HYDROCHLORIDE AND ITS ROTATION.

8 gms. of the d-amine were dissolved in 10 ccs. of absolute ether, and a solution of dry hydrochloric acid in 75 ccs. absolute ether gradually added, with cooling. The hydrochloride, precipitated in thick white curdy masses, was filtered off, dissolved in 10 ccs. absolute alcohol, and absolute ether (about 20 ccs.) added until tufts of needles began to separate. These were filtered, and washed with ether. M.P. 169°. (See also p. 8.)

A solution of 30% concentration in water was first prepared; parts of this were diluted to 20, 10, and 4% and polarimetric readings taken in a 1 dcm. tube.

C.	t°.	α	$[\alpha]^{t}_{D}$
30	11·7	2·5	8·33
	14·	2·45	8·166
	15·5	2·44	8·13
	18·	2·41	8·03
	20·	2·40	8·0
	25·	2·37	7·9
	30·	2·35	7·83
	42·	2·29	7·63
20	12·	1·25	6·25
	15·	1·20	6·00
	20·	1·19	5·95
	26·	1·16	5·80
	31·	1·14	3·70
	40·	1·01	5·05
10	20·	0·52	5·2
	26·	0·50	5·0
	31·5	0·47	4·7
	40·	0·42	4·2
4	15·	0·21	5·25
	18·	0·21	5·25
	21·	0·19	4·75
	26·	0·18	4·5
	31·	0·17	4·25
	40·	0·14	3·5

The table readings, compiled (Ber. 38. 806) by Marckwald and Meth, for the l-amine hydrochloride is given for comparison. They do not mention temperatures.

C	α	$[\alpha]_D^t$
31·45	−5·20	−8·27
25·18	−3·53	−7·01
18·87	−2·24	−5·93
10·00	−0·91	−4·57
4·00	−0·28	−3·50

d-α- PHENYLETHYLAMINE SULPHATE.

Separate solutions of 5 gms. d-amine and of 2·5 gms. conc. sulphuric acid - each in 10 ccs. of absolute alcohol, were ice-cooled and mixed. Small granular crystals separated which after being filtered off and washed, were dissolved in boiling 90% alcohol. On cooling and adding absolute alcohol in which they are almost insoluble, glistening plates, M.P. 262° (decomp.) were obtained. $(C_8H_{11}N)_2 H_2SO_4$ requires S=9·61%; found S=9·47%. Sulphuric acid in excess of the above quantity causes the salt first precipitated to redissolve. Concentrations of 12, 10 and 4% were examined polarimetrically :-

C.	t°.	α	$[\alpha]_D^t$
	13·	1·14	4·75
	16·	1·15	4·79
12	20·5	1·19	4·96
	25·5	1·19	4·96
	31·	1·2	4·99
	40·	1·24	5·16
	9·	0·91	4·55
	14·5	0·93	4·65
10	21·	0·97	4·85
	27·	0·97	4·85
	33·	0·97	4·85
	41·	0·98	4·90
	12·5	0·168	2·1
	17·25	0·207	2·6
4	22·	0·24	3·0
	27·	0·25	3·13
	32·	0·25	3·13
	43·	0·26	3·25

2 dcm. tube used.

RECOVERY OF MALIC ACID.

The alkaline liquor (p. 25) was diluted with one-half its volume of water and filtered through asbestos from solid impurities. The filtrate was kept cold and gradually neutralised with 15% hydrochloric acid of which an excess of 20 ccs. was also added. Sodium Chloride and gummy matter were filtered off and the hot filtrate treated with milk of lime until alkaline. On cooling, the whole solidified to a gelatinous mass which was filtered off and treated on a water bath with hot dilute nitric acid (1 part 60% acid to 10 parts water) until a clear solution was obtained. Calcium hydrogen malate separated on cooling, and a further crop was obtained by evaporating the mother liquor to a quarter of its volume. This salt was recrystallised from water heated to 58°. A solution in water of the concentration (1·8 gms. per 100 ccs.) of the salt (1 mol.) was prepared, heated to 50°, and at this temperature mixed with a 50% solution of lead acetate ($2\frac{1}{2}$ mols.) also at 50°. The mixture was allowed to cool, and when separation was complete, the lead malate was filtered off, transferred to a large flask, mixed with hot water, and hydrogen sulphide passed through the warm mixture for two hours as well as when cooling. The lead sulphide was filtered off and washed, and the filtrate concentrated on water bath till syrupy, after which it was left to stand in a large desiccator until crystals of malic acid separated.

SUMMARY.

1. A review of the literature on the preparation and resolution of α-phenylethylamine, and on the applications of the optically active forms of the base as resolving agents, is given, and further applications of the active base are indicated.

2. The reduction of acetophenone oxime to α-phenylethylamine is achieved by a 'sodium-alcohol' method which should find

extensive application for similar reductions.

3. Details are given for the isolation of the dexto- and laevo- forms of the base in good yield.

4. The rotatory powers of the hydrochloride and sulphate of the d-base have been examined.

5. Improvements in the preparation and purification of acetophenone oxime are recorded.

6. A method is given for the recovery of the malic acid used in the resolution.

7. The isolation of d-α-phenylethylamine by the processes given would be a most suitable laboratory exercise in optical resolution.

CHAPTER II

The ACTION of AMINES on SEMICARBAZONES

PART I

Borsche and his collaborators (Ber. 1901, 34, 4297; 1904, 37, 3177; 1905, 38, 831) found that semicarbazones react with aromatic amines on heating, according to the scheme :-

$C(RR):N \cdot NH \cdot CO \cdot NH_2 + R \cdot NH_2 \longrightarrow C(RR):N \cdot NH \cdot CO \cdot NHR + NH_3$

ammonia being evolved and δ-substituted semicarbazones formed.

The action of aniline, the toluidines, and the naphthylamines on such semicarbazones as those of acetone, acetophenone, benzophenone, β-methylhexanone, l-menthone, d-camphor, pulegone and d-carvone, was studied by Borsche, with the results indicated by the above equation.

In some instances Borsche obtained a number of bye products as well as the δ-substituted semicarbazone. The formation of these (sym-substituted ureas, azines and hydrazodicarbonamides) is explained by the following equations :-

$C(RR):N \cdot NH \cdot CO \cdot NHR + R \cdot NH_2 \longrightarrow C(RR):N \cdot NH_2 + CO(NHR)_2$

$$2C(RR):N\cdot NH_2 \longrightarrow C(RR):N\cdot N:\ C(RR) \quad + \quad NH_2\cdot NH_2$$

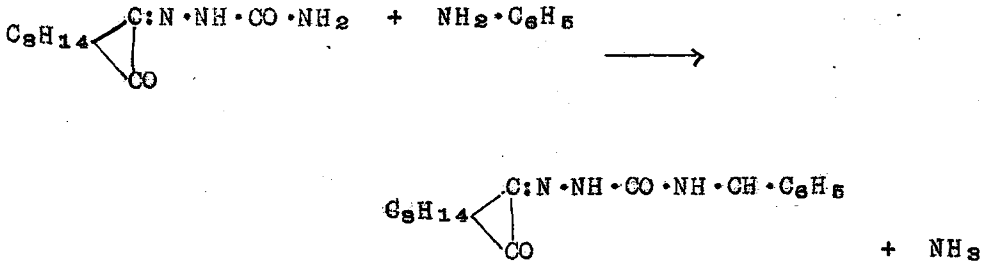
$$2C(RR):N\cdot NH\cdot CO\cdot NHR \longrightarrow C(RR):N\cdot N:C(RR) \quad + \quad RNH\cdot CO\cdot NH\cdot NH\cdot CO\cdot NHR$$

Work on this reaction has been continued by other investigators. Heilbron and Wilson (J. C. S. 1913, 103, 1504), by the action of boiling aniline on the α-and γ-forms of phenylstyryl ketone semicarbazone, prepared the α-and γ-stereoisomerides of phenylstyryl ketone δ-phenylsemicarbazone

$$C_6H_5\cdot CH:CH\cdot\ C(C_6H_5):N\cdot NH\cdot CO\cdot NH_2 \quad + \quad NH_2C_6H_5 \longrightarrow$$

$$C_6H_5\cdot CH:CH\cdot\ C(C_6H_5):N\cdot NH\cdot CO\cdot NH\cdot C_6H_5 \quad + \quad NH_3$$

When camphor quinone semicarbazone is heated with aniline it undergoes the change described by Borsche giving rise to camphorquinone phenylsemicarbazone, with liberation of ammonia (Forster and Zimmerli, J. C. S. 1910, 97, 2157).



$$C_8H_{14}\begin{cases} C:N\cdot NH\cdot CO\cdot NH_2 \\ CO \end{cases} + \quad NH_2\cdot C_6H_5 \longrightarrow$$

$$C_8H_{14}\begin{cases} C:N\cdot NH\cdot CO\cdot NH\cdot CH\cdot C_6H_5 \\ CO \end{cases} + \quad NH_3$$

Wilson and Hopper - working with α-phenylethylamine (p. 41), and Wilson and Crawford working with benzylamine, have found (J.C.S. 1922, 121, 866) that aromatic amines containing the amino group in a side chain react with acetone semicarbazone, after the fashion of simple aromatic amines, yielding acetone -δ-α-phenylethylsemicarbazone or acetone -δ- benzylsemicarbazone and ammonia :

$$C(CH_3)_2{:}\ N{\cdot}NH{\cdot}CO{\cdot}NH_2 + NH_2R \longrightarrow$$

$$C(CH_3)_2{:}\ N{\cdot}NH{\cdot}CO{\cdot}NH{\cdot}R + NH_3.$$

(where R= α-phenylethyl or benzyl).

The method adopted for α-phenylethylamine (for preparation see p. 1) consisted in mixing acetone semicarbazone (heated to 180°) with slightly more than one equimolecular proportion of the amine (also at 180°). Vigorous evolution of ammonia took place immediately and the acetone semicarbazone quickly dissolved. As soon as solution had been effected (requiring only a few minutes) the reaction mixture was cooled somewhat and diluted with an equal volume of alcohol. The product (acetone -δ-α-phenylethylsemicarbazone) was precipitated by the addition of ice and a few drops of dilute acetic acid (to neutralise residual amine), after which it was recrystallised from alcohol.

While Borsche used a large excess of amine, it was found here that the theoretical quantity (1 mol.per mol.of semicarbazone) of α-phenylethylamine gave the best results. This was a desirable economy.

A similar plan was adopted for the preparation of active -acetone-δ-α-phenylethylsemicarbazone fromd-α-phenylethylamine (for preparation see p. 43). It is noteworthy that the active compound melts at a lower temperature(84°) than the racemic form (M.P.114°).

Acetone -δ-α-phenylethylsemicarbazone is readily hydrolysed by heating on the water bath with 10 times its weight of N-hydrochloric acid, the products — acetone and

δ-α-phenylethylsemicarbazide hydrochloride - going into solution.

$$C(CH_3)_2:N\cdot NH\cdot CO\cdot NH\cdot CH(CH_3)\ C_6H_5 + H_2O + HCl =$$

$$HCl\cdot NH_2\cdot NH\cdot CO\cdot NH\cdot CH(CH_3)\ C_6H_5 + CO(CH_3)_2$$

Concentration of this solution yields the hydrochloride, which can be purified by recrystallisation from absolute alcohol.

The advantage of using acetone semicarbazone for these preparations is twofold; firstly, the acetone δ-substituted semicarbazone is so readily hydrolysed; and secondly, the removal of the ketone following hydrolysis is effected during the concentration of the solution. This removal is not necessary - as would have been the case had the semicarbazone of acetophenone or benzophenone been used.

The hydrochloride of the active semicarbazide, in melting at 189°, behaves like the majority of active compounds in having a higher melting point than the inactive form (M.P. 165°). The active hydrochloride is dextrorotatory in aqueous solution, while the acetone (p. 45), benzaldehyde (p. 99) and benzoin (p. 188) derivatives are laevorotatory.

It is intended to apply this optically active semicarbazide to the resolution of certain racemic aldehydes and ketones. A resolution of benzoin by this means is given on p. 185. The only optically active semicarbazide hitherto prepared appears to be the camphoryl ψ-semicarbazide of Forster and Fierz (J. C. S. 1905, 87, 722).

EXPERIMENTAL.

δ-α-PHENYLETHYLSEMICARBAZIDE.

Inactive and Active Forms of its Hydrochloride and Acetone Derivative.

Finely powdered acetone semicarbazone (1 mol.) and α- phenylethylamine (1·5 mols.) were heated separately in a bath to 180° and mixed, the mixture being maintained at this temperature. Vigorous evolution of ammonia took place and the acetone derivative quickly dissolved - solution being complete in a few minutes. Heating was continued for about 3 minutes longer, during which, evolution of ammonia continued. The product was then withdrawn from the bath, diluted with an equal volume of alcohol, and a few pieces of ice added. After acidification with dilute acetic acid to remove excess of α- phenylethylamine, and dilution with water, a white finely divided precipitate of acetone δ-α-phenylethylcarbazone was at once thrown down. This product was filtered, washed with water, and dissolved in the minimum quantity of hot alcohol, from which the semicarbazone separated in colourless prisms on cooling in ice. Acetone δ-α- phenylethylsemicarbazone is very soluble in alcohol or benzene, and almost insoluble in light petroleum or water ; it is best recrystallised from a mixture of benzene and light petroleum. It melts at 114° and is readily hydrolysed by heating with dilute hydrochloric acid. Found; N=19·04. $C_{12}H_{17}ON_3$ requires N=19·17 per cent.

r-δ-α- phenylethylsemicarbazide hydrochloride.

The above acetone semicarbazone was heated with ten times its weight of N-hydrochloric acid in a boiling water bath, and the solution, when cold, was extracted with ether to remove impurities, the aqueous portion being evaporated to dryness on a water bath. The residue was recrystallised from absolute alcohol, from which the hydrochloride separated in plates or prisms melting at 165° with decomposition. Found: Cl=16·47. $C_9H_{13}ON_3,HCl$ requires Cl=16·47 per cent.

These experiments were then repeated using d-α- phenylethylamine (p. 24). The base employed gave $[\alpha]^{15}_{D}$ + 40·8°.

Active - Acetone δ-α- phenylethylsemicarbazone.

The reaction was carried out in the same way as in the preparation of the recemic semicarbazone, and a similar plan was adopted in working up the product, which was finally recrystallised from light petroleum; a small insoluble residue remained. The petroleum solution deposited beautiful rhombic prisms of the semicarbazone which, after one further recrystallisation, melted at 84°.

The insoluble residue mentioned above, while insoluble in petroleum ether, was slightly soluble in a petroleum ether solution of the semicarbazone. During the primary crystallisation of the acetone δ-α- phenylethylsemicarbazone from petroleum, sometimes after a crop of prisms had continued to grow for a time, the supernatant liquid suddenly became cloudy and a white amorphous precipitate gradually separated. In such a case, as soon as cloudiness appeared, the supernatant solution was agitated and decanted, and the prisms washed with a few ccs. of cold N- hydrochloric acid which readily dissolved the amorphous precipitate. From the solution which had been decanted, the precipitate continued to separate for some time, but afterwards prisms again began to appear. At this stage gentle heat was applied, when the prisms redissolved much more readily than the precipitate, which was then filtered off. In this way a separation could be effected. The precipitate, after recrystallisation from benzene melted with decomposition at 185°. The quantity was too small for investigation.

The active - acetone δ-α- phenylethylsemicarbazone is extremely soluble in alcohol or benzene, and moderately soluble in petroleum. It is readily hydrolysed by warm dilute hydrochloric acid. Found: N=19·14 per cent.

$C_{12}H_{17}ON_3$ requures N=19·17 per cent. It is laevorotatory in alcoholic solution; 0·7820 gm. in 10 ccs. of alcohol gave $\alpha_D^{12^\circ}$ - 5·26° (l=1 dcm.) whence $[\alpha]_D^{12^\circ}$ - 67·3°. Both the racemic and the active semicarbazones become bright red on the addition of concentrated sulphuric acid, and ultimately give an orange coloured solution.

Active δ-α- Phenylethylsemicarbazide hydrochloride.

The active acetone derivative was heated on the water bath with ten times its weight of N- hydrochloric acid, and the solution concentrated until crystals appeared. After cooling, these were collected, washed with a very little water, dried on the pump, and thoroughly washed with benzene.

The hydrochloride forms beautiful pearly plates, soluble in water, soluble in hot alcohol, and insoluble in benzene. It melts at 189° (with decomposition). Found: Cl=16·40 per cent, $C_9H_{13}ON_3$,HCL requires Cl=16·47 per cent. It is dextrorotatory in aqueous solution.

0·9766 gm. in 10 c.c. of water in a 1 dcm. tube gave $\alpha_D^{12\cdot 2^\circ} = +\ 6\cdot 56^\circ$, whence $[\alpha]_D^{12\cdot 2^\circ} = +\ 66\cdot 0^\circ$. While the hydrochloride is dextrototatory, like the α- phenylethylamine from which it was prepared, it is noteworthy that the above acetone derivative, as well as the benzaldehyde (p. 99) and benzoin (p.188) derivatives, are laevorotatory.

CHAPTER III

The ACTION of AMINES on SEMICARBAZONES

PART II

While the author's work on this subject was mainly concerned with the action of racemic and optically active α-phenylethylamine, he has had occasion to repeat the work of Borsche (on aniline) and of Crawford (on benzylamine) for the purpose of preparing large quantities of δ- phenyl and δ- benzylsemicarbazides; and as he has made considerable improvements on the first published method (J. C. S. 1922, 121, 866) for making δ-α- phenylethylsemicarbazide hydrochloride, these improvements have been applied to the preparation of its phenyl and benzyl analogues, and are therefore given in detail in the following experimental part.

Borsche by heating aniline and acetone semicarbazone at 180°, obtained a considerable bye product of diphenylurea.

Wilson, Hopper and Crawford (loc. cit.) carried out the reactions with benzylamine and α- phenylethylamine at 180°, and obtained small quantities of urea derivatives.

It has now been found that aniline, benzylamine and α-phenylethylamine react with acetone semicarbazone at temperatures much below, 180°. When equimolecular parts of benzylamine or α-phenylethylamine and acetone semicarbazone are mixed and heated up to 129°, a moderate evolution of ammonia takes place - bubbling up through the mixture.

$$R\cdot NH_2+NH_2\cdot CO\cdot NH\cdot N:C(CH_3)_2\longrightarrow NH_3+R\cdot NH\cdot CO\cdot NH\cdot N:C(CH_3)_2$$

(Reaction I)

If heating be continued at this temperature the mixture becomes entirely fluid and, in about an hour, the end-point of Reaction I is clearly defined by the almost complete cessation of ammonia bubbles. At this stage, if the temperature be raised to about 150°, evolution of alkaline vapours begins again, and heating for any length of time at this temperature, causes an increased amount of urea derivatives amongst the products of the experiment.

$$R\cdot NH\cdot CO\cdot NH\cdot N:C(CH_3)_2+R\cdot NH_2\longrightarrow NH_3\cdot N:C(CH_3)_2+CO(NH\cdot R)_2$$

(Reaction II).

With aniline and acetone semicarbazone Reaction I begins at 125°, though here it is evident from the much slower evolution of ammonia that aniline has a less energetic action on the semicarbazone than have the more aliphatic amines — benzylamine and α-phenylethylamine.

Borsche (Ber.1905.88.832) heated acetone semicarbazone (1 mol.) with aniline (12·5 mols.) for 5 minutes at 130°. On repeating this experiment the author found that a considerable amount of sym-diphenyl urea was formed. If, however, a mixture of the semicarbazone (1 mol.) and aniline (1 mol.) is heated (see p. 56) for about an hour at 140°, practically no urea body is formed, and a better yield of acetone δ-phenylsemicarbazone is obtained.

In the following experiments, the acetone (-δ-phenyl, -δ-benzyl, or-δ-α- phenylethyl-) semicarbazones, obtained by pouring the reaction mixture (mixed with alcohol) into water, were not purified. The product was hydrolysed with the theoretical quantity (1 mol - calculated on amine used in the reaction) of 5 per cent. hydrochloric acid, by heating on the water bath for 30 minutes,

$R{\cdot}NH{\cdot}CO{\cdot}NH{\cdot}N{:}C(CH_3)_2+H_2O+HCl \longrightarrow R{\cdot}NH{\cdot}CO{\cdot}NH{\cdot}NH_2{\cdot}HCL+CO(CH_3)_2$

the resulting solution of the hydrochloride being approximately saturated at laboratory temperature.

[In one experiment, using 10 per cent. hydrochloric acid for hydrolysis, the expected hydrochloride was not obtained; instead, the evolution of carbon dioxide was detected, and the other products were very soluble. Here it would appear that a decomposition of the δ-substituted semicarbazide hydrochloride into carbon dioxide, amine hydrochloride, and hydrazine dihydrochloride was taking place :-

$R{\cdot}NH{\cdot}CO{\cdot}NH{\cdot}NH_2+H_2O+3HCL \longrightarrow R{\cdot}NH_2{\cdot}HCL+CO_2+NH_2{\cdot}NH_2{\cdot}2HCL$

Thiele and Stange (Ann. 1894, 283, 3) found that on heating semicarbazide hydrochloride with concentrated hydrochloric acid, the resulting products were ammonium chloride, carbon dioxide, and hydrazine dihydrochloride :-

$NH_2{\cdot}CO{\cdot}NH{\cdot}NH_2+3HCL+H_2O \longrightarrow NH_4CL+CO_2+CO_2+NH_2{\cdot}NH_2{\cdot}2HCL$

A method of estimating semicarbazide is based on this decomposition (brought about with dilute sulphuric acid), the hydrazine formed being estimated by oxidation with standard potassium iodate solution (Maselli. C.1905,i,267). Hydrochloric acid stronger than 5 per cent. must therefore not be used for hydrolysis of the semicarbazone.]

The reaction product, after hydrolysis, was filtered to remove a slight quantity of insoluble matter consisting of substituted urea body, and the filtrate concentrated until it deposited crystals on cooling. It is better to remove the crops of hydrochloride in instalments by cooling in a freezing mixture following slight concentration, since the heating of concentrated solutions of the hydrochloride (under the conditions of the experiment) gives to a moderate extent a decomposition into hydrazine dihydrochloride and a substituted hydrazodicarbonamide :-

$$2R\cdot NH\cdot CO\cdot NH\cdot NH_2\cdot HCl \rightarrow R\cdot NH\cdot CO\cdot NH\cdot NH\cdot CO\cdot NH\cdot R + NH_2\cdot NH_2\cdot 2HCl$$

Finally the hydrochloride was recrystallised from absolute alcohol in which it is moderately soluble in the hot, but only slightly in the cold. Addition of ether to the alcoholic mother liquor brings about complete separation of the hydrochloride, but leaves the above mentioned bye products in solution.

The hydrochlorides of these δ-substituted semicarbazides, when pure, are beautiful compounds of great crystallising power and are quite stable on keeping. On heating to melting they decompose with evolution of much gas due to the formation of substituted hydrazodicarbonamides and hydrazine dihydrochloride (see last equation) — the latter substance evolving nitrogen. They are precipitated from their aqueous solutions by hydrochloric acid, but no further recovery can be made from the resulting mother liquor by evaporation since the decomposition (previously mentioned) of the hot acid solution takes place. Recrystallisation from alcohol was preferred to this method of purification.

Aqueous solutions of the hydrochlorides when treated with the theoretical quantity of alkali yield the free δ-substituted semicarbazide, which being sparingly soluble in water separates out. In consequence of this property the isolation of the free bases is easy compared with the isolation of semicarbazide itself. Semicarbazide is not stable on keeping (Bouvealt, Locquin, Bl. (3), 33, 183), and hence it would be advantageous if it could be quickly prepared, when required, from its stable hydrochloride. To isolate semicarbazide (Bouvealt, Lócquin, loc. cit.) however, is a tedious operation. Its hydrochloride in aqueous solution, is neutralised with potassium carbonate

$$NH_2\cdot CO\cdot NH\cdot NH_2\cdot HCL + K_2CO_3 = NH_2\cdot CO\cdot NH\cdot NH_2 + KCL + CO_2$$

and alcohol added to precipitate most of the potassium chloride, after which the precipitate is filtered off, and the semicarbazide recovered from the filtrate by evaporation in vacuo; the yield is very poor.

For work on semicarbazone formation requiring the use of a free carbamylhydrazide — and not its hydrochloride—

the three δ-substituted semicarbazides now under discussion are eminently suitable. They condense readily with aldehydes and ketones.

EXPERIMENTAL.

δ- PHENYLSEMICARBAZIDE.

$C_6H_5 \cdot NH \cdot CO \cdot NH \cdot NH_2$.

(a) Acetone δ-phenylsemicarbazone.

25 gms. of acetone semicarbazone (recrystallised from water) were mixed with an equal molecular proportion of freshly distilled aniline in a flask which was placed in a glycerine bath and heated. At 135° (bath temperature) evolution of ammonia commenced, and the solid gradually dissolved. The temperature was taken up to 140°, and maintained there until (about 1 hour) the evolution of gas ceased.

The flask was then withdrawn from the bath, cooled to about 100°, the contents mixed with an equal volume of alcohol, and quickly poured into 600 ccs. of well stirred ice cold water. The flask was washed out with some hot alcohol to remove completely the acetone δ-phenylsemicarbazone, some of which crystallised out on the sides of the vessel during the transference. On mixing with water the acetone derivative was quickly precipitated; after breaking up with a glass rod and standing for a few hours it became completely granular. It was filtered off and well washed with water.

(b) δ-phenylsemicarbazide hydrochloride.

The above crude acetone derivative was not purified at this stage, but was hydrolysed by heating in an actively boiling water bath for 30 minutes with an equal molecular proportion of hydrochloric acid in the form of a 5% aqueous solution. Hydrolysis took place readily and the phenylsemicarbazide hydrochloride being soluble passed into solution. There remained insoluble however, a light bulky precipitate of diphenylurea which was filtered off. The filtrate containing the phenylsemicarbazide hydrochloride, when cooled in a freezing mixture of ice and hydrochloric acid, gave a large crop of beautiful plates, which were filtered off and washed with a little very dilute hydrochloric acid, the washings being added to the filtrate, A succession of similar crops was obtained from the filtrate by alternately concentrating on the water bath and cooling in a freezing mixture. The total yield of hydrochloride, after draining well at the pump, was washed with ether which removed any colouring matter. It was then recrystallised in two portions from absolute alcohol, the mother liquor from the first lot being used for the recrystallisation of the second. Finally the addition of ether to the last alcoholic mother liquor caused almost complete separation of the hydrochloride in a pure form, but at the same time kept in solution the impurities - diphenylurea and colouring matter. Yield was excellent. M.P. 218°.

(c) δ- phenylsemicarbazide.

About one quarter of the above phenylsemicarbazide hydrochloride was dissolved in water to give a saturated solution at ordinary temperature. This solution was immersed in ice water and treated with a concentrated solution of caustic potash until a faint alkaline reaction was shown to phenolphthalein used as on external indicator. The free phenylsemicarbazide was quickly precipitated on addition of the alkali; it was filtered off and washed with water.

The filtrate plus washings were used to dissolve another quarter of the phenylsemicarbazide hydrochloride, and the resulting solution treated with alkali, as above described, to give the free base. δ-phenylsemicarbazide is slightly soluble in water and hence the preparation was carried out in two instalments to avoid using a larger volume of the solvent. Similarly the recrystallisation of the product from water was done in two instalments, the impurities present being insoluble. M.P. 125°. Yield was very satisfactory.

The remaining one-half of the δ-phenylsemicarbazide hydrochloride was used for the preparation of benzoin derivatives (p.163).

δ-BENZYLSEMICARBAZIDE.

$C_6H_5 \cdot CH_2 \cdot NH \cdot CO \cdot NH \cdot NH_2$.

(a) Acetone-δ-benzylsemicarbazone.

A mixture of 20 gms. finely ground acetone semicarbazone and 20 gms. benzylamine (slightly more than 1 mol) in a flask having a short air condenser attached was heated in a glycerine bath. When the bath temperature reached 129° evolution of ammonia began and the mass swelled. At 138° ammonia was much more vigorously discharged than was the case in the aniline experiment (p. 56); after 10 minutes at this temperature the acetone semicarbazone had completely dissolved; after 30 minutes the evolution of ammonia slackened, and at the end of 50 minutes — when the flask was withdrawn from the bath – the bubbling of ammonia had ceased.

The contents of the flask were mixed while hot with an equal volume of alcohol, and this solution along with alcoholic washings of the vessel, poured in a thin stream into a moderately large volume of ice water, well stirred. The acetone δ-benzylsemicarbazone, which separated at once, was broken up with a rod and left to stand overnight, after which it was filtered off and washed with cold water.

(b) δ- Benzylsemicarbazide hydrochloride.

The above crude acetone derivative while still moist was treated with a solution of 22 ccs. concentrated hydrochloric acid in 120 ccs. of water, and heated in a boiling water bath for 30 minutes. After cooling with water to ordinary temperature, some insoluble dibenzylurea was filtered off and washed with a little water. The filtrate was cooled in a freezing mixture of ice and hydrochloric acid, and a few drops of ether added which assists the separation; flaky crystals of benzylsemicarbazide hydrochloride separated. These were filtered off, washed first with a little dilute hydrochloric acid and then with ether to remove colouring matter - the ether washings being discarded. Further crops were obtained from the filtrate by alternately concentrating and freezing (as described for phenylsemicarbazide hydrochloride on p. 58). The purification from alcoholic solution was effected similarly to that of the phenyl-analogue (p 58). In this case the impurities are dibenzyl urea, probably a little dibenzylcarbamylhydrazine (p. 88), and a slight quantity of colouring matter. The yield of hydrochloride was 87% theoretical. When heated in a melting point tube to 194° it swelled up considerably but still remained solid; on further heating it melted at 225° with vigorous decomposition. Yield: 80 per cent, calculated on benzylamine used.

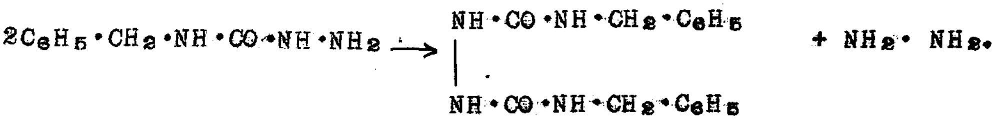
(c) δ-Benzylsemicarbazide.

Two portions of benzylsemicarbazide hydrochloride were taken, and one was dissolved in water so as to form an approximately saturated solution at ordinary temperature. This solution was then immersed in ice and carefully treated with a concentrated solution of sodium carbonate until effervescence ceased. Moderately pure Benzylsemicarbazide was precipitated at once, and was filtered off and washed with a little water. The second portion of the hydrochloride was dissolved in the filtrate and treated with sodium carbonate as before. After some time the second crop of the free base was filtered off and washed. The mother liquor on standing overnight yielded a little more in crystalline form.

The product was recrystallised in two portions from hot alcohol, the mother liquor from the first being used for dissolving the second. A little dibenzylcarbamylhydrazine

(p. 88) which is but slightly soluble, was eliminated. The base separated from concentrated alcoholic solution in beautiful large prisms, separating first on the surface and showing a fascinating movement during their growth. Melting Point 111°. Yield very good.

Later work (p. 68) which showed that δ-phenylethyl-semicarbazide when dissolved in alcohol gave diphenylethyl-carbamylhydrazine, suggested a similar experiment on δ-benzylsemicarbazide. Here it was found that formation of dibenzylcarbamylhydrazine took place, though very slowly.



$$2C_6H_5\cdot CH_2\cdot NH\cdot CO\cdot NH\cdot NH_2 \longrightarrow \begin{array}{l} NH\cdot CO\cdot NH\cdot CH_2\cdot C_6H_5 \\ | \\ NH\cdot CO\cdot NH\cdot CH_2\cdot C_6H_5 \end{array} + NH_2\cdot NH_2.$$

It is obvious therefore that it would have been a slight advantage to have recrystallised the yield of crude benzylsemicarbazide from water, as was done for its phenyl and phenylethyl analogues. From this medium it separates handsomely in large prisms.

δ-Benzylsemicarbazide and its hydrochloride thus prepared were identical with the compounds of these names prepared by Crawford (see Wilson, Hopper and Crawford J. C. S. 1922, 121, 866); the swelling up of the hydrochloride below its melting point has been noted (p. 62).

δ-α- PHENYLETHYLSEMICARBAZIDE.

$C_6H_5 \cdot CH(CH_3) \cdot NH \cdot CO \cdot NH \cdot NH_2$

Inactive acetone δ-α- phenylethylsemicarbazone

Finely powdered acetone semicarbazone (1 mol) and α-phenylethylamine (1 mol) were heated together at 188° for 80 minutes under a short reflux air condenser, and then for a further 80 minutes at 142° without the condenser. As with benzylamine a vigorous action took place. The reflux condenser prevents, during the first half of the experiment, loss of amine, which at the temperature, is very appreciably volatile in the current of ammonia. Later, the removal of the condenser permits the escape of a small quantity of oily product, which would otherwise appear as an emulsion during the recovery of the hydrochloride.

When the reaction mixture was cooled to about 100°, mixed with an equal volume of alcohol, and poured into a well stirred mass of crushed ice, a sticky solid separated, which on breaking up and standing overnight became quite solid. This crude acetone δ-α- phenylethylsemicarbazone could have been purified as described on p 42 , but was hydrolysed instead, the impurities being eliminated at the hydrochloride stage.

δ-α- phenylethylsemicarbazide hydrochloride.

The crude acetone derivative (1 mol) was heated in a boiling water bath with 5% hydrochloric acid (1 mol. - calculated on the α- phenylethylamine used) for 30 minutes. The insoluble matter which only amounted to a mere trace - showing that very little urea or hydrazodicarbonamide derivatives had been formed,—was filtered off, and on recrystallisation from alcohol and ether gave first amorphous matter M.P. 185° (probably diphenylethylcarbamylhydrazine - see p. 68) and later, long needles M.P. 135° (probably dl-α-phenylethylurea).

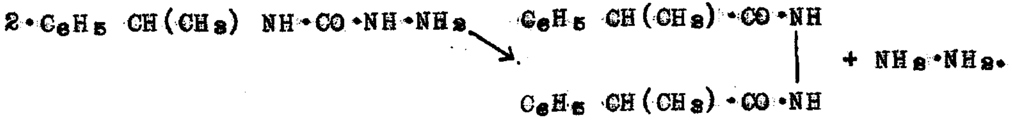
The filtrate from this insoluble matter, when extracted with ether to remove impurities, and cooled in a freezing mixture, gave crystals of the hydrochloride in the form of plates. Further crops were obtained from the mother liquor by concentrating and cooling alternately.

The product, recrystallised in instalments from alcohol, in the same manner as was described for δ-benzylsemicarbazide hydrochloride (p. 62), gave sometimes prisms, and sometimes plates - all melting at 165° with decomposition. Yield: about 75 per cent theoretical.

δ-α- Phenylethylsemicarbazide.

When a cold concentrated solution of sodium carbonate was added to a similar aqueous solution of δ-α- phenylethylsemicarbazide hydrochloride (cooled in ice) until effervescence ceased, a cloudiness first developed and later an oil separated, which, after scratching and cooling in a freezing mixture of ice and hydrochloric acid, solidified to a low melting point solid. This was filtered off, dissolved in the minimum quantity of hot water, and filtered from a little insoluble matter. From the filtrate, when cold, long white needles of the free base melting at 92° with decomposition, separated.

δ-α-phenylethylsemicarbazide is intensely soluble in alcohol or ether; it does not recrystallise from these solvents, but on long standing followed by spontaneous evaporation, diphenylethylcarbamylhydrazine (p. 90) separates, melting at 185°. This can only be explained by the loss of hydrazine from two molecules of the base .



$$2\cdot C_6H_5\,CH(CH_3)\,NH\cdot CO\cdot NH\cdot NH_2 \rightarrow \begin{array}{l} C_6H_5\,CH(CH_3)\cdot CO\cdot NH \\ \qquad\qquad\qquad\qquad\quad | \\ C_6H_5\,CH(CH_3)\cdot CO\cdot NH \end{array} + NH_2\cdot NH_2.$$

ACTIVE-ACETONE δ-α PHENYLETHYLSEMICARBAZONE.

This preparation was carried out exactly as described for the inactive product (p. 65), 43 gms. of acetone semicarbazone and 43·5 gms. of d-α-phenylethylamine being taken.

Active δ-α phenylethylsemicarbazide hydrochloride.

The crude acetone derivative was hydrolysed with 250 c.c. of 5 per cent hydrochloric acid as for the inactive product (p. 66), but as larger quantities of material were being worked with here, the bye products were obtained in greater bulk, and were more fully investigated.

The solution of hydrochloride, obtained after hydrolysis, contained about 8 gms. of insoluble amorphous matter, which was filtered off, washed with water, and recrystallised from alcohol in which it is sparingly soluble in the cold, thereby giving long thin needles, which melted at 208°, resolidified on cooling, and remelted at the same temperature. By analogy with all other work done on these lines, this product should be an optical form of sym-di -α- phenylethylurea. Found: N=10·85 and 10·39 per cent; di -α- phenylethylurea, $C_{17}H_{20}ON_2$ requires N=10·44 per cent. Further it was optically active; 0·2801 gms. dissolved in 50 ccs. alcohol gave a rotation of +0·95° in a 2 dcm. tube at 17°, and hence $[\alpha]^{17^\circ}_{D} = + 84{\cdot}8^\circ$.

When the aqueous solution of active-δ-α- phenylethylsemicarbazide hydrochloride was concentrated on the water bath during the recovery of the hydrochloride, an amorphous precipitate, as well as good crystals of the hydrochloride was obtained. It was established that this precipitate was due to a decomposition of the phenylethylsemicarbazide hydrochloride into diphenylethylcarbamylhydrazine and hydrazine hydrochloride.

$$2\cdot C_6H_5\cdot CH(CH_3)\ NH\cdot CO\cdot NH\cdot NH_2\cdot HCl \longrightarrow$$

$$N_2H_4\cdot 2HCl + C_6H_5\cdot CH(CH_3)\ NH\cdot CO\cdot NH\cdot NH\cdot CO\cdot NH\cdot CH\cdot(CH_3)\ C_6H_5$$

[Curtius (B. 27, 56; J. pr. chem. 11, 52, 465) has noted the decomposition of semicarbazide into hydrazodicarbonamide and hydrazine.]

The precipitate recrystallised from hot alcohol in well defined needles, insoluble in water, benzene, chloroform or petroleum ether, was optically inactive and melted at 220°. Found: N=17·19 per cent; diphenylethylcarbamylhydrazine, $C_{18}H_{22}O_2N_4$ requires N=17·18 per cent. The optical inactivity must be due to internal compensation similar to that existing in meso-tartaric acid — since inactive diphenylethylcarbamylhydrazine (p. 90) prepared from inactive δ-α phenylethylsemicarbazide melts at 185°. The latter body differs also in being much more soluble in alcohol.

The above argument is substantiated by the fact that there grew, in the last mother liquer from the recovery of δ-α phenylethylsemicarbazide hydrochloride, some very fine octahedral crystals of hydrazine dihydrochloride, which melted at 199° with vigorous decomposition.

Though so much prominence has been given <u>in</u> the above description to a consideration of the bye products formed, it must not be assumed that these dominated the other products of the experiment, which was carried out exactly as for the acetone derivative and the hydrochloride of inactive δ-α- phenylethylsemicarbazide (p p.65,66). The yield of active hydrochloride was 52 gms. (72 per cent.theoretical — calculated on α- phenylethylamine.) Its melting point and rotation were the same as given in Part 1 (p. 46). An exceptionally fine specimen of the active hydrochloride was obtained from an aqueous solution which had been left undisturbed for about a month in a desiccator over strong sulphuric acid. This consisted of large, almost rectangular plates.

CHAPTER IV

DERIVATIVES and Decomposition PRODUCTS of δ-substituted SEMICARBAZIDES

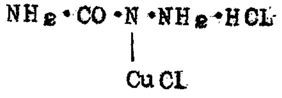
During investigation of the properties of the δ-substituted semicarbazides described in a previous section (p. 47) a number of their derivatives and decomposition products were prepared and examined. Thus δ- phenyl-, δ-benzyl- and δ-phenylethyl- semicarbazides or their hydrochlorides when dissolved in aqueous alcohol and treated with an alcoholic solution of oxalic acid, yield anhydrous oxalates. These salts consist of one molecule of the acid in union with one molecule of the base; they recrystallise rather slowly from aqueous alcohol, and are quite stable: their melting point varies somewhat according to the rate of heating; they are not hydrolysed by water, in which they are soluble.

Addition of sodium acetate to aqueous solutions of the hydrochlorides of these semicarbazides results in the immediate precipitation of the free bases. From this it would appear that these do not form acetates under the conditions; or that if acetates are capable of existence under any conditions, they are hydrolysed by water.

$$R\cdot NH\cdot CO\cdot NH\cdot NH_2\cdot HCl + NaOOC\cdot CH_3 \longrightarrow R\cdot NH\cdot CO\cdot NH\cdot NH_2 + NaCl + CH_3\cdot COOH.$$

In some papers dealing with semicarbazone preparation, authors have used the phrase 'by treatment with semicarbazide acetate', meaning 'by treatment with semicarbazide hydrochloride in presence of potassium acetate'. In view of the behaviour of these δ-substituted semicarbazides towards potassium acetate, the interaction of semicarbazide hydrochloride and potassium acetate was investigated. After removal of the potassium chloride (by precipitation with alcohol) and concentration of the mother liquor in vacuo, semicarbazide — and not its acetate — remained (p. 98).

An interesting series of compounds was obtained by the action of copper chloride on the hydrochlorides of the above semicarbazides in aqueous solution. These products are coloured and have similar properties to the double compound of semicarbazide hydrochloride and copper chloride, prepared by Thiele (Ann. 1905, 288, 1), and given by him the formula —



$$NH_2 \cdot CO \cdot \underset{\displaystyle CuCl}{\underset{|}{N}} \cdot NH_2 \cdot HCl$$

The double compounds (with copper chloride) about to be described are hydrated, and are given the general formula

$$RH_2 \cdot CO \cdot N(CuCl) \cdot NH_2 \cdot HCl,\ x \cdot H_2O.$$

With δ-benzylsemicarbazide two copper chloride compounds were isolated – an unstable royal blue product, and a comparatively stable olive green compound; these seem to differ only in the degree of hydration. All these copper chloride compounds are decomposed by water (or aqueous ammonia) giving a white precipitate the formation of which is not yet understood. They also decompose on heating alone ; water is first given off; then evolution of acid fumes sets in for a time; later the residue melts, and finally alkaline vapours are evolved. The stages of this decomposition should afford scope for further investigation.

The copper compound from phenylsemicarbazide is stable on keeping; the olive green compound from benzyl-semicarbazide is moderately stable; while the product from phenylethyl-semicarbazide is very unstable.

Like hydrazine and substituted hydrazines these δ-substituted semicarbazides react with nitrous acid to give azides.

$$R\cdot NH\cdot CO\cdot NH\cdot NH_2\cdot + HNO_2 \rightarrow R\cdot NH\cdot CO\cdot N_3 + 2H_2O$$

Phenylcarbamazide has been prepared and examined by Curtius (J.pr.Chem.1896,58,517;1898,88,205). For benzyl- and phenylethyl- semicarbazides the reaction was carried out by adding the theoretical quantity of sodium nitrite to cold concentrated solutions of their hydrochlorides. The azides formed, being insoluble in water, were precipitated at once. No odour of nitrous fumes was detected, and no indication of free nitrous acid was given on starch iodide paper. Treatment with standard sodium nitrite solution would probably serve for the estimation of these semicarbazides.

Curtius (loc.cit.) investigated the decomposition (by water) of phenylcarbamazide into diphenylurea -

$C_6H_5 \cdot NH \cdot CO \cdot N_3 \longrightarrow C_6H_5 \cdot NH \cdot \underline{COOH} \longrightarrow (C_6H_5 \cdot NH)_2CO + CO_2 + H_2O$

The small amounts of bye products (pp. 92, 95)encountered in the preparation of benzyl- and phenylethyl-carbamazides are therefore likely to be derivatives of urea.

Curtius (J.pr.Chem. 1898,88,205) has obtained hydrazodicarbonanilide (sym-diphenylcarbamylhydrazine) from δ-phenylsemicarbazide. Under the influence of heat or of iodine, or by long standing in alcoholic solution, δ-benzyl- and δ-α- phenylethyl- semicarbazides yield sym-dibenzyl - and diphenylethyl - carbamyl hydrazines.

$2R \cdot NH \cdot CO \cdot NH \cdot NH_2 \xrightarrow{r} R \cdot NH \cdot CO \cdot NH \cdot NH \cdot CO \cdot NHR + NH_2 \cdot NH_2$

With iodine the liberated hydrazine is at once decomposed.

δ-Benzylsemicarbazide when warmed with acetic anhydride readily gave an acetyl derivative, whereas δ-α- phenylethylsemicarbazide did not. This difference in behaviour may be due to decomposition (which takes place in alcoholic solution) into diphenylethylcarbamylhydrazine and hydrazine (see p. 91).

d-δ-α-phenylethylsemicarbazide hydrochloride combines readily (p. 99) with benzaldehyde, and the resulting semicarbazone has a high specific **rotation:** $[\alpha]_D^{18^\circ} = -296{\cdot}9^\circ$ for $c = 0{\cdot}8132$ in alcohol.

EXPERIMENTAL

δ-PHENYLSEMICARBAZIDE OXALATE.

$C_6H_5\cdot NH\cdot CO\cdot NH\cdot NH_2, (COOH)_2$.

0·4 gms. of δ-phenylsemicarbazide was dissolved in 4 ccs. cold alcohol and added to a cold solution containing 0·3 gm. oxalic acid in 3 ccs. alcohol. Heat was developed, and a white precipitate thrown down almost immediately. After a few hours the product was filtered, washed with 5 ccs. alcohol, and recrystallised from a hot solution of water and alcohol (1:2). Small well defined needle shaped crystals separated slowly. These decomposed slightly on slow heating at 165–166°, but did not actually melt until 220°. Found : N=17·34 per cent; $C_9H_{11}O_5N_3$ requires N=17·43 per cent.

δ-BENZYLSEMICARBAZIDE OXALATE.

$C_6H_5\cdot CH_2\cdot NH\cdot CO\cdot NH\cdot NH_2, (COOH)_2$.

0·4 gm. δ-benzylsemicarbazide hydrochloride, as a cold solution in 4 ccs. alcohol, was added to a cold solution of 0·3 gm. oxalic acid in 8 ccs. alcohol. A thick gelatinous precipitate was thrown down immediately which did not become granular on standing. It was filtered with difficulty owing to its consistency, then redissolved in aqueous alcohol (1:2) when it gave needles melting on slow heating at 185° with evolution of much gas.

Alternative method.

0·4 gm. δ-benzylsemicarbazide hydrochloride was dissolved in 2 ccs. water and added to 0·25 gm. oxalic acid dissolved in 8 ccs. alcohol. On scratching, or on seeding with a crystal from the first preparation, needles (M.P. 185°) slowly separated. Found N=16·36 per cent; $C_{10}H_{13}O_5N_3$ requires N=16·47 per cent.

δ-α- PHENYLETHYLSEMICARBAZIDE OXALATE.

$C_6H_5\cdot CH(CH_3)\cdot NH\cdot CO\cdot NH\cdot NH_2, (COOH)_2$.

0·45 gm. δ-α- phenylethylsemicarbazide hydrochloride was dissolved in 2 ccs. of water, and 0·25 gm. oxalic acid dissolved in 4 ccs. alcohol, added. After 8 hours, long prismatic needles separated which on recrystallisation from aqueous alcohol gave similar crystals melting with decomposition at 160°. Found N=15·67 per cent; $C_{11}H_{15}O_5N_3$ requires N=15·61 per cent.

δ-PHENYLSEMICARBAZIDE HYDROCHLORIDE COPPER CHLORIDE.

$C_6H_5\cdot NH\cdot CO\cdot N(CuCl)\cdot NH_2\cdot HCl, 10H_2O$.

2·5 gms. of δ-phenylsemicarbazide hydrochloride were dissolved in about 5 ccs. water, cooled and added to a cold solution of 1·8 gms. cupric chloride in 10 ccs. water. The mixture turned blue in colour, and almost immediately a light green precipitate was thrown down, which was filtered off and washed with a little water. From the mother liquor a little more separated on standing. The product when dried over concentrated sulphuric acid retained its bright green colour.

In contrast to the experiment (p. 84) with

δ-benzylsemicarbazide, only one product was obtained, and it differed from the benzyl-analogue in that it was quite stable on exposure to air, or when confined in a desiccator over concentrated sulphuric acid. On heating in an open tube, however, it did behave similarly to the above mentioned compound. At a gentle heat moisture was given off and the residue became white; then it melted, giving first acid vapours, and finally alkaline vapours.

Also, like the benzyl compound, it was unstable towards hot water, in which it decomposed with formation of a white product.

Three attempts to estimate the chlorine, by the Carius method, were unsuccessful; evidently great pressure was generated, as the tube burst each time.

To estimate the copper present, a portion was treated, until dissolved, with concentrated sulphuric acid, and taken carefully to dryness. The residue was moistened with nitric acid and taken to dryness, and this dual treatment repeated; and finally ignited to copper oxide. Found: Cu=13·7 per cent, $C_7H_9ON_3Cl_2Cu,10H_2O$ requires Cu=13·64 per cent.

δ-BENZYLSEMICARBAZIDE HYDROCHLORIDE COPPER CHLORIDE.

$$C_6H_5\cdot CH_2\cdot NH\cdot CO\cdot \underset{\substack{|\\ CuCl.}}{N}\cdot NH_2\cdot HCl,\ 4\tfrac{1}{2}H_2O.$$

2 gms. (1 mol.) δ-benzylsemicarbazide hydrochloride, dissolved in 20 ccs. cold water, were added to a filtered solution of 1·5 gms. (rather more than 1 mol.) cupric chloride in 15 ccs. cold water. The mixture assumed the colour of a dilute Fehling's solution and after a minute or so, suddenly deposited a crop of royal blue prismatic needles, which were quickly filtered off - but not washed. The filtrate continued to deposit crystals but these consisted of olive green plates, which were filtered off after standing overnight. A little more separated on longer standing.

Had the royal blue compound not been filtered off, but the reaction mixture left to stand about a week, the royal blue crystals would have slowly and completely changed to the olive green. The blue compound is moderately stable for a day or so in a cold atmosphere, but at a warm temperature (say near a steam bath) soon develops a greenish hue. Treatment with absolute alcohol converted it into the olive green compound, which is much more stable in air. Heating in a dry test tube gave results in very distinct stages; first, on very careful heating over a flame, moisture collected on the cooler parts of the tube and the mass turned green; then on raising the temperature, more moisture was evolved, and the residue became almost pure white; on further heating the mass melted giving off acid (i.e. to litmus) fumes which smelled distinctly of hydrochloric acid; and on still further heating alkaline (to litmus) fumes were given off. The olive green compound on heating behaved similarly i.e. as from the 'green' stage described above. The white product obtained during the heating turned green in contact with water.

Both compounds on treatment with concentrated ammonia solution were decomposed in the cold, giving rise to a small quantity of a white product, which in the crude state melted about 245°.

5 N. hydrochloric acid dissolved both compounds in the cold - the blue rather more readily, and the resulting solutions gave no precipitate on subsequent heating (compare action of ammonia), but were yellow when hot, turning to a blue green when cold.

Neither compound is for long stable in contact with cold water; the blue is the less resistant, changing first to a greenish colour; and both eventually change to a whitish product accompanied by a brownish, the latter being judged, from its solubility in acids and its stain on filter paper, to be cuprous oxide.

The above tests would indicate that the blue compound is a higher hydrate of the green, which also is a hydrate; and further that both are hydrates of the same product.

Estimation of the copper in the green substance was carried out by first treating with concentrated nitric acid, then concentrating very slowly in an air oven, and after a further treatment with nitric acid, finally igniting to cupric oxide. Found: Cu=16·5 per cent, $C_8H_{11}ON_3Cl_2Cu, 4\frac{1}{2}H_2O$ requires Cu=16·58 per cent. In the course of this estimation it was noticed that the melted compound, when treated with a few drops nitric acid in the cold, gave a bright red product.

δ-α- PHENYLETHYLSEMICARBAZIDE HYDROCHLORIDE COPPER CHLORIDE

$C_6H_5 \cdot CH(CH_3)NH \cdot CO \cdot N(CuCl) \cdot NH_2 \cdot HCl, x \cdot H_2O$.

When cold solutions of 1·5 gms. cupric chloride in 15 ccs. water and 2 gms. δ-α- phenylethylsemicarbazide hydrochloride in 20 ccs. water, were united, the mixture assumed a deep blue colour, and on standing overnight, a relatively small crop of olive green laminae separated, which were filtered, but not washed.

The product was very unstable, and when exposed to dry air on filter paper underneath a clock glass, it was noticed that the inner surface of the glass quickly became clouded with the moisture given off. Acid fumes, also, were evolved.

The substance was too unstable for examination. When heated quickly in a melting point tube, thus avoiding very much contact with air, it evolved gas at 135–142°; at 168° a white solid formed which melted about 190° with evolution of gas and charring. This behaviour is similar to what was noted for its phenyl, and benzyl analogues.

sym-DIBENZYL-CARBAMYL-HYDRAZINE.

$$\underline{C_6H_5\cdot CH_2\cdot NH\cdot CO\cdot NH\cdot NH\cdot CO\cdot NH\cdot CH_2\cdot C_6H_5.}$$

When 2 gms. δ-benzylsemicarbazide were heated in a owing to the presence of free iodine, was filtered off, washed with dilute sodium thiosulphate solution and with water, then dried, and recrystallised from a small quantity of glacial acetic acid. Glistening plates melting at 237°. These were insoluble in water, ether or benzene; very sparingly soluble in alcohol; insoluble in dilute hydrochloric acid or dilute caustic soda.

Found: $N=18 \cdot 69$ per cent; $C_{16}H_{18}O_2N_4$ requires $N=18 \cdot 79$. per cent.

sym-DIPHENYLETHYL-CARBAMYL-HYDRAZINE.

$C_6H_5 \cdot CH(CH_3) \cdot NH \cdot CO \cdot NH \cdot NH \cdot CO \cdot NH \cdot CH(CH_3) \cdot C_6H_5$.

Iodine Method.

When a solution of 2 gms. δ-α- phenylethylsemicarbazid in 30 ccs. of cold water was stirred and treated with the theoretical amount of iodine dissolved in aqueous potassium iodide, evolution of nitrogen and formation of a white precipitate quickly took place. After some time, the product which was slightly coloured owing to the absorption of unused iodine, was filtered off, washed with sodium thiosulphate solution and with water, and then recrystallised, by spontaneous evaporation of an alcoholic solution out of which it separated in long feathery needles of melting point 187°. The yield was very good. The compound, being easily soluble in alcohol, moderately soluble in ether and immensely soluble in glacial acetic acid, differs markedly from the corresponding phenyl(see Curtius. J. pr. Chem. 1898, 88, 205) and benzyl (p. 89) compounds, which are almost insoluble in alcohol and in ether, and which recrystallise readily from glacial acetic acid.

Found: N=17·22 per cent; $C_{18}H_{22}O_2N_4$ requires N=17·18 per cent.

Alcoholic Method.

When δ-α- phenylethylsemicarbazide was dissolved in alcohol with the intention of recrystallising it from this solvent, no product separated until, after several days, the solution had been reduced to small bulk through spontaneous evaporation, and then the separation of long feathery needles took place;these proved to be diphenylethyl-carbamyl-hydrazine.

BENZYLCARBAMAZIDE

$C_6H_5 \cdot CH_2 \cdot NH \cdot CO \cdot N_3$.

2 gms. of δ-benzylsemicarbazide hydrochloride was dissolved in 10 ccs. water; the solution was ice-cooled and treated with 1 gm. of sodium nitrite in the form of a 10 per cent. aqueous solution. There was neither evolution nor odour of nitrous fumes. The solution became quite thick with a white precipitate, which was filtered off, and washed with water. After drying in air, the product was treated with alcohol at about 50°. A small quantity remained undissolved and was filtered off; this was identical in appearance with dibenzyl urea (M.P.169°), it melted at 167° and when mixed with dibenzyl urea melted at 167°; probably it is dibenzyl urea (see p. 78).

The alcoholic filtrate from the 167° compound when cooled in ice, quickly gave a good crop of the pure azide (M.P.84°) in the form of beautiful six sided plates. These were filtered and washed with aqueous alcohol. The mother liquor was diluted with water to precipitate the product it contained. This fraction after drying in air was recrystallised from petroleum ether similarly to phenylethylcarbamazide (p. 95). It gave the pure azide and a meagre quantity of the compound M.P.167°. The yield was excellent.

Benzylcarbamazide melts at 84° without decomposition and the resulting liquid remains stable until 155° when it evolves gas and turns red. When heated in a dry tube it melts, and later a product distils, the vapours solidifying on the cooler parts of the tube to a white crystal mass. The azide is volatile in steam and these vapours produce a keen biting sensation in the nostrils. The grinding of the crystals induces intense sneezing. The compound which has great crystallising power appears to be insoluble in cold water ; soluble in hot petroleum ether, slightly soluble in the cold; very easily soluble in alcohol or benzene. No explosive properties were detected.

Found N=31·78 per cent; $C_8H_8ON_4$ requires N=31·8 per cent.

PHENYLETHYLCARBAMAZIDE.

$C_6H_5\cdot CH(CH_3)\cdot NH\cdot CO\cdot N_3$.

A solution of 2 gms. δ-α phenylethylsemicarbazide hydrochloride in 7 ccs. water was immersed in ice water for a short time so as to obtain a supersaturated solution, and to it while still in the cooling medium an ice cold solution of 1 gm. (excess) sodium nitrite in 4 ccs. water was gradually added, the mixture being agitated by swirling round, not by stirring which would cause crystallisation of the hydrochloride.

The first drops of nitrite caused the separation of an oily emulsion which required only a few seconds to solidify. Thereafter each drop of nitrite precipitated solid matter. At the end of the addition, a drop of the mixture on starch iodide paper showed no indication of free nitrous acid which is proof that the reaction between nitrous acid and the semicarbazide is very rapid.

Any lumps in the precipitated azide were broken up with a glass rod, after which it was filtered and washed with cold water. A drop or two of dilute hydrochloric acid added to the filtrate brought about a further slight precipitate; still more of the mineral acid caused evolution of nitrous fumes. Saturation of the filtrate with ammonium sulphate followed by extraction with ether recovered the last traces of azide.

The azide obtained by filtration, after drying in air on a porous plate, was added to the very small residue obtained from evaporation of the ethereal extract, and the whole boiled under reflux with 60-80° petroleum ether for a short time. A small quantity of substance, M.P. 157-165°, insoluble - or nearly insoluble in the solvent, was filtered off while hot. The mother liquor soon deposited a good crop of the azide in the form of coarse needles which adhered to the sides of the vessel. Later some flocculent amorphous matter (M.P. 150°) appeared, but as this remained suspended throughout the liquid, it was easily recovered by filtering the liquor decanted from the crystals. Concentration of this filtrate yielded beautiful well defined crystals of the pure azide. The first large crop was completely purified by one recrystallisation from petroleum ether. The yield was about 90 per cent. theoretical.

Phenylethylcarbamazide bears a close resemblance to benzylcarbamazide; when heated with water or alcohol the intense characteristic odour of hydrazoic acid is noted; when ground, the powder causes sneezing; it shows no explosive properties when rubbed, or when heated either alone or with copper oxide. It melts at 87°, resolidifies quickly on cooling and remelts at the same temperature; on heating to 148° it begins to evolve gas and gradually develops a brownish red colour – a behaviour which suggests that it loses nitrogen after the fashion,

$$' - CO \cdot N_3 + N_3 \cdot CO - \longrightarrow - CO \cdot N:N \cdot CO + 2N_2 \;'$$

yielding an azo body.

Found N=29·63 per cent; $C_9H_{10}N_4$ requires N=29·47 per cent.

ACETYL DERIVATIVE OF δ–BENZYLSEMICARBAZIDE.

$\underline{C_6H_5 \cdot CH_2 \cdot NH \cdot CO \cdot NH \cdot NH \cdot CO \cdot CH_3}$.

1 gm. of δ–benzylsemicarbazide and 4 ccs. of acetic anhydride were placed in a test tube provided with a calcium chloride tube and heated on a steam bath for 3 hours. The semicarbazide dissolved readily in the cold. The reaction product on standing at ordinary temperature for two days became a thick crystalline mass which was left for some time on a porous plate before being recrystallised from a mixture of alcohol and benzene. The product was obtained in glistening plates melting at 145°.

Found N=20·46 per cent; $C_{10}H_{13}O_2N_3$ requires N=20·3 per cent.

The Interaction of Semicarbazide Hydrochloride and Potassium Acetate.

Theoretical quantities of semicarbazide hydrochloride (in aqueous solution) and of potassium acetate (in alcoholic solution) were mixed, and the precipitate of potassium chloride filtered off. The filtrate was evaporated at 40–50° to dryness under greatly diminished pressure (less than 1 cm.). Acetic acid passed over in the distillate, and when the solid residue from the distilling flask was recrystallised from alcohol it proved to be free semicarbazide (M.P. 95°) mixed with potassium chloride.

ACTIVE BENZALDEHYDE-δ-α-PHENYLETHYLSEMICARBAZONE.

$C_6H_5 \cdot CH:N \cdot NH \cdot CO \cdot NH \cdot CH(CH_3) \cdot C_6H_5$.

1 gm. of benzaldehyde was shaken in a test tube with 3 gms. of d-δ-α-phenylethylsemicarbazide hydrochloride dissolved in 4 ccs. water. Reaction took place at once and the semi-solid product which formed was separated, washed with water, and when dry was recrystallised from petroleum ether. Long fine needles melting at 102-103° were obtained; these were very soluble in alcohol, chloroform, benzene or ethyl acetate, moderately soluble in petroleum ether, and insoluble in water. Found: N = 15·8 per cent; $C_{16}H_{17}ON_3$ requires N = 15·73 per cent. $[\alpha]_D^{18^\circ} = -296 \cdot 9^\circ$ for c = 0·8132 in alcohol.

CHAPTER V

BENZOIN SEMICARBAZONE

Biltz and his co-workers (Ann. 1905, 339, 243) have examined very fully the action of semicarbazide on benzoin and related products. The main features of their work which concern the present investigation are now discussed.

Biltz's recipe for benzoin semicarbazone is the following :-

'Benzoin semicarbazone is slowly formed when a solution of 8 gms. benzoin in 150 gms. alcohol is treated with a solution of 4 gms. semicarbazide hydrochloride in 10 gms. water and the mixture allowed to stand for 8 days. The reaction can be hastened when the solutions are warmed to about 60° and the mixture maintained at this temperature for some time.'

This recipe when taken in conjunction with the theoretical part preceding it, means that the reaction was carried out at room temperature. Since a solution of 8 gms. benzoin in 150 gms. alcohol begins to deposit crystals before room temperature is reached the instructions cannot be strictly followed. Wren (J.C.S. 1909, 95, 1591) interprets Biltz as having stated ' by the interaction of an alcoholic suspension of benzoin and an aqueous solution of semicarbazide hydrochloride', and in an attempt to prepare the semicarbazone of l-benzoin proceeded as follows :-

l-benzoin (2 gms.) was dissolved in boiling alcohol (47 ccs.) and quickly cooled to laboratory temperature whereupon a portion of the benzoin separated. After the addition of semicarbazide hydrochloride (1 gm.) dissolved in 3 ccs. water, the mixture was shaken in a thermostat at 25° for 5 days. The clear yellow solution so obtained was evaporated to dryness in vacuo. The residue when washed with water and recrystallised from alcohol proved to be slightly racemised benzoin. The failure of Wren's experiment to yield a semicarbazone is discussed later (p. 109).

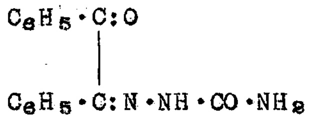
The author would amend Biltz's recipe for the preparation of benzoin semicarbazone to read as follows :-

----------when a solution of 8 gms. benzoin ___ dissolved in sufficient alcohol to maintain it in solution at room temperature is treated ----------- (see p. 101). The reasons for this modification being :-

(1) That 8 gms. benzoin is not soluble in 150 gms. alcohol at ordinary temperature.

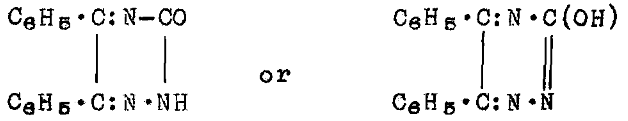
(2) That the larger volume of alcohol gives a better yield of benzoin semicarbazone, since the tendency to formation of diphenyloxytriazine is thereby reduced. This reason will be more easily understood after the preparation of benzoin benzylsemicarbazone has been discussed (pp. 132, 151).

Biltz has proved - as was also shown in this work - that when benzoin and semicarbazide hydrochloride interact, there are formed, considerable quantities of diphenyloxytriazine and diphenyliminazolone in addition to the semicarbazone. By means of some experiments with benzil he partly traced the formation of the first mentioned bye product. Thus benzil, when treated with semicarbazide hydrochloride and potassium acetate, gives the mono-semicarbazone ;



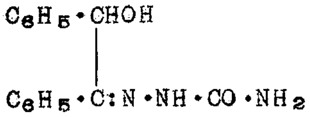
$$\begin{array}{l} C_6H_5\cdot C{:}O \\ \quad\;\; | \\ C_6H_5\cdot C{:}N\cdot NH\cdot CO\cdot NH_2 \end{array}$$

and this body when boiled in alcoholic solution for 6 hours undergoes intramolecular condensation with loss of water, yielding diphenyloxytriazine



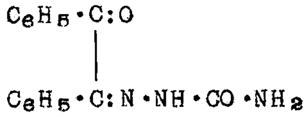
which had been previously described by Posner as a second form of benzil mono-semicarbazone. Diels (Ber. 1903, 36, 3190) has also effected the conversion of benzil semicarbazone into diphenyloxytriazine by treating with dilute caustic soda until dissolved, the sodium salt of the product being formed simultaneously. The author has conveniently effected the conversion by warming the semicarbazone in pyridine solution for a few minutes.

It is clear therefore, that the formation of diphenyloxytriazine from benzoin and semicarbazide, is due to the intermediate formation of benzil semicarbazone, or, to use Biltz's words ' the formation of diphenyloxytriazine (iii) along with benzoin semicarbazone is explained by the oxidation of a part of the benzoin or benzoin semicarbazone (i) to benzil or benzil semicarbazone (ii), and water splitting off from the latter yields the oxytriazine.'



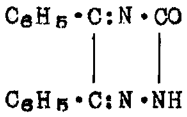
$$\begin{array}{l} C_6H_5\cdot CHOH \\ \quad | \\ C_6H_5\cdot C{:}N\cdot NH\cdot CO\cdot NH_2 \end{array}$$

(i)



$$\begin{array}{l} C_6H_5\cdot C{:}O \\ \quad | \\ C_6H_5\cdot C{:}N\cdot NH\cdot CO\cdot NH_2 \end{array}$$

(ii)



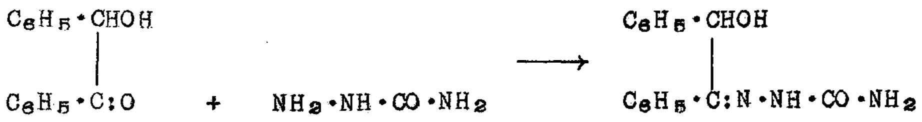
$$\begin{array}{l} C_6H_5\cdot C{:}N\cdot CO \\ \qquad |\quad\ \ | \\ C_6H_5\cdot C{:}N\cdot NH \end{array}$$

(iii)

Biltz made no reasonable attempt to explain the mechanism of this oxidation of benzoin or benzoin semicarbazone by means of semicarbazide which is a strong reducing agent. His detection of ammonia in the spent liquors from his experiments, and of diphenyliminazolone amongst the products of the reaction, is here made the basis of a theory (by the author) which suggests that benzoin, being an α-hydroxy ketone, reacts towards semicarbazide, after the fashion of α-hydroxy ketones and phenylhydrazine, yielding a semicarbazone of the corresponding α-β-diketone (e.g. benzil); the oxidation of the secondary alcoholic group being effected at the expense of the semicarbazide molecule, which is thereby split up into ammonia and urea. The urea then condenses with unchanged benzoin to form diphenyliminazolone.

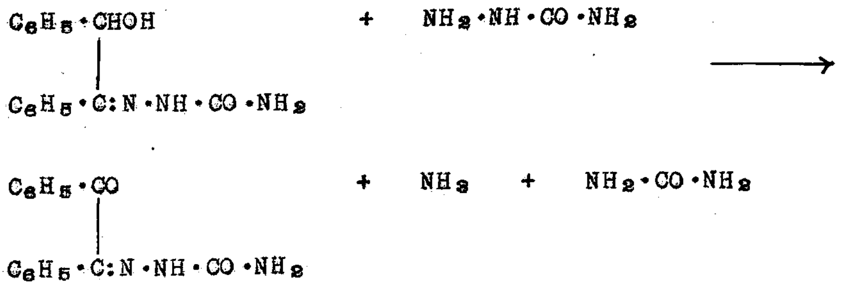
According to the foregoing theory the reaction between benzoin and semicarbazide would take place in the following stages:-

(1) Benzoin semicarbazone, being formed by the less energetic methods of procedure (e.g. at ordinary temperature and in dilute alcoholic solution), may be deemed the first product of the reaction.



$$\begin{array}{l} C_6H_5\cdot CHOH \\ \quad | \\ C_6H_5\cdot C{:}O \end{array} \quad + \quad NH_2\cdot NH\cdot CO\cdot NH_2 \quad \longrightarrow \quad \begin{array}{l} C_6H_5\cdot CHOH \\ \quad | \\ C_6H_5\cdot C{:}N\cdot NH\cdot CO\cdot NH_2 \end{array}$$

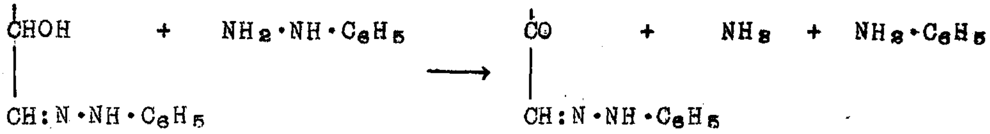
(2) Oxidation of benzoin semicarbazone to benzil monosemicarbazone.



$$\begin{array}{l} C_6H_5\cdot CHOH \\ \quad | \\ C_6H_5\cdot C{:}N\cdot NH\cdot CO\cdot NH_2 \end{array} \quad + \quad NH_2\cdot NH\cdot CO\cdot NH_2 \quad \longrightarrow$$

$$\begin{array}{l} C_6H_5\cdot CO \\ \quad | \\ C_6H_5\cdot C{:}N\cdot NH\cdot CO\cdot NH_2 \end{array} \quad + \quad NH_3 \quad + \quad NH_2\cdot CO\cdot NH_2$$

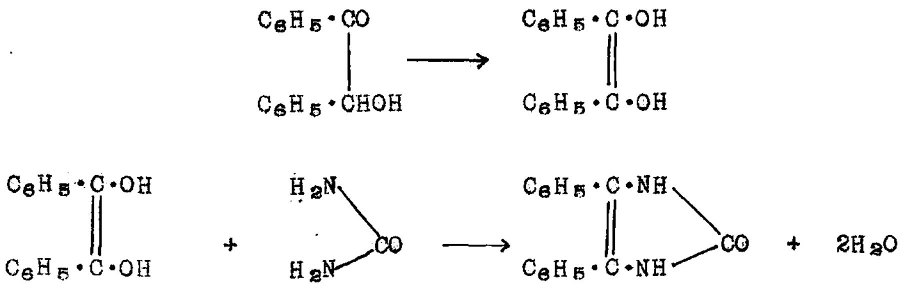
This is similar to the action of phenylhydrazine on glucose phenylhydrazone,



$$\begin{matrix}\mathrm{CHOH} \\ | \\ \mathrm{CH{:}N\cdot NH\cdot C_6H_5}\end{matrix} + \mathrm{NH_2\cdot NH\cdot C_6H_5} \longrightarrow \begin{matrix}\mathrm{CO} \\ | \\ \mathrm{CH{:}N\cdot NH\cdot C_6H_5}\end{matrix} + \mathrm{NH_3} + \mathrm{NH_2\cdot C_6H_5}$$

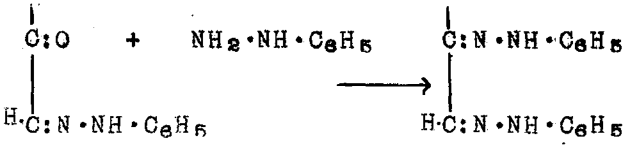
and explains the presence of ammonia in the spent liquors.

(3) Condensation of urea with benzoin to give diphenyliminazolone.



This stage of the theory is supported by the fact that urea has been condensed with benzoin in alcoholic (Anschutz, Ann, 1891, 261, 129; 1894, 284, 8) or in acetic acid solution (Biltz and Stellbaum, Ann. 1905, 339, 264) to give diphenyliminazolone in good yields. Incidentally there is here strong evidence that benzoin can behave in a dienolic form (see also p. 194).

(4) While glucosone phenylhydrazone reacts with a second molecule of phenylhydrazine to give an osazone,



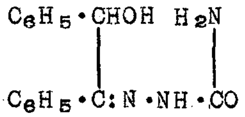
$$\begin{array}{l}\ |\\ C{:}O\\ |\\ H{\cdot}C{:}N{\cdot}NH{\cdot}C_6H_5\end{array} + NH_2{\cdot}NH{\cdot}C_6H_5 \longrightarrow \begin{array}{l}\ |\\ C{:}N{\cdot}NH{\cdot}C_6H_5\\ |\\ H{\cdot}C{:}N{\cdot}NH{\cdot}C_6H_5\end{array}$$

benzil mono-semicarbazone is more inclined (under the conditions of the experiment) to yield the internal condensation product (diphenyloxytriazine), than it is to react with a second molecule of semicarbazide; and hence the non-appearance of benzil mono-or di-semicarbazone amongst the products of the experiment.

Turning to Biltz's statement (Ann. 1905, 339, 246) 'that the formation of diphenyliminazolone is thought to be due to the emergence of the constituents of hydroxylamine from benzoin semicarbazone -

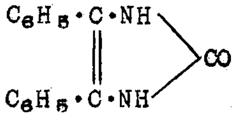
$$C_{15}H_{15}O_2N_3 = H_3NO + C_{15}H_{12}ON_2 \text{ ',}$$

there is no experimental foundation for the thought, which is evidently the outcome of an exercise in subtraction. His suggestion that hydroxylamine, (thought to be) formed during the change of benzoin semicarbazone into diphenyliminazolone, might serve for the oxidation of benzoin or benzoin semicarbazone to benzil or benzil semicarbazone, does not appear convincing. It would be difficult to depict, with structural formulae, the stages by which benzoin semicarbazone (I) could be converted into the iminazolone (II) and hydroxylamine.



$$\begin{array}{l} C_6H_5\cdot CHOH \quad H_2N \\ C_6H_5\cdot C{:}N\cdot NH\cdot CO \end{array}$$

(I)



(II)

[Note: The author draws attention to the fact that in Biltz's equation (Ann. 339, 246), diphenyloxytriazine should read benzoin semicarbazone].

Reverting to Wren's experiment (p. 102) it seems very probable to the author, that the clear yellow solution he obtained, contained diphenyloxytriazine, this colour being characteristic of its alcoholic solutions. If his reaction product had been poured into a large volume of water and allowed to stand for some time it is probable he would have obtained some of the bye products mentioned by Biltz (p. 103). Since Wren used equimolecular proportions of benzoin and semicarbazide hydrochloride, there was an excess of benzoin present (e.g. allowing for the semicarbazide used as oxidising agent) and this would account for the benzoin he recovered.

After benzoin δ-benzylsemicarbazone had been successfully prepared (p. 145) in pyridine solution it was thought that the interaction of benzoin and semicarbazide in this solvent might prove of interest. The results were very gratifying. Two isomerides (hereafter prefixed α- and β-) of benzoin semicarbazone were obtained. The combined yield of these was almost theoretical. No bye products other than slight colouring matter were obtained, even when the reaction mixture was heated on a water bath for a considerable time. The α-isomer was obtained in preponderating quantity; it melts at 206° and is identical with the benzoin semicarbazone hitherto described in the literature. The β-form is much more soluble and melts at 187°; on hydrolysis it yields benzoin, and on this fact coupled with its analysis and molecular weight, its identification is based; it is not dimorphous with the α-form (M.P. 206°) since a mixture of the two melts at 179°-200°.

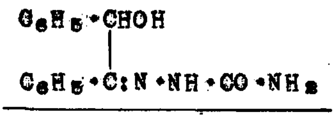
In this pyridine method, an aqueous solution of semicarbazide hydrochloride was added to a solution of benzoin in pyridine. After six days the product was precipitated in two instalments by addition of water, a large volume of which was required. The β-isomer was obtained from the second instalment and only in comparatively small proportion.

Biltz states that benzoin semicarbazone when heated with hydrochloric acid is at first split up into benzoin and semicarbazide, but that the benzoin is immediately reduced to hydrobenzoin by the semicarbazide. This statement probably means that he carried out the hydrolysis without the presence of a solvent.

The author has found however, that if the α-semicarbazone (that is the form used by Biltz) in alcoholic solution is heated for a short time with concentrated hydrochloric acid, hydrolysis takes places readily and benzoin separates out on cooling. The identity of this benzoin was confirmed by melting point, mixed melting point , crystalline form and solubility, and finally by its conversion into benzoin benzoate. Hydrolysis of the β-isomeride also gives benzoin.

EXPERIMENTAL

BENZOIN SEMICARBAZONE



$$\begin{array}{l} C_6H_5\cdot CHOH \\ \quad\quad\ \ | \\ C_6H_5\cdot C{:}N\cdot NH\cdot CO\cdot NH_2 \end{array}$$

8·5 gms. (1 mol.) of recrystallised semicarbazide hydrochloride dissolved in 20 ccs. of water were added to a solution of 16 gms. (1 mol.) benzoin in 160 gms. of pyridine. After six days at ordinary temperature, the solution, which had become somewhat coloured, was poured into 2400 ccs. of cold water vigorously agitated. The semicarbazone, which separated quickly as a white amorphous mass, was filtered off after an hour or so, and washed first with water, then with dilute hydrochloric acid (to remove traces of pyridine) and finally ~~in~~ with water. Crop 1 was thus obtained. When the filtrate diluted to about 8600 ccs. was allowed to stand overnight, a second crop (crop 2) separated which was collected and washed similarly to Crop 1. Further dilution of the liquor with water failed to produce a precipitate.

Crop 1 = 14 gms. approximately; M.P. 200-201°.
Crop 2 = 6 gms. approximately; M.P. 175-177°.

Crop 1 was dissolved in absolute alcohol by moderately long heating under reflux. The solution, after filtering and standing overnight, deposited large crystals which, after two further similar crystallisations from alcohol, melted at 206°, and proved to be that semicarbazone (α-form) of benzoin previously described by Biltz and Arnd (Ann. 1905, 339, 257).

The recrystallisation did not involve much loss since the isomer melting at 206° was very sparingly soluble in cold alcohol and there were no difficultly soluble products present, the impurities being a little of the more soluble isomer and colouring matter. The total mother liquors from the recrystallisation were united, concentrated at intervals and allowed to stand, so long as the melting point of the separating product was above 200°. After this, a little of the compound melting at 187° (see below) might be recovered.

Crop 2 was much more soluble than Crop 1 in refluxing alcohol, but from the solution so obtained there separated, after standing overnight, a moderate proportion of the higher melting isomer (206°) in a fairly pure form. This was filtered off and washed with alcohol, the washings being added to the filtrate. Concentration of the filtrate, followed by standing overnight, gave a product which did not completely redissolve on adding fresh alcohol and shaking. The residue consisting of the higher melting point isomer was filtered off and similar treatment of the filtrate repeated until there appeared tiny prism-shaped (almost cubical) crystals which separated at more or less regular intervals on the bottom of the flask, and which steadily grew for a few days as the solution evaporated spontaneously. The yield of these crystals was about one quarter of the original weight of Crop 2, and was purified by two or three recrystallisations from alcohol until the melting point remained constant at 186-187°. This product (β-form) crystallised slowly, and the best shaped crystals, almost cubical in form, were obtained by spontaneous evaporation. The mother liquors from this isomer, when diluted with water almost to incipient cloudiness, and then decolourised with animal charcoal of a neutral reaction (since acid would hydrolyse), yielded a little more of the compound. Owing to the slow recrystallisation of both forms of benzoin semicarbazone, the experiment was rather tedious and required at least two weeks for completion. Nothing in the way of bye-products was detected except the small quantity of colouring matter, which however has a marked influence, increasing the solubility of both forms of the semicarbazone, as well as retarding their separation.

Properties of Benzoin β-semicarbazone

Melting point 186-187° (with decomposition). In the absence of the colouring matter, it dissolves but slowlyin cold alcohol, and even in the hot it requires a considerable time, though it then gives a moderately concentrated solution. It is slightly soluble in boiling benzene or in boiling ether: insoluble in water.

Found N=15·78 per cent; $C_{15}H_{15}O_2N_3$ requires N=15·61 per cent.

Molecular Weight, by elevation of the boiling point of alcohol, gave 279; required 269.

When a portion (about 0·5 gm.), dissolved in aqueous alcohol, was treated with about 2 ccs. of concentrated hydrochloric acid, heated to active boiling for about a minute, then diluted with two volumes of water and left to cool, long needles separated which after recrystallisation from alcohol melted at 185°. The crystals so obtained had every appearance of benzoin (M.P. 185°), admixture with which did not alter the melting point. It was therefore concluded that the product had been hydrolysed into benzoin and semicarbazide hydrochloride.

When this β-semicarbazone (M.P. 187°) was mixed with the α-semicarbazone (M.P. 206°) in approximately equal proportions, the mixture melted with decomposition over a range of 179°-200°; thus proving that the two substances are not dimorphous.

Benzoin α-semicarbazone, the properties of which have been fully described by Biltz (loc. cit.) differs greatly from the β-semicarbazone in its solubility, its melting point and its crystalline form.

The following experiments were carried out in order to determine the effects of time and of temperature on the condensation of benzoin with semicarbazide in pyridine solution :-

Experiment I.

1 gm. of semicarbazide hydrochloride dissolved in 2 ccs. of water was added to a solution of 2 gms. benzoin in 20 ccs. pyridine, and the mixture allowed to stand for three hours at room temperature. Sufficient water to induce cloudiness was then added, and after standing overnight Crop 1 was filtered off. Crops 2, 3, and 4 were obtained in a similar manner.

Crop 1. M.P. 186°. Recrystallised from alcohol M.P. 206°.
2. 176°. " 206°.
3. 168°. " 170°.
4. 145°. " 148°.

When the third and fourth crops were fractionally crystallised from alcohol, the final products were the compound melting at 187°, together with unchanged benzoin, (M.P. 185°). As a fair quantity of benzoin was recovered it would seem that three hours was insufficient to bring about complete condensation.

A similar experiment when left for eighteen hours at room temperature before adding water, produced the products melting at 206° and 187°, as well as a small quantity of benzoin, and proved therefore, that eighteen hours is insufficient for complete condensation.

Experiment 2.

1 gm. of semicarbazide hydrochloride dissolved in 2 ccs. of water was added to a solution of 2 gms. of benzoin in 20 ccs. of pyridine. The mixture was heated to 100° and allowed to remain about that temperature for half an hour,

after which it was cooled, diluted with water in instalments, and the fractions crystallised from alcohol as before. The compounds melting at 205° and 187°, as well as a little benzoin were obtained; and hence the conditions were not sufficient to bring about complete condensation. More colouring matter was developed in this experiment.

During the time these small scale experiments were in progress, the larger experiment (p. 113) was carried to completion, and as it gave a satisfactory method of obtaining the two forms of benzoin semicarbazone without formation of bye products, the experiments on the effect of time and temperature were discontinued.

It was however established :-

1. That a period somewhere between 18 hours and 6 days was necessary to complete the condensation.

2. That both isomers were formed in the early stages of the reaction.

3. That the addition of a little water (i.e. short of enough to induce cloudiness) to the pyridine solution brought down the α-isomer in a practically pure form.

4. That under the conditions of the recrystallisation adopted, any benzoin present crystallised out intermediately between the separations of the α- and β-isomers, and hence its removal presented no difficulty.

Hydrolysis of Benzoin α-Semicarbazone.

4 gms. of finely ground benzoin α-semicarbazone (M.P. 205°) were heated under reflux with 30 ccs. alcohol and a few ccs. of concentrated hydrochloric acid for rather longer time than was necessary to effect complete solution. After cooling slightly the solution was filtered. In a short time needles separated, which after recrystallisation from

alcohol melted at 135°. A mixed melting point with benzoin (M.P. 135°) was 135°.

1 gm. of this hydrolysis product was treated with 4 gms. of benzoyl chloride in the manner described by Wren (J.C.S. 1909, 95, 1601.) for the preparation of benzoin benzoate (compare p. 147 for fuller details). Needles melting at 124° were obtained on recrystallisation of the benzoate formed. This confirms that under the conditions, benzoin - and not hydrobenzoin - is obtained by hydrolysis of benzoin semicarbazone. As mentioned in theoretical part (p. 111) Biltz stated that hydrobenzoin is obtained by the hydrolysis of the semicarbazone with hydrochloric acid. Hydrobenzoin <u>mono</u>- and di-benzoates melt at 160-161° and 247° respectively.

CHAPTER VI

BENZOIN δ-BENZYLSEMICARBAZONE

When optically active δ-α- phenylethylsemicarbazide hydrochloride had been prepared, it was decided to use it in an attempt to resolve some ketone or aldehyde containing an asymmetric carbon atom, and benzoin, being so readily accessible, naturally suggested itself. Before, however, proceeding to employ the δ-α- phenylethylsemicarbazide, it was deemed advisable to emperiment with the more accessible δ-benzylsemicarbazide, and to find out the best conditions for the preparation of benzoin δ-benzylsemicarbazone. It was thought that the conditions for the formation of benzoin δ-α- phenylethylsemicarbazone would be similar, and later this supposition was proved to be correct.

Taking as a guide, Biltz's instructions (Ann.1905,339,257) for the preparation of benzoin semicarbazone (see also p. 101) which seemed to be the only guidance obtainable from the literature, experiments were made on similar lines - using δ-benzylsemicarbazide hydrochloride.

Accordingly a solution of 4 gms. of benzoin in 75 ccs. of alcohol was mixed with a solution of 4 gms. of δ-benzylsemicarbazide hydrochloride in 8 ccs. of water, and the mixture kept about 60°. Another experiment using the same quantities of materials was carried out at ordinary temperature.

From both of these trials, (afterwards called preliminary experiments Numbers 1 and 2) a very good yield of a cream coloured product (melting at 222° when isolated, or at 239° when recrystallised) was obtained. The nitrogen content of this product being 16·4 per cent showed that it was not benzoin δ-benzylsemicarbazone which requires 11·6 per cent of nitrogen.

Further reference to Biltz's paper revealed the complicated courses which the interaction of semicarbazide and benzoin in alcoholic solution followed under slightly varying conditions, leading particularly to compounds of ring structure (see p. 103). At this stage it was decided to experiment on new lines and to use pyridine as solvent medium. This was a new departure so far as semicarbazone formation was concerned. Pyridine was chosen because it has proved so useful in altering or modifying a number of reactions (for example in the interconversion of isomeric aldoses by Fischer's method).

Accordingly an aqueous solution of δ-benzylsemicarbazide hydrochloride was mixed with a pyridine solution of benzoin; the results were wholly desirable, an excellent yield of benzoin δ-benzylsemicarbazone being obtained.

When this result had been achieved, the experiments using alcohol as solvent were not pursued further beyond preserving the products isolated from them, so that the fullest investigation was not given to them at the most suitable time. At a later period however, with the help of experience gained in working with the semicarbazones and δ-substituted semicarbazones of benzoin the products from these alcoholic preparations were investigated and an interpretation put upon the results.

Thus to review the facts briefly: when δ-benzylsemicarbazide hydrochloride (1 mol.) and benzoin (1 mol.) interacted in alcoholic solution, there were obtained three products :-

(1) A good yield of a cream coloured product melting at 239° (232° crude) which yielded benzil on hydrolysis and whose nitrogen content agreed with that of benzil dibenzylsemicazbazone. The identity of this product was confirmed by comparison with a sample of benzil dibenzylsemicarbazone prepared directly (p. 142) from benzil.

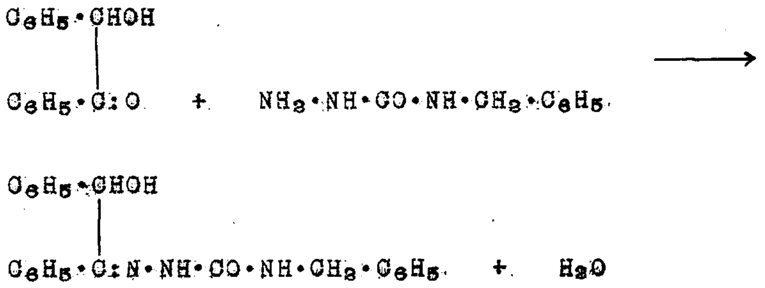
(2) A small proportion of a compound melting at 193° which yielded benzil on hydrolysis and whose nitrogen content agreed with that of benzil mono-

benzylsemicarbazone. Direct preparation of benzil mono-benzylsemicarbazone (p. 140) yielded a product which has not yet been fully examined; sometimes after recrystallisation it melted at 179°, sometimes about 208°, but more often over a range between these two temperatures. It might be a mixture of two dimorphous forms. Comparison with the compound melting at 198° was therefore, difficult and as this compound was only obtained in small quantity it might not be quite pure.

(3) A moderately large proportion of unchanged benzoin. This is in accordance with the succeeding theory.

The absence of derivatives of benzoin amongst the final products is not without a parallel in Biltz's work on benzoin semicarbazone which is reviewed on p. 108 . The work here described affords additional confirmation for the theory offered (p. 105) to explain the formation of bye products during the interaction of benzoin and semicarbazide hydrochloride in alcoholic solution.

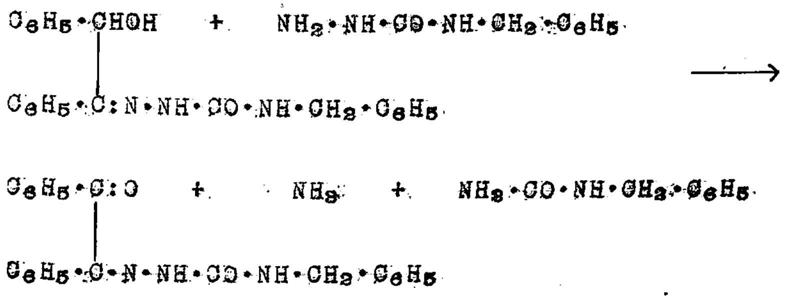
(1). Thus with benzylsemicarbazide, benzoin δ-benzylsemicarbazone is first formed :



$$\begin{array}{l} C_6H_5\cdot CHOH \\ \qquad | \\ C_6H_5\cdot C{:}O \quad + \quad NH_2\cdot NH\cdot CO\cdot NH\cdot CH_2\cdot C_6H_5 \end{array} \longrightarrow$$

$$\begin{array}{l} C_6H_5\cdot CHOH \\ \qquad | \\ C_6H_5\cdot C{:}N\cdot NH\cdot CO\cdot NH\cdot CH_2\cdot C_6H_5 \quad + \quad H_2O \end{array}$$

(2). Oxidation of the benzoin derivative to the corresponding derivative of benzil takes place at the expense of benzylsemicarbazide.

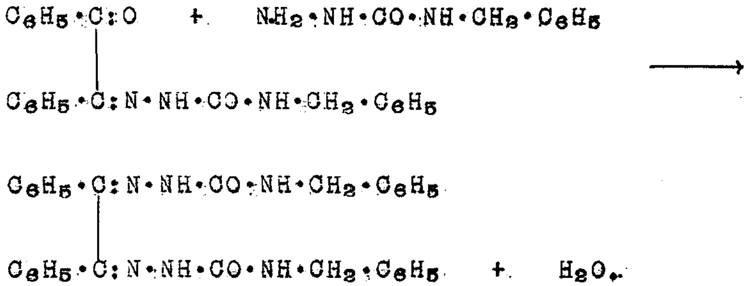


$$\begin{array}{l} C_6H_5\cdot CHOH \quad + \quad NH_2\cdot NH\cdot CO\cdot NH\cdot CH_2\cdot C_6H_5 \\ \qquad | \\ C_6H_5\cdot C{:}N\cdot NH\cdot CO\cdot NH\cdot CH_2\cdot C_6H_5 \end{array} \longrightarrow$$

$$\begin{array}{l} C_6H_5\cdot C{:}O \quad + \quad NH_3 \quad + \quad NH_2\cdot CO\cdot NH\cdot CH_2\cdot C_6H_5 \\ \qquad | \\ C_6H_5\cdot C\cdot N\cdot NH\cdot CO\cdot NH\cdot CH_2\cdot C_6H_5 \end{array}$$

(3). In benzil mono-benzylsemicarbazone the presence the benzyl radicle in the δ-position of the semicarbazone renders the formation of an oxtyriazine impossible (compare theory on benzil mono-semicarbazone p. 108).

The mono-derivative however reacts with a further molecule of δ-benzylsemicarbazide yielding the di-benzylsemicarbazone.



$$\begin{array}{l} C_6H_5\cdot C:O \\ \quad| \\ C_6H_5\cdot C:N\cdot NH\cdot CO\cdot NH\cdot CH_2\cdot C_6H_5 \end{array} + NH_2\cdot NH\cdot CO\cdot NH\cdot CH_2\cdot C_6H_5 \longrightarrow$$

$$\begin{array}{l} C_6H_5\cdot C:N\cdot NH\cdot CO\cdot NH\cdot CH_2\cdot C_6H_5 \\ \quad| \\ C_6H_5\cdot C:N\cdot NH\cdot CO\cdot NH\cdot CH_2\cdot C_6H_5 \end{array} + H_2O.$$

In the preliminary experiments described on pages 134 and 135, benzoin and δ-benzylsemicarbazide hydrochloride were taken in equimolecular proportions. Since benzil di-benzylsemicarbazone was formed in large quantity there must have been an excess of benzoin left over. This excess was actually recovered during the recrystallisation of the products.

According to the above theory, benzoin benzylsemicarbazone (1 mol.) and benzylsemicarbazide hydrochloride (2 mols.) should react in alcoholic solution to give benzil dibenzylsemicarbazone (1 mol.). Experiment (p. 144) using these proportions gave an almost theoretical yield, which is very considerable support for the theory.

While benzoin δ-benzylsemicarbazone is stable in alcohol, a cold concentrated alcoholic solution, to which a few drops of hydrochloric acid were added, was converted in the course of some days, into benzil dibenzylsemicarbazone. This conversion must be due in the first instance to the hydrolysis of a portion of the benzoin derivative into benzoin and benzylsemicarbazide, since otherwise there would be no free hydrazide to combine with the ketone group formed in the oxidation.

At a later period of the work, when geometric isomers were being looked for, the preparation (p. 148) of benzoin δ-benzylsemicarbazone was again attempted in alcoholic solution, but this time, in order to minimise the observed influence of hydrochloric acid (which in the preparation comes from the benzyl semicarbazide hydrochloride), almost twice the previous amount of alcohol was used as solvent. The more dilute solution gave rather different results, a moderate yield of benzoin benzylsemicarbazone being obtained, despite the formation of some benzil di-benzylsemicarbazone.

The preparation of benzil mono- and di-benzylsemicarbazone is given in the following experimental part since these compounds were required for comparison.

One characteristic of this pyridine method of semicarbazone preparation seems to have been established by the work on benzoin; namely that the oxidation of a :CHOH group in the α-position to a :CO group may not be effected by semicarbazides in pyridine solution. It is proposed to examine the interaction of other α-hydroxy ketones and aldehydes, in this solvent, with semicarbazides, hydrazine and phenylhydrazine.

EXPERIMENTAL

BENZOIN δ- BENZYLSEMICARBAZONE.

Preliminary Experiments.

Number 1.

A hot solution of 4 gms. benzoin in 75 ccs. alcohol was diluted with a solution of 4 gms. δ-benzylsemicarbazide hydrochloride in 8 ccs. water. The mixture was maintained at 60° (approximately) for 5 days, being cooled overnight. Each morning a crop of cream coloured product (M.P. 230-232°) was filtered off and washed with alcohol; the washings, being added to the filtrate, made good the loss of solvent due to evaporation.

After this time, nothing more separated on further heating, and the solution, being set aside, underwent spontaneous evaporation in the course of a fortnight, during which there separated a little more of the flocculent cream coloured product and long six sided plates. After swirling round, decanting, and washing with alcohol, the plates were separated. They melted at 198°, and remained unchanged on recrystallisation from boiling benzene. After the removal of the plates and flocculent matter, the reaction mother liquor gave, on further concentration, about 1 gm. of benzoin, and on still further concentration it gave a few drops of oil, but an insufficient quantity to purify.

Number 2.

4 gms. of δ-benzylsemicarbazide hydrochloride dissolved in 7·5 ccs. of water were added to a solution at 50° (to keep benzoin from separating out) of 4 gms. benzoin in 75 ccs. alcohol (i.e. one half of the alcohol subsequently used p. 148 ; compare theoretical discussion on pages 132 and 151). The mixture was immediately cooled to room temperature. No separation of benzoin took place at this stage.

After a day and continuing each day for 15 days, sufficient water to induce cloudiness was added. The separation took place of a moderately large quantity of a cream coloured powder, which during the period had been collected in 5 instalments. The first four crops melted between 200 and 232°. and when treated with boiling alcohol gave a compound M.P. 232° and a very little benzoin. The fifth crop, which required a larger volume of water for its precipitation, melted largely about 133° and completely about 190°; by recrystallisation from boiling alcohol in which it dissolved, it gave a small quantity of the product melting at 232°, and rather more than 1 gm. of benzoin.

After the removal of the fifth crop, the reaction liquor did not readily give a further precipitate on the addition of water, and was evaporated to dryness. The residue was heated with ether which removed a considerable amount of the colouring matter present, without dissolving much of the solid: this latter on recrystallisation from alcohol gave a little of the compound melting at 232°. and about 0·7 gm. of beautiful six sided plates melting at 198°.

Investigation of the Compounds melting at 232° and 198°.

Compound M.P. 232°.

When boiled under reflux with benzene, in which it did not seem to dissolve, then filtered, and washed with hot benzene, the residue melted at 239-240°, and was not changed by further treatment with benzene. This residue was recrystallised, by boiling under reflux, from a mixture of glacial acetic acid and alcohol (3:1); on cooling it separated out quickly in small uniform scales melting at 239-240°.

It is insoluble in water, ether or petroleum ether; almost insoluble in alcohol or benzene; soluble in glacial acetic acid. It does not seem to be effected by short boiling with dilute hydrochloric acid or caustic soda.

0·5 gm. was dissolved in glacial acetic acid, and a little water followed by 7 ccs. concentrated hydrochloric acid added to the hot solution which was then gently boiled for 40 minutes under reflux. After this time the solution was cooled slightly, diluted with water to induce faint cloudiness, filtered from a little amorphous matter (probably unhydrolysed product) while still warm, and set aside to cool. Long fine needles separated, melting at 94°, which, after recrystallisation by spontaneous evaporation from petroleum ether, gave well defined, stout, yellowish needles melting at 95°, and when mixed with benzil (M.P.95°) still melted at 95°. The form, colour and mixed melting point of this product, coupled with the analysis of the 239° compound, can scarcely leave any doubt that the latter was hydrolysed by the treatment outlined, into benzil and δ- benzylsemicarbazide, and hence was benzil dibenzylsemicarbazone. Its identity was confirmed by comparison with a sample of benzil dibenzylsemicarbazone prepared as described on p. 142

Found: N=16·55 per cent; $C_{30}H_{28}O_2N_6$ requires N=16·66.

Compound M.P.198°.

This dissolves by moderately long heating in alcohol and does not recrystallise out quickly. It is not affected by boiling with dilute hydrochloric acid, or with dilute caustic soda. Its alcoholic solution when boiled for a short time with hydrochloric acid, deposits, after cooling, the original compound; if however, boiling be continued under reflux for 2-3 hours, there separates out after cooling and standing, needles melting at 93°. This hydrolysis product was obtained in too small a quantity to purify thoroughly. After one recrystallisation from aqueous alcohol it still melted at 93°, and when mixed with benzil (M.P. 95°) the mixture melted at 93-95°; it is probable the compound is benzil. The nitrogen content of the original 198° compound is 11·5 per cent: benzil mono-benzylsemicarbazone $C_{22}H_{19}O_2N_3$ requires N=11·76 per cent.

BENZIL mono-δ-BENZYLSEMICARBAZONE.

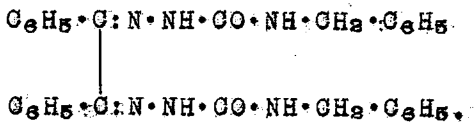
$$\begin{array}{l} C_6H_5\cdot C:O \\ \quad\quad | \\ C_6H_5\cdot C:N\cdot NH\cdot CO\cdot NH\cdot CH_2\cdot C_6H_5. \end{array}$$

0·5 gm. of potassium acetate was dissolved in 5 ccs. of alcohol, and 5 ccs. of water containing 1 gm. of δ-benzylsemicarbazide hydrochloride, added. The mixture was then poured into a solution of 1 gm. of benzil in 75 ccs. of alcohol, and after a few hours the precipitate of potassium chloride was filtered off. The filtrate was allowed to stand overnight and the benzylsemicarbazone which separated was filtered off and washed. On addition of water and again leaving overnight the remainder of the product was obtained.

The crude product melted at 176-178°; it was readily soluble in hot alcohol or hot benzene. Recrystallisation from alcohol or aqueous alcohol gave results which are not yet fully understood. In one case colourless needles melting at 179° were obtained; in another, a mixture of needles and plates, melting over a range from 180° to above 200°, was obtained; and in a third instance a product melting at 208° came down. Apart from dimorphic forms, there is here a possibility of the existence of two geometric isomers; fuller investigation will be given to these points at some future time. The experiment did not confirm or disprove the suggestion made on p. 128 that the compound melting at 198° is a form of benzil-mono-δ-benzylsemicarbazone.

The percentage of nitrogen in the crop of needles melting at 179° was 11·85; benzil mono-δ-benzylsemicarbazone, $C_{22}H_{19}O_2N_3$ requires N=11·76 per cent.

BENZIL Di-BENZYLSEMICARBAZONE.



$$\begin{array}{l} C_6H_5\cdot C:N\cdot NH\cdot CO\cdot NH\cdot CH_2\cdot C_6H_5 \\ \qquad | \\ C_6H_5\cdot C:N\cdot NH\cdot CO\cdot NH\cdot CH_2\cdot C_6H_5. \end{array}$$

1 gm. (1 mol.) of benzil dissolved in 10 ccs. hot alcohol was added to a warm solution of 5·8 gms. (3 mols.- e.g. 1 mol. excess) of δ-benzylsemicarbazide hydrochloride in 20 ccs. alcohol. The mixture was heated to gentle boiling under reflux for about 15 minutes and then left on the steam bath at about 60° for 2 hours. A product separated during the heating. After standing overnight Crop 1 was filtered off. The mother liquor on filtration deposited immediately a crop of δ-benzylsemicarbazide hydrochloride (about 1·5 gms.), excess of which was used in the preparation. The filtrate from the hydrochloride when treated with much water gave a precipitate (Crop 2).

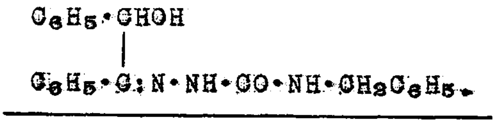
Crop 1 when washed with water (to remove hydrochloride) and with alcohol, and then recrystallised from a mixture of alcohol and glacial acetic acid, gave 1·4 gms. (83 per cent. theoretical) of benzil dibenzylsemicarbazone, melting at 239–240° with decomposition. Found : N = 16·5 per cent; $C_{30}H_{28}O_2N_6$ requires N=16·66 per cent. This product, which consisted of irregular plates was identical with the product (M.P. 239°) obtained from the interaction of benzoin and δ–benzylsemicarbazide hydrochloride (pp. 134, 135).

Crop 2 was too small for complete examination. In the crude state it melted at 178°. After recrystallisation from aqueous alcohol it was indistinguishable from benzil mono–δ–benzylsemicarbazone (p. 140) and melted about 208°.

Action of Benzylsemicarbazide Hydrochloride on Benzoin ______ δ-Benzylsemicarbazone.

1·1 gms. (2 mols.) of δ-benzylsemicarbazide hydrochloride dissolved in 2 ccs. of water was added to a solution of 1 gm. (1 mol.) of benzoin ____ -δ-benzylsemicarbazone dissolved in 10 ccs. of alcohol. The mixture was heated at about 60° for 18 hours. Early in the heating crystalline plates began to separate and the separation of these continued for a considerable time. After standing overnight in the cold the above product was filtered off, washed with alcohol, and recrystallised from a mixture of glacial acetic acid and alcohol. Irregular plates, melting at 239° were obtained; these were identical with the specimens of benzil dibenzylsemicarbazone described on pages 138 and 143. Found: N=11·5 per cent, $C_{30}H_{28}O_2N_6$ requires N=16·66 per cent. The yield of the compound was almost theoretical.

BENZOIN δ-BENZYLSEMICARBAZONE.



$$\begin{array}{l} C_6H_5\cdot CHOH \\ \quad\;\;| \\ C_6H_5\cdot C{:}N\cdot NH\cdot CO\cdot NH\cdot CH_2C_6H_5. \end{array}$$

Pyridine Method.

5 gms. (rather more than 1 mol,) of δ- benzylsemicarbazide hydrochloride dissolved in 5 ccs. of water were added to a solution of 5 gms. (1 mol,) of benzoin dissolved in 50 ccs. cold pyridine, and the mixed solution allowed to remain for 5 days at room temperature. After this time, 100 ccs. of water was added (just insufficient to induce cloudiness) and the solution poured into 2 litres of well stirred cold water, which caused the separation of the crude semicarbazone in a solid form.

The primary dilution of the pyridine solution with water rendered it less concentrated on coming in contact with the larger volume of water, and hence assisted in the precipitation of the product in a granular form. In a previous experiment it had been ascertained that either the dilution of the pyridine solution with a large volume of water, or the pouring of the pyridine solution into a moderate volume of water, gave a very sticky product, due to the influence of pyridine on the separating product. In order to obviate this influence as much as possible, the method of pouring a moderately diluted solution into a large volume of water was tried, and found successful.

The precipitate was collected, washed first with water, then with very dilute hydrochloric acid, and finally with water, and when well sucked at the pump was redissolved in the minimum of boiling alcohol. In comparison with the preparation of the semicarbazone by the alcoholic method (pp.134,148) there were no bye products to complicate the purification. The product, after two crystallisations from hot alcohol, out of which it separated quickly in long needles on cooling, was pure and melted at 115° (no decomposition even at 120°). The yield was about 90 per cent. theoretical.

Found: N=11·5 per cent; $C_{22}H_{21}O_2N_3$ requires N=11·6 per cent. It was readily soluble in alcohol, soluble in ether or benzene, very soluble in cold chloroform; insoluble in petroleum ether or water.

When an aqueous alcoholic solution was actively boiled for about a minute with concentrated hydrochloric acid, then diluted with water to incipient cloudiness, and left to cool, long needles of benzoin separated which after recrystallisation from alcohol were identified by melting point, and mixed melting point with benzoin. The identity of this hydrolysis product was confirmed by conversion into benzoin benzoate after the method of Wren (J.C.S. 1909,95,1601). 0·8 gms. of it along with 3·5 gms. benzoyl chloride were heated in a bath for 4 hrs. at 140° and finally raised to 180°, then cooled and diluted with aqueous alcohol. In a short time, short prisms separated, which were collected, washed with alcohol and with ether, and recrystallised from hot alcohol. Thin needles M.P.124° (Wren:124°-125°; Zinin.Ann.1857,104, 116, gives for benzoyl r-benzoin M.P.125°).

Alcoholic Method.

4 gms. (slight excess) δ-benzylsemicarbazide hydrochloride dissolved in 7·5 ccs. of water were added to a solution of 4 gms. (1 mol.) benzoin in 130 ccs. alcohol. The temperature on mixing was 33°, and though a few crystals of benzoin had separated just prior to mixing, it is noteworthy that the addition of the aqueous solution withheld further separation (compare p. 171). As nothing further separated within a few hours the crystals were filtered off and the solution left in the dark (in order to avoid the action of light on an alcoholic solution of benzoin) for nine days. A small quantity of benzil dibenzylsemicarbazone (pp. 142) had separated out; and the addition of 40 ccs. of water, followed by filtration, removed practically the whole of this compound. In an hour or so the filtrate

began to deposit crystals of benzoin δ-benzylsemicarbazone, the separation of which was rendered complete by the addition of water (about 30 ccs.). After filtering and washing with aqueous alcohol, this product was recrystallised from boiling 80 per cent. alcohol, in which benzil di-δ-benzylsemicarbazone is insoluble. Fine, long needles, M.P. 115° were obtained; these were identical with benzoin δ-benzylsemicarbazone prepared by the pyridine method (p.145). Yield 5 gms.

CHAPTER VII

BENZOIN δ-PHENYLSEMICARBAZONE

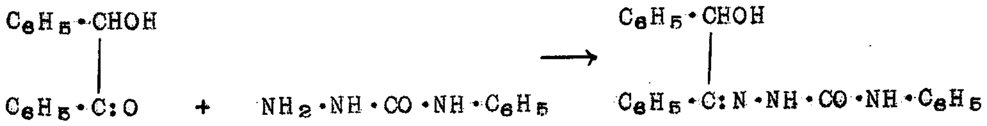
When it was found that :-

(1) A dilute aqueous alcoholic solution of benzoin and benzylsemicarbazide hydrochloride gave (p. 148) less bye products than did (p. 135) a more concentrated aqueous alcoholic solution of the same reagents;

(2) An alcoholic solution of benzoin benzylsemicarbazone to which a few drops of hydrochloric acid had been added, underwent change (p. 132) with formation of benzil dibenzylsemicarbazone;

it was concluded (a) that hydrochloric acid had a very pronounced influence on the interaction of benzoin with benzylsemicarbazide, and (b) that this influence could be moderated by the use of more alcohol as solvent.

When attempting the preparation of benzoin δ-phenylsemicarbazone



$$\begin{array}{l} C_6H_5\cdot CHOH \\ \quad | \\ C_6H_5\cdot C{:}O \end{array} \quad + \quad NH_2\cdot NH\cdot CO\cdot NH\cdot C_6H_5 \quad \longrightarrow \quad \begin{array}{l} C_6H_5\cdot CHOH \\ \quad | \\ C_6H_5\cdot C{:}N\cdot NH\cdot CO\cdot NH\cdot C_6H_5 \end{array}$$

a large volume of alcohol was therefore used to dissolve the benzoin.

The almost theoretical yield of the phenylsemicarbazone obtained is not attributed entirely to the large volume of solvent; it is thought to be due - in part at least - to the very sparing solubility of the product, which in consequence separates out, and does not take part in further reactions (compare the benzylsemicarbazone p. 130).

At some future time the author hopes to prove that under appropriate conditions (probably in the hot so as to maintain the benzoin phenylsemicarbazone in solution) benzil diphenylsemicarbazone can be obtained by the action of phenylsemicarbazide hydrochloride on benzoin in alcoholic solution.

While only one form of the phenylsemicarbazone was recovered from the alcoholic method, two isomers were obtained by the interaction of benzoin and phenylsemicarbazide in pyridine. The higher melting of these (M.P. 198°) forms the entire product from the alcoholic method and is the chief product from the pyridine method; it is named the α-isomeride. The β-isomeride is much more soluble and melts lower (169°). Both forms yield benzoin on hydrolysis.

In view of the almost universal acceptance of the Hantzsch-Werner hypothesis concerning isomeric oximes, it may reasonably be urged that the existence of the above pair of semicarbazones is due to the cis-trans type of isomerism. The same applies to the semicarbazones (p. 110) and phenylethylsemicarbazones (p. 170) of benzoin.

Stereoisomerism of Oximes and Semicarbazones.

While many examples of geometrical isomerism exist in the oximes of aldehydes and unsymmetrical ketones, comparatively few examples of this type of isomerism have been met with amongst semicarbazones. A sufficiently great number of isomeric semicarbazones however have been isolated to justify the claim that in semicarbazone formation isomerides may be encountered, due to considerations of the carbon-nitrogen linkage and of the spatial disposition of the groups around this linkage.

It might reasonably be asked 'are there any reasons for the prevalence of isomeric oximes and the paucity of isomeric semicarbazones', and the author here offers some suggestions in answer to the question.

(1) The Beckmann transformation of ketoximes, and the dehydration of aldoximes were powerful stimuli for drawing experimenters to the investigation of these compounds. If some reactions of equal interest were found concerning the semicarbazones, these discoveries would likely be followed up by the isolation of a large number of isomerides.

(2) Hantzsch's division of oximes into acid-stable and alkali-stable (Groundriss der Stereochemie 2nd.ed., p. 130) was possible owing to the inherent properties of the oximes, in that these compounds in a large number of cases at any rate, formed salts with acids or with alkalis. So far as the author is aware the

tendency of semicarbazones to salt formation is very rare. Wilson, Heilbron and Sutherland (J.C.S. 1914, 105, 2892) have shown that a large number of semicarbazones in the dry state will absorb hydrochloric acid, giving unstable products from which the halogen acid may be removed by a current of dry air. Read and Smith (J.C.S. 1922, 121, 1866) suggest that one form of piperitone semicarbazone is less basic than the other, and Forster and Zimmerli (J.C.S. 1910, 97, 2173) have found that only one form of camphorquinone semicarbazone is soluble in cold alkali. It may be confidently stated however that the semicarbazones do not possess the amphoteric properties displayed by the oximes. For this reason the conversion of one form into an isomeride by treatment with acids, very frequently met with in the oximes, may not be so general amongst the semicarbazones.

(3) Up to the present, the methods (see p. 205) of semi-

carbazone formation have not been so varied as those of oxime formation. For the former compounds the method of Baeyer (Ber. 1894, 27, 1918) has usually been followed; and whatever modifications have been introduced, the condensation has generally been effected in acid solution. The pyridine method developed during the work for this thesis is a new departure; it is generally applicable (see p. 206), and affords a means of carrying out the condensation in a faint alkaline medium. The results obtained in working with benzoin raise hopes of further success, and it is intended to continue the investigation of semicarbazone formation in this solvent and in the more basic solvent, piperidine. The use of caustic alkalis in semicarbazone formation seems to have been largely avoided. Read and Smith (J.C.S. 1922, 121, 1869), however have made the most interesting discovery that when piperitone and semicarbazide condense in presence of dilute caustic soda, an addition compound

$$C_9H_{16}:C(OH)\overset{NH}{\wedge}\cdot NH\cdot CO\cdot NH_2$$

is formed.

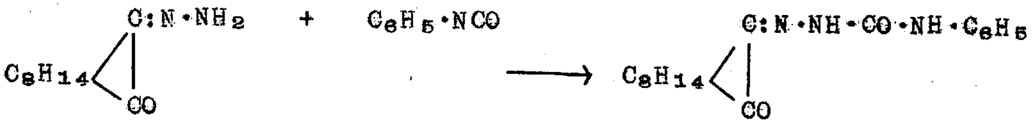
Review of Literature on Stereoisomeric Semicarbazones.

Wallach (Ber. 1895, 28, 1955) prepared stereoisomeric forms of the semicarbazones of isothujone, carvenone and tetrahydrocarvenone, but only obtained one form of the oximes of these ketones. The same author (Ber. 1896, 29, 2955, and Ann. 1898, 300, 269) showed that pulegone yields two semicarbazones.

Benzoylmethylthiodiazole (Wolff. Ann. 1902, 325, 173) and propaldehyde (Nef. Ann. 1904, 335, 202) each give two isomerides. Harries (Untersuchung uber das Ozon und seine Einwirkungen auf organische Verbindungen, Berlin, 1916, Springer) however records that the semicarbazone of propaldehyde is an oil. This record of Harries was brought to the notice of the author by Professor F.J. Wilson who was able to corroborate Nef's claim to the extent that semicarbazide condenses with propaldehyde to give solid products.

Knoevenagel and Samel (Ber. 1906, 39, 681) and later (Rupe and Dorschky. Ber 1906, 39, 2112) found that when semicarbazide acts on carvone in the cold, the product melts at 142° and is distinct from that (M.P. 162°) described by Baeyer (Ber. 1894, 27, 1918) ; it is however convertible into the latter by boiling with methyl alcohol or by heating to 170-175°.

Forster and Zimmerli (J.C.S. 1910, 97, 2156) in preparing camphorquinone semicarbazone by the modified method of Diels and von Dorp (Ber. 1903, 36, 3190) noticed that the mother liquor contained a more soluble isomeride (β-form) melting at a lower temperature. Both camphorquinone semicarbazones when heated with aniline undergo the change described on page 35 , yielding an equilibrium mixture of two camphorquinone phenylsemicarbazones which are separable by crystallisation. Condensation of camphorquinone with δ-phenylsemicarbazide gives a mixture of both forms of the phenylsemicarbazone, while the individual isomers may be obtained by the action of phenylcarbimide on the two forms of camphorquinone hydrazone.



$$C_8H_{14}\left\langle\begin{matrix}C{:}N\cdot NH_2\\ |\\ CO\end{matrix}\right. + C_6H_5\cdot NCO \longrightarrow C_8H_{14}\left\langle\begin{matrix}C{:}N\cdot NH\cdot CO\cdot NH\cdot C_6H_5\\ |\\ CO\end{matrix}\right.$$

Both the β-semicarbazone and the β-phenylsemicarbazone are convertible into the corresponding α-forms by the action of heat. Though Forster and Zimmerli indicate on a chart (p. 2159 in their paper) that this conversion is brought about with sulphuric acid, they do not give experimental details. Camphorquinone α-semicarbazone as distinguished from the β-isomeride dissolves immediately in cold alkali.

The most fruitful method of converting one form of a semicarbazone into an isomeride is by the action of ultra-violet light - a process which has been extensively studied by Wilson and his collaborators. It is noteworthy that generally there is obtained an equilibrium mixture of isomerides, the change not going to completeness in one direction.

Wilson and Heilbron (J. C. S. 1912, 101, 1482) found that phenylstyrylketone yields four stereoisomeric semicarbazones, two of which are stable under ordinary conditions, and two of which exist only in alkaline solution :-

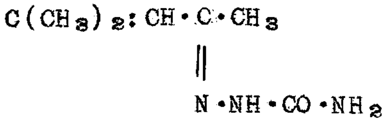
$C_6H_5 \cdot CH:CH \cdot C(C_6H_5):N \cdot NH \cdot CO \cdot NH_2$.

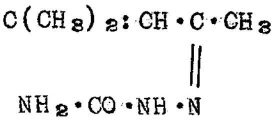
The same authors (J. C. S. 1913, 103, 1504) by the direct action of phenylsemicarbazide hydrochloride on phenylstyrylketone obtained two stereoisomerides (named α- and γ-) of phenylstyrylketone phenylsemicarbazone. The α-phenylsemicarbazone under the action of ultra-violet light was converted into an intensely yellow isomeride (δ-modification), while the γ-form under the same influence was converted into a yellow isomeride (β-form). In this as in the previous reference the existence of four isomers is attributed to a combination of carbon and nitrogen stereoisomerism :-

$C_6H_5 \cdot CH:CH \cdot C(C_6H_5):N \cdot NH \cdot CO \cdot NH \cdot C_6H_5$

Wilson and Heilbron (J. C. S. 1913, 103, 377) showed that mesityl oxide semicarbazone (M.P. 164°) prepared by the methods of Scholtz (Ber. 1896, 29, 612) or of Rupe and Kessler

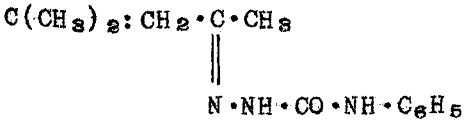
(Ber. 1909, 42, 4503), when exposed in chloroform solution to a mercury-vapour lamp, was partly converted into a stereoisomeride (β-modification) melting at 183-184°.

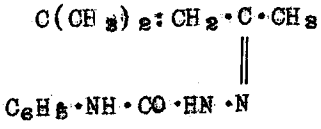

$$C(CH_3)_2{:}CH\cdot\underset{\substack{\|\\ N\cdot NH\cdot CO\cdot NH_2}}{C}\cdot CH_3$$


$$C(CH_3)_2{:}CH\cdot\underset{\substack{\|\\ NH_2\cdot CO\cdot NH\cdot N}}{C}\cdot CH_3$$

Either modification when exposed in this way yielded an equilibrium mixture of the two isomers. The β-form on heating above its melting point passed into the more stable α-form.

Wilson and Macaulay (J.C.S. 1924, 125, 841) found that only the stable form (M P. 134°) of mesityl oxide phenylsemicarbazone was formed by the direct action of phenylsemicarbazide on the ketone. This form however was partly changed into a less stable isomeride (M.P. 99-100°) by the action of ultra-violet light; and the latter form was largely converted into the stable isomer by boiling in alcoholic solution.

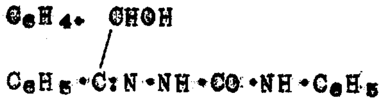

$$C(CH_3)_2{:}CH_2\cdot\underset{\substack{\|\\ N\cdot NH\cdot CO\cdot NH\cdot C_6H_5}}{C}\cdot CH_3$$


$$C(CH_3)_2{:}CH_2\cdot\underset{\substack{\|\\ C_6H_5\cdot NH\cdot CO\cdot HN\cdot N}}{C}\cdot CH_3$$

The above communication also includes a description of two forms of phenyl β-phenylstyryl ketone semicarbazone, both forms being obtained when an alcoholic solution of the ketone is boiled with semicarbazide hydrochloride. The isomers which melted at 171° and 204°, were interconvertible (to an equilibrium mixture) in alcoholic solution under the influence of ultraviolet light.

EXPERIMENTAL

BENZOIN δ-PHENYLSEMICARBAZONE



$$\begin{array}{l} C_6H_4\cdot\ CHOH \\ C_6H_5\cdot C{:}N\cdot NH\cdot CO\cdot NH\cdot C_6H_5 \end{array}$$

Alcoholic Method α-Form

4 gms. of δ-phenylsemicarbazide hydrochloride were dissolved in 8·5 ccs. of water and added to a solution of 4 gms. of benzoin dissolved in 180 ccs. of alcohol, the temperature on mixing being about 45°. After standing 18 hours at ordinary temperature a crop of crystals appeared, which were removed, washed with alcohol, and dried. A second crop of similar crystals appeared after 24 hours further standing; these were removed and the final traces of the product precipitated from the solution by addition of water. All three crops after two recrystallisations from alcohol yielded the same compound in the form of long fine woolly needles, M.P. 198° with decomposition.

Found: N =12·17 per cent; Benzoin δ-phenylsemicarbazone $C_{21}H_{19}O_2N_3$ requires N=12·18 per cent.

The product on hydrolysis in alcoholic solution with concentrated hydrochloric acid (compare hydrolysis p. 147) readily gave long needles of benzoin which after recrystallisation from alcohol were identified by their appearance, their melting point (185°) and their mixed melting point (185°) with benzoin (M.P. 185°).

This experiment is an excellent method of preparing the semicarbazone and the yield is almost theoretical.

Pyridine Method α-and β- Forms.

5 gms. (1 mol.) of δ-phenylsemicarbazide were added in the form of a dry powder to 6·5 gms.(rather less than 1 mol.) of benzoin dissolved in 45 ccs. pyridine, and left to stand in the dark for six days. Sufficient water to induce incipient cloudiness was then added and left overnight, during which time Crop 1 had separated. This was removed, washed with a little alcohol (not into the filtrate) and the filtrate again treated with water until incipient cloudiness. Crop 2 which had separated overnight was removed similarly to Crop 1. Further addition of water to the filtrate caused the separation of an oil which absorbed all the colouring matter in the solution, and this on standing, solidified in small hard spheres. These were removed and mechanically separated from other matter present, giving Crop 3 .

Crops 1 and 2 consisted of white needles melting at 189-191° and on recrystallisation from alcohol gave woolly needles M.P. 198° which were identical with that form of benzoin α-phenylsemicarbazone prepared by the alcoholic method (p.163).

Crop 3 was very soluble in alcohol, ether or benzene, and it was impossible to remove the colouring matter, which it held so tenaceously, by treatment with animal charcoal in these solvents. It was insoluble in petroleum ether, and when its ethereal solution was diluted with petroleum ether to incipient cloudiness, then boiled under reflux for a considerable time with animal charcoal, and filtered hot, practically the whole of the colouring matter was removed. This solution on standing overnight deposited a crop of hard stout prisms (still containing a little colouring matter) as well as a little of the α-compound melting at 198°. The prisms which were easily separated mechanically were redissolved in the minimum quantity of alcohol under reflux and allowed to crystallise by spontaneous evaporation. Beautiful clusters of needles separated, the melting point (169°) of which was not altered by recrystallisation. Found: $N=12{\cdot}26$ per cent; Benzoin δ-phenylsemicarbazone $C_{21}H_{19}O_2N_3$ requires $N=12{\cdot}18$ per cent. Benzoin was obtained by hydrolysis of the compound in alcoholic solution with concentrated hydrochloric acid (compare hydrolysis p. 147) and was identified by its shape, its melting point (135°), and its mixed melting point (135°) with benzoin (M.P. 135°). A mixed melting point of this 169° compound with the 198° isomer from the alcoholic method of preparation (p. 163) was 160–165° which showed the two forms are not dimorphous. The α-form M.P. 198° is difficultly soluble in alcohol and separates out quickly on cooling, whereas the β-form M.P. 169° is easily soluble in this solvent and only crystallises after spontaneous evaporation to small bulk.

CHAPTER VIII

BENZOIN-

δ-α-PHENYLETHYLSEMICARBAZONE

The interaction of benzoin and δ-α- phenylethylsemicarbazide hydrochloride was carried out in alcohol and in pyridine; from both of these media two isomeric forms of benzoin δ-α- phenylethylsemicarbazone were obtained, this being the only instance in the present work where two isomerides of a benzoin semicarbazone were obtained by the so-called 'alcoholic method' of preparation. From the pyridine method the α- and β- forms were obtained in almost equal proportions. This was the first time that the lower melting and more soluble form (β-isomer) of a benzoin semicarbazone was obtained in good yield. In comparison, the β-forms of benzoin semicarbazone and benzoin phenylsemicarbazone formed only minor parts of the yields from the experiments by which they were obtained.

In the pyridine method, the somewhat tedious procedure of gradually diluting (e.g. over a period of several days) an ethereal solution of the crude benzoin δ-α- phenylethylsemicarbazone with petroleum ether, was the only process which was found to give the second and further crops of the crude product in a granular form. Evaporation of ethereal solutions gave but gummy products, and other solvents behaved similarly. When the products had once assumed the granular form and had been filtered off, there was no difficulty in recrystallising them.

Both the α-and β- forms of the phenylethylsemicarbazone when hydrolysed in aqueous alcoholic solution with hydrochloric acid gave benzoin. This point is of particular importance in connection with the resolution of benzoin which was carried out (p. 185) using optically active δ-α- phenylethylsemicarbazide hydrochloride.

Throughout these experiments on the preparation of the semicarbazones and δ-substituted semicarbazones of benzoin, it was noted (mentioned p. 148) that when a warm alcoholic solution of benzoin, from which the ketone was either separating or about to separate, was treated with an aqueous solution of a semicarbazide hydrochloride, crystallisation was immediately arrested. This behaviour is suggestive of the formation of an additive compound between the ketone and the semicarbazide. Though benzoin semicarbazone and benzoin phenylsemicarbazone are sparingly soluble in alcohol, the separation of these does not commence until several hours after the mixing of the reagents in aqueous alcoholic solution. In this connection it is interesting to note that Read and Smith (J.C.S. 1922, 123, 1866) have actually isolated an additive compound of piperitone with semicarbazide, and to this they ascribe the formula :

$$C_9H_{16}:C(OH)\cdot NH\cdot NH\cdot CO\cdot NH_2$$

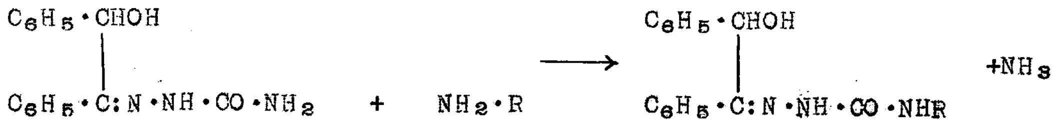
At this stage it is convenient to review the nomenclature suggested for the stereoisomeric forms of benzoin semicarbazone and benzoin δ-substituted semicarbazones. In all cases, the prefix α- is given to the form having the higher melting point; this form is also much less soluble in organic solvents. Judging from the reports of Wilson (p. 159), Wallach(p. 157) and Forster(p. 158) it seems in accordance with past practice to name the higher melting form of a semicarbazone (where there are two isomerides), the α-form. It is worthy of note that generally this form is the more insoluble and is obtained in the larger proportion. It would appear therefore, that the more stable form of a semicarbazone has the higher melting point.

A table, showing the melting points of these derivatives of benzoin, is given below.

	α-form	β-form
Semicarbazone	206°	187°
δ-Phenylsemicarbazone	198°	169°
δ-Benzylsemicarbazone	115°	
δ-Phenylethylsemicarbazone	174°	155°

The low melting point of benzoin benzylsemicarbazone, of which only one form was isolated, attracts attention. Is it a mixture ? Recrystallisation from various solvents failed to change its melting point. Apart from this benzyl-derivative there is a certain regularity in the other three pairs.

These benzoin δ-substituted semicarbazones might possibly be obtained by an indirect method, namely by heating benzoin semicarbazone with aniline, benzylamine and α-phenylethylamine.



$$\begin{array}{l} C_6H_5\cdot CHOH \\ \quad | \\ C_6H_5\cdot C{:}N\cdot NH\cdot CO\cdot NH_2 \end{array} + NH_2\cdot R \longrightarrow \begin{array}{l} C_6H_5\cdot CHOH \\ \quad | \\ C_6H_5\cdot C{:}N\cdot NH\cdot CO\cdot NHR \end{array} + NH_3$$

(compare 'the action of amines on semicarbazones' p. 85)

The investigation of this suggestion, particularly with a view to obtaining isomeric forms of benzoin δ-benzylsemicarbazone, will be undertaken at some future time.

The derivatives and decomposition products of semicarbazide, δ-phenylsemicarbazide, δ-benzylsemicarbazide and δ-phenylethylsemicarbazide when tabulated (see below) according to their melting points, form a very interesting table.

	S. C.	Ph. S. C.	Bz. S. C.	Ph. Et. S. C.
Free Base	96°	122°	111°	94°
Hydrochloride	173°	213°	227°	165°
Acetone derivative	187°	157°	113°	114°
Benzaldehyde do.	214°	174°	189°	103°
Benzoin do.	(205° 198°	(198° 169°	115°	(174° 155°
Acetyl do.	165°	169°	145°	-
Oxalate	-	220°	185°	160°

	S. C.	Ph. S. C.	Bz. S. C.	Ph. Et. S. C
$(R\cdot NH)_2CO$	132°	238°	169°	–
$R\cdot NH\cdot CO\cdot N_3$	93°	102°	84°	87°
$R\cdot NH\cdot COOC_2H_5$	50°	51°	48°	–
$R\cdot NH\cdot CO\cdot NH\cdot NH\cdot CO\cdot NHR$	259°	245°	237°	187°

S. C. = semicarbazide.

Ph. S. C. = δ-phenylsemicarbazide.

Bz. S. C. = δ-benzylsemicarbazide.

Ph. Et. S. C. = δ-phenylethylsemicarbazide.

R = hydrogen, phenyl, benzyl, and phenylethyl.

Only in the existence of one form of its benzoin derivative and in the low melting point of this derivative, does benzylsemicarbazide show a marked anomaly; it is of importance therefore, that this derivative should be further investigated.

The derivatives of semicarbazide with aldehydes and ketones are higher in melting point than the corresponding derivatives of the δ-substituted semicarbazides; for this reason the former hydrazide will be the more valuable as a reagent for giving solid and easily isolated condensation products, particularly in difficult cases.

Of the three substituted semicarbazides discussed, phenylsemicarbazide gives the highest melting derivatives and decomposition products. Regarding solubility in alcohol, which however was not determined quantitatively , it might be stated generally that this factor increases in the order :- compounds from semicarbazide; compounds from phenylsemicarbazide; compounds from benzylsemicarbazide; compounds from phenylethylsemicarbazide.

EXPERIMENTAL.

BENZOIN δ-α- PHENYLETHYLSEMICARBAZONE.

$$\begin{array}{l} C_6H_5\cdot CHOH. \\ \quad\ \ | \\ C_6H_5\cdot C:N\cdot NH\cdot CO\cdot NH\cdot CH(CH_3)\cdot C_6H_5. \end{array}$$

Pyridine Method.

Solutions of 8 gms. benzoin (1 mol.) in 80 ccs. pyridine and of 8·1 gms. (1 mol.) δ-α- phenylethylsemicarbazide hydrochloride in 10 ccs. water were prepared, mixed in the cold, and allowed to stand in a dark room. After six days the solution was diluted with water until faint turbidity, and then poured into a large volume of cold water which brought about the separation of a very sticky product (on the bottom of vessel) which did not solidify on standing. The supernatant aqueous liquor was poured off and the residue dissolved in ether in which it was readily soluble. The ethereal solution was shaken three times with water in a funnel to remove traces of pyridine, and then boiled under reflux with animal charcoal and sodium sulphate, and filtered while warm.

In the course of an hour or so a product began to separate and the solution was left for two days in order to complete the separation of Crop 1, which was filtered off, and washed until white, with ether - the washings being added to the filtrate.

The recovery of further solid product from the filtrate was difficult, but eventually it was found that addition of small quantities of petroleum ether over a period of two days brought down a somewhat discoloured solid in a filterable form which was collected (Crop 2) and washed with ether until white. The filtrate which had been considerably enlarged with the ether washings was diluted at intervals over a week with small amounts of petroleum ether. At this stage if on rubbing with a glass rod, the separating solid felt sticky, ether was carefully added until the product was quite granular. In this way crop 3 was obtained, and was filtered and washed as before. A small fourth crop was obtained in a similar manner, but over a longer period of time.

Purification of Crops.

Crop 1 in the crude state melted at 147-150°. When boiled under reflux with a large volume of ether in which it was difficultly soluble it slowly dissolved and the solution after cooling gave a crop of chipped plates melting at 153°. Recrystallisation from benzene in which it was more soluble did not alter the melting point, but recrystallisation from alcohol in which it was easily soluble gave long needles melting at 154° without apparent change. Found N=11·19 per cent. Benzoin δ-α- phenylethylsemicarbazone $C_{23}H_{23}O_2N_3$ requires N=11·26 per cent. When dissolved in aqueous alcohol and heated for a few minutes with concentrated hydrochloric acid (compare hydrolysis p. 147) the product was hydrolysed, and on cooling, long needles (M.P. 132-134°) separated; these on recrystallisation from alcohol had every appearance of benzoin melting at 135° and the melting point was not altered by admixture with benzoin (M.P. 135°). It was considered therefore that the compound melting at 154° was one form of benzoin δ-α- phenylethylsemicarbazone. For reasons explained in theory (p. 172) it is named the β-isomer.

Crop 2 which melted at 160-162° was appreciably less soluble than Crop 1 in the common organic solvents. By long heating under reflux with benzene it dissolved completely and a finely divided amorphous precipitate, melting at 172-173°, separated out quickly on cooling. By further recrystallisation from alcohol it was finally obtained in the form of rather stout needles melting at 174°. Found: N=11·23 per cent. Benzoin δ-α- phenylethylsemicarbazone $C_{23}H_{23}O_2N_3$ requires N=11·26 per cent. Hydrolysis of the product (compare hydrolysis p-147) with hydrochloric acid in alcoholic solution gave long needles which after recrystallisation melted at 135° and were identified as benzoin. The product melting at 174° was therefore taken to be a second form (α- isomer) of Benzoin δ-α- phenylethylsemicarbazone. A mixture of equal parts of the compounds melting at 174° and 154° melted at 140-145°, which excludes dimorphism.

Crops 3 and 4 melting at 130-140° when combined and dissolved in ether in which they were most readily soluble gave rise to a less soluble and a more soluble fraction. The less soluble fraction on further purification from alcohol proved to be the semicarbazone (melting at 154°) already mentioned, while the more soluble fraction after further recrystallisations from a mixture of ether and petroleum ether yielded a small amount of an apparently different compound in the form of long woolly needles melting at 137° and containing 11·37 per cent of nitrogen. Mixed melting points of this compound with the compounds melting at 174° and 154° would indicate that it is not a dimorphous form of either; lack of material prevented the further investigation of this product.

The yield of the α-isomer was 8 gms; of the β-isomer, 4 gms; and of the compound melting at 187°, 0·4 gms.

Alcoholic Method.

4 gms. of benzoin dissolved in 800 ccs. of alcohol were treated in the cold with the theoretical quantity (1 mol.) of δ-α- phenylethylsemicarbazide hydrochloride dissolved in a little water. After standing 6 days in the dark, the solution, from which nothing had separated out, was poured into a large volume of cold water. The soft - but filterable - product which separated, was collected, well pressed and washed with aqueous alcohol (1:1), after which it was dissolved in the minimum of alcohol under reflux. This solution on concentration and standing gave a crop which was fractionally crystallised from ether while a little gummy matter was eliminated in the alcoholic mother liquor. In the fractionation from

ether a moderate quantity of unchanged benzoin was first removed, and then it was noticed on further concentration of the solution that the separating product consisted of a mixture of long fine needles and prisms the melting point of which was about143 °. By reheating the mixture in its mother liquor the fine needles redissolved in a short time while the prisms required much longer for solution, so that by filtering the hot solution at the appropriate moment it was possible to make a fairly complete separation of the prisms. These after recrystallisation from alcohol gave stout needles melting at 174° and were proved to be identical with one form (α-isomer) of benzoin δ-α- phenylethylsemicarbazone (M.P.174°) already isolated in the pyridine method (p. 180).

The hot ethereal filtrate from the prisms on standing overnight gave a crop of needles mixed with a small proportion of prisms and the latter were removed by the 'reheating' treatment previously described. This time the hot ethereal filtrate was diluted with two volumes of light petroleum ether and left undisturbed overnight. Long fine needles grew which when collected, washed, and recrystallised from alcohol gave the second form of benzoin δ-α- phenylethylsemicarbazone previously obtained by the pyridine method (p.179). This product (β-isomer) consisted of fine rather flat needles M.P.154°.

So far as yield was concerned this alcoholic method of preparing the semicarbazone was very inferior to the pyridine process. There was adequate proof however that both forms of the semicarbazone were formed when the reaction took place in alcoholic solution.

CHAPTER IX

RESOLUTION of BENZOIN

The resolution of benzoin, about to be described, is the first instance of resolution which has been effected through the agency of an optically active semicarbazide.

Forster and Fierz (J.C.S. 1905,87,722) prepared the first optically active semicarbazide (camphoryl ψ semicarbazide) but do not appear to have carried out their expressed intention of using it for the resolution of racemic aldehydes and ketones.

Neuberg (Ber. 1903,36,976) has succeeded in resolving racemic arabinose by crystallising the hydrazone formed with l-menthyl hydrazine; and the same author in collaboration with Federer (Ber. 1905,38,868) resolved i-arabinose and i-galactose through the agency of d-amylphenylhydrazine. So far as the author is aware the above resolutions by Neuberg constitute the only examples of the resolution of racemic aldehydes or ketones accomplished through the operation of an optically active hydrazine.

The main objective of the work described in this thesis was the preparation of an optically active semicarbazide (δ-α- phenylethylsemicarbazide, p. 41).

$$C_6H_5 \cdot CH(CH_3) \cdot NH \cdot CO \cdot NH \cdot NH_2,$$

and the resolution, through its use , of some racemic aldehyde or ketone. Benzoin, being so accessible, naturally suggested itself as a suitable compound, and one optical enantiomorph of this hitherto un-resolved ketone has now been obtained in a pure form.

McKenzie and Wren (J.C.S. 1908,93,309) and Wren(J.C.S. 1909,95,1583) have already obtained the active forms of benzoin by a synthetic method. Starting out from active mandelic acid which they converted into the amide, they treated this with a Grignard reagent (magnesium phenyl bromide), and finally decomposed the resulting product with mineral acid. In this way the active forms of benzoin were obtained.

The interaction (p. 170) of benzoin with inactive -δ-α-phenylethylsemicarbazide was found to give two stereoisomeric semicarbazones. It follows therefore, that the optically active semicarbazide should give four isomerides. The separation of four nearly related products would, in most instances, be a matter of great difficulty. Only the first crop, however, of the crude benzoin r-phenylethylsemicarbazone was easily obtained (see p. 178) from an ethereal solution of the whole reaction product; and this crop was a moderately pure specimen of benzoin β-phenylethylsemicarbazone. When the reaction product from the corresponding experiment (p. 192), using d-δ-α-phenylethylsemicarbazide hydrochloride, was dissolved in ether a considerable time elapsed before any crystals appeared, but eventually a uniform crop of needles (M.P. 174–177°) grew, and these proved to be an almost pure sample of the active phenylethylsemicarbazone of d-benzoin. After two recrystallisations from alcohol, needles melting at 183°, and having $[\alpha]_D^{14^\circ} = -147^\circ$ for $C = 4{\cdot}9$ in alcohol, were obtained. On hydrolysis with oxalic acid in aqueous-alcoholic solution, d-benzoin was liberated; it melted at 181–183° [McKenzie and Wren: M.P. 181–132·5°], and gave $[\alpha]_D^{10\cdot5^\circ} = +118{\cdot}2^\circ$ for $C = 0{\cdot}99$ in acetone. For l-benzoin

McKenzie and Wren give $[\alpha]_D^{10\cdot5} = -118\cdot6°$ for $C = 0\cdot9232$ in acetone. Wren examined d-benzoin in a more dilute solution and recorded $[\alpha]_D^{11\cdot5} = +120\cdot5°$ for $C = 0\cdot4128$, in acetone.

Since only one isomeride of active benzoin phenylethylsemicarbazone was obtained in the crystallisation, the resolution here described gives only one active form of benzoin. It is evident however that the other enantiomorph (l-benzoin) could be obtained by using l-δ-α-phenylethylsemicarbazide hydrochloride (prepared from l-α-phenylethylamine: compare p. 37) in a manner similar to that described here for d-δ-α-phenylethylsemicarbazide hydrochloride.

EXPERIMENTAL.

To 8 gms. benzoin dissolved in 80 ccs. pyridine and cooled, were added 10 gms. d-δ-α-phenylethylsemicarbazide hydrochloride dissolved in 25 ccs. water. After 7 days the solution was placed in a separating funnel and fractionally precipitated by the addition of small instalments of water in the hope of effecting in this way a separation of optical isomers. Each addition of water caused the separation of an ~~oil~~ emulsion which in the course of 12 hours settled to the bottom of the funnel as a dark coloured oil. Each fraction of oil was run off into ether (about 5 volumes), the ethereal solution diluted with petroleum ether until faintly turbid, and immediately poured into a large volume of well agitated petroleum ether which caused the separation of a low melting point solid (M.P. 55–70°). The nine crops obtained in this way were so similar in appearance and melting point that it appeared doubtful if any separation of isomers was taking place: they were optically active however, and except for some anomaly in the first crop which had a specific rotation of -75·5° the specific rotation fell gradually from -86·0° for the second crop to -65·5° in the last. Samples of the first and last crops on hydrolysis with hydrochloric or oxalic acid in aqueous alcoholic solution gave inactive benzoin and their nitrogen content (11·02 and 11·1 per cent.) was in agreement with that (11·26 per cent.) of benzoin δ-α-phenylethylsemicarbazone, so it seemed likely that isomeric forms of this body were being dealt with. Alcohol, acetone, ethyl acetate and benzene were found unsuitable for the recrystallisation of the fractions as there was complete solubility in the cold and the products were only recovered in an oily condition. For some time it did appear that the only hope of effecting a separation lay in the repeated precipitation of the fractions from ethereal solution by petroleum ether since all other attempts at recovery from solvents resulted in oily products. When proceeding along these lines it was noticed that an ethereal solution which had stood over a week end (without petroleum ether having been added) had deposited long needle shaped crystals. In consequence of this observation the entire product of the experiment was dissolved in a small amount of ether and left a few days in a corked vessel until no more crystals separated. These crystals were removed and washed with ether, and the ethereal mother liquor plus washings preserved. The crystals were only moderately soluble in hot alcohol which was unexpected in view of the earlier behaviour of the products of the experiment towards solvents.

Needles separated quickly from the alcoholic solution on cooling, and after two recrystallisations in this way these were quite pure, melting at 188°. Found: N= 11·29 per cent; benzoin phenylethylsemicarbazone, $C_{23}H_{23}O_2N_3$ requires N = 11·26 per cent. ·049 gm. dissolved in 10 cc alcohol gave $\alpha = -0{\cdot}72°$ in a 1 dcm. tube at 14°, whence $[\alpha]_D^{14°} = -147°$.

Liberation of d-benzoin.

Preliminary experiments showed that the inactive phenylethysemicarbazones (p.170) of benzoin could be hydrolysed by heating in alcoholic solution with mineral acids or oxalic acid. The last mentioned acid was considered least likely to racemise the active benzoin, and hence it was selected for the following hydrolysis. The above active phenylethylsemicarbazone dissolved in hot alcohol was treated with a hot aqueous-alcoholic (1:1) solution containing 30 per cent of oxalic acid, and the mixture was boiled for a few minutes. On cooling and diluting with water, fine needles separated which after some time were collected, dried, and recrystallised from petroleum ether. Colourless needles melting at 131-133°, were obtained. ·099 gm. dissolved in 10 ccs. acetone gave $\alpha = +1\cdot17^\circ$ in a 1 dcm. tube at 10·5°, whence $[\alpha]_D^{10\cdot5^\circ} = +118\cdot2^\circ$. This d-benzoin when oxidised with 2·5 times its weight of concentrated nitric acid on the water bath gave rise to a product (e.g. benzil) which after recrystallisation from alcohol was identified by its appearance (faintly yellow needles), its melting point (94°-95°) and its mixed melting point (94°-95°) with benzil.

CHAPTER X

KETO-ENOLIC CHANGE of BENZOIN

The condensation of benzoin with urea (see p..107) and substituted ureas affords some evidence not hitherto brought forward in support of the claim that the ketone can also behave in a tautomeric dienolic form

$$C_6H_5\cdot CHOH\cdot CO\cdot C_6H_5 \rightleftharpoons C_6H_5\cdot C(OH):C(OH)\cdot C_6H_5.$$

The condensations of benzoin

(a) with UREA.

[Angeli. G. 1889, 19, 563; Anschutz and Gildermann, Ann. 1891, 261, 129; Anschutz and Schwickerath, Ann. 1894, 284, 8 ; Biltz and Horramann, Ber. 1907, 40, 4799. 4804]

(b) with mono-METHYLUREA.

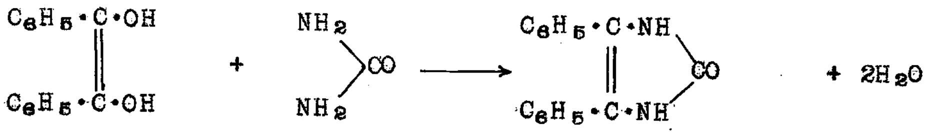
[Anschutz and Muller, Ann. 1894, 284, 33; Biltz and Horramann loc. cit.]

(c) and especially with sym-DIMETHYLUREA.

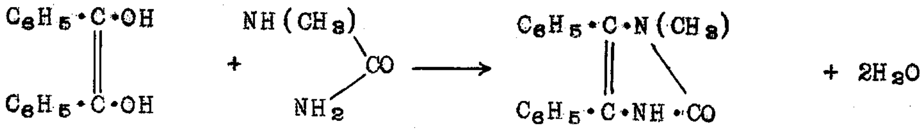
[Biltz and Horramann loc. cit.]

afford strong proof that the ketone passes into the form of ω-dihydroxystilbene before reacting. -

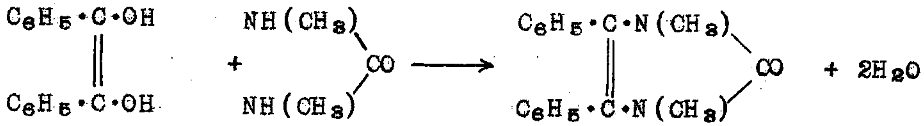
(a)



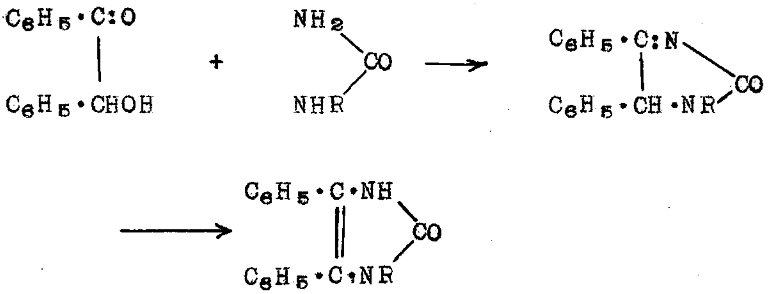
(b)



(c)

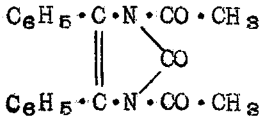


While the condensations (a) and (b) could be explained by the migration of a hydrogen atom following a primary condensation of the urea with the ketonic form of benzoin,

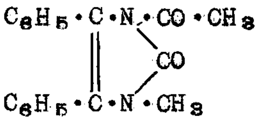


condensation (c) could not be explained in this way.

The acetyl derivatives of these iminazolone compounds are in agreement with the structures suggested. Thus α-β-diphenyliminazolone yields (Biltz, Ann. 1905, 339, 262) a diacetate (I), and α-β-diphenyl-N-methyliminazolone (Biltz, Ber. 1907, 40, 4808) gives only a mono-acetate (II) while α-β-diphenyl-N-N'-dimethyl-iminazolone does not form an acetate.

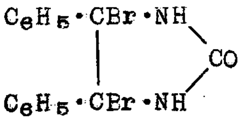


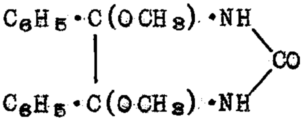
(I)



(II)

Further when α-β-diphenyliminazolone dissolved in methyl alcohol is treated with small quantities of bromine the formation of α-β-dimethoxy-α-β-diphenyliminazolone is probably due to the action of methyl alcohol on an intermediate dibromo-compound (Biltz. Ann. 1909, 368, 178).





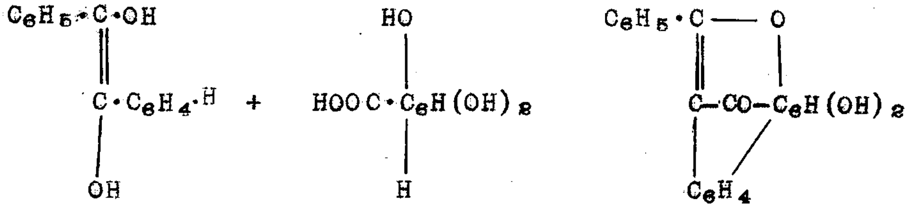
This is in agreement with the position suggested for the double bond.

The tautomerism of benzoin is amply illustrated in a number of other reactions, a summary of which is now given.

Graebe (Ber. 1898, 31, 2975) showed that benzoin under the influence of sulphuric acid condensed with gallic acid to give benzoin yellow. The reaction is explicable on the assumption that benzoin is first converted into ω-dihydroxystilbene,

$$C_6H_5\cdot CHOH\cdot CO;C_6H_5 \longrightarrow C_6H_5\cdot C(OH):C(OH)\cdot C_6H_5$$

which then reacts in accordance with the equation :



In a like manner, Haworth (J. C. S. 1909, 95, 486) explains the condensation of benzoin with the sodium derivative of ethyl-cyanoacetate :

$$\begin{array}{c} C_6H_5\cdot C\cdot OH \\ \| \\ C_6H_5\cdot C\cdot OH \end{array} \longrightarrow \begin{array}{c} C_6H_5\cdot C\cdot CH(CN)\cdot COOH \\ \| \\ C_6H_5\cdot C\cdot CH(CN)\cdot COOH \end{array}$$

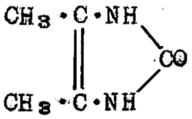
According to Thiele (Ann. 1899, 306, 142) the reverse transformation occurs when benzil is reduced to benzoin, e.g.

benzil ⟶ dihydroxystilbene ⟶ benzoin.

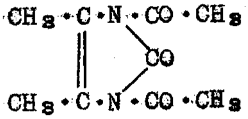
Although Thiele did not actually isolate the above intermediate compound, two stereoisomeric forms of its acetyl derivative were obtained when a solution of benzil in acetic anhydride to which a few drops of sulphuric acid had been added, was reduced with zinc dust. Similarly Nef (Ann. 1899, 308, 289) obtained one form of ω-diacetoxystilbene by the addition of acetic anhydride to the product of the action of sodium on a dry ethereal solution of benzil.

Wren (J. C. S. 1909, 95, 1594) attributes the easy racemisation of the active forms of benzoin in contact with alkali to the above keto-enolic change.

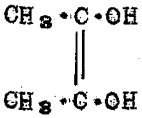
In this connection it might also be mentioned that dimethylketol condenses with urea to give dimethyliminazolone (Biltz. and Horramann, Ber. 1907, 40, 4801),



and that this compound gives a diacetate.

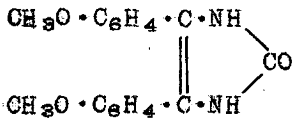


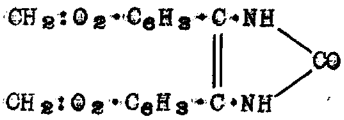
It might be inferred therefore that the above ketone can react in the form of a dihydroxybutylene.

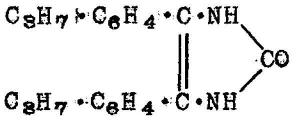


$$\begin{array}{c} CH_3 \cdot C \cdot OH \\ \| \\ CH_3 \cdot C \cdot OH \end{array}$$

Similarly the condensation of urea with anisoin, piperoin and cuminoin to give the following iminazolones (Biltz, Ann, 1905, 339, 265)

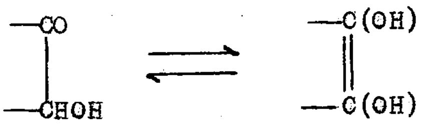






would suggest that these ketones can react as derivatives of ω-dihydroxystilbene.

Finally the author puts forward the view that the interaction of an α-hydroxyketone with urea, and especially with a sym-disubstituted urea, could be used generally for detecting isomeric change of the type :



CHAPTER XI

THE INTERACTION

of

δ-α-PHENYLETHYLSEMICARBAZIDE

and

d-GALACTOSE

The resolutions by Neuberg of i-arabinose and i-galactose have already been referred to (p. 186).

With a view to resolving i-galactose by means of active δ-α-phenylethylsemicarbazide, the interaction of the more accessible d-galactose with inactive δ-α-phenylethylsemicarbazide was examined to see if the resulting products were easily isolated and crystallised.

Work was carried out on the lines suggested by

? n Maqueene (Bl. 1904, iii, 31, 1078) and by Kahl (C. 1904, II, 1494) for preparing the semicarbazones of the hexoses. From both methods a thick syrup resulted which defied all attempts to crystallise it. In view of this no attempt was made to resolve i-galactose with active -δ-α-phenylethylsemicarbazide.

EXPERIMENTAL.

3·25 gms. inactive δ-α- phenylethylsemicarbazide (1·25 mol dissolved in a little alcohol was added to 2·7 gms. d-galactose dissolved in water. The solution was allowed to stand for a week, and then concentrated in vacuo over sulphuric acid. After 14 days the thick syrup remaining was treated with various solvents: it was completely and easily soluble in water, in ordinary alcohol, and in methyl alcohol; it was insoluble in ether, petroleum ether, benzene, chloroform, carbon tetrachloride, carbon disulphide and ethylene dichloride. From mixed solvents it came down syrupy. As only a few grains of galactose separated out from a solution in absolute alcohol, it was considered likely that the phenylethylsemicarbazone had been formed, this body being an uncrystallisable syrup.

A similar product was obtained by Kahl's method, e.g. by treating an aqueous solution of d-galactose with an aqueous-alcoholic solution containing phenylethylsemicarbazide hydrochloride and potassium acetate.

CHAPTER XII

PREPARATION of SEMICARBAZONES

in

PYRIDINE SOLUTION

In a number of instances, e.g. benzoin semicarbazone (Biltz, Ann, 1905, 339, 256) benz~~y~~aldehyde phenylethylsemicarbazone (p. 99), semicarbazones can be prepared by the action of an aqueous solution of semicarbazide hydrochloride on a solution or a suspension of an aldehyde or ketone in a neutral medium (water or alcohol).

Usually, however, semicarbazones are prepared according to the method of Baeyer(Ber. 1894, 27, 1918) who, acting on the suggestion of Thiele, mixed an aqueous solution of semicarbazide hydrochloride with an alcoholic solution of potassium acetate, and having filtered off the precipitated potassium chloride, added an alcoholic solution of an aldehyde or ketone to the filtrate. The reaction mixture was then allowed to stand at ordinary temperature for a period which varied from a few minutes up to five days, according to the semicarbazone being prepared. The success of the method is due to the fact that many carbonyl compounds will condense with semicarbazide in presence of acetic acid but not in presence of hydrochloric acid.

$$NH_2 \cdot CO \cdot NH \cdot NH_2 \cdot HCl + CH_3 \cdot COOK = NH_2 \cdot CO \cdot NH \cdot NH_2 + CH_3 \cdot COOH + KCl$$

$$NH_2 \cdot CO \cdot NH \cdot NH_2 + R \cdot CO \cdot R' = NH_2 \cdot CO \cdot NH \cdot N{:}C(RR') + H_2O$$

(see pp. 75 and 98 for interaction of semicarbazide hydrochloride and potassium acetate).

Tiemann prepared citral semicarbazone (see p. 211) by mixing an aqueous solution of semicarbazide hydrochloride with a solution of citral in glacial acetic acid, but his method does not seem to have been largely used.

The results of the present investigation prove that the use of pyridine as solvent facilitates the preparation of semicarbazones. No other reagent need be added to remove hydrochloric acid from the semicarbazide hydrochloride, pyridine itself being sufficiently basic for this purpose. A general outline of the method is as follows :-

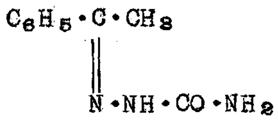
The aldehyde or ketone is dissolved in pyridine, and the theoretical amount of semicarbazide hydrochloride dissolved in a small quantity of water, added. [Pyridine hydrochloride being soluble under the conditions does not interfere]. Except for the semicarbazones of benzoin (previously discussed pp. 100–184) the condensation with all the other carbonyl compounds investigated is complete within 24 hours at ordinary temperature; in some cases the semicarbazone is precipated immediately. If the semicarbazone is soluble in pyridine it is precipated by addition of water; in a number of cases it was noticed that the method lends itself to the recovery of the resulting products by fractional precipitation (see benzoin semicarbazone p. 113 and acetophenone semicarbazone p. 208)

The purity of the reaction products is as good and sometimes better than that of the products from the Baeyer method of preparation; the yields are generally greater. In no case were there any side-reactions – due to the basic nature of pyridine, though some might have been expected(see acetoacetic ester semicarbazone p. 212). An attempt to use free semicarbazide in anhydrous pyridine was found unsuitable owing to the relative insolubility of the base in the solvent;

δ-benzylsemicarbazide may however be used in this fashion (p. 219).

The preparation of the following semicarbazones, most of which were previously known, illustrate the utility of the method. The hope of obtaining stereoisomerides as in the case of benzoin (p. 100) and perhaps methylethylketone (p. 216), was not realised.

ACETOPHENONE SEMICARBAZONE



$$C_6H_5\cdot C\cdot CH_3 \;\; \| \;\; N\cdot NH\cdot CO\cdot NH_2$$

This compound was obtained by Stobbe (Ann. 1899, 308, 123) who treated an alcoholic solution of acetophenone with an aqueous solution of semicarbazide hydrochloride in presence of sodium acetate. The yield was 95 per cent. theoretical and the M.P. 195-198°. Borsche (Ber. 1901, 34, 4301) prepared the semicarbazone in a similar manner and recorded its melting point as 198-199° (decomp.).

A solution of 5 gms. semicarbazide hydrochloride in 5 ccs. water was added to 30 ccs. of cold pyridine containing 5 gms. of pure acetophenone. The semicarbazone separated almost immediately, and after standing for 15 minutes was filtered off, washed first with water, then with dilute acetic acid and finally with water. A second crop was obtained by the addition of 20 ccs. water to the mother liquor.

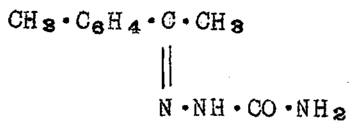
Crop 1. M.P. 198°: recrystallised, M.P. 198°.

Crop 2. M.P. 196°: recrystallised, M.P. 198°.

The semicarbazone crystallised from a mixture of alcohol and water in white plates melting at 198°; it is easily soluble in alcohol and in glacial acetic acid, moderately soluble in hot benzene, very sparingly soluble in cold benzene, petroleum ether, ether, or water. The yield was almost theoretical. It is noteworthy that the reaction product was almost pure.

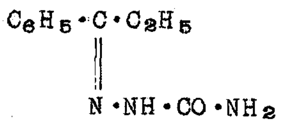
In a previous experiment using commercial acetophenone, the first two crops consisted of acetophenone semicarbazone, but a third crop after recrystallisation melted at 179°. The nitrogen content of this corresponded to compounds of the formulae:

(1)



$$CH_3\cdot C_6H_4\cdot \underset{\overset{\|}{N\cdot NH\cdot CO\cdot NH_2}}{C}\cdot CH_3$$

(2)



$$C_6H_5\cdot \underset{\overset{\|}{N\cdot NH\cdot CO\cdot NH_2}}{C}\cdot C_2H_5$$

The methyl-tolyl-ketone semicarbazones, of which there are three, melt at 192°, 188°, 200°. Ethyl-phenyl-ketone semicarbazone, however, melts about 179° (Stobbe, Ann. 1902, 321, 103, records M.P. 175°; and Blaise, C.r. 1901, 133, 1218, gives M.P. 182°) It is easily soluble in alcohol, soluble in hot benzene, insoluble in petroleum ether, ether or water. Its formation in this instance depended on the presence of ethylphenylketone in the commercial acetophenone; treatment with semicarbazide by the above method, evidently affords a means of detecting and separating this impurity.

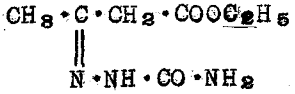
CITRAL SEMICARBAZONE.

$(CH_3)_2C:CH\cdot CH_2\cdot CH_2\cdot C(CH_3):CH\cdot CH:N\cdot NH\cdot CO\cdot NH_2$.

Tiemann and Semmler (Ber. 1895, 28, 2134), Barbier and Bouvealt (C.r. 1895, 121, 1159), and Tiemann (Ber. 1898, 31, 3330; 1899, 32, 115; 1900, 33, 881) have investigated this semicarbazone. Owing to the existence of two modifications of the aldehyde (citral a and citral b) there are two semicarbazones; these melt at 164° and 171°. When citral semicarbazone is prepared by the Baeyer method, it consists of a mixture and melts at 135°. If however, a solution of citral in glacial acetic acid is treated with an aqueous solution of semicarbazide hydrochloride, a separation of the semicarbazones may be effected (Tiemann). In the authors experience it is easy in this way to obtain the isomer melting at 164°, but not the other form. When however, citral is separated into its components by treatment with sodium bisulphite, these yield the corresponding semicarbazones melting at 164° (from citral a) and 171° (from citral b).

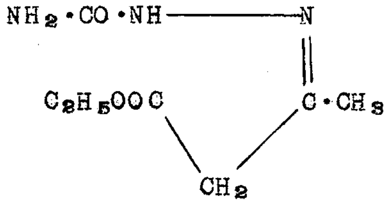
3 gms. of citral were dissolved in 20 ccs. of pyridine, and an aqueous solution (5ccs.) of 2 gms. semicarbazide hydrochloride added. After cooling in ice the semicarbazone was obtained as a white powder; addition of water to the mother liquor precipitated similar material. The product when crude melted at 129°, or when recrystallised from alcohol, at 132°. Thus the citral used was a mixture of the a and b citrals, and the pyridine method does not lend itself to the separation of the semicarbazones of these.

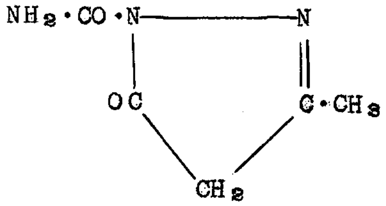
ACETOACETIC ESTER SEMICARBAZONE.



$$CH_3\cdot\underset{\underset{\displaystyle N\cdot NH\cdot CO\cdot NH_2}{\|}}{C}\cdot CH_2\cdot COOC_2H_5$$

Thiele and Stange (Ann. 1894, 283, 29) prepared this semicarbazone (M.P. 129° decomp.) by the method of Baeyer, and noticed the change into 1-carbonamid -3-methyl-pyrazolone





which it undergoes in contact with ammonia. This conversion is not brought about by pyridine.

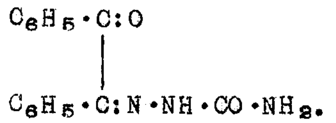
An aqueous solution (10 ccs.) of 7 gms. semicarbazide hydrochloride was added to a solution of 8·2 gms. acetoacetic ester in 30 ccs. pyridine. On shaking, the semicarbazone was immediately precipitated, and after standing for a short time was filtered off and washed first with water, then with dilute acetic acid and finally with water. A second crop was obtained after the addition of 20 ccs. water to the mother liquor.

Crop 1. M.P.127°; recrystallised M.P.129°(decomp).

Crop. 2. M.P.120°; recrystallised M.P.129°(decomp.)

The semicarbazone recrystallised from ether in needles, and the yield was almost theoretical.

BENZIL MONOSEMICARBAZONE.



$$\begin{array}{l} C_6H_5\cdot C:O \\ \quad\;\; | \\ C_6H_5\cdot C:N\cdot NH\cdot CO\cdot NH_2. \end{array}$$

Biltz and Arnd (Ann. 1905, 339, 250) prepared this semicarbazone by the Baeyer method, having allowed the reactants to stand for 3 days. They obtained plates melting about 174-175° (decomp.)

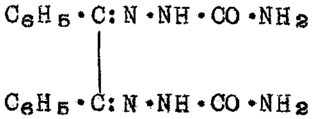
3 gms. of semicarbazide hydrochloride dissolved in the minimum quantity of water were added to a cold solution of 6 gms. benzil in 15 ccs. pyridine. After standing overnight the separated product was filtered off and washed. Two further crops were obtained by adding water to the mother liquor and allowing to stand an hour.

Crop.1 M.P. 165°; recrystallised from alcohol M.P.175°(decomp.)
Crop.2 M.P. 170°; do. do. M.P. do.
Crop.3 M.P. 175°; do. do. M.P. do.

Evidently the first crop is the least pure. The yield was

90 per cent. theoretical.

BENZIL DISEMICARBAZONE.



$$\begin{array}{l} C_6H_5\cdot C{:}N\cdot NH\cdot CO\cdot NH_2 \\ \qquad\ | \\ C_6H_5\cdot C{:}N\cdot NH\cdot CO\cdot NH_2 \end{array}$$

A mixture of benzil disemicarbazone and diphenyloxytriazine in the ratio of 1:4 was obtained by Biltz and Arnd (Ann. 1905, 339, 256) on heating an alcoholic solution of benzil with the requisite quantity (2 mols.) of semicarbazide hydrochloride and potassium acetate. The yield, which was very poor, consisted of leaflets melting at 243-244° (decomp.).

Three attempts to prepare benzil disemicarbazone were made by mixing semicarbazide hydrochloride (2 mols.) and benzil (1 mol.) in aqueous-pyridine solution.

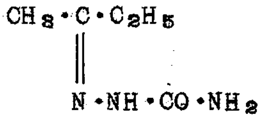
(1) No heating. Only the mono-semicarbazone obtained.

(2) 4 hrs. on water bath. Diphenyloxytriazine obtained.

(3) 8 hrs. on water bath. Diphenyloxytriazine obtained.

It seems probable therefore, that benzil monosemicarbazone does not react with semicarbazide in pyridine.

METHYLETHYL-KETONE SEMICARBAZONE.



$$\begin{array}{l} CH_3\cdot C\cdot C_2H_5 \\ \qquad \| \\ \qquad N\cdot NH\cdot CO\cdot NH_2 \end{array}$$

The data quoted in the literature respecting the melting point and crystalline form of methylethyl-ketone semicarbazone are discordant. For instance :

Scholtz (Ber.1896,29,610), plates from water,M.P.135-136°, Dilthey(Ber.1901,34,2122), needles from benzene and ligroin M.P.135-136°. Ponzio and Charrier(G.1907,37,I.508), prisms from benzene and ligroin M.P.143-144°. Blaise and Luttringer (Bl.1905,[3],33,818), M.P.(on quick heating) 145°. Robinson (J.C.S.1916,109,1044), M.P.148°.

These discordant data coupled with the observation made in the following experiments (that a sample of product melting at 143°, remelted after solidification at 136°) lead one to suggest that there might be two forms of the semicarbazone. The product was always obtained in the form of prismatic needles - not plates, as stated by Scholtz - on recrystallisation from water.

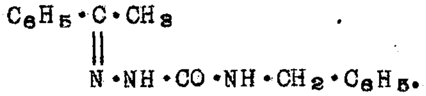
Experiment 1.

3·25 gms. semicarbazide hydrochloride in 2 ccs. water was added to a solution of 2 gms. methylethyl-ketone in 20 ccs. pyridine. The mixture was allowed to stand until no more needle shaped crystals separated. The yield of these amounted to 0·6 gm. (16 per cent. theoretical). They melted at 143°, and after resolidifying in the melting point tube, remelted at 136°.

Experiment 2.

5·7 gms. of semicarbazide hydrochloride in 5 ccs. water were shaken with 12 ccs. pyridine containing 3·5 gms. methylethylketone. After standing for a short time and then cooling in ice, the precipitated product was filtered off and washed. When crude it melted at 129°; after one recrystallisation from water the melting point rose to 136°, and after further recrystallisation to 143°. Yield 5 gms. (75 per cent. theoretical). A portion of the product melting at 136° was unchanged by recrystallisation from petroleum ether.

ACETOPHENONE δ-BENZYLSEMICARBAZONE.



$$\begin{array}{l}C_6H_5\cdot C\cdot CH_3\\ \qquad\quad\;\|\\ \qquad\quad\; N\cdot NH\cdot CO\cdot NH\cdot CH_2\cdot C_6H_5.\end{array}$$

A solution of 1·2 gms. acetophenone in 80 ccs. pyridine was mixed with an aqueous solution (2 ccs.) of 2 gms. δ-benzylsemicarbazide hydrochloride. After standing overnight the product was precipitated by the addition of water (about 80 ccs.) On recrystallisation from 90 per cent. alcohol colourless needles melting at 128° were obtained, and the yield was nearly theoretical. The product was easily soluble in hot alcohol, chloroform, benzene or ether, insoluble in petroleum ether or water. Found : N=15·7 per cent; $C_{16}H_{17}ON_3$ requires N=15·73 per cent.

BENZALDEHYDE δ-BENZYLSEMICARBAZONE.

$C_6H_5 \cdot CH \cdot N \cdot NH \cdot CO \cdot NH \cdot CH_2 \cdot C_6H_5$.

0·5 gm. benzaldehyde dissolved in pyridine (about 5 ccs.) was agitated with 0·5 gm. δ-benzylsemicarbazide which readily dissolved in the cold. As nothing had separated out during three days, the solution was diluted with 10 ccs. water which quickly induced the separation of crystals. These melted at 132-137°, and when recrystallised from alcohol gave stout rough prisms which melted at 139° and were identical with the product prepared by Crawford (see Wilson, Hopper and Crawford J.C.S. 1922, 121, 867).

CHAPTER XIII

HALOGENATION

in

ULTRAVIOLET-LIGHT

p-NITROBENZYLBROMIDE

While the broad general principles of halogenation, so far as the action of 'carriers' and of light are concerned, are fairly well understood, it appears to the author that much information of value - if not of novelty - would be gained by working out the details for the preparation of halogen compounds in mercury-vapour light. Bright sunlight is not always available and in consequence preparations requiring the solar stimulus are often held up for a considerable time.

The preparation of p-nitro-benzylbromide has been studied by Wachendorf (Ann. 1877, 185, 271) and by Reid (J. A. C. S. 1917, 39, 126). Wachendorf heated equimolecular proportions of p-nitrotoluene and bromine in a sealed tube for several hours at 125-130°. Reid obtained better yields when only one-half of the requisite quantity of bromine was at first introduced into the tube, the second moiety of halogen being added after the tube had been heated for an hour at 125-130° and reopened.

The most recent method published (Brewster, J. A. C. S. 1918, 40, 406) for making p-nitro-benzylbromide consists in adding a carbon tetrachloride solution of bromine to a boiling solution of p-nitro-toluene in the same solvent, a crystal of iodine being added to accelerate the reaction which is conducted in bright sunlight.

As the natural supply of actinic rays was very meagre at the time the present investigation was undertaken, Wachendorf's method was first examined.

On repeating Wachendorf's process and heating for 160 minutes, higher yields were obtained than were claimed by Reid for his modification of Wachendorf's method. The addition of a crystal of iodine caused an improvement. No further improvement was effected through the addition of borax to the reactants to remove halogen acid; it was therefore concluded that the hydrogen bromide generated had no harmful effect on the process. When however, commercial p-nitrotoluene was used, the incorporation of borax caused an improvement which was attributed to the neutralisation of traces of acid (probably from the mixture of sulphuric and nitric used in the nitration of toluene) in the nitro-compound. Attempts to repeat the process on a larger scale in an autoclave were not so successful although a moderate yield was obtained. Even when borax was incorporated, the solution of a small quantity of iron took place and this had a harmful effect on the yield. The influence of iron was studied by heating the reactants along with iron filings in a Carius tube, and in this case a lower yield was again obtained.

Later, Brewster's method was repeated, but the operation was conducted in the light of a quartz-mercury-vapour lamp and thereby rendered independent of the presence of sunlight at the time. Excellent yields were obtained; the reaction took place very readily, and it was possible to operate with fairly large quantities at a time.

p-Nitro-benzylbromide is moderately soluble in boiling petroleum ether but very sparingly in the cold. The improvement in yields is partly due to the recrystallisation of the cruder parts of the reaction products from this solvent.

EXPERIMENTAL.

Experiment 1.

5 gms. pure p-nitro-toluene and 2 ccs. bromine were heated for 160 minutes at 128-132° in a sealed tube. After cooling and opening the tube, the product was extracted with boiling alcohol (about 50 ccs.). A crop of needles separated from the solution on cooling, and a second crop was obtained after concentration. Water added to the mother liquor produced a precipitate which when collected and dried was heated under reflux with petroleum ether; colouring matter and some charred product were undissolved and adhered to the bottom of the vessel so that the boiling solution could be decanted cleanly. The decanted solution quickly deposited a crop of heavy prisms, the mother liquor from which was poured back to be used for further extraction of the charred and undissolved matter. This method of purification was very efficient since it obviated the use of filtration - a process always attended by some loss - and also since p-nitro-toluene is moderately

soluble in cold petroleum ether, whereas p-nitro-benzylbromide is very sparingly soluble in the cold solvent. Throughout the following experiments the product was purified in this way. Yield: 5·6 gms. (70 per cent. theoretical). M.P. 99-100°.

Experiment 2.

In this experiment which was carried out and worked up as in experiment number 1 a crystal of iodine was added to the reactants.

Yield: 6·4 gms. (80 per cent. theoretical). M.P. 99-100°.

Experiment 3.

10 gms. p-nitro-toluene dissolved in 100 ccs. of carbon tetrachloride to which a small crystal of iodine had been added were placed in a ~~silica~~ quartz flask provided with a reflux condenser and fixed near a mercury-vapour lamp. The solution was covered with a layer of water (about 30 ccs.) and heated to gentle ebullition. 12·7 gms. (4 ccs.) bromine dissolved in 50 ccs.

of carbon tetrachloride was placed in a tap funnel loosely inserted through the top of the condenser, and this solution was dropped in slowly (e.g. over a period of 20 minutes) on the boiling solution of p-nitro-toluene. After all the bromine had been added,heating was continued for a short time until the solution was practically colourless. The contents of the flask were then transferred to a separating funnel and the lower layer run off. After removing the carbon tetrachloride by distillation, the product was redissolved in boiling alcohol from which p-nitrobenzylbromide separated in needles on cooling. The small proportion dissolved in the alcoholic mother liquor was recovered and recrystallised from petroleum ether (see p. 224).

Yield: 12·6 gms. (80 per cent. theoretical). M.P. 99-100°.

[See "Systematic Organic Chemistry", Cumming, Hopper and Wheeler, p. 345].