16. *Reactions of Hydrazoic Acid. Part I.*

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Further applications of the Schmidt reaction have been investigated. Hydrazoic acid in the presence of concentrated sulphuric acid reacts smoothly with benzylideneacetone, methyl β-phenylethyl ketone, α-benzyl-α-methylacetone, and benzylmalonic acid to give cinnamomethylamide, aceto-β-phenylethylamide, aceto-β-phenyl*iso*propylamide, and phenylalanine respectively. The reactions with podocarpic acid, *o*-, *m*-, and *p*-toluic acids and stearic acid are also described. Esters such as methyl and ethyl benzoate react with the Schmidt reagent, forming aniline, and methyl azide decomposes similarly into hydrazoic acid in the presence of concentrated sulphuric acid, but ketones and acids are unaffected during the reaction.

A PUBLICATION of Adamson (J., 1939, 1564) on the preparation of amino-acids by an application of the Schmidt reaction with hydrazoic acid (*Acta Acad. Abœnsis math. phys.*, 1924, **2**, 38; *Ber.*, 1924, [*B*], **57**, 704; D.R.P. 1928, 500,435) has prompted us to record the results of our experiments with the same reagent, which are on somewhat similar lines.

A convenient method has been devised for the preparation of aceto-β-phenylethylamides, which are suitable intermediates for the preparation of *iso*quinoline derivatives by the Bischler–Napieralski method.

Benzylideneacetone reacts with hydrazoic acid and concentrated sulphuric acid to give cinnamomethylamide, which is resistant to hydrolysis:

$$\mathrm{CHPh{:}CH{\cdot}COMe} \xrightarrow{\mathrm{N_3H/H_2SO_4}} \mathrm{CHPh{:}CH{\cdot}CO{\cdot}NHMe}$$

Methyl β-phenylethyl ketone, however, with the same reagent gives a good yield of aceto-β-phenylethylamide:

$$\mathrm{CH_2Ph{\cdot}CH_2{\cdot}COMe} \xrightarrow{\mathrm{N_3H/H_2SO_4}} \mathrm{CH_2Ph{\cdot}CH_2{\cdot}NH{\cdot}COMe}.$$

That aceto-β-phenylethylamide was formed and not the isomeric β-phenylpropionomethylamide was proved by acid hydrolysis to β-phenylethylamine and conversion into 1-methyl-3 : 4-dihydro*iso*quinoline (Späth, Berger, and Kuntara, *Ber.*, 1930, **63**, 136).

Similarly, α-benzyl-α-methylacetone reacts with hydrazoic acid and sulphuric acid at 0° to give a good yield of aceto-β-phenyl*iso*propylamide. The constitution of the compound was proved by its conversion, by treatment with phosphoric oxide in boiling tetralin, into 1 : 3-dimethyl-3 : 4-dihydro*iso*quinoline, isolated as its picrate (cf. Hey, J., 1930, 20). Hydrolysis of the acetyl derivative with hydrochloric acid gave *dl*-β-phenyl*iso*propylamine, the inactive form of the physiologically active benzedrine.

In a further experiment to obtain compounds of physiological importance, benzylmalonic acid was treated with the Schmidt reagent in chloroform–dioxan solution at 40°, but the yield of *dl*-phenylalanine was only 16% (cf. a similar experiment with malonic acid by Adamson, *loc. cit.*).

Most of the acids so far studied in reaction with hydrazoic acid have been benzoic and related acids and aliphatic acids with the carboxyl group attached to a primary carbon atom. The action of hydrazoic acid on podocarpic acid, which apparently contains a carboxyl group attached to a tertiary carbon atom (Sherwood and Short, J., 1938, 1006), gives an amine in good yield, so there can be little steric effect in the Schmidt reaction.

The solvent as well as the catalyst in the Schmidt reaction has a marked effect on the yield. Schmidt records an 85% conversion of benzoic acid into aniline in chloroform solution. In benzene and anhydrous ether yields of 85·5% and 24% respectively have been obtained under similar conditions, and the use of 75% sulphuric acid reduces the yield to 15% in chloroform solution. In boiling chloroform the yield is decreased to 44%.

Esters as well as acids react with the Schmidt reagent, methyl and ethyl benzoate yielding 26% and 24% respectively of aniline in either benzene or chloroform.

In agreement with Oesterlin (*Angew. Chem.*, 1932, **45**, 536) we have found that the position of a substituent markedly influences the yield of the substituted aniline from the corresponding benzoic acid; *e.g.*, *o*-, *m*-, and *p*-toluic acids give yields of 46%, 24%, and 70% respectively of the corresponding toluidines with 50% excess of hydrazoic acid. A quantitative examination of a number of meta-substituted benzoic acids with this reagent has been completed, the results of which will be communicated shortly.

Schmidt (*loc. cit.*) suggests that hydrazoic acid reacts through the imino-radical. On this basis methyl azide might similarly give rise to the $\mathrm{CH_3{\cdot}N{:}}$ radical on decomposition, capable of reacting with ketones and acids to yield methylamides and secondary methylamines respectively. Although methyl azide decomposes similarly to hydrazoic acid, ketones and acids are unaffected during the reaction.

EXPERIMENTAL.

Action of Hydrazoic Acid on Benzylideneacetone.—Benzylideneacetone (5 g.; 1 mol.), dissolved in chloroform (75 c.c.), was mixed with a chloroform solution of hydrazoic acid (33 c.c. of 5·6% solution; 1¼ mols.) and cooled in ice–salt. Concentrated sulphuric acid (10 c.c.) was then added dropwise with stirring. After the rapid evolution of gas had ceased, the mixture was heated at 60° for 45 minutes. After cooling, the sulphuric acid layer was poured into water (250 c.c.), yielding a heavy brown oil, which solidified, m. p. 110° after recrystallisation from water. A further amount was obtained when the acid filtrate was made alkaline with ammonia. The crystals had the same m. p. 111° and physical properties as cinnamomethylamide (Orton, J., 1901, **79**, 1355; Vorländer, *Annalen*, 1902, **320**, 881).

Action of Hydrazoic Acid on Methyl β-*Phenylethyl Ketone.*—The ketone was prepared by catalytic hydrogenation of benzylideneacetone (Smith, J., 1914, **105**, 1706) and had b. p. 111—112°/10 mm., $n_D^{25°}$ 1·5140. The *dinitrophenylhydrazone* formed scarlet plates from alcohol, m. p. 131—132° (Found : N, 17·2. $C_{16}H_{16}O_4N_4$

requires N, 17·1%). To a rapidly stirred mixture of the ketone (20 g.; 1 mol.) in chloroform (10 c.c.) and concentrated sulphuric acid (36 c.c.) at 0°, a chloroform solution of hydrazoic acid (110 c.c. of 5·4% solution; 1 mol.) was added during 1 hour. After a further 45 minutes' stirring, the acid layer was poured into water (400 c.c.); it yielded to ether an oil, b. p. 126—127°/*ca.* 0·1 mm. (yield, 62·5%). Although the oil crystallised spontaneously on cooling (m. p. 42°), in agreement with other workers (Bischler and Napieralski, *Ber.*, 1893, **26**, 1905; Michaelis and Linow, *ibid.*, p. 2167; Decker, *Annalen*, 1913, **395**, 287), it could not be recrystallised from normal solvents. The constitution, however, was proved by hydrolysis with boiling concentrated hydrochloric acid to β-phenylethylamine, obtained as a viscous oil which formed a picrate, m. p. 170—171°, an oxalate, m. p. 180—180·5°, and a benzoyl derivative, m. p. 114—115° (the corresponding derivatives of β-phenylethylamine have m. p. 170—174°, 181°, and 114° respectively). Confirmation was obtained by conversion into 1-methyl-3 : 4-dihydro*iso*quinoline by heating with phosphoric oxide in boiling tetralin (Späth, Berger, and Kuntara, *loc. cit.*)—the picrate separated from methyl alcohol in long needles, m. p. 192° (Späth *et al.* record m. p. 188—190°).

Action of Hydrazoic Acid on α-Benzyl-α-methylacetone.—α-Benzylidene-α-methylacetone, b. p. 132—133°/12 mm. (Bogert and Davidson, *J. Amer. Chem. Soc.*, 1932, **54**, 334) was hydrogenated under pressure (45 lb.) in glacial acetic acid solution in the presence of palladium–charcoal to give α-benzyl-α-methylacetone, b. p. 111°/10 mm. The *dinitrophenylhydrazone* crystallised from alcohol in yellow plates, m. p. 81° (Found : N, 16·5. $C_{17}H_{18}O_4N_4$ requires N, 16·4%).

A solution of hydrazoic acid in chloroform (105 c.c. of 5·25%; 1 mol.) was slowly added with stirring to a solution of α-benzyl-α-methylacetone (20 g.) in chloroform (10 c.c.) in presence of concentrated sulphuric acid (35 c.c.) at 0°. Brisk evolution of gas occurred and was complete in 2½ hours. The acid layer, when worked up in the usual way, gave an oil, b. p. 135—136°/0·1—0·2 mm., solidifying on standing to crystals, m. p. 63° (yield, 48%). Crystallisation from light petroleum yielded pure aceto-β-phenyl*iso*proylamide, m. p. 67° (Hey, *loc. cit.*, records m. p. 64°). The constitution was proved as in the previous case by acid hydrolysis to β-phenyl*iso*propylamine, which formed a picrate, m. p. 142·5—143° (lit., m. p. 143°), and conversion into 1 : 3-dimethyl-3 : 4-dihydro*iso*quinoline, isolated as the picrate, m. p. 135·5° (Hey records m. p. 136°).

Action of Hydrazoic Acid on Benzylmalonic Acid.—To a solution of benzylmalonic acid (6·5 g.; 1 mol.) in a mixture of chloroform (40 c.c.) and dioxan (5 c.c.) were added 40 c.c. of a 5% solution of hydrazoic acid in chloroform, followed dropwise by concentrated sulphuric acid (15 c.c.). The mixture was rapidly stirred for 2 hours at 40°, but the evolution of nitrogen was not brisk. The acid layer was poured into water (100 c.c.) containing crystalline sodium acetate (77 g.). On concentration *dl*-phenylalanine was obtained mixed with sodium sulphate. After crystallisation from hot water it had m. p. 256—257° (decomp.) (yield, 16%); the benzoyl derivative had m. p. 185—186° (lit., m. p. 186—187°).

Action of Hydrazoic Acid on Podocarpic Acid.—To a mixture of podocarpic acid (10 g.) in chloroform (80 c.c.) and hydrazoic acid in the same solvent (39 c.c. of 5% solution; 1¼ mols.) at 40°, concentrated sulphuric acid (10·5 c.c.) was added with stirring during 3 hours. The dark blue sulphuric acid layer was poured into water, yielding a white solid. The *sulphate* of the base so formed crystallised from dilute sulphuric acid in colourless plates, m. p. 279° (decomp.) (Found : C, 55·8; H, 7·4. $C_{16}H_{23}ON,H_2SO_4$ requires C, 55·9; H, 7·3%). The amine did not couple with β-naphthol after treatment with nitrous acid.

Action of Hydrazoic Acid on Methyl and Ethyl Benzoate.—Ethyl benzoate (5 g.) in chloroform solution (50 c.c.), when treated under the usual conditions with hydrazoic acid (1·5 mols.) at 40—45°, with concentrated sulphuric acid as catalyst, yielded 0·72 g. (23%) of aniline; from the chloroform layer, 3·5 g. (72%) of the ester were recovered by vacuum distillation. With 3 g. of the ester in benzene solution and similar treatment, 24% of aniline was obtained.

Similarly, methyl benzoate (5 g.) in chloroform (50 c.c.) yielded 0·92 g. (26%) of aniline, 3·5 g. (70%) of the ester being recovered.

Action of Hydrazoic Acid on o-, m-, *and* p-*Toluic Acids.*—The acids (5 g.), each dissolved in chloroform (40 c.c.), were allowed to react with hydrazoic acid in chloroform solution (1½ mols. of 4% solution) at 40—45° in the presence of concentrated sulphuric acid (13 c.c.). The products were worked up in the usual way, and the amines distilled in a vacuum and identified as their benzoyl derivatives. From the chloroform solutions the unchanged acids were obtained and purified. Yields of 46%, 70%, and 24% of the corresponding amines were obtained from *o*-, *m*-, and *p*-toluic acids respectively and 52%, 28%, and 74% of the original acids were recovered. A duplicate experiment with *p*-toluic acid gave almost identical results.

Action of Hyarazoic Acid on Stearic Acid.—15 G. of purified stearic acid, m. p. 69·5°, were dissolved in benzene (500 c.c.), concentrated sulphuric acid (30 c.c.) added, and the mixture stirred vigorously at 40°. Hydrazoic acid (52 c.c. of a 5·3% solution in benzene; 1·2 mols.) was then added slowly. After the reaction had ceased (2 hrs.) the acid layer was poured into water, precipitating the sulphate of heptadecylamine, which crystallised from alcohol in plates turning brown at 195° and decomposing at 200° (yield, 96%). The benzoyl derivative obtained therefrom had m. p. 81°, that recorded by von Braun and Sobecki (*Ber.*, 1911, **44**, 1473).

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