41. *Experiments on the Synthesis of Physostigmine (Eserine). Part I. Some Indolenine Derivatives.*

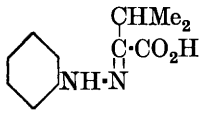
By ROBERT ROBINSON and HARUSADA SUGINOME.

THE initiation of experiments on the synthesis of physostigmine (eserine) has made it desirable to investigate more closely, as a preliminary, the methods available for the preparation of indolenine derivatives. In view of the ultimate object of the work, indolenines not bearing a substituent in position 2 were of special interest.

Brunner (*Monatsh.*, 1895, **16**, 849) has shown that the phenylhydrazone of *iso*butaldehyde when boiled with alcoholic zinc chloride affords a base $(C_{10}H_{11}N)_3$ and ammonia. Three years later, Plancher (*Chem.-Ztg.*, 1898, **22**, 37; *Ber.*, 1898, **31**, 1488) obtained a unimolecular base of the same indolenine type by applying Brunner's method to methyl *iso*propyl ketone phenylhydrazone.

It has recently been shown that intermediates for the synthesis of indole derivatives can be prepared in excellent yields by the application of the Japp–Klingemann reaction (Kalb, Schweizer, and Schlimpf, *Ber.*, 1926, **59**, 1858; Manske, Perkin, and Robinson, J., 1927, 2; Manske and Robinson, *ibid.*, p. 240).

With a view to the extension of the method to the synthesis of indolenine derivatives of type (III) the preparation of 3 : 3-dimethylindolenine has been studied as a preliminary. The starting point is ethyl *iso*propylacetoacetate, which can readily be converted into the phenylhydrazone of α-keto-β-methylbutyric acid (I) by the action of benzenediazonium chloride under alkaline conditions.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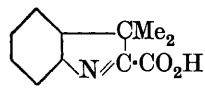
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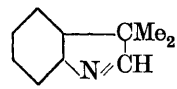
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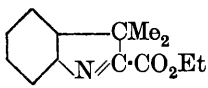
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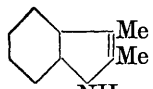
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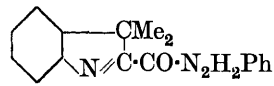

(VI.)

Brunner (*Monatsh.*, 1894, **15**, 763) has already treated this hydrazone (I), obtained from the ketonic acid, with 15% alcoholic sulphuric acid, the object being to obtain the ester. The final product was at first stated to be scatole and the reaction was attributed to the elimination of methylamine and carbon dioxide from the phenylhydrazone. Later, however, the same author (*Monatsh.*, 1895, **16**, 849) treated *iso*butaldehydephenylhydrazone with alcoholic zinc chloride and showed that the reaction products

were a new base and 2 : 3-dimethylindole and on the basis of these experiments he corrected the former supposition and suggested that the substance which was produced was 2 : 3-dimethylindole (V) and not scatole.

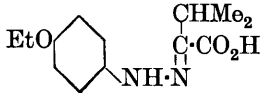
On repeating the experiment we have found that *ethyl* 3 : 3-*dimethylindolenine*-2-*carboxylate* (IV), 2 : 3-dimethylindole (V), and 3 : 3-*dimethylindolenine*-2-*carboxyphenylhydrazide* (VI) are produced.

It is worthy of note that 2 : 3-dimethylindole is obtained instead of 3 : 3-dimethylindolenine-2-carboxylic acid (II) : this is due to the instability of the acid, which easily parts with carbon dioxide, yielding 3 : 3-dimethylindolenine (III). This in its turn is changed by hot mineral acids into an indole derivative with migration of a methyl group. This view has been directly confirmed and the indolenine (III), heated with dilute sulphuric acid, yields 2 : 3-dimethylindole.

The phenylhydrazide (VI) may be formed by the condensation of ethyl 3 : 3-dimethylindolenine-2-carboxylate with phenylhydrazine produced from the original hydrazone (I) by hydrolysis; this view also has been substantiated by the synthesis of the hydrazide in the suggested manner.

The hydrazone (I) has also been treated with absolute alcoholic hydrogen chloride : 3 : 3-dimethylindolenine, 3 : 3-*dimethylindolenine*-2-*carboxylic acid* (II) and its ethyl ester are produced in satisfactory yield, the chief product being the carboxylic acid. When the carboxylic acid is heated, carbon dioxide and 3 : 3-dimethylindolenine (III) are obtained (compare Brunner, *loc. cit.*).

Substituting *p*-phenetidine for aniline in the first stage, we have applied a similar method to the preparation of the 5-ethoxyindolenines (VIII) and (IX) from the *p*-ethoxyphenylhydrazone (VII). The formation of these substances is a step in the approach to etheserole, which bears an ethoxyl group in this position in the indole nucleus.



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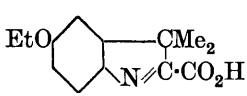
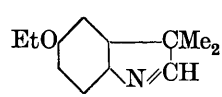


(VIII.)



(IX.)

EXPERIMENTAL.

α-*Keto*-β-*methylbutyric Acid Phenylhydrazone* (I).—A solution of ethyl *iso*propylacetoacetate (20·6 g.) in alcohol (150 c.c.) was mixed with one of sodium hydroxide (12 g.) in water (30 c.c.) and a solution of benzenediazonium chloride (from 9·3 g. of aniline, 6·9 g. of sodium nitrite, and 50 c.c. of concentrated hydrochloric acid) was quickly added. A heavy brown oil separated immediately and after a few

minutes it was isolated by means of ether and hydrolysed by alcoholic sodium hydroxide on the steam-bath. The solution was concentrated under diminished pressure, diluted with water (charcoal), filtered, and acidified with hydrochloric acid. The crystalline hydrazone acid which separated was washed with water (yield, 5·6—7·1 g.) and recrystallised from benzene or aqueous alcohol, forming yellow plates, m. p. 146—147° (decomp.) (Brunner, *loc. cit.*, gives m. p. 129°) (Found : N, 13·7. Calc. for $C_{11}H_{14}O_2N_2$: N, 13·6%).

Treatment of the Hydrazone Acid with Alcoholic Sulphuric Acid.—A solution of the hydrazone acid (15 g.) in alcoholic sulphuric acid (150 c.c., prepared from 22·5 g. of concentrated sulphuric acid and 150 g. of 95% alcohol) was refluxed for 4 hours on the steam-bath; then, after removal of the greater part of the alcohol, it was poured into water. A dark-brown tarry substance which separated was isolated by means of ether and distilled in steam. The distillate was again extracted with ether, and the solution dried over sodium sulphate and evaporated, giving a brown oil (4·5 g.), from which, on keeping, *ethyl* 3 : 3-*dimethylindolenine*-2-*carboxylate* separated in colourless stout prisms (0·83 g.), m. p. 79—80°, unaltered by recrystallisation from light petroleum (b. p. 40—60°) (Found : C, 72·5; H, 7·1; N, 6·5. $C_{13}H_{15}O_2N$ requires C, 72·3; H, 7·0; N, 6·5%). The ester gives an orange pine-shaving reaction, is readily soluble in ether, alcohol, or benzene but sparingly soluble in cold light petroleum, and does not afford a characteristic picrate. It is soluble in concentrated sulphuric acid and also in concentrated hydrochloric acid to a yellow solution which is not as intense as in the case of the ethoxy-compound (below) and on dilution with water the colour is discharged.

2 : 3-Dimethylindole can be isolated as the picrate from the mother-liquor of ethyl 3 : 3-dimethylindoleninecarboxylate. The reddish-brown derivative (2·8 g.) was collected and crystallised from alcohol; m. p. 156°, alone or mixed with a sample prepared from methyl ethyl ketone phenylhydrazone by Fischer's method (*Annalen*, 1886, **236**, 128, 131). 2 : 3-Dimethylindole, regenerated from the picrate by treatment with sodium bicarbonate, crystallised from light petroleum in leaflets, m. p. 105—106°, unchanged in admixture with an authentic specimen (Found : N, 10·0. Calc. for $C_{10}H_{11}N$: N, 9·7%).

3 : 3 - *Dimethylindolenine* - 2 - *carboxyphenylhydrazide* (VI).—The portion of the product of the above experiment which was not volatile in steam was a solid (3·8 g.), insoluble in alkali. When it was kept in alcoholic solution for several days, a brown crystalline substance separated which, recrystallised from alcohol, formed yellow rhombohedral crystals (0·3 g.), m. p. 155—156° (Found :

C, 73·4; H, 6·2; N, 14·9. $C_{17}H_{17}ON_3$ requires C, 73·1; H, 6·1; N, 15·1%). The *phenylhydrazide* is moderately easily soluble in methyl and ethyl alcohols, acetone, or benzene, but is less readily soluble in light petroleum. Its nature was disclosed by the results of the condensation of ethyl 3 : 3-dimethylindolenine-2-carboxylate with phenylhydrazine. A solution of the ester (0·22 g.) and phenylhydrazine (0·2 g.) in ethyl acetate (2 c.c.) was refluxed for 5 hours. The product was isolated as yellow crystals (0·32 g.) and was recrystallised from alcohol, forming yellow rhombohedra, m. p. 155—156°, alone or mixed with the specimen first obtained.

The alcoholic sulphuric acid treatment of the hydrazone acid (10 g.) was repeated but absolute alcohol was used and in this case 1·25 g. of ethyl 3 : 3-dimethylindolenine-2-carboxylate, 0·1 g. of the picrate of 2 : 3-dimethylindole, and 0·1 g. of the phenylhydrazide were isolated.

3 : 3-*Dimethylindolenine-2-carboxylic Acid* (II).—A solution of the hydrazone acid (I) (6·0 g.) in absolute alcohol (60 c.c.) was saturated with dry hydrogen chloride with cooling in running water, and then refluxed for 3 minutes, access of moisture being prevented; ammonium chloride immediately separated. After cooling, the solvent and the free hydrogen chloride were removed for the most part at room temperature in a vacuum, and an ethereal solution of the residue was shaken with sodium carbonate solution. For the treatment of the ethereal solution (A) see below. The aqueous solution was washed with ether, treated with charcoal, filtered, acidified with just sufficient dilute sulphuric acid, saturated with ammonium sulphate, and extracted with ether. The pale yellow ethereal solution was washed with water, dried over sodium sulphate, and evaporated, leaving 3 : 3-*dimethylindolenine-2-carboxylic acid* (II) as a pale yellow, crystalline substance (2·5 g.), pure enough for almost all purposes. It was recrystallised from ether–light petroleum, forming plates, m. p. 132—133° (decomp.) (Found : C, 70·2; H, 5·9; N, 7·5. $C_{11}H_{11}O_2N$ requires C, 69·8; H, 5·8; N, 7·4%).

This acid is readily soluble in methyl and ethyl alcohols, ether, acetone, or benzene and is also fairly readily soluble in water, especially when hot, but it is sparingly soluble in light petroleum. It gives no picrate, and the aqueous solution is strongly acid to litmus.

3 : 3-*Dimethylindolenine* (III).—3 : 3-Dimethylindolenine-2-carboxylic acid (1·0 g.) was heated at 135—140° in a glycerol-bath for 3 minutes, rapid evolution of carbon dioxide occurring. The resulting brown mass was triturated with a small quantity of benzene and the crystals were then collected and washed with the cold

solvent (yield, 0·6 g.; m. p. 185—190°). The base crystallised from benzene–alcohol in colourless plates, m. p. 214—215° (Brunner, *loc. cit.*, gives 215—216°) [Found: C, 82·9; H, 7·7; N, 10·2; *M*, 429 (camphor). Calc. for $(C_{10}H_{11}N)_3$: C, 82·7; H, 7·6; N, 9·7%; *M*, 435].

After being kept for a week, the compound had m. p. 152° and *M*, 235. Both specimens gave the same picrate, which was prepared in ethereal solution and obtained in well-formed yellow crystals, m. p. 146—147° (Brunner, *loc. cit.*, gives 135°) (Found: N, 15·0. Calc. for $C_{16}H_{14}O_7N_4$: N, 15·0%). On treatment with sodium bicarbonate solution the free base, m. p. 172—180°, was obtained.

Action of Dilute Sulphuric Acid on 3 : 3-*Dimethylindolenine-2-carboxylic Acid.*—The acid (0·5 g.) was boiled with 5% sulphuric acid for 8 hours and the cooled liquid was basified and repeatedly extracted with ether. 2 : 3-Dimethylindole (0·25 g.), thus isolated, crystallised from light petroleum in plates, m. p. 104—105°, undepressed on admixture with an authentic specimen; the picrate, m. p. 155°, was also prepared.

Examination of the Ethereal Solution (A).—The ethereal solution, which was highly fluorescent and possessed a terpene-like odour, was washed with water and dried over anhydrous sodium sulphate. A brown oily substance (2·8 g.) which remained after removal of the solvent crystallised when kept and was then stirred with a little alcohol (yield, 0·7 g.). On recrystallisation from alcohol–benzene, colourless crystals, m. p. 214—215°, were obtained. A mixed melting point with the 3 : 3-dimethylindolenine obtained above showed no depression and the picrate, m. p. 146—147°, was also prepared. On concentration of the alcoholic mother-liquor of the indolenine in a vacuum over sulphuric acid, ethyl 3 : 3-dimethylindolenine-2-carboxylate remained in prismatic needles (0·3 g.): the ester crystallised from light petroleum in colourless prisms, m. p. 79—80°, and was identified with the specimen previously obtained.

α-*Keto*-β-*methylbutyric Acid* p-*Ethoxyphenylhydrazone* (VII).—This acid was obtained in the same way as the phenylhydrazone of α-keto-β-methylbutyric acid, phenetidine being substituted for aniline. The yield was 53—56% of that theoretically possible. This *hydrazone acid* is easily soluble in most organic solvents, and it crystallises from benzene in yellow needles, m. p. 128—129° (Found: C, 62·7; H, 7·3; N, 11·5. $C_{13}H_{18}O_3N_2$ requires C, 62·4; H, 7·2; N, 11·2%).

5-*Ethoxy*-3 : 3-*dimethylindolenine*-2-*carboxylic Acid* (VIII).—A solution of the preceding *p*-ethoxyphenylhydrazone (10 g.) in alcohol (100 c.c.) was saturated with dry hydrogen chloride with cooling

in water. The greenish-yellow solution was refluxed for 5 minutes; thereafter ammonium chloride separated, and the alcohol was then removed under diminished pressure. The dark brown residue was dissolved in ether and shaken with aqueous sodium carbonate solution, and the aqueous layer again extracted with ether; on acidification with dilute sulphuric acid the *ethoxydimethylindolenine-carboxylic acid* was precipitated as a pale brown, crystalline solid. This was collected, washed with water, and dried (0·4 g. or 4·3% of that theoretically possible). It crystallised from benzene in colourless needles, m. p. 161—162° (decomp.) (Found: C, 66·5; H, 6·3; N, 6·0. $C_{13}H_{15}O_3N$ requires C, 66·9; H, 6·4; N, 6·0%). The acid is soluble in organic solvents with the exception of light petroleum but is sparingly soluble in water: the aqueous solution is acid to litmus. The solution in concentrated sulphuric acid is orange-yellow, and the acid is also fairly easily soluble in concentrated hydrochloric acid to give a yellow solution.

The poor yield of this acid is due to the ease with which it loses carbon dioxide.

5-*Ethoxy*-3 : 3-*dimethylindolenine* (IX).—The ethereal solution freed from acidic substances (see last section) was dried with anhydrous sodium sulphate, and the solvent removed, leaving a dark brown residue (7·5 g.). When this was kept in the ice-chest for a few hours, a brown substance crystallised, which was collected by means of a small volume of cold methyl alcohol (yield, 3·6 g. or 53% of that theoretically possible from the hydrazone acid) and purified through the *picrate*, obtained by treating an ethereal solution with picric acid: recrystallised from alcohol, this formed yellow needles, m. p. 145—146·5° (Found: N, 13·7. $C_{12}H_{15}ON,C_6H_3O_7N_3$ requires N, 13·4%).

A suspension of the picrate (5·0 g.) in ether (100 c.c.) was repeatedly shaken with aqueous sodium bicarbonate until the aqueous layer was colourless; the ethereal solution was finally shaken with water. After being dried over anhydrous sodium sulphate, the solution was concentrated and finally the ether was allowed to evaporate spontaneously. On being kept for a few days, the *indolenine* crystallised in large stout prisms (1·4 g.), m. p. 96—98° [Found: C, 76·3; H, 8·2; N, 7·7; EtO,* 20·6; *M*, 196 (camphor). $C_{12}H_{15}ON$ requires C, 76·2; H, 7·9; N, 7·4; EtO, 23·8%; *M*, 189]. The product was identified with the indolenine from the indolenine-2-carboxylic acid by the method of mixed melting points.

5-Ethoxy-3 : 3-dimethylindolenine-2-carboxylic acid (0·5 g.) was heated above its melting point; carbon dioxide was then readily

* For the ethoxyl determination hydriodic acid of *d* 1·96 was used together with phenol, and the experiment occupied an hour.

evolved. After cooling, the mass was dissolved in ether and shaken with aqueous sodium carbonate, and the extract washed with water. The indolenine was obtained from the ethereal solution in large prisms, m. p. 96—98°. It dissolved in acids without coloration.

Hydrochloride. A solution of 5-ethoxy-3 : 3-dimethylindolenine in dilute hydrochloric acid was evaporated over solid potassium hydroxide, leaving a buff-coloured crystalline solid. This was dissolved in absolute alcohol, ether added to produce a turbidity, and the mixture kept in a cold place; stellate clusters of anhydrous needles separated, m. p. 92—93° (Found : Cl, 15·6. $C_{12}H_{15}ON,HCl$ requires Cl, 15·7%).

Chloroplatinate. The precipitate obtained in the usual way changed on keeping into orange-yellow needles, which were collected, washed with water, and dried in the air. The substance darkened at 160° and decomposed at 270° (Found : Pt, 24·5. $2C_{12}H_{15}ON,H_2PtCl_6$ requires Pt, 24·8%). An attempt to prepare the chloroaurate was unsuccessful because a solution of the indolenine reduces auric chloride.

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