44. *Experiments on the Synthesis of Physostigmine (Eserine). Part IV. The Plancher Rearrangement of Indole Derivatives.*

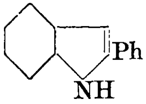
By Herbert S. Boyd-Barrett.

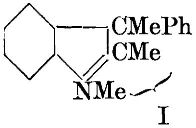
Numerous examples of the migration of alkyl groups in the indole series are well established, but in most cases a group migrates from nitrogen to carbon or from the 3- to the 2-position. For instance, Fischer and Schmitt (*Ber.*, 1888, **21**, 1071) observed the formation of 2-phenylindole from the phenylhydrazone of phenylacetaldehyde.

Plancher, however, has recorded (*Gazzetta*, 1898, **28**, ii, 374; *Atti R. Accad. Lincei*, 1900, v, **9**, 115) a number of migrations of alkyl and aryl groups from position 2 to position 3, and in relation to the synthetical work undertaken in the present series of memoirs it was important to gain further information respecting these novel transformations.

In order to avoid possible ambiguities where methyl and ethyl groups are concerned (due to the circumstance that methylation of the methyl group furnishes the ethyl group) a case has been re-investigated in which a phenyl group migrates from position 2 to position 3. Plancher (*loc. cit.*, p. 391) stated that the product of the interaction of 2-phenylindole (I) and methyl iodide is 3-phenyl-1 : 2 : 3-trimethylindoleninium iodide (II). [Actually (II) was represented as a methyleneindoline hydriodide.]

(I.)



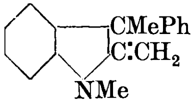


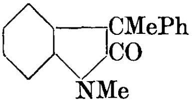
(II.)

No satisfactory proof of this view was, however, advanced apart from analogies.

The hypothesis has now been shown to be justified, because the methyleneindoline base (III) from (II) has been oxidised with formation of 3-*phenyl*-1 : 3-*dimethylindolinone* (IV) and the latter has been independently synthesised by an application of Brunner's reaction (*Monatsh.*, 1897, **18**, 597).

(III.)





(IV.)

The mechanism of the transformation is not clear (compare Plancher and Bonavia, *Gazzetta*, 1902, **32**, ii, 414), but it seems that ethyl, *iso*propyl, and phenyl have a greater migratory aptitude than methyl. The fact that phenyl and ethyl are thus found in the same category proves that the tendency to form the salt of a strong base is not the driving force in the reaction.

EXPERIMENTAL.

3-*Phenyl*-1 : 2 : 3-*trimethylindoleninium Iodide* (II).—This was obtained following Plancher (*loc. cit.*). It separated from methyl alcohol–ethyl acetate in long, almost colourless prisms or cubes, m. p. 227° (decomp.) (Found : C, 56·2 ; H, 5·0 ; I, 34·8. Calc. for $C_{17}H_{18}NI$: C, 56·2 ; H, 5·0 ; I, 34·4%).

A second product, m. p. 196° (decomp.), was isolated in substantial relative amount from a later preparation of the above substance, probably owing to loss of methyl iodide resulting in a lower pressure in the autoclave. It also was an *iodide* and was isolated from the ethyl acetate mother-liquor. Ultimately this readily soluble substance was crystallised from ethyl alcohol–ethyl acetate and obtained in long, slender, yellow needles, m. p. 196° (decomp.) (Found: C, 56·3; H, 5·2; N, 4·1; I, 35·3%). This salt is moderately easily soluble in alcohol or acetone, less readily in ethyl acetate, and almost insoluble in benzene and ether.

It is isomeric with Plancher's iodide (above) and is probably 2-phenyl-1 : 2 : 3-trimethylindoleninium iodide. The base, prepared from it by warming with dilute aqueous alkali, is quite stable, and this is in striking contrast to the isomeric base from the 3-phenylated iodide, which almost immediately assumes a red colour in the air. It is also possible that this by-product is a quinoline derivative and the result of ring enlargement, a phenomenon not unknown in this series.

3-*Phenyl*-1 : 2 : 3-*trimethylindoleninium Chloride*.—This was obtained from the iodide by addition of an excess of silver chloride to its boiling aqueous solution, with subsequent removal of water under reduced pressure; it proved to be unstable. The crude substance, isolated by grinding and washing the dried residue with pure acetone, was a light reddish crystalline solid, m. p. 92°, which darkened on exposure to air. This substance crystallised from pure acetone in faint pink clusters of needles, m. p. 94°. The crystals contained varying amounts of solvent of crystallisation, and unsatisfactory analyses were obtained. The chloride is moderately easily soluble in cold chloroform.

The *chloroplatinate* was a light salmon-coloured substance, m. p. 224° (decomp.) [Found: Pt, 22·4. $(C_{17}H_{17}N)_2,H_2PtCl_6$ requires Pt, 22·2%]. The *zincichloride*, prepared in alcoholic solution, separated in pale mauve prisms, and crystallised from alcohol in long, colourless, hexagonal prisms, m. p. 275° (decomp.) (Found: Cl, 25·8. $C_{17}H_{18}NCl,ZnCl_2$ requires Cl, 26·1%).

3-*Phenyl*-1 : 3-*dimethylindolinone* (IV).—Finely powdered potassium permanganate (20 g.) was gradually added to a solution of the chloride (10 g.) in pure acetone (250 c.c.), cooled in ice. The mixture was thoroughly agitated for 7 hours and kept in the ice-chest for 12 hours; the excess of permanganate was then decomposed by sulphur dioxide, and the liquor filtered. On removal of most of the acetone by distillation and addition of water, a yellow oil was obtained, which was isolated by means of ether as a reddish-yellow syrup (5·2 g.). On distillation a thick golden-yellow oil, b. p. 150—160°/2 mm., was obtained (Found: C, 80·6, 80·4; H, 6·4, 6·5; N, 6·2, 6·0. $C_{16}H_{15}ON$ requires C, 81·0; H, 6·3; N, 6·0%). After 2 months this specimen crystallised and had m. p. *ca.* 50°.

A well-defined *mononitro*-derivative of this neutral *indolinone* was obtained, and this serves for the characterisation of the substance. The indolinone (1 g.) was dissolved in nitric acid (5 c.c., *d* 1·42) and kept for 12 hours. The yellow substance precipitated by addition to ice-water was extracted in a Soxhlet apparatus with light petroleum and subsequently crystallised from absolute alcohol, forming light yellow prisms, m. p. 138° (Found : C, 68·1 ; H, 5·0 ; N, 10·0. $C_{16}H_{14}O_3N_2$ requires C, 68·1 ; H, 5·1 ; N, 10·1%).

α-Phenylpropionitrile, $C_6H_5{\cdot}CHMe{\cdot}CN$.—A new method for the alkylation of phenylacetonitrile has been investigated. The sodium derivative was prepared from the nitrile (145 g.) and sodamide (52 g.) (Upson and Thompson, *J. Amer. Chem. Soc.*, 1922, **44**, 182). A solution of methyl iodide (175 g.) in dry ether was gradually added with cooling during 2 hours, and the reaction mixture gently refluxed for a further 2 hours. The product was isolated by addition of water and dilute hydrochloric acid and extraction with ether. The crude substance (105 g.) had b. p. 215—245°. Unchanged phenylacetonitrile was removed by treatment with benzaldehyde and alcoholic sodium hydroxide, and the fraction, b. p. 220—245°, was collected and freed from any remaining traces of benzaldehyde by means of sodium bisulphite. The residue was again fractionated, α-phenylpropionitrile distilling at 229—233° (yield, 35 g.). Hydrolysis of this substance with 70% sulphuric acid for 5 hours gave α-phenylpropionic acid, b. p. 267—272° (29 g. from 35 g. of the nitrile). The *methylphenylhydrazide* of this acid was most readily obtained from α-phenylpropionyl chloride (7·6 g.) in dry ether, and methylphenylhydrazine (12·5 g.); the mixture was heated on the steam-bath for 1 hour. Dilute hydrochloric acid was then added, and the hydrazide was separated, dried, and crystallised from aqueous alcohol, forming colourless prisms, m. p. 128° (Found : C, 75·2 ; H, 7·1 ; N, 11·2. $C_{16}H_{18}ON_2$ requires C, 75·6 ; H, 7·1 ; N, 11·0%).

*Synthesis of 3-Phenyl-*1 : 3-*dimethyl-*2-*indolinone*.—The above hydrazide (5 g.), intimately mixed with finely powdered and freshly prepared quicklime (20 g.), was heated in a current of dry hydrogen at 200°, according to the method of Brunner (*loc. cit.*); after 12 hours, 70% of the theoretical amount of ammonia had been evolved. The contents of the flask were then treated with ice and dilute hydrochloric acid and the product was taken up in ether and isolated as a dark reddish syrup (3·3 g.). Subjected to distillation, it afforded a thick yellow oil (2 g.), b. p. 150—160°/2 mm. This specimen was converted into the mononitro-derivative, m. p. 138°. The melting-point was not depressed on admixture with a specimen of the nitro-compound obtained from the oxidation product.

α-Phenyl-α-methylacetone, CHPhMe·COMe.—This was obtained in moderate amount from β-phenyl-Δ^{β}-butylene (Tiffeneau, *Ann. Chim.*, 1907, **10**, 362), but could not be purified except through the semicarbazone, hydrolysis of which was best effected with 10% hydrochloric acid; the pure ketone had b. p. 212—214°. The methylphenylhydrazone of this ketone, obtained by heating equimolecular quantities of the substances on the steam-bath, was not isolated, but the crude substance was heated with alcoholic zinc chloride for 2 hours and 3-phenyl-1 : 2 : 3-trimethylindoleninium zincichloride was isolated. Purified by several recrystallisations from absolute alcohol, the substance finally separated as almost colourless, hexagonal prisms, m. p. 275° (decomp.) (Found : Cl, 25·8%). Compared with the zincichloride described above, no differences were observed, the two substances having identical general properties and reactions. No depression of melting point was observed on admixture, and the two compounds gave similar red colorations when warmed with diphenylformamidine in acetic anhydride.

3 : 3′-*Diphenyl*-1 : 3 : 1′ : 3′-*tetramethyl*-2 : 2′-*indocarbocyanine Chloride*.—The formation of this dye is a proof of the occurrence of a methyl group in the 2-position in the indoleninium chloride. 3-Phenyl-1 : 2 : 3-trimethylindoleninium chloride (2 mols.) and diphenylformamidine (1 mol.) were refluxed with acetic anhydride and after 1 hour dilute hydrochloric acid was added, causing a separation of sticky red material. This was collected, and a further small quantity of the dye salted out from the filtrate. The crude substance, warmed with alcohol and dilute hydrochloric acid, separated as reddish crystals with a coppery lustre.

Thrice crystallised from alcohol and dilute hydrochloric acid, the *chloride* separated in minute red plates with a green reflex, m. p. 255—258° (decomp.) (Found : C, 76·1, 76·1; H, 6·7, 6·6; N, 5·1, 5·0; Cl, 6·8, 6·9. $C_{35}H_{33}N_2Cl,2H_2O$ requires C, 76·0; H, 6·7; N, 5·1; Cl, 6·4%). The dye is moderately readily soluble in alcohol, acetone, and glacial acetic acid, giving intensely red solutions, but it is sparingly soluble even in boiling water, forming a rose-red solution, the colour of which is discharged on addition of alkali. The related base is soluble in benzene and ether.

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