

286. *Studies in the Indole Series. Part I. Derivatives of 2-Phenylindole.*

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THE structure of the compounds which are readily formed by the action of nitrous acid on the indoles has been studied by several investigators, and two formulæ, of types (I; R = H) and (II; R = H), have been proposed (for summary, see Angeli, "Neue Studien in der Indol- und Pyrrolgruppe," 1911). Möhlau (*Ber.*, 1882, **15**, 2487; 1885, **18**, 166) obtained



from 2-phenylindole a "nitroso-compound" to which he assigned the *isonitroso*-structure (I; R = H), but Fischer (*Ber.*, 1888, **21**, 1073; *Annalen*, 1886, **236**, 116) considered it to be a true nitroso-compound (II; R = H). The nitrosoamine structure was discarded, for the properties of the compound differed entirely from those of the known *N*-nitrosoindoles, in that it did not give the Liebermann reaction, was reduced to 3-amino-2-phenylindole (instead of 2-phenylindole), melted at a high temperature, and was insoluble in the common organic solvents.

Angeli and Angelico (*Gazzetta*, 1900, **30**, 268) objected to Fischer's formula (II; R = H) on the grounds that the properties of the "nitroso-compounds" are quite different from those of true *C*-nitroso-compounds (*e.g.*, nitrosobenzene), which possess low melting points, and dissolve readily in organic solvents to give an intense blue or green solution; they therefore revived Möhlau's suggestion that the substance was an *isonitroso*-compound, which accounts for the solubility in sodium hydroxide solution, the formation of ethyl ethers, and the production of quinazoline derivatives by the action of phosphorus pentachloride at room temperature. This formulation is also in accord with the fact that *isonitroso*- are much more stable than the corresponding nitroso-compounds.

In spite of this body of evidence, however, it can still be argued that the properties of the compounds differ markedly from those of the true oximes, which are usually colourless, readily soluble in the common organic solvents, and fairly low-melting.

Since no true *C*-nitroso-indoles are described in the literature, a compound of this type has now been prepared for the purpose of comparison. In 3-nitroso-2-phenyl-1-methylindole (II; R = Me) a representative of a third and quite distinctive type of nitrosoindole has been obtained for the first time. It crystallises from ligroin in emerald-green plates, m. p. 144°, dissolves in most organic solvents, and is decomposed by glacial acetic acid. In concentrated sulphuric acid it gives a deep red colour. Although undoubtedly an authentic *C*-nitroso-compound, it does not exhibit the typical reactions of such compounds; *e.g.*, it neither gives the Liebermann reaction nor condenses with aniline or hydroxylamine. It therefore appears that there is no conclusive chemical test for the presence of the nitroso-group in organic compounds. Consequently, Angeli and Angelico's conclusions, based as they are on purely chemical evidence, cannot be regarded as definitely established, so further confirmation has been sought by examining the absorption spectra of "nitroso"-2-phenylindole, its methyl ether, and 3-nitroso-2-phenyl-1-methylindole. The curves thus obtained (see fig.) show clearly the similarity in structure of the "nitroso"-2-phenylindole and its methyl ether (I; R = Me), the curve of the true *C*-nitroso-compound (II; R = Me) being quite different. As the structures of compounds (I; R = Me) and (II; R = Me) are known with certainty, the "nitroso-compound" must be the *isonitroso*-compound (I; R = H). If it is a tautomeric mixture, the proportion of true nitroso-compound present must be very small.

This structure was confirmed by the preparation of the oxime of 2-phenyl-3-indolone by means of hydroxylamine hydrochloride. The oxime was shown to be identical with "nitroso"-2-phenylindole or, at least, tautomeric with it, so the substance must be regarded as the *isonitroso*-compound.

It follows that 2-phenylindole reacts in the indolenine form with nitrous acid. On the other hand, it can react in the normal form, as shown by its condensation with triphenylcarbinol, a substance similar in many ways to nitrous acid (Baeyer and Villiger, *Ber.*, 1902, **35**, 3019).

The determination of the molecular weight of the "nitroso-compound" by Rast's method showed it to be monomeric, so its remarkable properties cannot be ascribed to molecular complexity.

In the course of our work it was necessary to prepare and identify the benzoyl-2-phenylmethylindoles. A detailed study was accordingly made of the several methods available for preparing these compounds, and as the accepted methods of identifying such indoles were found unsatisfactory, new methods were devised. The most generally used process for the preparation of the substituted indoles is that of Fischer (*loc. cit.*, 1886), which proved to be the most satisfactory in our work, a suitable fusion temperature being essential for good yields. By this means 2-phenylindole and 2-phenyl-5- and -6-methylindole were prepared. The structure of the first two indoles follows from the method of synthesis, but that of the last, prepared from acetophenone-*m*-tolylhydrazone, had to be elucidated by another method.

Bischler's method (*Ber.*, 1892, **25**, 2860) was less satisfactory than the Fischer synthesis, but it afforded 2-phenyl-7-methylindole in 43% yield, this indole being unobtainable by Fischer's synthesis. An essential catalyst for the reaction is the hydrobromic acid usually found as an impurity in the anilides used. Madelung's synthesis (*Ber.*, 1912, **45**, 1131) was used to prepare the isomeric 2-phenyl-4- and -6-methylindoles, the former being unobtainable by either Bischler's or Fischer's method; this synthesis serves to determine the orientation of the methyl groups in the above indoles. The relative values of the three syntheses may be inferred from the observation that 2-phenylindole was prepared by the methods of Madelung, Bischler, and Fischer respectively in yields of 4.5%, 16%, and 70% of the theoretical.

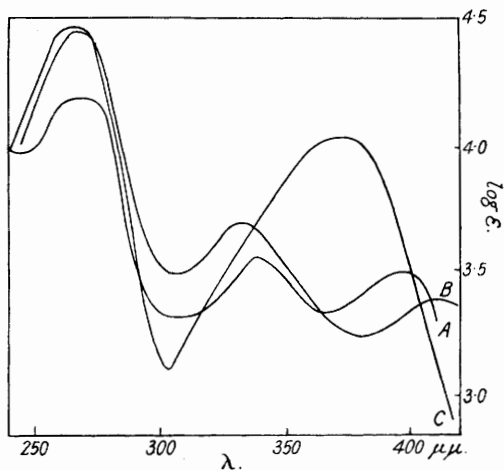
Among the derivatives we used for characterising the indoles, the picrates and benzylidene compounds were not satisfactory, the *isonitroso*-compounds were suitable only if specially purified, and the acetyloximino-, benzoyloximino-, and benzeneazo-compounds were very satisfactory.

The mechanism of the Fischer indole synthesis has been the subject of much speculation, and Robinson's theory (J., 1924, **125**, 827) is now generally accepted as the most probable (Neber, *Annalen*, 1929, **471**, 113). The only other theory which has been seriously considered is that of Reddelien (*ibid.*, 1912, **388**, 165), but we have now shown this to be erroneous, for both acetophenone-*p*- and -*o*-toluidine when fused with phenylhydrazine zincchloride gave 2-phenylindole and not the 5- or the 7-methyl homologue. Bodfors (*Ber.*, 1925, **58**, 775) carried out the same experiment, but his methods of identifying his products were inadequate.

EXPERIMENTAL.

Spectroscopic Measurements.—A Bellingham and Stanley "medium" quartz spectrograph was used, giving the spectrum from 205 μ to the red region on a 10 \times 4 in. plate. The solutions were 0.0004*N* in ordinary absolute alcohol. An iron spark was used as a source of light, and by using the rotating-sector method, a quantitative determination of the absorption curves was made.

Properties of 3-isoNitroso-2-phenylindole.—This compound does not condense with aniline



A. "Nitroso"-2-phenylindole.
B. Methyloximino-2-phenylindolenine.
C. 3-Nitroso-2-phenyl-1-methylindole.

or hydroxylamine hydrochloride under ordinary conditions, and it does not yield a blue coloration on addition of bromine (Piloty's test for many isonitroso-compounds). 0.0086 G. depressed the m. p. of 0.1493 g. of camphor by 9°; whence $M = 231$ (Calc. for $C_{15}H_{12}ON_2$: M , 236).

2-Phenyl-3-triphenylmethylindole.—2-Phenylindole (0.4 g.) and triphenylcarbinol (0.9 g.) were dissolved separately in boiling glacial acetic acid, and mixed; a purple solution was immediately formed. On the addition of water a reddish-grey substance was precipitated; recrystallised from alcohol, it formed colourless truncated prisms, m. p. 212°; yield 36% (Found: N, 3.2. $C_{33}H_{25}N$ requires N, 3.2%). In alcoholic solution this shows a much stronger fluorescence than the parent indole. It gives Ehrlich's test, but not the pine-splint test.

Action of Hydroxylamine Hydrochloride on 2-Phenylindolone.—2-Phenylindolone (Kalb and Baeyer, *Ber.*, 1912, 45, 2150) and hydroxylamine hydrochloride, dissolved separately in alcohol, were mixed and boiled for an hour; powdered sodium acetate was then added, and after a further hour's boiling the yellow precipitate which had separated was filtered off, washed successively with alcohol, water, alcohol, and ether, and recrystallised from amyl acetate, forming an orange-coloured substance, m. p. 280° (decomp.), not depressed on admixture with "nitroso"-2-phenylindole. The identity of the two substances was further established by benzylation, both giving identical products (m. p. and mixed m. p.).

3-Methyloximino-2-phenylindolone.—Sodium (0.46 g.) was dissolved in methyl alcohol (25 c.c.) and 3-isonitroso-2-phenylindole (4.44 g.) added. To the deep red solution thus obtained, methyl iodide (2.84 g.) was added, and the mixture boiled under reflux for 1 hour. On evaporating the alcohol and washing the residue with dilute sodium hydroxide solution, a dark red substance was obtained. This was dissolved in benzene, dried over sodium hydroxide, and the benzene evaporated; the viscid, dark red syrup thus obtained (3.3 g.) was extracted with light petroleum (b. p. 40–60°) (Soxhlet), the extract evaporated to dryness, and the dark red syrup placed in a desiccator evacuated to 0.5 mm. After a week, the substance began to solidify to a bright red crystalline mass, but complete solidification occupied several weeks. The solid distilled in a Pregl micro-vacuum-distillation apparatus at 193–194°/0.4 mm.; m. p. 54° (Found: N, 11.8. $C_{15}H_{12}ON_2$ requires N, 11.9%), and was very soluble in the common organic solvents.

2-Phenyl-1-methylindole.—Acetophenonephenylmethylhydrazone, prepared from the freshly distilled hydrazine (B.D.H.), required distillation in a vacuum before being used for the next stage; the fraction, b. p. 186–192°/11 mm., was obtained a viscid pale yellow syrup which solidified with extreme slowness. Recrystallised from ligroin, it had m. p. 49–50°. 8 G. of the hydrazone, when fused with 40 g. of zinc chloride at 200° for 2 mins., afforded 4 g. of the indole; this is an improvement on Degen's method (*Annalen*, 1886, 236, 154).

3-Nitroso-2-phenyl-1-methylindole.—The above indole was dissolved in cold glacial acetic acid and treated with ca. 0.5 g. of sodium nitrite in concentrated aqueous solution; the red solution was poured into water, and the yellow-green precipitate washed with water, and crystallised twice from ligroin, affording long, narrow, emerald-green plates, m. p. 144°; yield 85% (Found: N, 12.0. $C_{15}H_{12}ON_2$ requires N, 11.9%).

Preparation of Hydrazones.—These were usually obtained by heating together equimolecular quantities of the hydrazine and ketone in the steam-oven for 15–30 mins., but difficulty was sometimes experienced, for *m*-tolylhydrazine which had not been freshly distilled showed no hydrazone formation even after 3 days' intermittent heating on the steam-bath, whereas the freshly distilled hydrazine gave a 92% yield of hydrazone in 20 mins.

Acetophenone-o-tolylhydrazone formed colourless crystals, m. p. 101°, (yield 80%) (Found: N 12.5. $C_{15}H_{16}N_2$ requires N, 12.5%). The *m*-tolylhydrazone, long colourless crystals, m. p. 81°, yield 92%, distils at 214–223°/12 mm., forming a viscid yellow syrup which very slowly crystallises as pure white prismatic needles (Found: N, 12.4%); and the *p*-tolylhydrazone formed colourless leaflets, m. p. 125° (yield 67%).

Synthesis of Indoles.—(i) *By Fischer's method* (*loc. cit.*, 1886). 2-Phenylindole was prepared by 2 mins.' fusion at 190°, m. p. 189°; yield 70% (42% as indole and 28% as the isonitroso-compound); and its 5-methyl homologue, m. p. 216°, was obtained after 1½ mins.' fusion at 175°.

2-Phenyl-6-methylindole was prepared in ½ min. at 280°; yield 78% (44% as indole, 34% as isonitroso-compound), m. p. 193° (Found: C, 86.9; H, 6.5; N, 6.8. $C_{15}H_{13}N$ requires C, 86.9; H, 6.3; N, 6.8%). Its *picrate* formed purple needles, m. p. 145.5° (Found: N, 12.9. $C_{21}H_{16}O_7N_4$ requires N, 12.8%), readily decomposed by water, and difficult to obtain free from its components.

2-Phenyl-7-methylindole could not be prepared at any temperature between 120° and 400°.

(ii) *By Bischler's method.* Phenacylaniline and phenacyltoluidines were prepared in the usual way. Phenacyl-*m*-toluidine forms long flat prisms from alcohol, m. p. 110° (Found:

N, 6.2. $C_{15}H_{15}ON$ requires N, 6.2%). 2-Phenylindole and its 7-methyl homologue (m. p. 117°) were prepared in yields of 16% and 43% respectively; and the 6-methyl homologue (yield 50% as *isonitroso*-compound) was identified with the substance prepared by method (iii) by m. p. and mixed m. p. of the 3-*isonitroso*- and 3-acetyloximino-compounds.

This method was abandoned because of the difficulty of purifying the crude product either by recrystallisation or by distillation in a vacuum.

(iii) *By Madelung's method.* 2-Phenyl-6-methylindole was prepared from the benzoyl derivative of *p*-xylylidine (m. p. 150°) in 3.5% yield, 40% of the starting material being recovered unchanged. Crystallised from alcohol, it had m. p. 192.5°, and was identified (m. p. and mixed m. p.) with the substance prepared by methods (i) and (ii). 2-Phenyl-4-methylindole was prepared from the benzoyl derivative of *o*-3-xylylidine; the yield was so small that the product was converted into the insoluble *isonitroso*-compound (see below), the yield of which was 5.5%.

Derivatives of the Indoles.—Benzeneazo-compounds. These were made by the method of Plancher and Soncini (*Gazzetta*, 1902, 32, 447). 3-Benzeneazo-2-phenylindole formed dark red cubes, and was obtained in two forms, m. p.'s 137° and 165°. 3-Benzeneazo-2-phenyl-5-methylindole, long golden-brown prisms, m. p. 193°; yield 98% (Found: N, 13.3. $C_{21}H_{17}N_3$ requires N, 13.5%); the corresponding 6-methyl compound, dark brown cubes, m. p. 177°; yield 81% (Found: N, 13.4%); and the 7-methyl analogue, long dark red plates, m. p. 155° (yield 51%), from ligroin or alcohol (Found: N, 13.4%).

isoNitroso-compounds. These were prepared by the action of sodium nitrite and glacial acetic acid on the indoles. They had previously been obtained by other workers only in an impure state; from amyl acetate, however, they crystallise well in tiny, diamond-shaped plates, insoluble in most organic solvents. They melt at high temperatures with decomposition but have perfectly reproducible m. p.'s. They give very low results on analysis by the ter Meulen method. Highly impure *isonitroso*-compounds can be purified by the following procedure. The compound is dissolved in a little boiling pyridine, just sufficient boiling water is added to give a permanent cloudiness, and the mixture is boiled and allowed to cool; the black sludge which is deposited is filtered off, washed at once with ether, and recrystallised once from amyl acetate. Owing to their insolubility, these compounds are of service in the isolation of indoles.

3-*isoNitroso*-2-phenylindole is an orange-coloured compound, m. p. 280° (decomp.), and not a yellow substance, m. p. 258°, as described by all previous workers (Found: C, 75.5; H, 4.7; N, 12.3. Calc. for $C_{14}H_{10}ON_2$: C, 75.7; H, 4.5; N, 12.5%). The 4-methyl homologue is a yellow, microcrystalline substance, m. p. 251° (decomp.) (Found: N, 11.8. $C_{15}H_{12}ON_2$ requires N, 11.9%); the 5-methyl homologue has m. p. 273° (decomp.); the 6-methyl compound, m. p. 237° (decomp.) (Found: N, 11.9%); and the 7-methyl compound melts at 244°.

Benzoyloximino-compounds. These were prepared by benzylation of the *isonitroso*-compounds in sodium hydroxide solution (Spica and Angelico, *Gazzetta*, 1899, 29, 59). 3-Benzoyloximino-2-phenylindolenine has m. p. 153° (Found: N, 8.5. Calc. for $C_{21}H_{14}O_2N_2$: N, 8.6%) (Spica and Angelico give N, 9.18%). Its 4-methyl homologue has m. p. 145.5° (Found: N, 8.1. $C_{22}H_{16}O_2N_2$ requires N, 8.2%); 5-methyl compound, m. p. 159–160° (Found: N, 8.4%); 6-methyl compound, m. p. 142–143° (Found: N, 8.3%); 7-methyl compound, m. p. 163° (Found: N, 8.4%).

Acetyloximino-compounds. These were readily obtained by the action of acetic anhydride on the *isonitroso*-compounds (Spica and Angelico, *loc. cit.*). 3-Acetyloximino-2-phenylindolenine, m. p. 117° (Found: N, 10.5. Calc. for $C_{16}H_{12}O_2N_2$: N, 10.6%) (Spica and Angelico give N, 11.0%). The 4-methyl compound has m. p. 142° (Found: N, 10.0. $C_{17}H_{14}O_2N_2$ requires N, 10.1%); the 5-methyl compound, m. p. 169.5° (Found: N, 9.9%); 6-methyl compound, m. p. 118–119° (Found: N, 10.3%); 7-methyl compound, m. p. 122.5° (Found: N, 10.3%).

Disproof of Reddelien's Theory.—Acetophenone-*o*-toluidine (25 g.) and phenylhydrazine zincchloride (21 g.) were heated together to 250°, the mixture cooled, and extracted with chloroform. The indole obtained by evaporation of the chloroform was crystallised twice from alcohol, and shown by m. p. and mixed m. p. (189°) to be 2-phenyl- and not 2-phenyl-7-methylindole. The 3-benzeneazo-, 3-*isonitroso*-, and 3-benzoyloximino-compounds were prepared and shown by m. p. and mixed m. p. to be identical with the corresponding derivatives of 2-phenylindole and different from those of 2-phenyl-7-methylindole. A similar experiment with acetophenone-*p*-toluidine yielded only 2-phenylindole (identified as above).

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