26. *The Structure of the Nitroindazoles and their* N-*Methyl Derivatives.*

By Ian M. Barclay, Neil Campbell, and George Dodds.

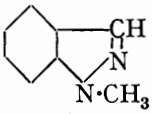
The bromine reactivity of the *N*-methyl derivatives of three 3-bromonitroindazoles has been measured, and the results discussed in relation to the structures of indazole and its derivatives. Evidence is given for the quinonoid formula for 2-alkylindazoles. There are indications that indazole resembles in structure the 1-alkyl compounds, and this is confirmed by absorption-spectra measurements.

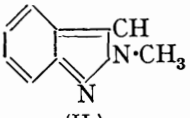
The validity of the Auwers rule for the alkylation of indazoles is questioned.

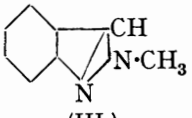
The structure of indazole and its derivatives has been intensively studied by Auwers and others (see, *e.g.*, Auwers and Duesberg, *Ber.*, 1920, **53**, 1179; Auwers and Schwegler, *ibid.*, p. 1211; Auwers, *Annalen*, 1924, **437**, 70; Meisenheimer and Diedrich, *Ber.*, 1924, **57**, 1715; Fries, *Annalen*, 1927, **454**, 303) both by chemical and by physical methods. By analogy with other heterocyclic compounds there can be little doubt that indazole

and its derivatives are resonance hybrids, the resonance being largely due to that of the benzene nuclei (cf. Pauling and Sherman, *J. Chem. Physics*, 1933, **1**, 606), though the necessary data are lacking to test the matter quantitatively. The present paper deals mainly with the structure of the heterocyclic ring.

1-Methylindazole is represented without ambiguity by (I), but the structure of the 2-compound has not yet been settled. Auwers (*loc. cit.*, 1924) rejects (III) and accepts


(I.)

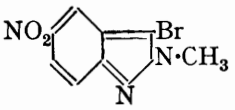

(II.)

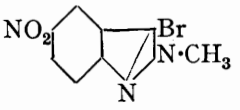

(III.)

(II), pointing out the difficulty of constructing a molecule with a three-membered ring. Meisenheimer (*loc. cit.*) supports this view, but Fries (*loc. cit.*) prefers (III), as the 2-alkylindazoles are colourless and show no quinonoid properties. Our results show that one of the forms contributing to the hybrid is the quinonoid structure.

It is known that, if a bromo-group is separated from a nitro-group by a double bond or conjugated system of double bonds, the bromine is reactive towards piperidine (*e.g.*, McLeish and Campbell, J., 1937, 1103) and this method of double-bond detection is applied in the present paper to derivatives of the nitroindazoles.

Consideration of the possible formulæ for the methyl derivatives of all the 3-bromo-*x*-nitroindazoles shows that reactive bromine will be found only in one compound, *viz.*,

(IV.) 


(V.)

3-bromo-5-nitro-2-methylindazole and then only if it possesses a quinonoid structure as one of the contributory forms (IV). That this is indeed the case is shown by the following table giving the removal of bromine by piperidine under different conditions.

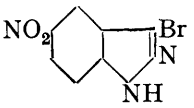
Compound.	Removal of bromine, %. i.	ii.	iii.
3-Bromo-4-nitroindazole		0	
3-*Bromo-4-nitro*-1-*methylindazole*	0	0	
3-Bromo-4-nitro-2-methylindazole	0	0	
3-*Bromo-5-nitroindazole*	0	4	0 1
3-*Bromo-5-nitromethylindazole*, m. p. 188°	2	30	44 45
3-*Bromo-5-nitromethylindazole*, m. p. 225°	0	0	0 0
3-Bromo-6-nitroindazole			0 2
3-*Bromo-6-nitro*-1-*methylindazole*	0	0	0 2
3-*Bromo-6-nitro-2-methylindazole*	0	0	0 0

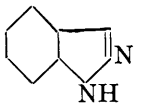
Col. i. Piperidine at 45° for 1 hour.
Col. ii. Piperidine at 45° for 24 hours.
Col. iii. Piperidine at 95° for 3 hours.

It therefore is necessary to assign an *o*-quinonoid structure to 3-bromo-5-nitro-2-methylindazole, and by analogy it is probable that all 2-alkylindazoles possess this structure. This conclusion is supported by Auwers's refractivity measurements (*Annalen*, 1937, **527**, 291). It might be argued that the three-membered ring formula (V) would account for the reactivity by the N_1–C_3 bond, but if this were so the 2-alkyl derivatives of all 3-bromoindazoles should show bromine reactivity. This is not the case.

The results of the bromination of the 5-nitromethylindazoles were as follows: methyl compound, m. p. 163° ⟶ bromo-compound, m. p. 225°; methyl compound, m. p. 129° ⟶ bromo-compound, m. p. 188°. As the bromo-compound, m. p. 188°, is reactive, it must be methylated in the 2-position, and hence its precursor, m. p. 129°, must also be the

2-derivative. Hence the isomer, m. p. 163°, is 5-nitro-1-methylindazole. This is the opposite of the formula assigned by Fries (*loc. cit.*), who, however, noted that his evidence was inconclusive.

(VI.) 

 (VII.)

The small reactivity of 3-bromo-5-nitroindazole indicates that structure (VI) is the main contributing form, and suggests that the corresponding form (VII) holds for indazole. This is in agreement with Auwers's conclusion (previous reference) that indazole closely resembles the 1-alkyl derivatives, *e.g.*, (I). Further support for this conclusion is provided by the absorption spectra of indazole, 5- and 6-nitroindazoles, and their *N*-methyl-

FIG. 1.

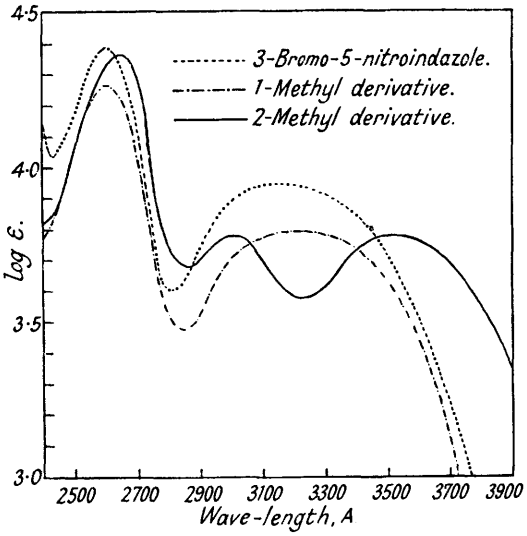
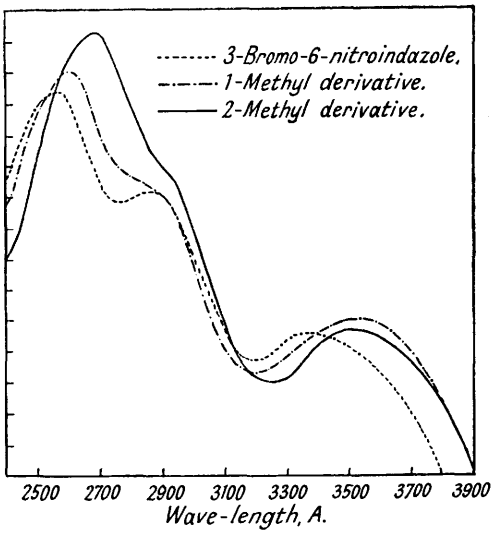
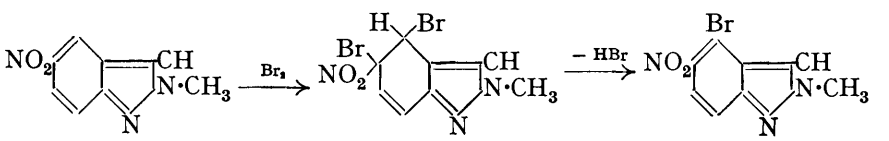


FIG. 2.



derivatives. Little can be deduced from the curves of 6-nitroindazole, but in the other two cases there is a close similarity between the parent indazole and its 1-methyl derivative but a decided difference from the 2-methyl isomer.

Following other workers in the field (*e.g.*, Witt, Noelting, and Grandmougin, *Ber.*, 1890, **23**, 3635), we have assumed throughout that bromination of indazoles occurs in position 3. There is, however, the possibility that, if (say) 5-nitro-2-methylindazole has the quinonoid structure, addition of bromine, followed by elimination of hydrogen bromide (cf. J., 1931, 3308), might occur to give 4-bromo-5-nitro-2-methylindazole (VIII) :

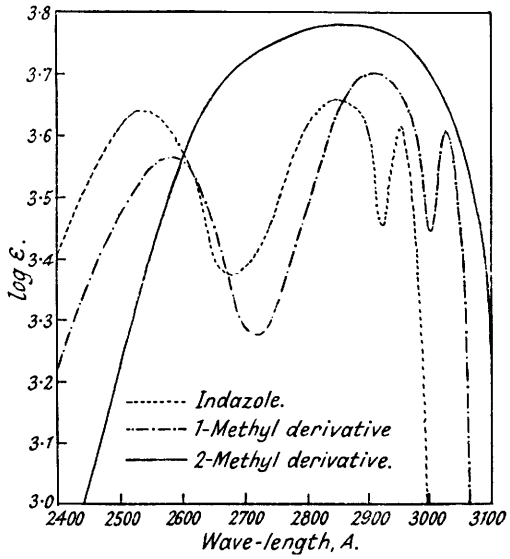
 (VIII.)

(The bromine in this compound would be reactive to piperidine and its reactivity would sustain the argument for the quinonoid form.) Formation of the 4-bromo-compound is possible, but in our opinion extremely unlikely in view of the reactive 3-position of indazoles and the presence of the nitro-group in the benzene ring. Further, if bromination did occur preferentially in the 4-position, further bromination to give the 3 : 4-dibromo-compound would be expected. No indication of this was found, although in the several cases investigated excess bromine was used.

Attempts to prepare 5-nitro-1-methylindazole from the methylhydrazone of 2-chloro-

5-nitrobenzaldehyde were unsuccessful. This is rather surprising in view of the ease with which Fries (*loc. cit.*) effected ring-closure of the phenylhydrazone of 2-chloro-5-nitrobenzophenone, though on the other hand Meyer (*Ber.*, 1893, **26**, 1253) could not effect closure of a ring in the phenylhydrazone of 2-chloro-5-nitrobenzaldehyde.

FIG. 3.



Auwers and Duesberg (*loc. cit.*) formulated the rule that alkylation of indazoles in alkaline solution takes place mainly in the 1-position. Exceptions to the rule are known (*e.g.*, Auwers and Dereser, *Ber.*, 1919, **52**, 1340). We have found other exceptions in the methylation of 6-nitroindazole and 3-bromo-6-nitroindazole, and are inclined to doubt the general validity of this rule, as the quantitative separation of the isomers produced is a matter of difficulty.

EXPERIMENTAL.

Unless otherwise stated, the methods of preparation, properties, and purification of compounds used are those given in the literature. The purity of the compounds was checked by the sharpness of their m. p.'s on the Kofler micro-apparatus (*Mikrochem.*, 1934, **15**, 242). Analyses were done by Drs. Weiler and Strauss, Oxford, and Mr. Brown, Edinburgh. The reactivity measurements were carried out as in previous papers (Campbell and McLeish, *loc. cit.*).

Spectroscopic Measurements.—A Bellingham and Stanley "medium" quartz spectrograph was used, giving the spectrum from 2400 A. to the red region on a 10 × 4 in. plate. The solutions were 0·0001M in ethyl alcohol. An iron spark was used as the source of light, and by using the rotating-sector method, a quantitative determination of the absorption curves was obtained.

Indazole.—Precise instructions are lacking for the preparation of indazole by the method of Jacobson and Huber (*Ber.*, 1908, **41**, 2574). The following method was finally adopted (cf. Auwers, *Ber.*, 1919, **52**, 1335; Haworth and Hey, J., 1940, 365). Benz-*o*-toluidide (20 g.) was dissolved in a hot mixture of acetic acid (50 c.c.) and acetic anhydride (50 c.c.) and rapidly cooled with stirring to obtain fine crystals. The mixture was then cooled to 3°, and nitrous fumes passed in at the rate of one or two bubbles per second. A deep green colour was obtained after about 20 mins., the temperature of the solution never having exceeded 10°. Immediately a clear solution was obtained it was poured into water (100 g.) and ice (100 g.). The oil which separated soon solidified on being stirred. The precipitate was washed with cold water until only a faint odour of acetic acid remained, pressed on tile, and dried at room temperature for 2 hours. The nitroso-compound (characterised by its "flash" on heating) was added to sodium-dried benzene (150 c.c.), the solution kept overnight, refluxed for 1 hour, and 100 c.c. of benzene distilled off. The solution was separated from benz-*o*-toluidide, shaken with sodium carbonate solution (50 c.c.), washed with water, and extracted with 2N-hydrochloric acid (100 c.c.). Treatment with sodium hydroxide gave indazole, which, crystallised from hot water, had m. p. 146° (lit., 146°); yield of pure compound, 1 g. The *picrate* (Auwers and Duesberg, *loc. cit.*) crystallised from ether in yellow needles, which were converted into orange prisms on standing in suspension; m. p. 136° (lit., 136—137°). It had not previously been analysed (Found: N, 19·5. $C_{13}H_9O_7N_5$ requires N, 20·2%).

N-Methyl Derivatives of 3-Bromo-4-nitroindazole.—Great difficulty was experienced in preparing 6-nitro-*o*-toluidine required for making 4-nitroindazole. The preparation from 2 : 4 : 6-trinitrotoluene (Tiemann, *Ber.*, 1870, **3**, 218; Beilstein, *ibid.*, 1880, **13**, 243) gave very poor yields of 2 : 6-dinitro-4-aminotoluene, although many modifications of the method were tried, and removal of the amino-group gave only a 5% yield of the nitrotoluidine. Korner and Cortardi (*Atti R. Accad. Lincei*, 1916, **25**, 339) claimed a 60% yield by the reduction but the

promised experimental details were never published. Cohen and Dakin (J., 1902, **81**, 26) could not obtain the amino-compound directly. *o*-Toluic acid was therefore nitrated, and the resulting mixture separated by the rather unsatisfactory method of Scherpenzeel (*Rec. Trav. chim.*, 1901, **20**, 173). p-*Nitrobenzyl* 4-*nitro*-o-*toluate* formed leaflets (acetic acid), m. p. 149° (Found: N, 8·6. $C_{15}H_{12}O_6N_2$ requires N, 8·8%), and p-*nitrobenzyl* 6-*nitro*-o-*toluate*, prisms (alcohol), m. p. 108—114° (Found: N, 9·3%). 6-Nitro-*o*-toluamide gave a poor yield of 6-nitro-*o*-toluidine by the Hofmann reaction, but Curtius degradation of the azide gave good results. The acid chloride of 6-nitro-*o*-toluic acid (11 g.) was dissolved in benzene (100 c.c.), and powdered sodium azide (3 g.) was slowly added, the solution being vigorously shaken. The solution was finally heated gently and then boiled with an equal volume of concentrated hydrochloric acid for 4 hours. The benzene was removed, and the hydrochloride of 6-nitro-*o*-toluidine converted into the base by trituration with concentrated aqueous ammonia; crystallised from alcohol, it had m. p. 91° (lit., 92°); yield, 40%. 4-Nitroindazole was obtained by Noelting's method (*Ber.*, 1904, **37**, 2582). The indazole was methylated by a quicker method than that of Auwers and Frese (*Ber.*, 1925, **58**, 1369). 4-Nitroindazole (4 g.), potassium hydroxide (3 g.), methyl iodide (9 g.), and methyl alcohol (25 c.c.) were heated under reflux for 4 hours, and the solution poured into water. The precipitate obtained was dried on porous plate, dissolved in ether, and separated by the method of Auwers and Frese (*loc. cit.*). 4-Nitro-1-methylindazole, crystallised from light petroleum (b. p. 80—100°), had m. p. 136° (lit., 138—139°); yield, 0·8 g. The 2-methyl compound, crystallised from water, had m. p. 98° (lit., 101—103°); yield, 0·3 g. The methyl derivatives were brominated by suspending them in dilute hydrochloric acid, adding bromine water, and stirring vigorously for ½ hour. The precipitate was washed with water, and crystallised from alcohol. 3-*Bromo*-4-*nitro*-1-*methylindazole* had m. p. 216—220° (Found: Br, 29·4. $C_8H_6O_2N_3Br$ requires Br, 31·2%). There was only sufficient of the 2-methyl isomer, m. p. 195—199°, for the reactivity measurements.

3-*Bromo*-5-*nitroindazole*.—5-Nitroindazole (1 g.) was brominated in dilute hydrochloric acid as above. The precipitate was boiled with water to remove any unchanged nitroindazole, and obtained in colourless, cubic prisms (alcohol), m. p. 221°; it sublimes in the same form; yield, 1 g. (Found: Br, 31·3. $C_7H_4O_2N_3Br$ requires Br, 33·0%).

N-*Methyl Derivatives of* 3-*Bromo*-5-*nitroindazole*.—The 5-nitromethylindazoles, prepared by the method of Fries (*loc. cit.*), were obtained as colourless needles when crystallised from light petroleum (b. p. 80—100°). From the isomer of m. p. 163°, 3-*bromo*-5-*nitro*-1-*methylindazole* was obtained as pale yellow needles (alcohol–acetic acid) or colourless needles (light petroleum, b. p. 80—100°), m. p. 225°; it sublimes in prisms (Found: Br, 30·6. $C_8H_6O_2N_3Br$ requires Br, 31·2%). From the other isomer, m. p. 129°, 3-*bromo*-5-*nitro*-2-*methylindazole* was obtained in yellow needles (alcohol) or pale yellow needles (light petroleum, b. p. 80—100°), m. p. 188°, subliming in cubic prisms (Found: Br, 30·2%).

Attempted Preparation of 5-*Nitro*-1-*methylindazole*.—2-Chloro-5-nitrobenzaldehyde (Erdmann, *Annalen*, 1893, **272**, 153) gave the 2 : 4-*dinitrophenylhydrazone* as orange prisms (tetralin) or needles (methyl alcohol), m. p. 280° (decomp.) (Found: N, 19·1. $C_{13}H_8O_6N_5Cl$ requires N, 19·1%). 2-*Chloro*-5-*nitrobenzaldehydemethylhydrazone* was prepared by heating the aldehyde (0·85 g.), methylhydrazine sulphate (0·7 g.), and crystalline sodium acetate (0·7 g.) in aqueous alcohol for 10 minutes. Water was added, and the precipitate crystallised first from aqueous methyl alcohol and then from light petroleum (b. p. 60—80°); yellow needles, m. p. 121—122°, subliming (Found: N, 20·2. $C_8H_8O_2N_3Cl$ requires N, 19·7%). All efforts to close the ring in this compound with potassium hydroxide were unsuccessful.

N-*Methyl Derivatives of* 6-*Nitroindazole*.—These were prepared from 6-nitroindazole by the method used for the 5-compound. Auwers and Schwegler (*loc. cit.*) obtained only one of the isomers in the pure state. We effected separation of the mixture by fractional crystallisation from methyl alcohol, 6-nitro-2-methylindazole separating from the hot solution in yellow prisms, m. p. 160° (lit. 159—160°). Addition of water to the filtrate gave the 6-nitro-1-methylindazole, which separated as colourless needles from light petroleum (b. p. 60—80°), m. p. 125° (lit., 105—108°) (Found: C, 54·5; H, 3·9. Calc. for $C_8H_7O_2N_3$: C, 54·3; H, 3·9%). The yield of the 2-methyl is three times that of the 1-methyl derivative.

N-*Methyl Derivatives of* 3-*Bromo*-6-*nitroindazole*.—These were prepared either by methylation of 3-bromo-6-nitroindazole (5·0 g.) or by bromination of the 6-nitromethylindazoles by methods given above. In the first case, the isomers were separated by ether. The insoluble isomer was crystallised three times from ethyl alcohol, yellow needles, m. p. 175°; yield 2·5 g. (50%) (Found: Br, 31·6. $C_8H_6O_2N_3Br$ requires Br, 31·2%). As the compound is identical with that obtained by the bromination of 6-nitro-2-methylindazole, it is 3-*bromo*-6-*nitro*-2-*methyl*-

indazole. The soluble 1-*methyl* isomer was crystallised several times from methyl alcohol, forming colourless, elongated prisms, m. p. 156°; it sublimed in compact prisms. Yield 0·7 g. (14%) (Found : Br, 31·5%).

Colour of Nitroindazole Derivatives.—Some of the nitroindazole derivatives are stated in the literature to be coloured (*e.g.*, Fries, *loc. cit.*). It was found, however, that when crystallised from light petroleum most of them were colourless, the exceptions being 3-bromo-5- and -6-nitro-2-methylindazole (both yellow).

We wish to thank several of the advanced students in the Department for preparing intermediates, the Carnegie Trust for the Universities of Scotland for a teaching fellowship to one of us (N. C.), and the Moray Fund for a grant.

UNIVERSITY OF EDINBURGH. [*Received, November 21st,* 1940.]