Methylation of Indazoles and Related Reactions

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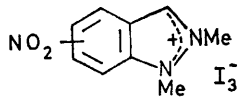
When methylated under neutral conditions, 4-, 6- and 7-nitroindazole gave the 2-methyl derivatives as the main products, whereas 5-nitroindazole formed mainly the 1-methyl derivative. On methylation under acidic conditions, 6-nitroindazole yielded only the 1-methyl derivative and 5-nitroindazole solely the 2-methyl derivative. 6-Hydroxyindazole was methylated to give 6-methoxyindazole and 6-hydroxy-2-methylindazole. 1,2-Dimethylindazoline was conveniently synthesised in high yield from 3-chloroindazole. Treatment of 6-nitroindazole with formalin in methanolic hydrochloric acid at 60° gave solely 1-methoxymethyl-6-nitroindazole.

THE literature on alkylation of indazoles is confusing and often contradictory.[1] Most of the work reported was done before the introduction of dipolar aprotic solvents and the extensive application of chromatography.

We decided to examine the potential as alkylating agents of alkyl halides in dimethyl sulphoxide and of alkyl toluene-*p*-sulphonates in nitrobenzene, initially for the methylation of mononitroindazoles. We expected that the results obtained for methylation would apply to alkylation with higher unbranched homologues, in accord with previous experience with alkyl 2,4-dinitrobenzene sulphonates [2] and recent findings [3] for the lower alkyl halides in dimethyl sulphoxide.

Mononitroindazoles reacted with methyl toluene-*p*-sulphonate in nitrobenzene at 90° and yielded the 2-methyl derivatives as the main products, except for



(I)

the case of 5-nitroindazole, which gave the 1-methyl derivative predominantly, as in the methylation by methyl iodide. In these reactions, starting material was isolated rather than quaternary periodides (Table).

Methylation of mononitroindazoles

Indazole	Products (%) MeI–Me_2SO, 70°	*p*-TsOMe–$PhNO_2$, 90°	CH_2N_2 in dioxan + BF_3, 18°	Cryst. from	M.p. (°C)	Lit m.p. (°C)
4-NO_2			1-Me (50)		140	136 [a,b]; 139 [d]
	2-Me (50)	2-Me (60)	2-Me (50)	MeOH	101	98 [a]; 81—82° [c]; 101—103° [b,d]
	Periodide (20)	S.m.* (20)		H_2O	187	
5-NO_2	1-Me (50)	1-Me† (60)			127	129 [e,f]
	2-Me (10)	2-Me† (10)	2-Me (50)	H_2O	163	163 [e]
	Periodide (17)	S.m.* (30)		MeOH	220	
6-NO_2	1-Me (10)		1-Me (75)	H_2O	125	125 [a,g]; 122 [i]
			1-Me (16)			108 [j]
			2-Me (8)	MeOH		116—118 [k]
	2-Me (50)	2-Me (50)	(In the absence of BF_3–Et_2O)	MeOH	160	160 [a,g,h]
	Periodide‡ (17)	S.m.* (25)		MeOH	170—172	
7-NO_2	2-Me (30)	2-Me† (40) S.m.* (50)		Et_2O	140	143 [i]

* Starting material. † $\nu_{max.}$ 3110—3100 (NH), 1570—1520, and 1390—1380 (NO_2) cm^{-1}. ‡ (Found: C, 19·1; H, 1·75; N, 7·3; I, 67·3. $C_9H_{10}N_3O_2I_3$ requires C, 18·85; H, 1·75; N, 7·35; I, 66·2%).

[a] I. M. Barclay, N. Campbell, and G. Dodds, *J. Chem. Soc.*, 1941, 113. [b] K. V. Auwers and E. Frese, *Ber.*, 1925, **58B**, 1369. [c] E. Noelting, *Ber.*, 1904, **37**, 2556. [d] R. Sureau, *Chimia (Switz.)*, 1961, **15**, 195. [e] K. Fries and H. Tampke, *Annalen*, 1927, **454**, 303. [f] H. R. Synder, C. B. Thompson, and R. L. Hinman, *J. Amer. Chem. Soc.*, 1952, **74**, 2009. [g] M. Kamel, M. A. Allam, F. I. A. Hay, and M. A. Osman, *J. prakt. Chem.*, 1966, **31**, 100. [h] G. Hahn and F. Just, *Ber.*, 1932, **65**, 717. [i] R. R. Davies, *J. Chem. Soc.*, 1955, 2412. [j] K. V. Auwers and K. Schwegler, *Ber.*, 1920, **53B**, 1211. [k] K. V. Auwers and W. Demuth, *Annalen*, 1927, **451**, 282.

Treatment of 4-, 5-, 6-, and 7-nitroindazole with methyl iodide in dimethyl sulphoxide at 70° gave the 2-methyl derivative as the main product in each case, except for that of 5-nitroindazole, which gave the 1-methyl derivative predominantly. Quaternary periodides (I) were also isolated in small amounts from these reactions (Table), formed by association of molecular iodine with the quaternary salts. Iodine was evolved when these periodides were boiled with methanol.

4-, 5-, and 6-Nitroindazole reacted with diazomethane in the presence of boron trifluoride–ether complex at 18°. 4-Nitroindazole gave equal amounts of the 1- and 2-methyl derivatives, 5-nitroindazole gave exclusively the 2-methyl derivative (50%) and 6-nitroindazole yielded the 1-methyl derivative (75%) (Table), in contrast to methylation under neutral conditions. This reaction probably involves an intermediate *N*-boron complex. A similar mechanism has been proposed for

[1] L. C. Behr, 'Chemistry of Heterocyclic Compounds,' ed. A. Weissberger, vol. 22, part 3, 1967, p. 310, gives a table of alkylation products with references.

[2] A. J. Nunn and J. T. Ralph, *J. Chem. Soc.* (*C*), 1966, 1568.

[3] H. Heaney and S. V. Ley, *J.C.S. Perkin I*, 1973, 499.

the *O*-methylation of alcohols by diazomethane in the presence of a Lewis acid.[4]

Isomers were separated on neutral alumina columns. The 1-methyl isomer was eluted first in each case. The same order of elution was observed when a known mixture of 1- and 2-methyl-6-nitroindazoles was subjected to g.l.c. on a 5% methylsilicone gum (E30) column. This behaviour reflects to some extent the relative polarity of the two isomers.

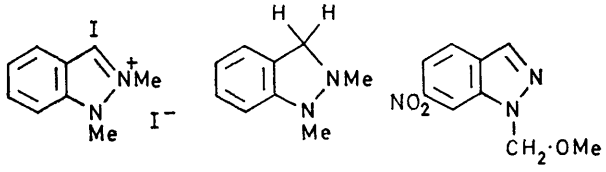
6-Hydroxyindazole reacted with methyl iodide in the presence of sodium methoxide at 65° to give 6-methoxyindazole (25%); likewise with dimethyl sulphate in the presence of aqueous potassium hydroxide at 45° it gave 6-methoxyindazole (40%).

Diazomethane reacted with 6-hydroxyindazole at room temperature, with and without boron trifluoride–ether, to yield 6-methoxyindazole (10%) and 6-hydroxy-2-methylindazole (70%) in each case. Treatment of 6-methoxyindazole and 6-hydroxy-2-methylindazole with diazomethane and yielded a yellowish oily residue in each case. These products, which showed identical i.r. spectra, appeared to be 6-methoxy-2-methylindazole, which was also obtained from the reactions with methyl iodide and with dimethyl sulphate. It is surprising that *N*-methylation takes place predominantly rather than *O*-methylation, especially in the absence of catalyst. Diazomethane in the presence of fluoroboric acid [4] or boron trifluoride–ether [5] has been used for *O*-methylation of alcohols. The formation of a methyldiazonium cation intermediate [4] in these reactions has been postulated.

6-Methoxyindazole was synthesised independently. Treatment of the *p*-nitrophenylhydrazone of anisaldehyde with polyphosphoric acid gave 6-methoxy-1-*p*-nitrophenylindazole. Addition of nitrobenzene to the reaction mixture increased the yield from 25% [6] to 54%. This compound was reduced to the amine, which was cleaved by chromic acid to yield 6-methoxyindazole.

1,2-Dimethylindazoline was synthesised by an unambiguous route from the readily available 3-chloroindazole. Treatment of the latter with methyl iodide in concentrated methanolic potassium hydroxide yielded a mixture of 1- and 2-methyl-3-chloroindazole, which was heated with methyl iodide at 100° to give 1,2-dimethyl-3-iodoindazolium iodide (II) (63%), nucleophilic displacement of chlorine having occurred. The iodide (II) was treated at room temperature with aqueous methanolic potassium hydroxide to give 1,2-dimethylindazolin-3-one, which was reduced by lithium aluminium hydride to 1,2-dimethylindazoline (III) (79%). König and Huisgen [7] have reported the formation of 1,2-dimethylindazoline in 67% yield by the action of phenyl-lithium on 1-(3-chlorobenzyl)-1,2-dimethylhydrazine.

6-Nitroindazole reacted with formalin at room temperature in the presence of 20% hydrochloric acid to yield 1-hydroxymethyl-6-nitroindazole.[8,9] However, with formalin in the presence of 20% hydrochloric acid and



(II) (III) (IV)

methanol at 60°, it yielded only 1-methoxymethyl-6-nitroindazole (IV); no 2-methyl isomer was formed. The formation of 1-methoxymethyl-6-nitroindazole (IV) might have taken place by acylation with a hemiacetal, formed from formalin and protonated methanol.

EXPERIMENTAL

Neutral alumina (Brockmann activity I; 240 mesh) was used for column chromatography. Chromatography columns were prepared in petroleum (b.p. 40—60°). Solvents were evaporated under vacuum with a rotary evaporator. Petroleum refers to the fraction of b.p. 40—60°.

Methylation of Mononitroindazoles.—(a) *By methyl iodide in dimethyl sulphoxide. General method.* The nitroindazole (1 g, 0·006 mol) and methyl iodide (2·82 g, 0·02 mol) in dimethyl sulphoxide (15 ml) were stirred for 5 h at 70°. The mixture was cooled and concentrated under reduced pressure. The residues were extracted with hot ether. The extracts were treated with crystals of sodium thiosulphate, dried (Na_2SO_4), and evaporated. Crystallization of the residue from methanol yielded the 2-methyl derivative. In the case of 6-nitroindazole, dilution of the mother liquor with water yielded 1-methyl-6-nitroindazole. M.p.s and yields of the products are given in the Table. The ether-insoluble residues were boiled with methanol and charcoal. Concentration of filtrates yielded quaternary periodides (Table).

1-*Methyl- and* 2-*methyl-*5-*nitroindazole.* In the case of 5-nitroindazole the ethereal solution was evaporated and the residue, dissolved in benzene, was chromatographed on alumina to separate the 1- and 2-methyl isomers [elution with benzene–ether (1 : 1) and methanol].

(b) *By methyl toluene-*p-*sulphonate. General method.* Methyl toluene-*p*-sulphonate (1·1 g, 0·006 mol) was added to a solution of the mononitroindazole (1 g, 0·006 mol) in nitrobenzene (30 ml). The mixture was stirred for 5 h at 90°, allowed to cool, and then filtered. The filtrate was chromatographed on alumina. Nitrobenzene was eluted first with petroleum. The isomeric products and unchanged starting materials were then eluted with benzene, or benzene–ether. M.p.s and yields are shown in Table.

The best conditions for the quantitative estimation of isomer ratios in a reaction mixture by g.l.c. involved use of a 5% E30 column (made by dispersion of methylsilicone gum on Chromosorb P) at 250°. When a known mixture of 1- and 2-methyl-6-nitroindazoles in nitrobenzene was treated in this way, nitrobenzene appeared first, followed by the 1- and 2-methyl isomers clearly separated.

[4] M. Caserio, J. D. Roberts, M. Neeman, and W. S. Johnson, *Tetrahedron*, 1959, **6**, 36.
[5] E. Muller and W. Rundel, *Angew. Chem.*, 1958, **70**, 105.
[6] E. B. Dennler and A. R. Frasca, *Tetrahedron*, 1966, **22**, 3131.
[7] H. König and R. Huisgen, *Chem. Ber.*, 1959, **92**, 429.
[8] F. T. Pozharskii, M. A. Kazanbieva, and B. A. Tertov, *J. Gen. Chem. (U.S.S.R.)*, 1964, **34**, 3409.
[9] J. Elguero, A. Fruchier and R. Jacquier, *Bull. Soc. chim. France*, 1969, 2064.

(c) *By diazomethane. General method.* Diazomethane (0·1 mol) in ether was added dropwise to a stirred solution of the nitroindazole (0·03 mol) in dioxan containing boron trifluoride–ether complex (1 ml). The mixture was stirred at room temperature for 6 h, the white inorganic residue was filtered off, then acetic acid (1 ml) was added to the filtrate. The solvent was removed under reduced pressure and the residue was taken up in methanol and chromatographed on alumina [elution with benzene, benzene–petroleum (1 : 1), or petroleum]. M.p.s and yields are given in the Table. Treatment of 6-nitroindazole with diazomethane in the absence of boron trifluoride–ether gave a mixture of 1- and 2-methyl-6-nitroindazole and 6-nitroindazole.

(d) *By methyl iodide and sodium methoxide.* 7-Nitroindazole (0·646 g, 0·003 mol) was added to sodium methoxide [from sodium (0·12 g)] in methanol (10 ml). Methyl iodide (1·04 g, 0·007 mol) was then added and the mixture was stirred at 60° for 4 h. After filtration and removal of the solvent under reduced pressure, the residue was taken up in benzene and chromatographed on alumina. The first fraction eluted with benzene–petroleum (1 : 1) gave 1-methyl-7-nitroindazole (100 mg, 14%) m.p. 102° (lit.,[10] 98°). The second band, eluted with ether, gave 2-methyl-7-nitroindazole (400 mg, 56%), m.p. 142° (lit.,[10] 143°). Indazole was methylated in a similar manner and the product was chromatographed on silica gel. Elution with petroleum eluate yielded unchanged indazole (500 mg, 50%). Elution with benzene then gave 2-methylindazole (110 mg, 10%) m.p. 50° (lit.,[11] 56°), and finally elution with benzene–ether (10 : 1) yielded 1-methylindazole (330 mg, 30%), m.p. 60° (lit.,[11] 60—61°).

Methylation of 6-Hydroxyindazole.—(a) *By methyl iodide and sodium methoxide.* Treatment as already described gave 6-methoxyindazole (25%), m.p. 123—124°.

(b) *By dimethyl sulphate and alkali.* 6-Hydroxyindazole (4 g, 0·027 mol) was dissolved in aqueous potassium hydroxide (2 g in 20 ml) and dimethyl sulphate (3·8 g, 0·03 mol) was added. The mixture was stirred for 3 h on a water-bath at 40—50°, then extracted with benzene and ether; the combined extract was dried ($MgSO_4$) and evaporated. The oily residue gave 6-methoxyindazole (1·77 g, 40%), m.p. 124° (from petroleum), mixed m.p. 124°, $\nu_{max.}$ (KBr) 3300 (NH) and 1630 cm^{-1}.

(c) *By diazomethane.* Diazomethane (1·3 g, *ca.* 0·03 mol) in ether was prepared from *N*-nitrosotoluene-*p*-sulphonamide. 6-Hydroxyindazole (4 g, 0·027 mol) was added and the mixture was stirred at room temperature overnight, and then for 1 h at 40°. The ether was evaporated off and the residue was extracted with benzene. The extract yielded 6-methoxyindazole (440 mg, 10%), m.p. 122—124°. The benzene-insoluble residue, recrystallised from boiling methanol, gave 6-hydroxy-2-methylindazole (3 g, 70%), m.p. 170° (lit.,[12] 167—169°) (Found: C, 64·25; H, 5·5; N, 18·55. Calc. for $C_8H_8N_2O$: C, 64·9; H, 5·45; N, 18·95%), $\nu_{max.}$ (KBr) 3100, 2780, 2660, and 1635 cm^{-1}.

In a parallel experiment, but with addition of boron trifluoride–ether (1 ml), identical yields were obtained.

Formation of 6-methoxy-2-methylindazole. Diazomethane (0·42 g, *ca.* 0·001 mol) in ether was added slowly to a solution of 6-methoxyindazole (0·148 g, 0·001 mol) in dioxan (10 ml) containing boron trifluoride–ether (1 drop). The mixture was stirred at room temperature for 24 h, filtered, and evaporated to yield 6-methoxy-2-methylindazole as an oily residue (38 mg, 25%) which was not purified; $\nu_{max.}$ (film) 3010, 2940, and 1630 cm^{-1}. In like manner, 6-hydroxy-2-methylindazole also yielded 6-methoxy-2-methylindazole (38 mg, 25%), with an identical i.r. spectrum.

6-Methoxyindazole.— 6-Methoxy-1-(*p*-nitrophenyl)indazole [6] (2·7 g, 0·01 mol) dissolved in acetic acid (36 ml) was reduced with tin(II) chloride and hydrochloric acid to yield 1-(p-*aminophenyl*)-6-*methoxyindazole* (1·3 g, 56·6%), m.p. 100° (from ether) (Found: C, 71·0; H, 5·4; N, 16·85. $C_{14}H_{13}N_3O$ requires C, 70·35; H, 5·5; N, 17·6%), $\nu_{max.}$ (KBr) 3420, 3340 (NH_2) 3230, and 1625 cm^{-1}. Oxidation of this material (1 g, 0·004 mol) with acidified dichromate then gave 6-methoxyindazole (16·6%), m.p. and mixed m.p. 124°.[13]

1,2-Dimethylindazoline.—(a) *3-Chloro-1- and 2-methylindazole.* 3-Chloroindazole (10 g, 0·06 mol) was dissolved in concentrated methanolic potassium hydroxide (20 ml) and methyl iodide (26 g, 0·18 mol) was added. The mixture was refluxed at 50° for 7 h and then stirred at room temperature overnight. The white inorganic residue was filtered off. The filtrate was concentrated under reduced pressure. The residue was treated with water and extracted with benzene. Evaporation of the extract yielded a mixture of 3-chloro-1- and 2-methylindazoles (6·54 g, 60%) as a yellowish oil, b.p. 68° at 3 mmHg, $\nu_{max.}$ (film) 3060, 2860, and 1620 cm^{-1}.

(b) *3-Iodo-1,2-dimethylindazolium iodide.* The mixture of 3-chloro-1- and 2-methylindazoles (3·3 g, 0·018 mol) was heated with methyl iodide (7·5 g, 0·05 mol) in a sealed tube at 100° for 7 h. The residue was boiled with methanol and charcoal and the product was filtered. The filtrate was concentrated under reduced pressure and the residue crystallised from methanol giving 3-iodo-1,2-dimethylindazolium iodide, m.p. 220° (lit.,[14] 220°).

(c) *1,2-Dimethylindazolin-3-one.* Potassium hydroxide (2·5 g, 0·04 mol) was dissolved in water (25 ml) and methanol (25 ml) and 3-iodo-1,2-dimethylindazolium iodide (4·22 g, 0·01 mol) was added. The suspension was stirred for 0·5 h at room temperature (until a clear solution had been obtained). Stirring was continued for 4 h then the solvent was evaporated off under reduced pressure. The residue was treated with water and extracted with ether. The extract was concentrated to give 1,2-dimethylindazolin-3-one (1·368 g, 90%), m.p. 60° (from petroleum) (lit.,[15] 66°), $\nu_{max.}$ (KBr) 2880, 1670, and 1620 cm^{-1}.

(d) *1,2-Dimethylindazoline.* Lithium aluminium hydride (4 g, 0·05 mol) was suspended in ether (50 ml) and 1,2-dimethylindazolin-3-one (7 g, 0·03 mol) in ether (100 ml) was added slowly; immediately a vigorous reaction took place. The mixture was then stirred at room temperature overnight. The complex was decomposed with water and extracted with ether. The extract was dried (Na_2SO_4) and evaporated, leaving 1,2-dimethylindazoline (5 g, 79·3%) as an oil, b.p. 48—50° at 3 mmHg (lit.,[7] 90—92° at 12 mmHg) (Found: C, 72·25; H, 8·4; N, 19·65. Calc. for $C_9H_{12}N_2$: C, 73·05; H, 8·15; N, 18·95%), $\nu_{max.}$ (film) 3050, 2860, 2780, and 1610 cm^{-1}.

1-Methoxymethyl-6-nitroindazole.—6-Nitroindazole (1·63 g,

[10] R. R. Davies, *J. Chem. Soc.*, 1955, 2412.
[11] K. V. Auwers and M. Düesberg, *Ber.*, 1920, **53B**, 1179.
[12] K. V. Auwers and W. Demuth, *Annalen*, 1927, **451**, 282.
[13] H. Tiefenthaler, W. Dörscheln, H. Göth, and H. Schmid, *Helv. Chim. Acta*, 1967, **50**, 2244.
[14] K. W. Auwers and A. Lohr, *J. prakt. Chem.*, 1924, **108**, 297.
[15] R. Sureau, G. Kremer, and V. Dupro, Fr.P., 1,297,123/1962.

0·01 mol) was dissolved in methanol (40 ml) and 20% hydrochloric acid (20 ml), and aqueous formalin (40%; 5 ml) was added. After 10 min a yellow precipitate started to appear, which disappeared on refluxing at 60° for 4 h. The solvent was then removed; crystallisation of the yellow residue from methanol gave *1-methoxymethyl-6-nitroindazole* (1·2 g, 58%), m.p. 124° (Found: C, 52·2; H, 4·5; N, 20·45. $C_9H_9N_3O_3$ requires C, 52·2; H, 4·4; N, 20·3%), $\nu_{max.}$ (KBr) 3105, 2840, 1595, and 1530 cm^{-1}, τ ($CDCl_3$) 6·64 (3H, CH_3) 4·14 (2H, $N{\cdot}CH_2$), 2·01 (1H, aromatic), 1·50 (1H, aromatic), and 1·81 (2H).

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