963. *Reactions of Lead Tetra-acetate. Part III.*[1] *The Synthesis of 3-Alkyl-1-arylindazoles*

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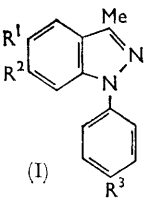
Further exploratory studies are reported of the synthesis of 3-alkyl-1-arylindazoles from ketone arylhydrazones by treatment with lead tetra-acetate followed by a Lewis acid. The variations of yields with conditions are described and discussed. Data for the nitration of some of the indazoles are reported.

We have previously described the synthesis of a number of 1-arylindazoles by the treatment of the arylhydrazones of aromatic ketones with lead tetra-acetate to give azo-compounds (azoacetates [2]), followed by cyclisation with a Lewis acid.[1] The intermediate azo-compound need not be isolated, and overall yields of the 1,3-diarylindazoles from the arylhydrazones ranged from 28 to 72%. We now report the results of further experiments designed to explore the scope and limitations of this procedure as a synthetic method for indazoles. Since our earlier study showed that the yield from acetophenone phenylhydrazone is lower than those generally obtained from the arylhydrazones of benzophenones, attention is here directed to methods for obtaining improved yields from acetophenone and its derivatives.

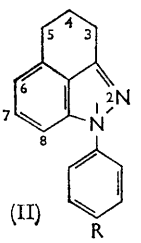
The azo-compounds have been prepared by mixing solutions of the arylhydrazone and lead tetra-acetate at 0—10°, either in methylene chloride,[2] or in benzene containing 10% of acetic acid to prevent the precipitation of lead compounds on to the suspended arylhydrazone.

Five procedures have been used for the conversion of the azo-compound into the indazole: (*A*) treatment with a considerable excess (>2 mol.) of aluminium trichloride suspended in benzene; (*B*) as for (*A*), but with an approximately equimolar amount of aluminium trichloride; (*C*) treatment with boron trifluoride–ether complex; (*D*) treatment of the arylhydrazone in methylene chloride with lead tetra-acetate, followed by boron trifluoride–ether complex; (*E*) treatment of the crude azo-compound in benzene with boron trifluoride–ether complex. The results are summarised in the Table, yields being based on the arylhydrazone.

Yields of indazoles from the arylhydrazones of acetophenones and related compounds



(I)



(II)

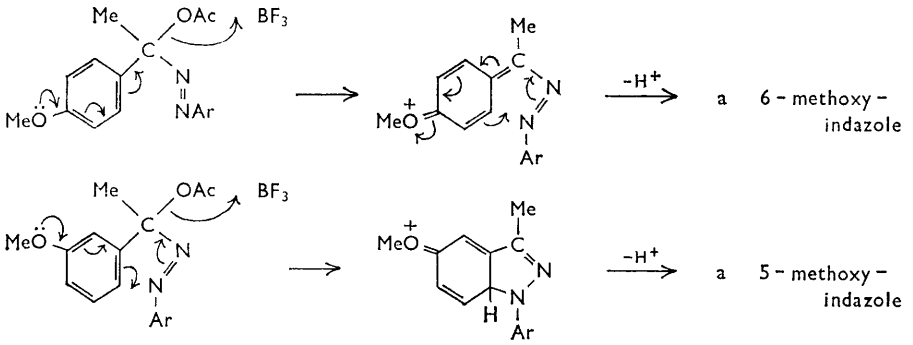
R^1	R^2	R^3	Method	Yield (%)
H	H	H	(*A*)	42
			(*C*)	11
			(*D*)	16
H	H	NO_2	(*A*)	31
			(*B*)	46
			(*C*)	0
			(*E*)	24
OMe	H	H	(*A*)	22
			(*D*)	58
OMe	H	NO_2	(*C*)	60
			(*D*)	66
			(*E*)	82
H	OMe	NO_2	(*A*)	10
			(*D*)	21
			(*E*)	84
	R			
	H		(*A*)	*ca.* 50
			(*D*)	0
	NO_2		(*A*)	14
			(*B*)	19
			(*D*)	0

[1] Part II, W. A. F. Gladstone and R. O. C. Norman, *J.*, 1965, 3048.
[2] D. C. Iffland, L. Salisbury, and W. R. Schafer, *J. Amer. Chem. Soc.*, 1961, **83**, 747.

The use of excess of aluminium trichloride gives relatively poor yields. These are improved somewhat by reducing the amount of Lewis acid {compare methods (*A*) and (*B*) for 3-methyl-1-*p*-nitrophenylindazole and 1,3,4,5-tetrahydro-1-*p*-nitrophenylbenz[*cd*]-indazole}, and a further study of the preparation of 1,3-diphenylindazole from benzophenone phenylhydrazone showed that the yield is increased from 49% using 4·8 mol. of aluminium trichloride [1] to 86% using 0·8 mol. Benzene appears to be the best solvent for ring-closure using the boron trifluoride–ether complex.

Further confirmation is provided that the azo-compound need not be isolated:[1] slightly higher yields were obtained by method (*D*) than method (*C*), where these were compared.

It is notable that method (*E*) gives much higher yields of the 5- and 6-methoxyl-substituted than of unsubstituted 3-methyl-1-*p*-nitrophenylindazole, and in the last case acetophenone *p*-nitrophenylhydrazone is formed as a by-product in 22% yield. The effect of the *m*-methoxyl group in the azo-compound in aiding ring-closure is in accord with our previous findings,[1] and the effect of *p*-methoxyl is suggestive of there being considerable carbonium-ion character in the transition state of the cyclisation, *p*-methoxyl facilitating reaction by enhancing the ease of departure of acetate ion, and *m*-methoxyl assisting formation of the C–N bond, as represented, respectively:



The by-products usually isolated when the indazole is formed in low yield are the arylhydrazone and the ketone, nitrogen being evolved. The dark alkali-extract of the cyclised product, which was observed in some instances when *p*-nitrophenylhydrazones were the starting materials, may indicate the formation of *p*-nitrophenol, which is known to resinify in alkali. The isolation of 1-*p*-nitrophenylazonaphthalene as a by-product of the reaction with α-tetralone *p*-nitrophenylhydrazone is suggestive of the occurrence of acid-catalysed β-elimination on the azoacetate, and the formation of a trace of *p*-nitrobiphenyl when cyclisation of this azoacetate was carried out in benzene is a strong indication of there being some homolytic decomposition (giving the *p*-nitrophenyl radical). It is apparent that azoacetates undergo various reactions which compete with cyclisation, and that in general the yield of the indazole is likely to be increased by incorporation of electron-donating substitutents in the aromatic ring of the original ketone.

Nitrations.—The only mononitro-product isolated from the nitration of 5-methoxy-3-methyl-1-phenylindazole (I; $R^1 = OMe$, $R^2 = R^3 = H$) was different from the indazole (I; $R^1 = OMe$, $R^2 = H$, $R^3 = NO_2$) derived from the cyclisation of *m*-methoxyacetopheone *p*-nitrophenylhydrazone. It is assigned as the 4-nitro-derivative on the basis of its proton magnetic resonance (p.m.r.) spectrum, which had an AB quartet (2H, $J = 9{\cdot}6$ c./sec.). Since 1,3-diphenylindazole is nitrated in the *para*-position of the 1-phenyl substituent,[1] it is evident that the course of nitration of the methoxyindazole is determined by the activating influence of methoxyl on the positions *ortho* to it, 4- predominating over 6-substitution just as β-methoxynaphthalene is more reactive towards electrophiles at the 1- than the

3-position. The nitroindazole (I; $R^1 = OMe$, $R^2 = H$, $R^3 = NO_2$) is also nitrated at the 4-position, the product being identical with that from the dinitration of (I; $R^1 = OMe$, $R^2 = R^3 = H$).

The nitration of 1,3,4,5-tetrahydro-1-phenylbenz[*cd*]indazole gave two mononitro-products. One was identical with the product (II; $R = NO_2$) of cyclising α-tetralone *p*-nitrophenylhydrazone. The other was identified as the 6-nitro-derivative of (II; $R = H$) on the basis of its p.m.r. spectrum; this had an AB quartet (2H, $J = 9$ c./sec.) and resonances due to methylene protons at τ 6·90 (3-position), 7·75 (4-position), and 6·52 (5-position); the last of these shows a considerable shift to lower field compared with the corresponding methylene group in (II; $R = H$), as expected by comparison with the resonances due to the methyl group in toluene and *o*- and *p*-nitrotoluene (τ 7·66, 7·47, and 7·57, respectively).[3]

Experimental

The materials used were as described previously.[1] P.m.r. spectra were measured in deuterochloroform on a Perkin-Elmer 60 Mc. spectrometer; A_2B_2 quartets due to *p*-nitrophenyl moieties were similar to those described for *p*-nitrotoluene and related compounds ($J_{AA} \sim J_{BB} \sim 2$ c./sec.; $J'_{AB} \sim 0$),[4] and τ values quoted for A_2B_2 and AB quartets refer to the centres of gravity of the A and B groups. Ultraviolet (u.v.) spectra were determined for solutions in ether unless stated otherwise. Chromatography was on alumina, Spence's type H.

Arylhydrazones were prepared by standard methods, and had the properties previously reported. m-*Methoxyacetophenone* p-*nitrophenylhydrazone* had m. p. 177—179° (from ethanol) (Found: C, 63·0; H, 5·3; N, 15·0. $C_{15}H_{15}N_3O_3$ requires C, 63·1; H, 5·3; N, 14·7%).

Azoacetates, where isolated, were prepared by the method of Iffland *et al.*,[2] except that the products were not distilled *in vacuo*. 1,2,3,4-*Tetrahydro*-1-p-*nitrophenylazo*-1-*naphthyl acetate*, from α-tetralone *p*-nitrophenylhydrazone in 87% yield, had m. p. 136—138° (from light petroleum) (Found: C, 63·05; H, 5·1; N, 12·0. $C_{18}H_{17}N_3O_4$ requires C, 63·7; H, 5·0; N, 12·4%). 1-p-*Nitrophenylazo*-1-*phenylethyl acetate* and 1-m-*anisyl*-1-p-*nitrophenylazoethyl acetate* were unstable orange oils (carbonyl stretch at 1750 $cm.^{-1}$ and no NH absorption).

3-*Methyl*-1-p-*nitrophenylindazole*.—(i) Boron trifluoride–ether complex (100 ml.) was added at −40° to 1-*p*-nitrophenylazo-1-phenylethyl acetate [prepared from acetophenone *p*-nitrophenylhydrazone (13 g.)]. After 10 min. at 100°, the cooled mixture was poured into water. The chloroform extract was chromatographed on alumina to give only acetophenone *p*-nitrophenylhydrazone (5 g.; 38%).

(ii) The crude azoacetate prepared as above was dissolved in benzene (300 ml.) and crushed aluminium trichloride (30 g., 4·3 mol.) was added. After heating under reflux for 1 hr. the cooled mixture was poured into water. The benzene layer and the chloroform extract of the aqueous layer were combined, and dried ($MgSO_4$); the solvents were distilled, and the residue was chromatographed on alumina. Elution with light petroleum–chloroform (2 : 3, v/v) gave 3-*methyl*-1-p-*nitrophenylindazole* (4 g.; 31%), m. p. 151—152°; $\lambda_{max.}$ 233, 257sh, 266sh, 284sh, 303, and 349 mμ (Found: C, 65·8; H, 4·4; N, 17·4. $C_{14}H_{11}N_3O_2$ requires C, 66·4; H, 4·4; N, 16·6%).

(iii) Lead tetra-acetate (16 g., 1·3 mol.) was added gradually to a suspension of acetophenone *p*-nitrophenylhydrazone (6·6 g.) in benzene (350 ml.) and acetic acid (50 ml.). After 2 hr. with occasional shaking, the mixture was poured into water (600 ml.), and hydrazine hydrate was added dropwise until the brown suspension of lead dioxide disappeared on shaking. The benzene layer was added to more water and a further small quantity of hydrazine hydrate was added. After being dried (K_2CO_3) the benzene solution was treated with aluminium trichloride (3·5 g., 1 mol.), and heated under reflux for 10 min. The cooled mixture was poured into dilute hydrochloric acid, and the dried benzene layer was distilled. Addition of a small quantity of ethanol to the residue precipitated 3-methyl-1-*p*-nitrophenylindazole (3·0 g.; 46%)

(iv) The azo-compound, prepared as in (iii) from acetophenone *p*-nitrophenylhydrazone (8 g.), was isolated in benzene (400 ml.). Boron trifluoride–ether complex (125 ml.) was added,

[3] L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, Oxford, 1959, p. 58.
[4] R. E. Richards and T. P. Schaefer, *Trans. Faraday Soc.*, 1958, **54**, 1280.

with stirring, and the solution was heated to boiling and poured, cold, into water. The benzene layer and the chloroform extract of the aqueous layer were combined, washed with dilute sodium hydroxide solution (dark extract), dried ($MgSO_4$), and distilled. Chromatography of the residue gave, with light petroleum–ether (6 : 1, v/v), 3-methyl-1-*p*-nitrophenylindazole (1·9 g.; 24%) and, with light petroleum–ether (1 : 1, v/v), acetophenone *p*-nitrophenylhydrazone (1·8 g.; 22%).

5-*Methoxy*-3-*methyl*-1-*phenylindazole*.—(i) Solutions of *m*-methoxyacetophenone phenylhydrazone (17 g.) in methylene chloride (100 ml.) and of lead tetra-acetate (43 g., 1·3 mol.) in methylene chloride (300 ml.) were mixed at 0°. After 2 hr. at room temperature, boron trifluoride–ether complex (100 ml.) was added, with stirring, and the solution stood overnight. After hydrolysis, the organic layer was washed with water and with dilute sodium hydroxide solution (dark extract), dried ($MgSO_4$), and distilled. The residue was filtered through alumina in light petroleum to give the indazole (10 g.) contaminated with a small amount of *m*-methoxyacetophenone (very weak absorption at 1695 $cm.^{-1}$). This material was heated on a water-bath for 10 min. with 2,4-dinitrophenylhydrazine (0·4 g.) in ethanolic hydrochloric acid (100 ml.). The filtrate was partitioned between water (400 ml.) and light petroleum–chloroform (4 : 1, v/v) (200 ml.). The organic layer was washed, dried ($MgSO_4$), diluted with light petroleum (200 ml.), and filtered through alumina. The filtrate was distilled, finally *in vacuo*, to give 5-*methoxy*-3-*methyl*-1-*phenylindazole*, b. p. 176—178°/0·7 mm.; $\lambda_{max.}$ 260 and 322 mμ (Found: C, 76·2; H, 6·25; N, 11·2. $C_{15}H_{14}N_2O$ requires C, 75·6; H, 5·9; N, 11·8%).

(ii) This indazole was also prepared in 22% yield as for 3-methyl-1-*p*-nitrophenylindazole, method (iii), except that 2·5 mol. aluminium trichloride was used.

5-*Methoxy*-3-*methyl*-1-p-*nitrophenylindazole*.—1-*m*-Anisyl-1-*p*-nitrophenylazoethyl acetate, from *m*-methoxyacetophenone *p*-nitrophenylhydrazone (29 g.), was treated with boron trifluoride–ether complex (100 ml.), causing a vigorous reaction. The yellow solid isolated after hydrolysis was washed with ethanol to give 5-*methoxy*-3-*methyl*-1-p-*nitrophenylindazole* (17 g., 60%), m. p. 186—187° from n-butanol (charcoal); $\lambda_{max.}$ 222, 239, 317, and 361 mμ (Found: C, 63·4; H, 4·6; N, 14·4. $C_{15}H_{13}N_3O_3$ requires C, 63·6; H, 4·6; N, 14·8%).

This indazole was also prepared in 66% yield by method (i) for 5-methoxy-3-methyl-1-phenylindazole and in 82% yield by method (iv) for 1-*p*-nitrophenyl-3-methylindazole.

6-*Methoxy*-3-*methyl*-1-p-*nitrophenylindazole*.—*p*-Methoxyacetophenone *p*-nitrophenylhydrazone (18·5 g.) was treated with lead tetra-acetate (35 g.) in benzene (1 l.) and acetic acid (100 ml.). A solution of the azoacetate in benzene was obtained [as in method (iii) for the preparation of 3-methyl-1-*p*-nitrophenylindazole]. Boron trifluoride–ether complex (200 ml.) was added, with stirring, and after 5 min. the solution was poured into water. The yellow solid was filtered off, and the benzene layer was washed with dilute sodium hydroxide solution (dark extract) dried ($MgSO_4$), and distilled. The residue, together with the yellow solid, was recrystallised from n-butanol (1 l.) to give 6-*methoxy*-3-*methyl*-1-p-*nitrophenylindazole* (15·5 g.; 84%), m. p. 213° from n-butanol (charcoal); $\lambda_{max.}$ 233, 281, and 348 mμ (Found: C, 63·3; H, 4·6; N, 14·5. $C_{15}H_{13}N_3O_3$ requires C, 63·6; H, 4·6; N, 14·8%).

This indazole was also prepared in 21% yield as for 5-methoxy-3-methyl-1-phenylindazole, method (i), and in 10% yield as for 3-methyl-1-*p*-nitrophenylindazole, method (iii), except that 2·5 mol. aluminium trichloride was used. In the former case, chromatography of the products also yielded *p*-methoxyacetophenone *p*-nitrophenylhydrazone (35%). In both cases alkali-soluble by-products were formed.

1,3,4,5-*Tetrahydro*-1-*phenylbenz*[cd]*indazole*.—Treatment of α-tetralone phenylhydrazone (14 g.) according to method (iii) for 3-methyl-1-*p*-nitrophenylindazole (3 mol. aluminium trichloride) gave a colourless oil (7·1 g.) which was boiled for 10 min. in ethanol (200 ml.) containing *p*-nitrophenylhydrazine (4 g.). The filtrate was partitioned between water and benzene, and the dried ($MgSO_4$) organic layer was filtered through alumina. Evaporation of the eluate gave a colourless oil exhibiting no carbonyl absorption.

The picrate (1·4 g.) of this material, from the oil (1·5 g.) and a saturated solution of picric acid (2 g.) in hot ethanol, decomposed on attempted recrystallisation. The original oil was recovered by treatment with ammonia and extraction into petroleum and was characterised as 1,3,4,5-*tetrahydro*-1-*phenylbenz*[cd]*indazole* as follows. Absorption maxima were at 246sh, 252, 267, and 309 mμ, the spectrum being almost identical with that of 3-methyl-1-phenylindazole. The p.m.r. spectrum had a multiplet (8H), *ca.* τ 2·7; triplets (each 2H), centred at τ 7·03, 7·17 (J = 6 c./sec.); and a quintet (2H), centred at τ 7·92 (J = 6 c./sec.). Nitration

(see below) gave two mononitro-derivatives, one of which was identical (m. p., mixed m. p., and infrared spectrum) with 1,3,4,5-tetrahydro-1-*p*-nitophenylbenz[*cd*]indazole.

When treated as in method (i) for 5-methoxy-3-methyl-1-phenylindazole, α-tetralone phenylhydrazone gave a black tar. Filtration in light petroleum through alumina gave a colourless eluate which darkened on distillation at 40°. The residue showed strong N–H absorption at 3320 cm.$^{-1}$, aromatic-NH absorption at 1135 and 1250 cm.$^{-1}$ (each as in the spectrum of α-tetralone phenylhydrazone), and carbonyl absorption at 1680 cm.$^{-1}$ (as in the spectrum of α-tetralone). α-Tetralone phenylhydrazone was found to darken similarly on being heated.

1,3,4,5-*Tetrahydro*-1-p-*nitrophenylbenz*[cd]*indazole*.—Treatment of 1,2,3,4-tetrahydro-1-*p*-nitrophenylazo-1-naphthyl acetate as in method (ii) for 3-methyl-1-*p*-nitrophenylindazole (2 mol. $AlCl_3$) gave 1,3,4,5-*tetrahydro*-1-p-*nitrophenylbenz*[cd]*indazole* (16%), m. p. 142—144° (from ethanol); $\lambda_{max.}$ 237, 259sh, 267sh, and 358 mμ; p.m.r. spectrum: A_2B_2 quartet (4H), τ 1·69, 2·07 (J_{AB} = 9 c./sec.), multiplet (3H), *ca.* τ 2·7, quartet (4H), centred at τ 6·97 (J = 6 c./sec.), quintet (2H), centred at τ 7·80 (J = 6 c./sec.) (Found: C, 68·6; H, 4·9; N, 14·8. $C_{16}H_{13}N_3O_2$ requires C, 68·8; H, 4·7; N, 15·0%).

This experiment was repeated using a smaller quantity of aluminium trichloride (1 mol.) and heating at 50° for 4 hr. Chromatography as above gave the indazole in 22% yield and 4-nitrobiphenyl (0·05 g.), identical (m. p. and mixed m. p.) with authentic material.

Treatment of α-tetralone *p*-nitrophenylhydrazone as in method (i) for 5-methoxy-3-methyl-1-phenylindazole gave a mixture of products. Chromatography on alumina gave, successively, α-p-*nitrophenylazonaphthalene* (2%), as a feathery red solid, m. p. 154—156° (from ethanol); $\lambda_{max.}$ 284, 297sh, and 400 mμ (p.m.r. spectrum: A_2B_2 quartet (4H), τ 1·62, 1·90 (J_{AB} = 9·6 c./sec.), multiplet (7H), *ca.* τ 2·0 (Found: C, 68·7; H, 4·0; N, 16·0. $C_{16}H_{11}N_3O_2$ requires C, 69·3; H, 4·0; N, 15·2%); and α-tetralone *p*-nitrophenylhydrazone (25%).

1,3-*Diphenylindazole*.—A solution of α-phenyl-α-phenylazobenzyl acetate [2] (5 g.) in benzene (150 ml.) containing suspended aluminium trichloride (2·5 g., 1·25 mol.) was heated under reflux for 10 min. and 1,3-diphenylindazole (3·0 g., 73%) was isolated as described previously.[1] The use of 0·8 mol. of aluminium trichloride increased the yield to 86%. 1-*p*-Nitrophenyl-3-phenylindazole [1] was obtained similarly in 95% yield, using 1·0 mol. aluminium trichloride.

Nitrations.—A solution of 5-methoxy-3-methyl-1-phenylindazole (3·5 g.) in acetic anhydride (30 ml.) was treated at 0° during 10 min. with fuming nitric acid (*d* 1·5; 0·63 ml.). After 1 hr. the mixture was poured into water and warmed, with shaking, to decompose acetic anhydride. The oily solid was treated with a little methanol to remove starting material, and chromatography of the resulting solid on alumina gave, (i), with light petroleum–chloroform (9 : 1, v/v), 5-*methoxy*-3-*methyl*-4-*nitro*-1-*phenylindazole* (1·5 g.), m. p. 108—109° (from methanol); p.m.r. spectrum: AB quartet (2H), τ 2·32, 2·84 (J = 9·6 c./sec.), multiplet (5H), τ *ca.* 2·6, singlets (each 3H), τ 6·1, 7·5 (Found: C, 63·7; H, 4·7; N, 14·7. $C_{15}H_{13}N_3O_3$ requires C, 63·6; H, 4·6; N, 14·8%); and (ii), with chloroform, 5-*methoxy*-3-*methyl*-4-*nitro*-1-p-*nitrophenylindazole* (0·2 g.), m. p. 264° (from chloroform) (Found: C, 54·6; H, 3·6; N, 17·1. $C_{15}H_{12}N_4O_5$ requires C, 54·9; H, 3·7; N, 17·1%).

A suspension of 5-methoxy-3-methyl-1-*p*-nitrophenylindazole (3·2 g.) in acetic anhydride (100 ml.) was treated dropwise at 0° (agitation) with fuming nitric acid (0·5 ml.). After a further 20 min. the mixture was poured with stirring into warm water. Chromatography of the resulting solid gave, with light petroleum–chloroform (9 : 1, v/v), starting material (2·0 g.), and, with chloroform, 5-methoxy-3-methyl-4-nitro-1-*p*-nitrophenylindazole (0·8 g.), identical (m. p. and mixed m. p.) with the compound prepared as above.

A solution of 1,3,4,5-tetrahydro-1-phenylbenz[*cd*]indazole (5·5 g.) in acetic anhydride (100 ml.) was treated at 0° with fuming nitric acid (1·0 ml.). After 30 min. the mixture was poured, with stirring, into warm water, and the viscous yellow oil was extracted into ether. The dried ($MgSO_4$) ethereal solution was distilled, and the residue was chromatographed on alumina. Elution with light petroleum–benzene in which the benzene concentration was gradually increased to 20% gave four fractions of 2 l. each. The solid from the first fraction gave, after three recrystallisations from ethanol, 1,3,4,5-*tetrahydro*-6-*nitro*-1-*phenylbenz*[cd]*indazole* (0·4 g.), m. p. 130—131°; $\lambda_{max.}$ (in methanol) 233, 268, 316, and 347 mμ; p.m.r. spectrum: AB quartet (2H), τ 1·80, 2·52 (J = 9 c./sec.), multiplet (5H), *ca.* τ 2·3, triplets (each 2H), centred at τ 6·52, 6·90 (J = 6 c./sec.), quintet (2H), centred at τ 7·75 (J = 6 c./sec.) (Found: C, 69·2; H, 5·0; N, 14·7. $C_{16}H_{13}N_3O_2$ requires C, 68·8; H, 4·7; N, 15·0%). The fourth fraction, treated

similarly, gave 1,3,4,5-tetrahydro-1-*p*-nitrophenylbenz[*cd*]indazole (0·5 g.), identical (m. p. and mixed m. p.) with the material prepared from α-tetralone *p*-nitrophenylhydrazone (above). The second and third fractions (0·8 g.) were mixtures of these mononitro-products.

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