560. *Reactions of Lead Tetra-acetate. Part II.*[1] *A New Synthesis of 1-Arylindazoles*

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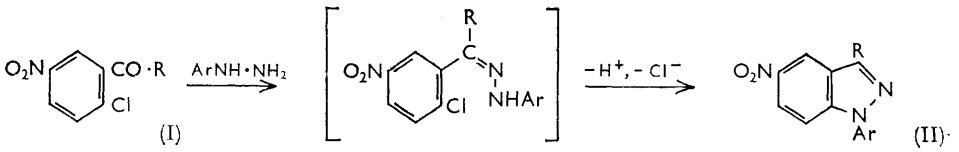
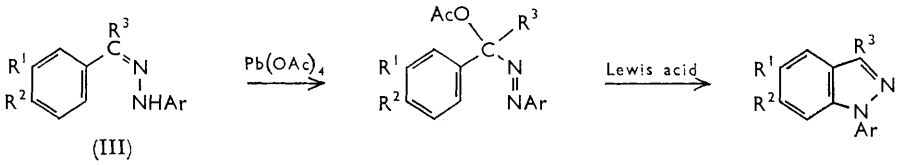
The arylhydrazones of six aromatic ketones have been converted by lead tetra-acetate into azoacetates which undergo cyclisation in the presence of a (Lewis) acid to 1-arylindazoles. The reactions provide a short and efficient method for obtaining this heterocyclic system.

The general methods for preparing indazoles are multi-stage processes.[2] For example, the trisubstituted ketone (I) and an arylhydrazine form the 1-arylindazole (II) with elimination of the chloro-substituent as chloride ion:



The nitro-group is necessary to activate the benzenoid ring to nucleophilic substitution and may then be removed *via* the amino- and diazonium-derivatives. Two obvious limitations to this method are that other nitro-substituents required in the indazole might also be removed, and the tetrasubstituted benzenes required to give indazoles substituted in the benzo-ring, other than in the 5-position, are difficult to obtain. The difficulty of obtaining the starting materials is also a limitation of other general methods of synthesis.

We now report a convenient two-step method for preparing 1-arylindazoles from the arylhydrazones of aromatic ketones. The hydrazone (III) is first treated with lead tetra-acetate in methylene chloride to give the azo-compound (IV), as previously described by Iffland *et al.*,[3] and cyclisation to the indazole (V) is then induced by a Lewis acid.



	R^1	R^2	R^3	Ar
(IV) a:	H	H	Ph	Ph
b:	H	H	Ph	*p*-NO_2·C_6H_4
c:	OMe	H	Ph	Ph
d:	H	NO_2	Ph	Ph
e:	NO_2	H	Ph	Ph
f:	H	H	Me	Ph

	R^1	R^2	R^3	Ar
(V) a:	H	H	Ph	Ph
b:	H	H	Ph	*p*-NO_2·C_6H_4
c:	OMe	H	Ph	Ph
d:	H	H	*p*-NO_2·C_6H_4	Ph
e:	H	H	*m*-NO_2·C_6H_4	Ph
f:	H	H	Me	Ph

The azo-compounds (which have been given the general name azoacetates [3]) have mostly been obtained in greater than 70% yield. Some are easily purified, but those from the phenylhydrazones of acetophenone and *p*-nitrobenzophenone are unstable and have been used, immediately after preparation, without purification.

The yield of the indazole from the azoacetate varies widely, depending on the structure of the azoacetate, the nature of the Lewis acid (boron trifluoride–ether complex and aluminium trichloride have been used), and the temperature of the reaction. We can, however, make certain general observations about the optimum conditions.

Mild conditions, namely, treatment with boron trifluoride–ether complex at room

[1] Part I, D. R. Harvey and R. O. C. Norman, *J.*, 1964, 4860.

[2] R. C. Elderfield in "Heterocyclic Compounds," ed. R. C. Elderfield, vol. 5, John Wiley and Sons, Inc., New York, 1957, p. 162.

[3] D. C. Iffland, L. Salisbury, and W. R. Schafer, *J. Amer. Chem. Soc.*, 1961, **83**, 747.

temperature, result in the conversion of the azoacetate (IVc), which contains the electron-releasing methoxyl group, into the indazole (Vc) in 90% yield. On the other hand, the nitro-substituted azoacetate (IVd) is unaffected in these conditions at room temperature or in 10 min. at 100°, but undergoes ring-closure (in 65% overall yield from the phenylhydrazone) when refluxed in boron trifluoride–ether complex. The latter conditions also lead to the indazoles (Va), (Vb), and (Ve) in 85, 95, and 40% yield from the respective azoacetates.

Boron trifluoride–ether complex is a more effective reagent than aluminium trichloride (suspended in refluxing benzene) for the azoacetate (IVa): the latter procedure gives 1,3-diphenylindazole in only 49% yield. On the other hand, the azoacetate (IVf) derived from acetophenone gives 1-phenyl-3-methylindazole (Vf) in 42% yield with aluminium trichloride but in only 11% yield with boron trifluoride. The low yield in the latter case results from side-reactions discussed subsequently.

Isolation and purification of the azoacetate are not essential. Preparation of the azoacetate (IVa) in methylene chloride followed by removal of the solvent and treatment of the residue with boron trifluoride–ether complex for 15 min. on the water-bath gives 1,3-diphenylindazole in 76% yield, which is approximately the same as the overall yield when the intermediate azoacetate is isolated. However, combination of the two stages is less satisfactory: addition of benzophenone phenylhydrazone to a solution of lead tetra-acetate and boron trifluoride–ether complex in methylene chloride, followed by heating at 40°, gives 1,3-diphenylindazole in 57% yield. The lower yield than that obtained by the two-stage process is possibly the result of oxidation of the indazole by lead tetra-acetate in the presence of boron trifluoride–ether complex: this is a very powerful oxidising system which gives cation-radicals with benzenoid compounds containing strongly electron-releasing groups,[4] and, consistently with this interpretation, 1,3-diphenylindazole gives an electron spin resonance spectrum when treated with lead tetra-acetate and boron trifluoride–ether complex in methylene chloride.

Concentrated sulphuric acid in place of a Lewis acid gives only 40% of 1,3-diphenylindazole from the azoacetate (IVa). Since indazoles are reactive towards electrophilic reagents (see, *e.g.*, below), a Lewis acid is the more suitable reagent.

Direction of Ring-closure.—Ring-closure of an azoacetate derived from an unsymmetrical diaryl ketone might occur in either aromatic nucleus. The azoacetate (IVc) gives 90% of (Vc) with boron trifluoride, no isomer being detectable, *i.e.*, ring-closure occurs preferentially, and essentially specifically, *para* to the methoxyl group. On the other hand, the azoacetates (IVe) and (IVd) do not undergo ring-closure into the nitro-substituted rings to give the known 5- (or 7-) and 6-nitro-1,3-diphenylindazoles, but give instead mononitro-1,3-diphenylindazoles which are evidently (Ve) and (Vd), respectively. These observations, together with the fact that the methoxy-compound (IVc) cyclises more readily than the nitro-compound (IVd), indicate that the reaction involves electrophilic attack on the benzene ring, probably *via* a cation formed on removal of the acetate group by the Lewis acid.

Nitration of 1,3-Diphenylindazole.—The only mononitro-derivative isolated after treatment of 1,3-diphenylindazole with fuming nitric acid in acetic anhydride was identical with the indazole (Vb) derived from benzophenone *p*-nitrophenylhydrazone. This not only provides structural confirmation for the product from the azoacetate (IVb) but also shows that the *para*-position of the 1-phenyl substituent in 1,3-diphenylindazole is the most reactive in nitrating conditions. Despite its participation in the π-system of the heterocyclic nucleus, the unshared electron-pair on $N_{(1)}$ is evidently available to delocalise the positive charge in the transition state of electrophilic substitution.

Experimental

Materials.—Lead tetra-acetate was the B.D.H. laboratory reagent, which was moist with acetic acid. Immediately before use, the reagent was filtered off under suction and washed

[4] D. L. Allara and R. O. C. Norman, unpublished observations.

with light petroleum. The resulting material was assumed to be 95% pure.[1] Boron trifluoride–ether complex (Hopkin and Williams) contained 40% boron trifluoride (w/w). Anhydrous aluminium trichloride (B.D.H.) was ground to a powder before use. Methylene chloride was dried over calcium chloride and benzene was dried over sodium. Alumina was Spence's type " H." Light petroleum used in recrystallisations had b. p. 60—80° and that for chromatography had b. p. 40—60°.

Arylhydrazones were prepared by standard methods and had the properties previously reported, except for *m*-nitrobenzophenone phenylhydrazone which had m. p. 119—122° (from ethanol containing a little ethyl acetate) (lit.,[5] 116°) (Found: C, 72·1; H, 4·8; N, 13·2. Calc. for $C_{19}H_{15}N_3O_2$: C, 71·9; H, 4·7; N, 13·2%). m-*Methoxybenzophenone phenylhydrazone* had m. p. 107—108° (from ethanol) (Found: C, 78·9; H, 6·2; N, 9·3. $C_{20}H_{18}N_2O$ requires C, 79·5; H, 6·0; N, 9·3%).

1,3-*Diphenyl-5-methoxyindazole.*—2-Chloro-5-nitrobenzophenone (67 g.), phenylhydrazine (29 g.), and methanol (150 ml.) were heated on a boiling water-bath for 2 hr. The mixture was then placed in a *large* flask and *very slowly* heated on an oil-bath. At about 150—160° a vigorous reaction began suddenly, with evolution of hydrogen chloride and a spontaneous rise of temperature to 190° (*care must be exercised in this reaction*). After being kept at 200° for 18 hr., the black residue was cooled and dissolved in boiling chloroform. Precipitation with ethanol (600 ml.) gave a dark green solid which was mixed with alumina and repeatedly extracted in a boiling mixture of light petroleum (2 l.) and chloroform (100 ml.). On cooling, the concentrated filtrate deposited 1,3-diphenyl-5-nitroindazole [6] as bright yellow crystals (38 g.; 46%), m. p. 178°. This material (34 g.) and palladium–charcoal (10%) (4 g.) were suspended in dimethylformamide (400 ml.) containing hydrazine hydrate (250 ml.). After 2 hr. at 100° volatile material was removed (100°/12 mm.) and the residue was diluted with ethanol (200 ml.). The filtrate was poured into brine (5 l.), the oily solid amine removed, and hydrochloric acid (20 ml.) added to precipitate the remaining amine as the hydrochloride. The combined solids were dissolved in warm acetic acid (1 l.) and water (200 ml.) was added. Sodium nitrite (10 g.) in water (50 ml.) was added during 20 min. at 5°, and the resulting solution, after reaching room temperature, was poured into a stirred solution of sodium fluoroborate (130 g.) in ice-cold water (3 l.). After 20 min. at 0°, the precipitate was washed with water, sucked dry, and triturated with chloroform containing a little ethanol. The solid was filtered, washed with chloroform until the washings were colourless, and dried in vacuo, giving 1,3-diphenylindazol-5-yldiazonium fluoroborate (30 g.) as bright yellow crystals.

The diazonium fluoroborate (2 g.) was heated in boiling methanol (150 ml.) for 2 hr. After distillation of the methanol, a solution of the residue in chloroform was washed with aqueous sodium carbonate and dried ($MgSO_4$). After removal of the solvent, addition of a little ethanol precipitated 1,3-diphenylindazole (0·8 g.; 51%), m. p. 100—101° (from light petroleum), identical (m. p., mixed m. p., and infrared spectrum) with authentic material; [6] $\lambda_{max.}$ (in ether), 244, 262, and 318 mμ.

A solution of the diazonium fluoroborate (11 g.) in acetic acid (125 ml.) and acetic anhydride (45 ml.) was refluxed for 18 hr. and poured into water while still warm. The ether extract was washed with aqueous sodium carbonate, dried ($MgSO_4$), and distilled, leaving a pale pink oil which could not be crystallised after chromatography (ester absorption at 1760 $cm.^{-1}$). A solution of this material in ethanol (200 ml.) containing sodium hydroxide (5 g.) was refluxed for 2 hr., the ethanol was distilled, and the residue was acidified with hydrochloric acid and extracted into chloroform. Removal of the chloroform left a brown, viscous oil which, after trituration with a little chloroform, gave 1,3-*diphenyl-5-hydroxyindazole* (1·8 g.; 22%), m. p. 199—200° (from chloroform containing a little light petroleum); $\lambda_{max.}$ (in ether), 225, 254, 275, and 338 mμ; whose *toluene*-p-*sulphonate* had m. p. 125—127° after chromatographic purification and recrystallisation from ethanol (Found: C, 70·5; H, 4·8; N, 5·9; S, 7·4. $C_{26}H_{20}N_2O_3S$ requires C, 70·9; H, 4·5; N, 6·4; S, 7·3%).

A mixture of 1,3-diphenyl-5-hydroxyindazole (1·7 g.), dimethyl sulphate (10 ml.), aqueous 2N-sodium hydroxide (25 ml.), and dioxan (20 ml.) was refluxed for 24 hr. After dilution with water, the chloroform extract was dried ($MgSO_4$) and distilled and the residue in light

[5] I. Heilbron and H. M. Bunbury, " Dictionary of Organic Compounds," Eyre and Spottiswoode, London, 1953, vol. III, p. 642.
[6] W. Borsche and W. Scriba, *Annalen*, 1939, **540**, 83.

petroleum–chloroform (9 : 1, v/v) was filtered through alumina to give 1,3-*diphenyl-5-methoxyindazole* (0·9 g.), m. p. 103—105° (from light petroleum); $\lambda_{max.}$ (in ether), 222, 254, 272, and 334 mμ (Found: C, 79·8; H, 5·45; N, 9·3. $C_{20}H_{16}N_2O$ requires C, 80·0; H, 5·3; N, 9·3%).

Azoacetates.—In cases where these were isolated, the method of Iffland *et al.*[3] was followed, except that the products were not distilled *in vacuo* but were filtered in solution through alumina. α-Phenyl-α-phenylazobenzyl acetate had m. p. 101—102° (from light petroleum containing a little chloroform) (lit.,[3] 101—103°). *α-Phenyl-α-p-nitrophenylazobenzyl acetate* (76%) had m. p. 133° (from light petroleum containing a little chloroform) (Found: C, 66·8; H, 4·6; N, 10·6. $C_{21}H_{17}N_3O_4$ requires C, 67·2; H, 4·5; N, 11·2%). *α-m-Nitrophenyl-α-phenylazobenzyl acetate* (70%) had m. p. 110—111° (from light petroleum containing a little chloroform) (Found: C, 67·0; H, 4·45; N, 10·9. $C_{21}H_{17}N_3O_4$ requires C, 67·2; H, 4·5; N, 11·2%). *α-m-Methoxyphenyl-α-phenylazobenzyl acetate* (72%) was a yellow oil (carbonyl stretch at 1745 cm.$^{-1}$) which was separated from other products by chromatography but not further purified. *α-p-Nitrophenyl-α-phenylazobenzyl acetate* and *1-phenyl-1-phenylazoethyl acetate* were unstable oils (ester absorption at 1755 and 1750 cm.$^{-1}$, respectively) which decomposed on attempted purification and were therefore used immediately after preparation.

Indazoles.—Method (*i*). Boron trifluoride–ether complex (150 ml.) was added slowly, with stirring, to a solution of *α-m*-methoxyphenyl-α-phenylazobenzyl acetate (30 g.) in ether (200 ml.) at −10°. After 2 hr. at room temperature the solution was poured into water and the ethereal extract was washed with aqueous sodium carbonate, dried ($MgSO_4$), and distilled, leaving *1,3-diphenyl-5-methoxyindazole* (23 g.; 90%), m. p. 104—106° (from light petroleum), identical (m. p., mixed m. p., and infrared spectrum) with the material prepared as above (Found: C, 79·8; H, 5·45; N, 9·3. Calc. for $C_{20}H_{16}N_2O$: C, 80·0; H, 5·3; N, 9·3%).

Method (*ii*). A solution of α-phenyl-α-*p*-nitrophenylazobenzyl acetate (20 g.) in boron trifluoride–ether complex (200 ml.) was refluxed for 1 hr., cooled, and poured into water. The solid which separated was filtered through alumina in light petroleum–chloroform (9 : 1, v/v) to give *1-p-nitrophenyl-3-phenylindazole* (16 g.; 95%), m. p. 161—162°; $\lambda_{max.}$ (in ether) 229, 249sh, 270sh, 319, and 353 mμ (Found: C, 72·1; H, 4·2; N, 13·3. $C_{19}H_{13}N_3O_2$ requires C, 72·4; H, 4·1; N, 13·3%).

When treated similarly, α-phenyl-α-phenylazobenzyl acetate gave 1,3-diphenylindazole (85%), identical (m. p., mixed m. p., and infrared spectrum) with the authentic material;[6] *α-m*-nitrophenyl-α-phenylazobenzyl acetate gave *1-phenyl-3-m-nitrophenylindazole* (40%), m. p. 143—144° (from light petroleum containing a little chloroform); $\lambda_{max.}$ (in ether), 246, 262, and 317 mμ (Found: C, 71·9; H, 4·2; N, 13·4. $C_{19}H_{13}N_3O_2$ requires C, 72·4; H, 4·1; N, 13·3%); and crude *α-p*-nitrophenyl-α-phenylazobenzyl acetate gave *1-phenyl-3-p-nitrophenylindazole* (65% from the phenylhydrazone), m. p. 148—150° (from ethanol); $\lambda_{max.}$ (in ether) at 249, 319sh, and 348 mμ (Found: C, 72·0; H, 4·2; N, 12·9. $C_{19}H_{13}N_3O_2$ requires C, 72·4; H, 4·1; N, 13·3%).

Method (*iii*). A solution of acetophenone phenylhydrazone (12 g.) in benzene (300 ml.) was added to lead tetra-acetate (26 g.) in benzene (300 ml.) at 5°. After 15 min. at room temperature, the mixture was heated to 40°, washed with water, aqueous sodium hydrogen sulphite, and aqueous sodium carbonate, and dried ($MgSO_4$). The dry solution was added to a suspension of aluminium trichloride (20 g.) in benzene (100 ml.). This mixture was refluxed for 1 hr., kept overnight, and poured into water. The benzene layer was washed, dried ($MgSO_4$), and concentrated to 50 ml. Filtration in light petroleum through alumina gave 1-phenyl-3-methylindazole (5·1 g.; 42·5%), m. p. 73° (from light petroleum) (lit.,[7] 73—74°) (Found: C, 81·0; H, 5·7; N, 13·5. Calc. for $C_{14}H_{12}N_2$: C, 80·8; H, 5·8; N, 13·5%).

Method (*iv*). A solution of benzophenone phenylhydrazone (13·5 g.) in methylene chloride (100 ml.) was added to lead tetra-acetate (22 g.) in methylene chloride (200 ml.) at 0—5°. After 10 min. the volume was halved by distillation, boron trifluoride–ether complex (100 ml.) was added, and the mixture was heated on the water-bath for 15 min. and poured into ice-cold water. Extraction and purification as in method (ii) gave 1,3-diphenylindazole (10·3 g.; 76%).

Method (*v*). A solution of benzophenone phenylhydrazone (14 g.) in methylene chloride (100 ml.) was added during 5 min. to methylene chloride (100 ml.) containing lead tetra-acetate (23 g.) and boron trifluoride–ether complex (250 ml.) cooled in ice. The blue solution was

[7] W. Borsche and W. Scriba, *Annalen*, 1939, **541**, 283.

allowed to warm to room temperature, and after 1 hr., when the colour had changed to purple, the mixture was heated to 40° and poured, with stirring, into water. The organic layer and the ether extract of the aqueous layer were combined, washed with aqueous sodium carbonate, and dried ($MgSO_4$). Purification as in method (ii) gave 1,3-diphenylindazole (8 g.; 57%).

Method (*vi*). Concentrated sulphuric acid (150 ml.) was added slowly to finely powdered α-phenyl-α-phenylazobenzyl acetate (6 g.). The temperature of the solution rose spontaneously to 50° and the colour changed from blue to purple. After being heated on the water-bath for 5 min. the solution was cooled and poured into water. Extraction and purification of the product as in method (ii) gave 1,3-diphenylindazole in 40% yield.

In addition, 1,3-diphenylindazole was obtained in 49% yield by method (iii); 1,3-diphenyl-5-methoxyindazole was obtained in 59 and 44% yields by methods (iv) and (v), respectively; 1-phenyl-3-methylindazole was obtained in 11 and 16% overall yields by methods (ii) and (iv), respectively, but could not be detected as a product of method (v).

Nitration of 1,3-*Diphenylindazole*.—Fuming nitric acid (2·05 ml.) was added during 15 min. to a solution of 1,3-diphenylindazole (11·9 g.) in acetic anhydride (40 ml.) at 0°. After 1 hr., addition of the solution to warm water, with shaking, gave a yellow solid which was separated into two components by chromatography on alumina. One component, after being chromatographed again, had m. p. 161—162° and was identical (mixed m. p. and infrared spectrum) with 1-*p*-nitrophenyl-3-phenylindazole (see above). The second, which sublimed with decomposition above 270° and could not be further purified, corresponded to a mixture of di- and tri-nitro-derivatives (Found: N, 16·5%).

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