Synthesis of 3-Alkyl-1-aryl-6,7-dihydro-6,6-dimethylindazol-4(5*H*)-ones, 2,3-Diaryl-4,5,6,7-tetrahydroindazoles, and Related Compounds

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1,2-Dimethyl-7a-hydroxy-4-oxo-1,4,5,6,7,7a-hexahydroindazole hydrochloride (I) was obtained in moderate yield from cyclohexane-1,3-dione, formaldehyde, and *NN'*-dimethylhydrazine. 3-Alkyl-1-aryl-6,7-dihydro-6,6-dimethylindazol-4(5*H*)-ones (VII) were prepared from 2-acyl-5,5-dimethylcyclohexane-1,3-diones and arylhydrazines. 2,3-Diaryl-4,5,6,7-tetrahydroindazoles (XI) resulted from the reaction of 3'-arylspiro[cyclohexane-2'-oxiran]-2-ones with arylhydrazines.

THE reaction of cyclohexane-1,3-dione with formaldehyde and *NN'*-dimethylhydrazine hydrochloride under aqueous conditions yielded a basic product, isolated as its hydrochloride, $C_9H_{14}N_2O_2$,HCl. The mass [M^+ (*m/e* 182), $M - 18$, $M - 32$, $M - 47$, and $M - 60$] and i.r. [$\nu_{max.}$ 3 530 (OH) and 1 680 and 1 650 cm^{-1} (C:C·C:O)] spectra suggested structure (I) or (II), either of which on electron impact could give an $M - 32$ intermediate (III) which would be expected[1] to breakdown in a retro-Diels–Alder manner to yield $C_6H_6N_2O$, *m/e* 122 (IV). The n.m.r. spectrum showed a singlet at τ *ca.* 1.4 (in CF_3·CO_2D or D_2O) corresponding to an olefinic proton at C-3. The slight shift downfield by comparison with the value for the corresponding proton in the hydrazo-compound (VI; $R^1 = R^2 = H$) and the related indazole (VII) may be due to further deshielding by the adjacent N^+. The OH singlet was superimposed on an *N*-methyl singlet at τ 5.84 and was not observed in

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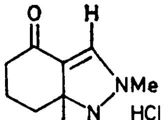
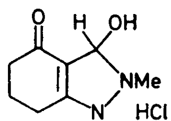
[1] H. E. Audier, J. Bottin, M. Fetizon, and J. C. Tabet, *Bull. Soc. chim. France*, 1971, **8**, 2911.

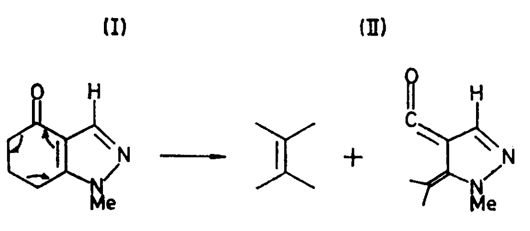
D_2O. Similarly, in $(CD_3)_2SO$ the OH signal was present as a broad peak overlapping the methyl singlets at τ 5.78 and 5.94. These data establish the structure (I).



(I)

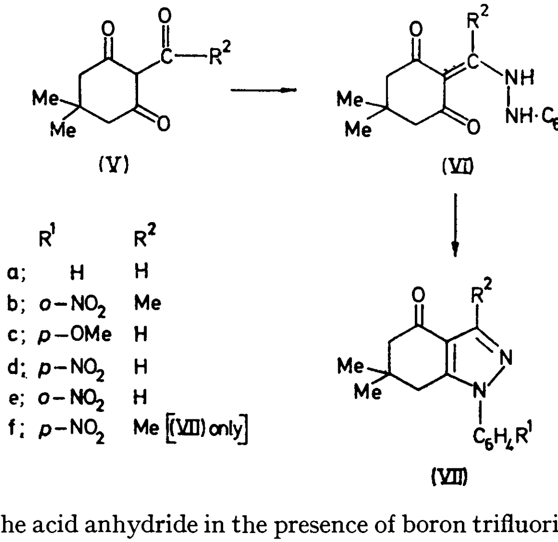


(II)

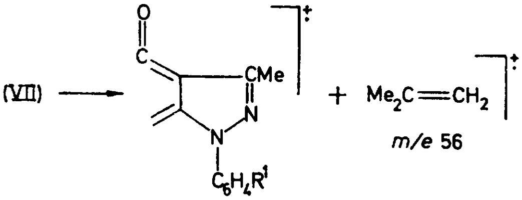


The foregoing reaction could not be adapted to the synthesis of other *N*-substituted indazoles; when non-aqueous solvents were used 3,4,5,6,7,9-hexahydro-2*H*-xanthen-1,8-dione was the main product.

The reaction of 1-α-chlorobenzylidene-2-phenylhydrazine with dimedone did not give the indazolone (VII; $R^1 = H$ $R^2 = Ph$) by dipolar addition, but instead afforded 1-benzoyl-2-(5,5-dimethyl-3-oxocyclohex-1-enyl)-1-phenylhydrazine in high yield. 6,7-Dihydroindazol-4(5*H*)-ones (VII) were however prepared by extension of the reported reaction between phenylhydrazine and 2-acetylcyclohexane-1,3-dione.[2] The 2-acyl-5,5-dimethylcyclohexane-1,3-diones (V) were obtained by the reaction of dimedone with a mixture of the appropriate anhydride and acid under reflux, with the acid anhydride in the presence of boron trifluoride gas at 0 °C. As reported previously,[3] a range of 3-alkyl-1-aryl-6,7-dihydroindazol-4(5*H*)-ones can be synthesised in this way. Subsequently it was found that the reaction between 2-formyl-5,5-dimethylcyclohexane-1,3-dione (V; $R^2 = H$) and arylhydrazines afforded the hydrazo-compound (VI; $R^2 = H$) and not the indazole. The n.m.r. spectrum showed three low-field one-proton signals at τ 3.00, 1.69 (d, *J* 10 Hz), and −2.00 (d, *J* 10 Hz). The signals at τ 3.00 and −2.00 disappeared in D_2O and the doublet at τ 1.69 collapsed to a singlet. This last signal is due to the olefinic proton and the low-field signal at τ −2.00 to the more deshielded NH proton. The involvement of the exocyclic carbonyl group in reaction with arylhydrazine is shown by the equivalence of the two pairs of α-methylene protons. Sucrow and his co-workers[4] prepared the indazole (VII; $R^1 = H$, $R^2 = Me$) by cyclisation of a characterised product obtained from dimedone and acetaldehyde phenylhydrazone, identical with that obtained from 2-acetyl-5,5-dimethylcyclohexane-1,3-dione (V; $R^2 = Me$) and phenylhydrazine,[3] which shows that the initial reaction occurred at the exocyclic carbonyl group and was followed by cyclisation, (V) → (VI) → (VII). The hydrazo-compound (VI; $R^1 = o\text{-}NO_2$, $R^2 = Me$) from 2-acetyl-5,5-dimethylcyclohexane-1,3-dione was also isolated. Treatment of these intermediates with polyphosphoric acid at 110—120 °C achieved the required cyclisation. The physical properties of the hydrazo-compounds (VI) and the corresponding 6,7-dihydroindazol-4(5*H*)-ones (VII) are summarised in Tables 1 and 2.* The mass spectra of these indazoles showed that they fragmented in a retro-Diels–Alder manner. The main fragmentation involved the loss of 56 mass units, with, for example, formation of an intense peak at *m/e* 243 in the case of the indazole (VII; $R^1 = p\text{-}NO_2$, $R^2 = Me$).



	R^1	R^2
a;	H	H
b;	o-NO_2	Me
c;	p-OMe	H
d;	p-NO_2	H
e;	o-NO_2	H
f;	p-NO_2	Me [(VIII) only]



The synthesis of tetrahydroindazoles with *o*-nitrophenyl substituents at N-1, N-2, or C-3 was of interest for the preparation of triazapentalenes.[5] Our attempted route to 1-methyl-3-(*o*-nitrophenyl)-6,7-dihydroindazol-4(5*H*)-one (IX) was the reaction of cyclohexane-1,3-dione and *o*-nitrobenzaldehyde *N*-methylhydrazone in benzene and acetic acid in the presence of air.[4] However the product isolated, in excellent yield, was the hydrazone (VIII). Cyclisation was not effected by refluxing in glacial acetic acid, nor with ethanolic hydrogen chloride, nor with polyphosphoric acid at 120—130 °C.

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* Tables 1—4 are available as Supplementary Publication No. SUP 21497 (5 pp.). For details of Supplementary Publications see Notice to Authors No. 7, *J.C.S. Perkin I*, 1974, Index issue.

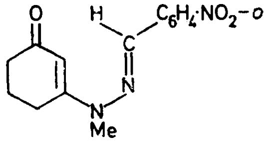
[2] (*a*) H. Smith, *J. Chem. Soc.*, 1953, 803; (*b*) I. A. Strakova, A. Strakov, A. Ya. M. Strautzele, and E. Gudriniece, *Latv. P.S.R. Zinat. Qkad., Vest. Khim. Serv.*, 1968, **5**, 597 (*Chem. Abs.*, 1969, **70**, 47,363f).

[3] A. J. Nunn and F. J. Rowell, *J.C.S. Perkin I*, 1973, 3391.

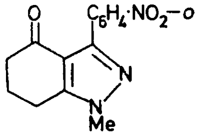
[4] W. Sucrow, M. Slopianka, and A. Neophytou, *Chem. Ber.*, 1972, **105**, 2143.

[5] A. J. Nunn and F. J. Rowell, *J.C.S. Perkin I*, 1975, 629.

4,5,6,7-Tetrahydro-2,3-diphenylindazoles (XI) were obtained by the reaction of phenylhydrazines with 2′-arylspiro[cyclohexane-2′-oxiran]-2-ones (X) compounds in 70—80% yields. The spiro-oxirams were

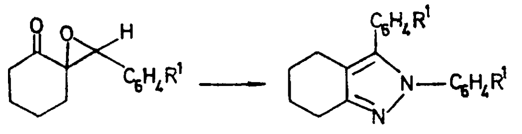


(VIII)



(IX)

prepared by the action of aqueous hydrogen peroxide on methanolic solutions of the corresponding olefins.[6] The physical properties of the epoxides and the corresponding indazoles are summarised in the Supplementary Publication (Tables 3 and 4). Neither *ortho*- nor *para*-methoxyphenyloxirans could be obtained by this method.

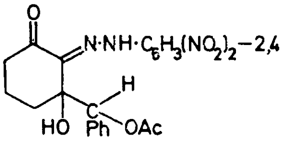


(X) (XI)

	R^1
a;	H
b;	o-Me
c;	p-Cl

	R^1	R^2
a;	H	H
b;	o-Me	o-NO_2
c;	p-Cl	o-NO_2
d;	H	o-NO_2

The reaction of (Xa) with 2,4-dinitrophenylhydrazine did not give the expected 2-(2,4-dinitrophenyl)-4,5,6,7-tetrahydro-3-phenylindazole. The product isolated in this case (XII) was identified by its i.r., n.m.r., and mass spectral data.



(XII)

EXPERIMENTAL

I.r. spectra were measured for potassium bromide discs and ^{1}H n.m.r. spectra for solutions in [^{2}H]chloroform unless otherwise stated (at 60 MHz, with tetramethylsilane as internal standard). Mass spectral determinations were performed by the Physico-Chemical Measurements Unit, Harwell. The alumina for column chromatography was neutral and of activity I. Petroleum had b.p. 60—80°.

1,2-*Dimethyl*-7a-*hydroxy*-4-*oxo*-1,4,5,6,7,7a-*hexahydroindazole Hydrochloride* (I).—To a solution of cyclohexane-1,3-dione (1.12 g) and *NN*′-dimethylhydrazine hydrochloride (176 mg) in water (20 ml) was added aqueous formaldehyde (40%; 1 ml). The solution was refluxed for 30 min, then cooled, and the precipitated hexahydroxanthen-1,8-dione (160 mg) removed. The filtrate was basified and extracted with ether. The extract was dried (K_2CO_3) and treated with ethereal hydrogen chloride; on cooling, white crystals of the *indazole* (I) slowly separated (611 mg, 36%); m.p. 187—187.5° (from methanol–ethyl acetate), $\nu_{max.}$ 3 530, 1 680, 1 650, 1 558, 1 445, 1 246, 1 141, 1 130, and 795 cm^{-1}; τ($CF_3{\cdot}CO_2H$) 1.4 (1 H, s), 5.70 (3 H, s), 5.84 (3.4 H, s), 6.82 (2 H, t), 7.12 (2 H, t), and 7.52 (2 H, m); τ (D_2O) 1.38 (1 H, s), 5.82 (3 H, s), 5.96 (3 H, s), 6.92 (2 H, t), 7.35 (2 H, t), and 7.72 (2 H, q); τ [$(CD_3)_2SO$] 0.88 (1 H, s), 5.78 (3.5 H, s), 5.94 (3.5 H, s), 6.92 (2 H, t), *ca*. 7.45 (overlapping solvent peak), and 7.82 (2 H, q) (Found: C, 49.5; H, 6.55; N, 12.6%; $M^+ - 32$, 150.0795. $C_9H_{14}N_2O_2$,HCl requires C, 49.45; H, 6.9; N, 12.8%. $C_8H_{10}N_2O$ requires *m/e*, 150.0793).

Attempted Preparation of the Indazole (VII; R^1 = H, R^2 = Ph).—1-α-Chlorobenzylidene-2-phenylhydrazine (230 mg) and dimedone (116 mg) in benzene (5 ml) were treated with triethylamine (0.5 ml). The solution was refluxed for 4 h, then shaken with aqueous sodium hydroxide (10%), dried (K_2CO_3), and evaporated to yield a white solid (283 mg, 91%). This was recrystallised from ethanol to yield 1-*benzoyl*-2-(5,5-*dimethyl*-3-*oxocyclohex*-1-*enyl*)-1-*phenylhydrazine*, mp 231—232°, $\nu_{max.}$ 3 200, 1 684, 1 600, 1 558, 1 409, 1 247, 700, and 690 cm^{-1}, τ −0.62 (1 H, s, disappears on shaking with D_2O), 2.28 (2 H, q), 2.68 (6 H, s), 2.76 (2 H, m), 4.50 (1 H, s), 7.80 (4 H, s), and 8.98 (6 H, s) (Found: C, 75.7; H, 6.4; N, 8.1%; M^+, 334.1681. $C_{21}H_{22}N_2O_2$ requires C, 76.3; H, 6.4; H, 8.1%; *M*, 334.1681).

1-*Aryl*-6,7-*dihydro*-6,6-*dimethylindazol*-4(5H)-*ones* (VII).—Equivalent quantities of 2-formyl-5,5-dimethylcyclohexane-1,3-dione and arylhydrazine were refluxed in absolute ethanol for 2 h. The solvent was removed under vacuum and the residue chromatographed on alumina in petroleum. Elution with petroleum–benzene (1 : 1 v/v) gave the hydrazo-intermediate (VI) (see Table 1), which was heated in polyphosphoric acid at 110—120 °C for 20 min. The solution was added to ice–water, and extracted with chloroform. This extract was dried (Na_2SO) and evaporated to yield the indazolone (VII). The reaction between *o*-nitrophenylhydrazine and 2-acetyl-5,5-dimethylcyclohexane-1,3-dione proceeded in a similar manner. The reaction with *p*-nitrophenylhydrazine gave the indazole directly without treatment with polyphosphoric acid. The properties of these compounds are summarised in Table 2.

Attempted Preparation of the 3-(o-*Nitrophenyl*)*indazole* (IX).—*o*-Nitrobenzaldehyde *N*-methylhydrazone (17.8 g) was refluxed in benzene (200 ml) and glacial acetic acid (6.0 ml) with cyclohexane-1,3-dione (11.2 g) for 4 h with passage of air through the solution. Cooling afforded yellow crystals of o-*nitrobenzaldehyde* N-(3-*oxocyclohex*-1-*enyl*)-N-*methylhydrazone* (VIII) (23.9 g, 81%), m.p. 172—173°, $\nu_{max.}$ 1 640, 1 578, 1 550, 1 527, 1 260, 1 094, and 755 cm^{-1}; τ 1.78 (1 H, s), 1.90 (2 H, m), 2.43 (2 H, m), 4.36 (1 H, s), 6.52 (3 H, s), 7.00 (2 H, t), 7.26 (2 H, t), and 7.92 (2 H, m) (Found: M^+, 273.1113. $C_{14}H_{15}N_3O_3$ requires *M*, 273.1113).

3′-*Arylspiro*[*cyclohexane*-2′-*oxiran*]-2-*ones* (X).—These were prepared by treatment of a mixture of the 2-benzylidene[7] (0.052 mol) and aqueous hydrogen peroxide (30%; 5 ml, 0.052 mol) in methanol (35 ml) with aqueous 6N-sodium hydroxide (2.5 ml, 0.015 mol). The mixture was stirred for 2 h at 15 °C then diluted with 2 volumes of cold

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[6] H. O. House and R. L. Wasson, *J. Amer. Chem. Soc.*, 1956, **78**, 4394.

[7] (*a*) W. S. Rapson and R. G. Shuttleworth, *J. Chem. Soc.*, 1940, 636; (*b*) J. Colonge and J. Sibend, *Bull. Soc. chim. France*, 1952, 786; (*c*) A. C. Huitric and W. D. Kumler, *J. Amer. Chem. Soc.*, 1956, **78**, 1147.

water; the *epoxide* separated and was filtered off (see Table 3).

4,5,6,7-*Tetrahydro*-2,3-*diphenylindazoles* (XI).—The spiro-oxiran (X) (0.005 mol) in absolute ethanol (50 ml) and glacial acetic acid (2 ml) was treated with *o*-nitrophenylhydrazine (0.005 mol). The solution was refluxed for 4 h and evaporated to dryness, and the residue was applied to a neutral alumina column. Gradient elution (0—50% v/v benzene–petroleum) gave the *diphenylindazoles* (XI) (Table 4).

Reaction of 3′-*Phenylspiro*[*cyclohexane*-2′-*oxiran*]-2-*one with* 2,4-*Dinitrophenylhydrazine*.—The oxiran (Xa) (1.86 g) and 2,4-dinitrophenylhydrazine (1.98 g) were refluxed in absolute ethanol (25 ml) and glacial acetic acid (2 ml) for 4 h. The solution was cooled and the yellow crystals, which separated afforded α-[2-(2,4-*dinitrophenylhydrazono*)-1-*hydroxy*-3-*oxocyclohexyl*]*benzyl acetate* (XII) (2.918 g, 80%), m.p. 256—257° (decomp.), $\nu_{max.}$ 3 450, 3 320, 1 720, 1 620, 1 590, 1 334, 1 258, and 1 249 cm^{-1}; τ ($CF_3{\cdot}CO_2H$) 1.55 (1 H, s), 2.06 (1 H, d), 2.48 (5 H, s), 2.63 (1 H, m), 3.35 (1 H, d), 5.92 (1 H, s), 7.25 (2 H, m), 7.50 (2 H, m), 7.68 (4 H, m), and 7.92 (3 H, s) (Found: C, 56.7; H, 5.1; N, 12.6%; M^+, 442. $C_{21}H_{22}N_4O_7$ requires: C, 57.0; H, 5.0; N, 12.7%; M, 442).

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