Semmler–Wolff Aromatisation and Abnormal Beckmann and Schmidt Reactions of 3-Alkyl-4-oxo-1-phenyl-4,5,6,7-tetrahydroindazoles and their Oximes in Polyphosphoric Acid

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(*E*)-3-Alkyl-4-hydroxyimino-1-phenyl-4.5.6.7-tetrahydroindazoles (XII) reacted in polyphosphoric acid to give mainly 3-alkyl-4-amino-1-phenylindazoles (XIII) and the abnormal Beckmann products. 3-alkyl-4-oxo-1-phenyl-1.4.5.6.7.8-hexahydropyrazolo[4.3-*c*]azepines (XIV). The use of deuteriated polyphosphoric acid showed that the azepine did not arise from ring expansion of an azirine formed from a nitrenium ion and moreover that no interaction occurred between the nitrenium ion and 3-alkyl substituents. 3-(*m*-Methoxyphenyl)-1.6.6-trimethyl-4-hydroxyimino-4.5.6.7-tetrahydroindazole (XX) gave. in addition to the corresponding 4-aminoindazole (XXI) and 4-oxo-lactam (XXII). a product (XXIII) arising by bond insertion into the nitrenium ion from the 3-(*m*-methoxyphenyl) group. The Schmidt reaction on 3-alkyl-6.6-dimethyl-4-oxo-1-phenyl-4.5.6.7-tetrahydroindazoles (XXIV) gave mainly the 4-oxo-lactam (XIV). plus some 5-oxo-lactam (XV). together with the corresponding amine formed on aromatisation (XIII). indicating that reaction proceeded through a different intermediate. Both 6.6-dimethyl-4-oxo-1-phenyl-4.5.6.7-tetrahydroindazole and its (*Z*)-oxime underwent normal Beckmann and normal Schmidt reactions to give the 4-oxo-lactam.

BECKMANN rearrangements with associated Semmler–Wolff aromatisation have been observed in αβ-unsaturated oximes.[1] On the basis of the reactions of the oximes of 1-tetralones, a mechanism has been proposed [2] for the Semmler–Wolff aromatisation. This mechanism accommodates the observations that 8-methyl-1-tetralone oximes (I) fail to undergo a Semmler–Wolff aromatisation in Beckmann's mixture,[3] giving only the lactam (II) resulting from phenyl migration, and also that 2-substituents reduce the yield of Semmler–Wolff product with a corresponding increase in the yield of the lactam (III) arising from alkyl migration.[4] Conley and Balling [2] proposed that isomerisation of the oxime is initially required to produce the (*Z*)-configuration. The mechanism (Scheme 1) further requires that the C–H bond α to the oxime and the hydroxyimino-group attain a *trans* and *anti*-parallel relationship. In this configuration the electrons of the α-C–H bond approach the developing nitrenium ion as the N–O bond synchronously dissociates with the formation of an intermediate azirine (V). Aromatisation to the 1-aminonaphthalene (IV) follows on protonation of the azirine nitrogen with subsequent ring opening to the imine and proton transfer. Thus when a methyl substituent is present at the C-8 position the initial isomerisation of the oxime is blocked and the

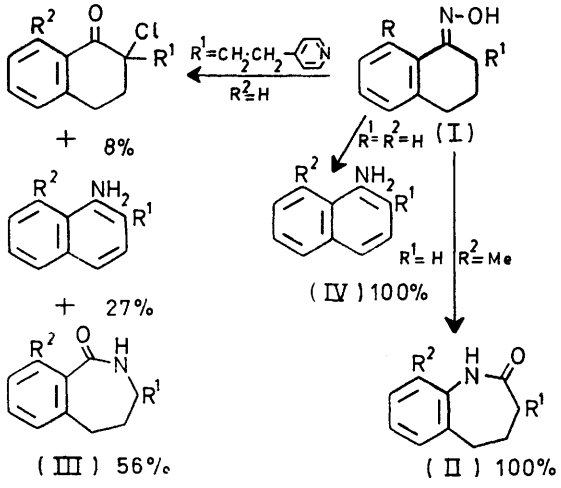
[1] R. T. Conley and S. Ghosh, 'Abnormal Beckmann Rearrangements,' in Mechanisms of Molecular Migrations, ed. B. S. Thyagarjan, vol. IV, Wiley-Interscience, New York and London, 1971, p. 197.

[2] R. T. Conley and P. J. Balling, Abstract 151st National Meeting Amer. Chem. Soc., Pittsburg, Pa., March 1966.

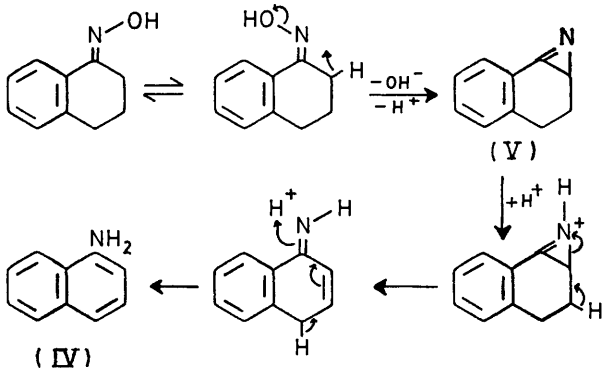
[3] G. Schroeter, A. Gluschke, G. Gotzky, J. Huang, G. Irmisch, E. Laves, D. Schrader, and G. Stier, *Ber.*, 1930, **63**, 1308.

[4] L. Bauer and R. E. Hewitson, *J. Org. Chem.*, 1962, **27**, 3982.

lactam (II) is formed by rearrangement of the (*E*)-isomer. With a bulky substituent at C-2, the attainment of the *trans* and *anti*-parallel disposition of the



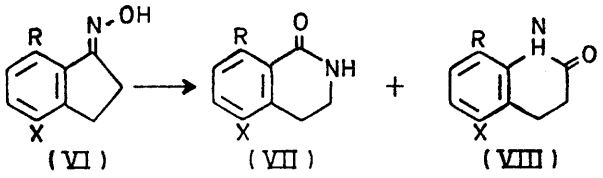
C(2)–H bond to the hydroxyimino-group is hindered as the bulky substituent tends to assume the more stable equatorial configuration, thereby slowing the aromatisation relative to the alkyl migration. The reactions of 2-substituted and unsubstituted 1-tetralones in polyphosphoric acid, however, generally give little or no aromatised product or lactam derived from alkyl migration. Instead, the major product is the lactam



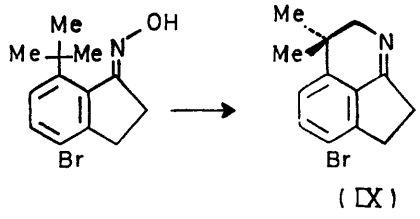
SCHEME 1

(II).[2] For example, the 1-tetralone oxime (I; R^1 = 4-C_5H_4N·CH_2CH_2, R^2 = H) gives the single lactam (II; R^1 = 4-C_5H_4N·CH_2CH_2, R^2 = H) in 72% yield.[4] Thus the oxime appears to assume the (*E*)-configuration in polyphosphoric acid, and gives ring expansion by phenyl migration.

The less flexible 7-alkyl-1-indanone oxime system (VI) reacted in an anomalous manner in polyphosphoric acid [5,6] to that predicted by the foregoing mechanisms. In this case increasing the size of the 7-alkyl substituent progressively increased the proportion of lactam (VII) arising from alkyl migration, compared to that arising from the phenyl migration (VIII). Thus when R = H, the lactam mixture consisted of 10% (VII) and 90% (VIII) whereas when R = t-butyl the relative yields were reversed. Thus it appeared that the lactam (VII)



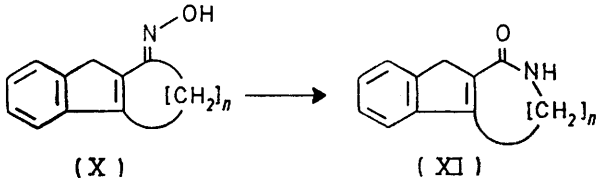
was not arising from the hindered (*Z*)-oxime in the normal concerted Beckmann fashion, but arising from an intermediate nitrenium ion formed by fission of the hydroxyimino N–O bond in the (*E*)-oxime. This was further demonstrated by the isolation of products [*e.g.* (IX)] formed by C–H bond insertion from the 7-alkyl



group onto the nitrenium ion. The intermediate formation of a nitrenium ion has also been proposed to explain the exclusive formation of the lactams (XI) by alkyl migration in the oximes of 3,8-dihydrocyclopent[*a*]inden-1(2*H*)-one (X; $n = 2$) and 3,4-dihydrofluorene-1(2*H*)-one (X; $n = 3$) in polyphosphoric acid.[7]

In our work, the reaction of 3-alkyl-4-oxo-1-phenyl-4,5,6,7-tetrahydroindazole oximes in polyphosphoric acid gave lactams arising from alkyl migration, but due to the greater flexibility of the system, also gave 3-alkyl-4-amino-1-phenylindazoles (XIII) from the Semmler–Wolff aromatisation.

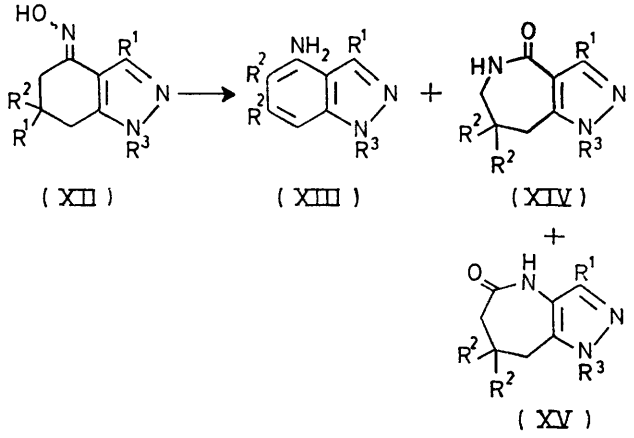
The absolute configurations of the oximes were determined from the ^{1}H n.m.r. spectra of the oximes and their parent ketones.[8] For compound (XIId) the (*Z*)-isomer



was isolated, whereas for compounds (XIIa—c) the major oximes isolated were the (*E*)-isomers. The products obtained on heating these oximes in polyphosphoric acid at 120—130° for 60 min are summarised in Table 1.

[5] P. T. Lansbury, J. G. Colson, and N. R. Mancuso, *J. Amer. Chem. Soc.*, 1964, **86**, 5225.
[6] P. T. Lansbury and N. R. Mancuso, *J. Amer. Chem. Soc.*, 1966, **88**, 1205.
[7] R. M. Pinder, *J. Chem. Soc.* (*C*), 1969, 1690.
[8] G. Slomp and W. J. Wechter, *Chem. and Ind.*, 1962. 41; C. W. Shoppee, M. I. Akhtar, and R. F. Lack, *J. Chem. Soc.*, 1964, 3392.

It can be seen that alkyl migration to give 3-alkyl-4-oxo-1-phenyl-1,4,5,6,7,8-hexahydropyrazolo[4,3-*c*]-azepine (XIV) was the major mode of rearrangement since only traces of 3-alkyl-5-oxo-1-phenyl-1,4,5,6,7,8-hexahydropyrazolo[4,3-*b*]azepine (XV) were detected.



(XII) (XIII) (XIV)

(XV)

a; R^1 = Me, R^2 = H, R^3 = Ph
b; R^1 = R^2 = Me, R^3 = Ph
c; R^1 = Pr^i, R^2 = Me, R^3 = Ph
d; R^1 = H, R^2 = Me, R^3 = Ph
e; R^1 = R^2 = Me, R^3 = *p*-$MeOC_6H_4$
f; R^1 = *m*-$MeOC_6H_4$, R^3 = Me

TABLE 1

Rearrangement products of oximes (XII) on heating in polyphosphoric acid

	Oxime	(XIII)(%)	(XIV)(%)	(XV)
(XIIa)	*E*	66	34	*
(XIIb)	*E*	65	35	*
(XIIc)	*E*	80	20	*
(XIId)	*Z*	Trace	100	*

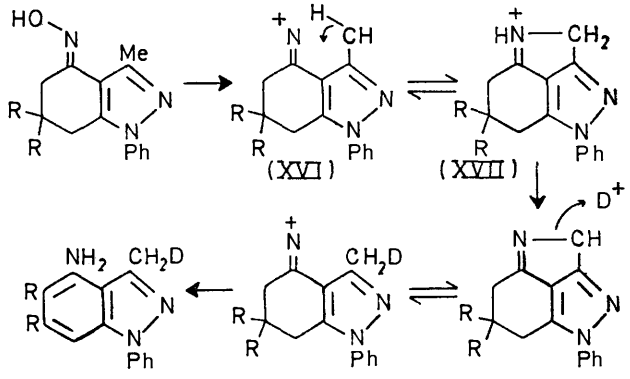
* Trace present (from t.l.c.).

Also, exclusive methyl migration from C-6 to C-5 was observed during the aromatisation for compounds (XIIb) and (XIIc). This was unambiguously demonstrated in the case of 1-(*p*-methoxyphenyl)-3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydroindazole oxime (XIIe); the amine product (XIIIe) was deaminated and gave an indazole showing a distinct two-proton singlet in its n.m.r. spectrum between the A_2B_2 quartet of the *p*-methoxyphenyl protons, consistent with the *para*-disposition of the indazole protons at C-4 and C-7 with $J_{4,7}$ 0 Hz.

It should be noted that the (*Z*)-oxime (XIId) underwent a clean Beckmann rearrangement predominantly with alkyl migration to give the 4-oxo-lactam (XIVd). Also, an increase in the size of the 3-alkyl substituent from methyl to isopropyl resulted in an increase in the yield of aromatised product. This is not expected if the aromatisation proceeds with prior isomerisation of the oximes to the (*Z*)-isomer since an increase in 3-alkyl size should hinder formation of the (*Z*)-oxime and result in a decrease in the yield of the aromatised product with a corresponding increase in the yield of lactam derived from phenyl migration. The reaction appears to parallel those of the 7-alkylindan-1-one oxime (X; $n = 2$), and (X; $n = 3$) oxime systems in proceeding *via* fission of the N–O bond of the (*E*)-oxime with formation of the nitrenium ion, followed by either alkyl migration to the 4-oxo-lactam (XIV) or, in this more flexible system, formation of an azirine intermediate [*e.g.* (XVIII)] when the nitrenium ion and the α-C–H bond attain coplanarity. The azirine then aromatises in the usual way.

Comparison of molecular models of 1-tetralone oxime (I), 7-methylindan-1-one oxime (VI), and 1-phenyl-3-methyl-4-oxo-4,5,6,7-tetrahydroindazole oxime (XII), demonstrates that the distances between the (*Z*)-oxime oxygen atom and the 3-methyl group in compound (XII) and the 7-methyl group in compound (VI) are approximately equal and that the corresponding distance between the (*Z*)-oxime oxygen and the hydrogen at C-8 in the tetralone oxime (I) is much larger, thus making isomerisation in the 1-tetralone oxime molecule less sterically hindered.

Owing to the apparent formation of an intermediate nitrenium ion in the 3-alkyl-4-oxotetrahydroindazole system described, the reactions of the oximes (XIIa) and (XIIb) were performed in deuteriated polyphosphoric acid. It was anticipated that interaction between the nitrenium ion (XVI) and the 3-methyl group could lead to insertion of a C–H methyl bond with the formation of a tricyclic pyrrolium ion (XVII) (Scheme 2). A similar intermediate has has been observed in the reaction of 4,7-dimethylindan-1-one oxime.[6] Ring opening of the strained intermediate in deuteriated polyphosphoric acid could result in incorporation of deuterium into the 3-methyl group (Scheme 2). No such incorporation was observed.



(XVI) (XVII)

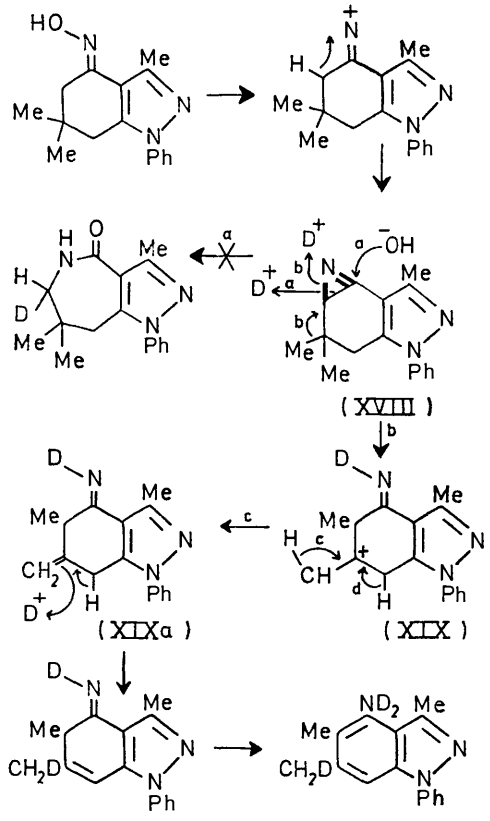
SCHEME 2

The amine from compound (XIIa) had deuterium at C-5 and C-7 due to subsequent exchange of the protons at these carbon atoms once the amine had been formed. This was demonstrated by the fact that this deuterium was re-exchanged when the amine (XIIIa) was reheated in ' normal ' polyphosphoric acid. The amine now gave an n.m.r. spectrum in which the aromatic proton multiplet at τ 2·70 showed seven protons and the C-5 aromatic proton at τ 3·72 integrated for one proton and showed the normal split doublet ($J_{5,6}$ 7·5, $J_{5,7}$ 3·0 Hz), whereas

the deuteriated amine showed six protons at τ 2·70 and 0·25—0·72 protons at τ 3·78 which appeared as a simple doublet with $J_{5.6}$ 7·5 Hz and $J_{5.7}$ absent.

The amine from compound (XIIb) showed dueterium incorporation (*ca.* 10%) at the C-6 methyl group. This was inferred from the n.m.r. spectra of the 4-amino-indazole (XIIIb) and its deamination product, 3,5,6-trimethyl-1-phenylindazole. A downfield shift (0·3 p.p.m.) of the amine methyl singlet at τ 7·92 was observed while the methyl singlet at τ 7·65 (which carried the deuterium) showed a downfield shift of only 0·03 p.p.m. on deamination. Thus the deuteriated methyl group was β to the amino-group.

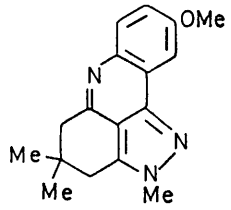
The deuterium at the C-6 methyl group possibly arises from an intermediate in the Semmler–Wolff aromatisation which carries a carbonium ion site at C-6 [*e.g.* (XIX)], as would be formed after the migration of a methyl group from C-6 to C-5. Elimination of a proton onto the carbonium ion site can occur from the C-6 methyl group (route c, Scheme 3) or from one of the methylene protons at C-7 (route d). Subsequent loss of a C-7 methylene proton from the *exo*-eliminated product (XIXa) would result in deuterium incorporation at the C-6 methyl group (Scheme 3).



SCHEME 3

The 4-oxo-lactams (XIV) from both oximes showed less than 0·2% deuterium content. Thus they appear to originate directly from the nitrenium ion intermediate (XVI) and not by ring expansion of the azirine (XVIII) since this would have given lactams monodeuteriated at C-6. The results of the reactions in deuteriated polyphosphoric acid are summarised in Table 6.

Since no deuteriation was observed at the 3-methyl groups and also since no product attributable to bond



(XX)

insertion onto the nitrenium ion or by hydride abstrac tion by the nitrenium ion were observed,[6] it may be concluded that no reaction between the 3-alkyl substituents and the nitrenium ion took place. This reflects the greater flexibility of the 3-alkyl-4-oxo-1-phenyl-4,5,6,7-tetrahydroindazole system and the lower energy required for azirine formation, thereby giving the observed aromatisation.

The reaction of 4-hydroxyimino-1,6,6-trimethyl-3-(*m*-methoxyphenyl)-4,5,6,7-tetrahydroindazole (XIIf) in polyphosphoric acid was also investigated. The major product was the amine (XIIIf) (81%) plus the 4-oxo-lactam (XIVf) (7%). A compound isolated in 2% yield was assigned the structure (XX) from its n.m.r. spectrum, which showed three aromatic protons, from its i.r. spectrum, and from mass spectral data. This compound clearly arises by bond insertion into the nitrenium ion intermediate from the adjacent *m*-methoxyphenyl substituent in a similar fashion to that observed for the formation of (IX) in the 7-t-butylindan-1-one oxime system.

The Schmidt reactions on the 3-alkyl-4-oxo-1-phenyl-4,5,6,7-tetrahydroindazoles (XXI) in polyphosphoric acid at 50—60° were also examined. The results are shown in Table 2. For compounds (XXIb and c) the

TABLE 2

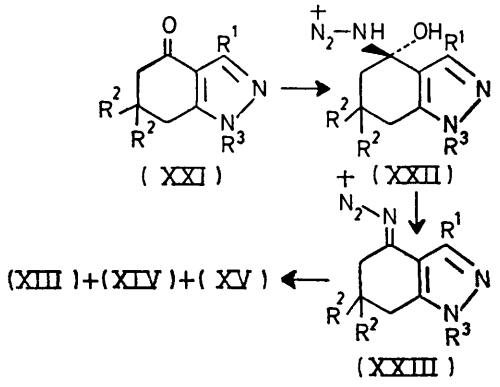
Products obtained by the Schmidt reaction on (XXI)

	(XIII)(%) [a]	(XIV)(%) [b]	(XV)(%) [b]
(XXIb)	18	74	26
(XXIc)	17	80	20
(XXId)	Trace [c]	*ca.* 100	Trace [c]

[a] Percentage of total product (from n.m.r.). [b] Percentage based on lactams only (from n.m.r.). [c] Not detectable by n.m.r. but indicated by t.l.c. (alumina; chloroform).

yields of amine (XIII) are considerably reduced while the yields of the 5-oxo-lactams (XV) are increased compared with the yields from the reactions of the corresponding oximes. These results parallel those observed for the Schmidt reactions on the 7-alkylindan-1-one system in which it was proposed that the ring expansion to the lactam possibly proceeds through the α-azidohydrin

intermediate (XXII) rather than the more sterically hindered azide (XXIII).[6]



b; $R^1 = R^2 = Me$, $R^3 = Ph$
c; $R^1 = Pr^i$, $R^2 = Me$, $R^3 = Ph$
d; $R^1 = H$, $R^2 = Me$, $R^3 = Ph$

EXPERIMENTAL

I.r. spectra were measured for potassium bromide discs. ^1H N.m.r. spectra were performed in [^2H]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 1. Petroleum had b.p. 60—80°.

2-Acetylcyclohexane-1,3-dione.—This was prepared by refluxing a solution of cyclohexane-1,3-dione with excess of acetic anhydride and sodium acetate (method a).[9]

2-Acetyl-5,5-dimethylcyclohexane-1,3-dione.—This was prepared by saturating a solution of dimedone in acetic anhydride and acetic acid with boron trifluoride (method b) [10] and also *via* method a.

2-Formyl-5,5-dimethylcyclohexane-1,3-dione.—This was prepared *via* hydrolysis of the anil of 2-formyl-5,5-dimethylcyclohexane-1,3-dione, formed by heating dimedone and *NN'*-diphenylformamidine (method c).[10]

2-Butyl-5,5-dimethylcyclohexane-1,3-dione.—This was prepared by saturating a solution of dimedone in iso-butyric anhydride and iso-butyric acid with boron trifluoride (method b).[10]

The 2-acyl derivatives were isolated and characterised as their copper chelates (Table 3).

3-Alkyl-4-oxo-1-phenyl-4,5,6,7-tetrahydroindazoles (XXI).—These were prepared by refluxing equivalent quantities of the 2-acylcyclohexane-1,3-dione and phenylhydrazine in absolute ethanol for 2 h. The solution was evaporated to dryness under vacuum and the residue chromatographed on alumina in petroleum. Elution with petroleum–benzene [1 : 1 (v/v)] gave the required product. The properties of these products are summarised in Table 4.

3-Alkyl-4-hydroxyimino-1-phenyl-4,5,6,7-tetrahydroindazoles (XII).—These were prepared by refluxing the 4-oxotetrahydroindazole (XXI) with 5 equiv. of hydroxylamine hydrochloride and fused sodium acetate in absolute ethanol for 5 h. The solution was then added to ice–water and the precipitate filtered off and recrystallised from acetone. The properties of these oximes are shown in Table 4.

Reactions of the 4-Hydroxyiminotetrahydroindazoles (XII) *in Polyphosphoric Acid*.—The oxime (XII) (300 mg) was stirred in polyphosphoric acid (13 g) at 130—140° for 1 h when solution was complete. The cold solution was added to ice–water and neutralised with sodium hydroxide. The solution was extracted with ether and the extract washed with water, dried (Na_2SO_4), then evaporated to dryness. The residue was applied to an alumina column in petroleum. Elution with petroleum–benzene [1 : 1 (v/v)] gave *3-alkyl-4-amino-1-phenylindazole* (XIII) (Table 5). Elution with chloroform gave *3-alkyl-4-oxo-1-phenyl-1,4,5,6,7,8-hexahydropyrazolo*[4,3-c]*azepine* (XIV) (Table 5).

4-Acetylamino-3-methyl-1-phenylindazole.— 4-Amino-3-methyl-1-phenylindazole (XIIIa) (100 mg) was dissolved in benzene (5 ml) and the solution was treated with triethylamine (0·5 ml) and acetic anhydride (0·2 ml) and left at room temperature for 12 h. Petroleum (10 ml) was added, and crystals of *4-acetylamino-3-methyl-1-phenylindazole* separated (75 mg) (63%), m.p. 190—191°, $\nu_{max.}$ 3280, 1660, 1500, 1280, 755, 696, and 681 cm^{-1}, τ 2·55 (9H, m), 7·25 (3H, s), and 7·79 (3H, s) (Found: C, 71·4; H, 5·8; N, 15·6. $C_{16}H_{15}N_3O$ requires: C, 71·9; H, 5·6; N, 15·7%).

Deamination of the 4-Aminoindazole (XIIIe).—4-Amino-1-(*p*-methoxyphenyl)-3,5,6-trimethylindazole (XIIIe) hydrochloride (95 mg), was dissolved in hypophosphorous acid (5 ml), and sodium nitrite (40 mg) in water (2 ml) was added dropwise at 0 °C over 10 min. The mixture was stirred at 5° for 30 min then left at room temperature for 4 h. The solution was made alkaline with potassium hydroxide and the product extracted into ether. The extract was washed with water, dried (K_2CO_3), and then applied to an alumina column in petroleum. Elution with petroleum gave *1-(p-methoxyphenyl)-3,5,6-trimethylindazole* (40 mg) (50%), m.p. 85—86°, $\nu_{max.}$ 2890, 1498, 1435, 1243, and 798 cm^{-1}, τ (CCl_4) 2·45 (2H, d, *J* 10 Hz), 2·68 (2H, s), 3·07 (2H, *J* 10 Hz), 6·18 (3H, s), 7·48 (3H, s), and 7·66 (3H, s) (Found: C, 76·0; H, 7·0; N, 10·6%; M^+, 266·1415. $C_{17}H_{18}N_2O$ requires C, 76·8; H, 6·8; N, 10·5%; *M*, 266·1419).

Deamination of the 4-Aminoindazole (XIIIb).—The 4-aminoindazole (XIIIb) (127 mg) was deaminated as described for (XIIIe). *3,5,6-Trimethyl-1-phenylindazole* (86 mg, 72%), m.p. 75·5—76°, was obtained, $\nu_{max.}$ 2921, 1603, 1516, 1499, 1450, and 750 cm^{-1}, τ (CCl_4) 2·50 (5H, m), 2·68 (1H, s), 7·46 (3H, s), and 7·62 (3H, s) (Found: C, 80·2; H, 6·8; N, 11·1%; M^+, 236·1308. $C_{16}H_{16}N_2$ requires C, 81·3; H, 6·8; N, 11·8%; *M*, 236·1313).

3-(m-Methoxyphenyl)-1,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydroindazole.—Dimedone (7·0 g) and the hydrazone (8·2 g) from *N*-methyl hydrazine and *m*-anisaldehyde in benzene (200 ml) were refluxed with glacial acetic acid (6·0 ml) for 2 h with a slow passage of air through the solution.[11] The solution was then added to aqueous 10% sodium hydroxide solution and extracted with ether. The extract was washed with water, acidified with conc. hydrochloric acid, washed with water, dried (Na_2SO_4), then evaporated to dryness. The residue was recrystallised from benzene–petroleum to yield *3-(m-methoxyphenyl)-1,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydroindazole* (3·18 g, 22%), m.p. 112—113°, $\nu_{max.}$ 3075, 2962, 1668, 1504, 1435, 1230, 1060, and 792 cm^{-1}, τ 2·60 (4H, m), 6·11 (3H, s), 6·20 (3H, s), 7·35 (2H, s), 7·60 (2H, s), and 8·86 (6H, s) (Found: C. 71·9; H, 7·3; N, 9·8. $C_{17}H_{20}N_2O_2$ requires C, 71·9; H, 7·1; N, 9·8%).

4-Hydroxyimino-3-(m-methoxyphenyl)-1,6,6-trimethyl-4,5,6,7-tetrahydroindazole (XIIIf).—3-(*m*-Methoxyphenyl)-1,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydroindazole (2·84 g)

[9] H. Smith, *J. Chem. Soc.*, 1953, 803.
[10] N. Rodgers and H. Smith, *J. Chem. Soc.*, 1955, 344.
[11] W. Sucrow, M. Slopianka. and A. Neophytou, *Chem. Ber.*, 1972, **105**, 2143.

TABLE 3

Properties of the copper chelates of 2-acylcyclohexane-1,3-diones

C-2	C-5	M.p. (°)	Analysis: Found C	Found H	Required C	Required H	Yield/% (method)	$\nu_{max.}$ (cm^{-1})
MeCO	H	264—265 *					61(a)	
MeCO	Me	262—263	55·9	6·2	56·2	6·1	60(a), 65(b)	3570, 3460, 2965, 1630, 1570, 1385
Pr^{i}CO	Me	224—225	59·2	7·2	59·6	7·0	24(b)	2970, 1645, 1580, 1420
HCO	Me	290—291	54·9	5·5	54·7	5·6	44(c)	3250, 2960, 1655, 1590, 1370

* Lit.,[9] 263—265°.

TABLE 4

Properties of the 3-alkyl-4-oxo-1-phenyl-4,5,6,7-tetrahydroindazoles (XXI) and their oximes (XII)

Compound	M.p. (°)	Yield (%)	Analyses and molecular ions: Found (%) C(%)	Found H(%)	Found N(%)	M+	Formula	Required C(%)	Required H(%)	Required N(%)	M	^{1}H n.m.r./τ(CDCl$_3$) Substituent at C-3	C-5	$\nu_{max.}$(KBr)/cm^{-1}
(XIIa)	128—129 *	39										7·58	7·73	
(XXIb)	135—136 †	48	76·2	7·4	11·2		$C_{16}H_{18}N_2O$	75·6	7·1	11·0		7·57	7·78	1660, 1510, 1480, 764, 696
(XXIc)	95—96	10	76·5	7·9	9·9		$C_{18}H_{22}N_2O$	76·7	7·9	9·9		6·56	7·75	1665, 1505, 1490, 768, 718, 698
(XXId)	100—101	53	75·4	6·9	11·2		$C_{15}H_{16}N_2O$	74·2	6·8	11·5		1·96	7·60	1676, 1600, 1503, 769, 696
(XXIe)	128—129	18	72·0	7·3	9·8	284·1527	$C_{17}H_{20}N_2O_2$	71·8	7·0	9·9	284·1228	7·58	7·80	1670, 1520, 1490, 1250, 1045. 1032, 837
(XIIa)	209—210	82	69·5	6·2	17·3	241·1215	$C_{14}H_{15}N_3O$	69·7	6·3	17·4	241·1215	7·50	7·18	3200, 1690, 1635, 1600, 980, 898
(XIIb)	210—211	89	71·0	7·0	15·6	269·1533	$C_{16}H_{19}N_3O$	71·4	7·1	15·6	269·1528	7·52	7·34	3300, 1645, 1602, 1558, 1509, 1429, 762
(XIIc)	148—149	95	71·2	8·0	13·8		$C_{18}H_{23}N_3O$	72·7	7·8	14·1		6·58	7·39	3220, 1630, 1600, 1548, 1500, 1450 914
(XIId)	203—204	74	70·4	6·6	16·6	255·1364	$C_{15}H_{17}N_3O$	70·6	6·7	16·6	255·1372	1·58	7·61	3200, 1665, 1604, 1505, 1420, 958, 795
(XIIe)	221—222	75	68·8	7·2	13·9	299·1646	$C_{17}H_{21}N_3O_2$	68·2	7·2	14·0	299·1634	7·54	7·45	3200, 1640, 1525, 1456, 1265, 1027

* Lit.,[9] 129°. † Lit.,[11] 136°.

TABLE 5

Properties of the products from the Schmidt and attempted Beckmann reactions on 4-oxoindazoles (XXI) and their oximes (XII)

Compound	^{1}H n.m.r./τ(CDCl$_3$) (J in Hz)	$\nu_{max.}$(KBr)/cm^{-1}
(XIIIa)	2·65 (7H, m), 3·72 (1H, d, $J_{5.6}$ 7·5, $J_{5.7}$ 3), 5·81 (2H, s), 7·22 (3H, s)	3480, 3395, 1623, 1594, 1513, 1496. 1360, 1300
(XIIIb)	2·6 (5H, m), 3·10 (1H, s), 5·94 (2H, s), 7·25 (3H, s), 7·66 (3H, s), 7·92 (3H, s)	3500, 3405, 1615, 1595, 1512, 1496. 1354. 795
(XIIIc)*	2·43 (5H, m), 6·37 (1H, m), 7·57 (6H, m), 8·25 (6H, d, J 6)	2480, 1600, 1558, 1505, 1267, 1100. 765. 700, 691
(XIIIe)†	2·75 (q, J 9), 3·22 (1H, s), 5·86 (2H, s), 6·20 (3H, s), 7·24 (3H, s), 7·65 (3H, s), 7·90 (3H, s)	2600. 1590, 1520, 1460, 1255, 835
(XIVa)	2·61 (5H, s), 3·58 (1H, t), 6·64 (2H, m), 7·10 (2H, t), 7·43 (3H, s), 7·95 (2H, m)	3280, 3200, 3060, 1645, 1486, 804, 766
(XIVb)	2·54 (5H, s), 3·52 (1H, t), 6·98 (2H, d, J 6), 7·36 (2H, s), 7·46 (3H, s), 8·97 (6H, s)	3520, 3420, 3280, 3240, 1650, 1500, 1284. 1079, 758
(XIVc)	2·57 (5H, s), 3·48 (1H, t), 6·40 (1H, m), 7·02 (2H, d, J 6), 7·38 (2H, s), 8·62 (6H, d), 8·96 (6H s)	3220, 3085, 1650, 1500, 1460. 1384. 773
(XIVd)	1·82 (1H. s), 2·53(5H, s), 3·08 (1H, t), 6·84 (2H, d. J 6), 7·29 (2H, s), 8·93 (6H, s)	3280. 3170, 3050, 1648, 1555, 1485. 960, 769. 696
(XVb)	1·88 (1H, s), 2·14 (5H, s), 7·35 (2H, s), 7·40 (2H, s). 7·75 (3H, s), 8·89 (6H, s)	3305, 3210, 3150, 3050, 1660, 1600. 1503. 1396. 1369, 755, 695
(XVc)	2·52 (6H, s), 6·90 (1H, s), 7·25 (2H, s). 7·46 (2H, s), 8·59 (6H. d), 8·80 (6H, s)	3310, 3200, 3120, 3030, 1663, 1500, 1405. 1390, 1380. 768, 695

* Data for the hydrochloride; n.m.r. spectrum recorded in CD_3OD. † I.r. data recorded for hydrochloride.

	M.p. (°)	Yield (%)* A	Yield (%)* B	Analyses and molecular ions: Found C(%)	Found H(%)	Found N(%)	M+	Formula	Required C(%)	Required H(%)	Required N(%)	M
(XIIIa)	90—91	66		75·8	5·7	18·7	223·1115	$C_{14}H_{13}N_3$	75·3	5·9	18·8	233·1110
(XIIIb)	133—134	65	18	76·6	6·8	16·8	251·1425	$C_{16}H_{17}N_3$	76·5	6·8	16·7	251·1422
(XIIIc)	69—70	80	17	77·3	7·4	15·0	279·1736	$C_{18}H_{21}N_3$	77·5	7·5	15·0	279·1735
(XIIIe)	137—138	67		72·9	7·0	15·0	281·1530	$C_{17}H_{19}N_3O$	72·6	6·8	14·9	281·1528
(XIVa)	226—227	34		69·6	6·4	17·3	241·1220	$C_{14}H_{15}N_3O$	69·8	6·3	17·4	240·1215
(XIVb)	133—134	34	61	69·9	7·2	15·5	269·1528	$C_{16}H_{19}N_3O$	71·4	7·1	15·6	269·1528
(XIVc)	176—177	20	67	72·7	8·0	14·3	299·1850	$C_{18}H_{23}N_3O$	72·5	7·8	14·4	297·1841
(XIVd)	177—178	*ca.* 100	*ca.* 100	69·9	6·8	16·5	255·1373	$C_{15}H_{17}N_3O$	70·6	6·7	16·5	255·1372
(XVb)	196—197		21	70·9	7·3	15·5	269·1525	$C_{16}H_{19}N_3O$	71·4	7·1	15·6	269·1528
(XVc)	183—184		16	72·3	8·1	14·0	297·1844	$C_{18}H_{23}N_3O$	72·5	7·8	14·4	297·1841

* A = Percentage of product isolated from the attempted Beckmann reaction; B = percentage of product isolated from the Schmidt reaction.

was refluxed in absolute ethanol (150 ml) with hydroxylamine hydrochloride (3·5 g) and fused sodium acetate (3·5 g) for 20 h. The solution was evaporated to dryness then treated with water. The solid was filtered off, washed with water, and recrystallised from ethanol to give 4-*hydroxyimino*-3-(m-*methoxyphenyl*)-1,6,6-*trimethyl*-4,5,6,7-*tetrahydroindazole* (XIIf) (2·15 g, 72%), m.p. 184·5°, $\nu_{max.}$ 3200, 2980, 1620, 1586, 1470, 1290, 1225, 1060, 948, and 783 cm^{-1}, τ 1·76 (1H, s), 2·70 (4H, m), 6·22 (3H, s), 6·32 (3H, s), 7·40 (2H, s), 7·49 (2H, s), and 8·89 (6H, s) (Found: C, 67·3; H, 7·3; N, 13·8. $C_{17}H_{21}N_3O_2$ requires C, 68·2; H, 7·1; N, 14·0%).

Reaction of Oxime (XIIf) *in Polyphosphoric Acid.*—The 4-hydroxyimino-tetrahydroindazole (XIIf) (1 g) was added to stirred polyphosphoric acid (15 g) at 130°. After 15 min the solution was added to ice cold, aqueous sodium hydroxide solution and rapidly extracted into ether. The extract was dried (K_2CO_3) and evaporated to dryness. The residue (864 mg) was applied to an alumina column in petroleum. Gradient elution with 10% increments of benzene in petroleum (in 100 ml portions) yielded 4-*amino*-3-(m-*methoxyphenyl*)-1,5,6-*trimethylindazole* (XIIIf) (700 mg, 81%), m.p. 45—46°, $\nu_{max.}$ 3485, 3400, 2940, 1620, 1495, 1345, 1290, 1258, 1042, 810, and 794 cm^{-1}, τ (CCl_4) 2·80 (3H, m), 3·20 (1H, m), 3·55 (1H, s), 6·10 (5H, s), 6·20 (3H, s), 7·55 (3H, s), and 7·98 (3H, s) (Found: C, 72·4; H, 7·2; N, 14·6%; M^+, 281·1535. $C_{17}H_{19}N_3O$ requires C, 72·6; H, 6·8; N, 14·9%, M^+, 281·1528). Elution with 5% ethyl acetate in benzene yielded 9-*methoxy*-2,4,4-*trimethyl*-2,3,4,5-*tetrahydropyrazolo*[3,4,5-kl]*acridine* (XX) (17 mg, 2%), m.p. 188—189°, $\nu_{max.}$ 2920, 1620, 1574, 1415, 1232, 1025, and 824 cm^{-1}, τ (100 MHz) 2·05 (1H, d, *J* 9 Hz), 2·28 (1H, d, *J* 3 Hz), 2·79 (1H, dd, *J* 9 and 3 Hz), 5·92 (3H, s), 6·06 (3H, s), 7·14 (2H, s). 7·21 (2H, s), and 8·84 (6H, s) (Found: M^+, 281·1535. $C_{17}H_{19}N_3O$ requires *M*, 281·1528). Elution with ethyl acetate yielded 3-(m-*methoxyphenyl*)-1,7,7-*trimethyl*-4-*oxo*-1,4,5,6,7,8-*hexahydropyrazolo*[4,3-c]*azepine* (XIVf) (60 mg, 7%), m.p. 168—169°, $\nu_{max.}$ 3300, 3200, 3060, 2950, 1665, 1485, 1446, 1240, 1049, 894, 803, and 786 cm^{-1}, τ 2·60 (4H, m), 3·48 (1H, t), 6·18 (6H, s), 7·15 (2H, d, *J* 6 Hz), 7·40 (2H, s), and 8·82 (6H, s) (Found: C, 68·1; H, 7·3; N, 13·9%; M^+, 299·1635. $C_{17}H_{21}N_3O_2$ requires C, 68·2; H, 7·1; N, 14·0%; *M*, 299·1634).

Schmidt Reactions of 3-*Alkyl*-6,6-*dimethyl*-4-*oxo*-1-*phenyl*-4,5,6,7-*tetrahydroindazoles* (XXI).—The 4-oxo-tetrahydroindazole (XXI) (300 mg) was dissolved in polyphosphoric acid (13 g). To the stirred solution at 50° was added sodium azide (1·5 equiv.) over 1 h. The mixture was then stirred at 50—60° for 12 h. The cold solution was added to ice–water, neutralised with sodium hydroxide, and extracted with ether. The extract was washed with water, dried (Na_2SO_4), and evaporated to dryness. The residue was applied to an alumina column in petroleum. Elution with petroleum–benzene [1 : 1 (v/v)] liberated 3-alkyl-4-amino-5,6-dimethyl-1-phenylindazole (XIII) (Table 5). Elution with benzene yielded 3-*alkyl*-7,7-*dimethyl*-5-*oxo*-1-*phenyl*-1,4,5,6,7,8-*hexahydropyrazolo*[4,3-b]*azepine* (XV) (Table 5), and finally elution with chloroform liberated 3-alkyl-7,7-dimethyl-4-oxo-1-phenyl-1,4,5,6,7,8-hexahydropyrazolo-[4,3-*c*]azepine (XIV) (Table 5).

Reactions of 4-*Hydroxyiminotetrahydroindazoles* (XIIa *and* b) *in Deuteriated Polyphosphoric Acid.*—The oxime (XIIa or b) (300 mg) was added to stirred deuteriated polyphosphoric acid [5] (13 g) at 120—130°. After 60 min the solution was poured dropwise into a rapidly stirred mixture of aqueous 10% sodium hydroxide solution and ether at 5°. The ether phase was separated and dried (Na_2SO_4). The deuteriated 3-alkyl-4-amino-1-phenylindazoles (XIIIa or b) were isolated either by alumina column chromatography as described above (method a), or by treatment of the dry ethereal solution with ethereal hydrochloric acid (method b) or perchloric acid (method c) and filtration to give the amine salts. The lactams were isolated by the usual chromatographic technique. The properties of the compounds isolated from these reactions are shown in Table 6.

TABLE 6

Properties of the compounds isolated from the reaction of compounds (XIIa and b) in deuteriated polyphosphoric acid

Compound	Method of isolation *	M^+	^{1}H n.m.r./τ
(XIIIa)	a		(in CCl_4) 2·70 (6H, m), 3·88 (0·25—0·8H, d, *J* 7·5 Hz), 5·97 (2H, s) 7·32 (3H, s)
(XIIIa) acetate	Prepared as described for normal (XIIIa)	267·1333; $C_{16}H_{13}D_2N_3O$ requires 267·1341. 266·1270: $C_{16}H_{14}DN_3O$ requires 266·1278	(in CD_3OD) 2·55 (6H, m), 2·98 (0·6H, d, *J* 7·5 Hz), 7·38 (3H, s), 7·82 (3H, s)
(XIIIa)	After reheating in PPA and isolation		(in CCl_4) 2·7 (7H, m), 3·90 (1H, dd, *J* 7 and 3Hz), 5·95 (2H, s), 7·33 (3H, s)
(XIIIb)	b		(in CCl_4) 2·50 (5H, m), 3·12 (1H, s), 6·02 (2H, s), 7·32 (3H, s), 7·70 (2·7H, s) 799 (3H, s)
	c	252·1464; $C_{16}H_{16}DN_3$ requires 252·1485	(in C_5D_5N) 7·11 (3H. s), 7·68 (2·6H, s). 7·82 (3H. s)
(XIVa)	a	0·14% †	
(XIVb)	a	<0·1% †	

* See Experimental section. † From comparison the mass spectra of the deuteriated and nondeuteriated compounds.

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