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Antiimplantation Agents: Part III—1,2-Diaryl-4,5-polymethylenepyrroles & 1,2-Diaryl-4-oxo- & 1,2-Diaryl-4-hydroxy-4,5,6,7-tetrahydroindoles[a,b,c]

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2-Phenacylcycloalkanones (**3**) and anilines give rise to polymethylenepyrroles (**4**). Pyrrolopiperidine (**10**) is likewise obtained from 2-phenacylpiperidone (**9**). 2-Phenacylcyclohexane-1,3-diones undergo condensation with anilines to form 1,2-diaryl-4-oxo-4,5,6,7-tetrahydroindoles (**15**) and with a variety of other amines to give **28**, while 2-acetonyldimedone and *p*-fluoroaniline afford **32**. Some members of **15**, and **28a** and **32** are reduced to alcohols **20**, **29** and **33** respectively. Attempted dehydration of **20d** and acylation of **33** lead to the formation of dimers **21** and **34**, while hydrogenolysis of the former transforms it to **22**. **15c** and **15n** are converted into azepinones **24c** and **24a** via oximes **16c** and **16a**. **24a** is aminoalkylated to **24b** and reduced to **27**. **4e** and **15c** undergo Mannich reaction at β-position of the pyrrole ring to form **5** and **18a**, while **15n** is attacked at a position α to the C = O group giving a mixture of **18b** and **19b**. Perhydroindoline **36** is obtained from 2-allyldimedone. 1,2-Diaryl-4-acetyl-5-methylpyrroles **38a** and **38b** made available from triketone **37** are reduced to alcohols **39a** and **39b**. Several compounds of the study exhibit antiimplantation activity in the rat, among which the ethers **4m**, **4n** and **4p** of 1-(*p*-hydroxyphenyl)-2-phenyl-4,5-polymethylenepyrroles, 1,2-diaryl-4-oxo-4,5,6,7-tetrahydroindoles (**15e**, **15n**, **15w** and **15z**), 1,2-diaryl-4-hydroxy-4,5,6,7-tetrahydroindoles [**20a**, **20d** (C 6924-Go) and **20e**] and the desoxy derivative **22** of **22d** are effective at a dose of 10 mg/kg p.o. × 6 days or less. Compounds **4p** (MED_{100} 1 mg), **20d** (MED_{100} 2 mg) and **22** (MED_{100} 1 mg) show no dissociation between antiimplantation and estrogenic activities. Detailed studies on C-6924 reveal that it owes its activity to weak estrogenic-antiestrogenic properties.

In the previous paper[1], we presented the antiimplantation properties of a series of 1,2-diaryl-1,2,3,4-tetrahydroisoquinolines. We report in this paper, the structure-activity relationships in a series of 1,2-diaryl-4,5-polymethylenepyrroles and 1,2-diaryl-4-oxo-4,5,6,7-tetrahydroindoles and their derivatives which had similar properties.

Chemistry

Polymethylenepyrroles

The polymethylenepyrroles **4** (Table 1) and **6** (Table 6) were obtained by heating phenacyl cycloalkanones (**3**) with amines, especially anilines at 170-180°. Ketones **3** in turn were obtained from the pyrrolidine enamines (**2a-2c**) of cyclopentanone (**1a**), cyclohexanone (**1b**) and cycloheptanone (**1c**) by treatment with phenacyl bromides by a procedure known for **3b**[2]. Some members of **4** are reported to undergo dehydrogenation to 1,2-diarylindoles[3]. The aminoalkyl ethers, e.g. **4b**, **4h** and **4p** were prepared from the respective phenols. **7a** was obtained from **3b** and N-aminopiperidine in refluxing ethanol containing acetic acid. Mannich reaction of **4e** with formaldehyde and morpholine afforded **5** which did not show the pyrrole β-proton signal in the PMR spectrum. This signal was seen at δ 6.25 in the PMR spectrum of **4e**. The major product from **7a**, formaldehyde and morpholine was an oil, probably **7b**. However, a crystalline product obtained in low yield was the methylene-bis-derivative formed by bridging the β-position in 2 moles of **7a** by a CH_2 group; its PMR spectrum did not exhibit a signal at δ 5.95 observed for **7a**.

Compound **3b** and isonicotinic acid hydrazide gave **8**, while the 3-phenacyl derivative (**9**) of N-benzyl-4-piperidone and *p*-fluoroaniline afforded **10**. The former reaction could conceivably yield a cinnoline[4,5]. However, structure **8** was supported by the presence, in the PMR spectrum (DMSO-d_6), of a singlet at δ 6.13 ppm (pyrrole β-proton) and another at 11.67 (NH). Further, the base peak in the mass spectrum of **8** was a fragment formed by the loss of isonicotinamide ($M^+ - 122$). Pyrryl ethers **11a** and **11b** included as monocyclic derivatives in this study were prepared from 1-(*p*-hydroxyphenyl)-2,5-dimethylpyrrole[6].

4-*Keto*-4,5,6,7-*tetrahydroindoles and transformation products*

Fusion of the ketones **13** (Table 2) with appropriate anilines at 170-180° gave compounds of the general structure **15** (Table 3) in good yields. For the synthesis of **15cc**, refluxing acetic acid was found to be a suitable medium. Derivatives **13** where R = Me were conveniently synthesised in moderate to good yields by

*Contribution No. 724 from Research Centre.
[b]Part II: Nagarajan K., Talwalker P. K., Kulkarni C. L., Shah R. K., Shenoy S. J. & Prabhu S. S., *Indian J. Chem.*, **24B** (1985) 83.
[c]Dedicated to Dr. Nitya Anand on his 60th birth anniversary.
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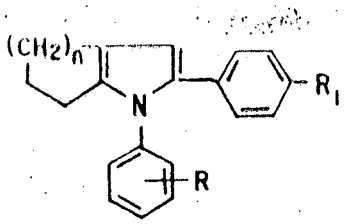
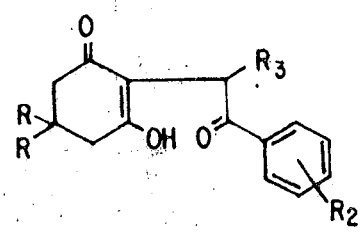
Table 1 Diaryl-4,5-polymethylenepyrroles



Compd*	n	R	R_1	Mol. formula	m.p./b.p. (mm) C	Crystallised from†	Anti-implantation activity (rat) MED_{100} (mg/kg/day p.o. ×6 days)
4a	1	4-OH	H	$C_{19}H_{17}NO$	151-52	A+C	>100
4b	1	4-(N-Pyrrolidino)ethoxy	H	$C_{25}H_{28}N_2O$	93-94	E	50
4c	2	3-Cl	H	$C_{20}H_{18}ClN$	99-100	F+B	ϕ
4d	2	3-(N-Pyrrolidino)ethoxy	H	$C_{26}H_{30}N_2O$	250(10^{-3})	(Oil)	100
4e	2	4-F	H	$C_{20}H_{18}FN$	129-30	F+B	ϕ
4f	2	4-OMe	H	$C_{21}H_{21}NO$	132-33	F+B	ϕ
4g	2	4-OH	H	$C_{20}H_{19}NO$	187-78	B	ϕ
4h	2	4-$OCH_2CH_2NEt_2$	H	$C_{26}H_{32}N_2O$	220(5×10^{-3})	(Oil)	50
4i (maleate)	2	4-(N-Pyrrolidino)ethoxy	H	$C_{30}H_{34}N_2O_5$	156-57	B+D	25
4j	2	4-(N-Pyrrolidino)ethoxy	Cl	$C_{26}H_{29}ClN_2O$	113-14	E	25
4k (maleate)	2	4-(N-Piperidino)ethoxy	H	$C_{31}H_{36}N_2O_5$	158-59	B+D	25
4l	2	4-(N-Morpholino)ethoxy	H	$C_{30}H_{34}N_2O_6$	178-79	A+B	>100
4m	2	4-$OCH_2CH_2CH_2NMe_2$	H	$C_{25}H_{30}N_2O$	92-94	E	10
4n	2	4-(N-Piperidino)propoxy	H	$C_{28}H_3N_2O$	88-90	E	10
4o	3	4-OH	H	$C_{21}H_{21}NO$	153-55	B+C	ϕ
4p	3	4-(N-Pyrrolidino)ethoxy	H	$C_{27}H_{32}N_2O$	115-57	D+E	1
4q	2	3-OH	H	$C_{20}H_{19}NO$	Gum		
4r	2	4-OH	Cl	$C_{20}H_{18}ClNO$	169-70	B	

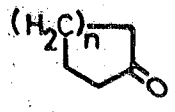
*All the compounds gave satisfactory analyses for C, H and N. The data are available with the authors.
†A = Methanol, B = ethanol, C = water, D = ether, E = hexane, F = acetone.

Table 2 —2-Phenacylcyclohexane-1,3-diones (13)



Compd*	R	R_2	R_3	Mol. formula	m.p. C	Crystallised from†
13a	H	H	H	$C_{14}H_{14}O_3$	148-49	B
13b	Me	H	H	$C_{16}H_{18}O_3$	180-82	B+C
13c	Me	H	Me	$C_{17}H_{20}O_3$	143-45	A
13d	Me	2-NO_2	H	$C_{16}H_{17}NO_5$	172-74	B
13e	Me	4-Br	H	$C_{16}H_{17}BrO_3$	172-74	B
13f	Me	4-Cl	H	$C_{16}H_{17}ClO_3$	234-38	B
13g	Me	4-NO_2	H	$C_{16}H_{17}NO_5$	202-4	B
13h	Me	4-OMe	H	$C_{17}H_{20}O_4$	167-68	B+C
13i	Me	4-F	H	$C_{16}H_{17}FO_3$	157-60	B+C

*All the compounds gave satisfactory analyses for C, H and N. The data are available with the authors.
†A = methanol, B = ethanol, C = water.



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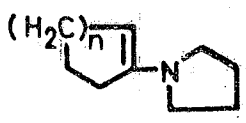
1b n = 2
1c n = 3



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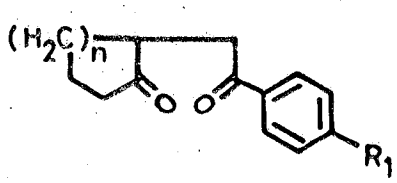
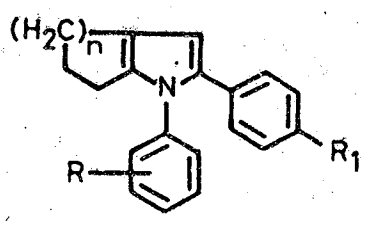
2b n = 2
2c n = 3



3a n = 1 R_1 = H
3b n = 2 R_1 = H
3c n = 3 R_1 = H
3d n = 2 R_1 = H



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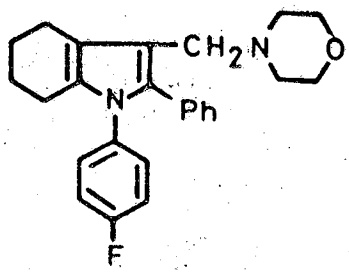

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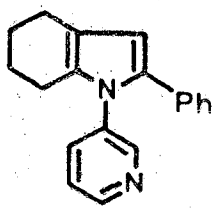

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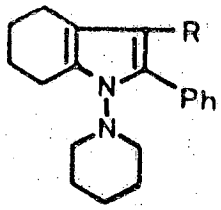
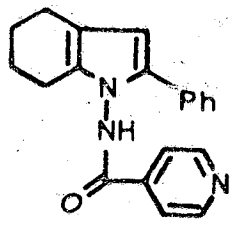


7a R = H
7b R = CH_2NO



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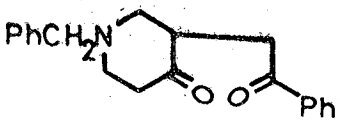

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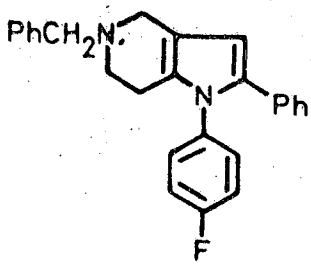

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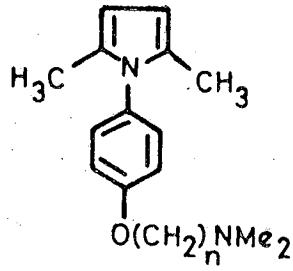
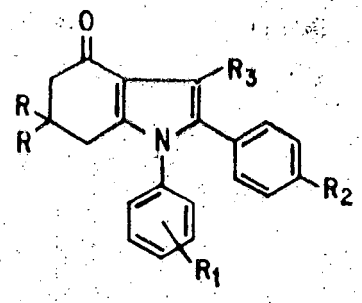


11a n = 2
11b n = 3

the reaction of dimedone (**12b**) with phenacyl bromides in chloroform in the presence of potassium carbonate[5]. In some cases neutral products resulting from O-alkylation were obtained[5]. But in the preparation of **13d**, the neutral byproduct was the xanthene **14**. We rationalise its formation on the basis of the presence of small amounts of ω,ω-dibromo-*o*-nitroacetophenone in the alkylating agent. C-Alkylation of dimedone by this dibromide, followed by cyclodehydration would lead to **14**. For the alkylation of **12a**, the literature procedure[7] was found to be better. Phenylacetic acid **15l** was the hydrolysis product of **15k** which arose from the reaction of **13b** and ethyl *p*-aminophenylacetate. Direct condensation of **13b** with *p*-aminophenylacetic acid was less satisfactory. Amine **15q**, the reduction product of **15s**

Table 3—1,2-Diaryl-4-keto-4,5,6,7-tetrahydroindoles (15)

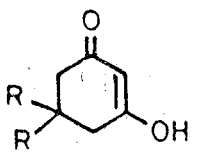


Compd*	R	R_1	R_2	R_3	Mol. formula	m.p. °C	Crystallised from†	Antiimplantation activity (rat) MED_{100} (mg/kg/day p.o. ×6 days)
15a	H	H	H	H	$C_{20}H_{17}NO$	199-201	B	ϕ
15b	H	4-F	H	H	$C_{20}H_{16}FNO$	164-65	A	ϕ
15c	Me	H	H	H	$C_{22}H_{21}NO$	209-10	F+A	50
15d	Me	2-Me	H	H	$C_{23}H_{23}NO$	170-72	A+C	ϕ
15e	Me	2-F	H	H	$C_{22}H_{20}FNO$	205-6	A+C	10
15f	Me	3-CF_3	H	H	$C_{23}H_{20}F_3NO$	145-57	B	ϕ
15g	Me	3-F	H	H	$C_{22}H_{20}FNO$	185-87	B	25
15h	Me	3-OH	H	H	$C_{22}H_{21}NO_2$	199-200	A	ϕ
15i	Me	4-CF_3	H	H	$C_{23}H_{20}F_3NO$	165-67	B	ϕ (at 50 mg)
15j	Me	4-Me	H	H	$C_{23}H_{23}NO$	193-94	B	>100
15k	Me	4-CH_2CO_2Et	H	H	$C_{26}H_{25}NO_3$	162-65	A	—
15l	Me	4-CH_2CO_2H	H	H	$C_{24}H_{23}NO_3$	250-51	A	ϕ
15m	Me	4-Cl	H	H	$C_{22}H_{20}ClNO$	188-89	F+A	50
15n	Me	4-F	H	H	$C_{22}H_{20}FNO$	205-6	F+A	10
15o	Me	4-F	Br	H	$C_{22}H_{19}BrFNO$	243-44	F+A	ϕ
15p	Me	4-F	Cl	H	$C_{22}H_{19}ClFNO$	234-35	F+A	ϕ
15q	Me	4-F	NH_2	H	$C_{22}H_{21}FN_2O$	283-85	F+A	ϕ
15r‡	Me	4-F	NHR_4	H	$C_{26}H_{27}FN_4OS$	207(d)**	A	ϕ
15s	Me	4-F	NO_2	H	$C_{22}H_{19}FN_2O_3$	280-81	F+B	ϕ
15t	Me	4-F	OMe	H	$C_{23}H_{22}FNO_2$	221-23	F+A	25
15u	Me	4-F	H	Me	$C_{23}H_{22}FNO$	193-94	F+A	25
15v	Me	4-OH	H	H	$C_{22}H_{21}NO_2$	296-98	F+A	ϕ
15w (HCl.$2H_2O$)	Me	4-(N-Pyrrolidinoethoxy)	H	H	$C_{28}H_{33}ClN_2O_2$ $2H_2O$	184 (−H_2O at 180)	B+D	3
15x	Me	4-OMe	H	H	$C_{23}H_{23}NO_2$	183-84	B	>100
15y	Me	4-NH_2	H	H	$C_{22}H_{22}N_2O$	268-70	A	ϕ
15z	Me	4-$NHNH_2$	H	H	$C_{22}H_{23}N_3O$	208(d)	H+E	10
15aa	Me	4-NHNHCSNHMe	H	H	$C_{24}H_{26}N_4OS$	271(d)	DMF+D	ϕ
15bb	Me	NMe_2	H	H	$C_{24}H_{26}N_2O$	189-90	F+A	>100
15cc	Me	NO_2	H	H	$C_{22}H_{20}N_2O_3$	196-99	A	ϕ
15dd	Me	H	4-F	H	$C_{22}H_{20}FNO$	187-89	F+A	ϕ

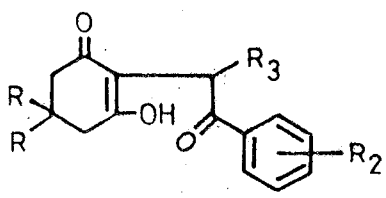
*All the compounds gave satisfactory analyses for C, H and N. The data are available with the authors.
†A = Methanol, B = ethanol, C = water, D = ether, E = hexane, F = acetone.
‡R_4 = $NHCSNHCH_2CH=CH_2$; from hydrazine, m.p. 230-31°.
**Softening at 170°.

was further converted into the allyl thiosemicarbazide (**15r**) through the hydrazine formation. Similarly, the amine **15y**, prepared from the acetamide (obtained from **13b** and *p*-aminoacetanilide), was converted into the hydrazine **15z** and thence into the methyl thiosemicarbazide **15aa**. The pyrrolidinoethoxy derivative **15w** was obtained from phenol **15v** by alkylation.

Ketotetrahydroindoles **15n** and **15c** were transformed into the oximes **16a** and **16c** respectively (Table 4), and the former into the methyl thiosemicarbazone **16b**. Reaction of **15n** with semicarbazide took an anomalous turn to afford a dimeric product tentatively formulated as **17** on the basis of C, H and N analyses. The highest peak in its mass spectrum was at *m/z* 662, corresponding to the loss of −NHCONH− unit from



12 a R = H
12 b R = Me



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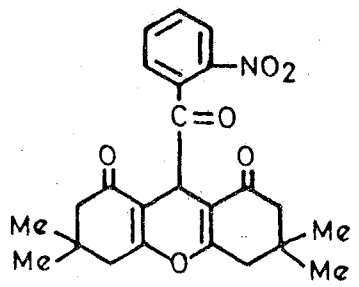

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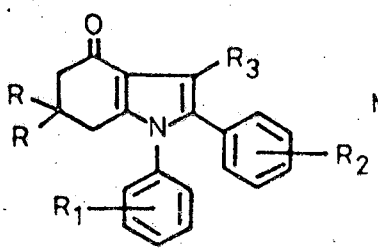

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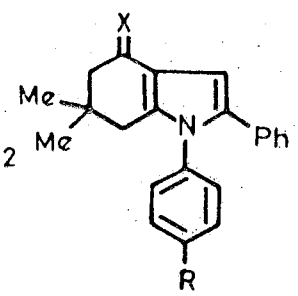
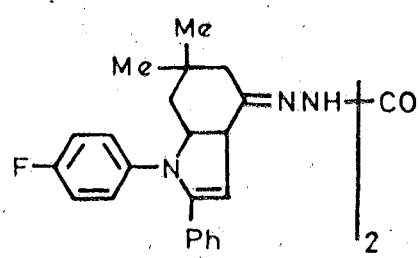


16a X = NOH, R = F
16b X = NNHCSNHMe, R = F
16c X = NOH, R = H



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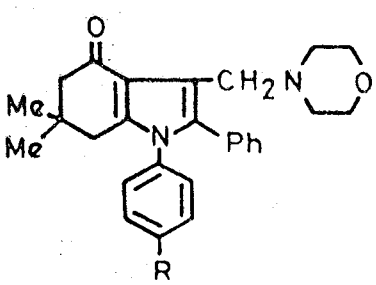
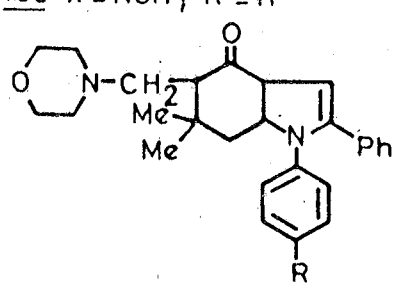
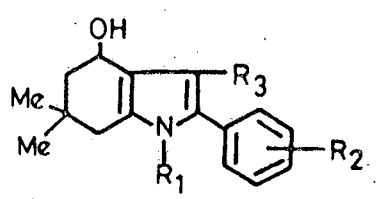


18 a R = H
18 b R = F



19a R = H
19 b R = F



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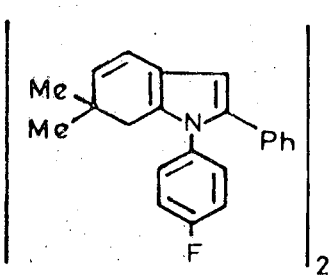

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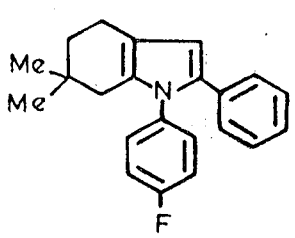

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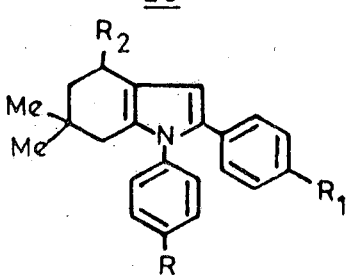


23a R = F, R_1 = H, R_2 = OMe
23 b R = H, R_1 = F, R_2 = OH
23c R = H, R_1 = F, R_2 = OEt
23d R = F, R = Br, R_2 = OH

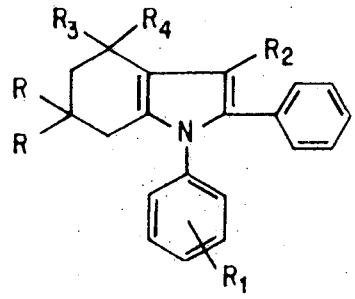
the molecular ion (720). Hydrazine and monosubstituted hydrazines undergo reaction with **13** to give perhydrocinnolines[4,5]. While **3b** and N-aminopiperidine lead to the formation of the expected 1-(N-piperidino)perhydroindoles **7a**, **13** and N,N disubstituted hydrazines form 3-aminoindoles by an anomalous reaction[8]. Mannich reaction on **15c** and **15n** proceeded very slowly and partially to afford products in low yields. The reaction can occur either on the pyrrole or on the CH_2 group adjacent to C=O group. The product from **15c** (M^+ at *m/z* 414) was homogeneous and readily recognized as **18a** (one singlet

for 2 × Me at δ 1.09, a singlet for N−CH_2 at 3.78; no signal for pyrrole β-proton); on the other hand, the product from **15n** was a mixture (TLC) of **18b** and **19b** (**18b**: one singlet for 2Me at δ 1.09, N−CH_2 singlet at 3.73; **19b**: *two* Me singlets at δ 1.04 and 1.13, pyrrole β-proton singlet at 6.73) in the ratio of about 3:5.

Reduction of ketones **15** to alcohols **20** (Table 4) proceeded somewhat sluggishly with sodium borohydride but more readily with lithium aluminium hydride. However, these alcohols were fairly reactive and underwent secondary reactions to give byproducts. Thus, during the large scale preparation and crystallisation of **20d** from THF−MeOH, a small amount of a highly soluble product was obtained and identified as the methyl ether **23a** [M^+ at *m/z* 349; PMR($CDCl_3$): δ 6.80-7.44 (*m*, aromatic H), 6.47 (*s*, pyrrole β−H), 4.46 (*t*, C*H*−OMe), 3.5 (*s*, OMe), 1.33-2.22 (*m*, two CH_2 groups), 1.08 (*s*, Me), 0.99 (*s*, Me)]. Similarly in another case, the alcohol **23b** arising in the incomplete reduction of **15dd** seemed to have formed the ethyl ether **23c** in the process of purifying by crystallization from ethanol [M^+ at *m/z* 363; NMR/($CDCl_3$): −C*H*$_3$CH$_2$, *t* at δ 1.27; C*H*$_2$−CH$_3$, *q* at 3.71; two nonequivalent methyl singlets at 0.98 and 1.07; pyrrole β-proton at 6.4 ppm; multiplets for other protons]. During reduction of ketone **15o**, the bromine atom was lost partially to afford besides the expected alcohol **23d**, **20d** also the extent of 15% (M^+ at *m/z* 335 and other fragments observed in the mass spectrum of **20d** (Found: Br, 16.84. Calc.: Br, 16.40%). For the synthesis of **22**, a convenient procedure was the catalytic hydrogenolysis of **20d**. An attempt to dehydrate **20d** under acid catalysis led to a product with the right elemental analysis, but the high melting point and the mass spectrum (M^+ at *m/z* 634) showed it to be the dimer **21** of undeduced structure. Likewise an attempted acetylation of **20d** led to a product with the right elemental analysis for the expected product. But the high m.p. and mass spectrum require it to be formulated as a dimer; however, the IR spectrum lacking any C=O band was puzzling.

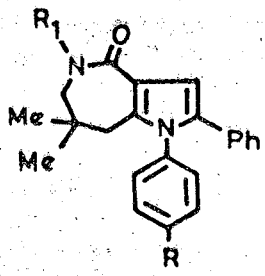
Beckmann rearrangement of the oxime **16a** with PPA afforded an azepinone (**24**) which was further aminoalkylated to **24b** and also reduced to **27**. The ring-enlarged product was formulated as **24a** rather than **25** on the basis of PMR data. Thus, the pyrrole β-protons in **24a** and **24b** appeared as singlets at δ 6.7 and 6.9 respectively, downfield from its 'normal' position because of the effect of an adjacent C=O group (*cf* 6.77 ppm for the same proton in **15n**). In the reduction product **27**, this signal moved upto its normal position at δ 6.25 ppm. Further in the spectrum of **27**, the ring methylene groups were seen as singlets at δ 3.88, 2.90 and 2.45 corresponding to the protons at C-4, C-6 and C-8 respectively. Additionally, it was noted that in **24b** the protons at C-6 and C-8 were seen as insulated

Table 4 Oximino and Hydroxy-perhydroindoles (**16**, **20** and **22**)



Compd*	R	R_1	R_2	R_3	R_4	Mol. formula	m.p. °C	Crystallised from†	Antiimplantation activity (rat) MED_{100} (mg/kg/day p.o. ×6 days)
16a	Me	4-F	H	=NOH		$C_{22}H_{21}FN_2O$	274-77(d)	B	ϕ
16b	Me	4-F	H	=NNHCSNHMe		$C_{24}H_{25}FN_4S$	263-65	E+A	ϕ
16c	Me	H	H	=NOH		$C_{22}H_{22}N_2O$	260-61	B	
20a	Me	H	H	H	OH	$C_{22}H_{23}NO$	186-88	D	10
20b	Me	3-F	H	H	OH	$C_{22}H_{22}FNO$	192-96	D	50
20c	H	4-F	H	H	OH	$C_{20}H_{18}FNO$	85-85	C	ϕ
20d	Me	4-F	H	H	OH	$C_{22}H_{22}FNO$	192-93	THF+A	3
20e	Me	4-F	Me	H	OH	$C_{23}H_{24}FNO$	165-68	A	3
22	Me	4-F	H	H	H	$C_{22}H_{22}FN$	138-40	C	1

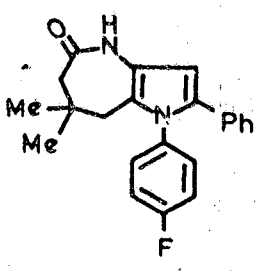
*All the compounds gave satisfactory analyses for C, H and N. The data are available with the authors.
†A = Methanol, B = ethanol, C = hexane, D = benzene, E = chloroform.



24 a. R = F, R_1 = H

24 b. R = F, R_1 = $(CH_2)_3NMe_2$

24 c. R = R_1 = H



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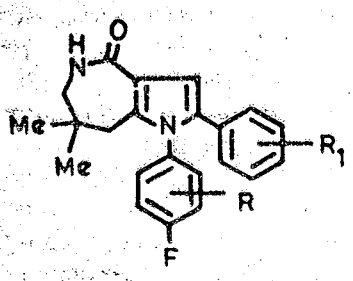
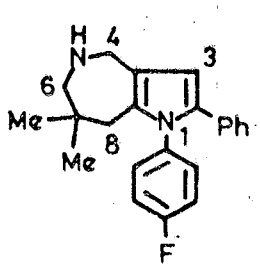


26 R = H, R_1 = SO_3H or vice versa



27

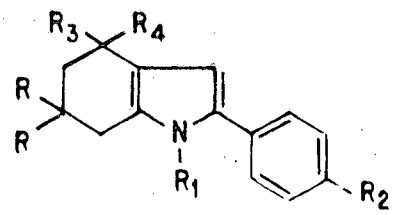
singlets at δ 3.05 and 2.38 respectively. Literature precedent[9] exists to support the direction of ring enlargement of similar molecules. The oxime **16c** underwent similar rearrangement to azepinone **24c**.

The use of conc. sulphuric acid to effect Beckmann transformation of the oxime **16a** resulted in ring expansion and sulphonation to afford **26**, which also arose from **24a** under similar conditions. The PMR spectrum in DMSO-d_6 showed that one of the two aryl groups (undetermined) had got sulphonated. The pyrrole β-position remained intact (singlet at δ 6.8). The sulphonic acid group was not located on the lactam nitrogen since the signals for protons at C-6 (δ 3) and C-8 (δ 2.4) had not moved appreciably from their locations in **24a** (δ 2.93 and 2.38).

Reactions of some ketones (**13**) with miscellaneous amines like 3-aminopyridine, aminoethanol, morpholinopropylamine, *p*-chlorobenzylamine and cyclohexylamine afforded tetrahydroindoles of the structure **28** (Table 5). Of these, **28a** was reduced to the alcohol **29**. The 2-methylketotetrahydroindole **32** (Table 6) became available by reaction of acetonyldimedone (**30**) or 2-propargyldimedone (**31**) with *p*-fluoroaniline, while 2-allyldimedone (**35**) and the same aniline gave the dihydroindole derivative (**36**). Formulation of the product as the perhydroindole (**36**), rather than as the isomeric perhydroquinoline was supported by PMR data [δ 4.3 (*m*, 1H, C_2 – H), 1.2 (*d*, 3H, C_2 – Me), 1.07 (*s*, 3H, C_6 – Me), 1.00 (*s*, 3H, C_6 – Me)]. Reduction of **32** afforded the oily alcohol **33**, which under the conditions of benzoylation formed dimer the **34** of undeduced structure.

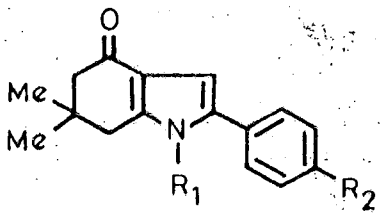
Lastly, some monocyclic analogues of active compounds were prepared from the ketone **37** and aniline or *p*-fluoroaniline. Acetylpyrroles **38a** and **38b** thus produced were reduced to the alcohols **39a** and **39b** respectively (Table 6).

Table 5—Miscellaneous 1-Substituted 4-Keto-4,5,6,7-tetrahydroindoles and Related Alcohols



Compd*	R	R_1	R_2	R_3	R_4	Mol. formula	m.p. °C	Crystallised from†	Antiimplantation activity (rat) MED_{100} (mg/kg/day p.o. × 6 days)
28a	Me	3-Pyridyl	H		=O	$C_{21}H_{20}N_2O$	198-99	A	25
28b	H	CH_2CH_2OH	H		=O	$C_{16}H_{17}NO_2$	147-49	D	ϕ
28c	H	CH_2CH_2OH	OMe		=O	$C_{17}H_{19}NO_3$	140-42	B	ϕ
28d	Me	CH_2CH_2OH	OMe		=O	$C_{18}H_{21}NO_3$	160-61	B	ϕ
28e	Me	3-(N-Morpholino)propyl	H		=O	$C_{23}H_{30}N_2O_3$	128-30	A	ϕ
28f	Me	4-Chlorobenzyl	H		=O	$C_{23}H_{22}ClNO$	138-40	B	ϕ
28g	Me	Cyclohexyl	H		=O	$C_{22}H_{27}NO$	159-60	B + C	ϕ
29	Me	3-Pyridyl	H	H	OH	$C_{21}H_{22}N_2O$	180-84	E + B	25

*All the compounds gave satisfactory analyses for C, H and N. The data are available with the authors.
†A = Methanol, B = ethanol, C = water, D = benzene, E = acetone.



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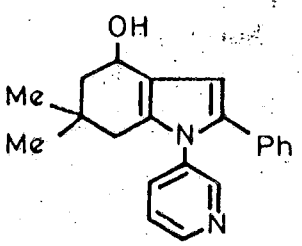

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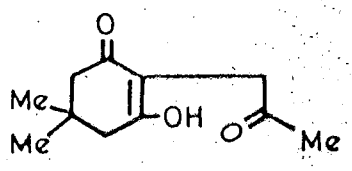

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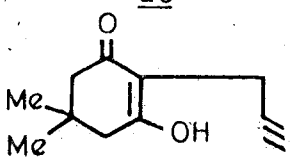

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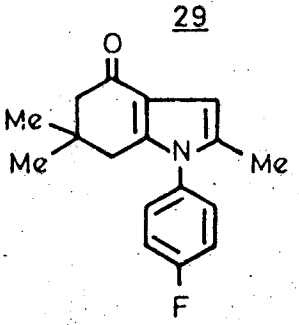

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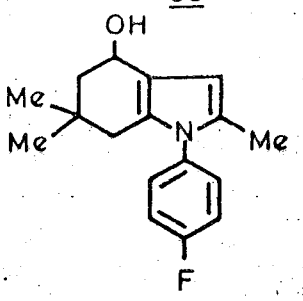

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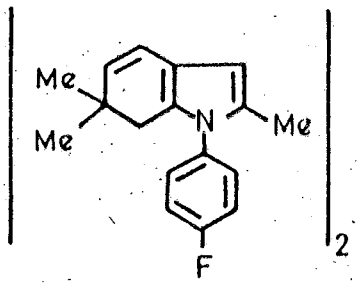

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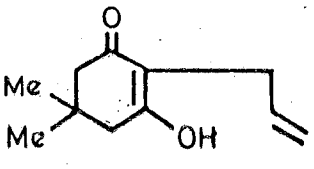

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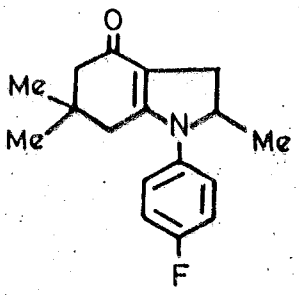

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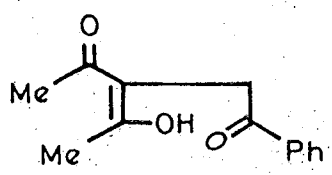

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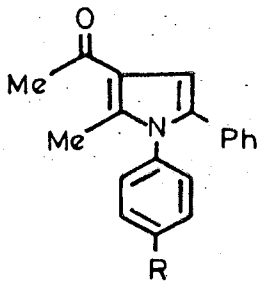
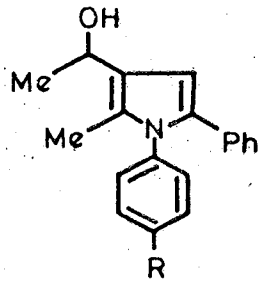


38 a R = H

38 b R = F



39 a R = H

39 b R = F

Biology

Several polymethylenepyrroles, ketotetrahydroindoles and derived products were subjected to the basic test for assessing their antiimplantation activity. A very small number of highly active preparations were studied in a few more tests. Compound **20d**, one of the most potent members of the series was studied extensively in the following tests, the details of which have been given earlier[1].

Test 1: *Inhibition of implantation in mated female rats*—MED_{100}/kg/day p.o. for 6 days; compounds inactive at screening dose of 100 mg are marked ϕ.

Test 2: *Uterotropic activity in the immature mouse*—Dose in mg/kg p.o, ×3 days causing significant increase in uterine weight, comparable to the effect of 1 μg/kg/day of s.c. estradiol was determined.

Test 3: *Vaginal opening test in the immature mouse*—Dose in mg/kg p.o. ×4 days causing vaginal opening

Table 6—Miscellaneous perhydroindoles, pyrroloazepines and pyrroles

Compd*	Mol. formula	m.p. °C	Crystallised from†	Antiimplantation activity (rat) MED_{100} (mg/kg/day p.o. × 6 days)
5	$C_{25}H_{27}FN_2O$	101-3	E	ϕ(as HCl)
6	$C_{19}H_{18}N_2$	100-102	F+A	ϕ
7a	$C_{19}H_{24}N_2$	108-10	B	ϕ
8	$C_{20}H_{19}N_3O$	230-31	B	ϕ
10	$C_{26}H_{23}FN_2$	187-88	B+G	ϕ
11a (tosylate)	$C_{23}H_{30}N_2O_4S$	195-96	B	
11b	$C_{17}H_{24}N_2O$	68-70	B+C	ϕ
24a	$C_{22}H_{21}FN_2O$	270-72 (d)	F+B	100
24b	$C_{27}H_{32}FN_3O$	127-30	D+E	
24b (HCl)	$C_{27}H_{33}ClFN_3O.H_2O$	225-27	A+D	ϕ
24c	$C_{22}H_{22}N_2O$	320	THF+A	—
27	$C_{22}H_{23}FN_2$	154-55	D+E	
27(HCl)	$C_{22}H_{24}ClFN_2.H_2O$	245-47	A+D	ϕ
32	$C_{17}H_{18}FNO$	155-57	A	ϕ
36	$C_{17}H_{20}FNO$	108-10	D	
36 (tosylate)	$C_{24}H_{28}FNO_4S$	160-63	B+D	ϕ
38a	$C_{19}H_{17}NO$	99-101	A	ϕ
38b	$C_{19}H_{16}FNO$	120-21	A+C	ϕ
39a	$C_{19}H_{19}NO$	94-96	E	ϕ
39b	$C_{19}H_{18}FNO$	102-3	D+E	ϕ

*All the compounds gave satisfactory analyses for C, H and N. The data are available with the authors.
†A = Methanol, B = ethanol, C = water, D = ether, E = hexane, F = acetone, G = chloroform.

in 100% of the mice was noted (= 3 μg s.c. for 3 days of estradiol).

Test 4: *Uterotropic activity in the immature castrated rat*—Dose in mg/kg p.o. × 4 days giving 100% increase in uterine weight was assessed.

Test 5: *Vaginal opening test in the immature castrated rat*—Dose in mg/kg p.o. × 4 days causing vaginal opening in 100% of rats (= 3 μg s.c. for 3 days of estradiol).

Test 6: *Vaginal smears (Allen Doisy test) in the castrated rat*—Dose in mg/kg p.o. × 3 days producing positive vaginal smears in 50% of the treated rats (= 2.5 μ s.c. for 3 days of estradiol).

Test 7: *Induction of uterine withdrawal bleeding in the immature rhesus monkey*—Dose in mg/kg p.o × 20 days inducing withdrawal bleeding (= 2.5 μg estradiol s.c. × 20 days).

Test 8: *Antiuterotropic activity in the immature mouse*—Dose in mg/kg p.o. × 3 days significantly inhibiting uterine weight gain due to 2 μg estradiol s.c. administered concurrently.

Test 9: *Antiuterotropic activity in the immature castrated rat*—Dose in mg/kg p.o. × 7 days significantly inhibiting uterine weight gain due to concurrent administration of 0.8 μg s.c. of estradiol.

Test 10: *Effect on deciduoma formation in the pregnant and pseudopregnant rat*—Minimum inhibitory dose in mg/kg p.o. × 4 days.

Test 11: *Effect on ovarian compensatory hypertrophy in the hemicastrated rat*—Minimum dose in mg/kg p.o. × 14 days significantly reducing increase in weight of the left ovary.

Test 12: *Effect on gonadotropin secretion in the immature male rat*—Minimum dose in mg/kg i.v. p.o. × 14 days decreasing significantly the weights of ventral prostate, seminal vesicles and testes.

Activities in test 1 are reported in Table 1 and 3-6

Discussion of results

Among the 1,2-diaryl-4,5-polymethylenepyrroles **4** (Table 1), slight antiimplantation activity is seen for 1-(*p*-hydroxyphenyl)cyclopentapyrrole (**4a**) and the activity is enhanced in the corresponding pyrrolidinoethyl ether (**4b**). Among the tetrahydroindoles **4c-4n**, activity is seen only for the basic ethers. Of these, aminopropyl ethers **4m** and **4n** are more active than the aminoethyl ethers **4h-4l**. Shifting of the pyrrolidinoethoxy group from position 4 to 3 in the phenyl group at position-1 of pyrrole (**4i**→**4d**) causes a four-fold reduction in activity. The most active preparation among the polymethylene pyrroles is the cycloheptapyrryl ether **4p** (MED_{100} 1 mg). At this dose it was estrogenic in the mouse (tests 2 and 3). Since it was also quite toxic, the preparation was not developed further. The Mannich base **5**, pyrrolopyridine **10** as well as the monocyclic pyrrole derivative **11b** were inactive.

Among the ketotetrahydroindoles **15** (Table 3), activity was fairly widespread when R was a methyl group. Thus cyclohexane-1,3-dione derived products **15a** and **15b** were inactive at 100 mg, while the corresponding derivatives **15c** and **15n** in the dimedone series were active at 50 and 10 mg respectively. The effect of substituting the N-phenyl group in **15c** by a fluorine atom is to enhance the activity in the order 4-F = 2-F > 3F, while Cl at position-4 (**15m**) does not affect it. A methyl group at position-4 (**15j**) or position 2 (**15d**) reduces or annihilates the activity. CF_3 or OH at position-3 or CF_3, CH_2CO_2H, OH, NH_2 or NO_2 at position-4 causes total loss of the activity in **15c**, while OMe or NMe_2 at position-4 diminishes it. Etherification of inactive **15v** with pyrrolidinoethyl chloride leads to the highly potent preparation **15w** (MED_{100} 3 mg). Hydrazine **15z** is quite potent, but the derived methyl thiosemicarbazide **15aa** is inactive: The last compound was inspired by the high antifertility activity of Go. 2696[10].

Substitution studies were carried out on the phenyl group at position-2 in **15n**. Bromine or chlorine atom or amino, thiosemicarbazide or nitro group in the *para*-position (**15o-15s**) abolished the activity of **15n**, while a methoxy group diminished it (**15t**). Addition of an extra methyl group in **15n** at position-3 affords **15u** again with somewhat diminished activity, while interchange of the *p*-fluorophenyl and phenyl groups in **15n** leads to inactive **15dd**. Lastly, replacement of the phenyl group in **15c** by a 3-pyridyl moiety (**28a**) (Table 5) improves the activity, while alkyl (**28d**, **28e**), aralkyl (**28f**) and cyclohexyl (**28g**) substitution has the reverse effect. The antifertility activity is likewise absent in 1-(*p*-fluorophenyl)-2-methylindole (**32**) or its dihydro derivative **36** (Table 6). Inactivity extends to **38a** and **38b**, which may be considered to be monocyclic versions of **15n**.

Manipulations were then carried out on the keto group in **15n**. The oxime **16a** and methylthiosemicarbazone **16b** were inactive (Table 4). Compound **24a**, the pyrroloazepinone (Table 6) obtained by the rearrangement of **16a**, was active at 100 mg, but neither its aminoalkyl derivative **24b**, nor its reduction product **27** was implantation inhibiting. Reduction of active ketones of the type **15** to alcohols **20** (Table 4) generally enhanced the antiimplantation potency, although this was not observed in the conversion **15b** → **20c** or **15g** → **20b**. Reduction of **15c** to **20a**, **15n** to **20d** and **15u** to **20e** enhanced the activity by factors of 5, 3.3 and 8.3 respectively. On the other hand, transformation of the 3-pryidyl ketone **28a** to the alcohol **29** (Table 5) left the activity untouched. Among the group of alcohols, again **39a** and **39b** (Table 6) representing the monocyclic analogues of **20a** and **20d** respectively were inactive. The most potent transformation product **22** (Table 4) of **15n** was obtained when the carbonyl group was reduced to a methylene group. Its effective antiimplantation dose (1 mg) was paralleled by estrogenic potency (tests 2 and 3). The very limited availability of **22** precluded further extensive testing. However, the dramatic contrast between the activity of **22** (1 mg) and its des-dimethyl derivative **4e** (inactive at 100 mg/kg) and of the pairs **15n** and **15b** and **20d** and **20e** is worth noting. Our study thus showed that in this perhydroindole series, antiimplantation activity is elicited by 1,2-diaryl or 1-heteryl-2-aryl compounds only when position-6 is substituted with methyl groups.

Table 7 — Biological Properties of **20d** (C 6924-Go)

Test No.	Effective dose (mg)
1	3
2	100
3	> 100
4	< 1
5	3
6	< 3.3 > 1
7	> 30
8	30
9	< 10 > 3
10	1
11	< 3.3
12	10

From the highly active preparations described above, **20d** (C 6924-Go) was chosen for detailed studies. It inhibited implantation in the rat — MED_{100} 3 mg/kg/day p.o. given days 1-3 or 1-6 of pregnancy and 12 mg/kg/day given days 4-6 of pregnancy. The MED_{100} for inhibition of implantation in the mouse was 20 mg/kg/day p.o. administered days 1-6 postmating, while in the rabbit, it was < 6.25 mg/kg/day p.o. for 6 days. On the other hand, implantation could not be inhibited in the hamster even at a dose of 75 mg/kg/day p.o. for 5 days. Results of other tests are provided in Table 7. Most of the responses elicited by C 6924-Go at least in the rat can be explained on the basis of its weak estrogenic and antiestrogenic activities, the mechanism probably being acceleration of tubal transport of ova. C 6924-Go was not toxic to rat at 1500 mg/kg p.o. and was not dismorphogenic in this species at 4.5 mg/kg p.o.[11]

Experimental Procedure

2-Phenacylcycloalkanones **3** *and* 3-phenacylpiperidone **9**

These were prepared using the procedure reported[2] for **3b**. Their characterization data are as follows: **3a**: b.p. 152-55°/2 mm; **3b**: b.p. 175-185°/3-4 mm, m.p. 40-43°; **3c**: b.p. 180-190°/4 mm; **3d**: b.p. 200-210°/3-4 mm, m.p.

49-50° (Found: C, 67.3; H, 6.0. $C_{14}H_{15}ClO_2$ requires C, 67.1; H, 6.0); **9**: m.p. 105-8° [maleate m.p. 167-69° (from MeOH) (Found: C, 68.0; H, 6.1; N, 3.4. $C_{24}H_{25}NO_6$ requires C, 68.1; H, 6.0; N, 3.3%] accompained by a little 1-benzyl-3,3-bisphenacyl-4-piperidone, m.p. 136-37° (from MeOH) (Found: C, 79.2; H, 6.7; N, 4.0. $C_{28}H_{27}NO_3$ requires, C, 79.0; H, 6.4; N, 3.3%).

2-Phenacylcyclohexane-1,3-diones **13** (*Table 2*)

Compounds **13a-c**, **13e**, **13h** and **13i** have been reported earlier[5]. Similarly were synthesised **13d**, **13f** and **13g**. **13d** was accompanied by a small amount of alkali-insoluble perhydroxanthone **14**, m.p. 254-55° (from acetone-ethanol) (Found: C, 67.7; H, 5.59; N, 3.47. $C_{24}H_{25}NO_6$ requires C, 68.1; H, 6.0; N, 3.3%); νC=O at 1700, 1680, 1660 cm^{-1}; PMR($CDCl_3$): δ 8.42 (*dd*, 1H, Ar−*H ortho* to NO_2), 7.45-7.95 (*m*, 3H, 3Ar−*H*), 5.19 (*s*, 1H, ArC*H*), 2.51 (*s*, 4H, CH_2), 2.29 (*s*, 4H, CH_2), 1.17 (*s*, 3H, Me), 1.11 (*s*, 3H, Me).

Polymethylenepyrroles **4**, **6**, **8**, *and pyrrolopiperidine* **10**

These were prepared by the following general procedure:

A mixture of **3b** (4.3 g) and *p*-fluoraniline (2.2 g) was heated in a stream of nitrogen at 170-180° for 2 hr. After cooling, the product was crystallised from acetone-ethanol to give **4e** (4.9 g), m.p. 129-30°.

Aminoalkyl aryl ethers of Table 1 were prepared from the appropriate phenols as follows:

A mixture of **4a** (5 g), N-(2-chloroethyl)pyrrolidine (2.8 g) and sodium hydride (1 g; 50% suspension in mineral oil) in dioxane (30 ml) was stirred at 40° overnight. Ether (100 ml) was then added and the mixture filtered. The filtrate was evaporated and the residue treated with 50 ml 2*N* HCl and ether. The free base, recovered from the gummy HCl salt, became crystalline with hexane and was recrystallised from the same solvent to afford **4b** (1.7 g), m.p. 93-94°. In some cases, the gummy bases were transformed into crystalline maleate salts.

Compounds **11a** and **11b** (Table 6) were also obtained in a similar manner.

1-Piperidinoperhydroindole **7a**

A solution of **3a** (2.2 g) and N-aminopiperidine (2.0 g) in ethanol (5 ml) and acetic acid (1 ml) was heated under reflux for 3 hr and left to cool overnight. The crystalline product was collected and re-crystallised from ethanol to yield **7a** (1.3 g), m.p. 108-10° (Table 6).

Mannich reactions of **4e** *and* **7a**

A mixture of **4e** (4.5 g), paraformaldehyde (0.75 g), morpholine hydrochloride (5.0 g) and isopropanol (20 ml) was heated under reflux with stirring for 18 hr. Upon concentration and addition of ether, the hydrochloride of **5** separated out (5.8 g), m.p. 245-48° (softening at 210°). The free base **5** was crystallised from hexane, m.p. 101-3° (Table 6).

Similar treatment of **7a** (0.42 g) afforded the methylenebis derivative, m.p. 181-82° (from ethanol) (Found: C, 81.7; H, 8.7; N, 9.6; M^+ at *m/z* 572. $C_{39}H_{48}N_4$ requires C, 81.8; H, 8.5; N, 9.8%; M, 572); PMR ($CDCl_3$): δ 3.51 (*s*, 2H, ArCH_2Ar). The desired product **7b** was an oil.

1,2-Diaryl-4-oxo-4,5,6,7-tetrahydroindoles **15** *and* **28**

The method for **15c** consisted of heating **13b** (2.58 g) and aniline (0.93 g) at 170-180° for 2 hr in N_2 atmosphere and crystallising the product **15c** from acetone-methanol, yield 2.5 g, m.p. 209-10°. Other members of **15** are listed in Table 3 and those of **28** in Table 5.

1-(Carboxymethylphenyl)tetrahydroindole **15l**

Ester **15k** (5 g) in methanol (35 ml) was mixed with potassium hydroxide (5 g) in water (10 ml) and warmed on a water-bath for 2 hr. Addition of 2*N* HCl (100 ml) precipitated the product which was filtered and crystallised from methanol to give **15l**, m.p. 250-51°.

2-(p-Aminophenyl)tetrahydroindole **15q**

A solution of the nitro compound **15s** (10 g) in THF (400 ml) was shaken with hydrogen at atmospheric pressure and room temperature in the presence of platinum catalyst (from 0.5 g PtO_2) for 17 hr when 3 mol of hydrogen had been absorbed. The mixture was filtered and the filtrate evaporated to dryness. The product **15q** was recrystallised twice from acetone-methanol, 7.9 g, m.p. 283-85°.

Allylthiosemicarbazide **15r**

The foregoing amine (**15q**; 7.0 g) was dissolved in conc. HCl (50 ml) and water (50 ml) and diazotised at 0° with sodium nitrite (1.45 g) in water (10 ml). The diazonium solution was treated with stannous chloride (15 g) in conc. HCl (20 ml) and stirred at 0-5° for 2 hr. The mixture was filtered and the insoluble complex made strongly alkaline with conc. aq. sodium hydroxide. The hydrazine was filtered off and recrystallised from chloroform-ethanol, 4.2 g, m.p. 230-31° (d). A solution of the hydrazine (4.0 g) in dioxane (100 ml) was heated with allyl isothiocyanate (1.2 g) for 8 hr. Removal of dioxane and crystallisation of the residue from methanol gave **15r** (2 g), m.p. 207° (softening at 170°).

1-(p-Aminophenyl)tetrahydroindole **15y**

A mixture of **13b** (15.6 g) and *p*-aminoacetanilide (9.0 g) was heated at 180° for 2 hr. The product was

triturated with ethanol, filtered and crystallised from methanol to give the acetyl derivative of **15y**, 18.5 g, m.p. 267-68° (Found: C, 75.8; H, 7.2; N, 7.4. $C_{24}H_{24}N_2O_4.\frac{1}{2}H_2O$ requires C, 75.5; H, 6.6; N, 7.4%).

A mixture of the acetyl derivative (18 g), dioxane (90 ml) and 6*N* HCl (180 ml) was boiled under reflux for 3 hr, cooled and made alkaline to afford **15y** (8.1 g), m.p. 268-70° (from methanol-chloroform).

Hydrazine **15z** *and methyl thiosemicarbazide* **15aa** (*Table* 3)

Amine **15y** (5.0 g) was diazotised and the diazonium complex reduced with stannous chloride to give **15z** (4.3 g), m.p. 208°(d) (from $CHCl_3$-hexane). Reaction of **15z** (5.2 g) with methyl isothiocyanate (1.2 g) in hot dioxane (100 ml) for 6 hr gave **15aa** (4.5 g).

Pyrrolidinoethoxy derivative **15w** (*Table* 3)

Phenol **15y** (3.3 g) in DMF (25 ml) was stirred with sodium hydride (0.72 g; 50% suspension in mineral oil) at 50° for ½ hr and then treated with N-(2-chloroethyl)pyrrolidine (1.8 g) in DMF (10 ml). The mixture was stirred at 50° overnight and filtered. The filtrate was evaporated *in vacuo* and the residue treated with 2*N* HCl and ether when **15w** hydrochloride separated out as a gum which became crystalline on standing, 2.4 g.

Oximes **16a** *and* **16c** *thiosemicarbazone* **16b** (*Table* 4)

A mixture of **15c** (0.8 g), hydroxylamine hydrochloride (0.3 g) and pyridine (3 ml) was heated at 100° overnight. The product was filtered, washed with water and crystallized from a large excess of ethanol to give **16c** (0.6 g), m.p. 260-61°. Similarly **15n** (6 g) gave **16a** (6 g), m.p. 274-77° (from ethanol).

Likewise **15n** (2 g) and 4-methylthiosemicarbazide (1.4 g) when heated in pyridine (10 ml) for 20 hr gave **16b** (1.2 g), m.p. 263-65° (from chloroform-methanol).

Reaction of **15n** *with semicarbazide*

A mixture of **15n** (1 g), semicarbazide hydrochloride (0.35 g) and pyridine (3 ml) was heated at 100° overnight, water added to it and the resultant precipitate filtered and washed with THF to give **17**, insoluble in usual solvents (0.7 g), m.p. >300° (Found: C, 74.5; H, 6.1; N, 11.7. $C_{45}H_{42}F_2N_6O$ requires C, 75.0; H, 5.9; N, 11.7%).

Mannich reactions of **15n** *and* **15c**

15c (3.8 g), morpholine hydrochloride (1.8 g), paraformaldehyde (0.5 g) and methanol (50 ml) were heated under reflux overnight. The mixture was cooled when unreacted **15c** separated out and was filtered off (3.4 g). The filtrate was evaporated to dryness and treated with water. The aqueous solution was basified and the product **18a** crystallized from MeOH; 0.1 g, m.p. 220-1° (Found: C, 78.1; H, 7.3; N, 6.9. $C_{27}H_{30}N_2O_2$ requires C, 78.2; H, 7.3; N, 6.8%).

A similar treatment of **15n** (3.4 g) gave a mixture of **18b** and **19b**, 50 mg, m.p. 160-70° (from ether-hexane) (Found: C, 75.3; H, 6.9; N, 6.3. $C_{27}H_{29}FN_2O_2$ requires C, 75.0; H, 6.8; N, 6.5%).

1,2-*Diaryl*-4-*hydroxy*-4,5,6,7-*tetrahydroindoles* **20** (*Table* 4)

To a solution of **15n** (30 g) in dry THF (150 ml) was added LAH (3 g) in THF (50 ml). The mixture was heated under reflux with stirring for 5 hr, set aside overnight, decomposed with water, and resultant product crystallised from THF – MeOH to give **20d** (28 g), m.p. 192-93. Reduction of **15n** with $NaBH_4$ was slow and had to be repeated a few times for completion. **20a** and **20b** were obtained by the latter method while **20c**, **20e** and **29** (Table 5) were prepared using LAH. In a large scale preparation of **20d**, a hexane-soluble byproduct, **23a** was also obtained in a low yield, m.p. 99-101° (from hexane) (Found: C, 80.0; H, 7.3; N, 4.4. $C_{23}H_{24}FNO$ requires C, 79.1; H, 6.9; N, 4.0%).

15dd upon LAH reduction and crystallisation of the product **23b** first from chloroform-ethanol and then from hexane gave **23c**, m.p. 95-96° (Found: C, 79.8; H, 7.5; N, 4.4. $C_{24}H_{26}NFO$ requires C, 79.3; H, 7.2; N, 3.9%). LAH reduction of **15o** (3 g) afforded a crude product (2.8 g), m.p. 165-67°, which after two crystallisations from THF – MeOH rose to 185-87°. This was identified as **23d** containing about 20% of **20d** (Found: C, 66.1; H, 5.7; N, 3.5; Br, 16.8%. 85% $C_{22}H_{21}BrFNO$ + 15% $C_{22}H_{22}FNO$ requires C, 66.0; H, 5.2; N, 3.5; Br, 16.4%).

Dehydration of alcohol **20d**: *Formation of dimer* **21**

A solution of **20d** (1.0 g) in THF (25 ml) and methanol (25 ml) containing a few crystals of *p*-toluenesulphonic acid was heated under reflux for 1 hr. The crystals that separated on cooling were filtered off and washed with a little methanol to give **21**, m.p. >300° [Found: C, 83.1; H, 6.5; N, 4.6. $(C_{22}H_{20}FN)_2$ requires C, 83.3; H, 6.4; N, 4.4%].

4,5,6,7-*Tetrahydroindole* **22**

A solution of alcohol **20d** (4.2 g) in THF (200 ml) was shaken with hydrogen at 50° and 50 lbs/sq. inch pressure and 10% palladium-on-charcoal (0.5 g) for 8 hr. Filtration and removal of solvent *in vacuo* gave a syrup which was dissolved in hexane. The solution was concentrated and cooled to give **22** (1.8 g), m.p. 138-40° after a further crystallisation from hexane (Table 4).

Pyrroloazepinones **24a** *and* **24c** (*Table* 6)

The oxime **16a** (10 g) was heated with polyphosphoric acid (100 g) for 5 hr at 150°. Treatment of the resultant syrup with excess of water gave **24a** which crystallized from acetone-ethanol, 7.0 g, m.p. 270°(d). Compound **16c** was similarly transformed to **24c**, m.p. 320°.

Treatment of **16a** *with sulphuric acid: Formation of sulphonic acid* **26**

The oxime **16a** (2 g) was dissolved in conc. sulphuric acid (10 g) at 30° and the solution heated at 120° for 15 min. After cooling, ice was added when crystals separated out. These were filtered, washed with warm ethanol and crystallised from aq. methanol to yield **26** (0.3 g), m.p. >300° (Found: C, 61.7; H, 5.3; N, 6.5; S, 7.9. $C_{22}H_{21}FN_2O_4S$ requires C, 61.7; H, 4.9; N, 6.5; S, 7.5%).

Treatment of **24a** (0.6 g) with conc. sulphuric acid (4 g) at 120° for 15 min, addition of ice and crystallisation of the resultant gum from ethanol-ether also gave **26**, m.p. >300°.

Dimethylaminopropylazepinone **24b**

Lactam **24a** (4.4 g) was dissolved in dimethylformamide (40 ml), sodium hydride (1 g; 50% suspension in mineral oil) was added and the solution stirred at 50° for ½ hr and treated with 3-dimethylaminopropyl chloride (1 g) in the same solvent (10 ml). The mixture was heated at 50° overnight and filtered. The filtrate was evaporated *in vacuo*, and the residue triturated with 20 ml 3*N* HCl, when the sparingly soluble hydrochloride salt of **24b** was formed. This was filtered and crystallized from methanol-ether, 2.6 g, m.p. 225-27°. The free base **24b** was liberated from the salt and crystallised from ether-hexane, m.p. 127-130° (Table 6).

Azepine **27**

A solution of **24a** (3.7 g) in dry THF (40 ml) and dioxane (35 ml) was added with stirring to a suspension of lithium aluminium hydride (2 g) in THF (50 ml) heated under reflux. After further heating for 6 hr, the reaction mixture was decomposed with water, the product recovered by evaporation of the solvents and treated with 3*N* HCl to give the sparingly soluble salt of **27**, which was crystallised from methanol-ether, 1.5 g, m.p. 245-27°. The free base had m.p. 154-55° (from ether-hexane) (Table 6).

2-*Methyltetrahydroindole* **32**

Dimedone (28 g), chloracetone (18.6 g), anhyd. potassium carbonate (84 g) and chloroform (200 ml) were stirred together overnight and worked-up for the acidic product to give 2-acetonyldimedone **30** (17.5 g), m.p. 133-35° (from aq. ethanol) (Found: C, 67.5; H, 8.2. $C_{11}H_{16}O_3$ requires C, 67.3; H, 8.2%). *p*-Fluoroaniline (5.6 g) when heated with **30** (9.8 g) for 4 hr at 140° gave **32** (9.5 g), m.p. 155-57° (from methanol). It was also obtained as follows:

A mixture of dimedone (14 g), propargyl bromide (12 g), anhyd. potassium carbonate (42 g) and chloroform (150 ml) was stirred at room temperature for 1 week to give 2-propargyldimedone **31** (2.5 g), m.p. 138-40(from aq. ethanol) (Found: C, 73.7; H, 8.0. $C_{11}H_{14}O_2$ requires C, 74.1; H, 7.9%). Heating **31** (0.9 g) with *p*-fluoroaniline (0.6 g) at 140-150° for 2 hr gave **32** (0.15 g), m.p. and mixed m.p. 156-57°.

Reduction of **32** *to* **33** *and formation of dimer* **34**

The foregoing ketone **32** (5 g) was reduced with lithium aluminium hydride (1 g) in refluxing THF (150 ml) to give after the usual work-up, alcohol **33** (5 g) as a liquid. Treatment of **33** (0.55 g) with benzoyl chloride (0.3 g) in ether (20 ml) and saturated aq. sodium bicarbonate (20 ml) gave dimer **34**, m.p. 272-73° (from acetone-methanol) [Found: C, 79.7; H, 7.3; N, 5.3; M^+ at *m/z* 510. $(C_{17}H_{18}FN)_2$ requires C, 80.0; H, 7.1; N, 5.5%; M, 510].

2-*Methyltetrahydroindoline* **36**

Dimedone (21 g), allyl bromide (18 g), potassium carbonate (60 g) and chloroform (200 ml) when stirred together for a week gave 2-alkyldimedone **35** (9 g), m.p. 151-53° (from aq. methanol) (Found: C, 73.5; H, 9.0. $C_{11}H_{16}O_2$ requires C, 73.3; H, 9.0%). **35** (5.4 g) and *p*-fluoroaniline (3.3 g) were heated together at 150° for 3 hr, and the acid-soluble part of the product (6.8 g) was crystallised from ether to give **36** (3.5 g), m.p. 108-10°, which formed a crystalline toluenesulphonate salt, m.p. 160-63° (from ethanol-ether) (Table 6).

Acetylpyrroles **38a** *and* **38b** (*Table* 6)

3-Phenacylacetylacetone **37**[12] (3.3 g) and aniline (1.4 g) were heated together at 140-150° for 3 hr in nitrogen atmosphere. The cooled product was washed with dil. HCl and water and crystallised from methanol to give **38a** (2.8 g), m.p. 99-101°. **38b** (m.p. 120-21°) was synthesised likewise.

Reduction of **38a** *and* **38b** *to alcohols* **39c** *and* **39b**

Ketone **39a** (3 g) was reduced with lithium aluminium hydride (0.7 g) in a mixture of ether (100 ml) and THF (5 ml) overnight. The product was crystallised from ether-hexane to give **39a** (2 g), m.p. 94-96°. Compound **38b**, prepared likewise, had m.p. 102-3° (Table 6).

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