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Antiimplantation Agents: Part II[a]—1,2-Diaryl-1,2,3,4-tetrahydroisoquinolines[b,c]

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1,2-Diaryl-3,4-dihydroisoquinolinium derivatives (**5**) have been synthesised from N-aryl-N-aroyl-β-phenethylamines (**4**) and found to exhibit no antiimplantation activity in the rat whereas many of the corresponding tetrahydroisoquinolines (**6**) are active. Structure-activity relationships have also been studied. 1-(*p*-Fluorophenyl)-6-methoxy-2-phenyl-1,2,3,4-tetrahydroisoquinoline (**6u**) and its nor derivative (**6v**) are very potent, while the *ortho* (**6g**) and the *meta* (**6n**) fluoro analogues as well as the des-fluoro derivative (**6d**) are quite active. Extensive biological tests have been carried out on **6g**. The enantiomers (+)-**6p**.HCl and (−)-**6g**.HCl of **6n** have similar activity profiles as that of **6n** showing no separation of antiimplantation and estrogenic properties. Diastereoisomeric 2-(2-methyl-2-phenethyl)-1-phenyl-1,2,3,4-tetrahydroisoquinolines (**13a** and **13b**) show similar properties, while the tetracyclic derivative **19** is inactive. 2-Phenoxyethyl-1-phenyl-1,2,3,4-tetrahydroisoquinoline (**26**) shows moderate activity, but 1-(β-phenethyl)-2-phenyl-1,2,3,4-tetrahydroisoquinoline **29** is inactive.

The search for antifertility agents in general and antiimplantation agents in particular which are non-hormonal' in their action has yielded very few leads. Some of these are 4-methyl-1-(3,5-bistrifluoromethylphenyl)thiosemicarbazide (C 2696-Go)[1], 1-methyl-4-(α-methylallyl)bisthiocarbamoylhydrazine (ICI 33828)[2], 5-(*m*-trifluoromethylphenyl)oxymethyl-2-thiooxazolidinone (U-11634)[3], 2-(3-methoxyphenyl)-5*H*-*s*-triazolo[5,1-*a*]isoindole (L-10492)[4] and 2-(3-methoxyphenyl)-5,6-dihydro-*s*-triazolo[5,1-*a*]isoquinoline (L-10503)[4]. 5-Bromo-2-propionylthiophene thiosemicarbazone inhibits implantation in the rat but not in hamster and progesterone synthesis by the rat ovary[5]. There has been greater success in locating antifertility agents in exercises based upon the lead of triarylethylenes, although none has developed into a drug for human use. Among these may be mentioned 1,2-diarylindenes[6], 1,2-diaryl-3,4-dihydronaphthalenes[7] and 3,4-diarylchromenes[8] with a triarylethylene chromophore. Next in order could be mentioned classes of compounds where the ethylene bond is part of an aromatic system such as triarylfurans[9], 2,3-diarylbenzofurans and naphthofurans[10], 2,3-diarylbenzothiophenes[11], 1,2-diaryl[12]- or 2,3-diarylindoles[13] and 3,4-diarylcoumarins[14]. Somewhat more prolific have been the efforts in the area of triarylethanes and their aza isosters. Examples are thus known of triaryltetrahydrofurans[15] 1,2-diaryl-1,2,3,4-tetrahydronaphthalenes[16], 3,4-diarylchromans[17], 3,4-diaryl-3,4-dihydrocoumarins[18], 3,4-diarylthiochromas[11] and 1,2-diaryl-1,2,3,4-tetrahydroquinolines[12]. Systems which are a little more removed from the triaryl ethylene or ethane prototypes, are also known to have antifertility activity. Among such compounds are 1,2,3-triarylpropenes[19], diarylacrylophenones[20,21], 1-aryl-2-cyclohexyl-1,2-dihydroisoindolones[22] and 1-aryl-2-aralkyl-1,2,3,4-tetrahydroisoquinolines[23]. Significant activity has also been observed for systems incorporating the 1,1-diarylethylene group or its aza isoster, such as benzhydrylidenecyclohexanes (e.g. Fer 6060[24] or ORF 85-11[25]), 2,6-diphenyldibenzo[*b*,*f*][1,5]-diazocine[26] and 10-aryl-11-ethyldibenzothiepins[27]. A group of phenylcyclohexene carboxylic acids, e.g. ORF 385F[28] as well as a benzofuran-3-propionic acid[29] have antiimplantation properties. 2,6-Dibenzylcyclooctanone[30], reportedly active in this parameter, does not come under any of the above groups of compounds and is claimed to possess a different mode of action than estrogens.

Most of these preparations are estrogenic to varying degrees and a number of them are antiestrogenic. Many are considered to be 'impeded' estrogens and in general, the antiimplantation effect is attributed to frank or impeded estrogenicity.

During the course of our work in this area, we encountered good anti-implantation activity in a series of 1,2-diaryltetrahydroisoquinolines and 1,2-diaryl-4,5,6,7-tetrahydroindoles and explored the possibility of achieving a dissociation of antiimplantation and estrogenic properties among active congeners. We present in this paper our results on the study of tetrahydroisoquinolines.

[a]Contribution No. 723 from Research Centre.
[b]For Part I of the series, see ref. 1.
[c]Dedicated to Dr. Nitya Anand on his 60th birth anniversary.
[d]Prepared by Dr A Nagana Goud.

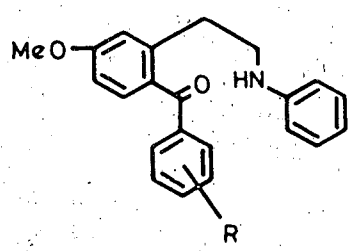
Chemistry

1,2-Diaryl-1,2,3,4-tetrahydroisoquinolines (**6**) were synthesised by the classical route shown in Scheme 1. Conversion of phenylacetic acids (**1**) to the anilides **2**, LAH reduction of **2** to N-aryl-β-phenethylamines (**3**), and aroylation of **3** to **4** were achieved in high yields (Tables 1-3). Cyclisation of the benzamide **4b** carrying no activating group *para* to the point of cyclisation afforded **5b** in 55% yield; but **5a** and **5d** were obtained only in 10% and 7% yields respectively, while **4ee** (Table 3) with a methoxy group *meta* to the point of cyclisation did not cyclise at all. On the other hand, amides **4f-4x** and **4bb-4dd** (Table 3) carrying activating groups underwent smooth cyclisation. The products (**5**; Table 4) were isolated generally as crystalline iodides in about 80% yield. Amide **4y** behaved anomalously during cyclisation, losing the bromine atom on the N-phenyl group, leading to **5f**, further identified by reduction to **6e**. The quaternary salts (**5**) were reduced in methanolic solution using $NaBH_4$ to tetrahydroisoquinolines (**6**) in high yields (Table 5). Compounds **6** were generally crystalline. However, the reduction product of **5s** was a gum and could not be characterised as such or as HCl salt. The synthesis of **6i** was achieved by catalytic reduction of **6h**. For the synthesis of the pyrrolidinoethoxy derivative **6z**, the benzyloxy amide **4u** was cyclised to the dihydroisoquinolinium derivative **5u**, which was reduced to **6x**, then debenzylated to **6y** and finally etherified. Demethylation of **6u** with HBr afforded the other phenol (**6v**).

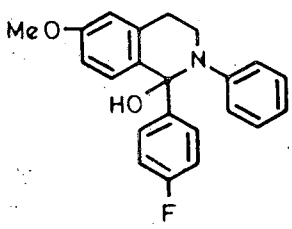
The free base, liberated from **5r** with aq. NaOH, appears to exist as ketone **7a** (IR $\gamma C=O$ 1660, γNH 3370 cm^{-1}) rather than as carbinolamine **8**.

The Birch reduction of **6d** was attempted to obtain an enone, but the experiment failed to give a characterisable product.

The bases **6g** and **6u** did not form stable salts with *d*-camphor sulphonic acid to allow optical resolution. But **6n** could be resolved into enantiomers which were



7a R = 4-F
7b R = 3-F



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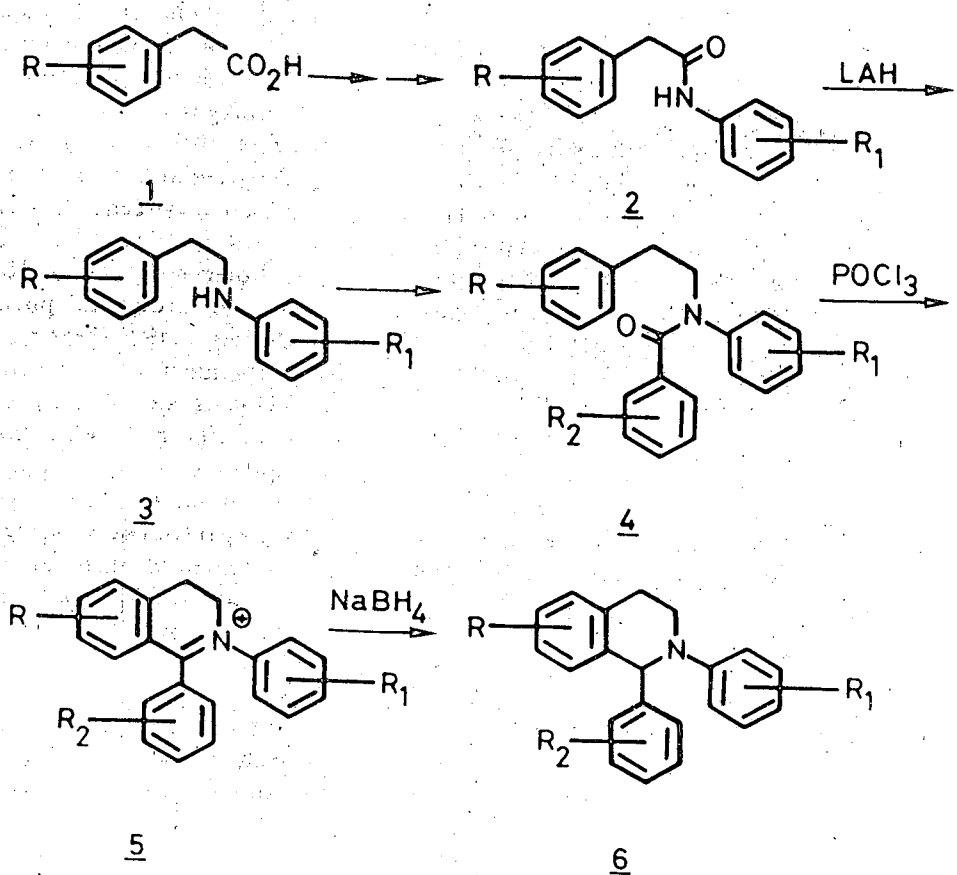
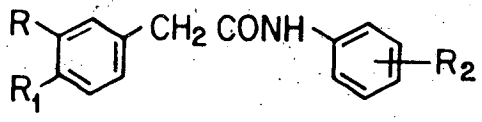


1 2 3 4 5 6

Scheme 1

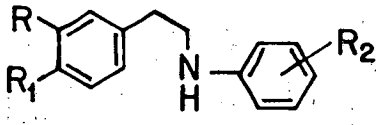
Table 1—Phenylacetanilides (2)



Compd	R	R_1	R_2	Yield (%)	m.p. °C	Crystallised from*	Mol. formula	Found (%) (Calc.) C	H	N
2a	H	H	H	90	119-20	A+C	$C_{14}H_{13}NO$	79.4 (79.6	6.0 6.2	6.3 6.6)
2b	H	H	3-CF_3	76	83-85	A+C	$C_{15}H_{12}F_3NO$	64.8 (64.5	4.4 4.3	5.0 5.0)
2c	OMe	H	H	85	108-9	A+C	$C_{15}H_{15}NO_2$	74.5 (74.7	6.2 6.3	5.6 5.8)
2d	OMe	H	2-Cl	71	108-10	B	$C_{15}H_{14}ClNO_2$	65.6 (65.3	5.1 5.1	5.2 5.1)
2e	OMe	H	2-Br	69	110-12	A+C	$C_{15}H_{14}BrNO_2$	55.8 (56.3	4.6 4.4	4.2 4.4)
2f	OMe	H	3-F	79	74-77	B+C	$C_{15}H_{14}FNO_2$	69.7 (69.5	5.5 5.4	5.4 5.4)
2g	OMe	H	3-Br	58	95-97	A	$C_{15}H_{14}BrNO_2$	55.7 (56.3	4.5 4.4	4.8 4.4)
2h	OMe	H	4-Br	76	139-40	B	$C_{15}H_{14}BrNO_2$	56.4 (56.3	4.7 4.4	4.5 4.4)
2i	H	OMe	H	78	118-19	B	$C_{15}H_{15}NO_2$	74.7 (74.7	6.6 6.3	6.0 5.8)
2j	OMe	OMe	H	80	110-11	A	$C_{16}H_{17}NO_3$	71.1 (70.8	6.6 6.3	5.5 5.2)
2k	$-OCH_2O-$		H	75	147-49	A	$C_{15}H_{13}NO_3$	70.2 (70.6	5.4 5.1	5.9 5.5)

*A = Methanol; B = Ethanol; C = Water.

Table 2—N-Aryl-β-phenethylamines (3)



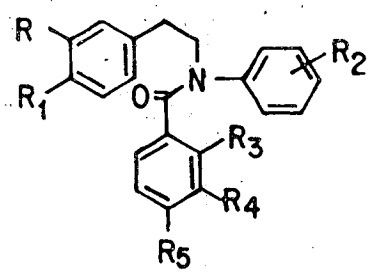
Copmd	R	R_1	R_2	Yield (%)	b.p. °C/mm	Mol. formula
3a	H	H	H	94	Liquid	$C_{14}H_{15}N$
3b*	H	H	3-CF_3	85	Liquid	$C_{15}H_{14}F_3N$
3c	OMe	H	H	72	205-10/3-4	$C_{15}H_{17}NO$
3d	OMe	H	2-Cl	82	173-76/1-1.5	$C_{15}H_{16}ClNO$
3e	OMe	H	2-Br	85	185-88/1.5-2	$C_{15}H_{16}BrNO$
3f	OMe	H	3-F	81	172-75/2	$C_{15}H_{16}FNO$
3g	OMe	H	3-Br	75	192-94/1-2	$C_{15}H_{16}BrNO$
3h	H	OMe	H	83	175-78/1-1.5	$C_{15}H_{17}NO$
3i	OMe	OMe	H	82	195-200/1.5	$C_{16}H_{19}NO_2$
3j	$-O-CH_2-O-$		H	71	200-202/1	$C_{15}H_{15}NO_2$

*3b.HCl, $C_{15}H_{15}ClF_3N$, m.p. 137-40° (from ethanol-ether) (Found: C, 60.0; H, 5.2; N, 4.4. $C_{15}H_{14}F_3N$.HCl requires C, 59.7; H, 5.0; N, 4.6%)

characterised as HCl salts [(+)-**6p**.HCl and (−)-**6q**.HCl] for biological evaluation.

A report on the facile racemisation of the alkaloid cryptostyline (I), a 1-phenyl-2-methyl-1,2,3,4-tetrahydroisoquinoline[31] derivative, on refluxing its solution in ether prompted us to examine the stability of the dextrorotatory base from (−)-**6q**.HCl. No loss in optical activity was observed on heating its ethereal solution under reflux for 6 hr. However, after prolonged standing, a small amount of a product was

Table 3—N-Aryl-β-phenylethylamides (4)



Compd	R	R_1	R_2	R_3	R_4	R_5	yield (%)	m.p. °C	Crystallised from*	Mol. formula	Found % (Calc.) C	H	N
4a	H	H	H	H	H	H	90	118-20	A+C	$C_{21}H_{19}NO$	83.4 (83.7	6.1 6.3	4.4 4.7)
4b	H	H	3-CF_3	H	H	H	60	108-9	A+C	$C_{22}H_{18}F_3NO$	71.4 (71.5	5.2 4.9	4.0 3.8)
4c	H	H	3-CF_3	F	H	H	62	69-70	A+C	$C_{22}H_{17}F_4NO$	68.3 (68.2	4.3 4.4	4.0 3.6)
4d	H	H	3-CF_3	H	Br	H	79	83-85	A+C	$C_{22}H_{17}BrF_3NO$	59.1 (58.9	3.9 3.8	3.6 3.1)
4e	H	H	3-CF_3	Cl	H	Cl	89	110-11	A+C	$C_{22}H_{16}Cl_2F_3NO$	60.1 (60.3	3.7 3.7	3.3 3.2)
4f	OMe	H	H	H	H	H	71	71-74	A	$C_{22}H_{21}NO_2$	79.8 (79.7	6.6 6.4	4.2 4.2)
4g	OMe	H	H	Br	H	H	76	98-100	A	$C_{22}H_{20}BrNO_2$	64.4 (64.4	5.2 4.9	3.9 3.4)
4h	OMe	H	H	Cl	H	H	62	96-98	A	$C_{22}H_{20}ClNO_2$	72.5 (72.2	5.5 5.5	4.2 3.8)
4i	OMe	H	H	F	H	H	79	Gum		$C_{22}H_{20}FNO_2$			
4j	OMe	H	H	NO_2	H	H	72	102-3	A	$C_{22}H_{20}N_2O_4$	70.5 (70.2	5.6 5.4	7.9 7.4)
4k	OMe	H	H	OMe	H	H	91	Gum		$C_{23}H_{23}NO_3$			
4l	OMe	H	H	Me	H	H	68	76-78	A	$C_{23}H_{23}NO_2$	80.1 (80.0	7.0 6.7	4.4 4.1)
4m (H_2O)	OMe	H	H	H	Br	H	49	74-76	A+C	$C_{22}H_{20}BrNO_2.H_2O$	61.4 (61.7	4.9 4.7	3.5 3.3)
4n	OMe	H	H	H	Cl	H	57	Gum		$C_{22}H_{20}ClNO_2$			
4o	OMe	H	H	H	F	H	74	65-67	D+E	$C_{22}H_{20}FNO_2$	76.0 (75.6	6.0 6.0	4.0 4.0)
4p	OMe	H	H	H	H	Br	52	79-99	A	$C_{22}H_{20}BrNO_2$	64.4 (64.4	5.0 4.9	3.4 3.4)
4q	OMe	H	H	H	H	Cl	61	88-89	B+C	$C_{22}H_{20}ClNO_2$	72.1 (72.2	5.6 5.5	3.6 3.8)
4r	OMe	H	H	H	H	F	92	Gum		$C_{22}H_{20}FNO_2$			
4s	OMe	H	H	H	H	NO_2	68	97-99	A	$C_{22}H_{20}N_2O_4$	70.5 (70.2	5.5 5.4	7.4 7.4)
4t	OMe	H	H	H	H	OMe	71	89-91	A	$C_{23}H_{23}NO_3$	76.4 (76.4	6.7 6.4	4.3 3.9)
4u	OMe	H	H	H	H	OCH_2PH	78	103-5	B	$C_{29}H_{27}NO_3$	79.0 (79.6	6.4 6.2	3.3 3.2)
4v	OMe	H	H	H	H	OCH_2CH_2OH	59	100-101	A+C	$C_{24}H_{25}NO_4$	(73.7 (73.6	6.8 6.4	3.8) 3.6)
4w Picrate	OMe	H	H	H	H	Piperidino-ethoxy	62	143-45	B	$C_{35}H_{37}N_5O_{10}$	61.3 (61.1	5.6 5.4	10.5 10.2)
4x	OMe	H	3-F	H	F	H	40	67-68	B+C	$C_{22}H_{19}F_2NO_2$	72.1 (71.9	5.2 5.2	4.2 3.8)
4y	OMe	H	2-Br	Br	H	H	68	Gum		$C_{22}H_{19}Br_2NO_2$			

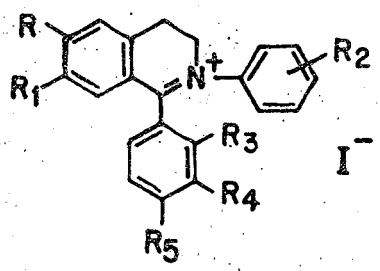
Contd

Table 3—N-Aryl-β-phenylethylamides (**4**)—*Contd*

Compd	R	R_1	R_2	R_3	R_4	R_5	yield (%)	m.p. °C	Crystallised from*	Mol. formula	Found (%) (Calc.) C	H	N
4z	OMe	H	2-Cl	F	H	H	71	67-70	D	$C_{22}H_{19}ClFNO_2$	68.7 (68.8	4.8 5.0	3.6 3.7)
4aa	OMe	H	3-Br	Br	H	H	86	Gum		$C_{22}H_{19}Br_2NO_2$			
4bb	OMe	OMe	H	Cl	H	H	65	141-43	A	$C_{23}H_{22}ClNO_3$	69.8 (69.8	5.8 5.6	3.9 3.5)
4cc	OMe	OMe	H	F	H	H	48	116-18	A	$C_{23}H_{22}FNO_3$	72.4 (72.8	6.0 5.8	4.1 3.7)
4dd	$-OCH_2O-$		H	F	H	H	93	Gum		$C_{22}H_{18}FNO_3$			
4ee	H	OMe	H	H	H	H	57	114-15	B	$C_{22}H_{21}NO_2$	79.7 (79.7	6.6 6.4	4.0 4.2)
4ff	OMe	H	H	H	CF_3	H	76	Gum		$C_{23}H_{20}F_3NO_2$			

*A = Methanol; B = ethanol; C = water; D = ether; E = hexane.

Table 4—1,2-Diaryl-3,4-dihydroisoquinolinium iodides (**5**)



Compd*	R	R_1	R_2	R_3	R_4	R_5	m.p. °C	Crystallised from†	Mol. formula	Found (%) (Calc.) C	H	N	Antiimplantation activity (MED_{100} in mg/kg p.o.)
5a	H	H	H	H	H	H	298 (d)	A	$C_{21}H_{18}IN$	61.4 (61.3	4.8 4.4	3.7 3.4)	
5b	H	H	3-CF_3	H	H	H	221-23 (d)	B + D	$C_{22}H_{17}F_3IN$	55.4 (55.1	3.9 3.6	2.9 2.9)	φ
5c	H	H	3-CF_3	F	H	H	Gum		$C_{22}H_{16}F_4IN$				
5d	H	H	3-CF_3	Cl	H	Cl	233-34 (d)	B + D	$C_{22}H_{15}Cl_2F_3IN$	48.2 (48.2	3.0 2.8	2.4 2.6)	φ
5e	OMe	H	H	H	H	H	227 (d)	B + D	$C_{22}H_{20}INO$	59.3 (59.9	4.8 4.6	3.0 3.2)	φ
5f	OMe	H	H	Br	H	H	203-5	B + D	$C_{22}H_{19}BrINO$	51.1 (50.8	4.0 3.7	2.8 2.7)	φ
5f (Cl^-)	OMe	H	H	Br	H	H	207-8	B + C	$C_{22}H_{19}BrClNO$	62.4 (61.6	4.7 4.5	3.2 3.3)	
5g	OMe	H	H	Cl	H	H	211-13 (d)	B + D	$C_{22}H_{19}ClINO$	55.1 (55.5	4.3 4.0	3.3 2.9)	
5h	OMe	H	H	F	H	H	190-93 (d)	B	$C_{22}H_{19}FINO$	57.5 (57.5	4.3 4.1	3.2 3.1)	
5h (Cl^-)	OMe	H	H	F	H	H	210 (d)	B + D	$C_{22}H_{19}ClFNO$	72.1 (71.8	5.4 5.2	4.2 3.8)	φ
5i	OMe	H	H	NO_2	H	H	197-200	A	$C_{22}H_{19}IN_2O_3$	54.0 (54.3	4.0 3.9	5.4 4.8)	
5j	OMe	H	H	OMe	H	H	Gum		$C_{23}H_{22}INO$				
5k	OMe	H	H	Me	H	H	216-18	A + D	$C_{23}H_{22}INO$	60.2 (6.7	5.0 4.9	3.2 3.1)	
5l	OMe	H	H	H	Br	H	204-6 (d)	A + D	$C_{22}H_{19}BrINO$	50.8 (50.8	3.9 3.7	2.9 2.7)	

Contd

Table 4—1,2-Diaryl-3,4-dihydroisoquinolinium iodides (5)—*Contd*

Compd*	R	R_1	R_2	R_3	R_4	R_5	m.p. °C	Crystallised from†	Mol. formula	Found (%) (Calc.) C	H	N	antiimplantation activity (MED_{100} in mg/kg p.o.)
5m H_2O	OMe	H	H	H	Cl	H	210-12 (d)	A+D	$C_{22}H_{19}ClINO.H_2O$	53.0 (53.5	4.2 4.3	3.0 2.8)	
5n H_2O	OMe	H	H	H	F	H	234-37 (d)	A+D	$C_{22}H_{19}FINO.H_2O$	55.6 (55.3	4.2 4.4	3.4 2.9)	
5o	OMe	H	H	H	CF_3	H	218-20	B+D	$C_{23}H_{19}F_3INO$	54.5 (54.2	4.1 3.8	3.1 2.8)	φ
5o (Cl^-)	OMe	H	H	H	CF_3	H	257-60 (d)	B+D	$C_{23}H_{19}F_3ClNO$	65.9 (66.1	4.8 4.6	3.5 3.4)	
5p	OMe	H	H	H	H	Br	229-31 (d)	B+D	$C_{22}H_{19}BrINO$	50.5 (50.8	4.1 3.7	3.1 2.7)	
5q	OMe	H	H	H	H	Cl	216-18	B+D	$C_{22}H_{19}INO$	55.6 (55.5	4.1 4.0	2.9 3.0)	φ
5r	OMe	H	H	H	H	F	190-92 (d)	A+D	$C_{22}H_{19}FINO$	57.8 (57.5	4.5 4.2	3.2 3.1)	
5r (Cl^-)	OMe	H	H	H	H	F	223 (d)	B+D	$C_{22}H_{19}ClFNO$	71.8 (71.8	5.3 5.2	4.0 3.8)	φ
5s	OMe	H	H	H	H	NO_2	214 (d)	A+D	$C_{22}H_{19}IN_2O_3$	54.4 (54.3	4.1 3.9	5.6 5.8)	φ
5t	OMe	H	H	H	H	OMe	185-87	A+D	$C_{23}H_{22}INO_2$	58.8 (58.6	4.6 4.7	3.0 3.0)	φ
5u	OMe	H	H	H	H	OCH_2Ph	137-42	B+D	$C_{29}H_{26}INO_2$	63.5 (63.6	4.8 4.8	2.5 2.6)	φ
5v (di-picrate)	OMe	H	H	H	H	Piperi-dino-ethoxy	165-67	B	$C_{41}H_{39}N_8O_{16}$	55.2 (54.7	4.7 4.4	13.2 12.5)	φ (as chloride)
5w	OMe	H	3-F	H	F	H	235-36	A+D	$C_{22}H_{18}F_2INO$	55.1 (55.4	4.0 3.8	3.4 2.9)	
5w (Cl^-)	OMe	H	3-F	H	F	H	294- (d)	B+D	$C_{22}H_{18}ClF_2NO$	68.2 (68.5	4.8 4.7	4.0 3.6)	
5x	OMe	OMe	H	Cl	H	H	216-17 (d)	A+D	$C_{23}H_{21}ClINO_2$	54.8 (54.6	4.3 4.2	3.0 2.8)	
5y	OMe	OMe	H	F	H	H	216-18 (d)	A+D	$C_{23}H_{21}FINO_2$	56.3 (56.5	4.2 4.3	3.0 2.9)	
5z	$-OCH_2O-$		H	F	H	H	Gum		$C_{22}H_{17}FINO_2$	—	—	—	
5aa	OMe	H	3-Br	Br	H	H	185-8 (d)	A+D	$C_{22}H_{18}Br_2INO$	44.4 (44.1	3.0 3.0	2.6 2.3)	

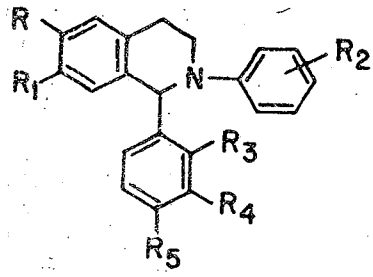
*Compounds were obtained in about 60-80% yield except for **5b-5d** which were obtained in 20-30% yield.
†A = Methanol; B = ethanol; C = benzene; D = ether.

isolated, which was identified as the pseudobase of the dihydroisoquinolinium derivative in the form of the ketone **7b** (IR: νC=O at 1640 and νNH at 3400 cm^{-1}).

2-Aralkyl-1-phenyl-1,2,3,4-tetrahydroisoquinolines, e.g. 2-(2-methyl-2-phenethyl)-1-phenyl-1,2,3,4-tetrahydroisoquinoline (**13**), are reported[22] to have potent anti-implantation properties. The latter (**13**) has been prepared and tested as a mixture of two diastereoisomeric racemates. We have been able to synthesise both diastereoisomeric racemates in the pure state in this study, our aim being to ascertain if one was more potent than the other as an antiimplantation agent and if there was a separation between this and estrogenic properties. Our first attempt involving quaternization of 1-phenyl-3,4-dihydroisoquinoline (**9**)[32] with 2-methyl-2-phenethyl chloride to give **10** failed. The successful route (Scheme 2) consisted of the acylation of 1-phenyl-1,2,3,4-tetrahydroisoquinoline (**11**)[32] with 2-phenylpropionyl chloride. The two diastereoisomeric amides **12a** and **12b** could be isolated in pure state at this stage by crystallization and then separately reduced to the desired tertiary bases **13a** and **13b** characterized as HCl salts. Unfortunately usual physical data, viz PMR spectra were of no avail in differentiating the stereochemistry of these products.

Dibenzoquinolizidine **19** was conceived as a cyclic version of **13** and was synthesised conventionally as

Table 5—1,2-Diaryl-1,2,3,4-tetrahydroisoquinolines (6)



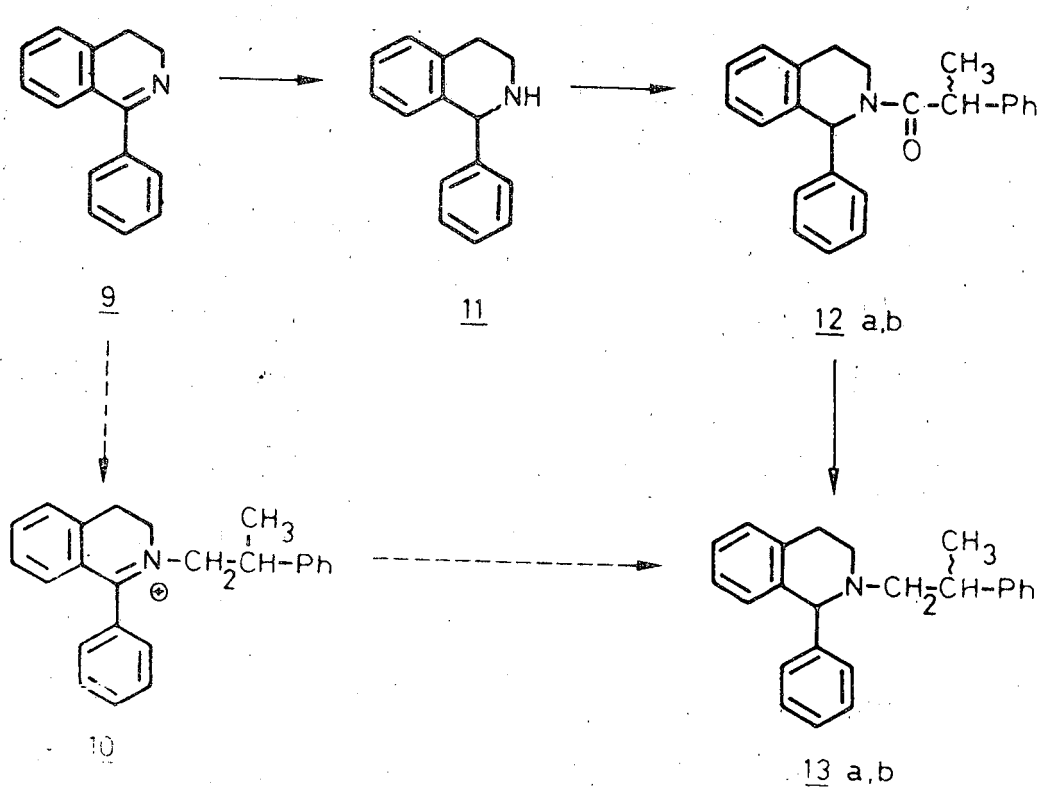
Compd*	R	R_1	R_2	R_3	R_4	R_5	m.p. °C	Crystallised from†	Mol. formula	Found (%) (Calc.) C	H	BN	Antiimplantation activity (MED_{100} in mg/kg p.o.)
6a .HCl	H	H	H	H	H	H	223-26	B+D	$C_{21}H_{19}N.HCl$	78.1 (78.4	6.6 6.3	4.6 4.4)	30
6b	H	H	3-CF_3	H	H	H	77-79	B	$C_{22}H_{18}F_3N$	74.6 (74.7	5.3 5.1	4.1 4.0)	φ
6c	H	H	3-CF_3	F	H	H	79-80	B	$C_{22}H_{17}F_4N$	71.5 (71.1	4.6 4.6	3.9 3.8)	φ
6d	OMe	H	H	H	H	H	107-8	F+A	$C_{22}H_{21}NO$	83.4 (83.1	6.9 7.0	4.3 4.6)	3
6e	OMe	H	H	Br	H	H	139-40	F+A	$C_{22}H_{20}BrNO$	66.9 (67.0	5.2 5.1	3.7 3.6)	50
6f	OMe	H	H	Cl	H	H	128-30	F+A	$C_{22}H_{20}ClNO$	75.6 (75.5	6.0 5.8	4.3 4.0)	25
6g	OMe	H	H	F	H	H	107-9	F+A	$C_{22}H_{20}FNO$	79.3 (79.3	6.0 6.1	4.5 4.2)	3
6h	POMe	H	H	NO_2	H	H	158-59	F+A	$C_{22}H_{20}N_2O_3$	73.3 (73.3	5.7 5.6	7.9 7.8)	φ (at 50); φ (at 10)
6i	OMe‡	H	H	NH_2	H	H	140-41	B	$C_{22}H_{22}N_2O$			8.6 (8.5)	
6j	OMe	H	H	OMe	H	H	181-83	F+A	$C_{23}H_{23}NO_2$	79.6 (80.0	6.9 6.7	3.7 4.1)	50
6k	OMe	H	H	Me	H	H	127-28	F+A	$C_{23}H_{23}NO$	83.6 (83.9	7.2 7.0	4.0 4.3)	3
6l	OMe	H	H	H	Br	H	129-30	F+A	$C_{22}H_{20}BrNO$	67.3 (67.0	5.2 5.1	3.9 3.6)	25
6m	OMe	H	H	H	Cl	H	116-17	G+E	$C_{22}H_{20}ClNO$	75.8 (75.5	6.0 5.8	4.4 4.0)	5
6n	OMe	H	H	H	F	H	87-88	G+E	$C_{22}H_{20}FNO$	79.5 (79.3	6.2 6.1	4.6 4.2)	3
6o .HCl	OMe	H	H	H	F	H	234-38 (d)	A+D	$C_{22}H_{21}ClFNO$	71.5 (71.4	5.7 5.7	3.8 3.8)	3
(+)6p .HCl	OMe	H	H	H	F	H	228-33	B+D	$C_{22}H_{21}ClFNO$	71.7 (71.4	5.6 5.7	3.6 3.8)	5
(−)6q .HCl	OMe	H	H	H	F	H	235-40	A+D	$C_{22}H_{21}ClFNO$	71.6 (71.4	5.8 5.7	4.2 3.8)	3
6r	OMe	H	H	H	CF_3	H	196-200	B+D	$C_{23}H_{20}F_3NO$	65.7 (65.8	5.0 5.0	3.5 3.3)	25
6s	OMe	H	H	H	H	Br	161-763	F+A	$C_{22}H_{20}BrNO$	66.9 (67.0	5.2 5.1	3.8 3.6)	φ
6t	OMe	H	H	H	H	Cl	126-28	C+E	$C_{22}H_{20}ClNO$	74.9 (75.5	6.0 5.8	4.2 4.0)	100**
6u	OMe	H	H	H	H	F	116-18	F+A	$C_{22}H_{20}FNO$	79.5 (79.3	6.2 6.1	4.1 4.2)	1
6v .HCl	OH	H	H	H	H	F	221-23	A+D	$C_{21}H_{19}ClFNO$	70.9 (70.9	5.9 5.4	4.1 3.2)	1

Contd.

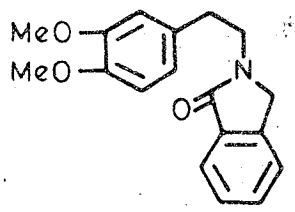
Table 5—1,2-Diaryl-1,2,3,4-tetrahydroisoquinolines (6)—*Contd*

Compd*	R	R_1	R_2	R_3	R_4	R_5	m.p. °C	Crystallised from†	Mol. formula	Found (%) (Calc.) C	H	N	Antiimplantation activity (MED_{100} in mg/kg p.o.)
6w	OMe	H	H	H	H	OMe	84-86	CH_2Cl_2+E	$C_{23}H_{23}NO_2$	79.7 (80.0	7.0 6.7	4.3 4.1)	<100**
6x	OMe	H	H	H	H	OCH_2Ph	Gum		$C_{29}H_{27}NO_2$				
6y .HCl	OMe	H	H	H	H	OH	199-202 (d)	B+D	$C_{22}H_{22}ClNO_2$	72.2 (71.8	6.2 6.0	3.6 3.8)	
6z	OMe	H	H	H	H	Pyrrolidino-ethoxy	Oil§		$C_{28}H_{32}N_2O_2$	78.5 (78.5	7.8 7.5	6.4 6.5)	3
6aa	OMe	H	H	H	H	Piperidino-ethoxy	Gum		$C_{29}H_{34}N_2O_2$	78.3 (78.7	7.8 7.7	5.8 6.3)	100
6bb	OMe	H	3-F	H	F	H	72-74	D+E	$C_{22}H_{19}F_2NO$	75.6 (75.2	5.4 5.5	3.8 4.0)	25
6cc	OMe	OMe	H	Cl	H	H	157-58	F+A	$C_{23}H_{22}ClNO_2$	72.6 (72.7	6.1 5.8	3.8 3.7)	φ
6dd	OMe	OMe	H	F	H	H	120-22	F+A	$C_{23}H_{22}FNO_2$	76.4 (76.0	6.3 6.1	4.2 3.9)	φ
6ee	$-OCH_2O-$		H	F	H	H	120-21	H+E	$C_{22}H_{18}FNO_2$	79.9 (76.1	5.4 5.2	4.3 4.0)	<100**

*Compounds were obtained in 80-90% yield.
†A = Methanol; B = ethanol; C = CH_2Cl_2; D = ether; E = hexane; F = acetone; G = benzene; H = chloroform.
‡Found: M^+ at m/z 330. Calc: M, 330.
**Not tested at lower doses.
§b.p. 180-90% 0/mm.



Scheme 2



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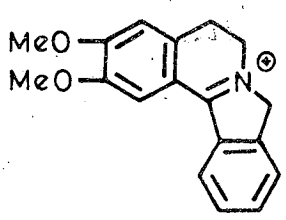

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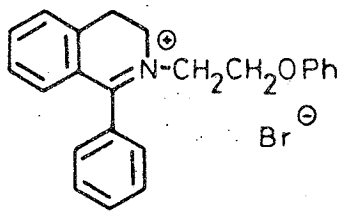

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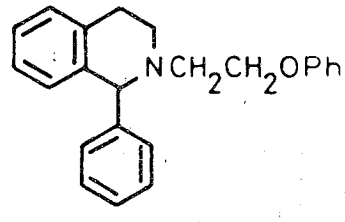

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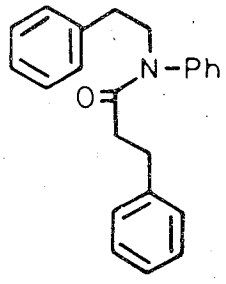

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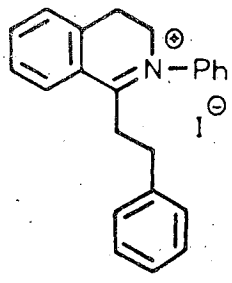

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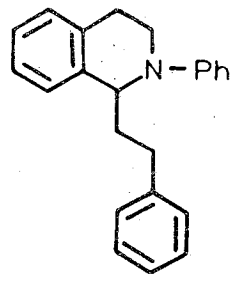

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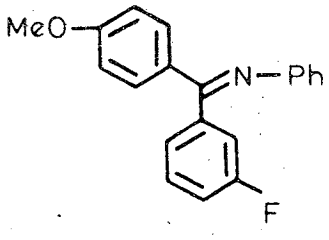

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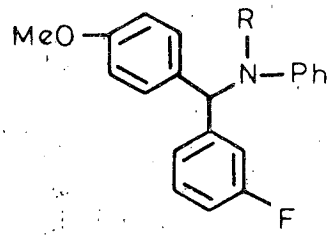


31 a R = H
31 b R = Et

Test 3: Vaginal opening in immature mouse—dose in mg/kg/p.o. producing significant effect.

Test 4: Vaginal smears (Allen Doisy) test in castrated rat—ED_{50} in mg/kg/p.o. eliciting a positive response in terms of absence of leukocytes in 50% of rats.

Test 5: Induction of uterine withdrawal bleeding in immature Rhesus monkey—ED_{50} in mg/kg/p.o. showing this property in 50% of monkeys treated.

Test 6: Antiuterotropic activity in immature mouse—*MED* in mg/kg p.o. significantly inhibiting increase in uterus weight of estradiol treated immature rats.

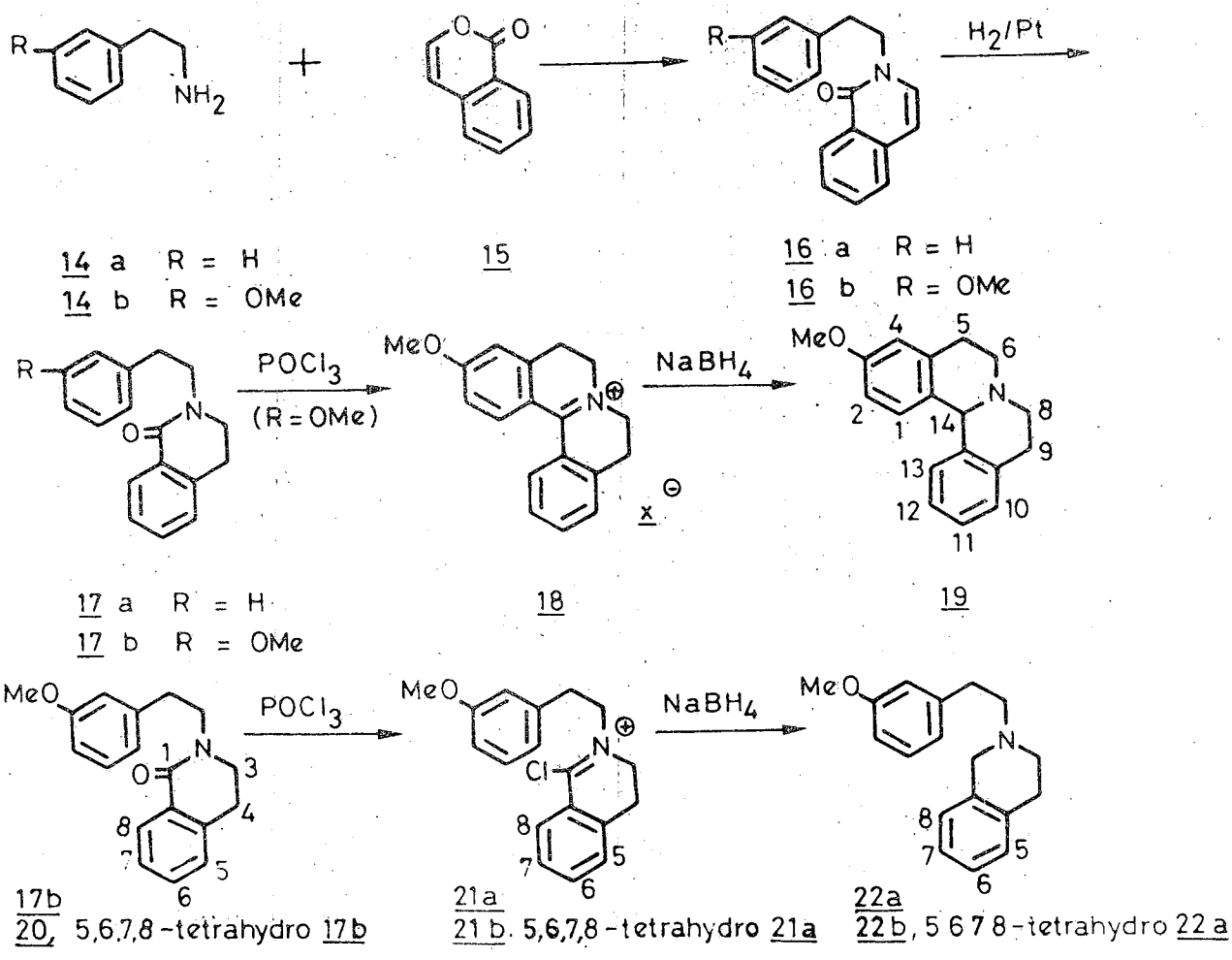
Test 7: Deciduoma formation in pregnant and pseudopregnant rats—*MED* in mg/kg/p.o. significantly inhibiting the deciduoma formation.

Test 8: Effect on ovarian compensatory hypertrophy in hemicastrated rat—*MED* in mg/kg day p.o. inducing 100% inhibition.

Test 9: Effect on gonadotropin secretion in immature male rat—minimum dose *MED* in mg/kg/day p.o. which significantly inhibits increase in the ventral prostate and seminal vesicle weights.

Discussion of results

All the dihydroisoquinolinium salts tested had no antiimplantation activity at 100 mg/kg p.o. for 6 days. Activity was observed for most of the 1,2-diaryltetrahydroisoquinolines (**6**). The prototype, 1,2-diphenyl-1,2,3,4-tetrahydroisoquinoline (6a) was active at 30 mg/kg, but the activity was lost on



Scheme 3

shown in Scheme 3. An attempted synthesis of desmethoxy **19** failed at the stage of cyclisation of **17a** due to lack of activation, while treatment of **16a** with $POCl_3$ merely gave 1-chloro-N-(β-phenethyl)isoquinolinium chloride. The byproduct, isolated in the preparation of **19** from crude **17b** through the uncharacterised salt **18**, was tentatively identified as a mixture of **22a** and **22b** in an approximate ratio of 1:3 on the basis of TLC and PMR and mass spectral evidences. Their genesis is traceable to the formation of a small amount of **20** during the catalytic reduction of **16b** to **17b** and subsequent conversion of **17b** and **20** to the immonium chlorides **21a** and **21b**. Further reduction with borohydride would lead to **22a** and **22b**.

Although adequately activated, isoindolinone **23** did not undergo cyclisation to **24**.

The synthesis of N-phenoxyethylisoquinolinium salt (**25**) (Table 6) was achieved from **9** by quaternisation with phenoxyethyl bromide. Alkylation of **11** with the same halide afforded **26**. 1-(2-Phenethyl)isoquinoline **29** was obtained from the amide **27** through the dihydroisoquinolinium salt **28**.

The schiff base **30** (Table 6) was prepared from the appropriate ketone via the dichloride and aniline with a view to reducing it to **31a** and then alkylating to **31b** which would be an acyclic version of **6n**. Unfortunately, the reduction product could not be properly characterised. An alternative approach involving condensation of the corresponding diphenyl chloromethane with N-ethylaniline also failed to yield the desired product.

Biology

The basic screening assessed the potency of compounds in inhibiting implantation in the rat. Other tests were also carried out to characterise highly active preparations. The tests are listed below. Details have been provided earlier[1].

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

Test 2: Uterotropic activity in immature mouse—effective dose in mg/kg/p.o. which induces 100% increase in uterus weight.

Table 6—Miscellaneous Compounds

Compd	Yield (%)	m.p. °C	Crystallised from	Mol. formula	Found (%) (Calc.) C	H	N	Antiimplantation activity (MED_{100} in mg/kg p.o.)
7a		75-76	Hexane	$C_{22}H_{20}FNO_2$	75.7 (75.6	6.6 5.8	4.0 4.0)	>100
7b	13	105-6	EtOH	$C_{22}H_{20}FNO_2$	76.1 (75.6	6.0 5.8	4.0 4.0)	
13a HCl	45	238-40	EtOH-ether	$C_{24}H_{26}ClN$	79.0 (79.2	7.5 7.2	3.8 3.9)	1
13b HCl	65	228-31	EtOH-ether	$C_{24}H_{26}ClN$	79.4 (79.2	7.5 7.2	4.1 3.9)	1
19 HCl	73	255	EtOH-ether	$C_{18}H_{20}ClNO$	71.6 (71.6	6.8 6.7	4.4 4.6)	φ
25	32	168-72	EtOH-ether	$C_{23}H_{22}BrNO$	67.4 (67.7	5.6 5.4	3.7 3.4)	φ
26	50	227-9	EtOH	$C_{23}H_{24}ClNO$	75.7 (75.5	6.9 6.6	3.9 3.8)	30
28	52	188-90	EtOH-ether	$C_{23}H_{22}IN$	63.1 (62.9	5.4 5.1	3.4 3.2)	φ
29 HCl	69	150-2	EtOH-ether	$C_{23}H_{24}ClN$	78.7 (79.0	7.1 6.9	4.1 4.0)	φ
30	40	86-7	Hexane	$C_{20}H_{16}FNO$	78.8 (78.7	5.4 5.3	4.8 4.6)	φ

introduction of a substituent (*m*-CF_3; **6b**) in the phenyl group at position-2 alone or with an extra substituent (2-F, **6c**) in the phenyl group at position-1. Further extensive structure-activity analysis was not carried out, since the synthesis of adequate quantities of required analogues posed problems. Poor yields in the conversion of **4** to **5** due to lack of an activating methoxy group was responsible for this.

1,2-Diaryl-1,2,3,4-tetrahydroisoquinolines (**6**) carrying a methoxy group at position-6 were widely studied. In this group, the bulk of the compounds investigated had an unsubstituted phenyl group at position-2. The parent compound (**6d**) itself was highly active (MED_{100} 3 mg/kg). Introduction of a halogen atom in the phenyl group modified the activity, generally decreasing it, the one (**6s**) carrying a bromine atom at position-4 was totally inactive. At any given position, the activity decreased in the order F > Cl > Br. Compound **6u**, carrying a fluorine atom at position-4 was the most active of the lot with MED_{100} 1 mg/kg; similar activity was shown only by the corresponding 6-hydroxytetrahydroisoquinoline (**6v**).

Among other substituents tried, NO_2 or NH_2 at position-2 (**6h** or **6i**) gave inactive compounds, while the 2-OMe derivative (**6j**) was moderately active and 2-methyl derivative (**6k**) quite potent. Apart from halogen atoms at position-3, the effect of 'pseudohalogen' group (CF_3) was tried and found to yield a moderately active compound (**6r**). At position-4, the presence of a piperidinoethoxy substituent led to the loss of activity (**6aa**; MED_{100} 100 mg/kg), while that of a pyrrolidinoethoxy group provided a highly potent derivative (**6z**; MED_{100} 3 mg).

Compared to **6f** and **6g**, compounds 6cc and **6dd** carrying an extra methoxy group at position-7 had lost their activity dramatically. Replacement of the two methoxy groups in **6dd** by a methylenedioxy group (**6ee**), however restored the activity partially. An extra substituent at position-3 of the N-phenyl group in **6n** such as fluorine atom (**6bb**) caused an eight-fold reduction in the activity.

Compound **13** has been reported as a mixture of racemic disastereoisomers and also to have good antiimplantation properties. The pure diastereoisomeric racemates **13a** and **13b** were prepared by us and found to be equally potent. Since 1-phenyl-2-phenethyltetrahydroisoquinoline is reported to be only a little less active[22], **19** was conceived as a hybrid and synthesised. However, it was devoid of any activity. The 2-phenoxyethyl analogue (**26**) of **13** was less active than **13**. 1-Phenethylisoquinoline (**29**) as well as the base **7b** were devoid of antifertility activity.

Some of the compounds in the present study showing hypocholesterolemic activity in the rat were: **6d** (ED_{65} 10 mg/kg), **6n** (ED_{70} 100 mg kg), 6cc (ED_{20} 3 mg/kg), **6u** (ED_{75} 10 mg/kg), and **6q** (ED_{60} 100 mg/kg).

Detailed studies carried out on a few compounds are discussed below.

Compound **6g**, one of the more potent compounds of the series, was available in quantities and was submitted to tests 2-8. The results presented in Table 7

show that it is a weak oral estrogen and also a weak antiestrogen and owes its activity to these properties. It was also found that at doses of 1, 3 or 10 mg/kg/day p.o., **6g** induced implantation in the rat wherein implantation had been delayed by daily injection of medroxyprogesterone acetate (15 mg/kg/day s.c.). Thus, **6g** was not blastolytic. From the data given in Table 7, it appears likely that **6g** exerts anti-implantation activity by acceleration of tubal transport of ova.

1,2-Diaryltetrahydroisoquinolines possess a chiral centre at position-1 and should therefore be resolvable into antipodes wherein one could perhaps expect a dissociation between antiimplantation and estrogenic properties. Accordingly, we attempted a resolution of **6g** which failed as noted earlier. **6u** which was again a potent implantation inhibitor and a weak estrogen was not resolvable. The *m*-fluorophenyl analogue (**6n**) was resolvable and we were thus able to compare the profiles of the racemate and the antipodes (+)-**6p**.HCl and (−)-**6q**.HCl. Data shown in Table 7 reveal that again there is no worthwhile separation of antiimplantation and estrogenic activities. These two properties ran parallel for three other compounds studied, viz. **6a**, **13a** and **13b**.

The present study thus provided a number of compounds which exhibited good antiimplantation and weak oral estrogenic activities, the former being a likely consequence of the latter and dissociation of the two was not achieved. For this reason and also because **6g** was teratogenic in the rat[33], the series was not investigated further, although it had low acute toxicity in the rat ($LD_{50} > 1000$ mg/kg p.o.).

Experimental Procedure

Arylacetanilides (**2**) *and N-(β-phenethyl)-benzanilides* (**4**)

The general procedure is illustrated for **2c**. *m*-Methoxyphenylacetic acid (20 g) and thionyl chloride (40 ml) were heated together in benzene (100 ml) under reflux for 1 hr. Excess thionyl chloride and solvent were removed *in vacuo*. The residue was dissolved in dry ether (40 ml) and the solution added during 15 min to a cooled (0°) and stirred mixture of aniline (14 g) in ether (100 ml). After stirring at room temperature overnight, the mixture was filtered and the residue washed successively with water, dil. HCl water and ether to give the amide **2c**. The ethereal filtrate was worked-up to give some more of the neutral amide; yield 24.9 g (86%), m.p. 108-9°. The arylacetanilides (**2**) and benzanilides (**4**) prepared in a similar manner are given in Tables 1 and 3 respectively.

N-Aryl-β-phenethylamines (**3**)

These were prepared by LAH reduction of **2** by the following procedure used for **3c**.

A solution of **2c** (24.8 g) in dry dioxane (70 ml) and ether (30 ml) was added to a stirred suspension of LAH (8.5 g) in ether (100 ml) during 30 min. After stirring overnight, the mixture was worked-up as usual to give **3c** as an oil (21 g; 91%). Distillation at 205-210 /3-4 mm gave the pure product (17 g; 74%). The amines (Table 2) were generally characterised as benzamides (**4**).

1,2-*Diaryl*-3,4-*dihydroisoquinolinium iodides* (**5**): (*i*) *Cyclisation of unactivated amide*

The amide **4b** (5.35 g) was heated under reflux for 24 hr with $POCl_3$ (30 ml) containing conc. HCl (4 ml). Excess $POCl_3$ and HCl were removed *in vacuo*, and water and ether added to the residue. The ether layer gave **4b** (1.5 g). The aqueous layer was treated with excess KI when the crystalline iodide **5b** was precipitated. This was recrystallised from ethanol-ether, yield 3.9 g (55%), m.p. 221-23° (d); **5a** and **5d** were however obtained only in 10% and 7% yields respectively.

(*ii*) *Cyclisation of activated amides*

Amide **4f** (1.92 g) and $POCl_3$ (10 ml) were heated together under reflux for 2 hr. The product was worked-up as earlier. There was negligible neutral

Table 7—Biological Properties of Some Tetrahydroisoquinolines

Compd	Biological Test No.								
	1	2	3	4	5	6	7	8	9
6a	30	10	10						
6g	3	<3		<1	1	1	<3	3.3	3.3
6n	3	1	1						
6n.HCl	3								
(+)-**6p**.HCl	5	1	3						
(−)-**6q**.HCl	3	1	1						
6u	1	1?							
13a.HCl	1	0.3	1						
13b.HCl	1	0.3	1						

material. The aqueous solution gave the quaternary iodide **5e**, 2.2 g (83%), m.p. 220° (d) (from ethanol-ether).

The quaternary salts (**5**), thus prepared are listed in Table 4. Passage of a methanolic solution of the iodide through an Amberlite column transformed it into the chloride.

A suspension of **5r** (2.5 g) in 10% aq. NaOH (10 ml) upon extraction with ether afforded **7a** (1.4 g), m.p. 75-76° (from hexane) (Table 6).

1,2-Diaryl-1,2,3,4-tetrahydroisoquinolines (**6**)

A solution of **5e** (10.7 g) in methanol (60 ml) was treated with $NaBH_4$ (2 g) during 1 hr. Addition of water precipitated **6d** which was collected and recrystallized from benzene-hexane, yield 6.1 g (78%), m.p. 107-8° (see Table 5 for physical data of **6**).

1-(2-Aminophenyl)-6-methoxy-2-phenyl-1,2,3,4-tetrahydroisoquinoline (**6i**)

Nitrophenylisoquinoline **6h** (1.3 g) in dioxane (10 ml) and methanol (10 ml) was reduced at 40° and atmospheric pressure using platinum catalyst (0.1 g PtO_2) during 18 hr to afford **6i** (0.7 g), m.p. 140-41° (from ethanol).

Pyrrolidinoethoxytetrahydroisoquinoline (**6z**)

Benzyloxytetrahydroisoquinoline **6x** (1 g) was heated with conc. HCl (10 ml) at 80-90° for 1 hr. The cooled solution after extraction with ether to remove neutrals (benzyl chloride) and standing, gave crystals of **6y** as the HCl salt, which was recrystallised from ethanol-ether, m.p. 199-202° (d). The free base (2.6 g), liberated from the salt from pooled experiments, was dissolved in dioxane (50 ml) and stirred with 50% suspension of sodium hydride in kerosene (0.43 g) for 45 min at room temperature. This was followed by addition of β-chloroethylpyrrolidine (1.3 g) in dioxane (5 ml), and the mixture stirred at 60° overnight. The basic product was dissolved in chloroform, and the solution chromatographed over silica gel (20 g), collecting 25 ml of chloroform eluates. Fractions 2 and 3 were combined and evaporated. The residue was purified by bulb to bulb distillation *in vacuo* to afford **6z** as an oil (1.07 g).

1-(p-Fluorophenyl)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydroisoquinoline (**6v**)

Methoxytetrahydroisoquinoline **6u** (1 g) was heated at 130° with 48% HBr (10 ml) for 2 hr in a nitrogen atmosphere. The supernatant liquid was decanted off from the residue which was washed with ether and dissolved in water. Treatment of the aq. solution with $NaHCO_3$ and extraction with ether gave crude **6v** which was chromatographed over silica (15 g) in benzene. **6v** was eluted with benzene-chloroform (1:1) as a gum which gave a crystalline HCl salt (0.23 g), m.p. 221-23° (from MeOH-ether).

Resolution of (±) *1-(m-fluorophenyl)-6-methoxy-2-phenyl-1,2,3,4-tetrahydroisoquinoline* (**6o**)

The racemic base **6o** (6.66 g) was dissolved in acetone (30 ml) and treated with *d*-camphor sulphonic acid monohydrate (4.64 g). The first crop of crystalline salt (4.7 g), m.p. 174-78°, was recrystallised twice from acetone to give 3.12 g, m.p. 180-83°. This was rubbed with 2*N* aq. NaOH to give the gummy base (2 g) which was converted into the crystalline HCl salt, (+)-**6p**.HCl (1.85 g) (from MeOH – EtOH), m.p. 275-80° (d) : with transition at 270°); $[\alpha]_D^{24} + 116°$ (*c*, 2 in MeOH).

The mother liquor from the original camphor sulphonate preparation was made basic and extracted with ether. The crude base was fractionally crystallised to remove (±)-**6o** in 3 crops (total 0.94 g), giving a gummy mixture and finally a fairly pure resolved enantiomer (2.3 g) which afforded (−)-**6q**.HCl (1.85 g), m.p. 275-80° (d) (with transition at 235-40°) (from MeOH – EtOH); $[\alpha]_D^{24} - 100°$ (*c*, 2 in MeOH).

Action of heat on optically active tetrahydroisoquinoline (**6g**)

The free base (0.523 g) liberated from (−)-**6q**.HCl was dextrorotaroy; $[\alpha]_D^{25} + 26.20$ (in Et_2O), and was recovered unchanged after heating under reflux with ether (50 ml) for 6 hr; $[\alpha]_D^{25} + 26.13°$ (in Et_2O). After keeping for 11 days in an open dish, the gummy base deposited some crystals. These were recrystallised from ethanol to afford **7b** (70 mg), m.p. 105-6°, identical with the product obtained by treating **5h** (as iodide) with aq. NaOH (Found: C, 76.1; H, 6.0; N, 4.0. $C_{22}H_{20}FNO_2$ requires C, 75.6, H, 5.8; N, 4.0%).

2(2-Methyl-2-phenylethyl)-1-phenyl-1,2,3,4-tetrahydroisoquinolines (**13a** *and* **13b**)

1-Phenyl-1,2,3,4-tetrahydroisoquinoline[32] (5.2 g) was treated with α-phenylpropionyl chloride (from 3.8 g acid with thionyl chloride) under the conditions used for **2c**. The neutral product (8.2 g) was triturated with hexane to give a slightly sticky solid (2.9 g), m.p. 140-45° which was crystallised from ether-hexane to afford **12a** (2.3 g), m.p. 155-56° (Found: C, 84.7; H, 6.9; N, 4.4. $C_{24}H_{23}NO$ requires C, 84.4; H, 6.8; N, 4.1%). The mother liquors on standing deposited crystals, m.p. 91-96°, which were recrystallised from hexane to yield **12b** (2.2 g), m.p. 95-98° (Found: C, 85.0; H, 7.2; N, 4.1. $C_{24}H_{23}NO$ requires C, 84.2; H, 6.8; N, 4.1%).

Reduction of **12a** (2.3 g) was carried out with LAH (0.8 g) in ether (100 ml). The mixture was decomposed

with water and the ether layer decanted off. The latter was shaken with 2*N* HCl when **13a**.HCl separated out and was filtered off (1.1 g). The aqueous layer from the filtrate was made basic to afford the base **13a** (1 g), which yielded more HCl salt (0.8 g). The combined salts were recrystallised from ethanol-ether to afford **13a**.HCl (1.8 g), m.p. 238-40°. **12b** was similarly reduced and the basic product converted into crystalline **13b**.HCl (1.6 g), m.p. 228-31° (from ethanol-ether), depressed by admixture with **13a**.HCl.

Isoquinolone **16b**

A mixture of isocoumarin (7.3 g) and *m*-methoxyphenethylamine (7.6 g) was heated at 140-50° for 16 hr. The product was taken up in ether and the ether layer washed successively with dil. HCl and water, dried and evaporated to give a solid (13.1 g) which was crystallised from hexane to yield **16b** (11.3 g), m.p. 55-58° (Found: C, 78.0; H, 6.3; N, 5.0. $C_{18}H_{17}NO_2$ requires C, 77.4; H, 6.1; N, 5.0%).

Dibenzoquinolizinium derivative (**18**)

The above amide (**16b**; 11.3 g) in acetic acid (100 ml) was hydrogenated at atmospheric pressure and room temperature during 24 hr using platinum catalyst (from 0.3 g PtO_2) to afford crude **17b** as a gum (11 g) admixed with some amount of **20**.

The crude **17b** (10 g) and $POCl_3$ (100 ml) were heated together under reflux for 20 hr. $POCl_3$ was removed *in vacuo* and the residue treated with ice chips and ether. The aqueous layer was treated with excess KI when an oil was formed. This was triturated with ethanol when crystalline **18** separated out. It was filtered (filtrate-A) and recrystallised from MeOH to give pure **18** (2.5 g), m.p. 257° (d) (Found: C, 55.4; H, 4.9; N, 3.7. $C_{18}H_{17}INO$ requires C, 55.3; H, 4.6; N, 3.6%).

Filtrate-A from above was treated with sodium borohydride (2 g). The basic product was worked-up and converted into HCl salt. It was crystallised from ethanol-ether to give **22a** + **b**.HCl (Found: C, 71.0; H, 8.3; N, 4.7; M^+ for base at *m/z* 267, 271).

Dibenzoquinolizidine **19**

A solution of **18** (2.3 g) in methanol (100 ml) was reduced with sodium borohydride (1 g) added in portions during 45 min. The product was worked-up by removal of solvent *in vacuo*, addition of water and extraction with ether. Treatment of the ether layer with HCl in ethanol gave the crystalline salt which was recrystallised from ethanol-ether to afford **19**. HCl (1.3 g), m.p. 253°; M^+ at *m/z* 265; PMR (D_2O): δ 5.7 (*s*, $C_{14}-H$), 3.7 (*s*, OMe), 3.55 (*t*, 8-CH_2); 3.25 (br, 5- and 6-CH_2), 3.12 (*t*, 9-CH_2).

Action of $POCl_3$ on isoquinolone **16a**

A mixture of **16a** (0.7 g) and $POCl_3$ (12 ml) was heated under reflux for 5 hr. Removal of $POCl_3$ and addition of water gave a solution which on treatment with KI afforded a crystalline product (0.9 g). Recrystallisation from ethanol-ether gave 1-chloro-2-(β-phenethyl)isoquinolinium iodide (0.35 g), m.p. 162-64° (Found: C, 51.2; H, 4.2; N, 3.8. $C_{17}H_{15}ClIN$ requires C, 51.6; H, 3.8; N, 3.5%). Passage of a solution of the salt in methanol through Amberlite IRA 400 resin regenerated **16a**.

Isoindolone **23**[d]

Homoveratryl amine (7.24 g) and α-bromo-2-cyanotoluene (3.14 g) were heated together in water (3.3 g) under reflux for 15 hr. The neutral product was filtered through a column of silica gel to yield **23** (0.1 g), m.p. 102-3° (from benzene-hexane) (Found: C, 72.8; H, 6.8; N, 4.9. $C_{18}H_{19}NO_3$ requires C, 72.7; H, 6.4; N, 4.7%).

Phenoxyethylisoquinolinium bromide **25**

1-Phenyl-3,4-dihydroisoquinoline **9** (5.25 g) and β-bromophenetole (5 g) were heated together in ethanol (30 ml) under reflux for 24 hr. The solvent was evaporated off and ether added to the residue when crude **25** separated out. It was crystallised from ethanol-ether to give pure **25** (3.4 g), m.p. 196-98°.

Phenoxyethyltetrahydroisoquinoline **26**

Isoquinoline **11** (4.2 g), β-bromophenetole (4.02 g), sodium bicarbonate (6.7 g) and ethanol (100 ml) were heated together under reflux for 20 hr. The mixture was filtered and the filtrate evaporated *in vacuo*. The residue was extracted with ether and the ether layer shaken with dil. HCl. The product was recovered from the acidic solution as an oil (5.1 g) which formed a crystalline HCl salt. Recrystallisation from ethanol gave **26**.HCl (3.7 g), m.p. 227-29°.

1-(*β-Phenethyl*)-2-*phenyl*-1,2,3,4-*tetrahydroisoquinoline* (**29**)

Amine **3a** (5.9 g) on treatment with β-phenylpropionyl chloride (from 4.5 g acid) gave amide **27** (9.0 g), m.p. 117-21°. Treatment of **27** with a mixture of polyphosphoric acid (75 g) and $POCl_3$ (20 ml) with stirring at 130-40° and work-up as usual gave the crystalline iodide **28** (4.1 g), m.p. 198-200° (from ethanol-ether) (Found: C, 63.1; H, 5.2; N, 3.3. $C_{23}H_{22}IN$ requires C, 62.9; H, 5.1; N, 3.2%). Reduction of **28** (3.0 g) with sodium borohydride (1.0 g) in 40 ml methanol and conversion of the product into the hydrochloride gave **29**.HCl (1.8 g), m.p. 150-52 (from ethanol-ether); M^+ at *m/z* 313.

Benzophenoneimine **30**

3-Fluoro-4'-methoxybenzophenone (6.9 g) was heated with oxalyl chloride (11.4 g) under reflux

overnight. Excess oxalyl chloride was evaporated off and aniline (9.8 g) in benzene (50 ml) added to the residue. The mixture was heated under reflux for 4 hr. The benzene layer was decanted off from the sludge, and evaporated to give a gum (9.0 g) which was extracted with hexane to give crude **30** (3.7 g). It was recrystallised from hexane to afford pure **30** (3.0 g), m.p. 86-87°.

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