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Antiimplantation Agents: Part IV—4-Benzhydrylidenepiperidines & Tetrahydropyran Analogues of F 6066[a,b,c]

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Several α-(4-pyridyl)benzhydrols (**8**) have been synthesised by Grignard reaction on 4-aroylpyridines (**6**) or ethyl isonicotinate (**7**). The quaternary salts **9** of **8** are reduced catalytically to α-(4-piperidyl)benzhydrols (**10**) which undergo dehydration to benzhydrylidenepiperidines (**11**). Demethylation of **11c** with HBr affords **11d** which is further acetylated to provide **11e**, an azaisoster of F 6066. Reduction of **9** with sodium borohydride furnishes the tetrahydropyridyl derivatives (**12**) which undergo acid-catalysed rearrangement to the benzhydrylidenepiperidin-3-ols **13** (**14**). Treatment of ethyl tetrahydropyran-4-carboxylate with *p*-anisylmagnesium bromide affords the benzhydrol (**19**), which is dehydrated to **20**. Among the compounds tested, **8b-8d** show moderate antiimplantation activity in rats.

Reports on the marked anti-implantation properties of some benzhydrylidene cyclohexanes **1**[1], **2**[2], **3**[3], **4**[4], **5**[5] and other similar compounds[6] prompted us to synthesise benzhydrylidenepiperidines (**11**) and benzhydrylidenetetrahydropyran **20** for biological evaluation.

The synthesis of **11** was carried out from the precursor **10** by dehydration. The tertiary piperidinemethanols **10** (Table 2) were obtained by catalytic hydrogenation of the quaternary salts **9** of **8** (Table 1) which in turn were prepared by the addition of arylmagnesium bromides to 4-aroylpyridines (**6**) or to ethyl isonicotinate (**7**). The target compound **11e** (Table 3) was prepared by demethylation of **11c** with hydrobromic acid followed by acetylation of the resultant **11d**. Reduction of quaternary salts **9** with sodium borohydride gave the tetrahydropyridines **12** (Table 4) which underwent acid-catalysed allylic rearrangement[7] to benzhydrylidenepiperidines **13** (**14**). The PMR spectra of the former were characterised by the presence of signals around δ 5.30 [1H, *t*, H(3)], 3.0 [2H, fine *q*, H(2)], 2.5 [2H, *t*, H(6)], 2.3 [3H, *s*, NCH_3] and 2.2 [2H, *hump*, H(5)], while those of the latter displayed signals around δ 4.4 [1H, poorly resolved *t*, H(3)] and 2.30 [3H, *s*, $N-CH_3$], the rest of the signals due to piperidine protons not being readily analyzable.

The allylic rearrangement of **12** will produce a single product **13** (=**14**) when **12** is a symmetrical substrate ($R=R_1$; **12d-f**), but a mixture of **13** and **14**, when $R\neq R_1$ (**12a-c**), since there is no factor supporting regiospecificity or selectivity. Surprisingly, the products from **12a-c** were homogenous on TLC and had reasonably sharp m.ps as maleates. The PMR spectra also showed a single resonance for the N-methyl protons. However, a careful study of their ^{13}C NMR spectra revealed that they could indeed be an approximately 1:1 mixture of **13a-c** and **14a-c**. Although there was again only one set of signals for methyl, methylene and methine carbon atoms resonating at high fields, the heterogenity became apparent in the aromatic region, especially looking at the signals due to the carbon atoms in the fluorine-containing phenyl group adjacent to the olefinic double bond. Thus, in the spectrum of the free base obtained from the rearrangement of **12a**, two doublets ($J_{CF}=20$ Hz) were seen for C-2[1] and C-4[1] *ortho* to the fluorine at 113.1, 113.3, 120.4 and 120.6 ppm. This has to be compared with the observation of two doublets at 112.8 and 113.8 ppm for both the C-atoms adjacent to the fluorine atom in **12a**. The products from **12b** likewise in comparison with the starting material and **11a** showed two sets of lines for C-2′ and C-6′ *meta* to the fluorine atom at 131.0 and 131.2 ppm.

In the course of this study, a number of ^{13}C NMR spectra were taken of compounds belonging to different structural types (**8-13**) in $CDCl_3$, DMSO-d_6 or a mixture of the two solvents. The data are pretreated in Table 5 to the extent resonances could be analysed. An interesting, and as yet unexplained, observation was made in the spectra of **12** carrying one or more halogen atoms (**12a-e**). These compounds exhibited in their proton-decoupled spectra, a signal at about 78 ppm right at the centre of the triplet due to the C-atom of $CDCl_3$. In the coupled mode, the signal became a doublet ($J=212$ Hz). This was not seen for another member of **12** (**12f**) not having a halogen atom,

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Table 1—Characterization Data of Benzhydrols **8** and Their Quaternary Salts (**9**)

Compd	R	R_1	Mol. formula	m.p. °C	Crystallised from*
8a	3-F	H	$C_{18}H_{14}FNO$	198-99	A
9a	(8a.CH_3I)		$C_{19}H_{17}FINO$	137-40	B+C
8b	4-Cl	4-Cl	$C_{18}H_{13}Cl_2NO$	175-77	B+D
9b	(8b.CH_3I)		$C_{19}H_{16}Cl_2INO$	Gum	—
8c	4-Cl	4-F	$C_{18}H_{13}ClFNO$	181-83	D
9c	(8c.CH_3I)		$C_{19}H_{16}ClFINO$	Gum	—
8d	4-F	H	$C_{18}H_{14}FNO$	188-90	D+E
9d	(8d.CH_3I)		$C_{19}H_{17}FINO$	205-7	A+C
9e	(8d.EtI)		$C_{20}H_{19}FINO$	Gum	—
8e	4-F	4-F	$C_{18}H_{13}F_2NO$	182-84	B
9f	(8e.CH_3I)		$C_{19}H_{16}F_2INO$	200-203	A+C
8f	4-OMe	4-OMe	$C_{20}H_{19}NO_3.H_2O$†	166-67	D+E
9g	(8f.CH_3I)		$C_{21}H_{22}INO_3$	224-25	A+C

*A = Methanol; B = ethanol; C = ether; D = chloroform; E = hexane.
†M^+ at *m/z* 321. Calc. M 321.

Table 2—Characterization Data of Diaryl(4-piperidyl)carbinols (**10**)

Compd	R	R_1	R_2	Mol. formula	m.p. °C	Crystallised from*
10a	4-F	H	Me	$C_{19}H_{23}FNO$	145-7	A
10a.HI	4-F	H	Me	$C_{19}H_{23}FINO$	243-4	A+C
10b	4-F	H	Et	$C_{20}H_{24}FNO$	124-6	A+D
10c	4-OMe	4-OMe	Me	$C_{21}H_{27}NO_3$	160-2	A

*A = Methanol; B = ethanol; C = chloroform; D = water.

Table 3—Characterization Data of 4-Benzhydrylidenepiperidines (**11**) and 4-Benzhydrylidene-3-piperidinols **13**(**14**)

Compd	R	R_1	R_2	R_3	Mol. formula	m.p. or b.p./mm °C	Crystallised from*
11a	4-F	H	Me	H	$C_{19}H_{20}FN$	140-45/ 5×10^{-3}mm	—
11b	4-F	H	Et	H	$C_{20}H_{22}FN$	140-50/ 10^{-2}mm	—
11c	4-OMe	4-OMe	Me	H	$C_{21}H_{25}NO_2$	210-20/ 5×10^{-3} m.p. 77-79	—
11d	4-OH	4-OH	Me	H	$C_{19}H_{21}NO_2$	255-57(d)	A
11d (HBr)	4-OH	4-OH	Me	H	$C_{19}H_{22}BrNO_2$	298-300	A+B
11e	4-OAc	4-OAc	Me	H	$C_{23}H_{25}NO_4$	122-24	B+C
13a(**14a**) (maleate)	3-F	H	Me	OH	$C_{23}H_{24}FNO_5$	110-12	B+D
13b(**14b**) (maleate)	4-F	H	Me	OH	$C_{23}H_{24}FNO_5$	163-64	B+D
13c(**14c**) (maleate)	4-F	4-Cl	Me	OH	$C_{23}H_{23}ClFNO_3$	180-81	B+D

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

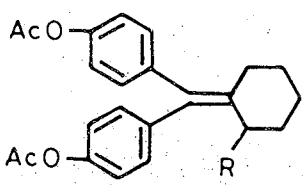
nor for any other type of compound of this study, irrespective of whether halogen atom was present or not. The signal is apparently due to $CHCl_3$, but the compounds themselves had no possibility of being contaminated with this solvent. In one case (**12d**), it was ascertained that the signal was not seen when the spectrum was run in DMSO-d_6 alone. Obviously **12a-e** were somehow catalysing the exchange of deuterium in $CDCl_3$ with the hydroxylic proton present in the molecules. Exchange with residual moisture in the solution can not be ruled out.

Attempts to prepare 2- and 3-piperidyl analogues of

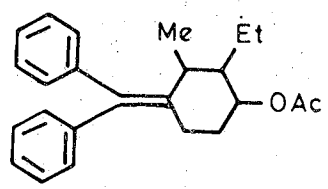
Table 4—Characterization Data of 4-(α-Hydroxybenzhydryl)-1,2,5,6-tetrahydropyridines (**12**)

Compd	R	R_1	R_2	Mol. formula	m.p. °C	Crystallised from*
12a	3-F	H	Me	$C_{19}H_{20}FNO$	177-79	A
12b	4-F	H	Me	$C_{19}H_{20}FNO$	174-75	A
12c	4-Cl	4-F	Me	$C_{19}H_{19}ClFNO$	165-67	A+B
12d	4-F	4-F	Me	$C_{19}H_{19}F_2NO$	152-54	B
12e	4-Cl	4-Cl	Me	$C_{19}H_{19}Cl_2NO$	178-81	C+D
12f†	4-OMe	4-OMe	Me	$C_{21}H_{25}NO_3 \cdot \frac{1}{2}H_2O$	170-72	A+B

*A = Methanol; B = benzene; C = ether; D = hexane.
†M^+ at *m/z* 339. Calc. M 339.



1 R = H (F 6066)
2 R = Me (F 6103)



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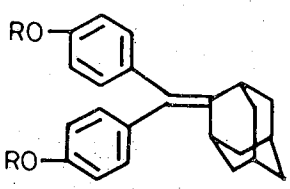

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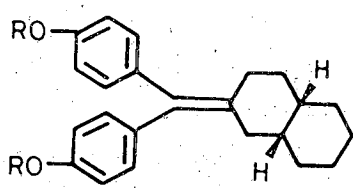

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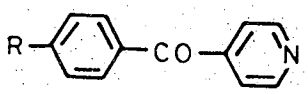

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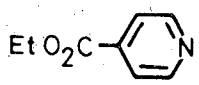

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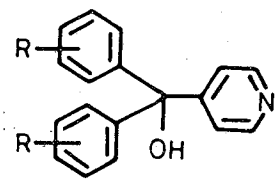

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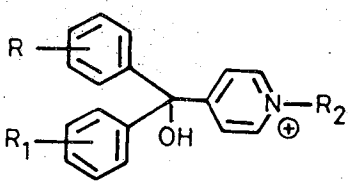

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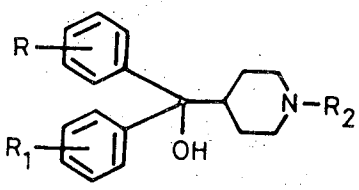

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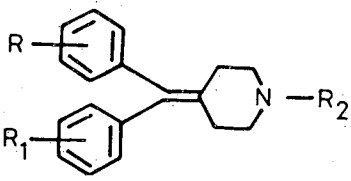

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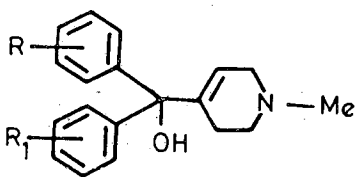

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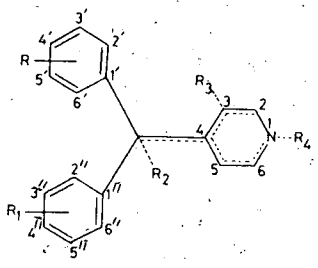
Table 5—^{13}C NMR Spectral Data of Compounds **8-13**



Compd	Table No.	δ (ppm) of C-atoms of phenyl rings	δ (ppm) of C-atom of pyridine ring					δ (ppm) of benzhydryl C-atom	δ (ppm) of other C-atoms
			C-2	C-3	C-4	C-5	C-6		
8c[a+b]	1	149.1(2, 6); 122.5(3, 5); 155.5(4) 142.0(1′); 129.6(2′, 6′); 114.4(3′, 5′) 161.3(4′); 145.0(1″); 129.4(2″, 6″); 127.7(3″, 5″); 132.4(4″)						79.4	
9d[a+b]	1	144.1(2, 6); 166.6(4); 140.2(1′); 130.2(2′, 6′); 115.3(3′, 5′); 160.2(4′)						80.8	48.6 ($N-CH_3$)
10a[a]	2	141.4(1′); 127.9(2′, 6′); 114.9(3′); 146.2(1″)	56.3	26.6	44.1	26.6	56.3	79.5	46.2 ($C-CH_3$)
12a[a+b]	4	148.9(1′); 112.8(2′); 161.8(3′); 113.8(4′); 128.5(5′); 123.3(6′); 145.1(1″); 127.1, 127.2(2″, 6″, 3″, 5″); 126.3(4″)	54.0	123.3	140.3	26.0	51.6	80.6	44.9 ($N-CH_3$) 78.6 ($CHCl_3$?)
12b[a+b]	4	141.6(1′); 129.8(2′, 6′); 114.1(3′, 5′); 145.8(1″); 127.9, 127.6, 126.9(2-6″); 161.5(4′)	54.8	123.9	141.1	26.6	52.4	81.4	45.6 ($N-CH_3$) 78.1 ($CHCl_3$?)
12c[a+b]	4	141.9(1′), 129.6(2′, 6′); 114.1(3′, 5′); 145.0(1″); 129.4(2″, 6″); 127.5(3″, 5″); 131.9(4″); 161.(4′)	54.5	123.9	140.8	26.5	52.1	80.3	45.3 ($N-CH_3$) 79.1 ($CHCl_3$?)
12d[b]	4	141.2(1′, 1″); 129.2(2′, 6′, 2″, 6″); 113.9(3′, 5′, 3″, 5″); 160.9(4′, 4″)	54.0	123.3	140.7	26.1	51.6	80.2	45.9 ($N-CH_3$)
12d[a+b]	4	141.7(1′, 1″); 129.7(2′, 6′, 2″, 6″); 114(3′, 5′, 3″, 5″); 161.9(4′, 4″)	54.7	124.1	141.4	26.6	52.4	81.2	45.6 ($N-CH_3$) 77.6 ($CHCl_3$?)
12e[a+b]	4	144.6(1′); 128.8(2′, 6′); 127.4(3′, 5′); 132.5(4′)	54.5	124.0	140.6	26.4	52.0	80.7	45.3 ($N-CH_3$) 78.8 ($CHCl_3$?)
12f[a+b]	4	138.6(1′); 129.0(2′, 6′); 113.0(3′,5′); 158.4(4′)	54.7	122.8	141.7	26.5	52.3	81.0	45.4 ($N-CH_3$) 55.2 (OCH_3)
11a[a]	3	138.6(1′); 131.3(2′, 6′); 114.9(3′, 5′); 160.5(4′); 142.6(1″); 129.8, 128.2, 126.5(2″-6″)	57.4	31.8	135.6?	31.8	57.4	135.4?	45.9 ($N-CH_3$)
13a[a] (**14a**)	3	113.1, 113.3, 120.4, 120.6(2′, 4′)	63.2	67.1	—	27.4	56.9	—	45.9 ($N-CH_3$)
13b[a] (**14b**)	3	131.0, 131.2(2′, 6′); 115.1(3′,5′)	63.2	67.3	—	27.4	56.9	—	45.6 ($N-CH_3$)

[a]$CDCl_3$; [b]DMSO-d_6.

diluted with water. The solid product **12b** was filtered and crystallised from MeOH, yield 1.4 g, m.p. 174-75°.

4-Benzhydrylidene-3-piperidinols **13a-c** (Table 3)

A solution of the foregoing tetrahydropyridine **12b** (2 g) in 1*N* HCl (40 ml) was stirred at room temperature for 36 hr. After neutralization with ammonia and extraction with ether, a gum was obtained which on trituration with hexane, deposited crystals of recovered starting material (**12b**). The product obtained as a gum from the filtrate was converted into maleate which was crystallized from EtOH-Et_2O to give **13b** maleate (1.6 g), m.p. 163-64°.

13a and **13c** were obtained likewise.

4-[Diaryl(4-pyridyl)methyl]morpholine (**15**)

Benzhydrol **8d** (1.1 g) was refluxed with thionyl chloride (10 ml) in dry $CHCl_3$ (25 ml) for 3 hr. Solvent and excess thionyl chloride were removed *in vacuo*. The residue was heated with morpholine (1 g) in $CHCl_3$ (10 ml) under reflux for 8 hr. After evaporation *in vacuo*, the residue was crystallised from methanol to afford **15** (0.15 g), m.p. 174-75° (Found: C, 76.0; H, 6.4; N, 8.4. $C_{22}H_{21}NF_2O$ requires C, 75.8; H, 6.1; N, 8.0%).

N-Benzhydrylpiperidines **16** *and* **17**

3-Fluoro-4'-methoxybenzophenone (8 g) was reduced with sodium borohydride (2.8 g) in methanol (70 ml) to give the carbinol (7.5 g) as an oil, from which the chloride was prepared by reaction with thionyl chloride (15 ml) in benzene (20 ml). The chloride was dissolved in $CHCl_3$ (20 ml) and heated with piperidine (12 g) under reflux for 20 hr. After removal of chloroform and piperidine *in vacuo*, the residue was partitioned between water and ether. The product was recovered from the ether layer and converted into HCl salt. Crystallisation from EtOH-Et_2O gave **16**.HCl (2.9 g), m.p. 209-11° (Found: C, 67.8; H, 7.2; N, 4.3. $C_{19}H_{23}ClFNO$ requires C, 68.0; H, 6.9; N, 4.2%).

The *p*-fluorophenyl analogue **17**, similarly prepared, was an oil (Found: C, 76.3; H, 7.5; N, 4.6. $C_{19}H_{22}NOF$ requires C, 76.2; H, 7.4; N, 4.7%). It formed a picrate, m.p. 183-84° (from MeOH) (Found: C, 57.1; H, 5.1; N, 10.4. $C_{25}H_{25}FN_4O_8$ requires C, 56.8; H, 4.8; N, 10.6%).

Tetrahydropyranylbenzhydrol **19**

Ethyl tetrahydropyran-4-carboxylate (14 g) was treated with *p*-anisylmagnesium bromide (from 6.0 g Mg and 46 g *p*-bromoanisole) to give **19** (10 g), m.p. 134-35° (from EtOH) (Found: C, 73.1; H, 7.7. $C_{20}H_{24}O_4$ requires C, 73.1; H, 7.4%).

Benzhydrylidenetetrahydropyran **20**

The foregoing carbinol (**19**; 1 g) was heated with potassium bisulphate (1 g) at 160-170° for 1 hr. Cooling, trituration with water and filtration gave a solid (0.8 g) which on crystallisation from EtOH afforded **20** (0.75 g), m.p. 113-16° (Found: C, 77.7; H, 7.4. $C_{20}H_{22}O_3$ requires C, 77.4; H, 7.1%).

References

1 Hanngren A, Einer-Jensen N & Ullberg S, *Nature*, **208** (1965) 461; Einer-Jensen N, *Acta Pharmacol Toxicol*, **23** (1966) 365.

2 Einer-Jensen N, *Acta Pharmacol Toxicol*, **25** (1967) 65; **26** (1968) supplement 1.

3 Karamas G, US 3,936,493 (to Orcho Pharmaceutical Corporation), February 3, 1976; *Chem Abstr*, **84** (1976) 164273b; Hahn D W, Allen G, McGuire J L & Dabenzo J P, *Contraception*, **9** (1974) 393.

4 Lee K T, US 3,711,556 (to du Pont de Nemours E I & Co), January 16, 1973; *Chem Abstr*, **78** (1973) 71672; Claassen V, *Ger Offen*, 1,810,343, to N N Philip's (Gloeilampenfabrieken), July 17, 1969; *Chem Abstr*, **71** (1969) 80812V.

5 Steinmen M, *Ger Offen*, 1,913,375; (to Scherico Ltd), January 27, 1969; *Chem Abstr*, **72** (1970) 43128b.

6 Lednicer D, *US Pat*, 3,636,166 (to Upjohn Co), January 18, 1972; *Chem Abstr*, **76** (1972) 112885.

7 Grisar J M, Hickey K R, Meyer D R & Levy A C, *J mednl Chem*, **11** (1968) 615.

8 Hanousek V & Prelog V, *Colln Czech Chem Commun*, **4** (1932) 259.

9 Nagarajan K, Talwalker P K, Kulkarni C L, Venkateswarlu A, Prabhu S S & Nayak G V, *Indian J Chem*, **23B** (1984) 1243.

10 Sperber N, Villani F J, Sherlock M & Papa D, *J Am chem Soc*, **73** (1951) 5010.