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Substituted 3-Amino-1,1-diaryl-2-propanols as Potential Antidepressant Agents

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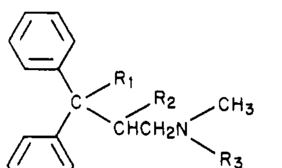
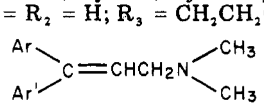
Received March 12, 1979

Following the discovery that 3-(dimethylamino)-1,1-diphenyl-2-propanol hydrobromide (**1**) possesses potent reserpine-prevention activity in mice, a series of analogues of **1** was synthesized and evaluated as potential antidepressant agents. Several routes to analogues of **1** were evaluated, the most generally applicable of which was the regiospecific ring opening of a suitably functionalized 1,1-diaryl-2,3-epoxypropane (obtained in three stages from the corresponding benzophenone) with the appropriate amine. The more interesting compounds of the series were evaluated for their propensity to cause undesirable peripheral anticholinergic effects, all compounds tested being markedly less active than imipramine on this parameter. On the basis of its good activity in biochemical and pharmacological animal models of depression, together with its relative lack of anticholinergic side effects, 1-(3-chlorophenyl)-3-(dimethylamino)-1-phenyl-2-propanol hydrochloride (**20**, BRL 14342) was chosen for further evaluation.

The discovery of a novel antidepressant free of monoamine oxidase inhibiting properties and without the untoward cardiovascular and anticholinergic effects of the tricyclic antidepressants remains a key target of medicinal research. During the reinvestigation of a series of diarylpropanamines, originally reported[1] to be devoid of significant pharmacological activity, several compounds, including **1**, were found to possess antireserpine activity in mice. Such activity is considered to be indicative of those antidepressants which are thought to exert their desired effects primarily by potentiating the actions of neuronal catecholamines (particularly noradrenaline). Antidepressant activity has been claimed for other diarylpropanamines (**2**,[2] **3**,[3] **4**,[4] and **5**[5]) and diarylpropenamines (**6**[2] and **7**[6]), although it should be noted that **7**, which is thought to act primarily by inhibiting neuronal 5-hydroxytryptamine uptake, possesses only a weak antireserpine effect.[7] This paper is concerned with the synthesis of novel analogues of **1** and their evaluation as potential antidepressants.



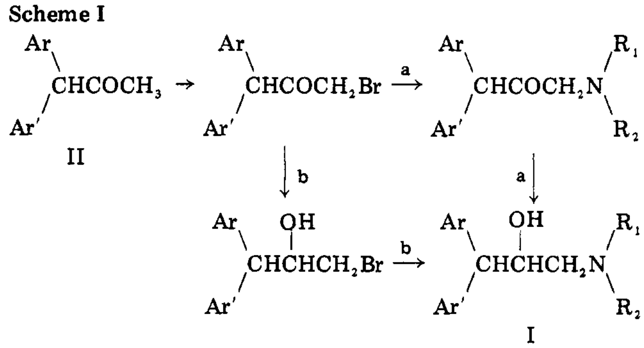
1, R_1 = H; R_2 = OH; R_3 = CH_3·HBr
2, R_1 = R_2 = H; R_3 = H, CH_3
3, R_1 + R_2 = CH_2; R_3 = H, CH_3
4, R_1 = OH; R_2 = H; R_3 = CH_3
5, R_1 = R_2 = H; R_3 = $CH_2CH_2CH_2OH$



6, Ar = Ar′ = C_6H_5
7, Ar = 4-BrC_6H_4; Ar′ = 3-pyridyl

Chemistry. Attention was first directed toward the synthesis of analogues (**8**–**33**) of **1** containing substituents in one or both of the phenyl groups and with a variety of substituted amino groups; the results are summarized in Table I.

Scheme I

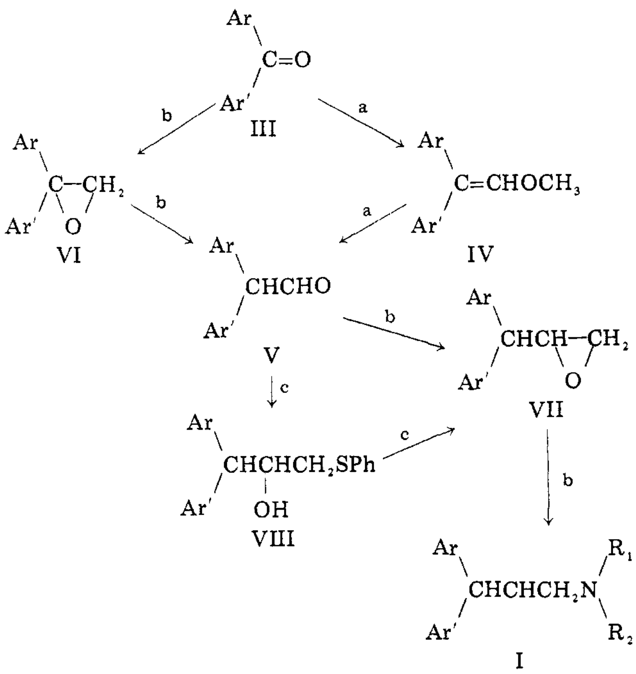


Initially, the required substituted 1,1-diaryl-3-amino-2-propanols I were prepared from the corresponding 1,1-diaryl-2-propanones II by the original (Scheme I, path a) or modified (Scheme I, path b) literature[1] procedure. Difficulties in the synthesis and nonregiospecific bromination of II prompted a search for alternative routes to I.

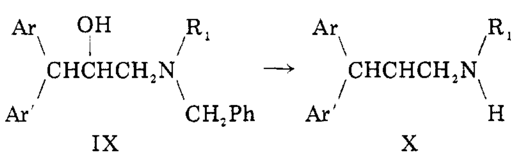
In one approach (Scheme II, path a) the appropriately substituted benzophenone III, which was either commercially available or readily synthesized, was reacted with methoxymethylenetriphenylphosphorane to give the vinyl ether IV, which on acid hydrolysis yielded the aldehyde V. Low yields in the Wittig reaction and difficulties in the purification of both IV and V necessitated an alternative synthesis of V (Scheme II, path b). Reaction of III with dimethylsulfoxonium methylide[8] gave the epoxide VI, which underwent smooth rearrangement with boron trifluoride etherate to give V. Further reaction of V with dimethylsulfoxonium methylide gave the epoxide VIII, which on treatment with the appropriate amine yielded I. No purification of intermediates V, VI, or VII was carried out.

The limiting stage in the above synthesis is the conversion of V to VII. With 2,2-diphenylethanal, a 90% yield

Scheme II

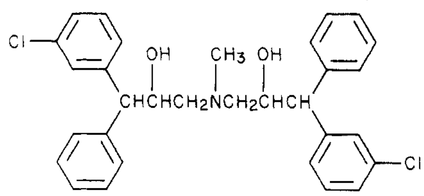


Scheme III



of 2,3-epoxy-1,1-diphenylpropane was obtained. Introduction of one electron-withdrawing substituent in either aromatic ring of V results in lower and variable yields, and introduction of a second such substituent in the same ring renders the synthesis impractical. These differences presumably reflect the relative ease of enolization of V. In an attempt to circumvent this problem, V was reacted with phenylthiomethyllithium (a reagent of enhanced nucleophilicity which is reported[9] to react smoothly with readily enolizable ketones) to give the β-hydroxy sulfide VIII, which on alkylation with triethyloxonium tetrafluoroborate, followed by treatment with base, yielded VII (Scheme II, path c). With 2,2-diphenylethanal, a 41% yield of the corresponding β-hydroxy sulfide VIII was obtained, but when one of the phenyl groups was replaced by 3-(trifluoromethyl)phenyl or 3,4-dichlorophenyl no significant amount of the required VIII was obtained and this route was abandoned.

The preparation of analogues of 1 containing primary and secondary amino groups proved troublesome. Reaction of VII with primary amines and ammonia in general proceeded less smoothly than with secondary amines, and in one case the adduct **34**, formed from 2 equiv of epoxide



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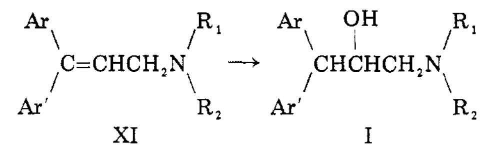
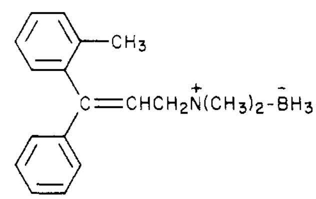
and 1 equiv of methylamine, was the sole isolable product, albeit in poor yield (16%). An alternative procedure via catalytic debenzylation of the appropriate amine IX was

Scheme IV



therefore investigated (Scheme III). Although this reaction proceeded satisfactorily for the unsubstituted (**9**) and 4-methyl (**28a,b**) analogues, it was less satisfactory for ring-halogenated analogues, no pure products being isolated. It was also not possible to prepare 3-amino-1,1-diphenyl-2-propanol (**8**) by this route, the required compound being more conveniently prepared by lithium aluminum hydride reduction of 2,2-diphenylethanal cyanohydrin.

An alternative approach to I is by hydroboration of the appropriately substituted 1,1-diaryl-3-aminopropene (XI, Scheme IV). Reaction of 3-(dimethylamino)-1,1-diphenyl-1-propene[2] with a large excess of diborane and subsequent peroxidation yielded **1** in 56% yield, while the corresponding 3,4- (**31**) and 3,5-dichlorophenyl (**32**) derivatives were obtained in 44 and 15% yield, respectively. In contrast, an attempt to hydroborate 3-(dimethylamino)-1-(2-methylphenyl)-1-phenyl-1-propene[2] with a lesser amount of diborane yielded only the borane–amine complex **35** in 83% yield.



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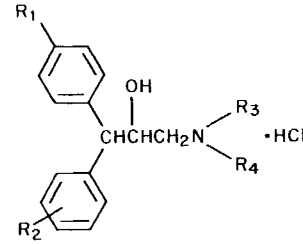
Other modifications of **1** were carried out. Analogues in which one of the phenyl groups was replaced by benzyl (**36**), phenethyl (**37**), 2-thienyl (**38**), or cyclohexyl (**39a,b**) were prepared by one of the methods already described. The 1-hydroxylated (**40** and **42**), 1-methoxylated (**41**), and ester (**43** and **44**) analogues were prepared by literature[1] methods. Two analogues containing a methyl or phenyl group at position 2 were prepared either by reduction of the cyanohydrin of 1,1-diphenyl-2-propanone (compound **45**) or by Grignard addition to 3-(dimethylamino)-1,1-diphenyl-2-propanone[1] (compounds **46** and **47**); the results are summarized in Table II.

Results and Discussion

Most analogues of **1** were isolated and pharmacologically evaluated as an undetermined mixture of the two possible diastereoisomers. In two cases (compounds **28** and **39**), the diastereoisomers were separated by fractional crystallization of the crude reaction product; in the case of compound **20** which is of especial interest pharmacologically, the initially obtained mixture of diastereoisomers was separated by fractional crystallization of the corresponding benzoate salts. In no case was a significant difference in pharmacological activity between the two diastereoisomers found. Similarly, **1** was resolved via its D-(−)- and L-(+)-mandelate salts into its enantiomers, but again no significant difference in pharmacological activity was detected.

Potential antidepressant activity (prevention of reserpine-induced hypothermia in mice) is detailed in Tables I and II. Replacement of one of the amino methyl groups of **1** by hydrogen (compound **9**), ethyl (compound **11**),

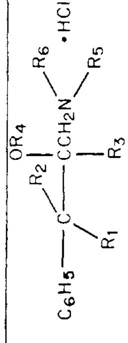
Table I. Physical Properties and Reserpine-Prevention Activities



no.[a]	R_1	R_2	R_3	R_4	mp, °C	purifn[b]	% yield[c]	method[d]	formula	anal.	reserpine prevention[e]: dose, mg/kg	reserpine prevention[e]: Δ6, °C
1[f]	H	H	CH_3	CH_3	169–171	A	24	A	$C_{17}H_{22}BrNO$	C, H, Br, N	5	5.3
8	H	H	H	H	210–215	B	59	B	$C_{15}H_{18}ClNO$	C, H, N; Cl[g]	100	I[h]
9	H	H	H	CH_3	187–188	A	75	C	$C_{16}H_{20}ClNO$	C, H, Cl, N	6	6.1
10	H	H	H	$CH_2C_6H_5$	165–166	A	40	D	$C_{22}H_{24}ClNO$	C, H, Cl, N	100	I[h]
11	H	H	CH_3	C_2H_5	159–161	A	27	E	$C_{18}H_{24}ClNO$	C, H, Cl, N	10[i]	10.2
12[j]	H	H	CH_3	$CH_2CH_2CH_2OH$	oil	C	26	F	$C_{19}H_{25}NO_2$	H, N; C[k]	30[l]	12.4
13	H	H	CH_3	$CH_2C_6H_5$	158–161	A	35	A	$C_{23}H_{26}ClNO$	C, H, Cl, N	10	6.1
14	H	H	C_2H_5	C_2H_5	162–163	A	58	D	$C_{19}H_{26}ClNO$	C, H, Cl, N	10	5.0
15	H	H	c-C_6H_5		194–196	A	67	D	$C_{20}H_{26}ClNO$	C, H, N; Cl[m]	100[n]	9.9
16	H	H	c-$C(CH_2CH_2)_2O$		186–188	A	65	D	$C_{19}H_{24}ClNO_2$	H, Cl, N; C[o]	100[n]	11.0
17[p]	H	H	c-$C(CH_2CH_2)_2N$-CH_3		250–252	D	28	D	$C_{20}H_{28}Cl_2N_2O$	H, Cl, N; C[q]	30	6.3
18	H	2-Cl	H	CH_3	165–170	A	30	G	$C_{16}H_{19}Cl_2NO$	C, H, N; Cl[r]	5	8.6
19	H	2-Cl	CH_3	CH_3	219–221	A	34	G	$C_{17}H_{21}Cl_2NO$	H, Cl, N; C[s]	1	6.6
20	H	3-Cl	CH_3	CH_3	186–188	A	24	G	$C_{17}H_{21}Cl_2NO$	C, H, Cl, N	1	5.3
21[t]	H	4-Cl	H	CH_3	foam	E	9	G	$C_{20}H_{26}ClNO_8$	C, H, N; Cl[u]	10	8.8
22[v]	H	4-Cl	CH_3	CH_3	147–149	A	20	G	$C_{21}H_{26}ClNO_5$	C, H, Cl, N	16	6.3
23[j]	H	4-F	CH_3	CH_3	55–57	C	40	A	$C_{17}H_{20}FNO$	C, H, N	5	5.8
24[j]	H	4-F	CH_3	$CH_2C_6H_5$	61–62	F	37	A	$C_{23}H_{24}FNO$	C, H, N	10	7.3
25	H	3-Br	CH_3	CH_3	154–159	A	22	G	$C_{17}H_{21}BrClNO$	C, H, Cl, N	5[w]	12.4
26	H	3-CF_3	CH_3	CH_3	113–116	A	50	G	$C_{18}H_{21}ClF_3NO$	C, H, N; Cl[x]	5	9.0
27	H	2-CH_3	CH_3	CH_3	218–219	A	58	G	$C_{18}H_{24}ClNO$	C, H, Cl, N	10	10.4
28a	H	4-CH_3	H	CH_3	186–188	A	36	C	$C_{17}H_{22}ClNO$	C, H, Cl, N	30	I[h]
28b	H	4-CH_3	H	CH_3	150–152	A	35	C	$C_{17}H_{22}ClNO$	C, H, Cl; N[y]	100	5.4
29[j]	H	4-CH_3	CH_3	CH_3	55–58	C	30	A	$C_{18}H_{23}NO$	C, H, N	100	I[h]
30	H	4-OCH_3	CH_3	CH_3	glass	E	13	G	$C_{18}H_{24}ClNO_2$	H, N; C, Cl[z]	10	5.9
31	H	3,4-Cl_2	CH_3	CH_3	100–104	A	44	H	$C_{17}H_{20}Cl_3NO$	C, H, N; Cl[aa]	10	7.2
32	H	3,5-Cl_2	CH_3	CH_3	148–149	A	15	H	$C_{17}H_{20}Cl_3NO$	C, N; H, Cl[ab]	3	6.2
33[j]	F	4-F	CH_3	CH_3	56–58	C	26	I	$C_{17}H_{19}F_2NO$	C, H, N	10	7.8

[a] With the exception of 1, all compounds are novel. [b] A, recrystallization from EtOH–Et_2O; B, recrystallization from EtOAc–Et_2O; C, column chromatography on alumina; D, recrystallization from EtOH; E, recrystallization from EtOAc–light petroleum (bp 60–80 °C); E, column chromatography on silica gel; G, recrystallization from light petroleum (bp 40–60 °C); H, recrystallization from Et_2O–light petroleum (bp 60–80 °C). [c] Overall yield from appropriate starting material; see Experimental Section for details. [d] See Experimental Section for details. [e] See Experimental Section for details and definition of Δ6. [f] Hydrobromide (lit. mp 169–170 °C), prepared as in ref 1. [g] Cl: calcd, 13.47; found, 12.91. [h] Inactive (Δ6 < 5 °C). [i] Inactive at 5 mg/kg. [j] Free base. [k] C: calcd, 76.25; found, 75.70. [l] Not tested at lower doses. [m] Cl: calcd, 10.71; found, 9.96. [n] Inactive at 30 mg/kg. [o] C: calcd, 68.37; found, 68.88. [p] Dihydrochloride. [q] C: calcd, 62.66; found, 62.05. [r] Cl: calcd, 22.76; found, 22.16. [s] C: calcd, 62.58; found, 62.99. [t] Hydrogen tartrate monohydrate. [u] Cl: calcd, 8.00; found, 7.42. [v] Hydrogen succinate. [w] Inactive at 3 mg/kg. [x] Cl: calcd, 9.87; found, 10.46. [y] N: calcd, 4.80; found, 4.22. [z] C: calcd, 67.19; found, 65.73. Cl: calcd, 11.04; found, 9.79. [aa] Cl: calcd, 29.54; found, 28.85. [ab] H: calcd, 5.55; found, 6.02. Cl: calcd, 29.54; found, 25.79.

Table II. Physical Properties and Reserpine-Prevention Activities



compd[a]	R_1	R_2	R_3	R_4	R_5	R_6	mp, °C	purifn[b]	% yield[c]	method	formula	anal.	reserpine prevention[e]: dose, mg/kg	reserpine prevention[e]: Δ6, °C
36	$C_6H_5CH_2$	H	H	H	CH_3	CH_3	164-166	A	18	A	$C_{18}H_{24}ClNO$	C, H, Cl, N	30	8.6
37	$C_6H_5CH_2CH_2$	H	H	H	CH_3	CH_3	137-139	A	14	A	$C_{19}H_{26}ClNO$	C, H, N	100	7.4
38[f]	2-thienyl	H	H	H	CH_3	CH_3	52-55	B	26	H	$C_{15}H_{19}NOS$	H, N; C[g]	60	8.4
39a	c-C_6H_{11}	H	H	H	CH_3	CH_3	219-222	A	14	G	$C_{17}H_{28}ClNO$	C, H, Cl, N	100	I[h]
39b	c-C_6H_{11}	H	H	H	CH_3	CH_3	162-164	A	11	G	$C_{17}H_{28}ClNO$	C, H, Cl, N	100	I[h]
40[i]	C_6H_5	OH	H	H	CH_3	CH_3	255-258	A	43	J	$C_{17}H_{22}ClNO_2$		30	5.5
41[j]	C_6H_5	OCH_3	H	H	CH_3	CH_3	206-208	C	14	K	$C_{18}H_{24}ClNO_2$		100	6.9
42	4-FC_6H_4	OH	H	H	CH_3	CH_3	222-224	A	32	J	$C_{17}H_{21}ClFNO_2$	C, H, Cl, N	10	7.5
43[k]	C_6H_5	H	H	$COCH_3$	CH_3	CH_3	228-230	A	75	M	$C_{19}H_{24}ClNO_2$		5[l]	10.2
44[d]	3-ClC_6H_4	H	H	COC_6H_5	CH_3	CH_3	77-79	D	70	M	$C_{24}H_{24}ClNO_2$	C, H, Cl, N	10	5.2
45	C_6H_5	H	CH_3	H	H	H	205-210	A	42	B	$C_{16}H_{20}ClNO$	C, H, Cl, N	100	I[h]
46	C_6H_5	H	CH_3	H	H	CH_3	272-273	A	79	L	$C_{17}H_{22}ClNO$	C, H, N; Cl[m]	30	8.9
47	C_6H_5	H	C_6H_5	H	CH_3	CH_3	260-263	A	28	L	$C_{23}H_{26}ClNO$	C, H, Cl, N	30	I[h]
imipramine											$C_{19}H_{25}ClN_2$		20	6.8

[a] Unless otherwise indicated by an appropriate footnote, all compounds are novel. [b] A, recrystallization from EtOH-Et_2O; B, recrystallization from light petroleum (bp 40-60 °C); C, column chromatography on alumina; D, recrystallization from Et_2O-light petroleum (bp 60-80 °C). [c] Overall yield from appropriate starting material; see Experimental Section for details. [d] See Experimental Section for details. [e] See Experimental Section for details and definition of Δ6. [f] Free base. [g] C: calcd, 69.98; found, 69.44. [h] Inactive (Δ6 < 5 °C). [i] Prepared as in ref 1 (lit. mp 245 °C). [j] Prepared as in ref 1 (lit. mp 206-207.5 °C). [k] Prepared as in ref 1 (lit. mp 223-224 °C). [l] Inactive at 4 mg/kg. [m] Cl: calcd, 12.20; found, 13.05.

Table III. Peripheral Anticholinergic Activity

compd	anti-pilocarpine, mg/kg sc[a]	mydriasis, mg/kg ip[a]	pA_2[b]
1	36 (27.2-51.3)	53 (47-60)	5.2
(+) 1	63 (48-83)	26 (21-37)	5.5
(-)-1	51 (37-72)	46 (41-52)	5.1
9	40 (5-52)	144 (116-118)	5.0
11	43 (38-50)	36 (33-40)	4.3
19	24 (18-125)	29 (23-41)	5.2
20	33 (22-51)	42 (40-46)	4.8
22[c]	71 (55-296)	40 (16-55)	5.1
23	>100	26 (22-34)	4.8
25	>100	49 (38-85)	5.1
26		26 (18-31)	5.8
imipramine	3.3 (2.1-4.5)	20 (18-22)	8.9

[a] Figures in parentheses are 95% fiducial limits. [b] See Experimental Section for definition of pA_2. [c] Free base.

3-hydroxypropyl (compound **12**), or benzyl (compound **13**) either retained or moderately reduced activity, but removal of both methyl groups (compound **8**) or incorporation of the amino function into a ring (compounds **15**–**17**) eliminated or substantially reduced activity.

Substitution of one or two halogen atoms into one of the phenyl groups (compounds **19**, **20**, **23**, **25**, and **32**) either retained or enhanced activity, the 2-chloro (**19**) and 3-chloro (**20**) derivatives being the most active compounds in the whole series. The 3-(trifluoromethyl) (**26**), 2-methyl (**27**), 4-methoxy (**30**), 3,4-dichloro (**31**), and 4,4′-difluoro (**33**) derivatives also possessed good activity, as did the two demethyl analogues **18** and **21**.

Acetylation of the hydroxyl group of **1** to give compound **43** essentially retained the activity of the parent compound, but benzoylation of **20** to give **44** markedly reduced activity.

The effect of replacing one of the phenyl groups of **1** by other groups was also examined. Replacement by benzyl (compound **36**), phenethyl (compound **37**) or 2-thienyl (compound **38**) markedly reduced activity, and in the case of the cyclohexyl analogue **39** this loss of activity was complete. Similarly, substitution of the 1-methine proton by hydroxy (compound **40**) or methoxy (compound **41**) reduced activity, although in the former case simultaneous introduction of a 4-fluoro substituent (compound **42**) resulted in only a minor reduction in activity. Analogues containing a methyl (compounds **45** and **46**) or a phenyl (compound **47**) group at position 2 were also much less active than **1**.

Several of the more potent compounds were evaluated for their propensity to cause undesirable peripheral anticholinergic effects. Three test systems were used: inhibition of pilocarpine-induced salivation and induction of mydriasis in mice and the in vitro antagonism of the effects of acetylcholine on the guinea pig ileum. The results detailed in Table III show that all of the compounds tested possessed significantly reduced peripheral anticholinergic properties compared with imipramine.

Compound **20** (BRL 14342) was chosen for further pharmacological and toxicological evaluation. The results of these studies, to be reported in detail elsewhere, can be summarized as follows.

Biochemical studies in vitro, following the procedure of Horn and Snyder,[10] have shown that **20** inhibits the uptake of radiolabeled noradrenaline (NA), 5-hydroxytryptamine (5-HT), and dopamine (DA) into whole rat brain synaptosomes at 1.2, 9.8, and 8.9 × 10^{-6} M (IC_{50}), respectively. Evidence of NA uptake inhibition in vivo was also obtained, since **20** (ED_{50} = 30 mg/kg po) inhibited 6-hydroxydopamine-induced depletion of brain NA. The antireserpine activity of **20** (and by extrapolation the other active members of the series) is, thus, probably due to its predominant NA uptake-inhibiting properties.

Because of its 5-HT and DA uptake-inhibiting properties in vitro, pharmacological studies with **20** have been undertaken to determine whether the former effects (seen at somewhat high concentrations) were reflected in vivo. Evidence of 5-HT-potentiating activity has been obtained using the procedure of Buus Lassen;[11] i.e., the anticonvulsant activity of L-5-hydroxytryptophan against maximal electroshock was potentiated by **20** (ED_{50} = 8.5 mg/kg po), whereas **20** alone (ED_{50} = 125 mg/kg po) possesses only weak anticonvulsant activity. The in vitro DA uptake-inhibiting properties, however, do not appear to be reflected pharmacologically in vivo. Thus, **20** at doses up to 50 mg/kg po, did not induce turning[12] in rats lesioned unilaterally in the substantia nigra, and in normal mice only slight CNS stimulation (at doses of 8 mg/kg po and above) was observed. No evidence of monoamine oxidase inhibiting properties was obtained either in vitro or in vivo.

On the basis of the above results, **20** appears to potentiate the central effects of NA and 5-HT and is therefore being progressed as a potential antidepressant agent.

Experimental Section

Chemistry. For most new compounds, the melting point, method of purification, overall yield, method of preparation, and analyses carried out are summarized in Tables I and II; details of other novel compounds are given later in this section. Each preparative method (Schemes I to IV) is illustrated by a representative sample. Overall yields quoted in Tables I and II are based on the following starting materials: methods A and E, the appropriate 1,1-disubstituted 2-propanone; method B, 2,2-diphenylethanal or 1,1-diphenyl-2-propanone; method C, the immediate 3-(*N*-benzyl-*N*-methylamino) precursor; method D, 2,3-epoxy-1,1-diphenylpropane; method F, 3-(methylamino)-1,1-diphenyl-2-propanol; method G, the appropriate benzophenone; method H, the immediate precursor propene; method I, 4,4′-difluorobenzophenone; method J, substituted or unsubstituted 1-hydroxy-3-(dimethylamino)-1,1-diphenyl-2-propanone; method K, 1-methoxy-1,1-diphenyl-2-propanone; method L, the appropriate 2-propanone precursor; method M, the 2-propanol precursor. The spectroscopic properties of all new compounds were consistent with their proposed structure. Melting points are uncorrected. The elemental analyses indicated were within 0.4% of the theoretical values.

Method A. 3-(*N*-Benzyl-*N*-methylamino)-1-(4-fluorophenyl)-1-phenyl-2-propanol (24). The procedure of Greenhill[1] was employed. Br_2 (14.85 g, 0.093 mol) in HOAc (200 mL) was added dropwise to a solution of 1-(4-fluorophenyl)-1-phenyl-2-propanone [20.1 g (0.088 mol), bp 134–142 °C (0.7 mm), prepared in 50% yield by the Friedel–Crafts reaction of 1-bromo-1-(4-fluorophenyl)-2-propanone with benzene in the presence of $AlCl_3$] in HOAc (200 mL) at 60–70 °C. After 30 min, the reaction mixture was poured onto ice and extracted with Et_2O to give crude 3-bromo-1-(4-fluorophenyl)-2-propanone (28 g).

Benzylmethylamine (21.8 g, 0.18 mol) was added to a solution of the crude bromo ketone (13.4 g, 0.044 mol) in Et_2O (250 mL), and the mixture was stirred at ambient temperature for 4 h and then extracted with 5 N HCl. The acidic layer was basified and extracted with Et_2O to yield an oil, which was purified by chromatography on silica gel in light petroleum (bp 40–60 °C) containing progressively increasing quantities of Et_2O to give 3-(*N*-benzyl-*N*-methylamino)-1-(4-fluorophenyl)-1-phenyl-2-propanone (6.7 g, 44%).

The amino ketone (6.7 g, 0.019 mol) in EtOH (75 mL) was treated with a solution of $NaBH_4$ (2.16 g, 0.057 mol) in H_2O (30 mL), and the resulting mixture was stirred at ambient temperature for 1 h. Excess $NaBH_4$ was decomposed with 5 N HCl, and the solvent was removed in vacuo. The residue was dissolved in 5 N HCl, washed with Et_2O, basified, extracted into Et_2O, and dried ($MgSO_4{\cdot}H_2O$).

Removal of the solvent gave an oil, which was chromatographed on silica gel in light petroleum (bp 40–60 °C) containing progressively increasing quantities of Et_2O to give **24** (5.7 g, 85%).

Method B. 3-Amino-1,1-diphenyl-2-propanol Hydrochloride (8). To 2,2-diphenylethanal (10.0 g, 0.051 mol) dissolved in dioxane (50 mL) was added a solution of NaCN (2.5 g, 0.051 mol) in H_2O (10 mL), and the resulting mixture was cooled to 15 °C. H_2SO_4, 30% (14 mL), was added dropwise with stirring and the resulting mixture was allowed to attain ambient temperature overnight. The next day Et_2O (50 mL) was added, and the organic layer was separated and dried ($MgSO_4{\cdot}H_2O$). Removal of the solvent in vacuo gave a gum (14.0 g) containing approximately 50% of the required 2,2-diphenylethanal cyanohydrin together with some unchanged starting material.

The crude cyanohydrin in dry THF (50 mL) was added dropwise with stirring to a suspension of $LiAlH_4$ (4.7 g, 0.12 mol) in dry THF (50 mL), and the resulting mixture was stirred under reflux for 4 h and then cooled. H_2O (5 mL), followed by 10% NaOH (15 mL), was added dropwise and the resulting organic layer was separated and dried ($MgSO_4{\cdot}H_2O$). Removal of the solvent in vacuo gave a gum which was dissolved in dry Et_2O and treated with Et_2O–HCl to precipitate **8** (7.9 g).

Method C. 3-(Methylamino)-1,1-diphenyl-2-propanol Hydrochloride (9). 3-(*N*-Benzyl-*N*-methylamino)-1,1-diphenyl-2-propanone (prepared in 86% yield by the reaction of 3-bromo-1,1-diphenyl-2-propanone[1] with benzylmethylamine) was reduced with $NaBH_4$ to give 3-(*N*-benzyl-*N*-methylamino)-1,1-diphenyl-2-propanol (80%) and converted to the hydrochloride, mp 158–161 °C.

A solution of the above propanol hydrochloride (2.0 g, 0.0054 mol) in EtOH (50 mL) was hydrogenated at ambient temperature and atmospheric pressure in the presence of 5% Pd on C (0.2 g) until hydrogen uptake ceased (ca. 24 h). The catalyst was removed by filtration, and the filtrate was evaporated to ca. 15 mL and then diluted with Et_2O to give **9** (1.1 g).

Method D. 3-(Benzylamino)-1,1-diphenyl-2-propanol Hydrochloride (10). Crude 2,3-epoxy-1,1-diphenylpropane [7.8 g (0.037 mol), prepared in 90% yield by the reaction of dimethylsulfoxonium methylide with 2,2-diphenylethanal in Me_2SO at 50 °C for 1 h] in EtOH (55 mL) was treated with benzylamine (4.07 g, 0.038 mol), and the resulting solution was allowed to stand overnight at ambient temperature. Removal of the solvent in vacuo gave 3-(benzylamino)-1,1-diphenyl-2-propanol (5.16 g, 44%), mp 123–124 °C, and converted to **10** with Et_2O–HCl.

Method E. 3-(*N*-Ethyl-*N*-methylamino)-1,1-diphenyl-2-propanol Hydrochloride (11). A modified Greenhill[1] procedure was used. Reduction of 3-bromo-1,1-diphenyl-2-propanone with $NaBH_4$ in MeOH gave 3-bromo-1,1-diphenyl-2-propanol (86%) as a yellow oil.

The above bromohydrin (2 g, 0.0069 mol) in EtOH (20 mL) was treated with ethylmethylamine (1 g, 0.017 mol) and the reaction was left to stand overnight at ambient temperature. Removal of the solvent in vacuo gave a brown oil which was partitioned between Et_2O and 5 N HCl. The aqueous layer was basified and extracted with Et_2O, and the organic layer was washed with H_2O and dried ($MgSO_4{\cdot}H_2O$). Removal of the solvent in vacuo gave 3-(*N*-ethyl-*N*-methylamino)-1,1-diphenyl-2-propanol (1.13 g, 61%) as a brown oil, which was converted to **11** with Et_2O–HCl.

Method F. 3-[*N*-(3-Hydroxypropyl)-*N*-methylamino]-1,1-diphenyl-2-propanol (12). A mixture of 3-(methylamino)-1,1-diphenyl-2-propanol (2.6 g, 0.011 mol) and 3-bromo-1-propanol (2.5 g, 0.018 mol) in EtOH (20 mL) was allowed to stand at ambient temperature overnight, then boiled under reflux for 7 h, and left to stand for a further 2 days at ambient temperature. The solvent was removed in vacuo and the residue was partitioned between Et_2O and 5 N HCl. The acid layer was separated, basified, and extracted with Et_2O, and the Et_2O extracts were washed with H_2O and dried ($MgSO_4{\cdot}H_2O$). Removal of the solvent in vacuo gave a yellow oil, which was chromatographed on alumina in light petroleum (bp 60–80 °C) containing increasing portions of EtOAc to give **12** (0.85 g, 26%) as a pale yellow oil.

Method G. 1-(3-Chlorophenyl)-3-(dimethylamino)-1-phenyl-2-propanol Hydrochloride (20). 3-Chlorobenzophenone (8.65 g, 0.04 mol) in Me_2SO (15 mL) was added under N_2 to a solution of dimethylsulfoxonium methylide [from 10.55 g (0.048 mol) of trimethylsulfoxonium iodide and 1.15 g (0.048 mol) of NaH], and the resulting mixture was stirred at 50 °C for 2 h, cooled, and poured into H_2O (45 mL). Extraction with Et_2O gave crude 1-(3-chlorophenyl)-1,2-epoxy-1-phenylethane (8.7 g, 95%).

$BF_3{\cdot}Et_2O$ (5 drops) was added to a solution of the crude epoxide (8.7 g, 0.038 mol) in dry C_6H_6 (250 mL). After 5 min, H_2O (100 mL) was added and the C_6H_6 layer was separated and washed with H_2O until the washings were no longer acidic. Removal of the C_6H_6 in vacuo gave crude 2-(3-chlorophenyl)-2-phenylethanal (5.07 g, 58%) as an oil.

Trimethylsulfoxonium iodide (1.37 g, 0.0063 mol) and NaH (0.15 g, 0.0061 mol) were mixed under N_2, and Me_2SO (4 mL) was then added slowly with stirring. A solution of 2-(3-chlorophenyl)-2-phenylethanal (1.28 g, 0.0056 mol) in Me_2SO (2 mL) was added over 15 min to this mixture, which was then heated to 55 °C for 3 h. After being cooled, the mixture was diluted with H_2O and extracted with Et_2O. The organic extract was washed with H_2O, dried ($MgSO_4{\cdot}H_2O$), and evaporated to give crude 1-(3-chlorophenyl)-2,3-epoxy-1-phenylpropane (1.26 g, 96%) as an oil.

The above epoxide (1.26 g, 0.0052 mol) was dissolved in Me_2NH–EtOH (4.0 mL, 33%, w/v, solution) and allowed to stand at ambient temperature for 48 h. Solvent and excess Me_2NH were removed in vacuo, the residue was dissolved in Et_2O and extracted with 2 N HCl, the acid extract was basified (2 N NaOH) and extracted with Et_2O, and the Et_2O extract was dried ($MgSO_4{\cdot}H_2O$). Removal of the solvent gave 1-(3-chlorophenyl)-3-(dimethylamino)-1-phenyl-2-propanol (0.41 g, 27%), which was converted to **20** (0.35 g, 76%) with Et_2O–HCl.

Method H. 1-(3,4-Dichlorophenyl)-3-(dimethylamino)-2-phenyl-2-propanol Hydrochloride (31). To a solution of 1-(3,4-dichlorophenyl)-3-(dimethylamino)-1-phenyl-1-propene [2.3 g (0.0075 mol), prepared via the Mannich base procedure of Jones et al.[2]] in dry THF (45 mL), stirred under N_2 at 0 °C, was added diborane (0.053 mol, 50 mL of a 2.1 M solution of BH_3 in THF), and the resulting solution was allowed to attain ambient temperature overnight. The reaction mixture was then cooled to 0 °C, carefully treated in succession with 40% NaOH (50 mL) and 30% H_2O_2 (50 mL), heated under reflux for 2 h, and cooled. The upper organic layer was separated and the lower aqueous layer extracted with Et_2O. The combined organic extracts were evaporated in vacuo, and the resulting oil was redissolved in Et_2O and extracted with dilute HCl at pH 5. Basification of the acidic layer and extraction with Et_2O gave 1-(3,4-dichlorophenyl)-3-(dimethylamino)-1-phenyl-2-propanol as a gum, which was converted to **31** (1.03 g) with Et_2O–HCl.

Method I. 1,1-Bis(4-fluorophenyl)-3-(dimethylamino)-2-propanol (33). PhLi (0.02 mol, 20 mL of a 1 M solution in Et_2O) was added under N_2 to a stirred suspension of $CH_3OCH_2P(Ph_3)^+Cl^-$ (6.88 g, 0.02 mol) in dry Et_2O (50 mL). After 10 min, 4,4′-difluorobenzophenone (4.56 g, 0.021 mol) in dry Et_2O (20 mL) was added, and the resulting mixture was stirred at ambient temperature for 2 h and then filtered. The filtrate was evaporated in vacuo and the residue chromatographed on alumina to yield 1,1-bis(4-fluorophenyl)-2-methoxyethene (3 g, 61%), which was dissolved in 50 mL of a solution of 10% H_2SO_4 in HOAc and allowed to stand for 30 min. The reaction mixture was then poured into H_2O and extracted with Et_2O, and the Et_2O extract was washed well with H_2O and then with $NaHCO_3$ and dried ($MgSO_4{\cdot}H_2O$). Evaporation of the solvent in vacuo yielded 2,2-bis(4-fluorophenyl)ethanal (2.2 g, 78%) after purification by chromatography on silica gel. The above aldehyde was converted to **33** in 55% yield as described in method C.

Method J. 1-(4-Fluorophenyl)-3-(dimethylamino)-1-phenyl-1,2-propanediol Hydrochloride (42). The procedure of Greenhill[1] was used. 1-(4-Fluorophenyl)-1-hydroxy-1-phenyl-2-propanone [prepared by the hydration of 1-(4-fluorophenyl)-1-phenylprop-2-yn-1-ol, itself prepared by the reaction of 4-fluorobenzophenone with sodium acetylide] was converted in 50% yield to 1-(4-fluorophenyl)-1-hydroxy-3-(dimethylamino)-1-phenyl-2-propanone (hydrochloride salt, mp 194–195 °C). Reduction of the latter with $LiAlH_4$, followed by treatment with Et_2O–HCl, gave **42**.

Method K. 1-Methoxy-3-(dimethylamino)-1,1-diphenyl-2-propanol Hydrochloride (41). This was prepared by the method of Greenhill.[1]

Method I. 3-(Dimethylamino)-1,1,2-triphenyl-2-propanol Hydrochloride (47). PhMgBr [from PhBr (12.4 g, 0.079 mol) and Mg (1.9 g, 0.079 mol) in dry Et_2O (50 mL)] was treated dropwise with stirring with a solution of 3-(dimethylamino)-1,1-diphenyl-2-propanone[1] (5 g, 0.02 mol) in dry Et_2O (25 mL), and the resulting mixture was stirred and boiled under reflux for 3 h. Workup with NH_4Cl, followed by chromatography of the crude product on alumina in light petroleum (bp 40–60 °C) containing progressively increasing proportions of Et_2O, gave 3-(dimethylamino)-1,1,2-triphenyl-2-propanol as an oil, converted to **47** with Et_2O–HCl.

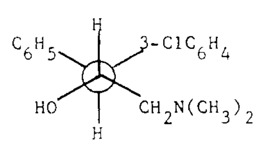
Method M. 2-(Benzoyloxy)-1-(3-chlorophenyl)-3-(dimethylamino)-1-phenylpropane (44). Benzoyl chloride (1.49 g, 0.011 mol) was added to 1-(3-chlorophenyl)-3-(dimethylamino)-1-phenyl-2-propanol (2.90 g, 0.01 mol) in dry pyridine (10 mL), and the solution was allowed to stand at ambient temperature for 4 h. The pyridine was removed in vacuo, and the residue was partitioned between Et_2O and 5 N HCl. The acid layer on basification and reextraction into Et_2O yielded **44** as a colorless solid.

Resolution of 1. 3-(Dimethylamino)-1,1-diphenyl-2-propanol dissolved in EtOAc was added to an equimolar amount of D-(−)-mandelic acid dissolved in EtOAc, and the resulting solution was evaporated in vacuo. The resulting D-(−)-mandelate salt was recrystallized five times from EtOAc (30–35 mL of solvent/g of salt), the melting point rising from 140–143 °C to a constant 153–154 °C. Regeneration of the free base gave (−)-3-(dimethylamino)-1,1-diphenyl-2-propanol, mp 61–62 °C, $[\alpha]^{20}{}_D$ −56° (*c* 1.6, EtOH), converted to (−)-1, mp 184–185 °C.

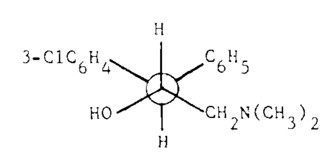
The mother liquors from the above recrystallizations were combined, evaporated, and reconverted to the free base enriched in the (+) isomer. Reaction of this base with an equimolar amount of L-(+)-mandelic acid, followed by purification as for the (−) enantiomer, gave (+)-3-(dimethylamino)-1,1-diphenyl-2-propanol, mp 60–61 °C, $[\alpha]^{20}{}_D$ +56° (*c* 1.6, EtOH), converted to (+)-**1**, mp 184–185 °C.

Separation of the Diastereoisomers of 20. To a solution of 1-(3-chlorophenyl)-3-(dimethylamino)-1-phenyl-2-propanol (**20**; 5.12 g, 0.018 mol) in EtOH (40 mL) was added a solution of $PhCO_2H$ (2.15 g, 0.018 mol) in EtOH (30 mL). The salt which immediately crystallized was filtered to give a colorless solid (5.46 g), mp 163–166 °C. A second crop (0.16 g), mp 149–149.5 °C, was obtained by concentration of the mother liquors. Two further crops (0.7 g, mp 133–148 °C, and 0.3 g, mp 110–116 °C) were obtained by evaporation of the EtOH filtrate and crystallization of the residue from Et_2O. Careful fractional crystallization of the above materials, with recombination of fractions of similar melting point range, led to the separation of two isomeric salts, mp 172–173 °C (2.05 g, 28%) and mp 117–142 °C (1.73 g, 24%). Each salt was converted first to its free base, which on treatment with HCl–Et_2O followed by crystallization from EtOH gave **20a**·HCl (1.38 g, 24%), mp 156.5–157 °C, and **20b**·HCl (1.11 g, 19%), mp 198–199 °C (with partial melting and resolidification at 110–120 °C), respectively.

The structures of **20a** and **20b** were deduced by means of a 90-MHz lanthanide-shift NMR study on each isomer using a compound/shift reagent [Eu(fod-d_9)$_3$] ratio of 0.95 and Me_4Si as internal standard. In the normal 90-MHz spectrum of each isomer, the aromatic protons appear as an unresolved multiplet (δ 6.8–7.7). Addition of the shift reagent (which is assumed to chelate mainly to the hydroxyl group) results in a greater downfield shift of the aromatic protons which are spatially nearer to the chelated europium atom than of those which are more remote. In the aromatic portion (δ 6.8–9.1) of the spectrum of **20a**, the 2-proton of the 3-chlorophenyl group occurs as a readily discernible singlet (δ 7.76). With **20b**, the aromatic protons occur in the same range as for **20a** but the corresponding 2-proton of the 3-chlorophenyl group is more deshielded (δ 8.89). On this basis, **20a** and **20b** have



20a



20b

been assigned the structures shown (for simplicity only one enantiomer is drawn for each structure).

Borane–Amine Complex of 3-(Dimethylamino)-1-(2-methylphenyl)-1-phenyl-1-propene (35). To a cooled solution of 3-(dimethylamino)-1-(2-methylphenyl)-1-phenyl-1-propene[2] (0.5 g, 0.002 mol) in dry THF (5 mL) under N_2 was added a solution of diborane (0.002 mol, 4 mL of a 1 M solution of BH_3 in THF), and the resulting mixture was stirred at ambient temperature for 1 h. NaOH, 40% (4 mL), was added to the mixture, which was then boiled under reflux during the addition of 30% H_2O_2 (4 mL). After 10 min at reflux, the mixture was cooled to ambient temperature and solid K_2CO_3 was added until two layers separated. The organic layer was separated and dried ($MgSO_4 \cdot H_2O$), and the solvent was removed in vacuo to give an oil (0.6 g) which was purified by chromatography on silica gel. Elution with light petroleum (bp 40–60 °C) containing progressively increasing proportions of Et_2O gave **35** (0.44 g, 83%). Anal. ($C_{18}H_{24}BN$) C, H, N. The suggested structure **35** was also supported by NMR, since the dimethylamino, allylic methylene, and vinyl protons of **35** were deshielded by 0.30, 0.42, and 0.30 ppm, respectively, compared with the propenamine (*E–Z* mixture) precursor.

Bis[3-(3-chlorophenyl)-2-hydroxy-3-phenylpropyl]methylamine (34). A mixture of crude 1-(3-chlorophenyl)-2,3-epoxy-1-phenylpropane (28.6 g, 0.12 mol) and $MeNH_2$ (500 mL of a 33%, w/v, solution in EtOH) was kept at ambient temperature for 2.5 h until TLC (silica-C_6H_6) indicated that no epoxide remained. Excess $MeNH_2$ and EtOH were removed in vacuo, and the residue was dissolved in Et_2O and treated with Et_2O-HCl to give **34** (5 g, 16%), mp 117–120 °C (with softening at 110 °C). Anal. ($C_{31}H_{32}Cl_3NO_2$) C, H, Cl, N.

1,1-Diphenyl-3-(phenylthio)-2-propanol and its Conversion to 1. The procedure of Shanklin et al.[9] was employed. *n*-BuLi (0.012 mol, 7.5 mL of a 1.6 M solution in hexane) was added over 10 min to a stirred solution of thioanisole (1.36 g, 0.011 mol) and Dabco (1.23 g, 0.011 mol) in THF (15 mL) at 0 °C under N_2. 2,2-Diphenylethanal (1.96 g, 0.01 mol) in THF (15 mL) was added dropwise and the resulting mixture was allowed to attain ambient temperature overnight. The next day the reaction mixture was poured into H_2O (100 mL) and extracted with $CHCl_3$ to give an oil, which was purified by chromatography on silica gel. Elution with light petroleum (bp 40–60 °C) containing progressively increasing quantities of Et_2O yielded 1,1-diphenyl-3-(phenylthio)-2-propanol (1.38 g, 41%) as an oil.

$Et_3O^+BF_4^-$ (0.86 g, 0.0045 mol) was added to a solution of the above propanol (1.3 g, 0.004 mol) in CH_2Cl_2 (20 mL), and when the resulting mixture became homogeneous aqueous 0.5 M NaOH (20 mL) was added and the resulting mixture was stirred overnight. The next day the organic layer was separated and dried ($MgSO_4 \cdot H_2O$) to give crude 2,3-epoxy-1,1-diphenylpropane, which was converted to **1** (78%) as described in method D.

Pharmacology. The potential antidepressant activity of the compounds has been assessed using a modification of the method of Spencer.[13] Two groups of five CFLP male mice (each mouse weighing 18–23 g) were given either an oral dose of test compound or control vehicle 24, 18, and 2 h before an intravenous injection of reserpine base (1 mg/kg). The esophageal temperatures of the mice were taken immediately before the administration of reserpine and at 2, 4, and 6 h afterwards. The mean temperature of the control group was subtracted from the mean of the test group at each of the three time points (2, 4, and 6 h), and these three differences were summed and adjusted to take into account any initial (time 0 h) temperature differences between the control and test groups. The resultant index of activity (measured in degrees Celsius) is called Δ6 in Tables I and II and, in general, active doses of test compound have been quoted such that Δ6 lies between 5 and 9 °C.

Anticholinergic activity was assessed by three methods: antagonism of pilocarpine-induced salivation, production of mydriasis, and inhibition of acetylcholine-induced contraction of the guinea pig ileum.

The pilocarpine test measures the degree of inhibition of salivation in mice induced by the cholinomimetic pilocarpine. Groups of eight male CFLP mice (each mouse weighing 18–23 g) were used for each test. Test drugs or vehicle were administered subcutaneously 20 min before the mice were anaesthetised with urethane (1.8 g/kg sc) and, after a further 10 min, pilocarpine (2 mg/kg sc) was administered.

These mice were then placed at the heads of 4-cm-wide columns ruled on sheets of chromatography paper with their front legs under their bodies. Every 5 min for 35 min the rows of mice were moved 4 cm down the column, and areas of salivation were measured using an Allbrit planimeter. Percentage change from control values for each dose level was calculated for each mouse and a regression against log dose was performed with subsequent calculation of the ED_{50} with fiducial limits according to the method of Goldstein.[14]

Mydriasis in mice was assessed by measurement of the pupil diameter. Groups of five CFLP male mice (each mouse weighing 18–23 g) were given vehicle or test compound (four dose levels typically) by the oral route. Pupil diameters were measured directly with a binocular microscope 20 min after drug. Percentage change from control values was calculated for each mouse, and the results were treated as for the pilocarpine group with the one difference that an ED_{200} value was calculated for these experiments. The ED_{200} was defined as a 200% increase in pupil diameter.

Inhibition of the contractions of the guinea pig ileum in vitro was assessed essentially by the method of Arunlkshana and Schild,[15] with the exception that the acetylcholine dose–response curves were fitted, using matrix manipulation techniques, to a sigmoid curve of the form:

$$p = \frac{D^E}{D^E + K^E}$$

where p is the response, D is the dose, K is the ED_{50}, and E is the slope. The generated ED_{50} values were then treated by the same method as that used by the original authors to produce a pA_2 value for acetylcholine antagonism, pA_2 being defined as the negative $\log_{10}$ of the molar concentration of compound (antagonist) which will reduce the effect of two equal doses of acetylcholine (agonist) to that of a single dose.

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