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Substituted 1,1-Diphenyl-3-aminoprop-1-enes and 1,1-Diphenyl-3-aminopropanes as Potential Antidepressant Agents

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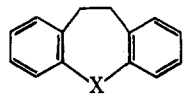
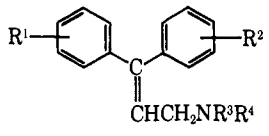
A series of substituted 1,1-diphenyl-3-aminoprop-1-enes and 1,1-diphenyl-3-aminopropanes has been prepared. These compounds display interesting properties as potential antidepressant agents.

The observation of antireserpine activity of a low order in compounds of the general structure I[1] and the structural relationship of these compounds to known antidepressant drugs, such as amitryptyline (II) and imipramine (III), led us to investigate the pharmacological properties of compounds of the general structures IV and V. 1,1-Diphenyl-3-aminoprop-1-enes (IV) and 1,1-diphenyl-3-aminopropanes (V) have previously been examined as potential analgetics,[2] antihistamines,[3] antispasmodics,[3,4] and analeptics.[5] This paper is concerned with the synthesis of new compounds of the generic structures IV and V and their evaluation as potential antidepressants.

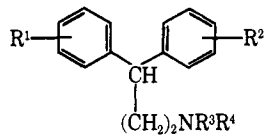
I



II, X = =CH(CH2)2NMe2
III, X = N(CH2)3NMe2



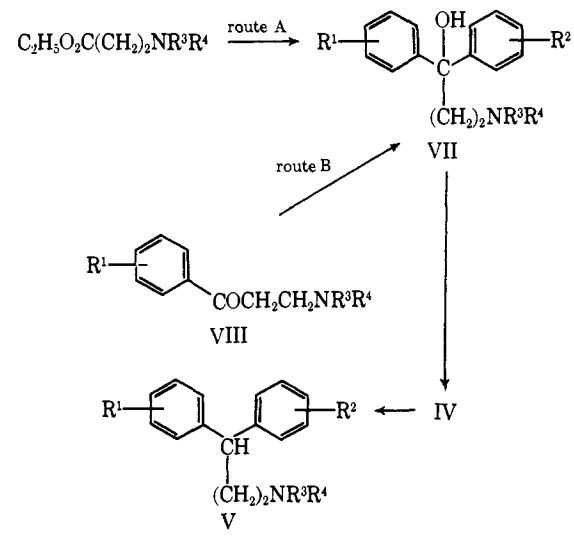
IV

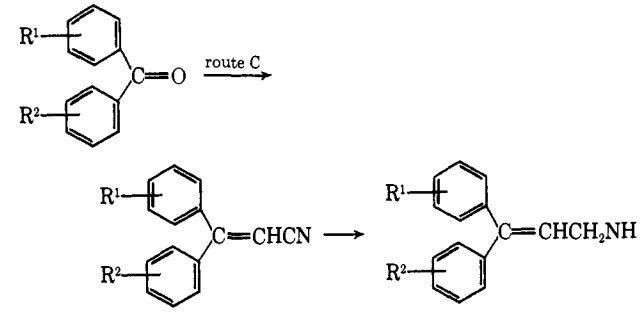


V

Chemistry.—The 1,1-diphenyl-3-aminoprop-1-enes IV were prepared in most cases by the methods illustrated below. The amino alcohols VII in which $R^1 = R^2$ were prepared best by reaction of a Grignard reagent with the appropriate ethyl β-aminopropionate derivative VI (route A). The alternative reaction of a Grignard reagent with a Mannich base VIII (route B) generally gave inferior yields, probably on account of enolization of the Mannich base.[6]

Dehydration of amino alcohols VII in which the aromatic rings have different substituents ($R^1 \neq R^2$) gave rise to mixtures of the geometrical isomers of the corresponding 1,1-diphenyl-3-aminoprop-1-enes. It was evident from the nmr spectra of these products that the geometrical isomers were generally formed in about equal proportions. Isomeric mixtures were tested as such in the form of either the HCl or oxalate salt.





Primary 1,1-diphenyl-3-aminoprop-1-enes (IV, $R^3 = R^4 = H$) were prepared by LAH reduction of the corresponding unsaturated nitriles (route C). When this reaction was carried out in Et_2O at room temp reduction of the conjugated double bond was significant, but at −20° reduction of the nitrile was not accompanied by reduction of the double bond.

1,1-Diphenyl-3-aminopropanes (V) were prepared by catalytic hydrogenation of the corresponding 1,1-diphenyl-3-aminoprop-1-enes (IV) or, in the case of secondary amines (V, $R^3 = H$), by hydrogenolysis of the corresponding 1,1-diphenyl-3-benzylaminoprop-1-enes (IV, $R^3 = CH_2C_6H_5$).

Structure–Activity Relationships.—The more active members of this series, *e.g.*, **6, 16,** and **17**, have activities comparable with those of known clinically effective antidepressants such as amitryptyline or imipramine, and some, particularly the monomethylamino compounds, *e.g.*, **5, 15,** and **18**, are more active in the pharmacological and biochemical tests reported.

In the olefinic series substitution in the Ph rings with halogen, especially F, marginally improves the

(*) To whom inquiries should be addressed.

(1) Unpublished observation from this laboratory.

(2) P. A. J. Janssen, "Synthetic Analgesics," Part 1, Pergamon Press, London, 1960.

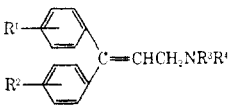
(3) A. C. White, A. F. Green, and A. Hudson, *Brit. J. Pharmacol*, **6**, 560 (1951).

(4) P. V. Petersen, *Acta Pharmacol. Toxicol.*, **7**, 51 (1951).

(5) K. Zipf, *Arzneimitt.-Forsch.*, **13**, 166 (1963).

(6) R. Baltzly and J. W. Billinghurst, *J. Org. Chem.*, **30**, 4330 (1965).

TABLE I



	R¹	R²	R³	R⁴	Method	Yield,[a] %	Mp of HCl or oxalate, °C	Formula[f]	Reversal of reserpine-induced hypothermia ED_{10}, mg/kg	% inhibition of 5-HT uptake at 10 μg/ml	Oral acute LD_{50} (mice) mg/kg
1	H	H	H	H	C	70	214–216	$C_{15}H_{15}N$[b]	>100		
2	2-CH_3	H	H	H	C	70	186–188	$C_{18}H_{18}ClN$	100		
3	2-F	H	H	H	C	50	180–182	$C_{15}H_{15}ClFN$	100		
4	4-F	H	H	H	C	48	189–190	$C_{15}H_{15}ClFN$	100		
5	H	H	CH_3	H	B	43	147–148	$C_{18}H_{18}ClN$[b]	1	96	201
6	H	H	CH_3	CH_3	A or B		168–170	$C_{17}H_{20}ClN$[b]	1.5	88	271
7	H	H	CH_3	C_2H_5	*c*	84	155–157 (ox)	$C_{20}H_{23}NO_4$	1–3		
8	H	H	$(CH_3)_2CH$	H	*d*	21	144–146	$C_{18}H_{22}ClN$	>100		
9	H	H	C_2H_5	C_2H_5	A or B		146–147	$C_{19}H_{24}ClN$[b]	30–100		
10	H	H	$CH_3CH{=}CH_2$	H	A	60	146–147	$C_{18}H_{20}ClN$	100		
11	H	H			A		165–167	$C_{19}H_{22}ClN$[b]	100		
12	H	H			A		209–210	$C_{20}H_{24}ClN$[b]	100		
13	H	H			A		218–219	$C_{19}H_{22}ClNO$[b]	100		
14	H	H			A	75	195–200	$C_{20}H_{26}Cl_2N_2$[b]	100		
15	4-F	H	CH_3	H	B	22	136–140	$C_{16}H_{17}ClFN$	0.6	96	177
16	4-F	H	CH_3	CH_3	B	10	188–190	$C_{17}H_{19}ClFN$	0.6	81	225
17	3-F	H	CH_3	CH_3	B	31	144–148	$C_{17}H_{19}ClFN$	0.5	78	352
18	4-Cl	H	CH_3	H	B	12	140–142	$C_{16}H_{17}Cl_2N$	0.7	98	110
19	4-Cl	H	CH_3	CH_3	B	12	210–212	$C_{17}H_{19}Cl_2N$	3	64	~400
20	4-Br	H	CH_3	CH_3	B	35	170–171	$C_{17}H_{19}BrClN$	0.6		180
21	3-CF_3	H	CH_3	CH_3	B	45	175–179	$C_{18}H_{19}ClF_3N$	3		118
22	2-CH_3	H	CH_3	H	B	20	156–160	$C_{17}H_{20}ClN$	15		281
23	2-CH_3	H	CH_3	CH_3	B	18	192–194	$C_{18}H_{22}ClN$	15		609
24	2-CH_3O	H	CH_3	CH_3	B	41	172–175	$C_{18}H_{22}ClNO$	8		284
25	4-F	4-F	CH_3	H	A	13	215–216 (ox)	$C_{16}H_{17}F_2NO_4$	3	97	
26	4-F	4-F	CH_3	CH_3	A	37	211–213	$C_{17}H_{18}ClF_2N$	3	74	287
27	4-F	4-F	CH_3	$CH_2C_6H_5$	A	33	130–132	$C_{23}H_{22}ClF_2N$	10–30		
28	3-F	3-F	CH_3	H	A	31	177–179	$C_{16}H_{18}ClF_2N$	2	99	<200
29	3-F	3-F	CH_3	CH_3	A	32	156–159	$C_{17}H_{18}ClF_2N$	2	66	164
30	3-CF_3	3-CF_3	CH_3	CH_3	A	47	158–160	$C_{19}H_{18}ClF_6N$	100		
31	4-Cl	4-Cl	CH_3	H	A	10	216–219 (ox)	$C_{18}H_{17}Cl_2NO_4$	2	94	472
32	4-Cl	4-Cl	CH_3	CH_3	B	40	230–232	$C_{17}H_{18}Cl_3N$	3	48	615
33	4-Cl	4-Cl	CH_3	$CH_2C_6H_5$	A	38	185–187	$C_{23}H_{22}Cl_3N$	60		
34	4-Cl	4-F	CH_3	CH_3	B	18	194–196	$C_{17}H_{18}Cl_2FN$	100	73	
35	4-Cl	3-F	CH_3	CH_3	B	20	145–147	$C_{17}H_{18}Cl_2FN$	4	67	409
36	4-Cl	2-CH_3O	CH_3	CH_3	B	25	156–159	$C_{18}H_{21}Cl_2NO$	7		
37	(*e*)	H	CH_3	CH_3	B	22	147–150	$C_{15}H_{18}ClNS$[b]	10		
	Amitriptyline								3	92	420
	Imipramine								7	94	680
	Desimipramine								0.8–1.6	92	
	Nortriptyline								1.0–2.0	94	

[a] Overall yield for both stages based on ester (A) or Mannich base·HCl (B). [b] Described in the literature. [c] Reduction of N-Ac derivative with LAH. See ref 12. [d] Reductive alkylation of amino compd with $NaBH_4$ and Me_2CO. See ref 12. [e] Ph replaced by thienyl. [f] All compounds, except those with footnote *b*, were analyzed for C, H, N.

activity; other substituents are usually dystherapeutic. High activity is retained only in compounds in which N is substituted with either N and Me or two Me radicals, the secondary amines being markedly superior in their ability to inhibit the uptake of 5-HT by human platelets. Substitution of the CH_2 adjacent to N with Me or substitution of the olefinic H with Me diminishes the activity. Replacement of propenyl by a butenyl skeleton is, unexpectedly in view of the amitryptyline structure II, dystherapeutic.

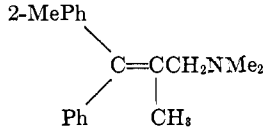
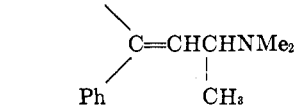
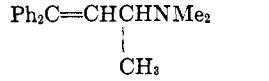
The saturated compounds are in general marginally less active, but with this reservation the same relationships hold as for the unsaturated series.

Experimental Section

Pharmacology. Test Methods.—The potential antidepressant activity of the test compounds was assessed by their ability to antagonize reserpine-induced hypothermia[7] in mice. In the case of the more active members of the series this test was supplemented by a detn of the compds' capacity to inhibit the uptake of 5-HT into human platelets.[8] The limitations of these tests in the prediction of clinically useful antidepressant activity are well known and have been documented.[9-11] One to four groups of 6 mice per treatment were given reserpine (2 mg of base/kg sc as the phosphate). Seventeen hours later the temp of the mice (T_0) was recorded, and the animals were dosed orally with the antidepressant treatment or saline. The temps (T_2, T_4, and T_6) were again recorded at intervals of 2, 4, and 6 hr. Gastric temps were measured by means of an orally inserted probe and displayed on an electric thermometer (type 3G10, Light Labo-

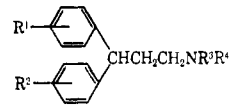
(7) J.-R. Boissier, J. Fichelle-Pagny, P. Simon, *Therapie*, **21**, 109 (1966).
(8) A. Todrick, A. C. Tait, *J. Pharm. Pharmacol.*, **21**, 751 (1969).
(9) L. Gyermek, *Int. Rev. Neurobiol.*, **9**, 95 (1966).
(10) L. J. Hekimian, S. Gershon, and A. Floyd, *Curr. Therapeutic Res.*, **10**, 282 (1968).
(11) S. Gershon, L. J. Hekimian, and A. Floyd, *Arzneimitt.-Forsch.*, **18**, 243 (1968).

TABLE II

		Yield,[a] %	Mp of HCl, °C	Formula[c]	Reversal of reserpine-induced hypothemia ED_{10}, mg/kg
38	$Ph_2C{=}C(CH_3)CH_2NMe_2$	26	188–190	$C_{18}H_{22}ClN$[b]	>30
39		29	181–182	$C_{19}H_{24}ClN$[b]	30
40		30	148–150	$C_{19}H_{24}ClNO$	>100
41	$Ph_2C{=}CH(CH_2)_2NMe_2$	20	180–182	$C_{18}H_{22}ClN$[b]	>100
42		12	158–161	$C_{18}H_{22}ClN$[b]	

[a] Compds **38–42** were prepd from PhMgBr and the corresponding aminoacetone followed by dehydration of the aminocarbinol. The overall yield is based upon the aminoacetone. [b] Described in the literature. [c] See footnote *f*, Table I.

TABLE III



	R^1	R^2	R^3	R^4	Yield, %	Mp of HCl or oxalate, °C	Formula[a]	Reversal of reserpine-induced hypothemia ED_{10}, mg/kg	% inhibition of 2-HT uptake a 10 μg/ml[b]
43	H	H	CH_3	H			$C_{16}H_{20}ClN$[b]		
44	H	H	CH_3	CH_3	78	169–170	$C_{17}H_{22}ClN$[b]	3	87
45	3-F	H	CH_3	CH_3	69	166–168	$C_{17}H_{21}ClFN$	2	
46	4-F	H	CH_3	CH_3	80	141–144	$C_{17}H_{21}ClFN$	3	
47	4-Cl	H	CH_3	CH_3	70	155–157	$C_{17}H_{21}Cl_2N$	50	90
48	3-CF_3	H	CH_3	CH_3	76	145–148	$C_{18}H_{21}ClF_3N$	8.5	
49	2-Me	H	CH_3	CH_3	86	164–166	$C_{18}H_{24}ClN$	20	
50	2-MeO	H	CH_3	CH_3	86	166–167	$C_{18}H_{24}ClNO$	15	
51	3-F	3-F	CH_3	CH_3	87	178–180	$C_{17}H_{20}ClF_2N$	2	
52	4-F	4-F	CH_3	CH_3	86	188–189	$C_{17}H_{20}ClF_2N$	10	81
53	3-CF_3	3-CF_3	CH_3	CH_3	77	198–200 (ox)	$C_{21}H_{21}F_6NO_4$	100	
54	4-Cl	4-Cl	CH_3	CH_3	62	190–194	$C_{17}H_{20}Cl_3N$	50	
55	4-F	4-Cl	CH_3	CH_3	85	173–176	$C_{17}H_{20}Cl_2FN$[c]	100	
56	4-F	4-F	CH_3	H	75	188–192 (ox)	$C_{18}H_{19}F_2NO_4$	10	97
57	4-Cl	4-Cl	CH_3	H	63	212–214 (ox)	$C_{18}H_{19}Cl_2NO_4$		
58	H	H				135–136	$C_{19}H_{24}ClN$[b]	10–30	
59	H	H				215–217	$C_{20}H_{26}ClN$[b]	>100	
60	H	H				208–209	$C_{19}H_{24}ClNO$[b]	>100	

[a] See footnote *f*, Table I. [b] Previously described. [c] N anal. only.

ratories, Brighton, England) which was read to an accuracy of ±0.05°. The effect of the compound was computed from the mean cumulative rise in temp at the intervals T_2, T_4, and T_6. The mean cumulative rise is thus defined as: $\Delta°C = T_2 + T_4 + T_6 - 3T_0$.

The hyperthermic effect was related to dose and, using suitable doses, a dose of drug could be defined which gave a cumulative rise in temp of 10° greater than controls, thus yielding the ED_{10} values recorded in Tables I, II, and III.

The inhibition of the uptake of 5-HT in platelets was detd as follows. A suspension of human platelets in saline was preincubated with drug for 5 min before adding ^{14}C-labeled 5-HT. After incubation for a further 20 min the suspension was chilled and filtered through a Millipore filter. The filter was washed and transferred to a vial of dioxan naphthalene–phosphor for counting. The radioactivity of the platelets is a measure of the uptake of 5-HT. The percentage inhibition produced by drugs as compared with saline-treated controls is recorded in Tables I and III.[12]

Logarithmically spaced doses of compd were administered orally to groups of 5–10 mice, and the percentage mortality at day 7 was detd by inspection. LD_{50}'s were computed by standard logit analysis, but results for selected compounds were tabulated.

N-Substituted ethyl β-aminopropionates (IV) were prepd by mixing equimolar proportions of the appropriate secondary or tertiary amine and ethyl acrylate and fractionally distg the product.[13]

Mannich base hydrochlorides (V) were prepd by standard methods from the appropriately substituted acetophenones.

N-Substituted 3-Amino-1,1-diphenylpropan-1-ols (VI).—The

(12) Full details will be published by A. R. Somerville in *Eur. J. Pharmacol.*

(13) D. W. Adamson, *J. Chem. Soc.*, S144, (1949).

general methods employed are illustrated for symmetrically or unsymmetrically substituted carbinolamines by the following 2 examples.

1,1-Di-(4-fluorophenyl)-3-dimethylaminopropan-1-ol.—A soln of 29.0 g (0.2 mole) of ethyl β-dimethylaminopropionate in 50 ml of anhyd Et_2O was added gradually with stirring to a cooled (0°) Et_2O soln of a Grignard reagent prepd from 105 g (0.6 mole) of p-BrC_6H_4F and 14.6 g (0.6 mole) of Mg. After stirring in the cold for 1 hr and then refluxing for 2 hr, the cooled mixture was decompd with 200 ml of a 10% w/v soln of NH_4Cl. Basification with NH_4OH and extraction with $CHCl_3$ (3 × 250 ml) afforded a $CHCl_3$ soln which on drying and evapn gave 58.0 g of a crude oil. This crude product was dehydrated without further purification.

3-Dimethylamino-1-(4-fluorophenyl)-1-phenylpropan-1-ol.—β-Dimethylaminopropiophenone·HCl (21.4 g, 0.1 mole) was added portionwise to a cooled (0°), stirred Et_2O soln of the Grignard reagent prepared from 35 g (0.2 mole) of p-BrC_6H_4F and 4.8 g (0.2 mole) of Mg. After stirring in the cold for 1 hr and then refluxing for 2 hr, the cooled mixture was decompd and worked up as above. The crude colorless solid (11 g) was dehydrated without further purification.

1,1-Di-(4-fluorophenyl)-3-dimethylaminoprop-1-ene (25).—A soln of 41.0 g (0.14 mole) of the carbinolamine in 250 ml of AcOH and 80 ml of concd HCl was refluxed for 30 min. The soln was concd under reduced pressure, dild with H_2O, and basified with NH_4OH. The base was extracted Et_2O, and Et_2O soln was dried and evapd. Distn under reduced pressure gave 20.5 g of an oil. The base was converted into its hydrochloride in anhyd Et_2O. Crystn of the hydrochloride from EtOAc–EtOH gave an anal. sample, mp 211–213°.

1,1-Di-(4-fluorophenyl)-3-dimethylaminopropane (53).—A soln of 5 g of the olefin·HCl in 20 ml of EtOH was hydrogenated at atm temp and pressure using 2.5 g of 5% Pd-C. After 1 mole of H_2 had been absorbed, the catalyst was filtered, the soln was concd, and the product was pptd with Et_2O. Filtration give 3.0 g of material. Crystn from EtOAc–EtOH gave an anal. sample, mp 188–189°.

1,1-Diphenylprop-1-enylamine (1).—Diethyl phosphonoacetate (106 g) was added dropwise to a stirred suspension of NaH (15 g) in dry dimethoxyethane (500 ml) at 0°. The mixture was stirred for 1 hr after the evoln of H_2 ceased, and a soln of benzophenone (91 g) in dimethoxyethane (100 ml) was then added dropwise. The mixture was stirred at 20° for 2 hr, then poured into H_2O (2000 ml), and extracted (Et_2O). Evapn and distn of the extract gave β,β-diphenylacrylonitrile (63 g, mp 48–49°). This (60 g) was added dropwise to a stirred soln of LAH (20 g) in dry Et_2O (500 ml) at −20°. The mixture was stirred for 2 hr at −20° and for 15 min at 0°. Excess LAH was destroyed by addn of H_2O, and the organic phase was sepd, dried ($MgSO_4$), and evapd. 1,1-Diphenylprop-1-enylamine (1) was isolated from the residual oil as its hydrochloride (58 g, mp 206–208°) by addn of ethereal HCl. The hydrochloride, recrystd from EtOH–Et_2O, had mp 214–216°.

Notes

Synthesis of 3-Trifluoromethyl Steroids[1a]

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The function of the carbonyl moiety of C-3 of steroid hormones in eliciting the biological response has been the subject of intensive study in this laboratory. Among C-2 and/or C-3 substituted steroids prepared to test the possibility that π bonding,[2] high electron density, or H bonding[2] might be important in terms of steroid–receptor interaction have been steroidal cyclopropanes[2] and nitro derivatives.[3] In the present study, the preparation of steroidal C-3 substituted CF_3 derivatives was undertaken, inasmuch as CF_3 represents a center which is both electron rich and capable of H bonding.

The introduction of a CF_3 group by photochemical addition of CF_3I across a double bond has been applied to 3β-ethoxy-17β-hydroxypregna-3,5-dien-20-one acetate[4] but such reactions with unconjugated olefinic steroids have not been reported. In the present study, several methods were tried in preparing the 3-CF_3 steroids. Attempted conversion of a 3-CO_2H substituent into a 3-CF_3 group by reaction with SF_4[4] failed. Likewise, reaction of a 3-keto steroid, dihydrotestosterone acetate, with F_3CMgI[5] yielded only starting material. Finally, employing a modified method of Godfredsen and Vangedal,[6] the 3-CF_3 steroid derivative was obtained.

A solution of 5α-pregn-3-en-20-one (**1**) in CCl_4, CF_3I, and a small amount of pyridine was irradiated with uv light for 8 hr under N_2. Only one product, 3α-trifluoromethyl-4β-iodo-5α-pregn-20-one (**2**), was isolated from the reaction mixture although 8 isomeric adducts (4 cis and 4 trans) could be formed from this reaction. The stereochemistry of **2** was established from further reactions as shown in Scheme I and from the nmr spectra of the adduct and its derivatives.

The C-19 Me peak of **2** was shifted 0.36 ppm downfield compared with **1** and upon hydrogenolysis of the iodo group with LAH, the C-19 Me resonance shifted 0.33 ppm upfield. As it is well known that electronegative groups produce a deshielding effect (0.25 ppm) on the C-19 Me group when they are in a 1:3 diaxial

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