Compounds Affecting the Central Nervous System. III. Substituted 1,1-Diaryl-*t*-aminopropanols and Related Compounds

D. I. BARRON, G. H. HALL, I. L. NATOFF, H. F. RIDLEY, R. G. W. SPICKETT, AND D. K. VALLANCE

Smith Kline & French Laboratories Ltd., Welwyn Garden City, Hertfordshire, England

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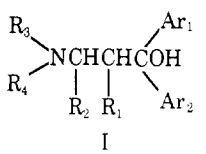
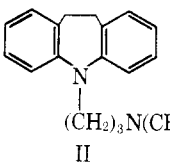
A series of substituted 1,1-diaryl-*t*-aminopropanols was prepared. Some of the compounds possessed a mixture of stimulant and depressant effects on the central nervous system and were also active as anticonvulsants and diuretics. The most active compounds were those with a branched chain, in which the amino groups were dimethylamino, pyrrolidyl, or piperidyl. Replacement of one or both of the aryl groups by heterocycles led to less active compounds as did substitution in the aromatic rings in the *meta* or *para* position.

In a previous publication[1] it was shown that 1,1-diphenyl-2-methyl-3-(*N*-methyl-*N*-phenethylamino)-1-propanol (I, $Ar_1 = Ar_2 = C_6H_5$; $R_2 = H$; $R_1 = R_3 = CH_3$; $R_4 = CH_2CH_2C_6H_5$) possessed a mixture of depressant (blockade of conditioned avoidance response in rats and anticonvulsant activity in mice) and stimulant activity (antireserpine activity and potentiation of picrotoxin convulsions in mice). In addition, it caused diuresis in rats. In some respects the profile of activity on the central nervous system resembled that of 5-(2-dimethylaminopropyl)-10,11-dihydro-5H-dibenz[*b*,*f*]azepine (imipramine, II). In view of the potential clinical interest in compounds with this type of activity, the preparation of related compounds was undertaken and this communication describes their synthesis and pharmacological properties.



I



II

1,1-Diaryl-*t*-aminoalkanols of general structure I have been investigated previously as antispasmodics[2-4] and as analgesics.[5-7] More recently 1-(2-chlorophenyl)-1-phenyl-3-dimethylaminopropanol (I, $Ar_1 = 2\text{-}ClC_6H_4$; $Ar_2 = C_6H_5$; $R_1 = R_2 = H$; $R_3 = R_4 = CH_3$) was shown[8,9] to be an effective antitussive agent. No other investigations of the effect on the central nervous system of compounds of type I have been recorded.

The compounds I ($Ar_1 = Ar_2$) (Table II) were synthesized by the addition of an aryllithium reagent to an appropriately substituted β-*t*-amino ester[10] (Table I). The unsymmetrical compounds I ($Ar_1 = Ar_2$) (Table III) were prepared by addition of an aryllithium reagent to an appropriately substituted β-*t*-amino ketone.[11] The esters of some of these tertiary alcohols and the corresponding olefins were prepared by standard methods.

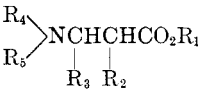
Biological Activity.—The methods used to assess the biological activity of these compounds have been described in previous papers,[1,12] and the results obtained are shown in Table IV.

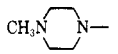
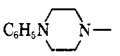
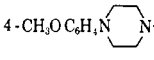
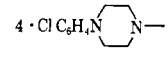
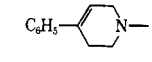
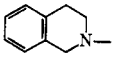
Initially it was thought that the effects on the central nervous system produced by compound **53** were caused by the presence of the arylalkyl group on the nitrogen atom since no CNS activity had been reported in the literature[2,13] for the dimethylamino derivative (**1**). Modifications retaining a phenylalkyl group on the nitrogen atom (**12**–**27**) showed no improvement in biological activity or were less active. Activity was lost when the following changes were made: removal of the methyl from the carbon adjacent to the alcohol group (**54**), moving the methyl to the position adjacent to the nitrogen atom (**12**), and lengthening the chain (**20** and **44**). Incorporation of the tertiary nitrogen atom into a 1,2,3,4-tetrahydroisoquinoline nucleus gave inactive compounds (**11**, **55**, and **56**). However, changing the arylalkyl group on the nitrogen to dimethylamino, to give 3-dimethylamino-2-methyl-1,1-diphenyl-1-propanol, led to a considerable increase in activity in all of the pharmacological tests.

When compared with imipramine, 3-dimethylamino-2-methyl-1,1-diphenyl-1-propanol (**1**) was found to be less active in reversing the ptosis caused by reserpine in mice, but was more active in potentiating picrotoxin-induced convulsions in mice. It was also considerably more active as an anticonvulsant against both electrical- and pentylenetetrazole-induced convulsions. In these two tests it has the same order of activity as diphenylhydantoin. Although the compound blocks the conditioned avoidance response in rats, this appears to be a nonspecific effect since the unconditioned response is blocked at doses only marginally greater (the closely related 3-dimethylamino-2-methyl-1-phenyl-1-(*o*-tolyl)-1-propanol (**28**) behaves similarly).[12] Kjaer and Peterson have reported[13] that this compound is devoid of analgesic activity and this was confirmed in our laboratories. As a diuretic, the compound (at 60 mg./kg.) causes a 65% increase in urine output in the rat. In the sodium-deficient rat at this dose level the output of Na^+ and K^+ was increased (control 0.47 mg./Na^+ excreted, with drug 5.80 mg./Na^+ excreted; control

(1) C. R. Ganellin and R. G. W. Spickett, *J. Med. Chem.*, **8**, 619 (1965).
(2) A. C. White, A. F. Green, and A. Hudson, *Brit. J. Pharmacol.*, **6**, 560 (1951).
(3) J. J. Denton, P. Schedl, W. B. Neier, and V. A. Lawson, *J. Am. Chem. Soc.*, **71**, 2054 (1949); **72**, 3795 (1950).
(4) A. W. Ruddy and J. S. Buckley, *ibid.*, **72**, 718 (1950).
(5) A. L. Morrison and H. Rinderknecht, *J. Chem. Soc.*, 1510 (1950).
(6) N. B. Eddy, C. F. Touchberry, and J. E. Lieberman, *J. Pharmacol. Exptl. Therap.*, **98**, 121 (1950).
(7) T. D. Perrine, *J. Org. Chem.*, **18**, 898 (1953).
(8) J. Y. P. Chen, H. F. Biller, and E. G. Montgomery, *J. Pharmacol. Exptl. Therap.*, **128**, 384 (1960).
(9) Detigon®; R. Gösswald, *Arzneimittel Forsch.*, **8**, 550 (1958).
(10) D. W. Adamson, *J. Chem. Soc.*, S144 (1949).
(11) J. J. Denton, V. R. Lawson, W. B. Neier, and R. J. Turner, *J. Am. Chem. Soc.*, **71**, 2050 (1949).
(12) D. I. Barron, G. H. Hall, I. L. Natoff, and D. K. Vallance, *J. Pharm. Pharmacol.*, **17**, 509 (1965).
(13) H. C. Kjaer and P. V. Peterson, *Acta Chem. Scand.*, **5**, 1145 (1957).

TABLE I
SUBSTITUTED β-t-AMINOPROPIONIC ESTERS



R_1	R_2	R_3	R_4	R_5	Formula	Yield, %	B.p. (mm.) or m.p., °C.
CH_3	CH_3	H	C_4H_8N		$C_9H_{17}NO_2$	54	53 (0.2)[a]
CH_3	CH_3	H	$C_5H_{10}N$		$C_{10}H_{19}NO_2$	44	56 (0.5)[a]
CH_3	CH_3	H	$C_6H_{12}N$		$C_{11}H_{21}NO_2$	73	60 (0.05)[b]
CH_3	CH_3	H			$C_{10}H_{20}N_2O_2$	50	60–62 (0.5)[c]
CH_3	CH_3	H			$C_{15}H_{22}N_2O_2$	76	96–97
CH_3	CH_3	H			$C_{16}H_{24}N_2O_3$	75	57–58
CH_3	CH_3	H			$C_{15}H_{21}ClN_2O_2$	60	64–65
CH_3	CH_3	H			$C_{16}H_{21}NO_2$	60	140 (0.15)
C_2H_5	H	CH_3			$C_{15}H_{21}NO_2$	36	114 (0.25)
C_2H_5	H	CH_3	$C_6H_5CH_2CH_2$	CH_3	$C_{15}H_{23}NO_2$	40	96 (0.3)
CH_3	CH_3	H	$C_6H_5CH_2CH_2$	C_2H_5	$C_{15}H_{23}NO_2$	52	96–100 (0.05)
CH_3	CH_3	H	$C_6H_5CH_2CH(CH_3)$	CH_3	$C_{15}H_{23}NO_2$	66	92 (0.05)
CH_3	CH_3	H	$3,4\text{-}CH_3OC_6H_3CH_2CH_2$	CH_3	$C_{16}H_{25}NO_4$	52	142 (0.02)
CH_3	CH_3	H	$C_6H_{11}CH_2CH(CH_3)$	CH_3	$C_{15}H_{29}NO_2$	77	80 (0.5)
CH_3	CH_3	H	$C_6H_5CH_2$	CH_3	$C_{13}H_{19}NO_2$	65	94 (0.3)
CH_3	CH_3	H	C_7H_{13}	CH_3	$C_{13}H_{25}NO_2$	25	96 (0.5)

[a] Ref. 10. [b] J. A. Hendry, F. L. Ross, and A. L. Walpole, *Brit. J. Pharmacol.*, **6**, 201 (1951). [c] Rhone-Poulenc and Co., French Patent 1,167,510 (1958); *Chem. Abstr.*, **55**, 8444 (1961).

3.26 mg./K^+, with drug 10.66 mg./K^+ excreted). The diuretic effect of this compound was confirmed in the dog, but the stimulating activity of the compound precluded testing above 6–8 mg./kg. i.v.[14] The related *o*-tolyl derivative (**28**) had a similar order of activity to 3-dimethylamino-2-methyl-1,1-diphenyl-1-propanol in all of the pharmacological tests for central nervous system activity. When its diuretic properties were compared with acetazolamide and chlorthiazide, it was found that, whereas chlorthiazide increased the urinary output of water, Na^+, K^+, and Cl^-, the *o*-tolyl derivative and acetazolamide also increased that of residual anion.[12]

Replacement of the dimethylamino group by pyrrolidyl and piperidyl groups gave compounds **2** and **3** with a similar order of activity, but if the ring size were further increased (**4**) activity decreased in all of the CNS tests except the antagonism of pentylenetetrazole-induced convulsions. Other substituents on nitrogen (**5**–**10**) gave inactive compounds.

When the aromatic groups (Ar_1 and Ar_2) in II (R_1 = R_3 = R_4 = Me; R_2 = H) are varied, CNS stimulant activity (antireserpine and picrotoxin potentiation) and anticonvulsant activity are retained when Ar_1 is phenyl, Ar_2 is *o*-tolyl (**28**), and Ar_1, Ar_2 = di(*o*-tolyl) (**36**). Activity is lost when one or both of the aromatic nuclei are substituted in the *meta* or *para* positions with chlorine, methoxyl, or methyl (**29**–**35**). Similar effects were noted in the pyrrolidyl series (**38**, **39**, and **43**), where it was additionally observed that replacement of one of the phenyl groups by 2-furyl, 2-thienyl, or 2-pyridyl gave compounds **40**–**42** with moderate-to-good stimulant activity but lower anticonvulsant activity than the parent compound.

The benzoates (**48** and **52**) and propionates (**50** and **51**) of I (3-dimethylamino-1,1-diphenyl-2-methyl-1-propanol and 1,1-diphenyl-2-methyl-1-pyrrolidyl-1-propanol) were active in the picrotoxin potentiation test but were much less active as anticonvulsants and had considerably less diuretic activity. The olefins (**45**–**57**) had no activity in the tests employed.

Thus optimum activity, in the depressant, stimulant, and anticonvulsant tests, occurs in structure I (R_3R_4N = dimethylamino or pyrrolidyl; R_1 = CH_3; R_2 = H; Ar_1Ar_2 = diphenyl or phenyl-2-tolyl). 3-Dimethylamino-2-methyl-1-phenyl-1-(*o*-tolyl)-1-propanol (**28**) was investigated clinically for antidepressant activity, but the main effects found were ataxia and drowsiness. When stimulant activity was observed it closely resembled that due to amphetamine. Toxic side effects prevented further investigation of the potential anticonvulsant activity of the compound in man.

Experimental Section[15]

1,1-Diphenyl-t-amino-1-alkanols (Table II).—The appropriate aryllithium reagent (0.2 mole) was prepared in anhydrous ether (150 ml.) under an atmosphere of nitrogen. To the cooled (0–5°) solution was added a solution of the appropriate β-*t*-amino ester (0.1 mole) in anhydrous ether (50 ml.). The mix-

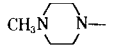
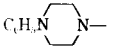
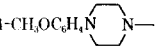
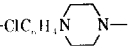
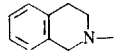
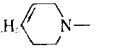
(14) We are grateful to Dr. G. Ullyot, Smith Kline & French Laboratories, Philadelphia, Pa., for the diuretic data on this compound.

(15) Melting points were recorded using an Electrothermal melting point apparatus comprising a gas-heated block and thermometer calibrated for exposed stem. Microanalyses are by Mr. M. Graham (Analytical Laboratories, Smith Kline & French Laboratories Ltd.). The infrared spectra of each compound was recorded.

TABLE II

DIPHENYL-*b*-AMINOALKANOLS

$$R_1NAC(OH)(C_6H_5)_2$$
$$|$$
$$R_2$$

No.	R_1R_2N	A	Formula	Crystn. solvent[a]	M.p., °C.	C, % Calcd.	C, % Found	H, % Calcd.	H, % Found	N, % Calcd.	N, % Found
1	$(CH_3)_2N$	$CH_2CH(CH_3)$	$C_{18}H_{23}NO$	1	94–96[b]	80.25	79.1	8.61	8.57	5.2	5.2
			$C_{18}H_{23}NO \cdot C_2H_2O_4$	1	155–156	66.8	66.7	7.01	7.12	3.9	4.0
2	C_4H_8N	$CH_2CH(CH_3)$	$C_{20}H_{25}NO$	2	117–119	81.3	81.6	8.53	8.66	4.7	4.8
3	$C_5H_{10}N$	$CH_2CH(CH_3)$	$C_{21}H_{28}NO$	2	121–122[c]	81.5	81.2	8.80	8.80	4.5	4.6
4	$C_6H_{12}N$	$CH_2CH(CH_3)$	$C_{24}H_{33}NO$	1	125–126	81.7	81.4	9.04	8.86	4.3	4.2
5	$C_7H_{13}NCH_3$	$CH_2CH(CH_3)$	$C_{22}H_{29}NO$	1	80–82	82.0	82.3	9.46	9.42	4.0	4.3
6	$(CH_3)_2N$	$CH_2CH(C_2H_5)$	$C_{19}H_{25}NO$	3	105–107[d]	80.5	80.5	8.89	8.98	4.9	4.9
7		$CH_2CH(CH_3)$	$C_{21}H_{28}N_2O$	2	143–145	77.75	77.6	8.70	8.84	8.6	8.55
8		$CH_2CH(CH_3)$	$C_{26}H_{30}N_2O$	4	127–128	80.8	80.5	7.82	7.73	7.25	7.5
9		$CH_2CH(CH_3)$	$C_{27}H_{32}N_2O$	4	131.5–133	77.85	78.0	7.74	7.68	6.7	6.85
10		$CH_2CH(CH_3)$	$C_{26}H_{29}ClN_2O$	4	152–153	74.2	74.1	6.94	6.98	6.7	6.9
11		$CH(CH_3)CH_2$	$C_{25}H_{29}NO$		92–93	84.0	83.7	7.61	7.72	3.9	4.1
			$C_{25}H_{29}NO \cdot HBr$	3	233–235	68.5	68.2	6.44	6.49	3.2	3.5
12	$C_6H_5(CH_2)_2NCH_3$	$CH(CH_3)CH_2$	$C_{24}H_{27}NO$	2	86–87	83.4	83.1	4.06	3.99	4.0	4.1
			$C_{24}H_{27}NO \cdot C_2H_2O_4$	3	150–151	71.7	71.9	6.70	6.65	...	...
13	$C_6H_5(CH_2)_2NC_2H_5$	$CH_2CH(CH_3)$	$C_{26}H_{31}NO \cdot C_2H_2O_4$	5	166–167	72.5	72.8	7.18	7.47	3.0	3.2
14	$C_6H_5CH_2CH(CH_3)NCH_3$	$CH_2CH(CH_3)$	$C_{26}H_{31}NO \cdot HCl$	1	205–207	76.2	76.1	7.87	7.95	3.4	3.7
15	$C_6H_5CH_2CH(CH_3)NCH_3$	CH_2CH_2	$C_{25}H_{29}NO \cdot HCl$	1	203–204	75.8	76.0	7.64	7.73	3.5	3.5
16	$3,4\text{-}(CH_3O)_2C_6H_3(CH_2)_2NCH_3$	$CH_2CH(CH_3)$	$C_{27}H_{33}NO_3 \cdot C_2H_2O_4 \cdot H_2O$	5	130–131.5	66.0	65.9	7.07	7.15	2.7	2.5
17	$C_6H_{11}CH_2CH(CH_3)NCH_3$	$CH_2CH(CH_3)$	$C_{26}H_{37}NO \cdot HCl$		184–185	75.1	74.8	9.24	9.19	3.4	3.7
18		$CH_2CH(CH_3)$	$C_{27}H_{29}NO \cdot C_2H_2O_4 \cdot H_2O$	4	157–158	70.9	71.1	6.77	6.88	2.8	3.1
19	$C_6H_5CH_2NCH_3$	$CH_2CH(CH_3)$	$C_{24}H_{27}NO \cdot C_2H_2O_4 \cdot H_2O$	1	150–151.5	70.85	71.0	6.77	7.88	2.8	3.1
20	$C_6H_5(CH_2)_2NCH_3$	$(CH_2)_3$	$C_{25}H_{29}NO$	2	70–71	83.5	83.5	8.13	8.24	3.9	4.0

[a] Solvents: 1, isopropyl alcohol; 2, petroleum ether (b.p. 60–80°); 3, ethanol; 4, benzene–petroleum ether; 5, ethanol–ether. [b] T. D. Perrine [*J. Org. Chem.*, **18**, 808 (1953)] gives m.p. 92–94°. [c] A. W. Ruddy and J. S. Buckley [*J. Am. Chem. Soc.*, **72**, 718 (1950)] give m.p. 120–121°. [d] Lit.[c] m.p. 103–104°.

TABLE III

DIARYLAMINOALKANOLS

$$R_1NAC(OH)(Ar_1)Ar_2$$
$$|$$
$$R_2$$

No.	R_1R_2N	A	Ar_1	Ar_2	Formula	Crystn. solvent[a]	M.p., °C.	C, % Calcd.	C, % Found	H, % Calcd.	H, % Found	N, % Calcd.	N, % Found
21	$C_6H_5(CH_2)_2NCH$	$CH_2CH(CH_3)$	C_6H_5	2-C_5H_4N	$C_{24}H_{24}NO_2 \cdot C_2H_2O_4 \cdot 0.5H_2O$	3	171–173	67.95	68.1	6.98	6.80	6.2	6.25
22	$C_6H_5(CH_2)_2NCH_3$	$CH_2CH(CH_3)$	2-C_4H_3S	2-C_4H_3S	$C_{21}H_{25}NOS \cdot C_2H_2O_4$	7	186–187	59.9	59.6	6.28	5.97	3.0	2.7

23	$C_6H_5(CH_2)_2NCH_3$	$CH_2CH(CH_3)$	2-C_4H_3O	$C_{21}H_{25}NO_3\cdot C_2H_2O_4$	3	149–150	64.3	64.3	6.34	6.28	3.3	3.3
24	$C_6H_5(CH_2)_2NCH_3$	$CH_2CH(CH_3)$	C_6H_5	$C_{26}H_{31}NO\cdot C_2H_2O_4$	3	185.5–186.5	72.5	72.6	7.18	7.39	3.0	3.2
25	$C_6H_5(CH_2)_2NCH_3$	$CH_2CH(CH_3)$	$C_6H_5CH_2$	$C_{27}H_{33}NO\cdot C_2H_2O_4$	3	157–159	72.9	73.3	7.38	7.41	3.0	2.8
26	$C_6H_5(CH_2)_2NCH_3$	CH_2CH_2	C_6H_5	$C_{24}H_{26}ClNO\cdot C_2H_2O_4$	3	189.5–190	66.45	66.3	6.00	6.08	3.0	3.1
27	$C_6H_5(CH_2)_2NCH_3$	CH_2CH_2	2-C_5H_4N	$C_{23}H_{26}N_2O_2\cdot C_2H_2O_4$	3	170.5–172	68.8	68.8	6.47	6.48	6.4	6.5
28	$(CH_3)_2N$	$CH_2CH(CH_3)$	C_6H_5	$C_{19}H_{25}NO\cdot HCl$	1	257	71.3	71.3	8.19	8.07	4.4	4.4
29	$(CH_3)_2N$	$CH_2CH(CH_3)$	4-$CH_3OC_6H_4$	$C_{20}H_{27}NO_2$	2	104–106	76.6	77.0	8.68	8.65	4.5	4.3
30	$(CH_3)_2N$	$CH_2CH(CH_3)$	4-$CH_3OC_6H_4$	$C_{20}H_{27}NO_2$	2	125–127	76.6	76.65	8.68	8.78	4.5	4.2
31	$(CH_3)_2N$	$CH_2CH(CH_3)$	C_6H_5	$C_{19}H_{25}NO\cdot C_2H_2O_4$	1	189–191	67.5	67.4	7.29	7.18	3.75	3.9
32	$(CH_3)_2N$	$CH_2CH(CH_3)$	C_6H_5	$C_{19}H_{25}NO_2$	2	98–99	76.2	76.0	8.42	8.50	4.7	4.4
33	$(CH_3)_2N$	$CH_2CH(CH_3)$	3-$CH_3C_6H_4$	$C_{19}H_{25}NO$	1	169–170	67.5	67.5	7.29	7.42	3.75	3.6
34	$(CH_3)_2N$	$CH_2CH(CH_3)$	4-ClC_6H_4	$C_{18}H_{22}ClNO\cdot C_2H_2O_4$	6	187–188	61.0	60.9	6.14	6.04	3.6	3.6
35	$(CH_3)_2N$	$CH_2CH(CH_3)$	$C{\equiv}CC_6H_5$	$C_{20}H_{23}NO$	2	84–85	81.9	81.6	7.90	7.93	4.8	4.6
36	$(CH_3)_2N$	$CH_2CH(CH_3)$	2-$CH_3C_6H_4$	$C_{20}H_{27}NO$	2	66–68	80.8	80.5	9.15	9.26	4.7	4.6
37	$(CH_3)_2N$	CH_2CH_2	C_6H_5	$C_{18}H_{23}NO$	1	133–134[b]	80.25	80.25	8.6	8.51	5.2	5.45
38	C_4H_8N	$CH_2CH(CH_3)$	C_6H_5	$C_{21}H_{28}NO$	2	121–122	81.5	81.3	8.8	8.79	4.5	4.2
39	C_4H_8N	$CH_2CH(CH_3)$	C_6H_5	$C_{21}H_{28}NO\cdot C_2H_2O_4$	6	185–187	69.1	68.7	7.32	7.31	3.5	3.0
40	C_4H_8N	$CH_2CH(CH_3)$	C_6H_5	$C_{18}H_{23}NO_2$	2	71.5–72.5	75.75	75.5	8.12	8.16	4.9	4.9
41	C_4H_8N	$CH_2CH(CH_3)$	C_6H_5	$C_{18}H_{23}NOS$	4	89–91	71.7	72.0	7.69	7.76	4.65	4.8
42	C_4H_8N	$CH_2CH(CH_3)$	C_6H_5	$C_{19}H_{24}N_2O$	1	115–116	77.0	77.2	8.16	8.18	9.45	9.6
43	C_4H_4N	$CH_2CH(CH_3)$	2-$CH_3C_6H_4$	$C_{22}H_{29}NO$	2	83–85	81.7	82.1	9.04	8.9	4.3	4.1
44	$C_6H_5(CH_2)_2NCH_3$	$(CH_2)_3$	C_6H_5	4-FC_6H_4	1	166–167	69.4	69.2	6.47	6.3	3.0	3.0

[a] Solvents: 1, isopropyl alcohol; 2, petroleum ether (b.p. 60–80°); 3, ethyl alcohol; 4, benzene–petroleum ether; 5, ethyl alcohol–ether; 6, isopropyl alcohol–water; 7, methyl alcohol–water. [b] A. L. Morrison and H. Rinderknecht [*J. Chem. Soc.*, 1510 (1950)] give m.p. 131–134°.

ture was then heated under reflux for 4 hr., cooled, and poured onto ice. The aqueous layer was extracted several times with ether, the extracts were dried ($MgSO_4$), and the solvent was distilled. The products were purified by crystallization or, if they were oils, as salts.

The preparation of 1,1-diphenyl-2-methyl-3-(N-methyl-N-phenethylamino)-1-propanol (Table II, **53**), 1,1-diphenyl-3-(N-methyl-N-phenethylamino)-1-propanol (**54**), 2-(3,3-diphenyl-3-hydroxy-2-methylpropyl)-1,2,3,4-tetrahydroisoquinoline (**56**), and 2-(3,3-diphenyl-3-hydroxypropyl)-1,2,3,4-tetrahydroisoquinoline (**55**) was described in a previous communication.[1]

The substituted *β-t*-aminopropionic esters (Table I) were prepared by the addition of the appropriate secondary amine to an *α,β*-unsaturated ester (methyl acrylate, methyl methacrylate, or ethyl crotonate), using the method of Adamson.[10] The crude esters were distilled and used immediately.

Unsymmetrical 1,1-diaryl-*t*-amino-1-alkanols (Table III) were prepared in a similar manner from a *β*-dialkylaminoalkyl ketone (0.1 mole) and an aryllithium reagent (0.1 mole). The products were purified by crystallization or if they were oils as salts.

The *β*-dialkylamino ketones were prepared by the Mannich reaction[16] from the appropriate secondary amine, formaldehyde, and the appropriate aralkyl ketone. The following compounds were prepared in this way: 3-dimethylaminopropiophenone, b.p. 80° (0.5 mm.), lit.[17] b.p. 83–87° (1–2 mm.); 3-dimethylamino-2-methylpropiophenone, b.p. 70–72° (0.3 mm.), lit.[4] b.p. 80–82° (1 mm.); 3-dimethylamino-2-ethylpropiophenone, b.p. 100–103° (0.5 mm.), lit.[4] b.p. 110° (1 mm.); 2-methyl-3-pyrrolidylpropiophenone, b.p. 115° (0.3 mm.), lit.[18] b.p. 117–118° (0.3 mm.); 3-(N-methyl-N-phenethylamino)-2-methylpropiophenone oxalate, which crystallized from methanol, m.p. 177° (*Anal.* Calcd. for $C_{19}H_{23}NO\cdot C_2H_2O_4$: C, 67.9; H, 6.78; N, 3.8. Found: C, 68.0; H, 6.52; N, 3.7.); 3-dimethylamino-2-methyl-*p*-methoxypropiophenone hydrochloride, which crystallized from isopropyl alcohol, m.p. 156–157° (*Anal.* Calcd. for $C_{13}H_{19}NO_2\cdot HCl$: C, 60.6; H, 7.82; N, 5.4. Found: C, 60.8; H, 7.73; N, 5.2.); 3-(N-methyl-N-phenethylamino)-2-methyl-*p*-methoxypropiophenone hydrochloride which crystallized from isopropyl alcohol, m.p. 161–163° (*Anal.* Calcd. for $C_{19}H_{23}NO_2\cdot HCl$; C, 68.35; H, 7.25; equiv. wt., 334. Found: C, 68.2; H, 7.43; equiv. wt., 338.).

1-Phenyl-4-(N-phenethyl-N-methylamino)butan-1-one.—A mixture of 4-chlorobutyrophenone (18.3 g., 0.1 mole), N-methylphenethylamine (13.5 g., 0.1 mole), triethylamine (10.1 g., 0.1 mole), and toluene (100 ml.) was heated under reflux for 40 hr. The precipitated triethylamine hydrochloride was filtered; the filtrate and washings were then extracted with dilute HCl, and the acid extracts were made alkaline with NH_3 and extracted with ether. The solvent was distilled from the dried ($MgSO_4$) ether extracts, and the residual oil was distilled *in vacuo* to yield 15.1 g. (54%) of the required product as a colorless mobile oil, b.p. 154° (0.1 mm.). The **maleate** crystallized from isopropyl acetate in colorless needles, m.p. 101–102°.

Anal. Calcd. for $C_{19}H_{23}NO\cdot C_4H_4O_4$: C, 69.5; H, 6.85; N, 3.5. Found: C, 69.7; H, 6.83; N, 3.3.

1-(4-Fluorophenyl)-4-(N-phenethyl-N-methylamino)butan-1-one was prepared in a similar manner from 4-chloro-4′-fluorobutyrophenone and N-methylphenethylamine. It was obtained as a colorless oil, b.p. 162° (0.01 mm.). The **maleate** crystallized in colorless needles, m.p. 110–111°.

Anal. Calcd. for $C_{19}H_{22}FNO\cdot C_4H_4O_4$: C, 66.5; H, 6.31; N, 3.4. Found: C, 66.4; H, 6.44; N, 3.4.

1,1-Diphenyl-2-methyl-3-(N-phenethyl-N-methylamino)-1-propene (45).—A mixture of 1,1-diphenyl-2-methyl-3-(N-phenethyl-N-methyl)aminopropan-1-ol (10.3 g.) and 85% H_2SO_4 (20 ml.) was heated on a steam bath for 20 min. and then poured onto ice. The mixture was made alkaline and extracted with chloroform; the $CHCl_3$ extracts were dried ($MgSO_4$) and the solvent was distilled to leave a viscous oil. Distillation of the residue gave the product as a viscous oil, b.p. 198–200° (0.1 mm). The **maleate** crystallized in rosettes of needles from isopropyl alcohol, m.p. 157–159°.

Anal. Calcd. for $C_{25}H_{27}N\cdot C_4H_4O_4$: C, 76.1; H, 6.83; N, 3.1. Found: C, 76.2; H, 6.69; N, 3.2.

(16) J. J. Denton, R. J. Turner, W. B. Neier, V. A. Lawson, and H. P. Schedl, *J. Am. Chem. Soc.*, **71**, 2048 (1949).

(17) H. R. Synder and J. H. Brewster, *ibid.*, **70**, 4230 (1948).

(18) A. Pohland and H. R. Sullivan, *ibid.*, **75**, 4458 (1953).

TABLE IV

BIOLOGICAL ACTIVITY OF DIARYLAMINOALKANOLS I

No.	LD_{50}, mg./kg.	Conditioned response[a]	Anti-amphetamine[b]	Anti-reserpine[c]	Picrotoxin potentiation[d]	Anticonvulsant[e] Electroshock	Anticonvulsant[e] Pentylene-tetrazole	Diuretic[f]	Anorectic[g]
1	250	3+[h]	−[h]	2+[h]	4+[h]	3+[h]	4+[h]	3+[h]	+[i]
2	190	3+	2+	2+	3+	3+	4+	4+	+
3	250	+	−	2+	3+	2+	3+	3−	+
4	750	−	−	−	+	+	4+	3+	...
5	750	...	...	...	...	+	+	−	...
6	190	2+	−	2+	...	2+	+	3+	+
7	190	+	+	−	+	−	−	+	...
8	2000	−	−	...	...	−	−	−	...
9	2000	−	−	...	...	−	−	−	...
10	2000	−	−	...	...	−	−	−	...
11	2000	−	−	...	...	−	−	−	...
12	2000	−	−	...	+	−	−	−	...
13	1500	−	−	2+	−	2+	+	+	...
14	500	−	+	...	...	+	−	...	...
15	500	−	−	3+	+	−	−	−	...
16	1000	−	−	−	−	−	−	−	...
17	1000	−	−	−	+	−	−	−	...
18	2000	−	−	...	...	−	−	...	...
19	750	−	−	2+	−	+	+	2+	...
20	250	−	−	2+	...	−	−	−	...
21	500	−	−	−	2+	−	−	±	...
22	1500	−	−	...	...	−	−	−	...
23	750	−	−	−	−	−	−	−	...
24	750	−	−	−	+	−	−	−	...
25	375	−	−	−	−	−	−	−	...
26	250	−	−	3+	−	−	−	−	...
27	250	−	−	2+	...	−	−	+	...
28	250	3+	2+	3+	3+	3+	4+	3+	+
29	375	−	−	+	−	+	−	+	...
30	750	−	−	−	−	−	−	+	...
31	750	−	−	−	−	−	−	+	...
32	375	−	−	−	−	−	−	2+	...
33	500	...	−	...	+	−	−	+	...
34	500	...	−	...	+	−	−	+	...
35	250	+	−	−	...	2+	...	+	...
36	375	2+	−	3+	3+	3+	+	3+	−
37	1200	−	−	2+	...	2+	3+	2+	−
38	250	−	−	−	−	−	−	+	−
39	250	+	+	...	...	2+	3+	2+	...
40	375	−	−	2+	2+	−	−	2+	−
41	190	−	...	2+	+	2+	2+	2+	−
42	250	−	...	2+	3+	3+	−	2+	−
43	500	−	−	+	3+	+	+	2+	−
44	375	−	−	−	+	−	−	−	...
45	1500	−	−	...	−	−	−	−	...
46	190	−	−	...	...	−	−	−	...
47	1000	−	−	...	−	−	−	−	...
48	750	+	...	−	...	3+	−	+	...
49	2000	−	...	−	...	−	−	−	...
50	1000	...	−	...	2+	+	+	4+	...
51	190	+	+	...	4+	+	+	3+	...
52	500	−	...	−	4+	+	−	−	...
53[j]	500	+	−	2+	−	2+	2+	2+	+
54[j]	2000	−	−	...	...	−	−	−	...
56[j]	1000	−	−	...	...	−	−	−	...
55[j]	1000	−	−	+	+	−	−	+	...
CPZ[k]	500	4+	4+	...	...	3+	4+	...	...
IMP[l]	350	...	+	4+	2+	2+	+	...	...
DH[m]	250	...	...	...	...	4+	4+	...	...
AMPH[n]	375	...	...	...	4+	4+	2+	+	+

[a] Blockade of conditioned avoidance response in rats. [b] Protection against amphetamine toxicity in aggregated mice. [c] Prevention of reserpine-induced ptosis in mice. [d] Potentiation of picrotoxin-induced convulsions in mice. [e] Protection against electroshock and pentylenetetrazole-induced convulsions in mice. [f] Diuresis in rats. [g] Anorectic activity in trained rats. [h] The method of presentation of activity in these columns is as follows: 4+ = ED_{50} < 10 mg./kg., 3+ = ED_{50} 10–25 mg./kg., 2+ = ED_{50} 25–50 mg./kg., + = ED_{50} 50–100 mg./kg. [i] + in this column indicates that the compound had anorectic activity in trained rats when tested at a dose level of 10–25 mg./kg./day for 5 days. [j] The preparation of these compounds was described in a previous publication.[1] [k] CPZ = chlorpromazine. [l] IMP = imipramine. [m] DH = diphenylhydantoin. [n] AMPH = *d*-amphetamine.

2-(3,3-Diphenylallyl)-1,2,3,4-tetrahydroisoquinoline (46) was prepared from the corresponding tertiary alcohol, as described above. The **base** was crystallized from isopropyl alcohol, m.p. 83–84°.

Anal. Calcd. for $C_{24}H_{23}N$: C, 88.6; H, 7.12; equiv. wt., 325. Found: C, 87.6; H, 7.14; equiv. wt., 323.

The **maleate** crystallized from ethanol; m.p. 174–175°.

Anal. Calcd. for $C_{24}H_{23}N \cdot C_4H_4O_4$: C, 76.2; H, 6.16; equiv. wt., 441.5. Found: C, 76.1; H, 6.12; equiv. wt., 441.

1-(4-Fluorophenyl)-1-phenyl-4-(N-phenethyl-N-methylamino)-1-butene (47).—The base was obtained as a viscous oil by dehydrating the corresponding tertiary alcohol with 85% H_2SO_4. The **maleate** crystallized from isopropyl alcohol–petroleum ether (b.p. 60–80°), m.p. 125–127°.

Anal. Calcd. for $C_{25}H_{26}FN \cdot C_4H_4O_4$: C, 73.4; H, 6.2; N, 2.95. Found: C, 73.5; H, 6.4; N, 3.2.

1-Benzoyloxy-1,1-diphenyl-2-methyl-3-pyrrolidylpropane (48).—To a solution of 1,1-diphenyl-2-methyl-3-pyrrolidyl-propan-1-ol (29.6 g., 0.1 mole) in a mixture of dry benzene (150 ml.) and dry ether (100 ml.) was added with cooling (0–5°) benozyl chloride (7 g., 0.05 mole). The mixture was allowed to stand at room temperature for 72 hr. The hydrochloride of the starting material was filtered, final traces being removed by washing with water. After drying, the solvents were distilled to leave a colorless viscous oil, which was converted to the **oxalate** salt. This was purified by crystallization from isopropyl alcohol, m.p. 170–172°, yield 7.1 g. (28%).

Anal. Calcd. for $C_{27}H_{29}NO_2 \cdot C_2H_2O_4$: C, 71.1; H, 6.38; N, 2.8. Found: C, 71.2; H, 6.50; N, 2.7.

1-Benzoyloxy-1,1-diphenyl-2-methyl-3-piperidylpropane (49) was prepared by treating the corresponding tertiary alcohol with benzoyl chloride; it crystallized from isopropyl alcohol as colorless prisms, m.p. 165–167°.

Anal. Calcd. for $C_{28}H_{31}NO_2$: C, 81.3; H, 7.56; N, 3.4. Found: C, 81.5; H, 7.68; N, 3.5.

1,1-Diphenyl-2-methyl-3-pyrrolidyl-1-propionyloxypropane (50).—A mixture of 1,1-diphenyl-2-methyl-3-pyrrolidylpropan-1-ol (3.0 g., 0.01 mole), pyrridine (4.0 ml.), and propionic anhydride (4.0 ml. 0.03 mole) was heated on a steam bath for 3 hr. The solvent was distilled *in vacuo* and the residual oil converted into its **oxalate.** Crystallization from ethyl alcohol–water gave the pure ester, m.p. 170–173°.

Anal. Calcd. for $C_{23}H_{29}NO_2 \cdot C_2H_2O_4$: C, 68.0; H, 7.08; equiv. wt., 220.8. Found: C, 67.7; H, 7.19; equiv. wt., 214.

3-Dimethylamino-1,1-diphenyl-2-methyl-1-propionoxypropane (51) was prepared from the corresponding tertiary alcohol (**1**) and propionic anhydride.[19] The oxalate crystallized from ethyl alcohol–water as colorless prisms, m.p. 152–153°.

Anal. Calcd. for $C_{21}H_{27}NO_2 \cdot C_2H_2O_4 \cdot 0.5H_2O$: C, 65.0; H, 7.12; N, 3.3. Found: C, 65.5; H, 7.38; N, 3.4.

The hydrochloride was characterized by Perrine.[19]

1-Benzoyloxy-3-dimethylamino-1,1-diphenyl-2-methylpropane (52) was prepared from the corresponding tertiary alcohol (**1**) and benzoyl chloride. The **base** crystallized from isopropyl alcohol as colorless prisms, m.p. 115–116°.

Anal. Calcd. for $C_{25}H_{27}NO_2$: C, 80.4; H, 7.29; N, 3.75. Found: C, 80.7; H, 7.51; N, 3.80.

(19) T. D. Perrine, *J. Org. Chem.*, **18**, 898 (1953).

Synthesis and Cholinergic Effects of Certain N-Methoxylated Quaternary Compounds[1a]

Laszlo L. Darko, Joseph G. Cannon,[1b]

Laboratory of Medicinal Chemistry, College of Pharmacy

John P. Long, and Thomas F. Burks

Department of Pharmacology, College of Medicine, University of Iowa, Iowa City, Iowa

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Analogs of acetylcholine, methacholine, carbachol, and bethanechol have been prepared, in which one of the N-methyl groups has been replaced by methoxy. Biological data are presented on these compounds.

The biological actions of the quaternary alkoxyamine moiety have not been studied thoroughly or systematically; the literature contains relatively few reports of testing of alkoxy analogs of quaternary ammonium drugs for their systemic effects. The chemical similarity between the alkylamino and the alkoxyamino groups suggests that organic molecules containing these moieties may be adsorbed at many of the same receptor sites in the body; differences in bulk and in electronic distribution may in some instances result in differences in the responses of the body to the two classes of compounds. Thus, it is possible that certain alkoxyamine derivatives may possess therapeutic advantages over their amine analogs.

Major and Hess[2] found that a quaternary N-methoxy congener of methantheline had atropine-like activity similar to methantheline itself. Rogers, *et al.*,[3] found that methoxy-, ethoxy-, or *n*-propyloxytrimethylammonium cations closely resemble their alkyltrimethylammonium counterparts in muscarinic properties. Palazzo and co-workers[4] reported that 1,10-bis(dimethylaminooxy)decane dimethiodide possessed anticholinesterase activity. Bruno, *et al.*,[5] found that 2-dimethylaminooxyethyl acetate methiodide (V) had similar biological activity to acetylcholine, and Schiatti and Maffii[6] reported that this compound was equal to 3-dimethylaminopropyl acetate methiodide as a substrate for acetylcholinesterase; although both were poorer substrates than acetylcholine, they were of the same order.

In the present work, certain significant structural variations in the acetylcholine molecule have been applied to the N-methoxy congeners. Thus, the N-methoxy analogs of acetylcholine (Ia), methacholine (IIa), carbachol (IIIa), and bethanechol (IVa) have

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(2) R. T. Major and H. J. Hess, *J. Med. Pharm. Chem.*, **2**, 461 (1960).

(3) E. F. Rogers, D. Bovet, V. G. Longo, and G. B. Marini-Bettolo, *Experientia*, **9**, 260 (1953).

(4) G. Palazzo, E. F. Rogers, and G. B. Marini-Bettolo, *Gazz. chim. ital.*, **84**, 915 (1954).

(5) I. Bruno, B. J. R. Nicolaus, G. Pagani, and E. Testa, *Helv. Chim. Acta*, **45**, 358 (1962).

(6) P. Schiatti and G. Maffii, *Boll. Soc. Ital. Biol. Sper.*, **38**, 1823 (1962).