0.12 mole), and *p*-toluenesulfonic acid (1.0 g.) in anhydrous benzene (100 ml.) was refluxed for 18 hr. as described under the preparation of 1-(*p*-toluenesulfonyl)-4-(N-pyrrolidino)-1,2-dihydroquinoline. When the solvent was removed and the residue was recrystallized from methanol, a crystalline solid (10.0 g., 67%) melting at 141–142° was obtained.

Anal. Calcd. for $C_{21}H_{24}N_2O_3S$: C, 65.60; H, 6.29; N, 7.28. Found: C, 65.04; H, 6.16; N, 7.57.

3-(2,3-Dihydro-4-quinolone)propionic Acid.—1-(*p*-Toluenesulfonyl)-4-(N-pyrrolidino)-1,2-dihydroquinoline (10.6 g., 0.03 mole) was treated with ethyl acrylate (9.0 g., 0.09 mole) in boiling methanol (100 ml.) for 20 hr., after which time water (10 ml.) was added, and the mixture boiled for another hour. After removal of the methanol, the residue was extracted with ether, and the ether layer was washed with 5% HCl and dried (Na_2SO_4). The residue (9.0 g.) could not be crystallized nor distilled *in vacuo* and was immediately hydrolyzed by boiling with HCl (30 ml.) in acetic acid (30 ml.) and water (10 ml.) for 4 hr. Solvents were then removed *in vacuo*, and the residue was titrated with water (10 ml.). The solid was recrystallized from ethanol–ether to give crystals (4.3 g., 65% based on the enamine), m.p. 160–161°.

Anal. Calcd. for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.74; H, 5.95; N, 6.39.

3-(8-Methoxy-2,3-dihydro-4-quinolone)propionic Acid.—When a solution of 1-(*p*-toluenesulfonyl)-4-(N-pyrrolidino)-8-methoxy-1,2-dihydroquinoline (3.8 g., 0.1 mole) and ethyl acrylate was boiled in methanol (100 ml.) for 20 hr. and worked up as described for the 8-desmethoxy analog, an oil (1.5 g.) was obtained. Hydrolysis of a 4.3-g. sample of such an oil was carried out with HCl (4.0 ml.) in acetic acid (12 ml.) and water (4.0 ml.) at reflux for 4 hr. Evaporation of the solvents and the addition of water (5 ml.) gave the product which crystallized from ethanol–petroleum ether (1.5 g., 60%), m.p. 139°.

Anal. Calcd. for $C_{13}H_{15}NO_4$: C, 62.64; H, 6.07; N, 5.62. Found: C, 62.62; H, 6.01; N, 5.61.

Amides of 3-(2,3-Dihydro-4-quinolone)propionic Acid and the 8-Methoxy Analogs.—To a suspension of acid (0.005 mole) in 100 ml. of anhydrous ether was added triethylamine (0.5 ml.). The resulting mixture was cooled to 5° and treated with ethyl chlorocarbonate (0.005 mole) and then stirred for 15 min. Ammonium hydroxide (5.0 ml.) or the amine (0.02 mole) was added, and the mixture was stirred an additional 15 min. The precipitated amide was removed by filtration, washed with water, and dried. The amides were purified by recrystallization from the designated solvent (see Table IV).

3-[3-(N-Pyrrolidinopropyl)]-1,2,3,4-tetrahydro-4-quinolinol.—To a solution of 3-(2,3-dihydro-4-quinolone)propion-N-pyrrolide (2.7 g., 0.01 mole) dissolved in tetrahydrofuran (40 ml.) was added in small quantities $LiAlH_4$ (1.5 g., 0.04 mole). The reaction mixture was warmed to 55–60° and stirred for 20 hr., at which time the excess $LiAlH_4$ was decomposed with 5% NaOH solution. Tetrahydrofuran was removed by distillation, and the reaction mixture was diluted with water and extracted three times with ether. The combined ether extracts were dried ($MgSO_4$), and the solvent was removed by distillation. The residue after recrystallization from ether weighed 1.25 g. (48%) and melted at 108°.

Anal. Calcd. for $C_{16}H_{24}N_2O$: C, 73.84; H, 9.29; N, 10.76. Found: C, 73.70; H, 9.44; N, 11.00.

Chemistry and Pharmacology of Some Esters Derived from Basic Alcohols

F. P. DOYLE,[1a] M. D. MEHTA,[1a] R. WARD,[1a] J. BAINBRIDGE,[1b] AND D. M. BROWN[1b]

Beecham Research Laboratories, Brockham Park, Betchworth, Surrey, England

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The preparation of a number of α-alkoxy-α,α-diphenylacetates derived from open-chain basic alcohols is described. Some of these compounds possess antitussive activity comparable to that of codeine phosphate and of the same order as that of their analogs which contain pyrrolidine or piperidine rings. 2-Diethylamino-1-(α-methoxy-α,α-diphenylacetoxy)propane rearranged on heating to 1-diethylamino-2-(α-methoxy-α,α-diphenylacetoxy)propane.

Chemistry.—2-Dimethyl- and 2-diethylaminoethyl α-alkoxy-α,α-diphenylacetates have been claimed to possess useful local anaesthetic, analgesic, or antispasmodic activity.[2] In a previous publication[3] we have described the preparation of some promising antitussives in which a number of α-alkoxy-α,α-diphenylacetic acids were esterified with a range of 1-alkylpyrrolidinyl or 1-alkylpiperidyl alcohols. In order to determine if a ring structure in the basic part of the molecule is essential for antitussive activity, we undertook the preparation of closely related compounds derived from open-chain basic alcohols carrying similar or different alkyl groups on the nitrogen atom. The basic esters were prepared from methyl or ethyl esters of the α-alkoxydiphenylacetic acids by transesterification with the appropriate amino alcohol.

During this synthetic work we observed the thermal rearrangement of 2-diethylamino-1-(α-methoxy-α,α-diphenylacetoxy)propane (I) to the isomeric 1-diethylamino-2-(α-methoxy-α,α-diphenylacetoxy)propane (II).

$$\underset{\text{Me}}{\underset{|}{\text{R—CH}_2\text{CHNEt}_2}} \xrightarrow{\Delta} \underset{\text{Me}}{\underset{|}{\text{RCHCH}_2\text{NEt}_2}}$$

I II

I and II, R = $Ph_2C(OMe)CO_2$

This rearrangement amplifies our earlier studies of the ester of the related 1-alkyl-2-hydroxymethylpyrrolidines[4a] and complements that of Kerwin, *et al.*,[4b] on 1-chloro-2-dialkylaminopropane.

Experimental

Melting points were determined in open glass capillaries using a Büchi apparatus and are uncorrected. The infrared absorption spectra for the ester rearrangement study were obtained by Mr. K. Austin using a Grubb-Parsons double-beam spectrometer with the specimens as approximately 2% solutions in $CHCl_3$.

(1) (a) Chemistry Department; (b) Pharmacology Department.

(2) A. Gilman, L. Goodman, J. M. Thomas, G. A. Haln, and J. M. Prutting *J. Pharmacol. Exptl. Therap.*, **74**, 290 (1942); R. Hirt, *Helv. Chim. Acta*, **32**, 87 (1949); Wander. A. G., British Patent 641,571 (1950); Boehringer Sohn, British Patent, 716,700 (1951); J. Büchi, H. Lauerner, R. Meyer, and R. Lieberherr, *Helv. Chim. Acta*, **34**, 373 (1951); F. F. Blicke and J. H. Biel, *J. Am. Chem. Soc.*, **76**, 3161 (1954); J. Klosa, *Arch. Pharm.*, **287**, 321 (1954); **288**, 42 (1955).

(3) F. P. Doyle, M. D. Mehta, G. S. Sach, R. Ward, and P. S. Sherman, *J. Chem. Soc.*, 578 (1964).

(4) (a) E. G. Brain, F. P. Doyle, and M. D. Mehta, *ibid.*, 633 (1961); (b) J. F. Kerwin, G. E. Ullyot, R. C. Fuson, and C. L. Zirkle, *J. Am. Chem. Soc.*, **69**, 2961 (1947).

TABLE I

$HOCH_2CH_2N<^{R}_{R^1}$

R	R¹	B.p., °C. (mm.)	n_D (°C.)	Method[a]	Yield, %	Derivative	M.p., °C.	Formula	Calcd., % C	Calcd., % H	Calcd., % N	Found, % C	Found, % H	Found, % N
Me	Et	51–56 (25)	1.4362[b] (22)	A	62	Picrate[c]	70–72	$C_{11}H_{16}N_4O_8$	39.75	4.85	16.9	39.5	5.3	16.7
Me	Pr	69 (27)	1.4379 (20.5)	B	59	Picrate[c]	74–75	$C_{12}H_{18}N_4O_8$	41.6	5.2	16.2	41.5	5.5	16.4
Me	*i*-Pr	57–60 (13)	1.4410[d] (20)	A	70	Picrate[c]	133–135	$C_{12}H_{18}N_4O_8$	41.6	5.2	16.2	41.7	5.2	16.5
Me	Bu	80–83 (22)	1.4404[f] (20)	B	53									
Me	Bz	78–81 (0.6)	1.5282[g] (19.5)	B	54	Picrate[c]	72–74	$C_{16}H_{18}N_4O_8$	48.7	4.6	14.2	48.9	4.7	14.2
						Methiodide[h]	146–148	$C_{11}H_{18}INO$	43.0	5.9	41.3[i]	43.1	6.2	41.3[i]
Et	*i*-Pr	58–61 (10)	1.4398[j] (20)	B	37	Picrate[c]	117–118	$C_{13}H_{20}N_4O_8$	43.3	5.6	15.55	43.3	5.9	15.5
Et	Bu	90–91 (22)	1.4422[k] (20)	A	61	Picrolonate[e]	133–135	$C_{18}H_{27}N_5O_8$	52.8	6.65	17.1	52.7	6.8	16.7
Et	*s*-Bu	105–110 (50)	1.4392 (21)	B[l]	74	Picrate[c]	78–79	$C_{14}H_{22}N_4O_8$	44.9	5.9	15.0	45.35	6.2	14.8
Et	*i*-Bu	98–99 (40)	1.4339 (20.5)	B[m]	73	Hydrogen di-*p*-toluoyl-D-tartrate[c,n]	171	$C_{28}H_{37}NO_4$	63.3	7.0		63.0	7.4	
Et	C_5H_{11}	96–98 (14)	1.4339 (20.5)	B	71	Acetate methiodide	119–121	$C_{12}H_{26}INO_2$	42.0	7.6	36.95[i]	42.2	7.6	36.9[i]

[a] Method A: F. Leonard and L. Simet, *J. Am. Chem. Soc.*, **77,** 2855 (1955); method B: J. B. Wright, E. H. Lincoln, R. V. Heinzelmann, and J. H. Hunter, *ibid.*, **72,** 3537 (1950). [b] Leonard and Simet[a] give b.p. 62–63° (25 mm.), $n^{20}D$ 1.4372. [c] Recrystallyzed from EtOH. [d] Wright, *et al.*,[a] give b.p. 84° (46 mm.), $n^{25}D$ 1.4379. [e] Recrystallized from benzene. [f] Wright, *et al.*,[a] give b.p. 97° (<39 mm.), $n^{25}D$ 1.4381. [g] W. Wilson [*J. Chem. Soc.*, 3527 (1952)] gives b.p. 129–132° (12 mm.), $n^{22}D$ 1.5270. [h] Recrystallized from MeOH. [i] Iodine analysis. [j] R. A. B. Bannard, J. H. Parkkari, and I. W. Coleman [*Can. J. Chem.*, **40,** 1909 (1962)] give b.p. 95° (57 mm.), $n^{25}D$ 1.4380. [k] H. C. Brill [*J. Am. Chem. Soc.*, **54,** 2484 (1932)] gives b.p. 195°. [l] 2-*sec*-butylaminoethanol was prepared by treating ethylene chlorohydrin with an excess of *sec*-butylamine; *cf.* A. C. Cope and E. M. Hancock, *ibid.*, **64,** 1503 (1942). [m] Prepared as in *l*; *cf.* M. Senkus, *ibid.*, **67,** 1515 (1945). [n] The use of di-*p*-toluoyl-D-tartaric acid for the characterization of amines is described by D. A. A. Kidd, *J. Chem. Soc.*, 4675 (1961).

Dialkylamino Alcohols.—2-Diethylaminopropanol and 1-diethylaminopropan-2-ol were prepared by known methods.[4b] A number of dialkylaminoethanols which are either new or had been inadequately characterized are included in Table I.

2-Ethylpropylaminoethanol.—2-Propylaminoethanol[5] (75 g.) was heated under reflux for 16 hr. with an excess of acetic anhydride (275 ml.). Distillation of the mixture yielded **2-(acetylpropylamino)ethyl acetate** (128 g., 94%) as a colorless oil, b.p. 100° (0.1 mm.), $n^{21}D$ 1.4511.

Anal. Calcd. for $C_9H_{17}NO_3$: C, 57.8; H, 9.2; N, 7.5. Found: C, 57.4; H, 9.1; N, 7.7.

This compound was reduced with $LiAlH_4$ in the usual manner[6] to give 2-ethylpropylaminoethanol (78%), b.p. 64–65° (9 mm.), $n^{20}D$ 1.4399; the **benzoate hydrochloride,** needles from ethyl methyl ketone, had m.p. 123.5–125.5°.

Anal. Calcd. for $C_{14}H_{22}ClNO_2$: C, 61.8; H, 8.2; Cl, 13.0; N, 5.15. Found: C, 61.9; H, 8.6; Cl, 13.1; N, 5.25.

The **picrate,** prisms from ethanol, had m.p. 51–53°.

Anal. Calcd. for $C_{13}H_{20}N_4O_8$: C, 43.3; H, 5.6; N, 15.55. Found: C, 43.0; H, 5.6; N, 15.3°.

3-Dimethylaminobutanol.—Reduction of ethyl β-dimethylaminobutyrate[7] with $LiAlH_4$ as above yielded 3-dimethylaminobutanol (66%), b.p. 72° (15 mm.), $n^{20}D$ 1.4431; the **benzoate hydrochloride,** colorless prisms from benzene, had m.p. 102°.

Anal. Calcd. for $C_{13}H_{20}ClNO_2$: C, 60.55; H, 7.8; Cl, 13.8; N, 5.4. Found: C, 60.4; H, 8.0; Cl, 13.4; N, 5.5.

The **picrate,** prisms from ethyl acetate, had m.p. 170°.

Anal. Calcd. for $C_{12}H_{18}N_4O_8$: C, 41.6; H, 5.2; N, 16.2. Found: C, 42.0; H, 5.4; N, 16.55.

Preparation of Esters.—The esters were prepared by the transesterification of an alkyl α-alkoxy-α,α-diphenylacetate with a basic alcohol in boiling heptane using sodium alkoxide as catalyst.[3] In addition to the tabulated compounds the following were prepared: **2-diethylamino-1-(α-methoxy-α,α-diphenylacetoxy)propane hydrochloride** (76%), prisms from ethyl methyl ketone, m.p. 129–131°.

Anal. Calcd. for $C_{22}H_{30}ClNO_3$: C, 67.4; H, 7.7; Cl, 9.05. Found: C, 67.3; H, 8.0; Cl, 9.2.

2-Diethylamino-1-(α-ethoxy-α,α-diphenylacetoxy)propane hydrochloride (52%), prisms from ethyl methyl ketone, m.p. 147–148°.

Anal. Calcd. for $C_{23}H_{32}ClNO_3$: C, 68.0; H, 8.0; Cl, 8.7. Found: C, 68.4; H, 8.0; Cl, 8.5.

1-Diethylamino-2-(α-methoxy-α,α-diphenylacetoxy)propane hydrochloride (75%), prisms from ethyl methyl ketone, m.p. 124–126°.

Anal. Calcd. for $C_{22}H_{30}ClNO_3$: C, 67.4; H, 7.7; Cl, 9.05. Found: C, 67.4; H, 7.4; Cl, 8.95.

1-Diethylamino-2-(α-ethoxy-α,α-diphenylacetoxy)propane hydrochloride (25%), prisms from ethyl methyl ketone, m.p. 169–171°.

Anal. Calcd. for $C_{23}H_{32}ClNO_3$: C, 68.0; H, 8.0; Cl, 8.7. Found: C, 67.9; H, 8.0; Cl, 8.8.

3-Dimethylamino-1-(α-methoxy-α,α diphenylacetoxy)butane hydrochloride (58%), prisms from ethanol–ether, m.p. 124–126°.

Anal. Calcd. for $C_{21}H_{28}ClNO_3$: C, 66.7; H, 7.5; Cl, 9.4. Found: C, 66.7; H, 7.3; Cl, 9.5.

3-Dimethylamino-1-(α-ethoxy-α,α-diphenylacetoxy)butane hydrochloride (52%), prisms from ethyl methyl ketone–ether, m.p. 102–104°.

Anal. Calcd. for $C_{22}H_{30}ClNO_3$: C, 67.4; H, 7.7; Cl, 9.05. Found: C, 67.7; H, 7.8; Cl, 9.1.

Rearrangement of 2-Diethylamino-1-(α-methoxy-α,α-diphenylacetoxy)propane.—The ester free base was heated at 200° for 4 hr. under nitrogen and then distilled to yield an oil, b.p. 138–142° (0.1 mm.), $n^{20}D$ 1.5280, which gave an infrared spectrum and a hydrochloride, m.p. 123–125° (mixture melting point not depressed), identical with those of 1-diethylamino-2-(α-methoxy-α,α-diphenylacetoxy)propane. After similar heating the latter was recovered unchanged, b.p. 168–172° (0.45 mm.), $n^{20}D$ 1.5280.

Pharmacology. Initial Screening for Antitussive Activity.—Guinea pigs weighing 400–800 g. were anesthetized with pentobarbital (36 mg./kg. i.p.), and the jugular vein was cannulated. The trachea was dissected out and cut transversely but not completely severed. In order to stimulate a cough, a piece of silver wire (26 gauge), the end of which had been rounded by heating in a bunsen flame, was passed into the slit in the trachea. When the tip of the wire touched the larynx or bifurcation, a cough occurred. If the anesthesia was too deep, a resonse could not be obtained. After eliciting several coughs at 2-min. intervals, a solution of the test compound in 1 *N* saline was injected intravenously and the cough stimulus was applied at 1 and 3 min If the response were abolished over this time, a positive result was recorded. Each pig was given at 0.5-hr. intervals 1, 3, 10, and 30 mg./kg. of the drug consecutively until the cough reflux was abolished. Where a compound showed promising activity,

(5) H. Mattes, *Ann.*, **315,** 104 (1901).

(6) F. P. Doyle, M. D. Mehta, G. S. Sach, and J. L. Pearson, *J. Chem. Soc.*, 4458 (1958).

(7) D. W. Adamson, *ibid.*, 885 (1950).

TABLE II: α-ALKOXY-α,α-DIPHENYLACETATES: $Ph_2C(OR)CO_2(CH_2)_nNR^1R^2$

No.	R	R¹	R²	n	Salt	Form	Solvent	M.p., °C.	Yield, %	Formula	Calcd., % C	Calcd., % H	Calcd., % Hal.	Found, % C	Found, % H	Found, % Hal.	Antitussive approx. ED_{50}, mg./kg.	I.v. toxicity, approx. LD_{50}, mg./kg.
1	Me	H	Me	2	HCl[a]	Needles	$COMe_2$	123–124	94	$C_{18}H_{22}ClNO_3$	64.4	6.6	10.55	64.3	6.85	10.85	Sl. active	80
2	Et	H	Me	2	HCl[b]	Needles	$COMe_2$	156–158	78	$C_{19}H_{24}ClNO_3$	65.2	6.9	10.1	65.6	7.2	10.35	Sl. active	20–40
3	Me	Me	Et	2	HCl	Needles	MeCOEt–EtOH	155–157	74	$C_{20}H_{26}ClNO_3$	66.0	7.2	9.7	66.1	7.5	10.0	2.7	41
4	Et	Me	Et	2	HCl	Needles	MeCOEt–EtOH	149–151	78	$C_{21}H_{28}ClNO_3$	66.7	7.5	9.4	66.6	7.6	9.5	3.5	<40
5	Me	Me	Pr	2	HCl	Needles	MeCOEt–Et_2O	137–139	58	$C_{21}H_{28}ClNO_3$	66.7	7.5	9.4	66.6	7.6	9.4	Inactive	
6	Et	Me	Pr	2	HCl	Needles	MeCOEt–Et_2O	151–153	71	$C_{22}H_{30}ClNO_3$	67.4	7.7	9.05	67.7	8.0	9.0	Inactive	
7	Me	Me	*i*-Pr	2	HCl	Prisms	MeCOEt–Et_2O	135	74	$C_{21}H_{28}ClNO_3$	66.7	7.5	9.4	66.9	7.4	9.4	3.5	<40
8	Et	Me	*i*-Pr	2	HCl	Prisms	MeCOEt–Et_2O	120–121	76	$C_{22}H_{30}ClNO_3$	67.4	7.7	9.05	67.3	7.8	9.0	3.5	<40
9	Me	Me	Bu	2	HCl[c]	Prisms	EtOAc–Et_2O	122–124	18	$C_{22}H_{30}ClNO_3$	67.4	7.7	9.05	67.2	8.0	9.2	Inactive	
10	Et	Me	Bu	2	HCl[c]	Needles	MeCOEt–Et_2O	147–149	50	$C_{23}H_{32}ClNO_3$	68.0	8.0	8.7	68.4	8.0	8.8	2.8	23
11	Me	Me	Bz	2	HCl[c]	Platelets	EtOH–Et_2O	144–145	70	$C_{25}H_{28}ClNO_3$	70.5	6.6	8.3	70.55	6.9	8.6	Sl. active	>80
12	Et	Me	Bz	2	HCl[c]	Needles	C_6H_6–petr. ether	122–124	59	$C_{26}H_{30}ClNO_3$	70.9	6.9	8.05	70.6	7.15	8.3	Inactive	>80
13	Me	Et	Pr	2	HCl[c]	Needles	MeCOEt	125–127	56	$C_{22}H_{30}ClNO_3$	67.4	7.7	9.05	67.3	7.6	9.2	3.3	51
14	Et	Et	Pr	2	HCl[c]	Needles	MeCOEt	137–138.5	34	$C_{23}H_{32}ClNO_3$	68.0	8.0	8.7	67.8	8.1	8.8	Sl. active	35
15	Me	Et	*i*-Pr	2	HCl[c]	Prisms	MeCOEt–Et_2O	111–112	42	$C_{22}H_{30}ClNO_3$	67.4	7.7	9.05	67.35	7.4	9.1	2.3	42
16	Et	Et	*i*-Pr	2	HCl[c]	Prisms	MeCOEt	133–135	56	$C_{23}H_{32}ClNO_3$	68.0	8.0	8.7	68.2	8.1	8.5	Sl. active	<40
17	Me	Et	Bu	2	HCl[c]	Needles	MeCOEt–Et_2O	131–132	57	$C_{23}H_{32}ClNO_3$	68.0	8.0	8.7	68.3	8.1	8.9	Sl. active	35
18[d]	Et	Et	Bu	2	HCl[c]	Needles	MeCOEt–Et_2O	135–136	75	$C_{24}H_{34}ClNO_3$	68.6	8.2	8.4	68.9	8.4	8.5	1.2	36
19	Me	Et	*i*-Bu	2	HCl[c]	Rosettes	MeCOEt–Et_2O	112–114	48	$C_{23}H_{32}ClNO_3$	68.0	8.0	8.7	68.0	8.0	8.8	Sl. active	40
20	Et	Et	*i*-Bu	2	HCl[c]	Needles	MeCOEt–Et_2O	134–136	29	$C_{24}H_{34}ClNO_3$	68.6	8.2	8.4	68.3	8.4	8.6	Sl. active	>80
21	Me	Et	*s*-Bu	2	HCl[c]	Rosettes	MeCOEt–Et_2O	123–125	53	$C_{23}H_{32}ClNO_3$	68.0	8.0	8.7	67.7	8.5	8.6	3.3	41
22	Et	Et	*s*-Bu	2	HCl[c]	Needles	MeCOEt–Et_2O	131–133	55	$C_{24}H_{34}ClNO_3$	68.6	8.2	8.4	68.4	8.4	8.8	3.7	51
23	Me	Et	C_5H_{11}	2	HCl[c]	Rosettes	MeCOEt–Et_2O	85–87	34	$C_{24}H_{34}ClNO_3$	68.6	8.2	8.4	68.3	8.3	8.6	Sl. active	43
24	Et	Et	C_5H_{11}	2	HCl[c]	Platelets	MeCOEt–Et_2O	95–96	43	$C_{25}H_{36}ClNO_3$	69.2	8.35	8.2	68.9	8.6	8.3	Sl. active	<40
25	Me	Pr	Pr	2	HCl[c,e]	Needles	MeCOEt–Et_2O	133–134	35	$C_{23}H_{32}ClNO_3$	68.0	8.0	8.7	68.0	8.2	8.6	Inactive	
26	Et	Pr	Pr	2	HCl[c,e]	Platelets	MeCOEt–Et_2O	156	71	$C_{24}H_{34}ClNO_3$	68.6	8.2	8.4	68.4	8.1	8.45	Inactive	
27	Me	*i*-Pr	*i*-Pr	2	HCl[c,f]	Needles	EtOAc–Et_2O	152–153	26	$C_{23}H_{32}ClNO_3$	68.0	8.0	8.7	68.2	8.05	9.0	Inactive	
28	Et	*i*-Pr	*i*-Pr	2	HCl[c,f]	Prisms	EtOAc–Et_2O	132–133	68	$C_{24}H_{34}ClNO_3$	68.6	8.2	8.4	68.4	8.45	8.5	Inactive	
29	Me	Bu	Bu	2	HCl[c,g]	Needles	MeCOEt–Et_2O	117–119	52	$C_{25}H_{36}ClNO_3$	69.2	8.35	8.2	69.1	8.5	8.4	Sl. active	<80
30	Et	Bu	Bu	2	HCl[c,g]	Platelets	MeCOEt–Et_2O	125–127	60	$C_{26}H_{38}ClNO_3$	69.7	8.55	7.9	69.4	8.65	8.0	Sl. active	>80
31	Me	Me	Et	3	HCl[h]	Prisms	MeCOEt–Et_2O	134–135	35	$C_{21}H_{28}ClNO_3$	66.7	7.5	9.4	66.9	7.7	9.3	Sl. active	40–80
32	Et	Me	Et	3	HCl[h]	Prisms	MeCOEt–Et_2O	114–116	43	$C_{22}H_{30}ClNO_3$	67.4	7.7	9.05	67.5	7.65	9.0	Sl. active	
33	Me	Et	Et	3	HCl[i]	Needles	EtOH–Et_2O	164–166	69	$C_{22}H_{30}ClNO_3$	67.4	7.7	9.05	67.1	7.9	9.2	Sl. active	40–80
34	Et	Et	Et	3	HCl[i]	Prisms	EtOH–Et_2O	138–140	53	$C_{23}H_{32}ClNO_3$	68.0	8.0	8.7	67.7	7.9	8.9	Sl. active	20–40
35[j]	Me	Me	Me	2													2.4	36
36[j]	Et	Me	Me	2													3.0	<40
37[j]	Me	Et	Et	2													Sl. active	<40
38[j]	Et	Et	Et	2													Codeine phosphate 3.8	80

[a] Obtained from 11 by hydrogenation in aqueous methanol over 10% Pd–C by the method of J. H. Biel, U. S. Patent 2,955,114 (1960). [b] Obtained from **12** by hydrogenation. [c] With these compounds it was necessary to remove traces of recovered basic alcohols by distillation before making a derivative. [d] This compound caused no salivation at 10 mg./kg. s.c. in cats. [e] 2-Dipropylaminoethanol was prepared by the standard method of W. W. Hartman in "Organic Syntheses," Coll. Vol. II, A. H. Blatt, Ed., John Wiley and Sons, Inc., New York, N. Y., 1943, p. 183. [f] 2-Diisopropylaminoethanol was prepared as in *e*. [g] 2-Dibutylaminoethanol was prepared as in *e*. It was characterized as the picrate, prisms from ethanol–ether, m.p. 64–65.5°. *Anal.* Calcd. for $C_{16}H_{26}N_4O_8$: C, 47.7; H, 6.5; N, 13.9. Found: C, 47.4; H, 6.7; N, 14.0. [h] 3-Ethylmethylaminopropanol was prepared by the method of Leonard and Simet, Table I, ref. *a*. [i] 3-Diethylaminopropanol was prepared as in *e*. [j] These were prepared as described by Klosa.[2]

10 animals were used, the number of positive results out of 10 being plotted against the dose on log probit paper and an ED_{50} (mg./kg.) was determined.

Acute Intravenous Toxicity.—Groups of 10 male albino mice 18–22 g. were injected intravenously with the compound in a volume of 0.1 ml./10 g. of body weight using a dose ratio of 1:1.1. The number dead in each group were recorded at 24 hr. An LD_{50} figure was determined for the more active compounds by the method of Litchfield and Wilcoxon.[8]

Results.—In tabulating the results, summarized in Tables II to V inclusive, the compounds have been classified as (a) active, where the approximate ED_{50} is recorded; (b) slightly active, showing activity below the toxic dose but with a small therapeutic ratio; (c) inactive, showing no activity in the initial antitussive test at subtoxic doses.

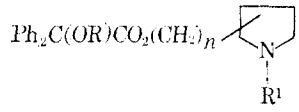
TABLE III[a]

$Ph_2C(OR^1)CO_2R^2 \cdot HCl$

No.	R^1	R^2	Antitussive approx. ED_{50}, mg./kg.	I.v. toxicity approx. LD_{50}, mg./kg.
39	Me	$CH_2CHMeNEt_2$[b]	1.8	39
40	Et	$CH_2CHMeNEt_2$	Inactive	
41	Me	$CHMeCH_2NEt_2$	1.0	44
42	Et	$CHMeCH_2NEt_2$	Inactive	
43	Me	$(CH_2)_2CHMeNMe_2$	Sl. active	38
44	Et	$(CH_2)_2CHMeNMe_2$	Sl. active	33

[a] The preparation of these compounds is described in the Experimental section. [b] This compound caused no salivation at 10 mg./kg. s.c. in cats.

TABLE IV[a]

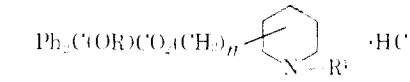


No.	R	R^1	n	Position in ring	Salt	Antitussive approx. ED_{50}, mg./kg.	I.v. toxicity approx. LD_{50}, mg./kg.
45	Me	Me	0	3	HCl	Sl. active	52
46	Me	Et	0	3	HCl	Sl. active	40
47	Et	Et	0	3	HCl	Sl. active	34
48	Me	Me	1	2	HCl	Sl. active	*b*
49	Et	Me	1	2	HBr	Active	34[b]
50	*n*-Pr	Me	1	2	HCl	1.6	40
51	*n*-Bu	Me	1	2	HCl	3.2	40
52	Bz	Me	1	2	HCl	Sl. active	56
53	Me	Et	1	2	HCl	1.7	48[b]
54	Et	Et	1	2	HCl	Sl. active	29[b]
55	Me	*n*-Pr	1	2	HCl	Active	<40
56	Me	*i*-Pr	1	2	HCl	2.7	37
57	Et	*i*-Pr	1	2	HCl	Sl. active	20
58	Me	Me	1	3	HCl	0.85	43
59	Me	Et	1	3	HCl	1.9	28
60	Et	Et	1	3	Citrate	Sl. active	40
61	Me	Me	2	2	HCl	Sl. active	<40
62	Et	Me	2	2	HBr	Sl. active	40
63	Me	Et	2	2	HCl	Sl. active	<40
64	Et	Et	2	2	HCl	Sl. active	

[a] The preparation of these compounds has been described by Doyle, *et al.*[3] [b] These compounds caused obvious prolonged salivation after intraperitoneal or subcutaneous administration to cats but not to rodents. The dose used was 5–10 mg./kg. Only a limited number of active compounds were tested in this way.

(8) J. T. Litchfield and F. Wilcoxon, *J. Pharmacol. Exptl. Therap.*, **96**, 99 (1949).

TABLE V[a]



No.	R	R^1	n	Position in ring	Antitussive approx. ED_{50}, mg./kg.	I.v. toxicity approx. LD_{50}, mg./kg.
65	Me	Me	0	3	Sl. active	61
66	Et	Me	0	3	Sl. active	<40
67	Bu	Me	0	3	Sl. active	40–80
68	Me	Et	0	3	3.8	37
69	Et	Et	0	3	2.1	38
70	Me	Me	0	4	3.4	56
71	Me	Et	0	4	Inactive	
72	Et	Et	0	4	Sl. active	20
73	Me	Me	1	2	1.0	41[b]
74	Et	Me	1	2	0.9	*b*
75	Et	Et	1	2	2.7	27
76	Me	Me	1	3	1.9	42
77	Me	Et	1	3	Inactive	
78	Et	Me	1	3	Inactive	
79	Et	Et	1	3	Inactive	
80	Me	Me	1	4	4.0	<40
81	Me	Et	1	4	2.7	26
82	Et	Me	1	4	Sl. active	<40
83	Et	Et	1	4	Sl. active	<20

[a] The preparation of these compounds has been described by Doyle, *et al.*[3] [b] These compounds caused obvious prolonged salivation after intraperitoneal or subcutaneous administration to cats but not to rodents. The dose used was 5–10 mg./kg. Only a limited number of active compounds were tested in this way.

Detailed pharmacology of 1-ethyl-3-(α-ethoxy-α,α-diphenylacetoxy)piperidine (69) was studied because it had good antitussive activity without obvious signs of toxicity and a tendency to cause salivation. There were more active compounds but on administration to cats and other species they all caused intense and persistent salivation which precluded further investigation. Its antitussive activity was determined in anesthetized guinea pigs as described before and in conscious guinea pigs as described below.

A guinea pig was placed in a box, 20.3 × 20.3 × 20.3 cm., the front and top of which were made of Perspex. Ammonia or SO_2 vapors were produced by blowing air into the box through a nebulizer. A reproducible flow of air was obtained by using a mercury manometer attached to a side arm in the supply tube. The animal was kept in the box for 2 min. during which time the number of coughs were counted by the experimenter.

The predrug mean number of coughs in a group of 10 guinea pigs was determined on the first and on the second day. Similar means were obtained 0.5 hr. after an intraperitoneal injection of the test compound had been given. The latter values were compared with the predrug mean to give the per cent change.

Antiacetylcholine Activity.—The antiacetylcholine activity was assessed on the isolated guinea pig ileum. The ileum was suspended in oxygenated Tyrode's solution at 37° in a 5-ml. bath, to which doses of acetylcholine (ACh) were added at 2-min. intervals until constant responses were obtained. The ACh was allowed to act for 30 sec. Atropine was added 30 sec. before the ACh and the depression of the ACh response was observed. When the response had returned to normal, the compound was added and a depression in the ACh response was again obtained. An estimate of the potency of the compound was obtained by bracketing the responses to fixed doses of atropine.

Mydriatic Activity.—Assays for mydriatic activity were carried out on the mouse according to the method of Puleska as modified by Ing, Dawes, and Wajda.[9] The pupil diameter was measured in arbitrary units with the aid of a micrometer scale set in the eyepiece of a dissecting microscope.

(9) H. R. Ing, G. S. Dawes, and I. Wajda, *Brit.*, **85**, 85 (1945).

Five mice (18–22 g.) were employed in each group. The compound was administered subcutaneously. The pupil diameters were measured at 30-min. intervals over a period of 2.5 hr. Atropine was used as a reference standard. The mean increase in pupil diameter for atropine and the compound was assessed for each time period.

Local anesthetic activity was determined by the intradermal wheal method as described by Somers and Edge.[10]

Constipating Activity.—The weight of feces excreted by a group of control mice, receiving normal saline, over a period extending from 15 min. to 6 hr. after subcutaneous injection was compared with those collected over the same period for three further test groups which received 25, 50, and 100 mg./kg. of codeine phosphate. The per cent inhibitions in weight caused by the three dose levels of codeine phosphate was compared with the inhibitions calculated for the same doses of the compound obtained with four further groups of mice.

On one day four groups of five mice (20–25 g.) were placed in metabolism cages and the feces were collected on filter paper. The three dose levels of the selected drug were administered and the same volume (0.2 ml.) of normal saline was given to the control group. This procedure was carried out on three further days for each drug, thereby giving a total of 20 mice/dose.

The Effect on Cardiovascular Activity.—Cats were anesthetized with ether and intravenous chloralose–urethan mixture (approximately 40 mg./kg. of chloralose and 160 mg./kg. of urethan). Blood pressure recordings were made from the carotid artery and injections were made *via* a polythene cannula inserted into the femoral vein. The drugs were dissolved in normal saline. The effect of the compound on the blood pressure response to ACh, histamine, epinephrine, norepinephrine, and dimethylphenylpiperazine was recorded.

Respiratory System.—Rabbits were anesthetized by intravenous injection of pentobarbital. The anesthetic was given very slowly until the desired plane of anesthesia was reached. The rabbits varied enormously in their anesthetic requirements and no recognized dose can be stated. The trachea was cannulated and respiration was recorded either by the method described by Gaddum[11] or by Paton.[12]

Analgesic activity was determined by the hot plate technique of Woolfe and Macdonald,[13] the hot plate being maintained at a constant temperature of 55° with boiling acetone. The mice were placed on the hot plate and the times taken for signs of discomfort were noted before and after the administration of the compound.

Potentiation of hexobarbital hypnosis by the compound was demonstrated by comparing the sleeping time in two groups of mice. Both received 60 mg./kg. of hexobarbital intravenously, but one group received 10 mg./kg. of the compound intraperitoneally 30 min. before the barbiturate.

Salivary Effects.—Cats were initially anesthetized with ether followed by intravenous chloralose–urethan (0.7% chloralose, 2.8% urethan, approximately 8 ml./kg.). Both Wharton's ducts were cannulated and connected, *via* a displacement bottle, to a drop recorder. Recordings of the drop rate were made on a smoked drum by means of a Thorp impulse counter. All drugs were given intravenously. After a constant response to 10 γ of carbachol had been obtained, the compound was administered and further doses of 10 γ of carbachol was given at varying intervals.

Results

Antitussive Activity in the Anesthetised Guinea Pig.—The comparative activities of codeine phosphate and **69** are illustrated in Figure 1. The antitussive activity in the conscious guinea pig is shown in Table VI.

Antiacetylcholine Activity.—The compound was found to be between 0.005 and 0.008 times as active as atropine sulfate on the isolated guinea pig ileum.

Mydriatic Activity.—The results are shown in Figure 2. After 30 min. the effect of atropine was at a maximum, but the response gradually wore off over the next 2 hr. On the other hand, the response to **69** while initially not as great as atropine sulfate was still significant at 150 min. after administration. At 25 mg./kg. the mydriatic effect was only slight.

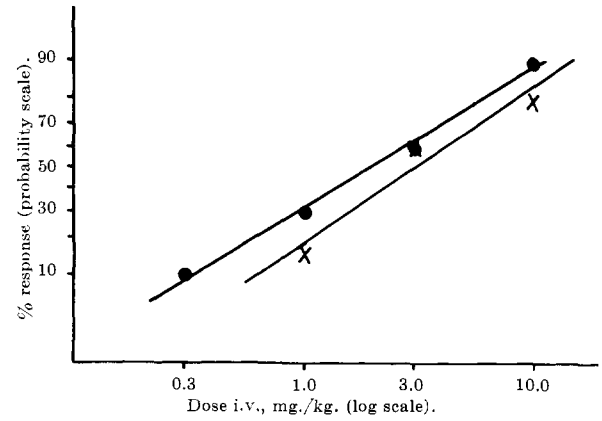


Figure 1.—Antitussive activity of codeine phosphate and **69** in the anesthetized guinea pig. The ordinate is the number of guinea pigs failing to cough in response to a mechanical stimulus of the trachea: ●—●, **69** (ED_{50} 2.1 mg./kg.); X—X, codeine phosphate (ED_{50} 3.0 mg./kg.).

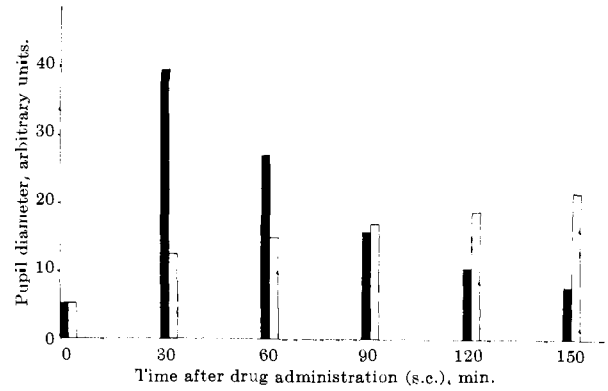


Figure 2.—Mydriatic effect in mice. The black columns represent the mean pupil diameter in arbitrary units after 0.1 mg./kg. of atropine sulfate, and the open columns represent the effect of 100 mg./kg. of **69**.

TABLE VI

COMPARATIVE ANTITUSSIVE ACTION OF **69**, CODEINE PHOSPHATE, AND MORPHINE HYDROCHLORIDE IN THE CONSCIOUS GUINEA PIG

Expt. no.	Drug	Dose, mg./kg.	Irritant vapor	Cough reduction, %[a]
1	**69**	40	SO_2	25
	Codeine phosphate	40	SO_2	15
2	**69**	40	NH_3	27
	Morphine·HCl	10	NH_3	48

[a] Reduction in number of coughs 0.5 hr. after drug administration.

Local Anaesthetic Activity.—The relative potency of **69** to procaine hydrochloride obtained by the intradermal wheal method was 1.66 (1.64–1.69), 5% limits of error.

Constipating Activity.—Compound **69** has little constipating activity compared with codeine phosphate (see Figure 3).

Cardiovascular System.—A transient vasodepressor action was produced with a dose of 2 mg./kg. of the

(10) G. F. Somers and N. D. Edge, *Quart. J. Pharmacol.*, **20**, 380 (1947).
(11) J. H. Gaddum, *J. Physiol.*, **99**, 257 (1941).
(12) N. D. Paton, *ibid.*, **57P**, 108 (1949).
(13) G. Woolfe and A. D. Macdonald, *J. Pharmacol. Exptl. Therap.*, **80**, 300 (1944).

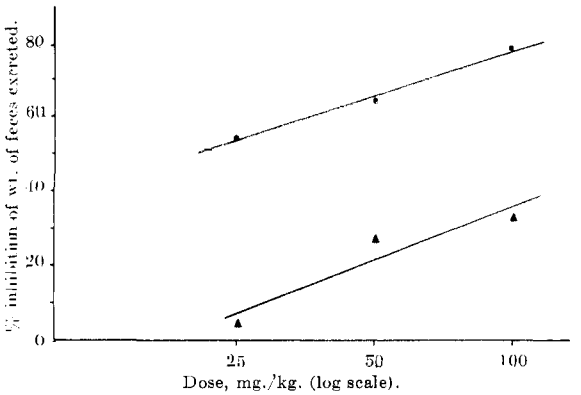


Figure 3.—Constipating activity in mice. The ordinate is the mean per cent reduction in the amount of feces produced by a group of 20 mice given **69** and codeine phosphate subcutaneously compared with control mice which received normal saline: ▲—▲, codeine phosphate; ●—●, **69**.

compound, but the response to 3 γ of epinephrine, 3 γ of norepinephrine, 3 γ of histamine, and 2 γ of ACh was unaffected. The response to 70 γ of dimethylphenylpiperazine was reduced approximately 70% by 4 mg./kg. of the compound but was unaffected at lower doses.

Respiratory Effect.—The compound has no depressant action on the respiration of the anesthetized rabbit but has in fact a slight stimulatory effect.

Analgesic Activity.—No analgesic activity was detected with the compound.

Hexobarbital Hypnosis.—The sleeping time of mice under hexobarbital was found to be increased from 705 (± 135) to 1595 (± 530) sec. after administration of the compound.

Salivary Effects.—The compound caused no increase in salivary flow, when administered at 5 mg./kg. i.v., neither did it block the salivation effected by carbachol injection.

Discussion

The compounds of this series have overcome some of the major drawbacks found with the standard drugs used for antitussive therapy. They neither have the respiratory depressant activity nor the constipating effects of morphine and its analogs.

In spite of some compounds having excellent antitussive properties (*e.g.*, **18, 39, 53, 73,** and **74**), they could not be used because they produced intense salivation in cats and dogs. This effect may come on shortly after administration or may not be noticeable until after 12 hr., persisting for fully 24 hr. Atropine in high doses prevents the salivation but as soon as its action wears off the flow of saliva returns. The compounds had no stimulatory action on other secretions apart from possibly the sweat glands, neither had they any anticholinesterase activity. Intestinal movement, pupil diameter, and central activity were not noticeably affected. The precise cause of the salivation has therefore not been determined but compounds having this property are rendered unsuitable for clinical use.

In the open-chain series (Table II) no obvious structure–activity relationships could be found. On the other hand, in the pyrrolidyl series (Table IV) good antitussive activity and relative freedom from the salivatory side effect occurred in the N-methyl- and N-ethyl-3-pyrrolidyl esters (**58** and **59**). However, trial of **58** in man revealed that the effective antitussive dose was too close to that producing antiacetylcholine activity.

In the piperidyl series (Table V) where $n = 1$, antitussive activity is generally greatest in the 2-substituted compounds, but unfortunately it is in this group that salivation is most evident.

Compound **69,** the most active nonsalivatory compound of the piperidyl series, has shown greater antitussive potency than codeine in animal tests and is free from both constipatory and atropine-like activity in therapeutic doses, though it may possibly cause slight mydriasis at high dosage. Its effect in potentiation of hexobarbitone hypnosis would suggest cautious use in initial clinical trials where patients are under barbiturate medication, although, since the compound has slight respiratory stimulant activity, serious effects would not be anticipated.

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