tracted with two 100-ml. portions of methylene chloride, and the combined methylene chloride extracts were washed with two 50-ml. portions of 10% hydrochloric acid. The wash solutions along with the original aqueous solution were made basic with sodium carbonate, then extracted with five 100-ml. portions of methylene chloride. After the combined methylene chloride extracts were dried over anhydrous sodium sulfate, the solvent was removed by distillation. The residue, which contained both pyridine and thiazole, was distilled through a six-inch Vigreux column under reduced pressure. Pyridine was collected at 2–4 mm. in a receiver cooled with Dry Ice while 54 g. (76%) of 4-methyl-5-(β-hydroxyethyl)-thiazole (V) was collected at 110–116° (0.7 mm.), $n^{20}D$ 1.5470. A pot residue of 7 g. remained.

When the reaction was conducted in the same manner as described above except that 68 g. (1.0 mole) of sodium formate was used in place of pyridine, the yield of thiazole was 68%.

A sample of V was redistilled, and a center cut boiling at 99–100° (0.20 mm.), $n^{20}D$ 1.5477, was analyzed.

Anal. Calcd. for C_6H_9NOS: C, 50.32; H, 6.33; N, 9.78. Found: C, 50.46; H, 6.36; N, 9.59.

Melting points of the **picrate**, m.p. 164–164.8°, and the ***p*-nitrobenzoate** of V, m.p. 124 to 125°, agreed with values previously reported in the literature.[8]

Thioformamide.—In a 5-l., three-necked flask equipped with a mechanical stirrer and thermometer were placed 3 l. of tetrahydrofuran and 300 g. (6.67 moles) of technical formamide. This solution was rapidly stirred while 330 g. (1.49 moles) of phosphorus pentasulfide was added in portions of about 50 g. during a period of one and one-half hours at 30–35°. During the addition and for a short time thereafter, it was occasionally necessary to cool the flask in an ice-bath in order to maintain this temperature. After the reaction mixture had been stirred at room temperature for six hours, a sticky solid which gradually formed in the reaction mixture was collected on a filter and discarded. Tetrahydrofuran was stripped from the filtrate under reduced pressure to leave a residue containing thioformamide, formamide and polymer. The residue was shaken with an equal part by weight of ether to dissolve thioformamide, leaving formamide and polymer undissolved. The ether solution was separated and concentrated under reduced pressure to give 201 g. (50%) of thioformamide.

The crude thioformamide is of sufficient purity to react satisfactorily with IV but if desired, it can be recrystallized from ethyl acetate at Dry-Ice temperature to give pure thioformamide, m.p. 32.0 to 33.8°.

Acknowledgment.—The authors wish to thank H. B. Copelin and J. S. Showell for their advice and assistance in the early phases of this work. Microanalyses were performed by J. M. Bauer and J. M. Amery.

NIAGARA FALLS, NEW YORK

[CONTRIBUTION FROM THE LILLY RESEARCH LABORATORIES]

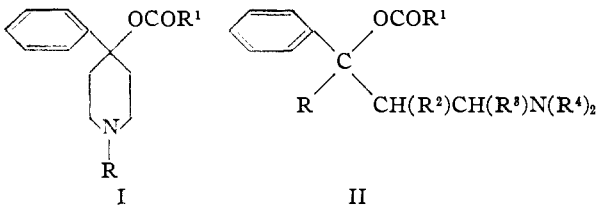
Analgesics: Esters of 4-Dialkylamino-1,2-diphenyl-2-butanols

BY A. POHLAND AND H. R. SULLIVAN

RECEIVED APRIL 25, 1953

Sixteen amino carbinols of the type $C_6H_5CH_2C(C_6H_5)OHCH(R^1)CH(R^2)N(R^3)_2$ have been prepared and eight of these separated into their diastereoisomeric forms. The carbinols have been converted to esters. Pharmacological studies in animals have shown that a number of these esters possess a high order of analgesic activity.

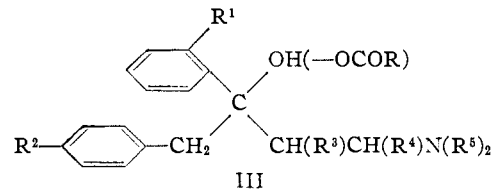
Acyl derivatives of 4-piperidinols[1,2] have been found to possess significant analgesic properties. These compounds (I) may be considered to be analogs of meperidine in which the ester function



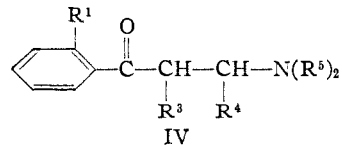
I II

is reversed. Similar open chain esters (II) have been prepared by other investigators[3–5] but according to the published pharmacological results, have failed to show any promising analgesic activity.

In our laboratories compounds of the type II have been under investigation as possible analgesic substances. Esters of 3-dialkylamino-1,1-diphenylpropanols were found to exhibit weak analgesic properties. These esters are unstable in aqueous solution, being readily hydrolyzed to the carbinol.[3] It was felt that more stable esters might possibly have greater analgesic activity, since the carbinols are devoid of activity. The present work is concerned with the preparation of 4-dialkylamino-1,2-diphenyl-2-butanols and their esters III.



III



IV

The intermediate β-dialkylaminopropiophenones and α-alkyl-β-dialkylaminopropiophenones (IV where R^1 is H or CH_3, R^3 is H or CH_3 or C_2H_5 and R^4 is H) were prepared by means of the Mannich reaction. The β-dialkylaminobutyrophenones (IV where R^1 and R^3 are H, R^4 is CH_3) were prepared by addition of the secondary amines to phenyl propenyl ketone.[6]

These aminoketones were allowed to react with benzylmagnesium chloride to yield the carbinols (Table I). The ketones containing an asymmetric

(1) K. A. Jensen, F. Lindquist, E. Rekling and C. G. Wolffbrandt, *Dansk Tids. Farm.*, **17**, 173 (1943).

(2) A. Ziering and J. Lee, *J. Org. Chem.*, **12**, 911 (1947).

(3) A. C. Kjaer and P. V. Petersen, *Acta Chem. Scand.*, **5**, 1145 (1951).

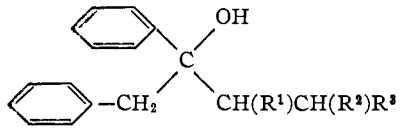
(4) J. H. Burckhalter and S. H. Johnson, Jr., THIS JOURNAL, **73**, 4827 (1951).

(5) M. B. Slomka and F. W. Schuller, *J. Am. Pharm. Assoc.*, **41**, 618 (1951).

(6) D. Shapiro, *J. Org. Chem.*, **14**, 839 (1949).

TABLE I

4-DIALKYLAMINO-1,2-DIPHENYL-2-BUTANOLS



Isomer	R^1	R^2	R^3	M.p., °C. HCl	Molecular formula	Nitrogen Calcd.	Nitrogen Found	Ionic chlorine Calcd.	Ionic chlorine Found
	H[a]	H	$(CH_3)_2N$	156–157	$C_{18}H_{23}NO\cdot HCl$	4.58	4.38	11.60	11.42
	H[b]	H	$C_5H_{10}N$[e]	232–233	$C_{21}H_{27}NO\cdot HCl$	4.05	4.20	10.25	10.40
α	CH_3[c]	H	$(CH_3)_2N$	231–232	$C_{19}H_{25}NO\cdot HCl$	4.38	4.57	11.08	11.11
β	CH_3[c]	H	$(CH_3)_2N$	197–199	$C_{19}H_{25}NO\cdot HCl$	4.38	4.26	11.08	11.39
α	C_2H_5	H	$(CH_3)_2N$	255–256	$C_{20}H_{27}NO\cdot HCl$	4.20	4.42	10.62	10.72
β	C_2H_5	H	$(CH_3)_2N$	153–154	$C_{20}H_{27}NO\cdot HCl$	4.20	4.32	10.62	10.54
α	CH_3	H	$(C_2H_5)_2N$	204–205	$C_{21}H_{29}NO\cdot HCl$	4.03	4.08	10.19	10.14
α	CH_3	H	C_4H_8N[f]	188–189	$C_{21}H_{27}NO\cdot HCl$	4.05	4.13	10.25	10.10
β	CH_3	H	C_4H_8N[f]	202–203	$C_{21}H_{27}NO\cdot HCl$	4.05	3.86	10.25	10.09
α	CH_3	H	OC_4H_8N[g]	219–220	$C_{21}H_{27}NO_2\cdot HCl$	3.87	3.81	9.80	9.85
β	CH_3	H	OC_4H_8N[g]	221 dec.	$C_{21}H_{27}NO_2\cdot HCl$	3.87	3.92	9.80	9.84
α	CH_3	H	$C_5H_{10}N$[e]	224–225	$C_{22}H_{29}NO\cdot HCl$	3.89	4.13	9.85	9.71
β	CH_3	H	$C_5H_{10}N$[e]	180–181	$C_{22}H_{29}NO\cdot HCl$	3.89	4.03	9.85	9.53
α	C_2H_5	H	$C_5H_{10}N$[e]	219–220	$C_{23}H_{31}NO\cdot HCl$	3.75	3.46	9.48	9.32
α	H[d]	CH_3	$(CH_3)_2N$	231–232	$C_{19}H_{25}NO\cdot HCl$	4.38	4.36	11.08	11.10
α	H	CH_3	C_4H_8N[f]	199–200	$C_{21}H_{27}NO\cdot HCl$	4.05	3.95	10.25	10.50
β	H	CH_3	C_4H_8N[f]	176–177	$C_{21}H_{27}NO\cdot HCl$	4.05	4.17	10.25	10.09
α	H	CH_3	$C_5H_{10}N$[e]	217–218	$C_{22}H_{29}NO\cdot HCl$	3.89	3.91	9.85	9.61
β	H	CH_3	$C_5H_{10}N$[e]	212–213	$C_{22}H_{29}NO\cdot HCl$	3.89	3.73	9.85	9.70

[a] Reference (7) reports base b.p. 138–139° (0.2 mm.). [b] Reference (7) reports base m.p. 85°. [c] Described in Experimental. Reference (7) reports b.p. 138–139° (0.1 mm.). [d] Free base melts at 96–97°. Reference (6) reports 94–95°. [e] Piperidine. [f] Pyrrolidine. [g] Morpholine.

center yielded predominantly one diastereoisomer. For example, β-dimethylaminoisobutyrophenone yielded 75% of the α-carbinol and only 15% of the β-isomer. Four of the carbinols have been previously reported,[6,7] but possible diastereoisomers were not isolated. Instead the free bases, isolated by distillation, were dehydrated to the 1,2-disubstituted-4-dialkylamino-2-butenes.[7]

The amino carbinol hydrochlorides were acylated at steam-bath temperatures using an equal weight of acetic or propionic anhydride and five times the weight of pyridine as a solvent. In cases where acylation could not be effected in this manner, less pyridine was used, and the reaction mixture refluxed at higher temperatures. The carbinols in ether solution were also acetylated by ketene. The higher acyl and benzoyl derivatives were prepared by the reaction of the acid chloride with the carbinols in toluene solution. The physical properties of the esters are summarized in Table II.

Carbinols and their acyl esters with substituted phenyls (compound III were R^1 is CH_3 or H, R^2 is H or Cl) were prepared. These are summarized in Table III.

In contrast to the esters of 3-dialkylamino-1,1-diphenylpropanols (II where R is C_6H_5, R^1 is alkyl), these acyl derivatives were quite resistant to hydrolysis. After 45 minutes reflux of a 5% aqueous solution, over 90% of the α,4-dimethylamino - 1,2 - diphenyl - 3 - methyl - 2 - propionyloxybutane hydrochloride was recovered unchanged. A 24-hour hydrolysis at reflux temperature, yielded 36% of unchanged ester along with both the α- and the β,4-dimethylamino-1,2-diphenyl-3-methylbutanols.

Preliminary pharmacological evaluation, using the rat-tail burn technique, has shown that a number of the esters are worthy of further study. Subcutaneous doses of 10 and 20 mg./kg. of α,4-dimethylamino - 1,2 - diphenyl - 3 - methyl - 2-propionyloxybutane hydrochloride in rats produced analgesic action similar to that of 1 and 2 mg./kg. of methadone hydrochloride. In anesthetized dogs, 1–2 mg./kg. intravenously or up to 20 mg./kg. subcutaneously caused no respiratory depression. The diastereoisomer, β,4-dimethylamino-1,2-diphenyl-3-methyl-2-propionyloxybutane, is devoid of analgesic action. α,1,2-Diphenyl-3-methyl-2-propionyloxy-4-pyrrolidinobutane, an analog in which pyrrolidine has replaced dimethylamine, is equally active as an analgesic. However, the acetyl compound, α,2-acetoxy-1,2-diphenyl-3-methyl-4-pyrrolidinobutane, is approximately twice as potent.

Experimental[8]

Aminoketones.—Many of the aminoketones used in this work have been fully described in the literature.[9–12] The free bases of the β-aminopropiophenones and β-aminobutyrophenones are unstable to distillation. For use in the Grignard reactions, the pure hydrochlorides were treated with excess cold dilute alkali and the bases dried in ether solution with magnesium sulfate. The Mannich bases from pro-

(7) W. G. Stoll, Ch. J. Morel and Ch. Frey, *Helv. Chim. Acta*, **33**, 1194 (1950).

(8) Melting points and boiling points are uncorrected.

(9) C. Mannich and G. Heilner, *Ber.*, **55**, 356 (1922).

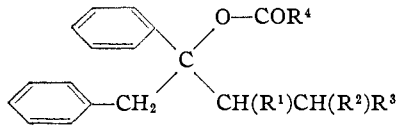
(10) J. H. Burckhalter and R. C. Fuson, THIS JOURNAL, **70**, 4186 (1948).

(11) A. W. Ruddy and J. S. Buckley, Jr., *ibid.*, **72**, 718 (1950).

(12) J. H. Burckhalter and S. H. Johnson, Jr., *ibid.*, **73**, 4827 (1952).

TABLE II

ESTERS OF 4-DIALKYLAMINO-1,2-DIPHENYL-2-BUTANOLS



Isomer	R^1	R^2	R^3	R^4	M.p., °C. HCl	Method	Molecular formula	Nitrogen Calcd.	Nitrogen Found	Ionic chlorine Calcd.	Ionic chlorine Found
	H	H	$(CH_3)_2N$	CH_3	227–228	B	$C_{20}H_{25}NO_2\cdot HCl$	4.03	3.82	10.19	10.34
	H	H	$(CH_3)_2N$	C_2H_5	188–189	B	$C_{21}H_{27}NO_2\cdot HCl$	3.87	3.95	9.80	9.78
	H	H	$(CH_3)_2N$	C_3H_7	169–170	D[a]	$C_{22}H_{29}NO_2\cdot HCl$	3.73	3.44	9.43	9.46
	H	H	$(CH_3)_2N$	C_6H_5	204–205 dec.	D	$C_{25}H_{27}NO_2\cdot HCl$	3.42	3.15	8.67	8.56
	H	H	$C_5H_{10}N$[b]	CH_3	157–158	C	$C_{23}H_{29}NO_2\cdot HCl$	3.61	3.66	9.14	9.25
α	CH_3	H	$(CH_3)_2N$	CH_3	187–188	B	$C_{21}H_{27}NO_2\cdot HCl$	3.87	3.59	9.80	9.71
α	CH_3	H	$(CH_3)_2N$	C_2H_5	170–171	A[a]	$C_{22}H_{29}NO_2\cdot HCl$	3.73	3.63	9.43	9.54
β	CH_3	H	$(CH_3)_2N$	CH_3	205–206 dec.	B	$C_{21}H_{27}NO_2\cdot HCl$	3.87	3.89	9.80	9.74
β	CH_3	H	$(CH_3)_2N$	C_2H_5	187–188 dec.	B[a]	$C_{22}H_{29}NO_2\cdot HCl$	3.73	3.73	9.43	9.61
α	C_2H_5	H	$(CH_3)_2N$	CH_3	156–157	B	$C_{22}H_{29}NO_2\cdot HCl$	3.73	3.66	9.43	9.58
α	C_2H_5	H	$(CH_3)_2N$	C_2H_5	169–170	B	$C_{23}H_{31}NO_2\cdot HCl$	3.59	3.75	9.09	9.19
β	C_2H_5	H	$(CH_3)_2N$	CH_3	155–156	B	$C_{22}H_{29}NO_2\cdot HCl$	3.73	3.54	9.43	9.23
β	C_2H_5	H	$(CH_3)_2N$	C_2H_5	175–176	B	$C_{23}H_{31}NO_2\cdot HCl$	3.59	3.30	9.09	9.02
α	CH_3	H	$(C_2H_5)_2N$	CH_3	191	C[a]	$C_{23}H_{31}NO_2\cdot HCl$	3.59	3.83	9.09	9.01
α	CH_3	H	C_4H_8N[c]	CH_3	202–203 dec.	A	$C_{23}H_{29}NO_2\cdot HCl$	3.61	3.57	9.14	9.06
α	CH_3	H	C_4H_8N[c]	C_2H_5	196–197 dec.	A	$C_{24}H_{31}NO_2\cdot HCl$	3.49	3.74	8.82	8.77
β	CH_3	H	C_4H_8N[c]	C_2H_5	169–170	A	$C_{24}H_{31}NO_2\cdot HCl$	3.49	3.41	8.82	8.87
α	CH_3	H	OC_4H_8N[d]	CH_3	195–196	A	$C_{23}H_{29}NO_3\cdot HCl$	3.47	3.44	8.78	8.70
α	CH_3	H	OC_4H_8N[d]	C_2H_5	190–191	A	$C_{24}H_{31}NO_3\cdot HCl$	3.35	3.50	8.48	8.63
β	CH_3	H	OC_4H_8N[d]	CH_3	177–178	A	$C_{23}H_{29}NO_3\cdot HCl$	3.47	3.41	8.78	8.70
β	CH_3	H	OC_4H_8N[d]	C_2H_5	160–161	A	$C_{24}H_{31}NO_3\cdot HCl$	3.35	3.35	8.48	8.18
α	CH_3	H	$C_5H_{10}N$[b]	CH_3	215–216	C	$C_{24}H_{31}NO_2\cdot HCl$	3.49	3.56	8.82	8.66
α	CH_3	H	$C_5H_{10}N$[b]	C_2H_5	191–192	A	$C_{25}H_{33}NO_2\cdot HCl$	3.37	3.29	8.52	8.74
β	CH_3	H	$C_5H_{10}N$[b]	CH_3	190–191	C	$C_{24}H_{31}NO_2\cdot HCl$	3.49	3.66	8.82	8.64
α	H	CH_3	$(CH_3)_2N$	CH_3	210–211	B	$C_{21}H_{27}NO_2\cdot HCl$	3.87	3.67	9.80	10.02
α	H	CH_3	$(CH_3)_2N$	C_2H_5	210–211	B	$C_{22}H_{29}NO_2\cdot HCl$	3.73	3.66	9.43	9.18
α	H	CH_3	C_4H_8N[c]	CH_3	203–204	A	$C_{23}H_{29}NO_2\cdot HCl$	3.61	3.72	9.14	8.85
α	H	CH_3	C_4H_8N[c]	C_2H_5	200	A	$C_{24}H_{31}NO_2\cdot HCl$	3.49	3.54	8.82	8.83
β	H	CH_3	C_4H_8N[c]	C_2H_5	187–188	A	$C_{24}H_{31}NO_2\cdot HCl$	3.49	3.78	8.82	9.05
α	H	CH_3	$C_5H_{10}N$[b]	CH_3	225–226	B	$C_{24}H_{31}NO_2\cdot HCl$	3.49	3.50	8.82	8.94
α	H	CH_3	$C_5H_{10}N$[b]	C_2H_5	229–230 dec.	A	$C_{25}H_{33}NO_2\cdot HCl$	3.37	3.32	8.52	8.29

[a] Described in Experimental. [b] Piperidine. [c] Pyrrolidine. [d] Morpholine.

piophenone and butyrophenone were stable to distillation at reduced pressures. The new Mannich ketones are described below.

β-Dimethylamino-*o*-methylisobutyrophenone Hydrochloride.—By the procedure of Maxwell[13] 95 g. (0.64 mole) of *o*-methylpropiophenone, 68 g. (0.83 mole) of dimethylamine hydrochloride, 26 g. (0.87 mole) of paraformaldehyde, 100 ml. of ethanol and 1 ml. of concentrated hydrochloric acid yielded 70 g. (46%) of product recrystallized from ethyl acetate–methanol solution, m.p. 134–135°.

Anal. Calcd. for $C_{13}H_{19}NO\cdot HCl$: N, 5.80; Cl, 14.67. Found: N, 5.56; Cl, 14.83.

β-Pyrrolidinoisobutyrophenone.—A reaction mixture containing 107.6 g. (1.3 moles) of pyrrolidine hydrochloride, 134 g. (1.0 mole) of propiophenone, 39 g. (1.3 moles) of paraformaldehyde, 200 ml. of ethanol and 2 ml. of concentrated hydrochloric acid was refluxed for 12 hours. The ethanol was removed *in vacuo* and the residue dissolved in water. The aqueous solution was washed with ether and then made basic by the addition of excess concentrated ammonium hydroxide. The oil was taken up in ether, dried over magnesium sulfate, and distilled. The product boiled at 117–118° (0.30 mm.); $n^{25}D$ 1.5302, 94 g. (44%).

β-Dimethylaminobutyrophenone Hydrochloride.—This compound has been prepared in crude form by Shapiro.[6] The procedure has been modified to give good yields of the pure product. A solution containing 6.8 g. (0.15 mole) of dimethylamine in 50 ml. of toluene was stirred and cooled to 10° during the dropwise addition of 14.6 g. (0.10 mole) of phenyl propenyl ketone. The reaction was allowed to stand overnight at room temperature and was then extracted with cold dilute hydrochloric acid. The acid aqueous layer was made basic with dilute ammonium hydroxide. The resulting oil was dried in ether solution over magnesium sulfate. The hydrochloride was prepared in ether using anhydrous hydrogen chloride and recrystallized from methanol–ethyl acetate solution, m.p. 134–135° dec.; 15 g. (66%).

Anal. Calcd. for $C_{12}H_{17}NO\cdot HCl$: N, 6.15; Cl, 15.57. Found: N, 6.16; Cl, 15.77.

β-Piperidinobutyrophenone Hydrochloride.—Following the procedure for the dimethylamino compound, 58.4 g. (0.4 mole) of phenyl propenyl ketone and 51.2 g. (0.60 mole) of piperidine in 150 ml. of toluene yielded 87 g. (81%) of the product which melted at 157–158°.

Anal. Calcd. for $C_{15}H_{21}NO\cdot HCl$: N, 5.03; Cl, 13.24. Found: N, 5.09; Cl, 13.20.

β-Pyrrolidinobutyrophenone Hydrochloride.—Following the procedure for the dimethylamino compound, 58.4 g. (0.4 mole) of phenyl propenyl ketone and 43 g. (0.6 mole) of pyrrolidine in 150 ml. of toluene yielded 40 g. (39%) of the product which melted at 120°.

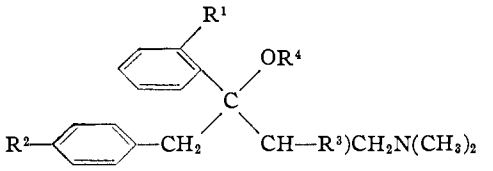
Anal. Calcd. for $C_{14}H_{19}NO\cdot HCl$: N, 5.52; Cl, 13.97. Found: N, 5.70; Cl, 14.00.

Preparation of α- and β,4-Dimethylamino-1,2-diphenyl-3-methyl-2-butenol Hydrochlorides.—Benzylmagnesium chlo-

(13) G. B. Maxwell, *Org. Syntheses*, **28**, 80 (1948).

TABLE III

4-DIMETHYLAMINO-1,2-DIARYL-2-BUTANOLS AND ESTERS



Isomer	R¹	R²	R³	R⁴	M.p., °C. HCl	Method	Molecular formula	Nitrogen Calcd.	Nitrogen Found	Ionic chlorine Calcd.	Ionic chlorine Found
	CH_3	H	H	H	169–170		$C_{19}H_{25}NO\cdot HCl$	4.38	4.42	11.08	11.14
	CH_3	H	H	CH_3CO	228–229	B	$C_{21}H_{27}NO_2\cdot HCl$	3.87	3.84	9.80	10.09
	CH_3	H	H	C_2H_5CO	197–198	B	$C_{22}H_{29}NO_2\cdot HCl$	3.73	3.67	9.43	9.31
α	CH_3	H	CH_3	H	234–235		$C_{20}H_{27}NO\cdot HCl$	4.20	4.36	10.62	10.75
α	CH_3	H	CH_3	CH_3CO	180–181	B	$C_{22}H_{29}NO_2\cdot HCl$	3.73	3.48	9.43	9.33
	H	Cl	H	H	163–165		$C_{18}H_{22}ClNO\cdot HCl$	4.12	4.06	10.42	10.42
	H	Cl	H	CH_3CO	215–216 dec.	B	$C_{20}H_{24}ClNO_2\cdot HCl$	3.66	3.40	9.27	9.34
α	H	Cl	CH_3	H	231–232 dec.		$C_{19}H_{24}ClNO\cdot HCl$	3.95	3.93	10.01	10.03
α	H	Cl	CH_3	CH_3CO	205–206 dec.	B	$C_{21}H_{26}ClNO_2\cdot HCl$	3.54	3.52	8.95	8.76
α	H	Cl	CH_3	C_2H_5CO	208–209 dec.	B	$C_{22}H_{28}ClNO_2\cdot HCl$	3.41	3.22	8.64	8.45
β	H	Cl	CH_3	H	221–222		$C_{19}H_{24}ClNO\cdot HCl$	3.95	3.79	10.01	10.01
β	H	Cl	CH_3	C_2H_5CO	190–192	B	$C_{22}H_{28}ClNO_2\cdot HCl$	3.41	3.31	8.64	8.97

ride was prepared from 127 g. (1 mole) of benzyl chloride, 30.8 g. (1.25 moles) of magnesium and 1400 ml. of ether. The Grignard solution was stirred at room temperature during the dropwise addition of 95.5 g. (0.5 mole) of β-dimethylaminoisobutyrophenone. The reaction mixture was stirred and refluxed for one hour and then decomposed with 190 ml. of saturated ammonium chloride solution. The ether was decanted from the granular solid and dried over magnesium sulfate. The hydrochloride was prepared in ether solution using anhydrous hydrogen chloride. After two recrystallizations from methanol–ethyl acetate (4:1), the α-isomer melted at 231–232°; 120 g. (75%).

The mother liquor was concentrated on a steam-bath to remove the methanol and ether was added to incipient crystallization. The crude β-isomer separated on cooling, m.p. 193–194°; 35 g. The β-isomer was recrystallized twice from methanol–ethyl acetate–ether solution, m.p. 197–199°; 25 g. (15%).

Preparation of the Esters: Method A for α,4-Dimethylamino-1,2-diphenyl-3-methyl-2-propionyloxybutane Hydrochloride.—A reaction mixture containing 50 g. (0.156 mole) of α,4-dimethylamino-1,2-diphenyl-3-methyl-2-butanol hydrochloride, 50 g. of propionic anhydride and 50 ml. of pyridine was heated at reflux for five hours. The reaction temperature rose to 140° during this time. The reaction mixture was cooled to 50° and ether was added to incipient turbidity. The crude product separated on further cooling, m.p. 161–166°; 57 g. After two recrystallizations from methanol–ethyl acetate solution the product melted at 170–171°; 41 g. (70%).

Anal. Calcd. for $C_{22}H_{29}NO_2\cdot HCl$: N, 3.73; Cl, 9.43. Found: N, 3.63; Cl, 9.54.

Method B for β,4-Dimethylamino-1,2-diphenyl-3-methyl-2-propionyloxybutane Hydrochloride.—A reaction mixture containing 2 g. of β,4-dimethylamino-1,2-diphenyl-3-methyl-2-butanol hydrochloride, 2 ml. of propionic anhydride and 10 ml. of pyridine was warmed on a steam-bath for two hours. Ether was added to incipient turbidity. The crude product was recrystallized from acetone–ether solution, m.p. 187–188° dec.; 1.50 g.

Anal. Calcd. for $C_{22}H_{29}NO_2\cdot HCl$: N, 3.73; Cl, 9.43. Found: N, 3.73; Cl, 9.61.

Method C for α,2-Acetoxy-4-diethylamino-1,2-diphenyl-3-methylbutane Hydrochloride.—A solution of 5.36 g. (0.017 mole) of α,4-diethylamino-1,2-diphenyl-3-methyl-2-butanol in 50 ml. of ether was allowed to react with excess ketene.[14] The hydrochloride was prepared from the ether solution and anhydrous hydrogen chloride and recrystallized from acetone, m.p. 191°; 4.0 g. (60%).

Anal. Calcd. for $C_{23}H_{31}NO_2\cdot HCl$: N, 3.59; Cl, 9.09. Found: N, 3.83; Cl, 9.01.

Method D for 2-Butyryloxy-4-dimethylamino-1,2-diphenylbutane Hydrochloride.—A reaction mixture containing 5 g. (0.019 mole) of 1,2-diphenyl-4-dimethylaminobutanol, 5 ml. of butyryl chloride and 75 ml. of toluene was warmed one hour on a steam-bath. The product was collected on a filter and recrystallized from methanol–ethyl acetate solution, m.p. 169–170°; 5.75 g. (82%).

Anal. Calcd. for $C_{22}H_{29}NO_2\cdot HCl$: N, 3.73; Cl, 9.43. Found: N, 3.44; Cl, 9.46.

Hydrolysis of α,4-Dimethylamino-1,2-diphenyl-3-methyl-2-propionyloxybutane Hydrochloride.—A solution of 10 g. of α-4-dimethylamino-1,2-diphenyl-3-methyl-2-propionyloxybutane hydrochloride in 200 cc. of water was refluxed for 45 minutes and then concentrated *in vacuo* to dryness. The residue was recrystallized from methanol–ethyl acetate solution, m.p. and mixed m.p. 167.5–170° with starting material, wt. 9.50 g.

Another run, with the addition of one drop of concentrated hydrochloric acid, was refluxed for 24 hours and then concentrated *in vacuo* to dryness. The residue was fractionally crystallized from methanol and methanol–ethyl acetate–ether to yield 2.75 g. of starting ester hydrochloride melting at 166–168°, 2.22 g. of α,4-dimethylamino-1,2-diphenyl-3-methyl-2-butanol hydrochloride melting at 231–232°, and 1.10 g. of β,4-dimethylamino-1,2-diphenyl-3-methyl-2-butanol hydrochloride melting at 196–198°.

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