was 186.6–189.8°. *Anal.* Calcd. for $C_{16}H_{24}N_6$: C, 62.47; H, 8.39; N, 29.14. Found: C, 62.71; H, 8.48; N, 29.14.

The following 2,4,6-trisubstituted-amino-*s*-triazines were also prepared by treating an excess of the amine with cyanuric chloride: **2,4,6-tri-1-piperidyl-*s*-triazine**[11]—yield 93%, m.p. 219–221.1° (from a toluene–ethanol mixture and then acetone). *Anal.* Calcd. for $C_{18}H_{30}N_6$: C, 65.42; H, 9.15; N, 25.43. Found: C, 65.65; H, 9.28; N, 25.41.

2,4,6-Tri-4-morpholinyl-*s*-triazine.—Yield 97%, m.p. 284–289° (dec.) (from ethanol). *Anal.* Calcd. for $C_{15}H_{24}N_6O_3$: C, 53.55; H, 7.19; N, 24.99. Found: C, 53.63; H, 7.13; N, 24.96.

(11) A. W. Hofmann, *Ber.*, **18**, 2779 (1885), obtained this compound by the reaction of the trimethyl ester of trithiocyanuric acid with piperidine, m.p. 213°.

Acknowledgments.—We are grateful to The Wm. S. Merrell Company for funds that made it possible for us to carry on this work and for many helpful discussions and suggestions. Our thanks are also due to the American Cyanamid Co. for generous supplies of cyanuric chloride, dicyandiamide and potassium dicyanoguanidine; to the Carbide and Carbon Chemicals Corp. for piperazine; to the Monsanto Chemical Company for piperidine and E. I. du Pont de Nemours and Co. for pyrrolidine.

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[CONTRIBUTION FROM THE CHEMICAL RESEARCH DIVISION OF LAKESIDE LABORATORIES, INC.]

Antispasmodics. I. Substituted Acetic Acid Esters of 1-Alkyl-3-hydroxypiperidine[1]

BY JOHN H. BIEL, HARRIS L. FRIEDMAN, HELEN A. LEISER AND EDWIN P. SPRENGELER

The method of Paul and Tchelitcheff for the preparation of 1-alkyl-3-hydroxypiperidines from furfural or tetrahydrofurfuryl chloride has been modified and consistently high yields of the aminoalcohols were obtained. A more rigorous proof of structure of the piperidinol derivatives *via* the catalytic hydrogenation of 3-hydroxypyridine has been accomplished. Partial cleavage was observed during the reduction of 3-hydroxypyridine and some of its esters. The cleavage products were identified. A series of substituted acetic acid esters of N-alkyl-3-piperidinol has been prepared. In the guinea pig ileum test these esters proved to be potent acetylcholine antagonists. The diphenylacetate of 3-hydroxypyridine was devoid of any spasmolytic properties.

In 1945, Paul and Tchelitcheff[2] published a two-step synthesis for the preparation of 1-alkyl-3-piperidinols from either furfural or tetrahydrofurfuryl chloride.

N-Ethyl and N-methyl-3-hydroxypiperidine are closely related in structure to diethylaminoethanol and tropine, respectively, the distance between the amino nitrogen and the alcoholic hydroxyl group being the same or nearly the same in the two pairs of aminoalcohols.[3] From these structural analogies it was tempting, therefore, to speculate on possible similarities in spasmolytic properties of some of the esters of the two aminoalcohols.

With the exception of the benzoate[2] no esters of N-alkyl-3-hydroxypiperidine have as yet been reported. However, esters of N-methyl-4-hydroxypiperidine have been synthesized and notably the diphenylacetate and 9-fluorene carboxylate[4] of this aminoalcohol were shown to possess potent spasmolytic properties.

We felt that a more rigorous proof of structure of the aminoalcohol was desirable than the one offered by the French workers. This was readily accomplished by the catalytic reduction of 3-hydroxypyridine hydrochloride,[5] N-alkylation of 3-hydroxypiperidine and conversion to the corresponding benzoate ester hydrochloride. The respective N-alkyl-3-piperidyl benzoate hydrochlorides were found to be identical with those obtained from the "furan" procedure of Paul and Tchelitcheff.[2]

While this work was in progress, Reitsema[6] published an alternate structure proof which involved the reduction of N-ethyl-3-piperidone to the alcohol and conversion of the latter to its benzoate hydrochloride.

The procedure for the synthesis of N-ethyl-3-piperidinol as described by Paul and Tchelitcheff[2] resulted in low yields when applied in this, as well as in other laboratories.[7] Through modification of their method (see Experimental) we succeeded in nearly doubling the yield of the desired aminoalcohol.

The esters were obtained by the condensation of the aminoalcohols with the appropriate acid chloride (procedure A), the action of the free acid on N-ethyl-3-chloropiperidine in refluxing isopropyl alcohol[8] (procedure B) or by the ester interchange in boiling xylene[9] (procedure C). Inasmuch as Reitsema[6] had reported a "ring contraction" to N-ethyl-2-benzylaminomethylpyrrolidine during the interaction of N-ethyl-3-chloropiperidine with benzylamine, it became necessary to verify the structure of the esters obtained from procedure B. This was accomplished in two ways: (1) The interaction of diphenylacetyl chloride with N-ethyl-3-hydroxypiperidine, as well as the action of diphenylacetic acid on N-ethyl-3-chloropiperidine yielded one product, N-ethyl-3-piperidyl diphenylacetate hydrochloride. (2) Hydrolysis of a product obtained by procedure B, presumably N-ethyl-3-piperidyl benzilate hydrochloride, followed by conversion of the resulting aminoalcohol to its benzoate hydrochloride yielded a compound which was identical with an authentic sample of N-ethyl-3-piperidyl benzoate hydrochloride.

An alternate route of arriving at N-alkyl-3-

(1) Presented in part before the Division of Medicinal Chemistry at the Cleveland Meeting of the American Chemical Society, April, 1951.

(2) R. Paul and S. Tchelitcheff, *Compt. rend.*, **221**, 560 (1945).

(3) C. Pfeiffer, *Science*, **107**, 94 (1948).

(4) R. R. Burtner and J. W. Cusic, THIS JOURNAL, **65**, 262 (1943).

(5) Chen-Heng Kao, *J. Chem. Eng. China*, **15**, 80 (1949); *C.A.*, **44**, 3993e (1950).

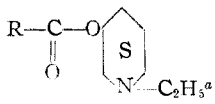
(6) R. R. Reitsema, THIS JOURNAL, **71**, 2041 (1949).

(7) R. C. Fuson and C. L. Zirkle, *ibid.*, **70**, 2760 (1948).

(8) H. Horenstein and H. Pählicke, *Ber.*, **71B**, 1644 (1938).

(9) C. H. Tilford, M. G. van Campen and R. S. Shelton, THIS JOURNAL, **69**, 2902 (1947).

TABLE I

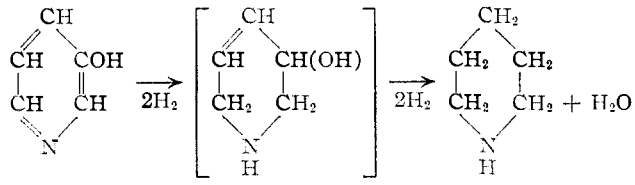


No.	R	Bases B.p., °C.	Mm.	Formula	Nitrogen, % Calcd.	Found	Salts Salt	Nitrogen, % Calcd.	Found	Halogen, % Calcd.	Found	M.p., °C.	Activity[e] (× 10^6)
I	$(C_6H_5)_2CH$	191–192	0.18	$C_{21}H_{25}NO_2$	4.33	4.21	HCl	3.89	3.85	9.87	9.79	195–196	4.0
II	$(C_6H_5)_2CH$[d]	173–175	.16	$C_{20}H_{23}NO_2$	4.53	4.49	HCl	4.06	4.13	10.29	10.31	193–194	5.0
III	$(C_6H_5)_2CH$	.....	..	$C_{21}H_{28}NO_2$	..	..	CH_3Br	3.35	3.40	19.15	19.11	168–169	18.0
IV	$(C_6H_5)(C_6H_{11})CH$	172–174	.55	$C_{21}H_{31}NO_2$	4.24	4.27	HCl	3.82	3.66	9.72	9.50	214–216	28.0
V	$(C_6H_5)(C_6H_{11})CH$	.....	..	$C_{22}H_{34}NO_2$	..	..	CH_3Br	3.31	3.27	18.83	18.49	126–127	435
VI	$(C_6H_5)_2COH$[b]	207–208	.50	$C_{21}H_{25}NO_3$	4.12	4.06	HCl	3.72	3.62	9.45	9.29	187–188	166
VII	$(C_6H_5)_2COH$	.....	..	$C_{21}H_{28}NO_3$	..	..	CH_3Br	3.23	3.23	18.45	18.30	179–180	1000
VIII	$(C_6H_5)(C_6H_{11})COH$[b]	166–167	.05	$C_{21}H_{31}NO_3$	4.06	4.03	HCl	3.67	3.66	9.30	9.11	215–217	....
IX	1-C_6H_5-C_6H_{11}[d,c]	.....	..	$C_{18}H_{28}NO_2$	..	..	HCl	4.14	4.20	10.50	10.28	215–216	9.1
X	9-Fluorene[b]	.....	..	$C_{21}H_{23}NO_2$	..	..	HCl	3.92	3.92	9.94	9.97	226–227	22.2
XI	9-Xanthene[b]	.....	..	$C_{21}H_{23}NO_3$	..	..	HCl	3.75	3.74	9.51	9.34	226–227	16.6
	Trasentine												4 0
	Atropine												500

[a] Unless otherwise indicated the esters were prepared by Procedure A. [b] Prepared by Procedure B. [c] Prepared by Procedure C. [d] N-Methyl for N-ethyl. [e] Effective dilution of the ester which afforded a 50% inhibition of guinea pig ileum spasms produced by acetylcholine (1:16,000,000) *in vitro*.

piperidyl esters is the condensation of commercially available 3-hydroxypyridine with an acid chloride, reduction to the 3-piperidyl ester, and subsequent alkylation with the desired alkyl halide.

This method was less practicable owing to the partial cleavage of the diphenylacetate ester during hydrogenation to piperidine, 3-hydroxypiperidine, diphenylacetic acid and ethyl diphenylacetate. We investigated more extensively the reduction of 3-hydroxypyridine hydrochloride and were unable to duplicate the results of Chen-Heng Kao[5] who claimed a quantitative conversion to 3-hydroxypiperidine hydrochloride. We found that 3-hydroxypiperidine was formed to the extent of only 30–40% and that the remainder was piperidine. As a possible mechanism we propose the formation of an intermediate "allyl" type alcohol which would be more prone to undergo hydrogenolysis inasmuch as 3-hydroxypiperidine once formed does not absorb hydrogen under the same conditions and can be recovered quantitatively.



The esters were screened, under the supervision of Mr. P. A. Nuhfer of our Pharmacology Division, for their antispasmodic action against acetylcholine on the excised guinea pig ileum, using both Trasentine and atropine as reference standards. Compounds (I) and (II) (see Table I) were equal to Trasentine in spasmolytic potency. Quaternization of (I) with methyl bromide (compound III) resulted in a four- to five-fold increase in activity over the parent compound.

Meier and Hoffman[10] similarly found the methochloride of 2-diethylaminoethyl diphenylacetate to be twice as potent as the hydrochloride. Nuclear hydrogenation of the diphenylacetate ester (compound IV) afforded a seven-fold increase in spasmolytic potency. Trasentine-6H has been reported to be eight times as potent as Trasentine in this test.[10] The 9-fluorenecarboxylate and 9-xanthenecarboxylate esters (compounds X and XI) were four to five times as potent as Trasentine. The corresponding esters in the diethylaminoethanol series had six to twelve times the spasmolytic potency of Trasentine.[4,11] The anti-acetylcholine activity of the benzilate ester (VI) was forty times that of Trasentine or one-third that of atropine. Similarly, the benzilate of 2-diethylaminoethanol has been reported to be one-fifth as active as atropine.[4] The methobromide of (VI) (compound VII) was found to be twice as active as atropine and the methobromide of the cyclohexylphenylacetate ester (V) equaled atropine in antispasmodic activity. Spasmolytic potency of the 1-phenylcyclohexane carboxylate ester (compound IX) proved to be twice that of either the diphenylacetate ester (II) or Trasentine. Tilford, Van Campen and Shelton[9] reported a five-fold activity increase of the 1-phenylcyclohexyl carboxylate of diethylaminoethanol over the corresponding diphenylacetate (Trasentine).

From the preliminary *in vitro* tests one may conclude that the replacement of diethylaminoethyl by the structurally related N-ethyl-3-piperidyl in some standard spasmolytic agents has yielded compounds of comparable activity. Whether the new compounds will have any therapeutic advantages over their parent compounds will have to be determined by more extensive pharmacological investigation and ultimate clinical trial.

Comparative spasmolytic activities of some esters of diethylaminoethanol and N-ethyl-3-piperidinol in the guinea pig ileum test are summarized in Table II.

Acknowledgment.—We wish to thank Dr. H. L. Daiell for his continued interest throughout the course of this project and Mr. H. C. Krahnke for supplying the analytical data.

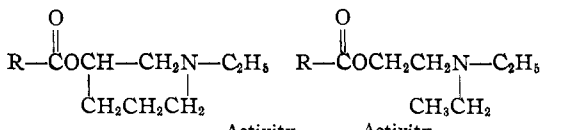
Experimental

N,N-Diethyltetrahydrofurfurylamine.—A mixture of 36.0

(10) R. Meier and K. Hoffman, *Helv. Med. Acad.*, **7**, 106 (1941).

(11) R. R. Burtner and J. W. Cusic, THIS JOURNAL, **65**, 1582 (1943).

TABLE II



R	Activity Trazentine = 1.0)	Activity Trazentine = 1.0)	Reference
$(C_6H_5)_2CH$[a]	1.0	1.0	
$(C_6H_5)_2CH$[b]	4.5	2.0	10
$(C_6H_5)(C_6H_{11})CH$	7.0	8.0	10
9-Fluorene	5.0	6.0	4
9-Xanthene	4.0	12.0	11
$(C_6H_5)_2COH$	40.0	10.0	4
1-(C_6H_5)-C_6H_{11}	2.3	5.0	9

[a] Unless otherwise indicated, the esters were tested in the form of their hydrochlorides. [b] Methyl halide salt.

g. (0.30 mole) of tetrahydrofurfuryl chloride,[12] 68.0 g. (0.90 mole) of diethylamine, 90.0 g. (0.60 mole) of sodium iodide and 150 cc. of abs. ethanol was heated for three days on the steam-bath in a citrate bottle. The reaction mixture was filtered and excess diethylamine and solvent removed by distillation through a 10" Vigreux column. The residue was dissolved in water, acidified with dilute hydrochloric acid and extracted several times with ether. The aqueous phase was saturated with solid potassium hydroxide and extracted repeatedly with ether. The ether extracts were dried with potassium carbonate, the ether removed by distillation and the residue distilled *in vacuo*, b.p. 64–65°, yield 25.4 g. (53%). *Anal.* Calcd. for $C_9H_{19}NO$: N, 8.92. Found: N, 8.75.

N-Ethyltetrahydrofurfurylamine.—This compound was prepared by the reductive aminolysis of furfural[13] in the presence of Raney nickel catalyst[14] according to the directions of Paul and Tchelitcheff.[2] A more satisfactory yield (71%) was obtained at a lower hydrogenation temperature (70–90°).

N-Ethyl-3-hydroxypiperidine. Method A.—Into a solution of 87.0 g. (0.68 mole) of N-ethyltetrahydrofurfurylamine (or 106 g. of N,N-diethyltetrahydrofurfurylamine) and 54 cc. of glacial acetic acid kept at 100–105° was passed 110 g. (1.40 moles) of hydrogen bromide gas during a period of two hours. The cooled reaction mixture was neutralized with a concd. potassium hydroxide solution keeping the temperature below 30°. A solution of 350 g. of potassium hydroxide in 300 cc. of water was then added and the alkaline mixture distilled until a small portion of the distillate no longer precipitated an oil on saturation with solid potassium hydroxide. The distillate was then saturated with potassium hydroxide and extracted with ether. The ether extract was dried with potassium carbonate and the ether removed by distillation. The residue was distilled *in vacuo* and 70 g. (80%) of product collected at 92–94° (15 mm.).[2] The benzoate ester of the above aminoalcohol was prepared, m.p. 199–200°.[2]

The Reduction of 3-Hydroxypyridine Hydrochloride.—A solution containing 39.1 g. (0.30 mole) of 3-hydroxypyridine hydrochloride in 250 cc. of abs. alcohol was subjected to hydrogenation at 60 lb. of hydrogen in the presence of 2.2 g. of platinum oxide. The catalyst was removed by filtration and the filtrate concentrated to dryness *in vacuo*. The solid residue was dissolved in water, the aqueous solution saturated with solid potassium hydroxide and extracted with ether. The ether extract was dried with potassium carbonate and the ether removed by distillation. The residue was distilled *in vacuo* and two fractions collected: (a) b.p. 40–42° (51 mm.), yield 13.5 g.; (b) b.p. 67–69° (2 mm.), yield 9.0 g. of 3-hydroxypiperidine, m.p. 61–63.[5] Fraction (a) was converted to its hydrochloride, m.p. 249–250°. A mixed m.p. with an authentic sample of piperidine hydrochloride gave no depression.

N-Ethyl-3-hydroxypiperidine. Method B.—A mixture of 3.8 g. (0.038 mole) of 3-hydroxypiperidine, 2.3 g. (0.038 mole) of potassium hydroxide and 5.9 g. (0.38 mole) of ethyl iodide in abs. alcohol was refluxed for 18 hours, cooled and the inorganic precipitate removed by filtration. The filtrate was acidified with concd. hydrochloric acid and concentrated to dryness *in vacuo*. The residue was dissolved in water and extracted with ether. The aqueous phase was then saturated with potassium hydroxide and worked up in the usual manner. The product was collected by vacuum distillation; b.p. 93–95° (15 mm.), yield 4.0 g. (82%). The benzoate ester hydrochloride[2] was prepared, m.p. 199–200°. A mixed m.p. with the ester obtained from method A showed no depression.

N-Methyl-3-hydroxypiperidine. Method A.—This aminoalcohol was prepared from N-methyltetrahydrofurfurylamine[2] in 70% yield by the procedure described for the N-ethyl derivative (method A), b.p. 80–82° (15 mm.); reported[2] b.p. 79° (15 mm.). The diphenylacetate hydrochloride melted at 193–194° (compound II in Table I).

Method B.—A solution containing 9.0 g. (0.090 mole) of 3-hydroxypiperidine, 13.1 g. (0.25 mole) of 88% formic acid and 8.9 g. (0.11 mole) of 37% formaldehyde was refluxed for 24 hours. To the reaction mixture was added 5 cc. of concd. hydrochloric acid. After concentration of the mixture *in vacuo* the residue was dissolved in water, the aqueous solution saturated with potassium hydroxide and extracted with ether. The ether extracts were dried with potassium carbonate and the ether removed by distillation. The residue was distilled *in vacuo* and the 7.0 g. (67%) of product collected, b.p. 81° (15 mm.). The diphenylacetate hydrochloride was prepared, m.p. 193–194°. A mixed m.p. of the two hydrochlorides obtained from methods A and B showed no depression.

α-Cyclohexylbenzylnitrile.—To 44.0 g. (1.1 moles) of sodamide in 150 cc. of dry benzene was added 117 g. (1.0 mole) of benzylnitrile during a period of 10 minutes with vigorous stirring. The mixture was stirred and refluxed for three hours. The heat was then removed and 163.0 g. (1.0 mole) of bromocyclohexane in 150 cc. of dry benzene was added at such a rate as to maintain a vigorous reflux. Stirring and refluxing were continued for eight hours. The reaction mixture was cooled and 250 cc. of water added. The water layer was discarded and the benzene removed from the organic phase by distillation. The residue was distilled *in vacuo* and 150 g. (75%) of product collected, b.p. 128–130° (0.2 mm.); m.p. 56–58°.[15]

Phenylcyclohexylacetic Acid.—The general procedure of Weston[16] was followed in the hydrolysis of the α-cyclohexylbenzylnitrile to phenylcyclohexylacetic acid. The latter was obtained in a 92% yield, m.p. 153–154°.[17] A mixed m.p. with an authentic sample of phenylcyclohexylacetic acid obtained from the hydrogenation procedure of Hoffmann[17] showed no depression.

Phenylcyclohexylglycolic Acid.—A hot (100°) solution of 22.8 g. (0.10 mole) of benzilic acid in 150 cc. of glacial acetic acid was hydrogenated at 60 lb. of hydrogen with an initial amount of 1.0 g. of platinum oxide. The hydrogenation mixture had to be heated several times and additional 0.5-g. portions of catalyst added in order to complete the uptake of the required amount of hydrogen. The catalyst was then removed by filtration and the filtrate concentrated to one-third its original volume. The white precipitate was filtered, washed with water and recrystallized three times from aqueous methanol; yield 12.7 g. (54%), m.p. 161–163°.[18]

Phenylcyclopentylglycolic Acid.—This acid was prepared in 28% yield by the method of Hoffmann and Schellenberg,[18] m.p. 147–148°.

Phenylcyclopentylglycolic Acid.—This acid was prepared in 28% yield by the method of Hoffmann and Schellenberg,[18] m.p. 147–148°.

3-Pyridyl Diphenylacetate Hydrochloride.—A mixture of 9.5 g. (0.10 mole) of 3-hydroxypyridine,[19] 23.6 g. (0.10 mole) of diphenylacetyl chloride[20] and 50 cc. of dry pyridine was refluxed for eight hours, chilled and poured into 600 cc. of ice-water. The aqueous mixture was extracted with several 300-cc. portions of ether and the combined ether

(12) W. E. Bachmann, *Org. Syntheses*, **25**, 84 (1945).

(13) Generously supplied by the Quaker Oats Co., Chicago, Ill.

(14) A. A. Pavlic and H. Adkins, THIS JOURNAL, **68**, 1471 (1946).

(15) E. D. Venus-Danilova and A. I. Bol'shukin, *J. Gen. Chem. (U. S. S. R.)*, **7**, 2823 (1937); *C. A.*, **32**, 2925[4] (1938); reported m.p. 55–56°.

(16) A. W. Weston, THIS JOURNAL, **68**, 2345 (1946).

(17) K. Hoffmann and L. Panizzon, U. S. Patent 2,346,027 (1944).

(18) K. Hoffmann and H. Schellenberg, *Helv. Chim. Acta*, **30**, 292 (1947).

(19) Kindly supplied by the Nepera Chemical Co., Yonkers, N. Y.

(20) H. Staudinger, *Ber.*, **44**, 1622 (1911).

extracts dried with potassium carbonate. The ether was removed by distillation and the ester distilled *in vacuo;* b.p. 188–190° (0.5 mm.), yield 26.0 g. (96%). The free base was dissolved in 80 cc. of isopropyl alcohol and 18 cc. of 5.0 *N* ethereal hyrochloric acid added. After cooling a white, crystalline precipitate appeared which was collected by filtration and washed with cold isopropyl alcohol; yield 28 g. (96%), m.p. 151–152°. Recrystallization from isopropyl alcohol did not raise the m.p.

Anal. Calcd. for $C_{19}H_{14}ClNO_2$: Cl, 10.91; N, 4.30. Found: Cl, 10.70; N, 4.20.

The Reduction of 3-Pyridyl Diphenylacetate Hydrochloride.—An alcoholic solution of 26.0 g. (0.08 mole) of the ester was hydrogenated at a pressure of 60 lb. of hydrogen in the presence of 0.5 g. of platinum oxide. Hydrogen uptake did not stop until 0.32 mole of hydrogen had been absorbed. The hydrogenation mixture was filtered and the filtrate concentrated *in vacuo*. The residue was suspended in 300 cc. of anhydrous ether and the mixture refluxed for one hour. The ether insoluble material was filtered, the solid dissolved in water and the aqueous solution saturated with potassium hydroxide. The ethereal extracts yielded 3 g. of piperidine on distillation. The hydrochloride was prepared and melted at 248–250°. A mixed m.p. with an authentic sample of piperidine hydrochloride showed no depression.

The ethereal filtrate was concentrated to dryness and 15 g. of a white precipitate recovered. The latter was suspended in 200 cc. of petroleum ether, the mixture refluxed for one hour, filtered hot and 6.6 g. of insoluble material isolated, m.p. 142–146°. On recrystallization from isopropyl alcohol the m.p. of the solid was raised to 146–148°. A mixed m.p. with an authentic sample of diphenylacetic acid showed no depression.

The petroleum ether filtrate was cooled in an ice–acetone-bath and 6.0 g. of a white, crystalline solid collected by filtration, m.p. 58–60°. The m.p. was raised to 60–60.5° after recrystallization from petroleum ether. The mixed m.p. of this material with an authentic sample of 2,2-diphenylethanol was 37–53°. A mixed m.p. with an authentic sample of ethyl diphenylacetate showed no depression.

2,2-Diphenylethanol.—Diphenylacetic acid was reduced with lithium aluminum hydride[21] to the alcohol[22] in 77% yield, m.p. 58–59°.

Ethyl Diphenylacetate.—Diphenylacetyl chloride was added to an excess of sodium ethoxide in absolute alcohol, the solution heated for a few minutes and then drowned in ice-water. The insoluble ester[23] was obtained in 80% yield, m.p. 59–60°.

3-Pyridyl Diphenylacetate Methiodide.—An anhydrous ether solution containing 5.0 g. (0.013 mole) of pyridyl diphenylacetate and 15.0 g. (0.105 mole) of methyl iodide was allowed to stand in the dark for two weeks. The yellow precipitate was collected by filtration; yield 2.1 g. (37%), m.p. 126–128°. *Anal.* Calcd. for $C_{20}H_{18}NO_2I$: I, 29.50. Found: I, 29.33.

The Synthesis of N-Alkyl-3-piperidyl Esters.—Three general procedures for the preparation of the piperidyl esters are described below.

Procedure A. N-Ethyl-3-piperidyl Diphenylacetate Hydrochloride.—A mixture of 46.0 g. (0.20 mole) of diphenylacetyl chloride, 25.8 g. (0.20 mole) of N-ethyl-3-hydroxypiperidine and 100 cc. of dry pyridine was refluxed for four hours, drowned in 800 cc. of ice-water and the aqueous phase extracted repeatedly with ether. The combined ether extracts were dried with potassium carbonate, the ether removed by distillation and the residue distilled *in vacuo*, b.p. 191–192° (0.18 mm.); yield 52.0 g. (80%).

To 51.0 g. (0.16 mole) of the basic ester dissolved in 250 cc. of isopropyl alcohol was added 30 cc. of a 5.3 *M* ethereal hydrochloric acid solution. The ester hydrochloride crystallized on cooling and was collected by filtration; yield 51.0 g. (90%), m.p. 195–196°.

Procedure B. N-Ethyl-3-piperidyl Benzilate Hydrochloride.—A solution containing 47.0 g. (0.207 mole) of benzilic acid, 30.5 g. (0.207 mole) of N-ethyl-3-chloropiperidine[7] in 130 cc. of dry isopropyl alcohol was refluxed for 72 hours, the solvent removed by distillation *in vacuo* and the residue drowned in 200 cc. of water. The aqueous mixture was acidified with concd. hydrochloric acid and extracted repeatedly with ether to remove any unreacted acid. The aqueous layer was then made alkaline with 12 g. of sodium hydroxide and extracted repeatedly with ether. The ether extracts were combined and dried with potassium carbonate. The product was collected by distillation *in vacuo;* b.p. 207–208° (0.5 mm.), yield 49.0 g. (73%).

To 49.0 (0.15 mole) of the ester base in 100 cc. of acetone was added an equivalent amount of ethereal hydrochloric acid. The product precipitated immediately and was collected by filtration; yield 50.0 g. (92%), m.p. 187–188°. After recrystallization from ethyl alcohol the m.p. was raised to 189–190°.

Method C. N-Methyl-3-piperidyl-1-phenylcyclohexylcarboxylate.—A mixture of 21.0 g. (0.091 mole) of ethyl phenylcyclohexylcarboxylate,[9] 17.0 g. (0.16 mole) of N-methyl-3-hydroxypiperidine, 0.3 g. of sodium and 100 cc. of dry xylene was heated at 165° in an oil-bath. Water and xylene were distilled slowly during a period of 16 hours. Water, xylene and excess aminoalcohol were distilled *in vacuo*. The residue was suspended in water, acidified with concd. hydrochloric acid and the aqueous acid suspension extracted several times with ether. The aqueous layer was made strongly alkaline with potassium hydroxide and extracted with ether. The ether extract was dried with potassium carbonate, the ether removed by distillation and unreacted aminoalcohol distilled at 5 mm. The residue was dissolved in anhydrous ether and acidified with ethereal hydrochloric acid. The precipitate was filtered and recrystallized from isopropyl alcohol yielding 3.6 g. (11%) of the desired ester hydrochloride, m.p. 215–216°.

Formation of Quaternary Ammonium Salts. N-Ethyl-3-piperidyl Diphenylacetate Methobromide.—Into 15.0 g. (0.046 mole) of the basic ester dissolved in 100 cc. of abs. alcohol was passed 15.0 g. (0.16 mole) of methyl bromide. The solution was allowed to stand at room temperature for three days and then concentrated to dryness *in vacuo*. The yellow oily residue was extracted several times with anhydrous ether to remove any unreacted basic ester. The ether washings were discarded and the oil crystallized from 150 cc. of methyl ethyl ketone; yield 10.0 g. (56%), m.p. 167–168°.

Structure Proof of N-Ethyl-3-piperidyl Benzilate Hydrochloride.—An alcoholic solution of 3.76 g. (0.01 mole) of the ester hydrochloride obtained from the reaction of benzilic acid and N-ethyl-3-chloropiperidine and 16.0 g. (0.30 mole) of potassium hydroxide was refluxed for 24 hours. The reaction mixture was clarified by filtration, acidified with concd. hydrochloric acid and the alcohol removed by distillation *in vacuo*. The residue was drowned in water and the aqueous mixture extracted with ether. The aqueous layer was saturated with potassium hydroxide, extracted with ether and the ethereal extracts dried with potassium carbonate. The ether was removed by distillation and the aminoalcohol distilled *in vacuo*, b.p. 86–88° (12 mm.); yield 1.2 g. The benzoate hydrochloride of the aminoalcohol was prepared, m.p. 198–199°. A mixed m.p. with an authentic sample of N-ethyl-3-piperidyl benzoate hydrochloride showed no depression.

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(22) Ramart-Lucas, *Compt. rend.*, **189**, 802 (1929); *C. A.*, **24**, 843 (1930); reported m.p. 61–62°.

(23) D. Vorlaender and E. Rack, *Ber.*, **56**, 1126 (1923); reported m.p. 59–60°.