ing point to 92–93°. The characteristic ester band at 5.81 μ was observed in the infrared spectrum.

Anal. Calcd. for $C_{25}H_{42}N_2O_6$: C, 66.64; H, 9.40. Found: C, 66.77; H, 9.26.

DL-*threo*-2-Dichloroacetamido-1-(*p*-nitrophenyl)-1-O-palmityl-1,3-propanediol (VII).—A suspension of 6.1 g. (0.0125 mole) of VI in 100 ml. of dry benzene with 3.0 g. (0.0125 mole) of dichloroacetic anhydride was heated at reflux for 16 hours. After filtration, the filtrate was evaporated *in vacuo* to a sirup which was taken up in a small volume of isopropyl alcohol and diluted with petroleum ether. After cooling at 5° overnight, 1.3 g. (19%) of white solid, m.p. 70–75°, was recovered. Recrystallization from ethanol raised the melting point to 88–89°. The melting point of a sample admixed with DL-chloramphenicol palmitate was depressed to 80–82°; E^1_1 185 at 264.5 mμ (in ethanol).

Anal. Calcd. for $C_{27}H_{42}Cl_2N_2O_6$: C, 57.75; H, 7.54. Found: C, 57.52; H, 7.23.

D-(−)-*threo*-2-Dichloroacetamido-1-(*p*-nitrophenyl)-1-O-palmityl-1,3-propanediol.—A solution of 9 g. (0.0185 mole) of D–O′ ester in 75 ml. of dry N,N-dimethylformamide was stirred while 3 g. (0.0204 mole) of dichloroacetyl chloride was added dropwise. After standing for 12 hours, the reaction mixture was poured into ether–sodium carbonate solution. The ether layer, after shaking, was separated, dried and evaporated *in vacuo*. The resulting sirup was taken up in hot xylene. Cooling caused the separation of 1.5 g. of the active form of amide V. The filtrate was diluted with petroleum ether and cooled to cause the separation of 1.5 g. (18%) of white solid, m.p. 101–102°. The solid was recrystallized from xylene to a melting point of 105–106°; E^1_1 179 at 267.3 mμ (in ethanol); $[\alpha]^{26}_D$ −39.5° (2% in ethyl acetate).

Anal. Calcd. for $C_{27}H_{42}Cl_2N_2O_6$: C, 57.75; H, 7.54. Found: C, 57.18; H, 7.79.

DETROIT, MICHIGAN

[CONTRIBUTION FROM THE COLLEGE OF PHARMACY, UNIVERSITY OF MICHIGAN]

Antispasmodics. XIX. Esters of 1-Methyl-2-(hydroxymethyl)-pyrrolidine and 1-Methyl-2-(hydroxymethyl)-piperidine

BY F. F. BLICKE AND CHI-JUNG LU[1,2]

RECEIVED MARCH 16, 1954

Salts of the diphenylacetate, benzilate, β-methyltropate and *p*-aminobenzoate of 1-methyl-2-(hydroxymethyl)-pyrrolidine and also the hydrochloride and methobromide of (1-methyl-2-pyrrolidyl)-methyl benzhydryl ether were prepared. The hydrochloride of the *p*-aminobenzoate of 1-methyl-2-(hydroxymethyl)-piperidine was synthesized. The hydrochlorides of the two basic alcohols underwent Mannich reactions. The pharmacological activity of some of the compounds has been reported.

Since a number of esters of basic alcohols, such as β-diethylaminoethanol, are active antispasmodics, it was of interest to prepare esters of 1-methyl-2-(hydroxymethyl)-pyrrolidine (I) and of 1-methyl-2-(hydroxymethyl)-piperidine (II). The basic alcohols I and II contain the same chain skeleton, N–C–C–OH, found in the simpler basic alcohol mentioned above.

In order to obtain the required alcohol I, diethyl glutamate was refluxed in xylene whereby it was converted into 2-carbethoxy-5-pyrrolidone; reduction of the pyrrolidone with lithium aluminum hydride yielded 2-(hydroxymethyl)-pyrrolidine. This pyrrolidine, in the form of its hydrochloride, reacted with formaldehyde and acetophenone to form the hydrochloride of the Mannich base, β-(2-hydroxymethylpyrrolidino)-propiophenone.

When 2-(hydroxymethyl)-pyrrolidine was treated with chloral,[3] the 1-formyl derivative was obtained; this substance was reduced with lithium aluminum hydride to the desired alcohol I.

Alcohol II was obtained in the following manner. α-Picoline was oxidized to α-picolinic acid which, in the form of the hydrochloride, was hydrogenated to α-pipecolinic acid hydrochloride. After esterification and reduction of the ester with lithium aluminum hydride, 2-(hydroxymethyl)-piperidine was obtained. In the form of the hydrochloride, this basic alcohol reacted with formaldehyde and acetophenone to yield the hydrochloride of the Mannich base, β-(2-hydroxymethylpiperidino)-propiophenone. 2-(Hydroxymethyl)-piperidine was converted by chloral into the 1-formyl derivative which was reduced by lithium aluminum hydride to the 1-methyl compound II.

The diphenylacetate of I was prepared by interaction of diphenylacetyl chloride with I. In order to obtain the benzilate, the alcohol I was converted into 1-methyl-2-(chloromethyl)-pyrrolidine (III) which was then allowed to react with benzilic acid according to the Horenstein–Pählicke process.[4] Since basic esters of tropic acid, in the form of salts, are often difficult to obtain in crystalline form,[5] it was decided to employ β-methyltropic acid[6] and to treat this acid with III by the Horenstein–Pählicke procedure. The hydrochloride of the ester formed, (1-methyl-2-pyrrolidyl)-methyl β-methyltropate, was obtained only as an oil but we were able to prepare the crystalline methobromide in poor yield.

Interaction of the alcohol I with diphenylbromomethane produced (1-methyl-2-pyrrolidyl)-methyl benzhydryl ether.

The hydrochlorides of the *p*-aminobenzoates of I and II were obtained by catalytic reduction of the hydrochlorides of the *p*-nitro esters.

The hydrochlorides of the diphenylacetate and the benzilate of I were tested at the Sterling–Winthrop Research Institute on the isolated rabbit in-

(1) This paper represents part of a dissertation submitted by Chi-Jung Lu in partial fulfillment of the requirements for the Ph.D. degree in the University of Michigan, 1952.

(2) American Foundation for Pharmaceutical Education Fellow.

(3) F. F. Blicke and Chi-Jung Lu, THIS JOURNAL, **74**, 3933 (1952).

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

(5) Unsuccessful attempts have been made in three different laboratories to obtain a crystalline salt of β-diethylaminoethyl tropate. See J. von Braun, O. Braunsdorf and K. Rath, THIS JOURNAL, **55**, 1666 (1922); R. R. Burtner and J. W. Cusic, *ibid.*, **65**, 262 (1943); H. Raffelson, Dissertation, University of Michigan, 1951, p. 69.

(6) This acid can be prepared readily by the use of the Ivanov reaction. See A. W. Weston and R. W. DeNet, THIS JOURNAL, **73**, 4221 (1951); F. F. Blicke and H. Raffelson, *ibid.*, **74**, 1730 (1952).

testine against acetylcholine-induced spasm. The maximum effective dilution for the former ester was found to be 1:870,000 and for the latter 1:54,000,000 (for atropine about 1:50,000,000).

The hydrochloride and methobromide of the benzhydryl ether of I were examined in The Wm. S. Merrell Company laboratories. The maximum effective dilution for both salts against acetylcholine was 1:3,000. Against barium chloride-induced spasm, the effectiveness of the hydrochloride is expressed by 1:100,000 and that of the methobromide by 1:<10,000 (papaverine, 1:100,000).

The hydrochlorides of the *p*-aminobenzoate of II and the Mannich base obtained from II were tested in the Parke, Davis and Company laboratories for local anesthetic activity on the rabbit cornea. Both compounds produced irritation and were not very active.

Experimental

β-(2-Hydroxymethylpyrrolidino)-propiophenone Hydrochloride.—A mixture of 5.5 g. of 2-(hydroxymethyl)-pyrrolidine hydrochloride,[7] 4.8 g. of acetophenone, 1.5 g. of paraformaldehyde, 20 cc. of absolute ethanol and a few drops of concentrated hydrochloric acid was refluxed for 12 hours. The solvent was removed under reduced pressure, the residue was covered with ether and placed in a refrigerator. After the product had become crystalline, it was recrystallized from isopropyl alcohol; yield 3.5 g. (32%), m.p. 135–136°.

Anal. Calcd. for $C_{14}H_{20}O_2NCl$: N, 5.19; Cl, 13.14. Found: N, 5.22; Cl, 13.07.

1-Formyl-2-(hydroxymethyl)-pyrrolidine.—2-(Hydroxymethyl)-pyrrolidine (45 g.) and 66 g. of chloral were allowed to react in the described manner[3]; yield 54 g. (93%), b.p. 122–124° (0.5 mm.).

Anal. Calcd. for $C_6H_{11}O_2N$: N, 10.84. Found: N, 10.74.

1-Methyl-2-(hydroxymethyl)-pyrrolidine.—Lithium aluminum hydride (16 g.), in 500 cc. of ether, was used to reduce 53 g. of the formyl derivative, dissolved in 250 cc. of ether, yield 38.5 g. (82%), b.p. 67–69° (12 mm.).

The methiodide melted at 293–294° dec. after recrystallization from isopropyl alcohol.

Anal. Calcd. for $C_7H_{16}ONI$: N, 5.45; I, 49.36. Found: N, 5.35; I, 49.14.

(1-Methyl-2-pyrrolidyl)-methyl Benzhydryl Ether.—A mixture of 8.0 g. of 1-methyl-2-(hydroxymethyl)-pyrrolidine, 17.3 g. of diphenylbromomethane and 9.6 g. of anhydrous potassium carbonate was stirred and heated in a nitrogen atmosphere at 150–160° (bath temperature) for 4 hours. After the addition of water, the mixture was extracted with ether and the extract was shaken with 5% hydrochloric acid. The acidic solution was made alkaline, the precipitated product was extracted with ether, the extract was dried over magnesium sulfate, the solvent was removed and the residue was fractionated; b.p. 114–117° (0.01 mm.), yield 11.7 g. (60%).

The hydrochloride melted at 177–178° after recrystallization from isopropyl alcohol.

Anal. Calcd. for $C_{19}H_{24}ONCl$: N, 4.41; Cl, 11.15. Found: N, 4.59; Cl, 11.08.

(7) The base of this compound was obtained by reduction of 2-carbethoxy-5-pyrrolidone with lithium aluminum hydride in 56% yield; b.p. 96–98° (14 mm.); reported b.p. 90–140° (10 mm.) (P. Karrer and P. Porfmann, *Helv. chim. Acta*, **31**, 2088 (1948)). The methiodide melted at 286–288° dec. after recrystallization from isopropyl alcohol. *Anal.* Calcd. for $C_6H_{14}ONI$: N, 5.76; I, 52.20. Found: N, 5.70; I, 52.03. The hydrochloride melted at 57–58° after recrystallization from isopropyl alcohol–ethyl acetate. Inadvertently, the total amount of the salt was used for other experiments before a sample could be reserved for analysis. The required 2-carbethoxy compound was obtained in 65% yield when the ester (E. Fischer and R. Baehner, *Ber.*, **44**, 1332 (1911)), obtained from glutamic acid, was refluxed for 12 hours in xylene.

The methobromide melted at 140–141° after recrystallization from isopropyl alcohol.

Anal. Calcd. for $C_{20}H_{26}ONBr$: N, 3.72; Br, 21.23. Found: N, 3.88; Br, 21.12.

(1-Methyl-2-pyrrolidyl)-methyl *p*-Nitrobenzoate Hydrochloride.—1-Methyl-2-(hydroxymethyl)-pyrrolidine (5.7 g.), 11.1 g. of *p*-nitrobenzoyl chloride and 100 cc. of benzene were refluxed for 3 hours and the mixture was then placed in a refrigerator. The precipitated hydrochloride was recrystallized from methanol; yield 13.5 g. (90%), m.p. 218–219°.

Anal. Calcd. for $C_{13}H_{17}O_4N_2Cl$: N, 9.31; Cl, 11.80. Found: N, 9.24; Cl, 11.71.

(1-Methyl-2-pyrrolidyl)-methyl *p*-Aminobenzoate Hydrochloride.—The *p*-nitro ester hydrochloride (4.1 g.), dissolved in 100 cc. of absolute ethanol, was shaken with hydrogen in the presence of 0.2 g. of platinum oxide catalyst, under an initial pressure of 50 pounds for about 1 hour after it appeared that the calculated amount of hydrogen had been absorbed. After filtration and removal of the solvent, the residue was covered with ether and placed in a refrigerator. The solidified hydrochloride was recrystallized from ethanol (yield 2.5 g.) and then from isopropyl alcohol; m.p. 175–177°.

Anal. Calcd. for $C_{13}H_{19}O_2N_2Cl$: N, 10.35; Cl, 13.11. Found: N, 10.23; Cl, 12.99.

(1-Methyl-2-pyrrolidyl)-methyl Diphenylacetate Hydrochloride.—1-Methyl-2-(hydroxymethyl)-pyrrolidine (5.7 g.), 13.6 g. of diphenylacetyl chloride and 100 cc. of benzene were refluxed for 12 hours. The solvent was removed, the residue was covered with ether and placed in a refrigerator. The partially solid product (10.2 g.) was recrystallized from isopropyl alcohol; m.p. 134–135°.

Anal. Calcd. for $C_{20}H_{24}O_2NCl$: N, 4.05; Cl, 10.26. Found: N, 3.98; Cl, 10.17.

1-Methyl-2-(chloromethyl)-pyrrolidine Hydrochloride.—A mixture of 11.5 g. of 1-methyl-2-(hydroxymethyl)-pyrrolidine, 13.1 g. of thionyl chloride and 100 cc. of benzene was refluxed for 5 hours and then placed in a refrigerator. The precipitated hydrochloride weighed 16.0 g. (94%). After recrystallization from isopropyl alcohol, with the addition of charcoal, the product weighed 12.0 g., m.p. 151–153°.

Anal. Calcd. for $C_6H_{13}NCl_2$: N, 8.23; Cl, 41.74. Found: N, 8.26, Cl, 41.55.

(1-Methyl-2-pyrrolidyl)-methyl Benzilate Hydrochloride.—A mixture of 8.0 g. of benzilic acid, 1-methyl-2-(chloromethyl)-pyrrolidine (obtained from 6 g. of the hydrochloride) and 100 cc. of isopropyl alcohol was refluxed for 4 hours. After removal of the solvent, the residue was covered with ether and placed in a refrigerator. The partially solidified product was recrystallized from isopropyl alcohol; yield 8.2 g. (63%), m.p. 160–161°.

Anal. Calcd. for $C_{20}H_{24}O_3NCl$: N, 3.87; Cl, 9.81. Found: N, 3.88; Cl, 9.82.

(1-Methyl-2-pyrrolidyl)-methyl β-Methyltropate Methobromide.—A mixture of 1-methyl-2-(chloromethyl)-pyrrolidine (obtained from 3.4 g. of the hydrochloride), 3.4 g. of β-methyltropic acid[6] and 30 cc. of isopropyl alcohol was refluxed for 4 hours. After removal of the solvent, the residue was dissolved in water, the ester base was liberated with sodium carbonate solution, extracted with ether and the extract was dried over magnesium sulfate. Excess methyl bromide was added whereupon the methobromide gradually precipitated as an oil. The oil was dissolved in isopropyl alcohol and the methobromide was precipitated by the addition of ether. After this process had been repeated a number of times, the oil became crystalline when rubbed under ether. The final yield was only 0.5 g., m.p. 137–140°.

Anal. Calcd. for $C_{17}H_{26}O_3NBr$: N, 3.76; Br, 21.46. Found: N, 3.54; Br, 21.26.

α-Pipecolinic Acid Hydrochloride.—α-Picoline was oxidized to α-picolinic acid,[8] and the hydrochloride was hydrogenated by a process similar to that used to convert nicotinic into nipecotic acid.[9] From 26.5 g. of the hydrochloride, 22.0 g. (80%) of the desired product was obtained, m.p. 258–260°.[10]

(8) A. W. Singer and S. M. McElvain, THIS JOURNAL, **57**, 1137 (1935).

(9) S. M. McElvain and R. Adams, *ibid.*, **45**, 2745 (1923).

(10) A. Ladenburg (*Ber.*, **24**, 640 (1891)), m.p. 259–261°.

2-(Hydroxymethyl)-piperidine.—Ethyl α-pipecolinate[11] (19 g.), in 100 cc. of ether, was reduced with 4.8 g. of lithium aluminum hydride in 300 cc. of ether. The mixture was refluxed for 6 hours; yield 12 g. (86%), b.p. 104–106° (10 mm.),[12] m.p. 67–69°.

The hydrochloride melted at 130–132° after recrystallization from isopropyl alcohol.

Anal. Calcd. for $C_6H_{14}ONCl$: N, 9.25; Cl, 23.38. Found: N, 9.08; Cl, 23.38.

The picrate, obtained by adding an alcoholic solution of picric acid to an ethereal solution of the base, melted at 135–137°.[13]

1-Formyl-2-(hydroxymethyl)-piperidine.—2-(Hydroxymethyl)-piperidine (6.9 g.), 10 cc. of chloroform and 8.9 g. of chloral yielded 6.3 g. (73.4%) of product, b.p. 144–146° (2 mm.).

Anal. Calcd. for $C_7H_{13}O_2N$: N, 9.78. Found: N, 9.68.

1-Methyl-2-(hydroxymethyl)-piperidine.—Six grams of the formyl derivative, dissolved in 150 cc. of ether, was reduced with 2.4 g. of lithium aluminum hydride in 150 cc. of ether. The mixture was refluxed for 6 hours; yield 3.5 g. (65%), b.p. 96–98° (19 mm.).

The methiodide melted at 300–302° dec. after recrystallization from absolute ethanol.

Anal. Calcd. for $C_8H_{18}ONI$: N, 5.16; I, 46.83. Found: N, 5.07; I, 46.87.

(11) R. Willstätter, *Ber.*, **29**, 390 (1896).

(12) R. R. Renshaw, M. Ziff, B. Brodie and N. Kornblum (THIS JOURNAL, **61**, 638 (1939)), b.p. 80–83° (1 mm.).

(13) Reference 13, m.p. 128–129.5°.

(1-Methyl-2-piperidyl)-methyl *p*-Nitrobenzoate Hydrochloride.—A mixture of 3.0 g. of 1-methyl-2-(hydroxymethyl)-piperidine, 5.6 g. of *p*-nitrobenzoyl chloride and 50 cc. of benzene was refluxed for 5 hours. After the mixture had been cooled in a refrigerator, the precipitate was filtered and washed with ether; yield 7.4 g. (90%), m.p. 192–193°, after recrystallization from absolute ethanol.

Anal. Calcd. for $C_{14}H_{19}O_4N_2Cl$: N, 8.91; Cl, 11.27. Found: N, 8.83; Cl, 11.10.

(1-Methyl-2-piperidyl)-methyl *p*-Aminobenzoate.—The nitro ester hydrochloride (3.1 g.) was reduced in the described manner; yield 2.5 g. (80%), m.p. 221–222° after recrystallization from methanol.

Anal. Calcd. for $C_{14}H_{21}O_2N_2Cl$: N, 9.85; Cl, 12.43. Found: N, 9.74; Cl, 12.40.

β-(2-Hydroxymethylpiperidino)-propiophenone Hydrochloride.—A mixture of 1.7 g. of 2-(hydroxymethyl)-piperidine hydrochloride, 0.9 g. of paraformaldehyde, 1.8 g. of acetophenone and 20 cc. of acetic acid was refluxed for 4 hours. The solvent was removed under reduced pressure, the residue was washed with ether, dissolved in water, the solution was made alkaline and the precipitate was extracted with ether. The extract was dried over magnesium sulfate and then treated with hydrogen chloride; the precipitate weighed 1.7 g. (50%), m.p. 191–192° after recrystallization from isopropyl alcohol.

Anal. Calcd. for $C_{15}H_{22}O_2NCl$: N, 4.93; Cl, 12.51. Found: N, 4.86; Cl, 12.43.

ANN ARBOR, MICHIGAN

[CONTRIBUTION FROM THE COLLEGE OF PHARMACY, UNIVERSITY OF MICHIGAN]

Antispasmodics. XX. Basic 1,3-Dioxolanes and 1,3-Dioxanes

BY F. F. BLICKE AND G. R. TOY[1]

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The preparation and antispasmodic activity of several 4-substituted 2,2-diphenyl- and 2-substituted 4,5-diphenyl-1,3-dioxolanes as well as of 5-substituted 2,2-diphenyl-5-methyl-1,3-dioxanes have been reported. In most instances the substituent was a (1-hexamethylenimino)-methyl or a (4-methyl-1-hexamethylenimino)-methyl group.

Earlier publications dealt with the preparation of basically-substituted 2,2-diphenyl-1,3-dioxolanes (I)[2,3] and 2,2-diphenyl-5-methyl-1,3-dioxanes (II).[4a,b] During this investigation we prepared compounds of types I and II and also basically substituted 4,5-diphenyl-1,3-dioxolanes (III) in which the basic substituent was a 1-hexamethylenimino or a 4-methyl-1-hexamethylenimino radical.

Interaction of 2,2-diphenyl-4-bromomethyl-1,3-dioxolane[2] with hexamethylenimine or 4-methylhexamethylenimine yielded compounds of type I. 2,2-Diphenyl-5-methyl-5-iodomethyl-1,3-dioxane[4a] reacted with the imines mentioned to form compounds of type II.

When hydrobenzoin was heated with bromoacetal, and the alcohol formed during the reaction was removed by distillation, 2-bromomethyl-4,5-diphenyl-1,3-dioxolane was obtained. Amination of this substance with piperidine, hexamethylenimine and 4-methylhexamethylenimine, respectively, produced compounds of type III.

The dioxolanes (Table I) and dioxanes were tested in The Wm. S. Merrell Company laboratories on the isolated rabbit jejunum against acetylcholine-induced spasm. The minimum effective concentrations were found to be as follows: 1:310,000 for 1 and 3; 1:200,000 for 4; 1:100,000 for 2 and 10; 1:31,000 for 5, 8 and 9; 1:10,000 for 6 and 7 (1:80,000,000 for atropine). The following minimum effective concentrations were found for barium chloride-induced spasm: 1:1,000,000 for 3; 1:500,000 for 4; 1:310,000 for 9 and 10; 1:31,000 for 1, 2, 5, 6 and 8; 1:10,000 for 7 (1:100,000 for papaverine).

Experimental

2-Bromomethyl-4,5-diphenyl-1,3-dioxolane.—A mixture of 21.4 g. of hydrobenzoin[5] and 19.7 g. of bromoacetal[6] was heated in a small distillation flask at 135–150° for 2 hours. During this time 9.2 g. (100%) of ethanol distilled from the mixture. The residue was recrystallized from 50 cc. of isopropyl alcohol with the addition of charcoal; yield 29.0 g. (91%), m.p. 89–90°.

Anal. Calcd. for $C_{16}H_{15}O_2Br$: Br, 25.04. Found: Br, 25.37.

The manner in which the compounds (1–8) listed in Table I were obtained is illustrated by the following procedure. The yields of the bases varied from 70–91%.

2,2-Diphenyl-4-(1-hexamethyleniminomethyl)-1,3-dioxolane Hydrochloride (1) and Methobromide (2).—A mixture of 25.0 g. (0.078 mole) of 2,2-diphenyl-4-bromomethyl-1,3-dioxolane,[2] 100 cc. of toluene and 39.6 g. (0.4 mole) of hexa-

(1) The Wm. S. Merrell Company Fellow.

(2) F. F. Blicke and F. E. Anderson, THIS JOURNAL, **74**, 1733 (1952).

(3) F. F. Blicke and E. L. Schumann, *ibid.*, **74**, 2613 (1952).

(4) (a) F. F. Blicke and E. L. Schumann, *ibid.*, **76**, 1226 (1954); (b) *ibid.*, **76**, 3153 (1954).

(5) J. S. Buck and S. S. Jenkins, *ibid.*, **51**, 2163 (1929).

(6) S. M. McElvain and D. Kundiger, *Org. Syntheses*, **23**, 8 (1943).