[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, COLLEGE OF PHARMACY, UNIVERSITY OF ILLINOIS]

Synthesis of Reserpine Analogs[1,2]

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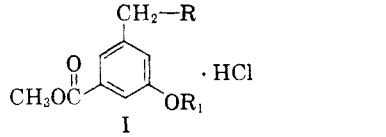
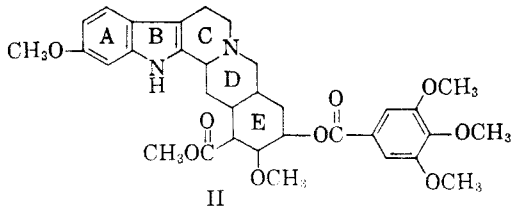
Esters of methyl 3-hydroxy-5-piperidinomethylbenzoate and of methyl 3-hydroxy-5-diethylaminomethylbenzoate were prepared and subjected to pharmacological testing. These compounds, resembling in structure a portion of the reserpine molecule, failed to show appreciable pharmacological activity. Esters of 3-piperidinomethylphenol, 3-diethylaminomethylphenol, 3-piperidinomethylbenzoic acid, and 3-diethylaminobenzoic acid were also prepared and were without pharmacological activity. All compounds were obtained as their hydrochlorides.

Esters of methyl 3-hydroxy-5-piperidinomethylbenzoate and of methyl 3-hydroxy-5-diethylaminomethylbenzoate (I) may be regarded as analogs of a portion of the reserpine molecule (II). The above



I



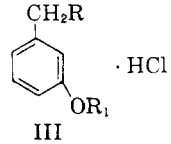
II

Ia. R = piperidino, R_1 = acetyl
Ib. R = diethylamino, R_1 = benzoyl
Ic. R = piperidino, R_1 = 3,4,5-trimethoxybenzoyl
Id. R = diethylamino, R_1 = 3,4,5-trimethoxybenzoyl

compounds possess ring E of the reserpine molecule as an aromatic ring, a portion of ring D, and all or a portion of ring C. The aromatic ring is substituted similarly to ring E of the reserpine molecule, except that the C-17 methoxyl group has been omitted. The presence of this group was deemed unnecessary to pharmacological activity since 17-desmethoxydeserpidine[3] has been shown to possess both the hypotensive and tranquilizing action of the naturally occurring alkaloids. The indole ring system, absent in the reportedly active diethylaminopropyl ester of 3,4,5-trimethoxybenzoic acid,[4] was also omitted.

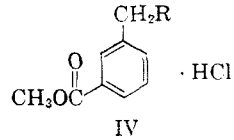
In an attempt to prepare compounds of simple chemical structure that possess both the tranquilizing and hypotensive activity of reserpine, the acetic acid ester (Ia) and the 3,4,5-trimethoxybenzoic acid ester (Ic) of methyl 3-hydroxy-5-piperidinomethylbenzoate, the benzoic acid ester (Ib) and the 3,4,5-trimethoxybenzoic acid ester (Id) of methyl 3-hydroxy-5-diethylaminomethylbenzoate were prepared as their hydrochlorides.

In the hope of observing the effects of further modification of molecular structure upon pharmacological activity, similar esters of 3-piperidinomethylphenol (IIIa and IIIc) and 3-diethylaminomethylphenol (IIIb and IIId), as well as the methyl esters of 3-piperidinomethylbenzoic acid (IVa) and 3-diethylaminomethylbenzoic acid (IVb), were also synthesized as their hydrochlorides.



III

IIIa. R = piperidino, R_1 = acetyl
IIIb. R = diethylamino, R_1 = acetyl
IIIc. R = piperidino, R_1 = 3,4,5-trimethoxybenzoyl
IIId. R = diethylamino, R_1 = 3,4,5-trimethoxybenzoyl



IV

IVa. R = piperidino
IVb. R = diethylamino

The esters of the 3-(*N*-substituted)aminomethylphenol (III) were prepared by photobrominating *m*-cresyl acetate to yield slightly impure 3-bromomethylphenyl acetate. This compound when reacted with piperidine or diethylamine yielded 3-piperidinomethylphenyl acetate and 3-diethylaminomethylphenyl acetate, respectively. The 3,4,5-trimethoxybenzoyl derivatives were prepared from the corresponding acetyl compounds by hydrolysis followed by esterification with 3,4,5-trimethoxybenzoyl chloride in a two phase Schotten-Baumann reaction.

The methyl esters of 3-(*N*-substituted)aminomethylbenzoic acids were similarly prepared from methyl *m*-toluate.

Esters of methyl 3-hydroxy-5-diethylaminomethylbenzoic acid and methyl 3-hydroxy-5-piperidinomethylbenzoic acid were somewhat more difficult to prepare and required the synthesis of 3-hydroxy-5-methylbenzoic acid (VII). The preparation of this

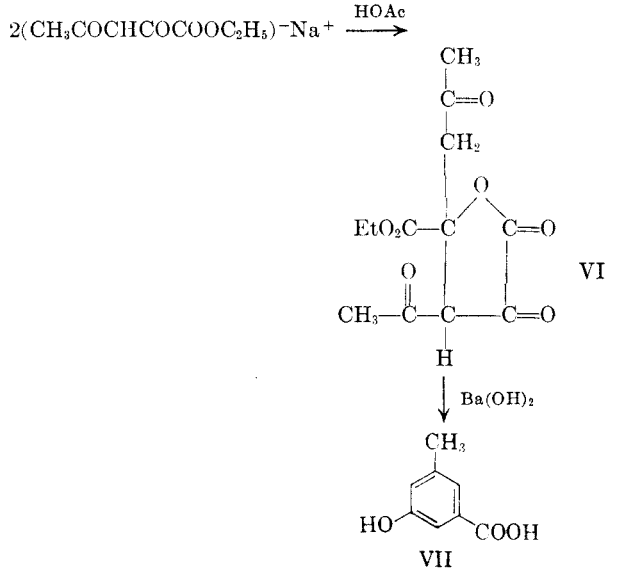
(1) Presented before the Medicinal Division at the 134th Meeting of the American Chemical Society, Chicago, Ill., September 1958.

(2) Abstracted from a thesis submitted by Fred A. Turner to the faculty of the University of Illinois in partial fulfillment of the requirement for the degree of Master of Science.

(3) F. Weisenborn, *J. Am. Chem. Soc.*, **79**, 4818 (1957).

(4) F. M. Miller and M. S. Weinberg, abstracts of papers, 130th Meeting, American Chemical Society, Atlantic City, N. J., Sept. 16–21, 1956.

compound from ethyl sodioacetopyruvate (V) by the following series of reactions was first reported by Claisen.[5] Unfortunately specific directions for carrying out the reactions which were later reported by Meldrum and Perkins[6] did not prove to be satisfactory for the synthesis of relatively large amounts of the compound. Difficulty was encountered in the isolation of Claisen's compound (VI) from the acetic acid used in its preparation. It was only after acetic acid was replaced with a mixture of equal volumes of water and acetic acid that a satisfactory yield of the compound was obtained. Conversion of Claisen's compound (VI) to 3-hydroxy-5-methylbenzoic acid (VII) also proved difficult. While Meldrum and Perkins reported that satisfactory yields of this acid were obtained by warming Claisen's compound with an aqueous suspension of barium hydroxide, we were able to obtain yields of only 20% of the theoretical. In attempts to substitute barium oxide, calcium oxide, and magnesium oxide for the prescribed barium hydroxide, magnesium oxide proved to be the most effective giving yields up to 50% of the theoretical.



VI

VII

In the preparation of the desired reserpine analogs, 3-hydroxy-5-methylbenzoic acid was then esterified with methyl alcohol, and the resulting ester acetylated. This diester was photobrominated to give slightly impure methyl 3-acetoxy-5-bromomethylbenzoate. When either diethylamine or piperidine was treated with methyl 3-acetoxy-5-bromomethylbenzoate, the products were methyl 3-hydroxy-5-diethylaminomethylbenzoate and methyl 3-hydroxy-5-piperidinomethylbenzoate rather than the expected acetyl derivatives. These compounds were identified as their hydrochlorides.

Attempts to prepare the acetate and the 3,4,5-trimethoxybenzoates of methyl 3-hydroxy-5-diethylaminomethyl or methyl 3-hydroxy-5-piperidinomethylbenzoate by a two phase Schotten-Baumann reaction failed, probably due to the hydrolysis of the carbomethoxyl group. Esterification was accomplished by warming the phenolic compounds with acetic anhydride and pyridine or with 3,4,5-trimethoxybenzoyl chloride and pyridine. Acetylation of methyl 3-hydroxy-5-diethylaminomethylbenzoate followed by treatment with hydrogen chloride yielded an oil which would not crystallize. In order to obtain a solid derivative for pharmacological testing the benzoate was prepared from benzoyl chloride in the presence of pyridine. None of these compounds when subjected to pharmacological testing showed appreciable pharmacological activity.

(5) L. Claisen, *Ber.*, **22**, 3271 (1889).

(6) A. N. Meldrum and W. H. Perkins, *J. Am. Chem. Soc.*, **95**, 1889 (1909).

EXPERIMENTAL[7]

γ-Lactone of 2,6-diketo-3-acetyl-4-carboethoxy-4-hydroxyheptanoic acid (Claisen's compound). A mixture of 321 g. (1.78 mol.) of ethyl sodioacetopyruvate,[8] 400 ml. of acetic acid, and 400 ml. of water was stirred for 2 hr. During this time the solid dissolved and the solution became gray. The contents of the flask was poured over 1 kg. of crushed ice in 150 ml. of sulfuric acid. The resulting acid, which was filtered and washed with cold water, weighed 205 g. (80%). It melted after recrystallization from water at 89–91°, lit. 90°.[5]

3-Hydroxy-5-methylbenzoic acid. To 1.5 l. of water, previously warmed on a steam bath, were added with stirring 190 g. (0.660 mol.) of Claisen's compound and 120 g. (3.0 mol.) of magnesium oxide. The mixture immediately became a deep reddish orange color which turned light brown in about 15 min. The stirring and heating was continued for about 30 min. after the addition of the solids.

The magnesium oxalate and excess magnesium oxide were removed by filtration, washed with warm water, and the filtrate was concentrated under vacuum to 200 ml. This concentrated solution was placed in an ice bath and treated with 150 ml. of 1:1 hydrochloric acid to precipitate the crude 3-hydroxy-5-methylbenzoic acid. The solid was filtered and washed with cold water. After recrystallization from water, 42.3 g. (42%) of a white solid melting at 206–207° was obtained (lit. 207–208°).[5]

Methyl 3-hydroxy-5-methylbenzoate. A solution of 41.6 g. (0.27 mol.) of 3-hydroxy-5-methylbenzoic acid, 100 ml. of methanol, and 10.0 ml. of sulfuric acid was refluxed on a steam bath for 5 hr. The excess methanol was removed by distillation and the residue was poured over 300 g. of crushed ice to precipitate the ester. The excess sulfuric acid was neutralized by the addition of sodium bicarbonate. The methyl 3-hydroxy-5-methylbenzoate was collected by filtration and washed with cold water. After drying, 41.5 g. (91%) of crude product was obtained. Upon recrystallization from ethanol-water, the white solid melted at 96–97°. The reported melting point is 97°.[9]

Methyl 3-acetoxy-5-methylbenzoate. A mixture of 41.5 g. (0.25 mol.) of methyl 3-hydroxy-5-methylbenzoate, 85 ml. of acetic anhydride, and 5 ml. of phosphoric acid was heated on a steam bath for 15 min. Then 100 ml. of water was carefully added to the hot solution to destroy the excess acetic anhydride. The resulting solution was poured over 500 g. of cracked ice to yield an oil which solidified after scratching

(7) All melting points are uncorrected. The carbon and hydrogen analyses were performed by Weiler and Strauss Analytical Laboratories, Oxford, England.

(8) *Org. Syntheses*, **Coll. Vol. I**, 238 (1941).

(9) E. Bernatek, *Acta Chem. Scand.*, **5**, 1318 (1951).

the side of the beaker. The solid was collected by filtration and washed with cold water. The crude methyl 3-acetoxy-5-methylbenzoate was purified by distillation under reduced pressure. A colorless oil boiling at 105–110°/0.2 mm. was obtained. It crystallized upon cooling. Yield 46.5 g. (91%). A sample after recrystallization from ethanol-water melted at 67°.

Anal. Calcd. for $C_{11}H_{12}O$: C, 63.45; H, 5.81. Found: C, 63.65; H, 5.64.

Photobromination of methyl 3-acetoxy-5-methylbenzoate. A 500-ml. ground glass three necked flask was equipped with an addition funnel containing 100 ml. of a 2*M* bromine solution in carbon tetrachloride and a reflux condenser connected to a gas adsorption trap. The third neck was closed with a glass stopper. A 500-watt clear glass tungsten lamp was placed about 1 in. from the flask. A solution of 41.6 g. (0.2 mol.) of methyl 3-acetoxy-5-methylbenzoate in 100 ml. of carbon tetrachloride was placed in the flask and gently refluxed upon the steam bath. The bromine solution was added at such a rate that the reaction mixture just retained a red color. The reaction was completed when all of the bromine solution had been added and the red color of the reaction mixture disappeared. This required from 20–30 min. The carbon tetrachloride was removed under vacuum and the residue was fractionally distilled. A colorless viscous oil consisting chiefly of methyl 3-acetoxy-5-bromomethylbenzoate was obtained. Yield 34.1 g. (59%) b.p. 158–164°/0.2 mm.

Photobromination of methyl m-toluate. Thirty g. (0.2 mol.) of methyl *m*-toluate[10] was photobrominated in the same manner as described above. A colorless oil boiling between 100–109° at 0.2 mm. pressure was collected. The yield of impure methyl 3-bromomethylbenzoate was 24.3 g. (53%).

Photobromination of m-cresyl acetate. Starting from 30.0 g. (0.20 mol.) of *m*-cresyl acetate,[11] 3-bromomethylphenyl acetate was prepared in the same manner as that described for the photobromination of methyl 3-acetoxy-5-methylbenzoate. The yield of impure colorless product boiling between 98–102° at 0.2 mm. pressure was 24.5 g. (54%).

Methyl 3-hydroxy-5-piperidinomethylbenzoate hydrochloride. To a solution of 17.2 g. (0.06 mol.) of methyl 3-acetoxy-5-bromomethylbenzoate in 150 ml. of dry benzene, was added a solution of 10.2 g. (0.12 mol.) of redistilled piperidine in 150 ml. of dry benzene. Almost immediately piperidine hydrobromide precipitated. The reaction mixture was refluxed for 1 hr. and then cooled in an ice bath. The piperidine hydrobromide was removed by filtration aud washed with benzene.

The benzene was distilled under vacuum and the brown liquid residue taken up in anhydrous ether. A small amount of additional piperidine hydrobromide precipitated from the ether and was removed by filtration. After drying over anhydrous magnesium sulfate, the ether solution was treated with hydrogen chloride gas and a gummy solid was obtained. The ether was decanted and the remaining gum was then dissolved in 20 ml. of cold methanol and anhydrous ether added until a faint turbidity was produced. Upon cooling, a white crystalline solid was obtained. The solid gave a purple color with ferric chloride solution and was soluble in an excess of 10% sodium hydroxide solution indicating that the 3-acetoxy group was hydrolyzed during the reaction. The yield of methyl 3-hydroxy-5-piperidinomethylbenzoate hydrochloride was 9.9 g. (58%), m.p. 234–235° (dec.).

Anal. Calcd. for $C_{14}H_{20}O_3NCl$: C, 58.85; H, 7.06; Cl, 12.41. Found: C, 58.45; H, 7.25; Cl, 12.34.

Methyl 3-hydroxy-5-diethylaminomethylbenzoate hydrochloride. From 17.2 g. (0.06 mol.) of methyl 3-acetoxy-5-bromomethylbenzoate and 8.8 g. (0.12 mol.) of redistilled diethylamine, methyl 3-hydroxy-5-diethylaminomethylbenzoate hydrochloride was prepared in the same manner as described above. Yield 8.9 g. (54%), m.p. 177–178°.

Anal. Calcd. for $C_{13}H_{20}O_3NCl$: C, 57.02; H, 7.36; Cl, 12.95. Found: C, 56.73; H, 7.19; Cl, 12.80.

3-Piperidinomethylphenyl acetate hydrochloride (IIIa). The condensation of 10.2 g. (0.12 mol.) of piperidine and 13.7 g. (0.06 mol.) of 3-bromomethylphenyl acetate was carried out in a manner similar to that described for the preparation of methyl 3-hydroxy-5-piperidinomethylbenzoate hydrochloride. In this reaction the white crystalline hydrochloride did not give a purple color with ferric chloride solution and was insoluble in an excess of sodium hydroxide solution, indicating that hydrolysis did not occur during the reaction. The yield of 3-piperidinomethylphenyl acetate hydrochloride was 6.7 g. (41%), m.p. 215–216°.

Anal. Calcd. for $C_{14}H_{20}O_2NCl$: C, 62.34; H, 7.48; Cl, 13.15. Found: C, 62.06; H, 7.49; Cl, 13.01.

3-Diethylaminomethylphenyl acetate hydrochloride (IIIb). From 13.7 g. (0.06 mol.) of 3-bromomethylphenyl acetate and 8.8 g. (0.12 mol.) of diethylamine, 6.12 g. (39%) of 3-diethylaminomethylphenyl acetate hydrochloride was prepared following the procedure for the preparation of 3-piperidinomethylphenyl acetate hydrochloride, m.p. 172–173°.

Anal. Calcd. for $C_{13}H_{20}O_2NCl$: C, 60.56; H, 7.82; Cl, 13.75. Found: C, 60.40; H, 7.70; Cl, 13.72.

Methyl 3-piperidinomethylbenzoate hydrochloride (IVa). The reaction between 10.2 g. (0.12 mol.) of piperidine and 13.7 g. (0.06 mol.) of methyl 3-bromomethylbenzoate was carried out in a manner identical to that used for the preparation of methyl 3-hydroxy-5-piperidinomethylbenzoate hydrochloride. The yield of methyl 3-piperidinomethylbenzoate hydrochloride was 6.25 g. (38%), m.p. 214–215°. A mixed melting point with 3-piperidinomethylphenyl acetate hydrochloride showed a marked depression 187–192°.

Anal. Calcd. for $C_{14}H_{20}O_2NCl$: C, 62.34; H, 7.48; Cl, 13.15. Found: C, 61.97; H, 7.41; Cl, 13.04.

Methyl 3-diethylaminomethylbenzoate hydrochloride (IVb). Starting with 13.7 g. (0.06 mol.) of methyl 3-bromomethylbenzoate and 8.8 g. (0.12 mol.) diethylamine, methyl 3-diethylaminomethylbenzoate hydrochloride was prepared following the procedure previously described for the preparation of methyl 3-hydroxy-5-piperidinomethylbenzoate hydrochloride. Yield 8.6 g. (55%), m.p. 147–148°.

Anal. Calcd. for $C_{13}H_{20}O_2NCl$: C, 60.56; H, 7.82; Cl, 13.75. Found: C, 60.92; H, 8.03; Cl, 13.72.

3-Piperidinomethylphenol hydrochloride. Ten g. (0.037 mol.) of 3-piperidinomethylphenyl acetate and 100 ml. of a 5% solution of hydrogen chloride in methanol were refluxed for 1 hr. The excess methanol was removed by distillation and the viscous residue was dissolved in 10 ml. of methanol. Anhydrous ether was added until a faint turbidity was produced. Upon cooling, the desired 3-piperidinomethylphenol hydrochloride crystallized. Yield 7.1 g. (84%), m.p. 163–164°.

Anal. Calcd. for $C_{12}H_{18}ONCl$: C, 63.40; H, 7.98; Cl, 15.60. Found: C, 63.29; H, 8.01; Cl, 15.49.

3-Diethylaminomethylphenol hydrochloride. The methanolysis of 10.0 g. (0.39 mol.) of 3-diethylaminomethylphenyl acetate hydrochloride was carried out in a similar manner to that described above. The yield of 3-diethylaminomethylphenol hydrochloride was 6.9 g. (82%), m.p. 133–134°.

Anal. Calcd. for $C_{11}H_{18}ONCl$: C, 61.25; H, 8.41; Cl, 16.44. Found: C, 61.03; H, 8.30; Cl, 16.33.

3,4,5-Trimethoxybenzoyl chloride. The method used for the preparation of 3,4,5-trimethoxybenzoyl chloride was that of Marsh and Stephen.[12] Twenty g. (0.9 mol.) of 3,4,5-tri-

(10) P. N. Raikow and P. Tischkow, *Chem. Ztg.*, **29**, 1269 (1905).

(11) A. Claus and J. Hirsch, *J. prakt. Chem.*, (2) **39**, 62 (1889)

(12) J. T. Marsh and H. Stephen, *J. Chem. Soc.*, **127**, 1633 (1925).

methoxybenzoic acid yielded 20.4 g. (94.2%) 3,4,5-trimethoxybenzoyl chloride, m.p. 79–80°, lit. 76–78.[13]

Methyl 3-acetoxy-5-piperidinomethylbenzoate hydrochloride (Ia). To a mixture of 7.0 g. (0.025 mol.) of methyl 3-hydroxy-5-piperidinomethylbenzoate hydrochloride and 150 ml. of pyridine contained in a 250-ml. glass-stoppered flask was added 15 ml. of acetic anhydride. The mixture after shaking for 3 hr. yielded a homogeneous solution which was allowed to stand overnight at room temperature. The pyridine was removed by distillation under reduced pressure and the residue dissolved in methanol. Anhydrous ether was added to the methanol solution until a faint turbidity was produced. The product then crystallized upon cooling, to yield 6.3 g. (78%) of methyl 3-acetoxy-5-piperidinomethylbenzoate hydrochloride, m.p. 177–178°.

Anal. Calcd. for $C_{16}H_{22}O_4NCl$: C, 58.62; H, 6.77; Cl, 10.82. Found: C, 58.47; H, 6.72; Cl, 10.92.

Methyl 3-benzoyloxy-5-diethylaminomethylbenzoate hydrochloride (Ib). Five g. (0.018 mol.) of methyl 3-hydroxy-5-diethylaminomethylbenzoate hydrochloride, 150 ml. of pyridine and 5 ml. of benzoyl chloride were placed in a glass-stoppered flask, shaken for 30 min. and allowed to stand for 24 hr. at room temperature. After removal of the pyridine under pressure, the residue was dissolved in isopropyl alcohol and anhydrous ether was added to produce a faint turbidity. Upon cooling, the product crystallized and 4.7 g. (68%) of methyl 3-benzoyloxy-5-diethylaminomethylbenzoate hydrochloride was obtained, m.p. 167–168° (dec.).

Anal. Calcd. for $C_{20}H_{24}O_4NCl$: C, 63.58; H, 6.40; Cl, 9.39. Found: C, 63.28; H, 6.13; Cl, 9.50.

Methyl 3-(3′,4′,5′-trimethoxybenzoyloxy-5-piperidinomethylbenzoate hydrochloride) (Ic). A mixture of 5.0 g. (0.018 mol.) of methyl 3-hydroxy-5-piperidinomethylbenzoate hydrochloride, 8.1 g. (0.036 mol.) of 3,4,5-trimethoxybenzoyl chloride and 250 ml. of pyridine was shaken for 4 hr. The homogeneous solution was then allowed to stand at room temperature for one day. Upon the removal of the pyridine under reduced pressure, a red solid was obtained. After recrystallization of the solid from methanol and ether, 6.3 g. (75%) of colorless methyl 3-(3′,4′,5′-trimethoxybenzoyloxy)-5-piperidinomethylbenzoate hydrochloride was obtained, m.p. 202–203° (dec.).

Anal. Calcd. for $C_{24}H_{30}O_7NCl$: C, 60.05; H, 6.30; Cl, 7.39. Found: C, 59.80; H, 6.21; Cl, 7.34.

Methyl 3-(3′,4′,5′-trimethoxybenzoyloxy-5-diethylaminobenzoate hydrochloride) (Id). From 5.0 g. (0.018 mol.) of methyl 3-hydroxy-5-diethylaminomethylbenzoate hydrochloride, 8.5 g. (0.036 mol.) of 3,4,5-trimethoxybenzoyl chloride, and 250 ml. of pyridine, 4.95 g. (58%) of methyl 3-(3′,4′,5′-trimethoxybenzoxy)-5-diethylaminomethylbenzoate hydrochloride was obtained when the procedure described for the preparation of methyl 3-(3′,4′,5′-trimethoxybenzoyloxy-5-piperidinomethylbenzoate hydrochloride) was followed, m.p. 191–192°.

Anal. Calcd. for $C_{23}H_{30}O_7NCl$: C, 59.04; H, 6.46; Cl, 7.58. Found: C, 59.34; H, 6.42; Cl, 7.48.

3′-Piperidinomethylphenyl 3,4,5-trimethoxybenzoate hydrochloride (IIIc). A solution of 6.1 g. (0.026 mol.) of 3,4,5-trimethoxybenzoyl chloride in 50 ml. of ether was added to a solution of 3.0 g. (0.013 mol.) of 3-piperidinomethylphenol hydrochloride in 25 ml. of 10% sodium hydroxide and the mixture was vigorously shaken for 20 min. The ether layer was separated and the aqueous layer was extracted with two 25-ml. portions of ether which were combined with the original ether solution. The combined ether extract was washed with 20 ml. of water and dried over anhydrous magnesium sulfate. Anhydrous hydrogen chloride when passed through the ether solution produced a white solid. After recrystallization of the solid from methanol and ether, 3.5 g. (53%) of 3′-piperidinomethylphenyl 3,4,5-trimethoxybenzoate hydrochloride was obtained, m.p. 163–164°. A mixed melting point with the starting hydroxyl compound showed a marked depression (142–147°).

Anal. Calcd. for $C_{22}H_{23}O_5NCl$: C, 62.63; H, 6.69; Cl, 8.40. Found: C, 62.74; H, 6.60; Cl, 8.32.

3′-Diethylaminomethylphenyl 3,4,5-trimethoxybenzoate hydrochloride (IIId). From 2.0 g. (0.009 mol.) of 3-diethylaminomethylphenol hydrochloride, and 4.3 g. (0.018 mol.) of 3,4,5-trimethoxybenzoyl chloride, 3.0 g. (79%) of 3′-diethylaminomethylphenyl 3,4,5-trimethoxybenzoate hydrochloride was prepared in a manner analogous to that described for 3′-piperidinomethylphenyl 3,4,5-trimethoxybenzoate hydrochloride, m.p. 166–167°.

Anal. Calcd. for $C_{21}H_{28}O_5NCl$: C, 61.53; H, 6.89; Cl, 8.65. Found: C, 61.47; H, 7.29; Cl, 8.77.

Acknowledgment. The authors are grateful to Abbott Laboratories for screening the compounds for pharmacological activity.

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(13) J. Koo, *J. Am. Chem. Soc.*, **75**, 720 (1953).

[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

Some Acetate Migration and Participation Reactions in Steroids[1]

ROBERT G. SCHULTZ[2]

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In an attempt to produce cholestan-3α,5α-diol-6-one-3,5-diacetate by solvolysis of cholestan-3β,5α-diol-6-one-3-tosylate-5-acetate in dimethylformamide, water, and potassium acetate, cholestan-3α,5α-diol-6-one-3-acetate was the only product isolated. When the reaction was carried out without added potassium acetate the product was cholestan-3α,5α-diol-6-one-5-acetate. The 5-acetate rearranged to the 3-acetate by treatment with dimethylformamide, water, and potassium acetate.

In the course of other synthetic studies, it became necessary to synthesize cholestan-3α,5α-diol-6-one diacetate (I). The route selected involved as a last step solvolysis of cholestan-3β,5α-diol-6-one-3-tosylate-5-acetate (II) with potassium acetate in a dimethylformamide-water system. The tosylate (II) was synthesized as shown.

Cholesterol (III) was oxidized to cholestan-3β,5α-diol-6-one (V) in a two-step procedure described by

(1) Presented in part at the 135th Meeting of the American Chemical Society, Boston, April 1959; Abstracts p. 23-O.

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