[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE RICE INSTITUTE]

THE SYNTHESIS OF ESTERS OF 2,6-DIMETHYL-4-AMINOBENZOIC ACID

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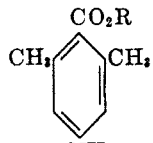
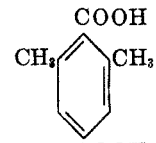
The recent discovery in plasma of an enzyme which catalyzes the hydrolysis of Novocaine to *p*-aminobenzoic acid and β-diethylaminoethanol (1) suggests that esters of *p*-aminobenzoic acid which are more difficultly hydrolyzed should exhibit a more prolonged local anesthetic effect. Such a requirement would most obviously be satisfied by *p*-aminobenzoic esters in which the ester group is sterically hindered by two *ortho* substituents. The present investigation was concerned with the synthesis of the simplest series of compounds of this type, the esters of 2,6-dimethyl-4-aminobenzoic acid (I).



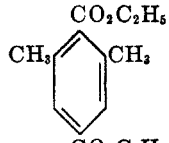
I



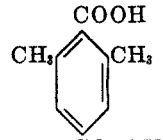
II

A synthetic sequence involving 2,6-dimethylterephthalic acid (II) as the starting material was employed. From this substance the requisite amino ester structure was obtained by esterification of the hindered carboxyl group and Curtius degradation of the unhindered carboxyl. The over-all method of synthesis, illustrated below by the preparation of the ethyl ester of the series I, therefore required the corresponding diester of II as an intermediate.

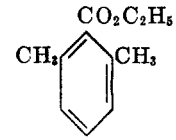
Diethyl 2,6-dimethylterephthalate (III) was prepared by several methods. Fischer esterification of II with ethanol yielded 4-carbethoxy-2,6-dimethylbenzoic acid (IV), which in turn was converted to III directly by means of Newman's procedure for the esterification of sterically hindered acids in 100% sulfuric acid. The hindered carboxyl of IV was esterified also by two classical methods.



III



IV



V

One of these involved reaction of the silver salt of the acid with ethyl iodide; the other consisted in the reaction with ethanol of the corresponding acid chloride, obtained by treatment of IV with thionyl chloride. A more direct route

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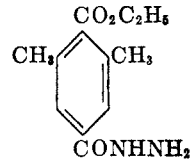
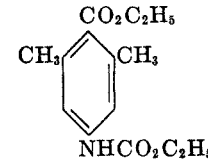
to III employed the diacid chloride of II as an intermediate. This substance could be obtained from the diacid by reaction with either phosphorus pentachloride or thionyl chloride. In the case of the latter reagent, isolation of the diacid chloride was unnecessary; the crude material underwent smooth conversion to the neutral ester on treatment with ethanol. Hydrolysis of III yielded 4-carbethoxy-3,5-dimethylbenzoic acid (V).

The diester III reacted with hydrazine to give 4-carbethoxy-3,5-dimethylbenzhydrazide (VI). Subsequent treatment of the hydrazide with nitrous acid and decomposition of the intermediate azide yielded the corresponding isocyanate, from which the ethyl urethan VII was obtained by reaction with ethanol. The final amine was then obtained by hydrolysis of the urethan.

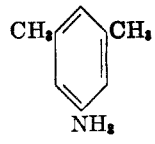


VI

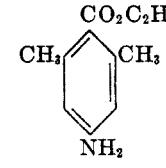


VII

The conventional method of converting a urethan to an amine which employs hydrolysis in concentrated hydrochloric acid yielded in the case of the urethan VII not the desired amino ester IX but 5-amino-1,3-dimethylbenzene (VIII). Apparently the xylidine derivative resulted from hydrolysis and decarboxylation of the hindered ester group. A similar mechanism for the elimination of the hindered carbomethoxy group of methyl mesitoate in sulfuric acid solution has been demonstrated by Schubert (2), and the ease with which 2,6-dimethyl-4-aminobenzoic acid undergoes decarboxylation in hydrochloric acid has been demonstrated by Noyes (3). Although acid hydrolysis of VII was unsatisfactory, the amino ester IX was obtained without difficulty by hydrolysis of the urethan in ethanolic potassium hydroxide.



VIII



IX

The *n*-propyl ester of the series I was prepared in a manner similar to that described above for the synthesis of the ethyl ester. Each of the hindered amino esters was characterized through its acetyl derivative. Preliminary tests on the tongue indicate that both the ethyl and *n*-propyl esters of 2,6-dimethyl-4-aminobenzoic acid appear to exhibit a significantly more prolonged local anesthetic effect than does Anesthesine, the related unhindered compound.

EXPERIMENTAL PART

Preparation of 4-carbethoxy-2,6-dimethylbenzoic acid. A solution of 0.50 g. (0.0026 mole) of 2,6-dimethylterephthalic acid, prepared according to the procedure of Hufferd and

Noyes (4), in 20 ml. of ethanol was saturated with dry hydrogen chloride and the mixture was heated under reflux for five hours; the bulk of the ethanol was then removed by distillation. To the residue, which crystallized on cooling, was added 20 ml. of water, and the precipitate was collected on a filter. The weight of the dried crude product, m.p. 145–153°, was 0.50 g. (87%). Recrystallization from dilute ethanol yielded 0.46 g. (80%) of fluffy white needles of 4-carbethoxy-2,6-dimethylbenzoic acid, m.p. 157–158°.

Anal. Calc'd for $C_{12}H_{14}O_4$: Neut. equiv., 222. Found: Neut. equiv., 220.

Sulfuric acid esterification of 4-carbethoxy-2,6-dimethylbenzoic acid. The procedure of Newman (5) was followed. From a solution of 2.41 g. (0.011 mole) of recrystallized 4-carbethoxy-2,6-dimethylbenzoic acid in 20 ml. of 100% sulfuric acid, added to 150 ml. of ethanol, there was obtained 1.8 g. (67%) of a yellow-brown oil; this crude diethyl 2,6-dimethylterephthalate was converted to the hydrazide without further purification. Acidification of the sodium carbonate extract of the crude reaction product yielded 0.7 g. (29%) of unchanged monoester.

Silver salt-ethyl iodide esterification of 4-carbethoxy-2,6-dimethylbenzoic acid. A solution of 1.7 g. (0.0076 mole) of the acid ester in dilute ethanol was neutralized to the phenolphthalein end point with 10% sodium hydroxide. Addition of 5% silver nitrate to this solution of the sodium salt resulted in the precipitation of 1.8 g. (71%) of the curdy, gray-white silver salt. The silver salt was suspended in a solution of 20 ml. of benzene and 10 ml. of ethyl iodide. After a reflux period of three hours, the clear supernatant solution was decanted from the silver iodide, the precipitate was washed with 5 ml. of ethanol, and most of the solvent was distilled from the combined filtrates. The residue was taken up in ether and extracted with 10% sodium carbonate. Evaporation of the solvent from the ether extract left 1.2 g. (88%) of a clear light-yellow oil; this crude diethyl 2,6-dimethylterephthalate was employed in the diester-hydrazine reaction. Acidification of the carbonate extract yielded 0.16 g. (13%) of the original acid ester.

Preparation of diethyl 2,6-dimethylterephthalate from 2,6-dimethylterephthalyl dichloride. (*a*) *Phosphorus pentachloride procedure.* The procedure of Bull and Fuson (6) was followed in the preparation of the diacid chloride from 2,6-dimethylterephthalic acid and phosphorus pentachloride. A solution of 1.0 g. (0.0043 mole) of the diacid chloride, b.p. 165–170° at 33 mm., 50 ml. of ethanol, and 10 ml. of benzene was heated under reflux for 16 hours. The bulk of the solvent was removed by distillation, and the residue was transferred to a Claisen flask. After the remaining low-boiling solvent had been removed at aspirator pressure, there was obtained 0.9 g. (83%) of diethyl 2,6-dimethylterephthalate, a colorless oil, b.p. 151–155° at 4 mm.

(*b*) *Thionyl chloride procedure.* In a flask fitted with a reflux condenser, calcium chloride tube, and hydrogen chloride trap there were placed 6.4 g. (0.033 mole) of 2,6-dimethylterephthalic acid and 75 ml. of Eastman practical-grade thionyl chloride. After a reflux period of eight hours, the excess thionyl chloride was distilled at the aspirator. To the yellow-white solid residue there was added 125 ml. of ethanol, and the mixture was heated under reflux for four hours. Most of the ethanol was removed by distillation, and to the residue there was added 60 ml. of water. The resulting suspension was extracted with two equal volumes of ether, and the combined ether extracts were washed with 10% sodium carbonate. Distillation of the solvent from the neutralized ether solution left 4.1 g. of a clear oily residue; the crude diester was converted to the ester hydrazide without further purification. On the assumption that all of the 2,6-dimethylterephthalyl dichloride present in the crude product of the thionyl chloride reaction gave the same 83% yield of diethyl ester afforded by the pure diacid chloride of the phosphorus pentachloride reaction, the yield of diacid chloride in the above preparation was 61%.

A completely analogous procedure was followed in the esterification with ethanol of 4-carbethoxy-2,6-dimethylbenzoic acid through its acid chloride.

Hydrolysis of diethyl 2,6-dimethylterephthalate. A solution of 0.50 g. (0.0020 mole) of the diethyl ester and 0.50 g. (0.0089 mole) of potassium hydroxide in 25 ml. of ethanol and 5 ml. of water was heated under reflux for two hours. After most of the solvent had been distilled, the basic residue was acidified, and the cheesy tan precipitate was collected on a filter.

The crude product was redissolved in 20% sodium carbonate solution and the resulting solution was decolorized with Norit; acidification of the clarified solution furnished 0.44 g. (99%) of 4-carbethoxy-3,5-dimethylbenzoic acid. Recrystallization of this product from cyclohexane yielded fluffy white needles, m.p. 129–130°.

Anal. Calc'd for $C_{12}H_{14}O_4$: Neut. equiv., 222. Found: Neut. equiv., 221.

Preparation of 4-carbethoxy-3,5-dimethylbenzhydrazide. A procedure similar to that of Curtius and Davidis (7) was followed. From 0.80 g. (0.0032 mole) of vacuum-distilled diethyl 2,6-dimethylterephthalate and a total volume of 1.2 ml. of 85% hydrazine hydrate, there was obtained 0.60 g. (80%) of crude ether-washed product, m.p. 168–171°. Recrystallization from ethanol yielded clusters of white needles, m.p. 174–175°; an additional recrystallization from benzene furnished pure 4-carbethoxy-3,5-dimethylbenzhydrazide, m.p. 175–176°.

Anal. Calc'd for $C_{12}H_{16}N_2O_3$: C, 61.00; H, 6.83.

Found: C, 60.87; H, 6.58.

Conversion of ethyl ester hydrazide to ethyl ester urethan. The generalized procedure of *Organic Reactions* (8) was employed with slight modification. The dried ether solution of the azide obtained from 1.95 g. (0.0083 mole) of 4-carbethoxy-3,5-dimethylbenzhydrazide was added to 10 ml. of toluene, and the solution was warmed on the steam-bath so that the ether slowly distilled. The remaining toluene solution was heated strongly on the steam-bath until evolution of nitrogen ceased. To the resulting solution of the isocyanate there was added 20 ml. of ethanol, and the mixture was heated under reflux for 15 hours. The toluene-ethanol solution was then evaporated under aspirator pressure; the residue consisted of 2.04 g. (93%) of crude ethyl ester urethan, part of which was oily and part crystalline.

Acid hydrolysis of ethyl ester urethan. A mixture of 1.0 g. (0.0038 mole) of the crude urethan and 15 ml. of concentrated hydrochloric acid was heated under reflux until the oily layer had disappeared; 45 hours were required. The aqueous solution was extracted with ether and then filtered, and the filtrate was saturated with hydrogen chloride. Cooling of this acidic solution resulted in the precipitation of clusters of white needles which were insoluble in ether and soluble in water. The amine hydrochloride did not melt below 300°, and resembled ammonium chloride on ignition; these are the properties of *sym-m*-xylidine hydrochloride (9). Schotten-Baumann acylation of the substance yielded an acetyl derivative, m.p. 141–142°, and a benzoyl derivative, m.p. 144–145°; both compounds were recrystallized from dilute ethanol. The mixture m.p.'s of these derivatives with authentic samples prepared from Eastman 5-amino-1,3-dimethylbenzene were not depressed. Although acetyl *sym-m*-xylidine has been described (9), the benzoyl derivative has not been reported.

Alkaline hydrolysis of ethyl ester urethan. A solution of 0.80 g. (0.0030 mole) of the crude urethan in 100 ml. of a 0.25 *N* solution of potassium hydroxide in 90% ethanol was heated under reflux for one hour. The bulk of the solvent was then distilled, until the volume of the residue was 5 ml. To this was added 25 ml. of water, and the turbid suspension was extracted with two 30-ml. portions of ether. The combined ether extracts, after drying over magnesium sulfate, were saturated with hydrogen chloride; glistening white needles and a heavy oil were precipitated. The mixture was filtered under a vacuum and the crystalline material was washed with ether; the weight of the ethyl 2,6-dimethyl-4-aminobenzoate hydrochloride, which did not melt below 300°, was 0.5 g. (72%). Evaporation of the ether from the combined filtrates left an oily residue, which appeared to be unchanged starting material. This substance could be subjected to further hydrolysis, and in this manner the yield of amino ester was nearly quantitative.

Schotten-Baumann acetylation of the above amino ester yielded an acetyl derivative which after successive recrystallization from toluene and water took the form of white needles, m.p. 140–141°. The m.p. of a mixture of this substance with the acetyl xylidine was depressed. Analysis indicated it to be the desired ethyl 2,6-dimethyl-4-acetamidobenzoate.

Anal. Calc'd for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28.

Found: C, 66.19, 66.32; H, 7.38, 7.22.

Note: The procedures employed in the preparation of the compounds of the *n*-propyl

series were similar in detail to those described above for the members of the ethyl series.

4-Carbopropoxy-2,6-dimethylbenzoic acid was obtained in 29% yield by Fischer esterification of 2,6-dimethylterephthalic acid with *n*-propyl alcohol. The product, after successive recrystallization from dilute *n*-propyl alcohol, cyclohexane, and carbon tetrachloride, consisted of small white granules, m.p. 115–119°; the main impurity appeared to be the parent dibasic acid.

Anal. Calc'd for $C_{13}H_{16}O_4$: Neut. equiv., 236. Found: Neut. equiv., 230.

Di-n-propyl 2,6-dimethylterephthalate was obtained in 65% yield by esterification of the silver salt of the above monoester with *n*-propyl bromide; an 11% yield of the original acid ester was also recovered. The intermediate silver salt was obtained in a yield of 80%. The diester was prepared in 49% yield by the reaction of *n*-propyl alcohol with 2,6-dimethylterephthalyl dichloride; the diacid chloride was obtained from the parent acid and thionyl chloride.

4-Carbopropoxy-3,5-dimethylbenzoic acid was obtained by hydrolysis of the di-*n*-propyl ester. After successive recrystallization from benzene and dilute ethanol, the substance took the form of white prisms, m.p. 110–111°.

Anal. Calc'd for $C_{13}H_{16}O_4$: Neut. equiv., 236. Found: Neut. equiv., 238.

4-Carbopropoxy-3,5-dimethylbenzhydrazide, m.p. 150–152°, was obtained from the diester in a yield of 95%. Recrystallization from benzene yielded fluffy white needles, m.p. 150–151°.

Reaction of the isocyanate obtained from the propyl ester hydrazide with ethanol furnished the corresponding urethan. Hydrolysis of the crude urethan in ethanolic potassium hydroxide yielded *n*-propyl 2,6-dimethyl-4-aminobenzoate, which was isolated as its hydrochloride and characterized through its acetyl derivative. The *n*-propyl 2,6-dimethyl-4-acetamidobenzoate, after recrystallization from toluene, consisted of clusters of white needles, m.p. 128–129°.

Anal. Calc'd for $C_{14}H_{19}NO_3$: C, 67.44; H, 7.68.
Found: C, 67.20, 67.32; H, 7.79, 7.68.

SUMMARY

The ethyl and *n*-propyl esters of 2,6-dimethyl-4-aminobenzoic acid have been synthesized and appear to exhibit a significantly more prolonged local anesthetic effect than does Anesthesine, the related unhindered ester. This result seems to be in agreement with the behavior which would be expected on the basis of the recently discovered detoxication of Novocaine through enzymatic hydrolysis.

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