2. The structure of the "alleged acetone anil" has been discussed. In agreement with the Reddelien formulation it was shown to be a trimethyldihydroquinoline.

3. The "anil" was found to polymerize readily. A dimer was isolated. The polymers were depolymerized easily.

4. A rapid method for the preparation of pure 2,4-dimethylquinoline was found which consisted in the decomposition of the "anil" in the presence of a metallic salt of an amine.

5. The acid decomposition of the "anil" was found to be related to its tendency to polymerize. One of the products was found to be 2,3,4-trimethylquinoline. This compound was also formed from the reaction of methyl ethyl ketone and aniline.

6. The following compounds were isolated when the reaction of aniline with acetone was conducted at higher temperatures than are usually used for the synthesis of the "anil": diphenylamine, phenyl-*p*-cumylamine, *p*-cumidine, 5,5-dimethylacridane and 5-methylacridine.

7. The reaction of acetone with diphenylamine was found to be more convenient for the preparation of the 5,5-dimethylacridane. As possible intermediate products in the formation of this compound *p,p'*-dianilino-2,2-diphenylpropane and *p*-isopropenyldiphenylamine were prepared and studied.

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[CONTRIBUTION FROM CHEMISTRY DEPARTMENT, NORTHWESTERN UNIVERSITY DENTAL SCHOOL]

Some Alkyl and Alkamine Esters of *p*-Aminomandelic Acid and Related Compounds

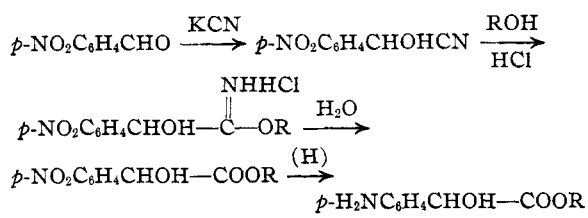
BY L. S. FOSDICK AND G. D. WESSINGER

The esters of *p*-aminobenzoic acid have been studied extensively since the preparation of novocaine.[1]

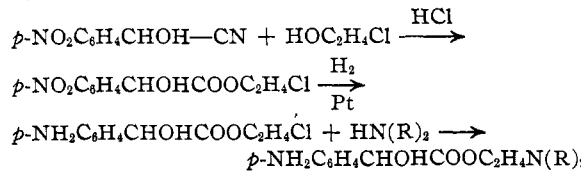
It is interesting to note that practically all of the effective analogs have a carbonyl group conjugated with the double bonds of the aromatic nucleus.[2] The esters of *p*-aminophenylacetic acid, a compound without this system, are quite devoid of anesthetic properties;[3] however, the esters of phenylacetic acid do have slight anesthetic properties.[4] On the other hand, all conjugated systems of this type do not produce anesthesia. The alkamine esters of β-aminocrotonic acid[2] are of this type.

In view of the above theoretical considerations it was thought that perhaps the esters of *p*-aminomandelic acid would be interesting compounds. The anesthetic efficiency should be less than that of novocaine due to the absence of the carbonyl group conjugated with the double bonds of the benzene ring but at the same time the presence of the secondary hydroxyl would make it less toxic.[5]

The normal esters of *p*-nitro- and *p*-aminomandelic acid were prepared by the reactions



The preparations of the alkamine esters are shown by the reactions



The toxicity and anesthetic efficiency were determined on diethylaminoethyl *p*-aminomandelate hydrochloride by Spruth and Olsen through the courtesy of Abbott Laboratories. The M. L. D. on white mice was 1400 mg./kg. compared with novocaine 180–200 mg./kg. The anesthetic efficiency on guinea pig wheals was not complete with a 2% solution while a 1% solution of novocaine gave anesthesia. The guinea pig wheals also produced a slight necrosis. A 2% solution of the same compound on human wheals produced anesthesia lasting twenty-five minutes while the same concentration of novocaine lasted thirty-five minutes. There was no tissue damage.

(1) Einhorn and Uhlfelder, *Ann.*, **371**, 131 (1909).
(2) Shriner and Keyser, THIS JOURNAL, **60**, 286 (1938).
(3) Pyman, *J. Chem. Soc.*, **111**, 167 (1917).
(4) Kurvahata, Ochiai and Nukita, *Folia Pharmacol. Japn.*, **7**, 408 (1928).
(5) Hartung, *Chem. Rev.*, **9**, 389 (1931).

TABLE I

Compound	Yield, %	M. p., °C. corr.	Nitrogen, % Calcd.	Found
p-$NO_2C_6H_4CHOHCOOCH_3$	51	87	[a]	
p-$NO_2C_6H_4CHOHCOOC_2H_5$	47	76–77	[a]	
p-$NO_2C_6H_4CHOHCOOC_3H_7$-*n*	55	84–84.5	5.85	5.81
p-$NO_2C_6H_4CHOHCOOC_4H_9$-*n*	63	44–45	5.53	5.58
p-$NH_2C_6H_4CHOHCOOCH_3$	60	162	7.73	7.68
p-$NH_2C_6H_4CHOHCOOC_2H_5$	52	119–119.5	7.18	6.94
p-$NH_2C_6H_4CHOHCOOC_3H_7$-*n*	64	84–84.5	6.69	6.62
p-$NH_2C_6H_4CHOHCOOC_4H_9$-*n*	45	104–105	6.27	6.11
p-$NH_2C_6H_4CHOHCOOC_2H_4N(C_2H_5)_2$	41			
p-$NH_2C_6H_4CHOHCOOC_2H_4N(C_2H_5)_2 \cdot HCl$	48	129–133, dec.	9.26	9.20
p-$NH_2C_6H_4CHOHCOOC_2H_4N(C_3H_7\text{-}n)_2$	38			
p-$NH_2C_6H_4CHOHCOOC_2H_4N(C_3H_7\text{-}n)_2 \cdot HCl$	43	135–140, dec.	8.47	8.35
p-$NH_2C_6H_4CHOHCOOC_2H_4N(C_4H_9\text{-}n)_2$	43			
p-$NH_2C_6H_4CHOHCOOC_2H_4N(C_4H_9\text{-}n)_2 \cdot HCl$	42	150–155, dec.	7.81	7.66
p-$NO_2C_6H_4CHOHCOOC_2H_4Cl$	59	79.5–80	Cl, 13.67	13.69
p-$NH_2C_6H_4CHOHCOOC_2H_4Cl$	68	95–96	Cl, 15.45	15.40

[a] These compounds were prepared by Engler and Zielke, *Ber.*, **22**, 207 (1899).

Experimental

***p*-Nitromandelonitrile.**—The method of Heller[6] for the preparation of *p*-nitromandelonitrile was utilized. Forty-three grams of *p*-nitrobenzaldehyde was suspended in about 3–4 times its mass of glacial acetic acid. About 10% in excess of the calculated quantity of potassium cyanide was dissolved in twice its mass of water. This potassium cyanide solution was added to the acetic acid suspension, the latter being stirred mechanically during the addition. It was also cooled in an ice-bath. The potassium cyanide solution was added over a period of about one hour.

After all the potassium cyanide had been added, the mixture was allowed to stand for two hours with occasional shaking. At the end of this time, the nitrile was precipitated by adding 3–4 volumes of cold water. The nitrile was filtered off and recrystallized from benzene.

The Preparation of the Normal Ester.—Twelve grams of *p*-nitromandelonitrile was dissolved (partly suspended) in 75 cc. of anhydrous ether, 0.1 mol. of the alcohol was added and the mixture cooled to 0°. Dry hydrogen chloride gas was passed into the mixture to saturation. The mixture was allowed to stand in the ice box overnight at 5°. The imino ether hydrochloride was removed by decantation and placed in a vacuum desiccator until the excess hydrogen chloride was removed. The dry imino ether hydrochloride was placed in a flask with 300 cc. of water and stirred for three hours at room temperature. The ester was removed by filtration and recrystallized from a water–alcohol mixture. The nitro esters were reduced under pressure by means of hydrogen with a platinum oxide catalyst and in alcohol solution.

Alkamine Esters of *p*-Aminomandelic Acid.—Five grams of β-chloroethyl *p*-aminomandelate was dissolved in 25 g. of the secondary amine and sealed in a bomb tube. The mixture was heated at 100° for one and one-half hours. An oily layer of the alkamine ester separated as did long white needles of the amine hydrochloride. The tube was cooled, opened and the excess amine decanted from the thick oily product. The oil was dissolved in dry acetone and the crystals of amine hydrochloride removed by filtration. The acetone was evaporated from the oily layer. The unstable alkamine ester was washed several times with dry ether to remove all traces of the free amine. The alkamine ester was then dissolved in hydrochloric acid and treated with norite to remove color. The mixture was allowed to evaporate *in vacuo;* yellow crystals of the hydrochloride separated.

The free base of the three alkamine esters prepared was in each case a liquid that could not be crystallized or distilled at 2 mm. For this reason the alkamine esters were purified and analyzed as the hydrochloride. The table gives the yield, melting point and analysis of the compounds prepared.

(6) Heller, *Ber.*, **46**, 280–294 (1913).

Summary

Several simple alkyl esters of *p*-nitromandelic acid have been prepared.

Several alkamine esters of *p*-aminomandelic acid have been prepared.

The simple alkyl and alkamine esters of *p*-aminomandelic acid possess anesthetic properties. They are, however, less efficient than the novocaine series. The toxicity of the novocaine analog is much less than novocaine and may be due to the hydroxyl group present.

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