termediate, but expt. no. 7 of Table I was stopped when a vigorous evolution of hydrogen bromide was observed after nine and one-half minutes.

While irradiation shortens the time of formation of the intermediate compound, it does not seem to noticeably influence the rate of its decomposition, for in Table V the 200-watt light was turned off at the first appearance of the orange-red precipitate after about three minutes and forty-five seconds, but the decomposition followed the same course as in Table IV.

TABLE V

DECOMPOSITION OF BROMINE–ACETOPHENONE INTERMEDIATE AFTER THE IRRADIATION WAS SHUT OFF

6.0 cc. Ketone + 100.0 cc. CCl_4 + 50.0 cc. Br_2 soln. (0.01 *m*), 30°, 200 watts, 6 inches for 3 min. 45 sec.

Time min.	Time sec.	% Bromination	Time min.	Time sec.	% Bromination
1	00	0.0	4	30	88.0
4	00	1.5	4	45	98.5

TABLE VI

DECOMPOSITION OF BROMINE–ACETOPHENONE INTERMEDIATE IN WATER

6.0 cc. Ketone + 0.5 cc. Water + 100.0 cc. CCl_4 + 50.0 cc. Br_2 soln. (0.01 *m*), 30°, 200 watts, 6 inches

Time min.	Time sec.	% Bromination	Time min.	Time sec.	% Bromination
1	00	0.0	39	15	98.6
27	00	1.0	39	50	100.0
35	45	2.2			

Water, on the other hand, not only delayed the time of formation of the intermediate but it prolonged the period of decomposition. In Table VI 0.5 cc. of water was added to the 6.0 cc. of acetophenone in 100.0 cc. of C. P. carbon tetrachloride; the intermediate compound was not observed until thirty-five minutes and forty-five seconds after the 50.0 cc. of bromine solution (0.01 *m*) was added, and it persisted for four minutes and five seconds.

Acknowledgment.—The authors wish to express appreciation for the active interest of Dr. E. Emmet Reid in this research.

Summary

1. Rates are given for the photochemical bromination of acetophenone, *p*-chloroacetophenone, *p*-bromoacetophenone, β-naphthylacetophenone, *o*-hydroxyacetophenone and *o*-methoxyacetophenone.

2. Water and sulfur are shown to be negative catalysts, while irradiation and hydrogen chloride shorten the time of bromination in carbon tetrachloride.

3. Factors influencing the rates of formation and decomposition of the intermediate bromoketone compounds have been studied.

GREENVILLE, SOUTH CAROLINA
RECEIVED JANUARY 9, 1941

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, NORTHWESTERN UNIVERSITY DENTAL SCHOOL]

Some Normal and Alkamine Esters of *m*-Aminomandelic Acid and Related Compounds

BY L. S. FOSDICK AND J. C. CALANDRA

The problem of the relation between chemical constitution and physiological activity has been widely studied. In the field of local anesthetics, much of the work has centered on variations of the procaine molecule. The amino alcohol[1] used to esterify the carboxyl group of *p*-aminobenzoic acid has been varied, and the amino group has been replaced by various substituents.[2] These studies have produced hundreds of compounds possessing local anesthetic action to a greater or lesser degree than procaine.

In nearly all instances the para substituted compounds have been prepared and their local anesthetic efficiency studied, but only a small amount of work has been done on the ortho and meta substituted compounds of each type of compound prepared. Some studies along this line have been the preparation of the esters of *o*- and *m*-aminobenzoic acids[3] and cinnamic acids.[4,5]

In 1938 Shriner and Keyser[6] suggested that a carbonyl group conjugated with double bonds in an aromatic nucleus enhanced anesthetic activity. On the basis of this consideration it was thought that the esters of *p*-aminomandelic should

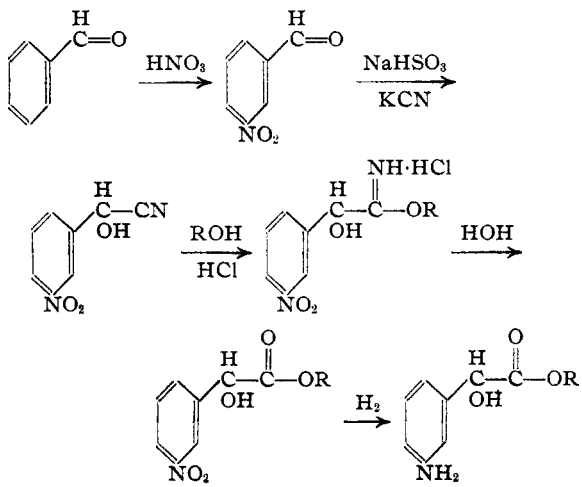
(1) Hirschfelder and Bieter, *Physiol. Rev.*, **12**, 190 (1932).
(2) Coles and Lott, THIS JOURNAL, **58**, 1989 (1936).
(3) German Patent 170,587 (1906).
(4) Wildman and Thorp, U. S. Patent 1,193,649 (1916).
(5) Kamm, THIS JOURNAL, **42**, 1030 (1920).
(6) Shriner and Keyser, *ibid.*, **60**, 286 (1938).

have less anesthetic activity than the analogous procaine compounds. These esters were prepared[7] and it was found that the prediction was correct. Pharmacological data indicated that although anesthetic activity was present it was much less than that produced from the analogous procaine compounds.

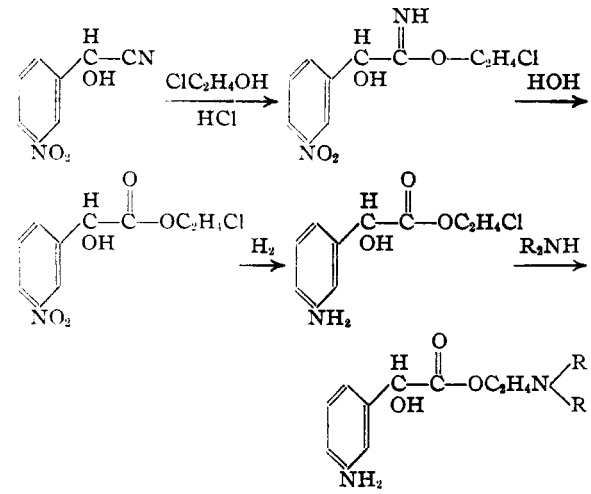
In the procaine series the anesthetic activity is considerably decreased if the amino group is substituted in the meta or ortho position.[8] On this basis the esters of *m*-aminomandelic acid should be less active than the corresponding esters of *p*-aminomandelic acid. This paper deals with the synthesis of the esters of *m*-aminomandelic acid.

The anesthetic activity of the series was so slight that the lower members of the series produced no anesthesia. Preliminary pharmacological data indicate that although the propyl, butyl and diethylaminoethyl esters possess anesthetic activity it is much less than that of the esters of *p*-aminomandelic acid.

These esters were prepared according to the series of reactions shown in the accompanying chart. Benzaldehyde was nitrated using a mixture of sulfuric acid and sodium nitrate. The *m*-nitrobenzaldehyde was then converted into the nitrile, which was treated with the appropriate alcohol and dry hydrogen chloride gas to form the imido ester. This was next hydrolyzed and converted to the nitro ester and followed by reduction to the amino ester. The β-chloroethyl *m*-aminomandelate was condensed with diethylamine in a sealed tube to form the alkamine ester.



(7) Fosdick and Wessinger, THIS JOURNAL, **60**, 1465 (1938).
(8) Brill, *ibid.*, **43**, 1320 (1921).



Experimental

***m*-Nitromandelonitrile.**—A mixture of a 10% solution of 48 g. of sodium bisulfite and 54 g. of *m*-nitrobenzaldehyde, prepared by adding benzaldehyde to a mixture of sodium nitrate and sulfuric acid,[9] was placed in a 3-liter round-bottom flask and 150 cc. of ether was added. The mixture was cooled in an ice-bath to 10° and 30 g. of potassium cyanide in a 20% solution was added over a period of a half-hour with mechanical stirring. During this time the bisulfite addition product separated out as a yellow solid, and redissolved upon the addition of a slight excess of potassium cyanide. The mixture was stirred for another half hour after the addition of the potassium cyanide. The ether layer was separated and the aqueous layer was extracted with several 50-cc. portions of ether. The nitrile was an oil and no attempt to isolate it was made. The ether extract was dried overnight over calcium chloride.

The Preparation of the Normal Esters.—To the dried ether solution of nitrile the calculated amount of the alcohol was added and dry hydrogen chloride gas was passed in until the solution was saturated. The hydrochloride of the imido ester started to separate after a few minutes and was completely precipitated after being allowed to stand in the icebox at 5° for an hour. The imido ester was filtered off and placed in a vacuum desiccator to remove the excess hydrogen chloride. The imido ester was then placed in 200 cc. of cold water and stirred for a half hour and the normal ester precipitated as a solid, which was recrystallized from alcohol. The nitro esters were converted into the amino ester by reduction with hydrogen under a pressure of 45 lb. using a platinum oxide catalyst.

Alkamine Esters of *m*-Aminomandelic Acid.—Ten grams of β-chloroethyl *m*-aminomandelate was dissolved in an excess of diethylamine and sealed in a Pyrex tube. The mixture was heated overnight on the steam-bath, cooled, opened and the excess diethylamine decanted. The residue was dissolved in dry acetone and the crystals of diethylamine hydrochloride filtered off. The acetone was evaporated and the oily layer was washed with dry ether to remove unchanged β-chloroethyl *m*-aminomandelate and diethylamine. The oil was dissolved in 0.5 *N* hydrochloric acid and treated with Norit several times.

(9) Friedlander and Henriques, *Ber.*, **14**, 2802 (1881).

TABLE I

Compound	Yield, %	M. p., °C., cor.	Nitrogen, % Calcd.	Found
m-$NO_2C_6H_4CHOHCOOCH_3$	80	66	6.63	6.50
m-$NO_2C_6H_4CHOHCOOC_2H_5$[a]	85	63	...	...
m-$NO_2C_6H_4CHOHCOOC_3H_7$-*n*	63	73	5.85	5.71
m-$NO_2C_6H_4CHOHCOOC_3H_7$-*i*	52	57	5.85	5.73
m-$NO_2C_6H_4CHOHCOOC_4H_9$-*n*	31	65	5.53	5.45
m-$NH_2C_6H_4CHOHCOOCH_3$	54	139	7.73	7.65
m-$NH_2C_6H_4CHOHCOOC_2H_5$	72	55	7.18	7.25
m-$NH_2C_6H_4CHOHCOOC_3H_7$-*n*	31	101	6.69	6.58
m-$NH_2C_6H_4CHOHCOOC_3H_7$-*i*	42	146	6.69	6.57
m-$NH_2C_6H_4CHOHCOOC_4H_9$-*n*	23	110	6.27	6.32
m-$NH_2C_6H_4CHOHCOOC_2H_4N(C_2H_5)_2$	36	...	...	...
m-$NH_2C_6H_4CHOHCOOC_2H_4N(C_2H_5)_2$·HCl	41	133	9.26	9.30
m-$NO_2C_6H_4CHOHCOOC_2H_4Cl$	63	76	5.39	5.44
m-$NH_2C_6H_4CHOHCOOC_2H_4Cl$	54	91	6.08	5.92

[a] Synthesized by Beyer, *J. prakt. Chem.*, **31**, 391 (1885).

The acid solution was evaporated to dryness in a vacuum desiccator and light brown crystals of the hydrochloride were obtained. The free base was unstable and was not analyzed as such. The physical constants and results of the analysis of the compounds prepared appear in the table.

Summary

The simple alkyl esters and the β-diethylaminoethyl ester of *m*-nitro- and *m*-aminomandelic acid have been synthesized. The local anesthetic activity of the esters with the amino group in the meta position was found to be much less than that of the corresponding para amino derivatives previously prepared.

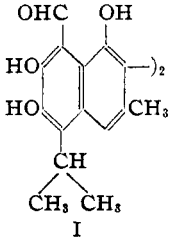
CHICAGO, ILLINOIS RECEIVED JANUARY 20, 1941

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

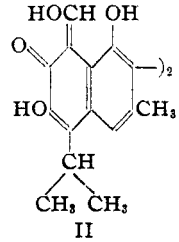
The Reactions of 2,8-Dihydroxynaphthaldehyde

BY ROGER ADAMS AND D. E. BURNEY[1]

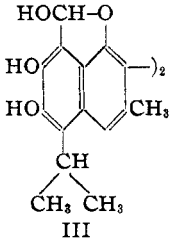
Gossypol has been demonstrated to have structure I.[2] With various reagents it gives derivatives of one of three tautomeric forms (I, II or III).



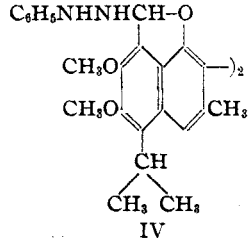
I



II



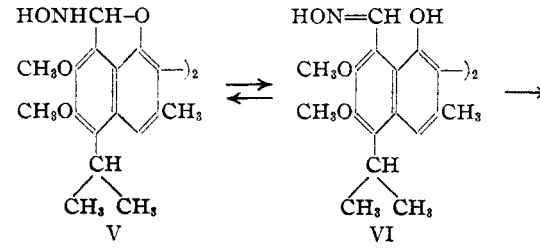
III



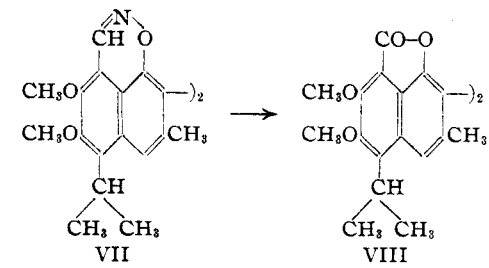
IV

Anhydrogossypol is derived from Formula II by loss of water between the peri groups, and gossypol hexamethyl ether has Formula III as its parent nucleus.

Treatment of gossypol hexamethyl ether with phenylhydrazine or hydroxylamine in ethanol solution failed to result in any reaction, but in acetic acid derivatives are obtained in which one methoxyl group in each half of the molecule has been eliminated (IV).[3] In the case of hydroxylamine two molecules of water also are lost with formation of orthoxazine rings; the sequence of the reactions involved is shown in Formulas V–VII.[2] Alkaline hydrolysis of the orthoxazine (VII) followed by treatment with acetic acid resulted in formation of the lactone (VIII); the mechanism of the conversion has been discussed in a previous communication.



V VI



VII VIII

The present investigation was undertaken to discover whether the reactions just described were typical of any 2,8-dihydroxynaphthaldehyde or whether they were dependent as well on the pres-

(1) In partial fulfillment of the requirements for the degree of Doctor of Philosophy in Chemistry.

(2) Adams, Morris, Geissman, Butterbaugh and Kirkpatrick, THIS JOURNAL, **60**, 2193 (1938).

(3) Adams and Geissman, *ibid.*, **60**, 2166 (1938).