[CONTRIBUTION NO. 1159 FROM THE STERLING CHEMISTRY LABORATORY OF YALE UNIVERSITY]

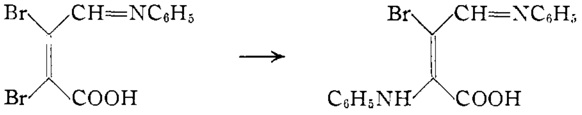
Studies on the Mucohalic Acids. IV. Replacement of Halogen in the Pseudo Ester Series

BY HARRY H. WASSERMAN AND FRANK M. PRECOPIO

RECEIVED JULY 13, 1953

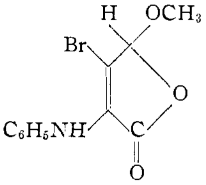
The reaction of aniline with pseudo methyl esters in the mucohalic acid series has been shown to involve replacement of the halogen beta to the carbonyl in each case, contrary to earlier proposals. This reaction course, which differs from the α-halogen replacement observed in the free acid series, is discussed.

The reactions of the mucohalic acids and their esters with aromatic amines were first studied by Hill,[1] and later, in greater detail, by Simonis.[2] Simonis found that with one mole of aniline, mucobromic acid was converted to the Schiff base (I), while with excess aniline, there was formed the dianilino derivative II in which the halogen alpha to the carboxyl group had been replaced.



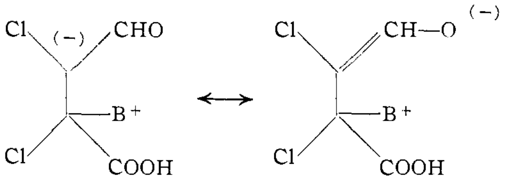
I II

On the other hand, reaction of aniline with the pseudo methyl ester[3] of mucobromic acid yielded only a monoanilino derivative involving displacement of halogen. Reasoning by analogy with the reactions of the free acid, Simonis proposed that the halogen alpha to the lactone carbonyl group had been replaced, and he formulated the "anilide" of the pseudo ester as an α-anilino-β-bromo-γ-methoxycrotonolactone (III).



III

Although it is well established that reactions of the mucohalic *acids* involving replacement of halogen takes place preferentially at the α-position,[2,4,5] it does not necessarily follow that the pseudo esters should react in an analogous way, since there is a considerable difference between the structures of the acids and the pseudo esters. In the acid series, an equilibrium exists between the open (aldehyde–acid) form and the cyclic (hemiacetal–lactone) form, whereas the pseudo esters exist exclusively as acetal–lactones. Displacement of halogen in the acid series by a base, B, takes place preferentially at the α-position since this reaction involves a more favored transition state stabilized by the strongly electron-attracting aldehyde group (IVa-b).

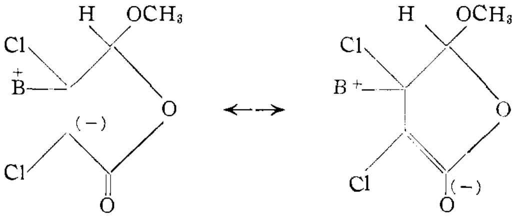


(a) (b)

IV

In the corresponding displacement at the β-position, the transition state would be stabilized less effectively by the carboxyl group.

On the other hand, one would expect reaction of bases with the pseudo esters to take place preferentially *at the β-position* since displacement at this site should involve a more favorable transition state stabilized by electronic interactions with the lactone carbonyl group (Va-b). In the ester series there can be no comparable stabilization arising from attack at the α-position



(a) (b)

V

That reaction of aniline with the pseudo esters does, in fact, take place at the β-position has been clearly established in the present work. In order to tag the α- and β-positions of the ester molecule, we have prepared the two chlorobromo esters, VIII and IX, from the corresponding acids of known structure,[6] and have subjected each ester to the action of aniline. Replacement of β-halogen in each case would lead to different products which should correspond to the anilino derivatives derivable from the esters of mucochloric and mucobromic acids, respectively. The accompanying chart I illustrates the reaction sequence as carried out.

α-Chloro-β-bromo-β-formylacrylic acid[6] (VI) was converted to the pseudo ester VIII, and thence to the chloro-anilino derivative (X). This anilino derivative X was identical with the product derived by the reaction of aniline with the pseudo ester of mucochloric acid (XII). A similar conversion of α-bromo-β-chloro-β-formylacrylic acid[6] (VII) led to the bromo-anilino derivative XI,

---

(1) H. B. Hill and R. W. Cornelison, *Am. Chem. J.*, **16**, 188, 277 (1895).

(2) H. Simonis, *Ber.*, **34**, 509 (1901).

(3) Simonis' assignment of the pseudo ester structure XIII to this methyl ester has been confirmed by infrared studies, H. Wasserman, doctoral dissertation, Harvard University, 1948, and, more recently, by D. Mowry, THIS JOURNAL, **72**, 2535 (1950).

(4) H. B. Hill and A. W. Palmer, *Am. Chem. J.*, **9**, 147 (1887).

(5) H. E. Sawyer, *Proc. Am. Acad. Arts Sci.*, **29**, 242 (1894).

(6) H. H. Wasserman, F. M. Precopio and T. C. Liu, THIS JOURNAL, **75**, 2527 (1953).

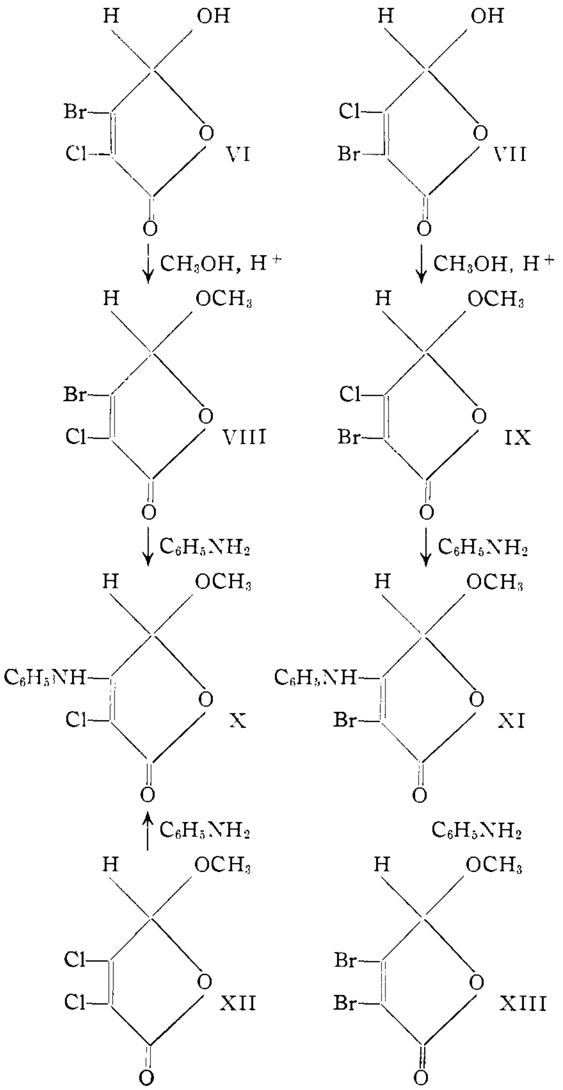
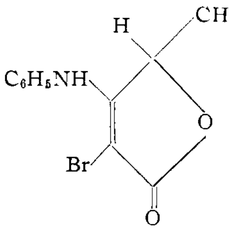


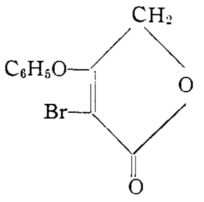
CHART I

identical with the product derived by the reaction of aniline with the pseudo ester of mucobromic acid (XIII).

The above transformations clearly disclose the nature of the halogen-replacement reactions in the pseudo ester series of the mucohalic acids and also provide a basis for formulating products of uncertain structure derived in analogous replacement reactions. Thus, the compound $C_{11}H_{10}O_2NBr$ obtained by the reaction of α,β-dibromo-γ-methyl crotonolactone with aniline[7] can be assigned the structure XIV involving replacement of β-halogen, and in like manner, the phenoxy derivative obtained by Hill[1] by reaction of α,β-dibromocrotonolactone with potassium phenylate should be reformulated as XV, rather than as the α-phenoxy derivative.



XIV



XV

Experimental

The following procedure, used to convert α-chloro-β-bromo-β-formylacrylic acid to the pseudo ester and thence to the anilino derivative, was employed in the conversions of all four of the acids in this series to the corresponding anilino derivatives.

α-Chloro-β-anilino-γ-methoxycrotonolactone (X).—A mixture of 9.5 g. of α-chloro-β-bromo-α-formylacrylic acid,[8] 50 ml. of anhydrous methyl alcohol and 10 drops of concentrated sulfuric acid was refluxed for 12 hours. The resulting yellow solution was poured into 200 cc. of water and extracted with benzene. The benzene solution was dried over anhydrous sodium sulfate and the solvent removed *in vacuo*, leaving a light yellow lachrymatory oil. Distillation of this oil, b.p. 53–54° (0.1 mm.), gave 8.3 g. (82%) of a colorless liquid, $n^{25}D$ 1.5148. This material gradually decomposed on standing.

Anal. Calcd. for $C_5H_4O_2ClBr$: C, 26.40; H, 1.77. Found: C, 26.89; H, 2.12.

A cold solution of 0.87 g. of aniline in 2 cc. of methanol was added to a solution of 1.0 g. of pseudo ester in 2 cc. of methanol and the resulting solution was cooled overnight in the refrigerator. Water was then added dropwise to the cold solution while stirring. By this method an oil separated which gradually solidified to a pale yellow solid. After several recrystallizations from methyl alcohol, the pure white product melted 123–125°. This product was identical in every respect with the anilino derivative obtained from the pseudo ester of mucochloric acid.

Anal. Calcd. for $C_{11}H_{10}O_3NCl$: C, 55.12; H, 4.21. Found: C, 55.12; H, 4.26.

α-Bromo-β-anilino-γ-methoxycrotonolactone (XI).—In a manner similar to the procedure described above, α-bromo-β-chloro-β-formylacrylic acid prepared by the method of Hill[9] was converted to the oily α-bromo-β-chloro-γ-methoxycrotonolactone (not isolated) and thence to the β-anilino derivative. The latter product, m.p. 116–117°, was identical with the anilino derivative obtained from the pseudo ester of mucobromic acid.

Anal. Calcd. for $C_{11}H_{10}O_3NBr$: C, 46.48; H, 3.55. Found: C, 46.32; H, 3.51.

NEW HAVEN, CONNECTICUT

---

[7] E. I. Vinogradova and M. M. Shemyakin, *J. Gen. Chem.* (*U. S. S. R.*), **16**, 709 (1946).

[8] This sample was kindly supplied by Dr. E. Kuh of the American Cyanamid Company.

[9] H. B. Hill and O. R. Jackson, *Am. Chem. J.*, **12**, 37 (1890).