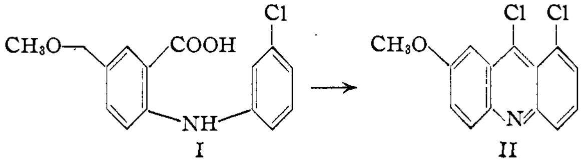
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF CALIFORNIA, BERKELEY]

A Synthesis of 2-Methoxy-8,9-dichloroacridine Utilizing the Chapman Rearrangement

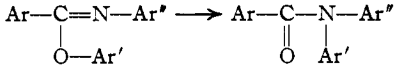
BY WILLIAM G. DAUBEN AND RUSSELL L. HODGSON

In the course of an earlier study on the synthesis of nuclear isomers of Quinacrine,[1] it was reported that when N-(3′-chlorophenyl)-5-methoxyanthranilic acid (I) was cyclized with phosphorus oxychloride only one pure compound could be isolated and this in low yield. The product was designated as 2-methoxy-8,9-dichloroacridine (II) on the basis of a comparison of the physical properties of the compound itself and the physical and biological properties of a Quinacrine type moiety derived from it with those of the previously known 6-chloro isomer. Shah, Kshatriga, Patel and Nargund[2] have reported, however, that ring closure of acid I yielded only the 6-chloro isomer. In order to further substantiate the structure II assigned to our compound, the 8-chloro isomer has been prepared unequivocally by a route utilizing the Chapman rearrangement.



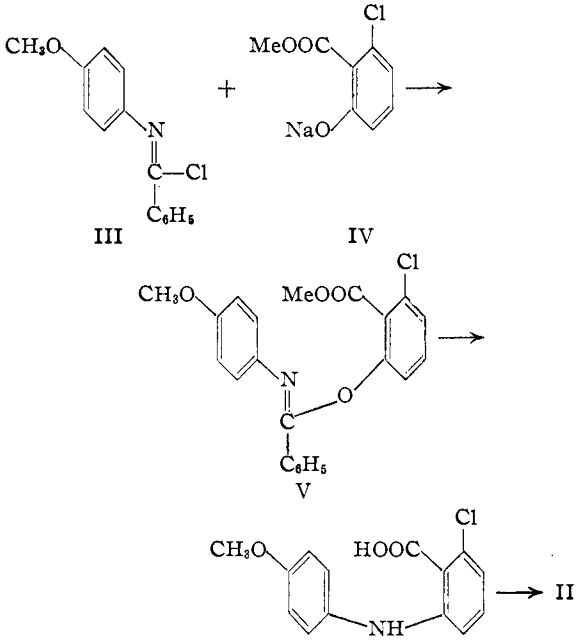
I II

It has been reported by Chapman[3] that when an aryl imido ester[4] is heated to 200°, intramolecular rearrangement to an acylated diphenylamine



$$\mathrm{Ar{-}\underset{\displaystyle O{-}Ar'}{C}{=}N{-}Ar''} \longrightarrow \mathrm{Ar{-}\underset{\displaystyle \overset{\|}{O}}{C}{-}\underset{\displaystyle Ar'}{N}{-}Ar''}$$

occurs. In such a migration it also has been shown that the migrating group itself does not undergo rearrangement. Jamison and Turner[5] have made use of this reaction for the preparation of substituted N-phenylanthranilic acids. They found that when the imido ester derived from methyl salicylate and N-phenylbenzimidyl chloride was heated to 270° and the rearrangement product hydrolyzed, N-phenylanthranilic acid was obtained in an over-all yield of 56%.



III IV

V

VI

The synthesis of N-(4′-methoxyphenyl)-6-chloroanthranilic acid (VI) was accomplished in a similar manner. The starting acid (IV), 2-chloro-6-hydroxybenzoic acid, was prepared from 2-chloro-6-nitrotoluene as described by Cohn.[6] The intermediate imido ester (V), prepared from the sodium salt of methyl 2-chloro-6-hydroxybenzoate (IV) and N-4-methoxyphenylbenzimidyl chloride (III), was not characterized but the crude reaction product directly subjected to rearrangement. It was found that the best yield of saponified rearranged product was obtained when the pyrolysis was conducted at 210° for seventy minutes. Under these conditions, N-(4′-methoxyphenyl)-6-chloroanthranilic acid (VI) was obtained in a yield of 28% (based on ester IV). The acid VI was cyclized and chlorinated by heating with phosphorus oxychloride in chlorobenzene and 2-methoxy-8,9-dichloroacridine (II) obtained in 37% yield. This dichloroacridine was found to be identical in all respects with the previously reported product obtained by ring closure of acid I.

Experimental[7]

2-Chloro-6-aminobenzoic Acid Hydrochloride.—This acid was prepared from 2-chloro-6-nitrotoluene following the procedures described by Cohn,[6] Ullmann and Panchard[8] and Huntress and Cliff[9] in an over-all yield of 47.3%. The product melts at 191-192° (dec.). Huntress and Cliff report 195° (dec.).

2-Chloro-6-hydroxybenzoic Acid.—The acid was prepared from the above hydrochloride by the general proce-

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[1] Dauben, THIS JOURNAL, **70**, 2420 (1948).

[2] Shah, Kshatriga, Patel and Nargund, *J. Univ. Bombay*, Sect. A, **15**, pt. 3 (Science No. 20), 42 (1946).

[3] Chapman, *J. Chem. Soc.*, 2462 (1930), and earlier papers.

[4] Previous investigators have employed the name imino ether for this type of compound; *Chem. Abstracts* suggests the name used in this paper.

[5] Jamison and Turner, *J. Chem. Soc.*, 1954 (1937).

[6] Cohn, *Monatsh.*, **22**, 473 (1901); *Chem. Centr.*, **72**, II, 925 (1901).

[7] Analyses by The Microanalytical Laboratory of the Department of Chemistry, University of California. All melting points are corrected.

[8] Ullmann and Panchard, *Ber.*, **37**, 1019 (1904).

[9] Huntress and Cliff, THIS JOURNAL, **55**, 2559 (1933).

dure of Cohn.[6] The by-product, *m*-chlorophenol, was separated from the desired acid by steam distillation and the crude acid recrystallized from water (Norit). The yield was 22% and the white crystals melt at 171.5–172.5°. Cohn[6] reported red crystals which melt at 166°.

Methyl 2-Chloro-6-hydroxybenzoate.—A solution of 1.3 g. (7.6 mmoles) of 2-chloro-6-hydroxybenzoic acid, 11 cc. of methanol and 1 cc. of concentrated sulfuric acid was heated under reflux for seventy-two hours, the reaction mixture concentrated under reduced pressure and then diluted with water. The residual oil was extracted with ether and the ethereal solution washed with freshly prepared sodium bicarbonate solution, dried and the ether distilled. The crude ester was recrystallized from aqueous methanol and the yield of white needles was 1.0 g. (71%), m. p. 47–48°.

Anal. Calcd. for $C_8H_7O_3Cl$: C, 51.49; H, 3.78. Found: C, 51.19; H, 3.92.

N-(4'-Methoxyphenyl)-6-chloroanthranilic Acid (VI).—To a solution of sodium ethoxide prepared from 0.11 g. (4.7 mmoles) of sodium and 10 cc. of absolute ethanol, cooled in an ice-bath, there was added in rapid succession 0.88 g. (4.7 mmoles) of methyl 2-chloro-6-hydroxybenzoate and a solution of 1.14 g. (4.7 mmoles) of N-4-methoxyphenylbenzimidyl chloride[3] in 30 cc. of dry ether. The reaction mixture was shaken vigorously whereupon a precipitate of sodium chloride began to form. The mixture was allowed to stand at room temperature for forty-eight hours, the solvent evaporated and the residue diluted with water. The resulting oily solid was removed by extraction with ether, the ethereal solution dried and the ether distilled.

The crude imido ester was heated in a nitrogen atmosphere at 210–215° for seventy minutes, then dissolved in 10.8 cc. of ethanol and the alcoholic solution diluted with 5.4 cc. of water and 5.4 cc. of a 1 *M* solution of ethanolic sodium ethoxide. The solution was refluxed for one and one-half hours, the alcohol evaporated on a steam-bath and the aqueous solution acidified with dilute hydrochloric acid. The dark oil which formed was separated by decantation and the crude benzoate of the substituted anthranilic acid dissolved in 22 cc. of ethanol. A solution of 7.2 g. of sodium hydroxide in 7.2 cc. of water was added and the mixture refluxed for one hour. The alcohol was evaporated and the solution acidified. The brown solid was extracted *exhaustively* with boiling water to remove the benzoic acid and the remaining brown solid recrystallized from aqueous ethanol. The yellow needle-like crystals melt at 139.5–140.5° (dec.), yield 0.36 g. (27.7%).

Anal. Calcd. for $C_{14}H_{12}O_3NCl$: C, 60.54; H, 4.36; N, 5.04; Cl, 12.76. Found: C, 60.58; H, 4.44; N, 5.63; Cl, 12.65.

2-Methoxy-8,9-dichloroacridine (II).—The ring closure and subsequent chlorination was conducted as described in an earlier publication[1] employing 0.2 g. (0.7 mmole) of acid VI, 1.6 cc. of phosphorus oxychloride and 4 cc. of chlorobenzene. The product was recrystallized from benzene, m. p. 180.3–181.3°, yield 0.08 g. (37.4%). No depression in melting point was noted upon admixture with the previously reported product.[1]

Anal. Calcd: for $C_{14}H_9ONCl_2$: C, 60.45; H, 3.26; N, 5.04; Cl, 25.50. Found: C, 60.80; H, 3.33; N, 5.40; Cl, 25.69.

Summary

Methyl 2-chloro-6-hydroxybenzoate and N-4-methoxyphenylbenzimidyl chloride were condensed in alkaline solution and the resulting imido ester rearranged to N-(4'-methoxyphenyl)-6-chloroanthranilic acid by pyrolysis. Subsequent ring closure and chlorination yielded 2-methoxy-8,9-dichloroacridine which was identical with the product previously reported.

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Derivatives of the Anomeric Glucopyranosylbenzenes

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In a series of recent papers Hurd and Bonner[1] have developed two methods for the synthesis of acetylated glycosylaromatic hydrocarbons, compounds in which a glycosyl radical is linked directly to an aromatic nucleus. The first of these involved the catalytic glycosylation of aromatic hydrocarbons with polyacetylglycosyl halides or acetates in the presence of aluminum chloride, and produced the desired glycosylaromatic compound in low yield along with a 1,1-diaryl-1-desoxyglycitol. The second synthesis employed the metathetical reaction of the halide function of polyacetylglycosyl halides with Grignard reagents, and permitted the extension of the glycosylation reaction to the aliphatic series. This method had the distinct advantages of high yield, greater generality, and ease of isolation of a pure product. All of the glycosylated hydrocarbons produced above by either method were isolated and characterized as their acetates.

In addition to the crystalline, low-rotating polyacetylglycosylaromatic compounds produced by the Grignard glycosylation, there was usually isolable from the crystallization mother liquors about one-fourth as much of a high-rotating sirup, assumed to be anomeric with the crystalline material. On the basis of their rotations, the crystalline substances were designated as the β-anomers (*e. g.*, tetraacetyl-β-D-glucopyranosylbenzene, m. p. 155–156°, $[\alpha]^{20}$D −18.6°) and the sirupy by-products as the α-anomers (*e. g.*, "tetraacetyl-α-D-glucosylbenzene," $[\alpha]^{20}$D 40°). While the sirupy "α-anomers" could not be purified and were therefore not analyzed, their constitutions were supported by the fact that they were readily oxidizable to the predicted aromatic carboxylic acids. The pyranose ring system in the β-anomers has been demonstrated by the periodate oxidation of crystalline β-D-xylopyranosylbenzene[2] which, besides the sirupy β-D-gluco-

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[1] Hurd and Bonner, THIS JOURNAL, **67**, 1664, 1759, 1972, 1977 (1945); Bonner, *ibid.*, **68**, 1711 (1946).

[2] Bonner and Hurd, unpublished work presented before the Division of Sugar Chemistry, 110th Meeting of the American Chemical Society, Sept., 1946.