[CONTRIBUTION FROM THE COBB CHEMICAL LABORATORY UNIVERSITY OF VIRGINIA]

Antitubercular Studies. 1,1,1-Trichloro-2,2-bis-(*p*-aminophenyl)-ethane

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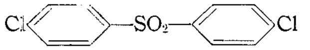
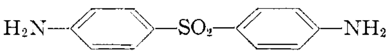
In their now classical study on the mode of insecticidal action, Laüger, Martin and Müller[3] observed the structural analogy of the stomach insecticide, bis-(4-chlorophenyl)-sulfone (I), and the antitubercular drug, bis-(4-aminophenyl)-sulfone (II). They attributed the increase of insecticidal action of DDT (III) over the sulfone I to the introduction of the lipid-solubilizing trichloroethyl group, and we considered it possible that the same electrophilic group, introduced into II, would give rise to a compound with increased antitubercular activity (IV). This might also be expected in view of the bacteriostatic properties of other structurally similar compounds containing cationoid groups, such as 4,4′-diaminobenzophenone[4] and 4,4′-diaminobenzil.[5]



I



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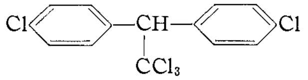
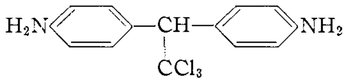


III

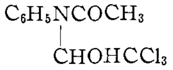


IV

We were unable to prepare the diamine IV because of the ease with which it loses hydrogen chloride, but here report the synthesis and structural proof of some of its acyl derivatives.

The reaction of aniline and chloral has been studied by Wallach,[6] who proved that in the various products formed the amino group always is involved in the condensation. Since concentrated sulfuric acid, the common condensing agent in the preparation of DDT, had not been tried, we treated aniline with chloral in this medium, but found that no reaction took place in the cold. When the mixture was heated, chloralide[6] was formed as the only reaction product in yields comparable to those obtained in the absence of aniline sulfate.

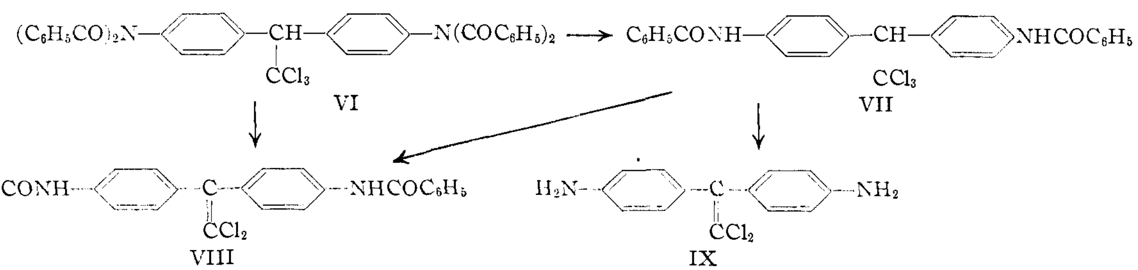
On the other hand, acetanilide and chloral could be condensed in sulfuric acid solution to give a complex mixture from which a small amount of N-(1-hydroxy-2,2,2-trichloroethyl)-acetanilide (V) was isolated. The structure of this compound was not confirmed but appears probable from its mode of formation in analogy to the addition of chloral to other amides.[7]



$$\begin{array}{l}C_6H_5NCOCH_3\\ \quad|\\ \quad CHOHCCl_3\end{array}$$

V

Therefore, it seemed advisable to treat chloral with N-disubstituted anilides which, having no available hydrogen in the amide groups, would force the condensation into the nucleus. Diacetanilide appeared unsuitable because of the ease with which the acetyl groups are removed by concentrated acids.[8] On the other hand, dibenzanilide has been reported more stable toward acids and was, therefore, chosen for our experiments. While it did not react with chloral in sulfuric acid solution at 5°, the condensation went smoothly at 28–29° and yielded a mixture of some 1,1,1-trichloro-2,2-bis-(*p*-dibenzamidophenyl)-ethane (VI), and much 1,1,1-trichloro-2,2-bis-(*p*-benzamidophenyl)-ethane (VII). Treatment of either of these compounds with ethanolic potassium hydroxide solution led to 1,1-dichloro-2,2-bis-(*p*-benzamidophenyl)-ethylene (VIII) and thus involved elimination of hydrogen chloride. Acid hydrolysis of VII furnished the diamine IX: even under mild conditions hydrogen chloride was split out from the trichloroethyl group.



The structure of VIII was proven by oxidative

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[1] Du Pont Fellow.

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[3] Läuger, Martin and Müller, *Helv. Chim. Acta*, **27**, 892 (1944).

[4] Auhagen, *Z. physiol. Chem.*, **274**, 48 (1942); Kuhn, Möller, Wendt and Beinert, *Ber.*, **75**, 711 (1942).

[5] Kuhn, Möller and Wendt, *ibid.*, **76**, 405 (1943).

[6] Wallach, *Ann.*, **193**, 1 (1878).

[7] Hurry and Meldrum, *J. Indian Chem. Soc.*, **11**, 535 (1934); Meldrum and Bhojraj, *ibid.*, **13**, 185 (1936); Rana, *ibid.*, **19**, 299 (1942); Hirwe and Kulkarni, *Proc. Indian Acad. Sci.*, **13A**, 49 (1941).

[8] Tassinari, *Gazz. chim. ital.*, **24**, **I**, 62, 445 (1894).

hydrolysis to bis-(*p*-benzamido)-benzophenone, which was synthesized for comparison from benzanilide and carbon tetrachloride.

The diamide VII was tested *in vitro* in the Merck Institute through the courtesy of Dr. Randolph T. Major. It inhibited the growth of *M. tuberculosis* in concentrations of 0.007 to 0.015 g. per liter, and showed considerable activity against *S. aureus*. In this connection it is interesting to note that 1,1,1-trichloro-2,2-bis-(*p*-nitrophenyl)-ethane has a marked chemotherapeutic effect in murine typhus.[9]

Experimental

N-(1-Hydroxy-2,2,2-trichloroethyl)-acetanilide.—A solution of 100 g. of chloral hydrate and 140 g. of acetanilide in 1 liter of concentrated sulfuric acid was agitated at room temperature overnight, and poured onto 3 liters of crushed ice. The viscous precipitate was extracted with ether, the extract dried and evaporated. The residual oil weighed 149 g. and consisted of a mixture of compounds including acetanilide and a high-melting product [m. p. 239–246° (dec.)], but no satisfactory separation was achieved. In the original extracted acid solution a colorless precipitate formed on standing. It was recrystallized from dilute ethanol and melted at 211–213° (dec.). The yield of pure product was 7 g.

Anal. Calcd. for $C_{10}H_{10}Cl_3NO_2$: C, 42.49; H, 3.57. Found: C, 42.47; H, 3.88.

Condensation of Dibenzanilide with Chloral.—Twenty grams of chloral and 40 g. of dibenzanilide were added in alternate portions to 600 cc. of 100% sulfuric acid with cooling and shaking, and the mixture was allowed to stand for four days at room temperature with occasional agitation. Four grams of an insoluble precipitate of 1,1,1-trichloro-2,2-bis-(*p*-dibenzamidophenyl)-ethane was removed by filtration through sintered glass. No adequate solvent was found for this material, and only a small sample was purified by crystallization from several liters of ethanol. The colorless compound melted at 178–179°.

Anal. Calcd. for $C_{42}H_{29}Cl_3N_2O_4$: N, 3.82. Found: N, 3.37.

The sulfuric acid filtrate from the insoluble tetrabenzoylamino derivative was poured onto 1 liter of crushed ice and the voluminous colorless precipitate filtered. The crude dried material weighed 40 g. and was recrystallized from dilute ethanol. Pure 1,1,1-trichloro-2,2-bis-(*p*-benzamidophenyl)-ethane melted at 167–169°.

Anal. Calcd. for $C_{28}H_{21}Cl_3N_2O_2$: C, 64.19; H, 4.04; N, 5.35. Found: C, 64.07; H, 3.61; N, 5.40, 5.09.

1,1-Dichloro-2,2-bis-(*p*-benzamidophenyl)-ethylene.—A suspension of 2 g. of 1,1,1-trichloro-2,2-bis-(*p*-dibenzamidophenyl)-ethane in 100 cc. of a 5% ethanolic potassium hydroxide solution was refluxed for two hours, the insoluble precipitate, apparently a potassium salt of the reaction product, was dissolved in water, and the basic solution acidified. The colorless ethylene derivative precipitated out and was recrystallized from ethanol. It melted at 97–97.5°, and the pure product weighed 0.25 g.

Anal. Calcd. for $C_{28}H_{20}Cl_2N_2O_2$: N, 5.75. Found: N, 5.90.

The same compound was obtained from the hydrolysis of 1,1,1-trichloro-2,2-bis-(*p*-benzamidophenyl)-ethane, dissolved in an ethanolic solution of potassium hydroxide.

1,1-Dichloro-2,2-bis-(*p*-aminophenyl)-ethylene.—A suspension of 100 g. of 1,1,1-trichloro-2,2-bis-(*p*-benzamidophenyl)-ethane in 4 liters of 6 *N* hydrochloric acid was refluxed for four hours. The material went slowly into solution, and benzoic acid separated out. The solution was cooled, benzoic acid filtered, the filtrate concentrated under reduced pressure and made alkaline with sodium carbonate. The reaction product was extracted into ether, the extract dried over sodium sulfate and evaporated. The brown solid residue weighed 40 g. and was recrystallized from acetone–ethanol. The colorless rhombohedra melted at 174–175°; the compound was soluble in dilute acids with a reddish color.

Anal. Calcd. for $C_{14}H_{12}Cl_2N_2$: C, 60.23; H, 4.33; N, 10.03. Found: C, 60.49; H, 4.70; N, 9.98.

Hydrolysis with 48% hydrobromic acid at 25° over a period of three days furnished 20% of the same product while 80% of the starting material was recovered.

Bis-(*p*-benzamido)-benzophenone.—(A) Five grams of chromium trioxide was added in small portions over a period of two hours to a cooled solution of 1.5 g. of 1,1-dichloro-2,2-bis-(*p*-benzamidophenyl)-ethylene in 30 cc. of glacial acetic acid. After completion of the initial reaction, the mixture was refluxed for four hours, cooled, and poured into 200 cc. of ice-water. The solution was made ammoniacal, and the benzophenone derivative extracted into ether. The brown residue from this extract was recrystallized from ethanol and from acetone. The colorless platelets melted at 151–152° and weighed 0.5 g. A mixture melting point with the ketone obtained by method B showed no depression.

The **semicarbazone** crystallized from ethanol as colorless needles, m. p. 156–157°. A mixture melting point with the semicarbazone from the ketone prepared by method B showed no depression.

Anal. Calcd. for $C_{28}H_{23}N_5O_3$: N, 14.67. Found: N, 14.26.

(B) To a suspension of 9 g. of aluminum chloride in 200 cc. of carbon tetrachloride cooled to 10–15° was added a mixture of 26 g. of benzanilide and 110 cc. of carbon tetrachloride in the manner described by Marvel and Sperry[10] in their preparation of benzophenone. The mixture was heated and worked up in a similar way, but the reaction product was extracted into ether. The residue from the ether extract was recrystallized from ethanol and acetone; the yield of colorless platelets melting at 151–152° was 9 g.

Anal. Calcd. for $C_{27}H_{20}N_2O_3$: N, 6.66. Found: N, 6.38.

The **semicarbazone** melted at 156–157°.

Summary

1. Condensation of chloral and acetanilide in concentrated sulfuric acid led to N-(1-hydroxy-2,2,2-trichloroethyl)-acetanilide.

2. Dibenzanilide and chloral were condensed to 1,1,1-trichloro-2,2-bis-(*p*-dibenzamidophenyl)-ethane. Complete hydrolysis of the dibenzamido groups of this compound was always accompanied by dehydrohalogenation leading to 1,1-dichloro-2,2-bis-(*p*-aminophenyl)-ethylene, but partial hydrolysis furnished 1,1,1-trichloro-2,2-bis-(*p*-benzamidophenyl)-ethane. This compound exhibited marked antitubercular activity *in vitro*.

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[9] Kikuth, unpublished results; Office of the Publication Board, Department of Commerce, Report No. 248, p. 63.

[10] Marvel and Sperry, "Org. Syntheses," Coll. Vol. I, 95 (1941).