[CONTRIBUTION FROM THE CHEMOTHERAPY SECTION, NATIONAL CANCER INSTITUTE, NATIONAL INSTITUTES OF HEALTH]

The Halogen-activating Effect of the N-Oxide Group in Chlorophenazine-N-oxides. Synthesis of an Isomer of Iodinin

BY DONALD L. VIVIAN

It is shown that the ordinarily non-reactive chlorine of 2-chlorophenazine and of 2,7-dichlorophenazine is made quite labile toward aqueous alcoholic alkali by conversion of the compounds to N,N'-dioxides, leading to the syntheses of 2-phenazinol-5,10-dioxide and 2,7-phenazinediol-5,10-dioxide. The latter is an isomer of iodinin. Further, it is demonstrated that only one chlorine, presumably the one para to the N-oxide group, is labile in 2,7-dichlorophenazine-5-oxide. Details are given of the reduction of the 2-phenazinol-5,10-dioxide to 2-phenazinol, affording the easiest method so far known of synthesizing the latter.

The fact that conversion of 2-chlorophenazine to the di-N-oxide labilizes the chlorine toward alkalies, yielding 2-phenazinol-5,10-dioxide by merely refluxing with aqueous alcoholic alkali, has previously been made known in a Communication to the Editor.[1] Reduction of this compound by sodium hyposulfite yielded the already well-known 2-phenazinol. The present paper reports details of these reactions, together with extensions to two other compounds, 2,7-dichlorophenazine-5,10-dioxide and 2,7-dichlorophenazine-5-oxide. The first of these gives 2,7-phenazinediol-5,10-dioxide, an isomer of iodinin, and the first dihydroxyphenazine di-N-oxide of known configuration to be synthesized. The second compound gives a chlorophenazinol-5-oxide. Since only one chlorine is replaced in this latter instance, probably the chlorine atom para to the N-oxide group, the resulting compound is presumed to be 7-chloro-2-phenazinol-5-oxide.

All three of the hydroxyphenazine-N-oxides are of interest because of their close relationship to iodinin, which is known to be 1,6-phenazinediol-5,10-dioxide.[2] Numerous reports have been published on the high antibacterial activity of iodinin and related compounds.[3,4]

Experimental Part

2-Chlorophenazine-5,10-dioxide.—This compound was prepared by use of the general method of Clemo and McIlwain.[5] Ten grams of 2-chlorophenazine, made from 4-chloro-2-nitrodiphenylamine by the method of Waterman and Vivian,[6] was dissolved in 500 cc. of warm glacial acetic acid, and 50 cc. of 30% H_2O_2 added. This mixture was heated 40 hours in an oven at 53-55°, and the product then precipitated by the addition of water. The yield of crude product, melting at 183°[7] with decomposition, was quantitative. Recrystallization from ethanol, in which it was only very sparingly soluble, gave red-orange microneedles, melting with decomposition at 190-191°. *Anal.*[8] Calcd. for $C_{12}H_7ClN_2O_2$: C, 58.4; H, 2.87. Found: C, 58.5; H, 3.06.

2-Phenazinol-5,10-dioxide.—A mixture of 8.5 g. of 2-chlorophenazine-5,10-dioxide, 400 cc. of 95% ethanol, 45 g. of KOH and 250 cc. of distilled water was refluxed for about 16-20 hours in a metal flask. The solution was now a deep reddish-violet color; it was allowed to cool, then filtered, and the phenazinol precipitated by a slight excess of dilute hydrochloric acid. There resulted after drying at room temperature 5.5 g. of red solid, which darkened at 205°. Recrystallization from a large volume of alcohol gave red-orange micro-plates, beginning to darken at 236°, but not completely melting by 280°.

Anal. Calcd. for $C_{12}H_8N_2O_3$: C, 63.2; H, 3.54. Found: C, 63.1; H, 3.87.

2-Phenazinol.—Two and one-half grams of 2-phenazinol-5,10-dioxide was dissolved in a solution of 2.5 g. of NaOH in 25 cc. of distilled water, and into this solution there was slowly stirred 4.5 g. of sodium hyposulfite ("sodium hydrosulfite"). Acidification with dilute acetic acid then gave 2.1 g. of dark olive-green crude, which was purified by vacuum sublimation and recrystallization from benzene. So obtained were pale yellow needles melting gradually with decomposition at 250-260°. *Anal.* Calcd. for $C_{12}H_8N_2O$: C, 73.4; H, 4.11. Found: C, 73.8; H, 4.25. As Kehrmann and Cherpillod[9] indicate in stating that this compound melts with decomposition at "approximately" 253-254°, 2-phenazinol does not have a well-defined melting point. The use of sodium hyposulfite for reduction of the di-N-oxide to the phenazinol follows Clemo and McIlwain,[5] who used it to reduce 1-phenazinol-5,10-dioxide to 1-phenazinol.

2,7-Dichlorophenazine.—This compound has been reported by Bamberger and Ham,[10] who prepared it from *p*-chloronitrosobenzene, and who gave m.p. 265.5° (cor.). The present method of synthesis was as follows:

(a) **4,5'-Dichloro-2'-methoxy-2-nitrodiphenylamine.**—A mixture of 826 g. of 5-chloro-2-anisidine, 1 kg. of 2,5-dichloronitrobenzene and 1 kg. of fused sodium acetate was heated in a flask bearing an air-condenser for 40 hours in an oil-bath at 210-225°. Following steam-distillation to remove unreacted material, the dried crude was extracted with ether in a Soxhlet, giving 412 g. of dark red product, pure enough to be used for the phenazine preparation given below. Recrystallization from glacial acetic acid (Norit) gave small red needles melting at 191-192°. *Anal.* Calcd. for $C_{13}H_{10}Cl_2N_2O_3$: C, 49.9; H, 3.22. Found: C, 49.5; H, 3.33.

(b) **2,7-Dichlorophenazine.**—The method of Waterman and Vivian[6] was again used. Five grams of the crude 4,5'-dichloro-2'-methoxy-2-nitrodiphenylamine in an open flask was heated with 5 g. of $FeC_2O_4 \cdot 2H_2O$ and 50 g. of granulated lead in an oil-bath at 260-265° until the internal temperature, which had reached a maximum of about 290°, began to fall. This required about 15 minutes from the time of putting the mixture in the hot oil-bath. Vacuum sublimation gave 1.3 g. of product melting at 240-260°. Recrystallization from benzene gave small sulfur-yellow needles melting at 266-268°. *Anal.* Calcd. for $C_{12}H_6Cl_2N_2$: C, 57.9; H, 2.43. Found: C, 58.1; H, 2.84.

2,7-Dichlorophenazine-5,10-dioxide.—The very low solubility of 2,7-dichlorophenazine in glacial acetic acid necessitated the use of a large volume of the solvent. Accordingly, 4 g. of the phenazine was dissolved in 4 l. of glacial acetic acid at 60°, and 400 cc. of 30% H_2O_2 added with stirring. Heating for 16 hours at 53-55°, and pouring the mixture into several volumes of water gave 3.75 g. red-orange platelets with a golden luster. These exploded at 220°. Recrystallization from glacial acetic acid gave a product shrinking at 228°, and exploding at 230°. *Anal.* Calcd. for $C_{12}H_6Cl_2N_2O_2$: C, 51.3; H, 2.15. Found: C, 51.6; H, 2.36.

2,7-Phenazinediol-5,10-dioxide.—A mixture of 3.2 g. of 2,7-dichlorophenazine-5,10-dioxide, 30 g. of KOH, 75 cc. of H_2O and 75 cc. of ethanol was refluxed in a metal flask for 6 days on the water-bath. The solution was allowed to cool, then filtered, leaving a considerable quantity of residue.

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[1] D. L. Vivian, THIS JOURNAL, **71**, 1139 (1949).

[2] G. R. Clemo and A. F. Daglish, *J. Chem. Soc.*, 1481 (1950).

[3] See, for example, H. McIlwain, *J. Chem. Soc.*, 322 (1943).

[4] C. N. Ihland, *Nature*, **161**, 1010 (1948).

[5] G. R. Clemo and H. McIlwain, *J. Chem. Soc.*, 479 (1938).

[6] H. C. Waterman and D. L. Vivian, *J. Org. Chem.*, **14**, 289 (1949).

[7] All melting points are corrected.

[8] Analyses by Mrs. M. M. Ledyard and Mrs. E. G. Peake, under the supervision of Mr. W. C. Alford.

[9] F. Kehrmann and F. Cherpillod, *Helv. chim. acta*, **7**, 975 (1924).

[10] E. Bamberger and W. Ham, *Ann.*, **382**, 91 (1911).

The resulting deep purplish-red solution was then made slightly acid by dilute HCl, and the very finely divided precipitate separated and washed to neutrality by centrifuging. Dried at 55°, the product weighed 1.8 g., and consisted of reddish-brown micro-plates, decomposing about 230°. *Anal.* Calcd. for $C_{12}H_8N_2O_4$: C, 59.0; H, 3.30. Found: C, 58.9; H, 3.52.

Longer refluxing with alkali than in the case of 2-chlorophenazine-5,10-dioxide still leaves considerable residue when 2,7-dichlorophenazine-5,10-dioxide is so treated; prolonged refluxing over a period of ten days or more has not yielded a residue-free solution. Moreover, the analytical data for samples of 2,7-phenazindiol-5,10-dioxide recrystallized from glacial acetic acid have never been satisfactory. These various phenomena are being investigated, with the aim of determining whether they are due to instability of the compound under the given conditions, etc.

7-Chloro-2-phenazinol-5(?)-oxide.—A mixture of 1.5 g. of 2,7-dichlorophenazine-5-oxide[10], 200 cc. of ethanol, 120 cc. of distilled water and 40 g. KOH was refluxed overnight in a metal flask, and the cooled and filtered reddish-violet solution made slightly acid with dilute HCl. There were precipitated very small deep yellow needles weighing 1.0 g. after washing to neutrality and drying. These, after two recrystallizations from glacial acetic acid, began to decompose at about 260°. *Anal.* Calcd. for $C_{12}H_7ClN_2O_2$: C, 58.4; H, 2.86; Cl, 14.4. Found: C, 58.3; H, 3.11; Cl, 14.7.

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[CONTRIBUTION FROM THE RICHARDSON CHEMICAL LABORATORY OF TULANE UNIVERSITY]

Alkylation with Long Chain *p*-Toluenesulfonates. I. Alkylation of Phenols with *n*-Octadecyl *p*-Toluenesulfonate

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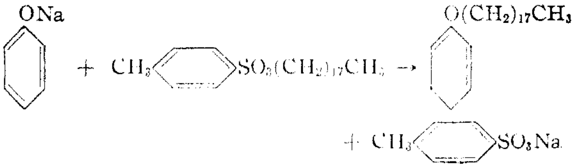
n-Octadecyl *p*-toluenesulfonate has been examined as an alkylating agent for phenols, and it has been found that the *n*-octadecyl aryl ethers are formed in 50 to 75% yields.

Esters of *p*-toluenesulfonic acid have been long established as alkylating agents for many organic types, including amines,[1,2,3] alkoxides,[4] phenoxides,[5] thiophenoxides,[6,2] Grignard reagents[4,7,8] and metallic salts.[1,9,10] The long chain (dodecyl and above) esters of *p*-toluenesulfonic acid have not been studied as alkylating agents except for the work of Sekera and Marvel[1] in 1933, who alkylated *n*-butylamine with dodecyl and hexadecyl *p*-toluenesulfonate and formed heptadecanonitrile from the hexadecyl ester and sodium cyanide.

We have undertaken in this Laboratory to examine the applicability of the long chain alkyl esters as alkylating agents. In this paper we are reporting the results of some experiments in which phenol and several phenolic types have been alkylated with *n*-octadecyl *p*-toluenesulfonate. The compounds alkylated were phenol, *o*- and *p*-nitrophenol, *p*-chlorophenol, *p*-cresol, α- and β-naphthol. The yields of octadecyl aryl ethers from the reaction varied from 51 to 75%.



n-Octadecyl *p*-toluenesulfonate was prepared from *n*-octadecanol and *p*-toluenesulfonyl chloride by a modification of the procedure of Sekera and Marvel[1,11] and we have obtained yields of the *n*-octadecyl ester of above 80%, an improvement over the earlier work by about 25%.

Experimental

***n*-Octadecyl *p*-Toluenesulfonate.**—Several modifications were made in the procedure given for the preparation of *n*-dodecyl *p*-toluenesulfonate.[11] To the cooled mixture of *n*-octadecyl alcohol, Eastman Kodak Co. white label (135 g.; 0.5 mole) and 300 g. of dry C.P. pyridine, 120 g. of *p*-toluenesulfonyl chloride was added. The mixture was stirred for 5 hours at a temperature below 15°. On pouring the mixture into one liter of ice-water the ester crystallized. It was collected on a Buchner funnel, washed several times with water, and sucked as dry as possible. It was purified as described previously from methanol. The yield of ester based upon the *n*-octadecyl alcohol used was 92%; m.p. 54–55°. This material was sufficiently pure for the work described below. After recrystallization from petroleum ether (b.p. 35–60°) using 5 ml. per 3 g., the melting point was 56° (reported,[11] 56°). The recovery was 90%.

Anal. Calcd. for $C_{25}H_{44}O_3S$: S, 7.55. Found: S, 7.46, 7.53.

***p*-Nitrophenyl *n*-Octadecyl Ether.**—In a 500-ml. three-necked, round-bottomed flask, equipped with a stirrer and a water condenser, were placed 7.5 g. (0.056 mole) of *p*-nitrophenol and 2.2 g. (0.055 mole) of sodium hydroxide dissolved in 100 ml. of water. To this mixture was then added 21.2 g. (0.050 mole) of *n*-octadecyl *p*-toluenesulfonate. The mixture was stirred and heated under reflux for about 20 hours. The hot reaction mixture was then poured into a 250-ml. separatory funnel and the water layer separated and discarded. The oil layer was washed with 6 *N* sodium hydroxide until a yellow color was no longer imparted to the alkaline wash layer. The organic material was then dissolved in benzene and washed twice with hot water. The benzene solution was cooled in an ice-bath, and the precipitated solid ether collected and dried on a Buchner funnel. This procedure yielded 11.4 g. of material melting from 68–71°. One recrystallization from ligroin (b.p. 65–90)) gave 11.1 g. of material melting at 70–71°. This corresponded to a 56.7% yield of ether based upon the ester.

Anal. Calcd. for $C_{24}H_{41}O_3N$: N, 3.58. Found: N, 3.65.

***p*-Aminophenyl *n*-Octadecyl Ether.**—In a 300-ml. round-bottomed flask were placed 5 g. (0.013 mole) of *p*-nitro-

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(1) Sekera and Marvel, THIS JOURNAL, **55**, 345 (1933).

(2) Slotta and Franke, *Ber.*, **63B**, 678 (1930).

(3) Rodionov, *Bull. soc. chim. France*, [4], **45**, 121 (1929).

(4) Ferns and Lapworth, *J. Chem. Soc.*, **101**, 273 (1912).

(5) Finzi, *Ann. chim. applicata*, **15**, 41 (1925); [*C. A.*, **19**, 2647 (1925)].

(6) Gilman and Beaber, THIS JOURNAL, **47**, 1449 (1925).

(7) Rossander and Marvel, *ibid.*, **50**, 1491 (1928).

(8) Gilman and Beaber, *ibid.*, **47**, 518 (1925).

(9) Cary, Vitcha and Shriner, *J. Org. Chem.*, **1**, 280 (1936).

(10) Slotta and Lorenz, *Ber.*, **58B**, 1320 (1925).

(11) Sekera and Marvel, *Org. Syntheses*, **20**, 50 (1940).