[CONTRIBUTION FROM THE ORGANIC CHEMICAL LABORATORY OF THE UNIVERSITY OF FLORIDA]

# Derivatives of Piperazine. IV. Reactions with Derivatives of Monochloroacetic Acid

BY DAVID E. ADELSON AND C. B. POLLARD

This paper is concerned with the reactions of the amino hydrogens of piperazine and the chlorine of various derivatives of monochloroacetic acid, *e. g.*, the esters, the nitrile, the amide and the corresponding alcohol. In all cases the compounds obtained are di-substituted piperazino derivatives. Optimum conditions for syntheses have been investigated and the inter-conversion of one type of compound into another has been studied. A few of these derivatives have previously been described;[1,2] the present methods of preparation and yields are decided improvements over the older ones.

Piperazino-1,4-bis-(alkyl acetates) (Table I) arise from the action of piperazine on the appropriate chloroacetic ester in ethanol solution in the presence of sodium carbonate. They are purified by distillation *in vacuo* or through intermediate conversion into the di-acid sulfate. These esters are soluble in the common organic solvents. The liquid members are colorless oils; the solid members are white and crystalline.

TABLE I

PHYSICAL CONSTANTS AND ANALYSES OF THE PIPERAZINO-1,4-BIS-(ALKYL ACETATES)[a]

| | | | | | | | Analyses, % N | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | Free base | | Di-acid sulfate | |
| Ester | M. p., °C. corr. | B. p., °C. corr. | Press., mm. | Bath, °C. | $d^{20}_{20}$ | $n^{25}$ | Calcd. | Found | Calcd. | Found |
| Methyl | 62.5 | 156–157 | 5 | 210 | ... | ... | 12.17 | 12.18 | ... | ... |
| Ethyl | 47.5 | 158.5–159 | 4 | 200 | ... | ... | 10.85 | 10.69 | 6.16 | 6.12 |
| *n*-Propyl | Oil | 177–178 | 5 | 220 | 1.052 | 1.462 | ... | ... | 5.80 | 5.73 |
| *n*-Butyl | Oil | 194–194.5 | 4 | 230 | 1.022 | 1.447 | ... | ... | 5.49 | 5.41 |
| *n*-Hexyl | 39.5 | 228–230[b] | 5 | 290 | ... | ... | ... | ... | 4.95 | 5.02 |

[a] Average yield: 80–85%. [b] Slight decomposition.

When shaken with concentrated ammonium hydroxide these esters yield piperazino-1,4-bis-(ethanamide) which chars over 250°. This compound is best recrystallized from water. Calcd. for $C_8H_{16}O_2N_4$: N, 27.99. Found: N, 27.90. This di-amide may be synthesized in 90% yield from piperazine, chloroethanamide and sodium carbonate by refluxing in toluene for two hours. After filtration, the solid residue is extracted with hot water. Found: N, 27.87.

Piperazino-1,4-bis-(ethanenitrile) is formed in 35% yield by dehydration of piperazino-1,4-bis-(ethanamide). It crystallizes from ethanol in long needles which melt at 165°. The compound can be synthesized directly from piperazine, chloroethanenitrile and sodium carbonate in quantitative yield. Calcd. for $C_8H_{12}N_4$: N, 34.14. Found: N, 33.98.

The di-acid sulfate of piperazino-1,4-bis-(acetic acid) arises in quantitative yield by treatment of piperazino-1,4-bis-(ethanamide) with concentrated sulfuric acid and sodium nitrite. After the evolution of nitrogen is complete, the desired product is precipitated as a white powder by addition of four parts of ice for every part of sulfuric acid used. Calcd. for $C_8H_{14}O_4N_2 \cdot 2H_2SO_4$: N, 7.03. Found: N, 6.86. Ammonia converts this compound into piperazino-1,4-bis-(acetic acid). The latter crystallizes from water with two molecules of water of crystallization and decomposes over 250°. Calcd. for $C_8H_{14}O_4N_2 \cdot 2H_2O$: N, 11.76; $H_2O$, 15.13. Found: N, 11.96; $H_2O$, 15.12. Analyses of the oven-dried material: Calcd. for $C_8H_{14}O_4N_2$: N, 13.86. Found: N, 13.96.

0.1 mole of piperazino-1,4-bis-(ethyl acetate) is dissolved in 400 cc. of freshly distilled *n*-butanol and 1.2 moles of sodium is added in large pieces. After the original violent reaction has subsided, the solution is refluxed until all of the sodium disappears, care being taken to maintain anhydrous conditions throughout. Water is added and the *n*-butanol is removed by steam distillation. Extraction of the strongly alkaline residue with hot amyl acetate and subsequent concentration of the latter yields (30%) piperazino-1,4-bis-(β-ethanol) which melts at 135–135.5°. A mixed melting point with an authentic specimen[3] shows no depression. Upon filtration of the concentrated alkaline reduction solution and boiling the residue with ethanol-water mixture (4:1 by volume), silky needles of piperazino-1,4-bis-(sodium acetate) are obtained. Calcd. for $C_8H_{12}O_4N_2Na_2$: N, 11.38. Found: N, 11.43. A sample of the material prepared from piperazine and sodium chloroacetate shows similar properties and 11.40% N upon analysis.

*n*-Hexyl chloroacetate, hitherto unreported in the literature, is prepared and purified in the usual fashion from molar proportions of chloroacetyl chloride and *n*-hexanol. The final yield after distillation is 80%. *n*-Hexyl chloroacetate is a colorless liquid that possesses a distinct fruity odor; b. p. 218.5–219.5° at 758 mm.; $d^{20}_{20}$ 1.026; $n^{25}$ 1.435.

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(1) Van Dorp, *Rec. trav. chim.*, **28**, 68 (1909).

(2) Franchimont and Kramer, *ibid.*, **31**, 40 (1912).

(3) Adelson, MacDowell and Pollard, unpublished work.

## Summary

1. The preparation and properties of compounds arising from the reaction between piperazine and derivatives of monochloroacetic acid have been described.

2. *n*-Hexyl chloroacetate has been synthesized and its physical constants reported.

3. The reaction between piperazino-1,4-bis-(ethanenitrile) and hydrogen peroxide is being studied.

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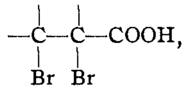
# The Dehalogenation of $\alpha,\beta$-Dibromo Acids. II. The Influence of the Acid Structure on the Yields of Bromoolefins

BY JAMES K. FARRELL AND G. BRYANT BACHMAN

Dehalogenation of $\alpha,\beta$-dibromo acids has been shown by many investigators to yield a large variety of products. In most cases these workers have interested themselves principally in the $\alpha$-bromoolefinic acids which usually make up the major portion of the products, and they have determined not only the yields of these acids but also the ratio in which their stereoisomeric forms arise. More recently a definite study of the preparation and properties of the bromoolefins which also arise in such dehalogenations under suitable conditions has been undertaken in this Laboratory.[1]

$$R_1R_2CBrCR_3BrCOOH \xrightarrow{-HBr} R_1R_2C{=}CR_3Br + CO_2$$

As a part of this program it was decided to investigate the effect of varying the structure of the dibromo acid on the yield of bromoolefin. The importance of such a study becomes readily apparent if one considers as an example the difference in behavior of cinnamic and crotonic acid dibromides upon dehalogenation with aqueous sodium carbonate. The former yields bromostyrene in 65% yields; the latter gives only a trace of bromopropene. The only difference between these two acids lies in the nature of the hydrocarbon radical attached to the $\beta$-carbon atom of the acid. Even if attention is confined to the aliphatic series alone, striking differences are manifested. Thus $\alpha,\alpha,\beta$-tribromobutyric acid gives 1,1-dibromopropene in 88% yields while $\alpha,\beta$-dibromopelargonic acid gives 1-bromooctene in only 30% yields when dehalogenated under the same conditions as the two acids mentioned above.

If one considers the basic skeleton of these dibromo acids as  $-\underset{Br}{\overset{|}{\underset{|}{C}}}-\underset{Br}{\overset{|}{\underset{|}{C}}}-COOH$, there are obviously three points at which different groups may be introduced into the molecule—one on the $\alpha$-carbon atom, and two on the $\beta$-carbon atom of the chain. In the present work most of the possible $\alpha,\beta$-dibromo acids of the aliphatic series up to and including those containing six carbon atoms have been studied. Whenever the structure of the acid permitted it, the corresponding $\alpha,\alpha,\beta$-tribromo acids were also prepared and their dehalogenation studied. In such cases dibromoolefins were formed.

$$R_1R_2CBrCBr_2COOH \xrightarrow{-HBr} R_1R_2C{=}CBr_2 + CO_2$$

In order to make comparisons valid all dehalogenations were carried out by standardized procedures, using pyridine or 20% aqueous sodium carbonate as the bases. The reasons for this selection of bases are discussed in the first paper of this series. More detailed descriptions of the procedures are given in the experimental part. In the following table (I) are shown the results. A few yields obtained in previous work are also included since they are pertinent to the general discussion.

It is apparent that the nature and position of the groups introduced, strongly influence the yield of bromoolefins obtained. With hydrogen in all three positions the yield of bromoolefin is practically zero and the principal product is the corresponding $\alpha$-bromoolefinic acid or its polymer.[2] Replacement of one hydrogen by a bromine atom in the alpha position or by an alkyl group in the alpha or beta positions gives acids which yield about 30% of bromoolefins. The nature of the alkyl group introduced does not exert much influence on the yield of bromoolefin. Thus it will be noted that a methyl, ethyl, propyl

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[1] Bachman, THIS JOURNAL, 55, 4279 (1933).

[2] An odor suggestive of bromoethylene was noted but none of this compound could be isolated.