SYNTHESIS OF QUATERNARY AMMONIUM DIBASIC ACIDS, ANHYDRIDES AND ESTERS OF MORPHOLINE PIPERIDINE AND DIETHYLAMINE

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ABSTRACT. — Several new organic dibasic acids, anhydrides and esters of morpholine, piperidine and diethylamine have been synthesized and characterized. Their molecular weights were determined potentiometrically with a silver, silver bromide indicating electrode versus a glass reference electrode. Morpholine, piperidine and diethylamine were dialkylated with ethyl bromacetate to form respectively, *N,N*-dicarbethoxymethylmorpholinium bromide (I) *N,N*-dicarbethoxymethylpiperidinium bromide (II) and diethyldicarbethoxylammonium bromide (III). These esters were hydrolyzed with concentrated hydrobromic acid to produce the dibasic acids, *N,N*-dicarboxymethylmorpholium bromide (IV), *N,N*-dicarboxymethylpiperidinium bromide (V) and dicarboxymethyldiethylammonium bromide (VIII), respectively. Compounds IV and V were successfully converted to their cyclic anhydrides, but compound VIII failed to produce the cyclic anhydride.

Morpholine, piperidine and diethylamine were successfully dialkylated with ethyl bromacetate to form *N, N*-dicarbethoxymethylmorpholinium bromide (I), *N,N*-dicarbethoxymethylpiperidinium bromide (II) and diethyldicarbethoxymethylammonium bromide (III). Hydrolysis of these esters with refluxing concentrated hydrobromic acid produced the corresponding dibasic acids. This method of synthesizing the dibasic acids proves to be a much more facile method than alkylating the secondary amines directly with bromoacetic acid. The monoacids are difficult to isolate and purify as shown by Remizov and Khromov-Bousov (1953).

N, N-dicarboxymethylmorpholinium bromide (IV) and *N,N*-dicarboxymethylpiperidinium bromide (V) were easily converted to their cyclic anhydrides (compounds VI and VII) by heating the dibasic acids below 90° in acetic anhydride.

Dicarboxymethyldiethylammonium bromide (VIII) could not be converted to the cyclic anhydride with acetic anhydride. Several other anhydride syntheses were attempted with similar results.

MATERIALS AND METHODS

Apparatus — The potentiometric titrations were run using a Leeds and Northrup Model 7401 pH meter, a Beckman glass reference electrode (No. 41263) and a laboratory constructed silver, silver bromide indicating electrode. The indicating electrode was constructed from a No. 14 gauge silver wire and coated with silver bromide by immersing the wire as an anode in a 37% hydrobromic acid solution with a platinum wire as the cathode. The silver bromide coating was formed in 30 seconds at 0.5 volt.

Monoester Preparation—The monoesters of morpholine, piperidine and diethylamine were prepared by reacting the corresponding amine with ethyl bromacetate in a two to

one ratio in ethyl acetate. The excess amine was required to remove the hydrogen bromide liberated. Without an excess of secondary amine, the monoester yield was consideraly reduced. The per cent yields (based upon the secondary amine hydrobromide salt) and the boiling points were:

ethyl 4-morpholine acetate (IX), 99% yield, 68± 4° at 0.600 mm
ethyl 1-piperidine acetate (X), 95% yield, b.p. 56± 2° at 0.150 mm
ethyl *N*,*N*-diethylglycinate (XI), 95% yield, b.p. 50± at 2° at 3.50 mm

Dister Preparation—The diesters (I, II, III) were prepared by alkylating the monoesters (IX, X, XI) with ethyl bromacetate in refluxing ethyl acetate. The morpholine (46% yield) and piperidine (64% yield) diesters (I & II) precipitated as a solid, but the diethylamine diester (III) formed as an insoluble viscous liquid. Several attempts to recrystallize III from chloroform, ethyl acetate, methoxyethanol, ethanol, benzene and mixed solvents of these proved fruitless.

Diester I and II were recrystallized from a mixed solvent of ethyl acetate and absolute ethanol. Compounds I and II were not hygroscopic and had mp of 157-58° and 131.5-32.5° respectively.

Diester I; Anal. Calcd. for $C_{12}H_{22}O_5NBr$: C, 42.36; H, 6.52; N, 4.12; Br, 23.49. Found: C, 42.42; H, 6.32; N, 3.97; Br, 23.30. *Mol. Wt.* Calcd. 340.22. Found: 341 ± 2.

Diester II; Anal. Calcd. for $C_{12}H_{22}NBr$: C, 46.16; H, 7.15; N, 4.14. Found: C, 46.07; H, 7.16; N, 4.18. *Mol. Wt.* Calcd. 338.24. Found: 339 ± 1.

Diacid Preparations—The diacids (IV, V, VIII) were prepared by refluxing the respective diesters (I, II, and III) in an excess of 48% hydrobromic acid for 3 hours. The solvent was removed by a rotary evaporator.

Diacid IV was recrystallized from acetic acid containing 4% water; mp 193°d and 40% yield. Diacid V and VIII were recrystallized from acetic acid containing 5% acetic anhydride: V, mp 174°d, 43% yield; VIII mp 192°d, 39% yield. (The yield of VIII was based on the monester (XI) since the diester III could not be recrystallized).

Diacid IV; Anal. Calcd. for $C_8H_{14}O_5NBr$: C, 33.82; H, 4.95; N, 4.93. Found: C, 33.75; H, 4.95; N, 5.00. *Mol. Wt.* Calcd. 284.1. Found: 285 ± 1.

Diacid V; Anal. Calcd. for $C_9H_{16}O_4NBr$: C, 38.31; H, 5.72; N, 4.96; Br, 28.32. Found: C, 38.37: H, 6.20; N, 4.94; Br, 28.32. *Mol. Wt.* Calcd. 282.1. Found: 284 ± 1.

Diacid VIII; Anal. Calcd. for $C_8H_{16}O_4NBr$: C, 35.57; H, 5.97; N, 5.19; Br, 29:58. Found: C, 35.56; H 5.42; N, 5.19; Br, 29.63. *Mol. Wt.* Calcd. 270. Found: 271 ± 1.
As similar to the diester (I and II), the diacids (IV and V) were not hygroscopic.

Anhydride Preparations—The anhydrides VI and VII were prepared by heating the diacids in an excess of acetic anhydride at 80-90° for 3 hours. If the temperature was allowed to increase above 90°, degradation of the reactants occurred. Approximately one third of the solvent was distilled under aspirator pres-

sure to verify the formation of acetic acid. The anhydride crystals were insoluble in acetic anhydride, consequently, they were easily isolated. After washing with ethyl ether, the anhydrides were recrystallized from acetic acid containing 5% acetic anhydride. Anhydride VI was synthesized and recrystallized in a 41.-5% yield; mp 190-192°d, while anhydride VII was produced in a 56.-5% yield; mp 185.5°d.

Anhydride VI; Anal. Calcd. for $C_8H_{12}O_4NBr$: C, 36.12; H, 4.51; N, 5.26. Found: C, 32.62; H, 5.61; N, 5.32. *Mol. wt.* Calcd. 266; Found: 267.2 ± 0.1.

All molecular weights are given as averages and ranges of three determinations. The exception to this was diester I which is based on two duplicate determinations.

Discussions and Results

The conversion of secondary amines to quaternary ammonium salts is a well established reaction and several kinetic studies have been published by Grimm (1931), Laidler (1938) and Coleman (1955). This laboratory studied the conversion of secondary amines to quaternary ammonium dibasic acids via the hydrolysis of the dibasic esters. Subsequent research involved the conversion of these dibasic acids to cyclic quaternary ammonium anhydrides as outlined in Figure 1.

The anhydrides of morpholine and piperidine (VI and VII) were successfully synthesized, however, the anhydride of diethylamine was not formed by heating (80° - 90°) the corresponding diacid with acetic anhydride. Only unreacted starting material was recovered. If the acetic anhydride reaction was heated above 90°C, degradation of the diacid (VIII) occurred. Degradation at temperatures above 90° was observed, also, for the diacid of morpholine and piperidine (VI and VII).

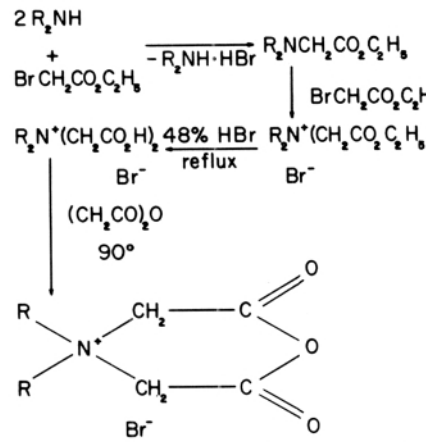

FIGURE 1. Synthesis of Quaternary Ammonium Dibasic Acids and Cyclic Anhydrides.

Three additional anhydride syntheses were unsuccessful with diacid VIII. The benzenesulfonyl chloride-pyridine synthesis for anhydrides by Brewster (1955) resulted in rapid degradation of the starting material at the beginning of the reaction with no external source of heat added.

In the phosgene anhydride synthesis by Rinderknecht (1964), diacid VIII was converted successfully to the triethylamine salt. However, when the cold phosgene (12% in benzene) solution was added to this salt, triethylamine hydrochloride and starting material were recovered. The variation of the reaction temperature from the recommended ice-bath temperature to room temper-

ature failed to alter the course of the reaction.

Ethoxyacetylene reacts with acids in methylene chloride to form anhydrides and ethyl acetate according to a procedure by Eglenton (1954). Unfortunately, diacid VIII was not soluble in refluxing methylene chloride. Consequently, when a solution of ethoxyacetylene in methylene chloride was refluxed with diacid VIII, no reaction occurred.. The unreactivity of diacid VIII compared with the facile anhydride formation of diacids IV and V was indeed surprising to observe, especially so when Bruice (1965) had synthesized ten different 3,3-substituted glutaric anhydrides. The substituents of Bruice's anhydrides were combination of methyl, ethyl, *n*-propyl, isopropyl, *t*-butyl and phenyl. Bruice synthesized the anhydrides from the corresponding dibasic acids by heating the acids at reflux (120° - 160°) with acetic anhydride for at least 2 hours.

Earlier anhydride syntheses from substituted glutaric acids were made by Howles (1900). Howles discovered that *cis*-1-methyl-2-isopropylglutaric acid formed the anhydride if heated with acetyl chloride, but the *trans*-2-methyl-3-isopropyglutaric acid did not. It is worth noting that Bruice was successful in synthesizing both the 3,3-methylisopropyl and the 3,3-methyl-*t*-butylglutaric acids. Undoubtedly, steric hindrance plus temperature effect (acetyl chloride, bp 51°) were operating to prevent anhydride formation in the *trans*-acid of Howles.

Stuart-Briegleb models were constructed for diacids IV, V and VIII to observe steric hindrance to anhydride formation. The preferred configuration to permit the maximum amount of free rotation appeared as shown in Figure 2. If free rotation of the ethyl groups occurred, the carboxyl groups could be prevented from reacting to form the anhydride. If one were permitted to go to higher temperatures (greater than 90°), the distortion in bond angles and lengths could possibly allow anhydride formation. This may explain why diacid VIII could not be converted to the anhydride while Bruice was successful in synthesizing the analogous anhydride of 3,3-diethylglutaric acid.

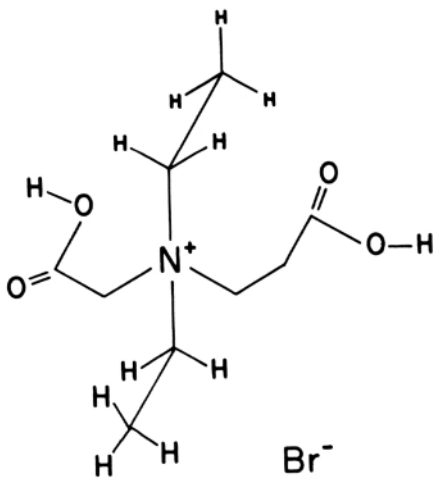

FIGURE 2. Conformation of Dicarboxymethyldiethylammonium Bromide.

In addition to the restriction in reflux temperature for diacid VIII (90°), it should also be emphasized that all of the quaternary ammonium dibasic acids (IV, V and VIII) were fairly insoluble in acetic anhydride. This probably was not the case with the 3,3-substituted glutaric acids of Bruice.

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