Eight-Membered Ring Heterocycles from Primary Amines, Hydrogen Sulfide, and Formaldehyde[1]

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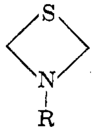
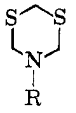
We have established, by molecular weight and spectral determinations, that the compounds having an equivalent content of nitrogen and sulfur which are obtainable from the reaction of a primary alkylamine, hydrogen sulfide, and aqueous formaldehyde possess eight-membered rings. Examples from methylamine and cyclohexylamine, respectively, are 3,7-dimethyl-1,5-dithia-3,7-diazacyclooctane (IIIa) and 3,7-dicyclohexyl-1,5-dithia-3,7-diazacyclooctane (IIIb).

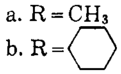
In the course of investigating transannular interactions between various combinations of functional groups, we wished to prepare certain cyclic models having sulfide and tertiary amino-nitrogen in juxtaposition. One structure of interest was that originally reported by Le Fèvre and Le Fèvre,[2] 3-methyl-1,3-thiazetidine (Ia), to result from the addition of aqueous methylamine saturated with hydrogen sulfide to formalin. Their report included the conversion of the C_3H_7NS compound, by warming in aqueous acetone, to 5-methyl-5,6-dihydro-1,3,5-dithiazane (IIa), $C_4H_9NS_2$, prepared much earlier by Wohl.[3]



I



II


a. R = CH$_3$
b. R =

A repetition of the synthesis of the "3-methyl-1,3-thiazetidine" yielded a compound of m.p. 127–130° (reported,[2] 138–139°) with correct analysis for the empirical formula C_3H_7NS. It was suspected immediately that this did not represent the molecular formula since the high melting point was unreasonable for the four-membered ring structure. Moreover, during purification it was found that the compound was *less* readily sublimed than the contaminant, 5-methyl-5,6-dihydro-1,3,5-dithiazane (IIa). The "3-methyl-1,3-thiazetidine" is not the sole suspect structure of the four-membered ring type. Braithwaite and Graymore[4,5] synthesized "3-cyclohexyl-1,3-thiazetidine" (Ib) from cyclohexylamine, hydrogen sulfide, and formaldehyde, and Collins and Graymore[6] determined its basicity. Again, the melting point of 117–118° (reported,[5] 118–119°) seemed out of line for a $C_8H_{15}NS$ structure (Ib) relative to Ia.

Accurate molecular weight determinations on the methyl and cyclohexyl compounds, which would solve the structural enigma, were troublesome. The molecular weight obtained for the cyclohexyl compound of empirical formula $C_8H_{15}NS$ in a Menzies-Wright ebullioscopic apparatus,[7] with benzene as the solvent, indicated that the value was at least twice that calculated (157.27) for 3-cyclohexyl-1,3-thiazetidine, but the individual results observed were erratic and the melting point of the material recovered following the determinations (m.p. 107–114°) showed that some decomposition had taken place. This decomposition was regarded as the principal cause of the nonintegral multiple of 157.27, within limits, for the observed molecular weight, since 5-cyclohexyl-5,6-dihydro-1,3,5-dithiazane (IIb), which did not decompose appreciably under the conditions of the determination, gave a reasonable value for $C_9H_{17}NS_2$ (calcd., 203.36; found, 214). When the $(C_3H_7NS)_x$ and $(C_8H_{15}NS)_x$ compounds were sublimed into a mass spectrometer (Type CEC 21–103) using the conventional inlet system at 140°, the highest mass numbers obtained were 135 and 203, respectively, corresponding to IIa and IIb, and indicating that decomposition had occurred in the inlet system. These experiments made firm our conviction that the "thiazetidines" actually consisted of larger rings, of either eight or twelve members, or, less hopefully, a mixture.

The problem of molecular weight was solved by utilizing a vapor pressure osmometer employing thermistors.[8] Operation at 37° in acetone permitted the determinations to be made without decomposition of the solutes. The *N*-methyl compound was found to have the molecular formula $C_6H_{14}N_2S_2$ (calcd., 178.30; found, 178); the *N*-cyclohexyl compound, $C_{16}H_{30}N_2S_2$ (calcd., 314.54; found, 313). The NMR and ultraviolet absorption spectra permitted a decision as to whether the symmetrical (III) or unsymmetrical (IV) eight-membered ring structures were correct. The

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[1] Partial support by a research grant (NSF-G14121) from the National Science Foundation is gratefully acknowledged.

[2] C. G. Le Fèvre and R. J. W. Le Fèvre, *J. Chem. Soc.*, 1142 (1932). Their statement was that the formulation (*i.e.*, I) was not improbable.

[3] A. Wohl, *Ber.*, **19**, 2344 (1886).

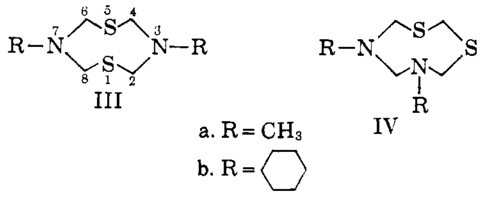
[4] E. R. Braithwaite and J. Graymore, *J. Chem. Soc.*, 208 (1950).

[5] E. R. Braithwaite and J. Graymore, *ibid.*, 143 (1953).

[6] D. J. Collins and J. Graymore, *ibid.*, 2893 (1958).

[7] A. W. C. Menzies and S. L. Wright, Jr., *J. Am. Chem. Soc.*, **43**, 2314 (1921).

[8] J. J. Neumayer, *Anal. Chim. Acta*, **20**, 519 (1959).



III

IV

a. R = CH_3

b. R =

NMR spectrum of the *N*-methyl compound showed two singlets at τ values of 7.58 and 5.62, with relative areas of 6:8, corresponding to methyl and methylene groups, and indicative of structure IIIa. The alternative structure IVa would require the fortuitous possibility that the methylene protons would all exhibit the same chemical shift, but this structure could be ruled out on the basis of the ultraviolet spectrum. Thus, Fehnel and Carmack[9] have shown that mercaptals exhibit characteristic absorption at 235–240 mμ (log ε *ca.* 2.8), and we find that 5-methyl-5,6-dihydro-1,3,5-dithiazane (IIa), which has the —SCH_2S— moiety, absorbs maximally at 209 mμ (log ε 3.62) with shoulders at 228 (log ε 3.36) and 251 mμ (log ε 2.83) in cyclohexane. By contrast, the $C_6H_{14}N_2S_2$ compound has a single absorption maximum at 208 mμ (log ε 3.86) in the same solvent. The structure is therefore confirmed as IIIa, 3,7-dimethyl-1,5-dithia-3,7-diazacyclooctane. Similarly, the structure of the *N*-cyclohexyl compound, $C_{16}H_{30}N_2S_2$, was shown to be IIIb, 3,7-dicyclohexyl-1,5-dithia-3,7-diazacyclooctane. The NMR spectrum showed a singlet at a τ value of 5.67 and multiplets centered at 7.10 and 8.52 of relative areas 8:2:20, and the ultraviolet spectrum in cyclohexane had a maximum at 209 mμ (log ε 3.94). 5-Cyclohexyl-5,6-dihydro-1,3,5-dithiazane (IIb) served as a spectral model for the alternative structure IVb. The eight-membered ring system of the 2N:2S compounds here determined, and presumably that of similar compounds obtained from other alkyl-[2] and aralkylamines,[4,5] bears close relation to those of S_8, octasulfur, and of $C_4H_8S_4$, the tetramer of thioformaldehyde.[10] At the stage in our work when the ebullioscopic molecular weight determinations of IIIa and b were inconclusive, the paper by Campbell[11] appeared, in which he showed that structure III (R = phenyl), 3,7-diphenyl-1,5-dithia-3,7-diazacyclooctane, should be assigned to the product from *N*-benzylideneaniline, hydrogen sulfide, and formaldehyde, previously regarded as "3-phenylthiazetidine."[12] We wish to record our recognition of Campbell's contribution; still, we continued our investigation until we established by independent and unequivocal means the structures of the *N*-alkyl analogs (III *vs.* I).

As a final check on the molecular weights of the eight-membered ring compounds IIIa and IIIb we turned again to mass spectrometry. When the separate samples were introduced from a glass capillary *directly* into the ion source of a time-of-flight mass spectrometer, the molecular ions of mass 178 (for $C_6H_{14}N_2S_2$) and 315 ± 1 (for $C_{16}H_{30}N_2S_2$) were observed.

Experimental[13]

5-Methyl-5,6-dihydro-1,3,5-dithiazane (IIa).—This compound was prepared by the method of Le Fèvre and Le Fèvre,[2] m.p. 65.2–66.0°; λ_{max} 209 mμ (log ε 3.62), shoulders at 228 (3.36) and 251 mμ (2.83).

5-Cyclohexyl-5,6-dihydro-1,3,5-dithiazane (IIb).—This compound was prepared following directions of Braithwaite and Graymore[4,5] and Le Fèvre and Le Fèvre[2]; colorless needles were crystallized from absolute ethanol, m.p. 56–57° (reported,[5] 58°); λ_{max} 209 mμ (log ε 3.70), shoulders at 228 (3.36) and 252 mμ (2.90). The infrared spectrum (carbon tetrachloride) showed no absorption in the N—H, O—H, or S—H stretching regions. The NMR spectrum (carbon tetrachloride) showed two singlets at τ values of 5.57 and 5.94 in addition to two broad multiplets at 6.57 and 8.55, with relative areas of 4:2:1:10.

Anal. Calcd. for $C_9H_{17}NS_2$: C, 53.15; H, 8.42; N, 6.89; mol. wt., 203.36. Found: C, 53.01; H, 8.45; N, 6.75; mol. wt., 202 (benzene).

3,7-Dimethyl-1,5-dithia-3,7-diazacyclooctane (IIIa).—Synthesized from aqueous methylamine, hydrogen sulfide, and formalin following directions of Le Fèvre and Le Fèvre,[2,14] colorless needles were obtained, m.p. 127–130° (reported,[2] 138–139°), λ_{max} 208 mμ (log ε 3.86). The infrared spectrum (chloroform) showed no bands corresponding to N—H, O—H, or S—H stretching. The NMR spectrum (deuterochloroform) showed two singlets at τ values of 5.62 and 7.58, with relative areas 8:6.

Anal. Calcd. for $C_6H_{14}N_2S_2$: C, 40.41; H, 7.91; N, 15.71; mol. wt., 178.30. Found: C, 40.62; H, 7.97; N, 15.61; mol. wt., 178 (acetone).

3,7-Dicyclohexyl-1,5-dithia-3,7-diazacyclooctane (IIIb).[5,6]—This compound, recrystallized several times from acetone, yielded colorless needles, m.p. 117–118° (reported,[5] 119°); λ_{max} 209 mμ (log ε 3.94). The infrared spectrum (carbon tetrachloride) showed no absorption in the O—H, N—H, or S—H region. The NMR spectrum (carbon tetrachloride) showed a singlet at τ values of 5.67 and multiplets centered at 7.10 and 8.52, with relative areas 8:2:20.

Anal. Calcd. for $C_{16}H_{30}N_2S_2$: C, 61.09; H, 9.61; N, 8.90; mol. wt., 314.54. Found: C, 61.13; H, 9.72; N, 9.17; mol. wt., 313 (acetone).

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(9) E. A. Fehnel and M. Carmack, *J. Am. Chem. Soc.*, **71**, 84 (1949).

(10) M. Schmidt and K. Blaettner, *Angew. Chem.*, **71**, 407 (1959).

(11) T. W. Campbell, *J. Org. Chem.*, **22**, 569 (1957).

(12) D. J. Collins and J. Graymore, *J. Chem. Soc.*, 4089 (1953).

(13) Melting points are corrected. Microanalyses and molecular weight determinations were carried out by Mr. Josef Nemeth and his associates. We are indebted to Mr. Dick Johnson for determination of the infrared and NMR spectra. The ultraviolet absorption spectra were obtained on a Bausch and Lomb Spectronic 505 spectrophotometer and/or a Cary Model 14 recording spectrophotometer in cyclohexane solution. The NMR spectra were obtained with a Varian Associates Model A-60, using tetramethylsilane as an internal standard. Molecular weight measurements reported in the Experimental were carried out utilizing thermistors.[8] The instrument used was a Mechrolab Inc., vapor pressure osmometer Model 301 A.

(14) Also prepared by Dr. T. W. Milligan, University of Illinois.

Acknowledgment.—We especially appreciate the kindness of Dr. D. J. Collins, Bournemouth Municipal College of Technology and Commerce, Lansdowne, Bournemouth, England, who prepared and sent us samples so that we might compare them directly with the compounds ($C_{16}H_{30}N_2S_2$ and $C_9H_{17}NS_2$) obtained in our laboratory. We are grateful to Professor Klaus Biemann, Massachusetts Institute of Technology, Cambridge, Mass., for determination of the mass spectra.

Crossed Cannizzaro Reactions

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Several pairs of aldehydes (including benzaldehyde, substituted benzaldehydes, and furfural) have been subjected to the conditions under which the Cannizzaro reaction usually occurs. Methods adequate for analyzing the resulting mixtures have been developed and tested. The observed disproportionations correspond qualitatively to what would be expected from (a) combined inductive and resonance influences contributed by *m*-nitro-, *p*-bromo-, and *p*-methoxy-substituents on benzaldehyde and (b) the previously observed furfural:benzaldehyde disproportionation ratio.

The work of Davidson and Bogert,[1] which involved the use of formaldehyde and an aromatic aldehyde in a crossed Cannizzaro reaction to give the corresponding aromatic carbinol in good yield, attracted some particular attention to this reaction and has become a frequently used preparative procedure. Soon after the publication of the work just mentioned, Bailar, Barney, and Miller[2] reported the results of a number of crossed Cannizzaro reactions involving pairs of aromatic aldehydes (benzaldehyde and substituted benzaldehydes). The reaction of a mixture of benzaldehyde and furfural with strong sodium hydroxide solution also has been investigated.[3]

This report includes results of experiments which represent extensions of the work of Bailar, Barney, and Miller and that on the benzaldehyde–furfural mixture. Substituted benzaldehydes with substituents of quite different types have been used, and furfural has been included as a component of three reaction mixtures. The pairs of aldehydes are listed in Table I. So far as possible, the crossed Cannizzaro reactions were carried out by the procedure used in the benzaldehyde–furfural study. It is to be noted, then, that the systems were *not* peroxide-free.

The purpose of the investigation was to determine the disproportionations which would occur when the components of the several aldehyde mixtures simultaneously undergo oxidation and reduction in the Cannizzaro reaction.

Analyses of the resultant alcohol and acid mixtures were necessary to determine the extents of the disproportionations. After considerable exploratory work with the various mixtures, methods were developed and tested—necessarily differing from one mixture to another—which yielded results adequate for the problems at hand. Details of the procedures are described in the Experimental, and some test data are listed also. Although complete agreement was not realized between alcohol-mixture and acid-mixture analytical data, the results are of similar magnitudes, and the averages permit an ordering of the several aldehydes representing relative individual susceptibilities to oxidation and to reduction in the Cannizzaro reaction.

From the data in Table I, it is obvious, for example, that *m*-nitrobenzaldehyde is (relatively) extensively oxidized as contrasted to *p*-anisaldehyde, which is much less extensively oxidized—*i.e.*, much more extensively reduced. On the bases of this and prior investigations,[2,3] the five aldehydes studied can be arranged (in order of diminishing susceptibility to oxidation): *m*-nitrobenzaldehyde, furfural, *p*-bromobenzaldehyde, benzaldehyde, and *p*-anisaldehyde. With reference to benzaldehyde and the substituted benzaldehydes, this order correlates with expected combined resonance and inductive influences of the substituent groups on the formyl group, as these should contribute to ease of (a) hydroxide ion attack and (b) hydranion transfer; the relative position of furfural in the series is in agreement with its relationship to benzaldehyde and indirectly, then, to its expected relationships to the substituted benzaldehydes.

Information concerning experimental details is included in the Experimental.

Experimental

Materials. Benzaldehyde.—Practical benzaldehyde was distilled fractionally under reduced pressure in an atmosphere of nitrogen, b.p. 71.5° (18 mm.) [lit.,[3] b.p. 69° (17 mm.)].

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[1] D. Davidson and M. T. Bogert, *J. Am. Chem. Soc.*, **57**, 905 (1935).

[2] J. C. Bailar, Jr., A. J. Barney, and R. F. Miller, *ibid.*, **58**, 2110 (1936); several earlier reports are listed in this publication.

[3] S. E. Hazlet and R. B. Callison, *ibid.*, **66**, 1248 (1944).