

method because tephrosin is eluted with chloroform from aluminum oxide more slowly than is deguelin. When chloroform solution of the two substances is passed through a column of the adsorbent, deguelin practically free from tephrosin is obtained in the first fractions while pure tephrosin is obtained in the subsequent fractions. An example follows:

A mixture of 1 g. of deguelin and 0.5 g. of tephrosin dissolved in 20 cc. of chloroform was passed through a 150 by 12 mm. column of aluminum oxide and eluted with chloroform. The first 50 cc. of percolate gave 0.7 g. of deguelin, melting at 170–171°. The second 50-cc. fraction gave 85 mg. of a mixture melting at 165–172°. The third fraction gave 180 mg. of tephrosin (m. p. 198–200°); the fourth 50-cc. fraction gave 40 mg. of tephrosin (m. p. 199–201°). The mother liquors were not reworked. There appeared to be some decomposition of the deguelin as it and its solution were somewhat yellow. However, passing the recovered deguelin dissolved in chloroform through a bed of norit removes all color and gives a sharp

melting product, melting at 171°. Repetition of the process upon the tephrosin fraction is necessary for complete purification.

Summary

1. Rotenone, dehydrorotenone, tephrosin, and two new compounds, one, $C_{21}H_{20}O_6$, m. p. 164–165°, and the second, $C_{23}H_{20}O_6$, m. p. 189–190°, have been isolated from the seeds of the African berebera tree.

2. A revision of the melting point of tephrosin from 198° to 201° and of isotephrosin from 252° to 260° has been made.

3. A procedure is suggested for the separation and purification of deguelin and tephrosin when the two substances occur together.

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The Configuration of Tervalent Nitrogen. A Bicyclic Hydrazine Derivative¹

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The problem of the configuration of trivalent nitrogen has held a peculiar fascination for chemists ever since the first indication that the bonds did not all lie in a common plane. Although the configuration of the ammonia molecule has now been determined to within narrow limits,² the organic chemists doubtless will consider the problem "solved" only when a structure of the type $R_1R_2R_3N$ has been separated into optical isomers. Despite many ingenious attempts at such resolutions not one has been successful.³ The consistent failure to isolate such optical isomers has now been rationalized by postulating a rapid inversion of configuration resulting from the vibration of the nitrogen through the plane of the three attached groups.

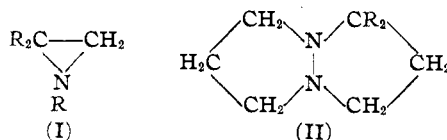
Accordingly, the more recent studies of the problem have centered around compounds in

(1) Most of the material reported herein was taken from the dissertation submitted by A. M. Moore in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the Johns Hopkins University. Preliminary work was carried out by F. Y. Wiselogle in the University of Illinois during the summer of 1940. He is grateful for the facilities which were made available and for many stimulating discussions with various members of the Chemistry Staff. We are indebted to the Hynson, Westcott and Dunning Research Fund for a grant-in-aid covering a part of the cost of this research.

(2) Migeotte and Barker, *Phys. Rev.*, **50**, 418 (1936).

(3) (a) Gilman, "Organic Chemistry, An Advanced Treatise," John Wiley and Sons, Inc., New York, N. Y., 1938, pp. 328–338; (b) "Annual Reports on the Progress of Chemistry," The Chemical Society, London, **36**, 239–246 (1939).

which the activation energy for the inversion of configuration would be increased through structural idiosyncrasies of the molecule. Thus several researchers have been studying substituted ethyleneimines, (I), in which one of the nitrogen



valency angles has been reduced to 63° through its incorporation in a three-membered ring.^{3b,4} Although theoretical calculations have indicated a stable configuration for such derivatives⁵ no optically active compounds have yet been obtained, largely owing to difficulties in the synthesis of requisite intermediates.

We have begun what we believe is a new approach to the problem since all of the valence angles remain normal and there is no structural strain within the molecule. In our projected structure the inversion restriction is achieved by locking two nitrogen atoms together in a bicyclic molecule in which the nitrogens are common to both rings. A representative member of such a class of compounds is a 3,3-disubstituted-1,2-trimethylenepyrazolidine (II). In this model

(4) Cairns, *THIS JOURNAL*, **63**, 871 (1941).

(5) Kincaid and Henriques, *ibid.*, **62**, 1474 (1940).

the four N-N-C bond angles must maintain values close to the normal value for open chain compounds since they are fixed by the strainless, planar, five-membered rings. If the C-N-C bond angles assume their normal values of 108° the two rings cannot be coplanar and the model resembles a butterfly. Such a model has no plane of symmetry in the normal state and must exist in enantiomorphous forms.

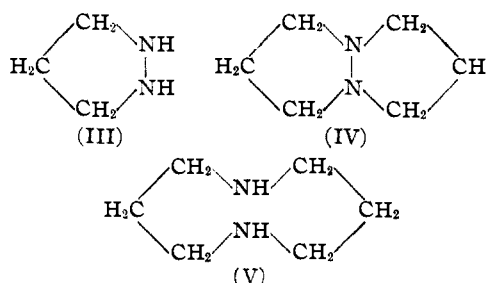
An inversion of configuration, *i. e.*, racemization, may take place in two ways. The molecule may assume, momentarily, a completely planar form followed by the coupled inversion of both nitrogen configurations. This coplanar state necessitates the simultaneous spread of both C-N-C angles from the normal value to 144° , a process which might be expected to require double the activation energy of a simple inversion process.

Alternatively, racemization may take place through a stepwise inversion of the two nitrogen configurations. This process would necessitate an intermediate having a multiplanar, "trans," structure of considerable energy due to the deviation of the bond angles in the rings from their normal values.⁶ By either racemization process the activated state should possess considerably higher energy than the corresponding state in compounds containing a single nitrogen atom in a chain or in a strainless ring. It is conceivable that both of these states would require so much energy that the rate of interconversion of enantiomorphs at ordinary temperatures would be measurably slow.

Bicyclic derivatives of hydrazine analogous to (II) have never been synthesized; indeed even the parent heterocycle, pyrazolidine (III), which should prove to be an important intermediate in any projected synthesis, has not yet been reported in the literature. The bicyclic hydrazines are similar in structure to tetraalkylhydrazines, R_2N-NR_2 , a class of compounds the very existence of which has long been questioned. Such compounds are now of unusual interest in connection with recent theories of the strength of the "normal" N-N bond.⁷ These compounds, having no N-H bonds, should be relatively resistant to oxidation processes and therefore should make possible direct experimental studies of the pri-

mary dissociation into "normal" divalent nitrogen radicals.

Accordingly, we have first undertaken the preparation of a representative member of the bicyclic hydrazine series in order to examine its stability and reactivity, in particular with respect to cleavage of the N-N bond. In this paper we report the synthesis of 1,2-trimethylenepyrazolidine (IV), which we have obtained from



the reaction between trimethylene dichloride, or dibromide, and hydrazine. In addition we have isolated substantial quantities of pyrazolidine (III), and of bis-trimethylenediimine (V).

Alkylation of Hydrazine with Trimethylene Dihalides.—The direct alkylation of hydrazine usually leads to trisubstituted azinium ions of the type $(R_3N-NH_2)^+$, which cannot be degraded to substituted hydrazines.⁸ The use of secondary alkyl halides and relatively large primary alkyl chlorides at high temperatures has, in a few cases, given substantial quantities of tri- and tetraalkylhydrazines.⁹

We have found that hydrazine and trimethylene dichloride, or dibromide, react rapidly in alcohol at reflux temperatures. In order to diminish the formation of quaternary azinium ions and to facilitate isolation of products we used a large excess of hydrazine and avoided any additional base. Even under these conditions about fifty per cent. of the reaction products consisted of quaternary ions. All attempts to isolate crystalline azinium salts were fruitless, however; neither were we able to extract the desired bases from the alkaline mixture. By adding an excess of potassium hydroxide to the reaction mixture and distilling off the free bases followed by a fractionation of the distillate under reduced pressure we have isolated pyrazolidine and 1,2-trimethylenepyrazolidine in total yield of thirty per cent. Although the ratio of the two bases varied over

(6) Such an intermediate would be isoelectronic with the strained *trans*-0,3,3-bicyclooctane recently synthesized by Barrett and Linstead, *J. Chem. Soc.*, 436 (1935).

(7) Cain and Wiselogle, *This Journal*, **62**, 1163 (1940); Lewis and Lipkin, *ibid.*, **63**, 3232 (1941).

(8) (a) Wieland, "Die Hydrazine," Ferdinand Enke, Stuttgart, 1913, p. 13; (b) Klages, *Ann.*, **547**, 39 (1941).

(9) (a) Klages, *Ann.*, **547**, 1 (1941); (b) Westphal, *Ber.*, **74**, 759 (1941).

considerable limits in individual experiments the sum was surprisingly constant. In addition we have found bis-trimethylenediimine in the mixture of volatile bases; it was preferable to isolate the dihydrohalide, however, by crystallization from the initial reaction mixture after removal of the unreacted hydrazine.

The pyrazolidine and 1,2-trimethylenepyrazolidine may be formulated as direct alkylation products of hydrazine. The surprisingly high yields may be attributed to the position of the halogen in the intermediary γ -halogen-propylhydrazine and the 1-(γ -halogen-propyl)-pyrazolidine. Pyrazolidine and 1,2-trimethylenepyrazolidine can then result by an intramolecular alkylation which is highly favored from a steric standpoint. The bis-trimethylenediimine is undoubtedly a reduction product of the bicyclic 1,2-trimethylenepyrazolidine.

Properties and Structure. Pyrazolidine.—The fraction distilling at 54–56° under 26 mm. pressure boiled without decomposition at 138° (760 mm.) and crystallized readily in an ice-bath, the large colorless plates melting at 10–12°, n_D^{20} 1.477, d_4^{20} 0.9952. The free base, although stable in air, is extremely hygroscopic, a property which explains our inability to obtain a sharp melting point. Pyrazolidine reduces Fehling solution and Tollens reagent rapidly at room temperature, reactions which are characteristic of N-arylpzazolidines and of *sym*-dialkylhydrazines.¹⁰ Treatment of pyrazolidine with benzoyl chloride and aqueous alkali gives a dibenzoyl derivative, melting at 147°. Another excellent crystalline derivative is the oxalate, melting at 115°.

1,2-Trimethylenepyrazolidine.—The fraction distilling at 74–75° under 26 mm. pressure boiled at 173° (760 mm.). The base crystallized in an ice-salt bath, the colorless plates melting at 1.5–2.5°, n_D^{20} 1.4895; d_4^{20} 1.0000. The compound is a monoacidic base in water having a basic dissociation constant of $1.0 \cdot 10^{-6}$ (Fig. 1). 1,2-Trimethylenepyrazolidine is about as strong a base as hydrazine, therefore, but considerably weaker than comparable tertiary amines.

1,2-Trimethylenepyrazolidine does not reduce Fehling solution at room temperature although a positive test is obtained when the mixture is warmed. Tollens reagent gives a mirror at room temperature and a solution of bromine in carbon tetrachloride is rapidly decolorized. 1,2-Trimethylenepyrazolidine absorbed no hydrogen under conditions that brought about the rapid hydrogenation of allyl chloride and allylhydrazine,¹¹ which indicates the absence of a carbon-carbon double bond. The hydrochloride and methiodide are extremely hygroscopic; on the other hand the picrate, melting at 159.5°, is an excellent crystalline derivative.

Bis-trimethylenediimine.—This interesting eight-membered ring was first obtained by Howard and Marckwald from *p*-toluene-sulfonamide and trimethylene dibromide

(10) Michaelis and Lampe, *Ber.*, **24**, 3738 (1891); Lochte, Bailey and Noyes, *THIS JOURNAL*, **43**, 2601 (1921).

(11) Gabriel, *Ber.*, **47**, 3031 (1914).

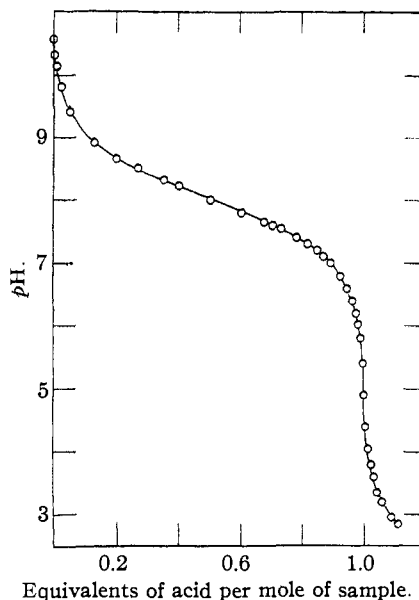


Fig. 1.—Titration of 1,2-trimethylenepyrazolidine with hydrochloric acid.

after hydrolytic removal of the *p*-toluenesulfonyl groups.¹² We obtained the free base in yields as high as 7% by fractionation of the mixture of volatile bases. Since bis-trimethylenediimine is not a simple alkylation product of hydrazine, however, it was necessary to prove that it was formed during the initial alkylation and did not result from the subsequent pyrolysis of 1,2-trimethylenepyrazolidine. Accordingly in an independent experiment, from trimethylene dibromide and hydrazine, the excess hydrazine was first removed with benzaldehyde; removal of the solvent from the acidified filtrate gave the crystalline dihydrobromide of bis-trimethylenediimine in 24% yield. The properties of our base and of its derivatives agreed in detail with the descriptions of Howard and Marckwald.

Experimental

Reaction between Hydrazine and Trimethylene Dibromide or Dichloride.—Several preliminary runs were made to determine the simplest procedure for the isolation of the products. The use of precipitated magnesium hydroxide, recommended by Westphal,^{9b} was unsatisfactory because the organic bases were adsorbed on the magnesium hydroxide. Attempts to salt out the bases from aqueous or aqueous-alcoholic solutions with potassium carbonate gave a layer of a mixture of quaternary azinium salts which evidently retained the hydrazine derivatives since repeated extractions with ether yielded no products in the ether layer. The quaternary salts could not be induced to crystallize. The most satisfactory procedure involved (1) use of a large excess of hydrazine; (2) addition of the organic halide to the warm solution of hydrazine in alcohol; (3) neutralization of the reaction mixture with potassium hydroxide and distillation of all volatile products under reduced pressure; (4) fractionation of the mixture.

In a 2-liter, 3-necked flask provided with mechanical stirrer, reflux condenser and dropping funnel were placed

(12) Howard and Marckwald, *ibid.*, **32**, 2038 (1899).

600 cc. of 95% alcohol and 3.0 moles of hydrazine.¹³ To the gently refluxing solution was added 150 cc. (1.5 moles) of trimethylene dibromide over a period of two and one-half hours and the refluxing was continued for an additional half-hour. During the reaction an oily precipitate of hydrazine monohydrobromide settled out. The mixture was cooled to 0° for several hours and the now crystalline hydrazine monohydrobromide was filtered off; approximately two gram-formula weights were recovered. A slight excess of solid potassium hydroxide was added to the cooled filtrate and the precipitated potassium bromide was removed by filtration. The alcohol was removed from the filtrate by fractionation, using a Vigreux column. The distilland was then distilled under reduced pressure, the distillate being divided into two fractions. The higher boiling fraction, b. p. 35–88°, was fractionated at reduced pressure through a 35-cm. wire spiral total reflux variable take-off fractionating column. The fractions obtained in one run are recorded in Table I. Essentially the same yields were obtained using trimethylene dichloride. Since the fractionation was extremely tedious we did not always strive for complete recovery of the higher boiling bis-trimethylenediimine.

TABLE I

| FRACTIONATION OF VOLATILE BASES | | | |
|---|------------------------------|-------------|-----------------------------------|
| Temperature ^a range, °C. | Weight of fraction, g. | Yield, % | Substance |
| 29–35 | 28.0 | | Water |
| 35–41 | 2.2 | | |
| 41–46 | 17.0 | | Hydrazine hydrate |
| 46–54 | 2.4 | | |
| 54–57 | 19.1 | 17.6 | Pyrazolidine |
| 57–74 | 1.9 | | |
| 74–75 | 12.0 | 14.3 | 1,2-Trimethylene- pyrazolidine |
| 75–106 | 7.3 | | |
| | Loss 15.5 | | |

^a Pressure, 26 mm.

Pyrazolidine.—All liquids were analyzed according to the procedure of Niederl and Niederl¹⁴ for hygroscopic substances. *Anal.* Calcd. for C₃H₅N₂: C, 50.0; H, 11.2. Found: C, 50.1, 49.7; H, 10.7, 10.9.

Pyrazolidine oxalate crystallized on mixing 280 mg. of the base dissolved in 5 cc. of absolute alcohol with 25 cc. of 0.5 molar oxalic acid in absolute alcohol. A yield of 450 mg. (72%) of material melting at 111–113° was obtained. Recrystallization from 95% alcohol raised the melting point to 114–115°. *Anal.* Calcd. for C₅H₁₀N₂O₄: C, 37.0; H, 6.2; N, 17.3. Found: C, 37.2; H, 6.0; N, 17.0.

Dibenzoylpyrazolidine precipitated when a mixture of 1.0 cc. of pyrazolidine and 3.5 cc. of benzoyl chloride was neutralized with 20% sodium hydroxide solution. The yield of crude product, melting at 141–146°, was 3.29 g. or 85%. Recrystallization from alcohol and ether gave colorless prisms melting at 146–147°.

(13) The volume of hydrazine to be used was calculated after its concentration had been determined according to the procedure of Kurtenacker and Wagner, *Z. anorg. Chem.*, **120**, 263 (1922). Most of the commercial samples described as 85% hydrazine hydrate actually were from 95–98%.

(14) Niederl and Niederl, "Organic Quantitative Microanalysis," revised edition, John Wiley and Sons, Inc., New York, N. Y., 1941, p. 47.

Anal. Calcd. for C₁₇H₁₄N₂O₂: C, 72.8; H, 5.8. Found: C, 72.9; H, 5.8.

1,2 - Trimethylenepyrazolidine.—*Anal.* Calcd. for C₆H₁₂N₂: C, 64.2; H, 10.8; N, 25.0. Found: C, 64.4; H, 11.0; N, 24.6.

For the acid titration samples of about 55 mg. were weighed into small glass stoppered bottles, transferred to a 30-cc. beaker and diluted with carbon dioxide-free water. The base was titrated with 0.1 N hydrochloric acid using a glass electrode and a Hellige pH meter. Duplicate titrations gave values of 113.0 and 114.3 for the equivalent weight compared with a calculated value of 112.2. The titration curve is reproduced in Fig. 1.

A 73% yield of the picrate melting at 158–159°, was obtained from 140 mg. of the base and 5 cc. of 0.2 molar picric acid in absolute alcohol. Recrystallization raised the melting point to 159.0–159.5°. *Anal.* Calcd. for C₁₂H₁₈O₇N₆: C, 42.3; H, 4.4; N, 20.6. Found: C, 42.2; H, 4.4; N, 20.6.

Bis-trimethylenediimine.—The free base, boiling at 70–73° under 15 mm. pressure was converted to the picrate, m. p. (dec.) 220–230°, and to the dibenzoyl derivative, m. p. 185–186°, following the directions of Howard and Marckwald.

A 92% yield of crude oxalate was obtained from 280 mg. of the base and 15 cc. of a 0.5 molar solution of oxalic acid in absolute alcohol. Recrystallization from 80% alcohol gave colorless crystals melting at 170.0–170.5°. *Anal.* Calcd. for C₁₀H₁₈N₂O₃: C, 40.8; H, 6.2; N, 9.5. Found: C, 40.8; H, 6.3; N, 9.7.

That bis-trimethylenediimine was formed in the initial reaction mixture was shown in an independent alkylation experiment from 0.993 mole of hydrazine and 0.49 mole of trimethylene dibromide in 250 cc. of 95% alcohol. After removal of the crystalline hydrazine monohydrobromide the solution was acidified with hydrobromic acid and treated with 50 cc. of benzaldehyde. The crystalline benzalazine was filtered and the filtrate, diluted with 200 cc. of water, was extracted with a total of 200 cc. of ether. Removal of the solvent from the aqueous layer left a partially crystalline residue of mixed salts. Digestion of the residue with 100 cc. of absolute alcohol left 10.6 g. of bis-trimethylenediimine dihydrobromide undissolved; an additional 6.6 g. crystallized from the alcohol on cooling, giving a total yield of 24%. The purified product melted with decomposition at 240–250°, the range depending on the rate of heating. The same product was obtained from the free base on acidification with hydrobromic acid. *Anal.* Calcd. for C₆H₁₂N₂Br₂: Br, 57.9. Found: Br, 57.9, 57.8.

Summary

The alkylation of hydrazine with trimethylene dibromide or dichloride in alcohol solution gives substantial quantities of pyrazolidine, of 1,2-trimethylenepyrazolidine and of bis-trimethylenediimine. The configurational stability of 1,2-trimethylenepyrazolidine and the stereoisomerism of its derivatives are discussed.