

washed with 10% aqueous sodium hydroxide and with water, and dried. The color phenomena observed during the reaction were the same as those found to take place in the cyclization of hydrocinnamic acid. The yield of crude ketone was 0.27 g. (76%), m. p. 123–128°. Recrystallization from methanol–water raised the melting point to 128–131°. The melting point was not depressed by admixture with a sample of 4-bromo-7-methoxy-1-indanone, m. p. 131.5–132.5°, prepared by the Friedel-Crafts reaction.<sup>9</sup>

When the reaction was carried out at 160° for one hour, the only substance isolated melted at 228–231° after recrystallization from 95% ethanol.

**$\alpha$ -Tetralone.**—Polyphosphoric acid, 133 g., was warmed to 90°, and 22 g. of molten  $\gamma$ -phenylbutyric acid<sup>24</sup> was added with rapid stirring. The temperature rose to 125° while the solution was heated and stirred for a total of two and one-half minutes. The mixture was allowed to cool for five minutes before it was decomposed with about 100 g. of ice. The aqueous mixture was extracted three times with 25 ml. of ether, and the combined ether extracts were washed twice with 30-ml. portions of 10% aqueous sodium hydroxide and with water. The washed organic extract was dried (Drierite), and the solvent was evaporated on the steam-bath. There remained about 17.5 g. of a brown oil which on vacuum distillation gave 13.0 g. (66%) of colorless liquid, b. p. 96° (2 mm.) (lit.,<sup>17,25</sup> 105–107° (2 mm.)),  $n_D^{20}$  1.5688 (lit.,<sup>26</sup> 1.5691). The semicarbazone was prepared; m. p. 216°, after one recrystallization from 95% ethanol (lit.,<sup>26</sup> 217°).

**Anthraquinone.**—A mixture of 17.14 g. of *o*-benzoylbenzoic acid and 35.8 g. of polyphosphoric acid was heated at 140–150° with vigorous stirring for forty minutes. A dark yellow solid deposited during this time. The warm

reaction mixture was decomposed with ice, and the cream-colored product was collected, washed with water and dried. After one recrystallization from glacial acetic acid there was obtained 16.7 g. of yellow needles, m. p. 281–284° (lit.,<sup>27</sup> 286°).

**1,2-Benzanthraquinone.**—A mixture of 6.4 g. of *o*-( $\alpha$ -naphthoyl)-benzoic acid and 18.7 g. of polyphosphoric acid was heated on a steam-bath with stirring for about twelve hours. The isolation method was similar to that of anthraquinone. The crude product was washed with 10% sodium hydroxide and with water and dried. One recrystallization from glacial acetic acid gave 2.6 g. (44%) of 1,2-benzanthraquinone, m. p. 160–164°. One recrystallization from benzene raised the melting point to 164–166° (lit.,<sup>28</sup> 168°).

### Summary

Polyphosphoric acid has been applied as a condensing agent in the synthesis of cyclic ketones. A procedure for the cyclization of hydrocinnamic acid to  $\alpha$ -hydrindone has been developed. The method has been extended to the cyclization of 2-bromo-5-methoxyhydrocinnamic acid.  $\alpha$ -Tetralone is obtained in 66% yield from  $\gamma$ -phenylbutyric acid. The cyclization of *o*-benzoylbenzoic acid to anthraquinone proceeds quantitatively, while 1,2-benzanthraquinone is obtained in 44% yield from *o*-( $\alpha$ -naphthoyl)-benzoic acid.

(27) Kempf, *J. prakt. Chem.*, [2] **78**, 257 (1908).

(28) Heller and Schuelke, *Ber.*, **41**, 3633 (1908); Elbs, *ibid.*, **19**, 2209 (1886).

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RECEIVED JANUARY 5, 1950

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(25) Thompson, "Org. Syntheses," **20**, 94 (1940).

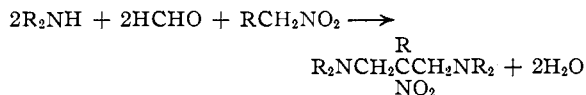
(26) v. Auwers, *Ann.*, **416**, 162 (1918).

[CONTRIBUTION FROM THE RESEARCH AND DEVELOPMENT DIVISION, COMMERCIAL SOLVENTS CORPORATION]

## The Preparation and the Hydrogenation of 5-Nitropentoxazolidines

BY MURRAY SENKUS

The experimental data presented in the papers on the reaction of amines with formaldehyde and nitroparaffins by Henry,<sup>1</sup> Mousset,<sup>2</sup> Duden<sup>3</sup> and Cerf<sup>4</sup> indicated that the reaction is limited to secondary amines and primary nitroparaffins as represented by the general equation



When it was discovered in this Laboratory that isopropylamine reacts with formaldehyde and 2-nitropropane to yield N-(2-nitroisobutyl)-isopropylamine<sup>5</sup> in good yield, it became apparent that the limitations that were advanced for the reaction of amines with formaldehyde and nitroparaffins by the earlier authors were not supported by sufficient experimental data. The reaction therefore has been reinvestigated and as

a consequence its scope has been greatly extended.

The new nitro amines which have been prepared during investigations in this Laboratory have been derived from primary amines and primary nitroparaffins,<sup>5</sup> primary amines and secondary nitroparaffins,<sup>5</sup> secondary amines and secondary nitroparaffins<sup>6</sup> as well as from ammonia and secondary nitroparaffins.<sup>7</sup> With the aid of a basic catalyst the reaction was also extended to aryl and alkaryl amines and primary and secondary nitroparaffins.<sup>8</sup> Finally it was reported that the reaction of two moles of a primary amine with three moles of formaldehyde and one mole of a primary nitroparaffin yields a 5-nitrohexahydropyrimidine.<sup>9</sup>

Work on the reaction of amines with formaldehyde and nitroparaffins has continued in this Laboratory. It has been found recently that one mole of a primary amine reacts with three moles of formaldehyde and one mole of a primary ni-

(1) Henry, *Bull. acad. roy. Belgique*, [3] **33**, 412 (1897).

(2) Mousset, *ibid.*, [3] **33**, 622 (1901).

(3) Duden, Bock and Reid, *Ber.*, **38**, 2036 (1905).

(4) Cerf, *Bull. soc. chim.*, [5] **4**, 1451 (1937).

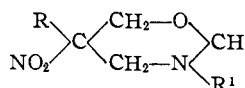
(5) Senkus, *This Journal*, **68**, 10 (1946).

(6) Johnson, *ibid.*, **68**, 12 (1946).

(7) Johnson, U. S. Patents 2,408,171 and 2,408,172.

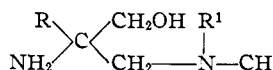
(8) Johnson, *This Journal*, **68**, 14 (1946).

(9) Senkus, *ibid.*, **68**, 1611 (1946).

TABLE I  
 SOME 5-NITROPENTOXAZOLIDINES OF THE TYPE


| R <sup>1</sup>   | R                             | M. p., °C. | B. p., °C. | Mm. | n <sub>D</sub> <sup>20</sup> | d <sub>4</sub> <sup>20</sup> | Formula   | Nitrogen, %<br>Calcd. | Found |
|--|-------------------------------|------------|------------|-----|------------------------------|------------------------------|---|-----------------------|-------|
| C <sub>7</sub> H <sub>15</sub> N <sub>2</sub> <sup>a</sup> | CH <sub>3</sub>               | 105.6      |            |     |                              |                              | C <sub>12</sub> H <sub>24</sub> N <sub>4</sub> O <sub>3</sub> | 20.59                 | 20.49 |
| C <sub>8</sub> H <sub>9</sub> O <sub>2</sub> <sup>b</sup>  | CH <sub>3</sub>               | 108.4      |            |     |                              |                              | C <sub>10</sub> H <sub>18</sub> N <sub>2</sub> O <sub>4</sub> | 11.38                 | 11.56 |
| C <sub>6</sub> H <sub>11</sub> <sup>c</sup>                | CH <sub>3</sub>               | 50.8       |            |     |                              |                              | C <sub>11</sub> H <sub>20</sub> N <sub>2</sub> O <sub>3</sub> | 12.27                 | 12.04 |
| CH <sub>3</sub>  | CH <sub>3</sub>               |            | 88-90      | 0.8 | 1.4708                       | 1.1713                       | C <sub>8</sub> H <sub>12</sub> N <sub>2</sub> O <sub>3</sub>  | 17.49                 | 17.57 |
| (CH <sub>3</sub> ) <sub>2</sub> CH                         | CH <sub>3</sub>               |            | 90-92      | .6  | 1.4710                       | 1.1054                       | C <sub>8</sub> H <sub>18</sub> N <sub>2</sub> O <sub>3</sub>  | 14.89                 | 14.91 |
| n-C <sub>4</sub> H <sub>9</sub>                            | C <sub>2</sub> H <sub>5</sub> |            | 103-105    | .4  | 1.4684                       | 1.0574                       | C <sub>10</sub> H <sub>20</sub> N <sub>2</sub> O <sub>3</sub> | 12.96                 | 12.74 |

<sup>a</sup> N,N,5-Trimethylhexahydropyrimidyl-5. <sup>b</sup> 5-Methyl-1,3-dioxanyl-5. <sup>c</sup> Cyclohexyl.

 TABLE II  
 SOME HYDROXYMETHYLETHANEDIAMINES OF THE TYPE


| R <sup>1</sup>   | R                             | °C.     | B. p., °C. | Mm. | n <sub>D</sub> <sup>20</sup> | d <sub>4</sub> <sup>20</sup> | Formula   | Nitrogen, %<br>Calcd. | Found |
|--|-------------------------------|---------|------------|-----|------------------------------|------------------------------|---|-----------------------|-------|
| C <sub>7</sub> H <sub>15</sub> N <sub>2</sub> <sup>a</sup> | CH <sub>3</sub>               | 127     |            | 0.3 | 1.4902                       | 0.9899                       | C <sub>12</sub> H <sub>28</sub> N <sub>4</sub> O              | 22.95                 | 23.56 |
| C <sub>8</sub> H <sub>9</sub> O <sub>2</sub> <sup>b</sup>  | CH <sub>3</sub>               | 143-145 |            | .4  | ....                         | ....                         | C <sub>10</sub> H <sub>22</sub> N <sub>2</sub> O <sub>3</sub> | 12.84                 | 12.98 |
| C <sub>6</sub> H <sub>11</sub> <sup>c</sup>                | CH <sub>3</sub>               | 98-101  |            | .1  | 1.4998                       | 1.0092                       | C <sub>11</sub> H <sub>24</sub> N <sub>2</sub> O              | 14.00                 | 14.03 |
| CH <sub>3</sub>  | CH <sub>3</sub>               | 58      |            | .3  | 1.4705                       | 0.9695                       | C <sub>8</sub> H <sub>16</sub> N <sub>2</sub> O               | 21.21                 | 20.93 |
| (CH <sub>3</sub> ) <sub>2</sub> CH                         | CH <sub>3</sub>               | 96-98   |            | .9  | 1.4700                       | .9631                        | C <sub>8</sub> H <sub>20</sub> N <sub>2</sub> O               | 17.50                 | 17.75 |
| n-C <sub>4</sub> H <sub>9</sub>                            | C <sub>2</sub> H <sub>5</sub> | 88-90   |            | .1  | 1.4698                       | .9398                        | C <sub>10</sub> H <sub>24</sub> N <sub>2</sub> O              | 14.89                 | 14.94 |

<sup>a</sup> N,N,5-Trimethylhexahydropyrimidyl-5. <sup>b</sup> 5-Methyl-1,3-dioxanyl-5. <sup>c</sup> Cyclohexyl.

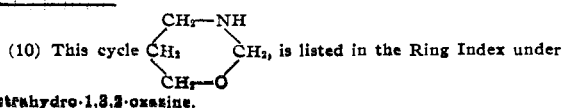
troparaffin to yield a 5-nitropentoxazolidine<sup>10</sup>; also, that hydrogenation of these new compounds yields diamino alcohols. This work is described in the present paper.

### Experimental

**Preparation of 5-Nitropentoxazolidines.**—Examples of each of the two procedures which were developed for the preparation of 5-nitropentoxazolidines are given below:

**Method A. 5-Nitro-3-(1-methyl-3,5-dioxacyclohexyl)-5-methylpentoxazolidine from 5-Amino-5-methyl-1,3-dioxane, Formaldehyde and Nitroethane.**—Two hundred and twenty-five milliliters (3 moles) of 36% aqueous formaldehyde was added to 117 g. (1 mole) of 5-amino-5-methyl-1,3-dioxane. The temperature rose to 50° in the mixture several minutes after the aldehyde had been added and then began to fall. Then 75 g. (1 mole) of nitroethane was added and the mixture was stirred for six hours. The mixture was allowed to stand for six hours during which time the product crystallized slowly. The mixture was filtered and the solid was washed with 500 ml. of methanol precooled to 0°. The dried product weighed 88 g.

**Method B. 5-Nitro-3-isopropyl-5-methylpentoxazolidine from Isopropylamine, Formaldehyde and 2-Nitro-2-methyl-1,3-propanediol.**—Seventy-five milliliters (1 mole) of 36% aqueous formaldehyde was added to 59 g. (1 mole) of isopropylamine at 0°. The non-aqueous layer which was separated weighed 70 g. (0.9 mole of N-hydroxymethylisopropylamine, assuming 100% purity). Then 105 g. (0.8 mole) of 2-nitro-2-methyl-1,3-propanediol and 500 ml. of benzene were added to this layer. The mixture was distilled slowly to remove the water of reaction. After water had ceased distilling, 500 ml. of petroleum ether was added to the residue and the solution was washed with three 500-ml. portions of water. Rectification of the washed solution gave 81 g. of 5-nitro-3-isopropyl-5-methylpentoxazolidine, b. p. 90-92° at 0.6 mm.



The 5-nitropentoxazolidines that were prepared are either white, crystalline solids or colorless liquids. They are soluble in acetone, benzene, ether and methanol. They are appreciably soluble in water, and on exposure to a large excess of water for an extended time, they yield a complex mixture of products. They are stable when stored at room temperature but when heated to 100-150°, they decompose with some force. The 5-nitropentoxazolidines that were prepared together with some properties and analytical data are listed in Table I.

**Hydrogenation of 5-Nitropentoxazolidines.**—Each of the 5-nitropentoxazolidines was hydrogenated according to the same procedure. The nitro compound (anywhere from 20 g. to 200 g.) was dissolved in 500 ml. of methanol and the mixture was hydrogenated in a stainless steel 1800-ml. rocking bomb in the presence of Raney nickel catalyst at 75 to 100° and a pressure of 1000 lb. per sq. in. Rectification of the filtered solution gave the product in good yield.

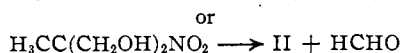
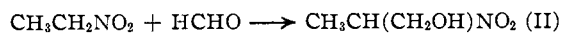
The diamino alcohols which were isolated are colorless liquids. They are soluble in aliphatic hydrocarbons. Their thermal stability is similar to that of other amino alcohols like 2-amino-1-ethanol. The compounds which were isolated are listed in Table II, together with some physical properties and analytical data.

### Discussion

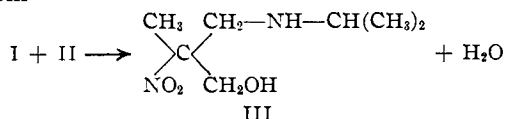
5-Nitropentoxazolidines can undoubtedly result from more than one series of reactions. The exact sequence in any series is indeterminate but the crucial intermediates are the same in any of the routes. For example in the formation of 5-nitro-3-isopropyl-5-methylpentoxazolidine from isopropylamine, formaldehyde and nitroethane the first important intermediates that are formed are N-(hydroxymethyl)-isopropylamine (from isopropylamine and formaldehyde)



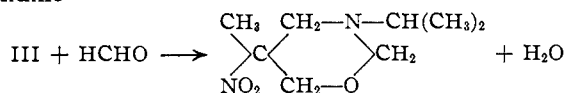
and 2-nitro-1-propanol (from nitroethane and formaldehyde or from 2-nitro-2-methyl-1,3-propanediol by dissociation into the nitro alcohol and formaldehyde)



These compounds then react according to the mechanism suggested by Henry<sup>1</sup> to give 2-nitro-2,5-dimethyl-4-azahexanol which possesses an amino group  $-\text{NH}[\text{CH}(\text{CH}_3)_2]$  and a hydroxyl group on carbon atoms removed by one carbon atom



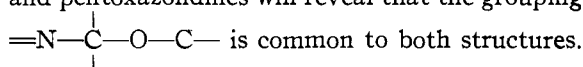
Inasmuch as amino alcohols with these structural features are known to yield pentoxazolines with aldehydes, it can be assumed that the final step in any route is the reaction of 2-nitro-2,5-dimethyl-4-azahexanol with formaldehyde to yield water and 5-nitro-3-isopropyl-5-methylpentoxazolidine



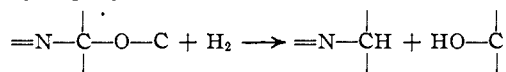
The structures chosen for the new compounds are supported by the analytical data. Further confirmation of their structure was obtained by studying the hydrogenation of these compounds and the examination of the reduced products.

An examination of the structures of oxazolines

and pentoxazolines will reveal that the grouping



is common to both structures. During the hydrogenation of the oxazolines,<sup>11</sup> the grouping at hand is split as shown



A similar splitting of this grouping in the 5-nitropentoxazolines would be expected to take place if these compounds were hydrogenated. A simultaneous reduction of the nitro group to the amino group should also occur. The hydrogenation of these compounds was tried. The nitrogen content of the product from each of these reductions agreed with that of the expected diamino alcohol. These data furnish additional support for the proposed structures of the 5-nitropentoxazolines.

### Summary

5-Nitropentoxazolines have been prepared by allowing one mole of a primary amine to react with three moles of formaldehyde and one mole of a primary nitroparaffin.

The hydrogenation of these new compounds was studied. Each nitro compound yielded a new diamino alcohol.

(11) Cope and Hancock, *THIS JOURNAL*, **64**, 1503 (1942); Senkus, *ibid.*, **67**, 1515 (1945).

TERRE HAUTE, IND.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, JAMES MILLIKIN UNIVERSITY]

## Preparation of Symmetrical N,N'-Disubstituted Piperazines and their Quaternary Ammonium Salts

BY D. R. SMITH, J. W. CURRY AND R. L. EIFERT

Domagk,<sup>1</sup> over a decade ago, found that the germicidal activity of quaternary ammonium compounds was increased when a large aliphatic group was attached to the quaternary nitrogen atom. This stimulated the study of the use of quaternary ammonium salts as germicides and, today, many commercial products<sup>2</sup> are on the market. However, only a few quaternary ammonium salts of heterocyclic bases have been tested. Hart and Niederl,<sup>3</sup> recognizing the importance of a cetyl group in bactericidal "invert soaps," prepared N-cetylthiomorpholine and studied several of its derivatives. Shepard and Shonle,<sup>4</sup> investigating topical antiseptics, used imidazole and imidazoline as nuclei and formed quaternary salts with long alkyl chains. Shelton, Van Campen, Tilford, Lang, Nisonger, Bandelin

and Rubenkoenig<sup>5</sup> made long chain alkyl quaternary salts using pyridine, picoline, lutidine, piperidine and morpholine and found definite germicidal properties. Later Niederl, Salzberg and Shatynski<sup>6</sup> prepared morpholinium sulfates and found that compounds in the N-hexadecyl series exhibited phenol coefficients of 500 to 600. Baltzly, Buck, Lorz and Schön<sup>7</sup> prepared the one piperazinium salt, containing a long aliphatic chain, that we found in the literature, but it was not tested for germicidal activity. Therefore, it was thought profitable to prepare and test some quaternary ammonium salts of piperazine.

Many N-monosubstituted<sup>7</sup> and N,N'-disubstituted<sup>8</sup> piperazines have been prepared. A new series of *sym*-disubstituted piperazines was first

(1) Domagk, *Deut. Med. Wochschr.*, **61**, 829 (1935).

(2) Lesser, *Drug and Cosmetic Ind.*, **64**, 558-560 (1949).

(3) Hart and Niederl, *THIS JOURNAL*, **66**, 1610 (1944).

(4) Shepard and Shonle, *ibid.*, **69**, 2269 (1947).

(5) Shelton, Van Campen, Tilford, Lang, Nisonger, Bandelin and Rubenkoenig, *ibid.*, **68**, 757 (1946).

(6) Niederl, Salzberg and Shatynski, *ibid.*, **70**, 618 (1948).

(7) Baltzly, Buck, Lorz and Schön, *ibid.*, **66**, 263 (1944).

(8) Forsee and Pollard, *ibid.*, **67**, 1788 (1935).