

TABLE III
EFFECT OF HYDROXIDE ION CONCENTRATION ON REACTION
OF SODIUM *p*-THIOCRESOLATE WITH HALOFORMS^a

Haloform	<i>p</i> -CH ₃ C ₆ H ₄ SNa reacted, % [OH ⁻] ₀ = 0.00	[OH ⁻] ₀ ~ 0.11
CHCl ₃	0.23	23.0
CHBrCl ₂	2.5	23.0
CHBr ₂ Cl	5.5	24.2
CHBr ₃	3.1	16.7

^a In 66²/₃% dioxane-water at 35.7° for enough time to use up ~ 0.1 *N* base; [CHX₃]₀ ~ 0.11 *M*, [*p*-CH₃C₆H₄SNa] ~ 0.14.

bromoform, the haloform thought most likely to give such side reactions.

Using a technique like that described earlier for the isolation of phenyl orthothioformate from sodium thiophenolate, sodium hydroxide and chloroform,² it was found that

6.8 g. of *p*-thiocresol, 3 ml. of bromoform and 235 meq. of alkali in 58-66% dioxane-water gave 18.3 meq. of unreacted sodium *p*-thiocresolate, and after three recrystallizations from aqueous ethanol, 3.6 g. (78% based on *p*-thiocresol used) of light yellow crystals, m.p. 108-109°. *p*-Tolyl orthothioformate is reported to melt at 109°¹⁶ and 111°.¹⁷

Acknowledgments.—We wish to acknowledge our indebtedness to the National Science Foundation for a grant in support of this investigation, to the Dow Chemical Co. for gifts of bromodichloromethane and dibromochloromethane and to the Kinetic Chemicals Division of E. I. du Pont de Nemours and Co. for a gift of fluoroform.

(16) J. Houben and K. M. L. Schultze, *Ber.*, **44**, 3235 (1911).

(17) F. Arndt, *Ann.*, **384**, 322 (1911).

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF FLORIDA]

Studies in the Mechanism of the Mannich Reaction. I. The Reaction of Methylenediamines with 2-Methyl-2-nitro-1-propanol¹

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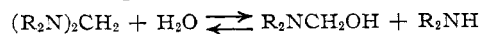
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Bis-(dialkylamino)-methanes will undergo reaction with 2-methyl-2-nitro-1-propanol to produce Mannich bases. This reaction has been applied to a number of bis-(dialkylamino)-methanes and the resulting Mannich bases were characterized.

It has been shown by Lieberman and Wagner² that methylene-bis-dibenzylamine can serve as an intermediate in the Mannich reaction with antipyrine under anhydrous condition, using dibenzylamine hydrochloride as catalyst. It also has been shown by Johnson³ that the reaction of aliphatic secondary amines with formaldehyde and primary or secondary nitroalkanes produces Mannich-like bases. This author also observed that the same products were produced either by first allowing the secondary amine to react with formaldehyde to produce an intermediate which was assumed to be the methylol derivative, and then allowing this intermediate to react with the nitroalkane, or by producing the nitroalcohol by reaction of formaldehyde with the nitroalkane, and then treating this intermediate with the secondary amine.

It has been shown by Henry⁴ that reaction of two equivalents of an aliphatic secondary amine with one equivalent of formaldehyde at 60° produces the methylenediamine. Recent work by Ingwalson⁵ in attempts to prepare the Mannich base of *N*-phenylpiperazine, formaldehyde and 2-nitropropane led to the conclusion that the only product of the reaction was bis-(*N*-phenylpiperazyl)-methane, as the properties of the product corresponded very closely with those reported by Prelog and Blazek,⁶ who prepared this compound by merely shaking a mix-

ture of *N*-phenylpiperazine and 40% formaldehyde solution. It has now been shown that the Mannich base is produced by reaction of *N*-phenylpiperazine with formaldehyde and 2-nitropropane. Owing to the ease of formation of bis-(*N*-phenylpiperazyl)-methane when *N*-phenylpiperazine is allowed to react with formaldehyde at room temperature, this compound appears to be an intermediate in the formation of the Mannich base, and can be substituted for *N*-phenylpiperazine and formaldehyde in the Mannich reaction with either 2-nitropropane or 2-methyl-2-nitro-1-propanol. This work has shown that bis-(dialkylamino)-methanes in general will react with 2-methyl-2-nitro-1-propanol to produce the Mannich bases, and tends to support the idea that the methylenediamine rather than the methylol derivative of the secondary amine is involved in the Mannich reaction. For a secondary amine which yields the corresponding methylenediamine in good yield immediately upon mixing with formaldehyde, the methylol derivative must arise in part from the equilibrium



if it is a necessary intermediate in the Mannich reaction, and a good yield of the Mannich base is to be obtained.

Experimental

Preparation of *N*-Phenyl-*N'*-(2-methyl-2-nitropropyl)-piperazine. a. Preparation of Bis-(*N*-phenylpiperazyl)-methane.⁶—To 4.1 g. (0.025 mole) of *N*-phenylpiperazine dissolved in 6 ml. of dioxane was added 1 g. (0.0125 mole) of 37% formaldehyde, and the solution was heated on a steam-bath for one hour. The crude product was isolated by addition of water to the dioxane solution and recrystallized.

(7) V. Prelog and G. J. Driza, *Coll. Czechoslov. Chem. Commun.*, **6**, 497 (1933).

(1) Presented in part before the Meeting-in-miniature, Florida section, American Chemical Society, Jacksonville, Fla., May, 1952.

(2) S. V. Lieberman and E. C. Wagner, *J. Org. Chem.*, **14**, 1001 (1949).

(3) H. G. Johnson, *THIS JOURNAL*, **68**, 12 (1946).

(4) L. Henry, *Bull. acad. roy. med. Belg.*, (3) **26**, 200 (1893).

(5) R. W. Ingwalson, M.S. Thesis, University of Florida, February, 1948.

(6) V. Prelog and Z. Blazek, *Coll. Czechoslov. Chem. Commun.*, **6**, 549 (1934).

zation of the crude precipitate from ethanol; yield 4 g., m.p. 127°, lit. value 124°.

b. Reaction of N-Phenylpiperazine with 2-Nitropropane and Formaldehyde.—To a solution of 8.9 g. (0.1 mole) of 2-nitropropane and 16.2 g. (0.1 mole) of N-phenylpiperazine in 30 ml. of dioxane was added 2 ml. of 2% sodium hydroxide solution and 8.2 g. (0.1 mole) of 37% formaldehyde solution. After stirring for one hour at room temperature, the solution was heated on a steam-bath for two hours. After cooling the product which crystallized was removed by filtration. An additional amount of product was obtained by adding an excess of water to the solution; combined yield 21 g. After recrystallization from ethanol, the product had a melting point of 128–130°; mixed m.p. with pure bis-(N-phenylpiperazyl)-methane, 100–105°. *Anal.* Calcd. for $C_{14}H_{18}N_4O_2$: C, 63.90; H, 7.98; N, 15.96. Found: C, 64.48; H, 7.91; N, 15.92. Calcd. for bis-(N-phenylpiperazyl)-methane, $C_{21}H_{28}N_4$: C, 75.00; H, 8.34; N, 16.69. The product is thus shown to be the expected Mannich base N-phenyl-N-(2-methyl-2-nitropropyl)-piperazine.

c. Reaction of N-Phenylpiperazine with 2-Methyl-2-nitro-1-propanol.—By a procedure similar to the above N-phenylpiperazine was converted to the Mannich base by substituting 2-methyl-2-nitro-1-propanol 11.9 g. (0.1 mole) for the 2-nitropropane and the formaldehyde; yield 17 g., m.p. 130°; mixed m.p. with bis-(N-phenylpiperazyl)-methane, 100–107°; mixed m.p. with above product, 129–130°.

d. Reaction of Bis-(N-phenylpiperazyl)-methane with 2-Methyl-2-nitro-1-propanol.—To 1.5 g. of bis-(N-phenylpiperazyl)-methane in 5 ml. of dioxane was added 0.5 g. of 2-methyl-2-nitro-1-propanol, and the mixture was heated on a steam-bath for two hours. The product was isolated as above and recrystallized from ethanol; m.p. 124°; mixed m.p. with pure bis-(N-phenylpiperazyl)-methane, 114°; mixed m.p. with pure N-phenyl-N-(2-methyl-2-nitropropyl)-piperazine, 125°.

Preparation of N,N'-Bis-(2-methyl-2-nitropropyl)-piperazine.—(a) To a solution of 98 g. (0.5 mole) of piperazine hexahydrate in 370 ml. of dioxane was added 90 g. (1 mole) of 2-nitropropane and 40 ml. of 2% sodium hydroxide. The solution was cooled with stirring to 5°. One mole, 82 g., of 37% formaldehyde was added through a dropping funnel at such a rate that the temperature was maintained below 10°. Stirring was continued for one hour. The solution was then heated on a steam-bath for one hour. After cooling, 400 ml. of water containing 2 ml. of 37% hydrochloric acid was added. The crystalline product which separated was recrystallized from ethanol; m.p. 170°, yield 128 g. *Anal.* Calcd. for $C_{12}H_{24}N_4O_4$: C, 50.0; H, 8.34; N, 19.44. Found: C, 50.0; H, 8.32; N, 19.52.

(b) Preparation of Polymethylenepiperazine.—To 43 g. (0.5 mole) of anhydrous piperazine dissolved in a mixture of 200 ml. of water and 100 ml. of dioxane was added with stirring 42 g. (0.5 mole) of 37% formaldehyde, dissolved in 100 ml. of water, at such a rate as to maintain the temperature below 50°. The polymethylenepiperazine began to precipitate immediately. When addition was complete, the mixture was heated on a steam-bath with stirring for two hours. The white precipitate was removed by filtration and dried in an oven at 75°; yield quantitative, m.p. 300° dec. *Anal.* Calcd. for $(C_4H_{10}N_2)_n$: C, 61.25; H, 10.20; N, 28.29. Found: C, 61.5; H, 10.61; N, 28.10. The product was insoluble in all solvents; however it decomposes in acid.

The reaction of formaldehyde with piperazine has been studied by Herz⁸ who reported the formation of a product which darkened at 170° and melted at 225°, the analysis of which supported the composition $C_4H_{10}N_2 \cdot 2CH_2O$. A product obtained by treating piperazine with methylene iodide and having properties similar to the product obtained in this work has been described.⁹

(c) Reaction of Polymethylenepiperazine with 2-Methyl-2-nitro-1-propanol.—To 75 ml. of dioxane was added 23.8 g. (0.2 mole) of 2-nitro-2-methyl-1-propanol, 9.8 g. (0.1 mole) of polymethylenepiperazine and 20 ml. of water. The mixture was stirred and heated on a steam-bath for four hours. The solution was filtered and the filtrate added to an excess of water. The crystalline precipitate was removed by filtration, and recrystallized from ethanol; m.p. 170–172°, mixed with pure sample 170–172°.

(8) W. Herz, *Ber.*, **30**, 1584 (1897).

(9) W. T. Forsee, Jr., and C. B. Pollard, *This Journal*, **57**, 2363 (1935).

Preparation of 3,5-Dimethyl-N,N'-bis-(2-methyl-2-nitropropyl)-piperazine.—(a) By a procedure similar to the preparation of the corresponding derivative of piperazine, this derivative was prepared from 2,5-dimethylpiperazine; m.p. 155–156°. *Anal.* Calcd. for $C_{14}H_{28}N_4O_4$: C, 53.20; H, 8.86. Found: C, 53.48; H, 8.78.

(b) Reaction of 3,5-Dimethylpiperazine with 2-Methyl-2-nitro-1-propanol.—By a procedure similar to that described above for the reaction of N-phenylpiperazine with this alcohol, the Mannich base of 3,5-dimethylpiperazine was prepared; m.p. 155–156; mixed m.p. with pure sample, 155–156°.

(c) Preparation of Polymethylene-3,5-dimethylpiperazine.—By a procedure similar to that used above for the corresponding piperazine derivative, this derivative of 3,5-dimethylpiperazine was prepared in 87% yield, m.p. 285–290° dec. *Anal.* Calcd. for $(C_7H_{14}N_2)_n$: C, 66.6; H, 11.10; N, 22.2. Found: C, 66.4; H, 10.90; N, 22.5.

(d) Reaction of Polymethylene-3,5-dimethylpiperazine with 2-Methyl-2-nitro-1-propanol.—By a procedure similar to that described above for the reaction of the corresponding derivative of piperazine with this alcohol, the Mannich base of 3,5-dimethylpiperazine was obtained; m.p. 154°; mixed m.p. with pure sample, 154–155°.

Preparation of Diallyl-(2-methyl-2-nitropropyl)-amine:

(a) From Diallylamine, 2-Nitropropane and Formaldehyde.—To a solution of 98 g. (1 mole) of diallylamine in 180 ml. of dioxane was added 90 g. (1 mole) of 2-nitropropane and 20 ml. of 2% sodium hydroxide solution. The solution was cooled to 5°, and 82 g. (1 mole) of 37% formaldehyde added at such a rate that the temperature did not rise above 10°. Stirring was continued for one hour, after which the solution was heated on a steam-bath for one hour. After cooling, 400 ml. of water containing 2 ml. of 37% hydrochloric acid was added. The upper layer was separated, dried, and distilled; b.p. 112° (14 mm.), 76° (2 mm.), yield 167 g. (89%), n_D^{25} 1.4610, d_4^{25} 0.9565; *MRD*, obsd. 56.82, calcd. 57.01. *Anal.* Calcd. for $C_{10}H_{18}O_2N_2$: C, 60.6; H, 9.10; N, 14.15. Found: C, 60.3; H, 8.82; N, 13.99. The infrared spectrum showed the characteristic absorption bands for the expected groups.

(b) From Bis-(diallylamino)-methane.—Bis-(diallylaminomethane) was prepared by adding 20.5 g. (0.25 mole) of 37% formaldehyde to 49 g. (0.5 mole) of diallylamine with stirring. Cooling was required to keep the temperature below 50°. The mixture was heated on a steam-bath for two hours, cooled, and the upper layer separated, dried, and distilled; b.p. 80° (4 mm.), yield 51 g. (83%), n_D^{25} 1.4668, d_4^{25} 0.8410; *MRD*, obs. 67.90, calcd. 68.26. *Anal.* Calcd. for $C_{18}H_{32}N_2$: C, 75.7; H, 10.68; N, 13.59. Found: C, 75.33; H, 10.50; N, 13.64. The infrared spectrum showed the characteristic absorption bands for the expected groups.

A solution composed of 20.6 g. (0.1 mole) of bis-(diallylaminomethane), 11.9 g. (0.1 mole) of 2-methyl-2-nitro-1-propanol, 8.9 g. (0.1 mole) of 2-nitropropane and 1 ml. of 2% sodium hydroxide in 40 ml. of dioxane was heated on a steam-bath for three hours. The product was separated by pouring the solution over an excess of ice, and the organic layer separated, dried and distilled; b.p. 76° (2 mm.), n_D^{25} 1.4622, d_4^{25} 0.9603. A comparison of the properties of this product with those of the pure Mannich base and bis-(diallylamino)-methane shows conclusively that the Mannich base is the chief product. The infrared spectrum was identical to that obtained above for the Mannich base.

Preparation of Dimethallyl-(2-methyl-2-nitropropyl)-amine.—(a) From Dimethallylamine, 2-Nitropropane and Formaldehyde.—By a procedure similar to that described above for the corresponding derivative of diallylamine, this Mannich base of dimethallylamine was prepared in 50% yield, b.p. 97° (2 mm.), n_D^{25} 1.4719, d_4^{25} 0.9060; *MRD*, obs. 69.90, calcd. 70.86. *Anal.* Calcd. for $C_{12}H_{22}O_2N_2$: C, 63.7; H, 9.74; N, 12.4. Found: C, 63.8; H, 10.21; N, 12.21. The infrared absorption spectrum showed the characteristic absorption bands for the expected groups.

(b) From Bis-(dimethallylamino)-methane.—Bis-(diallylaminomethane) was prepared in 79% yield by a procedure similar to that described above for the corresponding derivative of diallylamine; b.p. 105° (3 mm.), n_D^{25} 1.4758, d_4^{25} 0.8556; *MRD*, obs. 86.45, calcd. 86.72. *Anal.* Calcd. for $C_{12}H_{20}N_2$: C, 77.8; H, 11.4; N, 10.68. Found: C, 77.5; H, 11.61; N, 10.42. The infrared spectrum showed the characteristic absorption bands for the expected groups.

A solution of 23.8 g. (0.2 mole) of 2-methyl-2-nitro-1-

propanol and 26.2 g. (0.1 mole) of bis-(dimethylallylamino)-methane in 36 ml. of dioxane and 15 ml. of water was heated on a steam-bath with stirring for two hours. The organic layer was separated, dried and distilled; b.p. 102° (8 mm.), n_D^{20} 1.4710, d_4^{20} 0.9056. A comparison of the properties of this product with those of the pure Mannich base and bis-(dimethylallylamino)-methane shows that the Mannich base is the chief product. The infrared spectrum was identical to that obtained above for the Mannich base.

Because of the proximity of the boiling points of the Mannich base in this case and the bis-(dimethylallylamino)-methane, a sample of the above product, 29 g., was treated with 4 g. of 98% formic acid and 6 g. of 37% formaldehyde to convert any unreacted bis-(dimethylallylamino)-methane to methylaldimethylamine or a mixture of this amine and dimethylallylamine, which easily could be separated from the Mannich base by distillation. This is a special modification of the Leuckart reaction described by Clarke, Gillespie and Weisshaus.¹⁰ The product isolated by distillation dif-

fered only in insignificant amounts in physical properties from the pure Mannich base, and the infrared spectra were identical, indicating that the reaction of the methylenediamine with 2-methyl-2-nitro-1-propanol goes to completion.

Acknowledgment.—One of the compounds studied, N,N'-bis-(2-methyl-2-nitropropyl)-piperazine, was first prepared by the author by procedure (a) while employed by Rohm and Haas Co., Inc., Philadelphia, Pa., under the terms of OSRD Contract No. OEMsr-643. The analysis is by the R & H analytical laboratory. Permission to use this information has been granted by both Rohm and Haas Co. and the appropriate clearing agency for OSRD. Other analyses reported are by Peninsular ChemResearch, Inc., Gainesville, Fla., and the infrared spectra are by Mr. Robert S. Silas of this Laboratory.

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(10) H. T. Clarke, H. B. Gillespie and S. Z. Weisshaus, *THIS JOURNAL*, **55**, 4571 (1933).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF PURDUE UNIVERSITY]

Condensations of Nitroparaffins with Aldehydes. Preparation of γ -Dinitroparaffins¹

By G. BRYANT BACHMAN AND MARK T. ATWOOD²

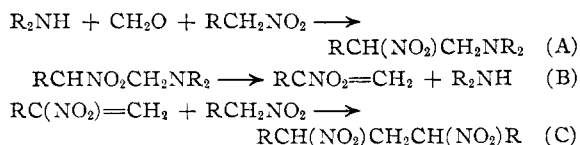
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The condensation of primary nitroparaffins with formaldehyde in the presence of small amounts of secondary amines to give γ -dinitroparaffins is reported. Only basic catalysts capable of forming Mannich base intermediates give good yields, although low yields are obtained even with a tertiary amine and with sodium carbonate. Diastereomers have been separated and shown to be interconvertible in the presence of base.

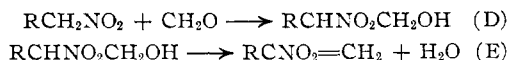
Relatively few γ -dinitroparaffins are known. Hass³ and others have condensed ketones with nitromethane to give compounds of the general structure $R_2C(CH_2NO_2)_2$. The condensation of nitroparaffins with nitroolefins has been utilized to prepare a few γ -dinitroparaffins.⁴ Snyder and Hamlin⁵ reacted Mannich type bases from primary nitroparaffins with nitroparaffins to obtain 3,5-dinitroheptane and 2-methyl-2,4-dinitrohexane. Heim⁶ condensed benzaldehyde with phenylnitromethane to obtain 1,3-dinitro-1,2,3-triphenylpropane.

It seemed to us that simple basic catalysis should be adequate to bring about a quite general condensation between the active methylene group of primary nitroparaffins and the carbonyl group of aldehydes, especially formaldehyde, to form γ -dinitro compounds. Accordingly, we have treated mixtures of two moles of various nitroparaffins and one mole of formaldehyde with catalytic amounts of primary, secondary and tertiary amines as well as with sodium carbonate and obtained the expected γ -dinitro compounds. The yields were best (up to 30%) when secondary amine catalysis was used, and we have therefore devised a reaction sequence

involving secondary amines to explain the formation of γ -dinitroparaffin products.



However, the fact that a carefully purified tertiary amine and sodium carbonate were also found to catalyze the formation of γ -dinitroparaffins makes it necessary to propose a somewhat different mechanism for the formation of the intermediate nitroolefins in such cases.



The relative ease of reaction (B) as compared to (E) probably accounts for the better results obtained with secondary amine catalysis. It should be noted that others⁷ have stated that Mannich-like bases are unlikely intermediates in the condensation of nitromethane with acetone. However our results clearly imply the presence of such intermediates in the condensation of higher nitroparaffins with formaldehyde.

In accord with the above proposals, secondary and tertiary nitroparaffins do not undergo this reaction, because they are incapable of forming the necessary nitroolefin intermediates. Instead, the reaction appears to stop with the formation of a nitroalcohol in the case of secondary nitroparaffins. Thus, 2-nitropropane, formaldehyde and small

(1) Presented before the Organic Division of the American Chemical Society at the Cincinnati meeting, March, 1955.

(2) From the Ph.D. thesis of M. T. Atwood, Purdue University, August, 1954. Commercial Solvents Corporation fellow, 1952-1954.

(3) H. B. Hass and J. Bourland, U. S. Patent 2,343,258 (March 7, 1946); M. S. Larrison and H. B. Hass, U. S. Patent 2,383,603 (August 28, 1945); H. B. Fraser and G. A. R. Kon, *J. Chem. Soc.*, 604 (1934).

(4) A. Lambert and H. A. Piggott, *ibid.*, 1489 (1947); also British Patent 584,789 (January 23, 1947); A. Lambert and A. Lowe, *J. Chem. Soc.*, 1517 (1947); also British Patent 589,515 (June 23, 1947).

(5) H. R. Snyder and W. E. Hamlin, *THIS JOURNAL*, **72**, 5082 (1950).

(6) F. Heim, *Ber.*, **44**, 2016 (1911).

(7) A. Lambert and A. Lowe, *J. Chem. Soc.*, 1518 (1947).