*Anal.* Calcd. for $C_{15}H_{13}ON$: C, 80.69; H, 5.87; N, 6.27. Found: C, 80.59; H, 5.79; N, 6.27.

**Attempted Preparation of *cis*-2-Iodostilbene.**—A solution of the diazonium salt prepared from 1.25 g. (5.4 mmoles) of *cis*-2-aminostilbene hydrochloride, 30 ml. of water, 1.3 ml. of concd. hydrochloric acid and 0.4 g. of sodium nitrite was cooled in an ice-bath and added to a solution of 0.83 g. of potassium iodide in 10 ml. of ice-cold water covered by a layer of 15 ml. of ether. After the reaction mixture had been stirred in the ice-bath for 5 hours the ether layer was washed twice with sodium thiosulfate and allowed to evaporate spontaneously. The orange solid residue (0.97 g.) upon steam distillation gave a white solid, m.p. 81–87°, which was shown by the infrared curve to be mainly phenanthrene contaminated by an unknown substance. The yield was 0.75 g. (78%). Further recrystallization from hexane raised the melting point to 97–98°.

**Attempted Preparation of *cis*-2-Cyanostilbene from Diazotized *cis*-2-Aminostilbene.**—A diazotized solution of 2.32 g. (10 mm.) of *cis*-2-aminostilbene hydrochloride was cautiously neutralized (litmus) by means of approximately 1.3 g. of sodium carbonate dissolved in a small amount of water. This solution was then added slowly with shaking to a cold (5°) mixture of 20 ml. of benzene and a solution of sodium cuprocyanide prepared from 3.12 g. of copper sulfate pentahydrate.[19] The benzene layer after drying (magnesium sulfate) and evaporation yielded a brown solid residue, shown by the infrared curve to be mainly phenanthrene; yield 1.47 g. (82.5%), m.p. 80–90°. Recrystallization from ethanol gave 0.91 g. (51%) of brownish flakes, m.p. 95–96°.

When the *trans*-amine was treated similarly the only products obtained were traces of *trans*-stilbene, m.p. 121–122°, and *trans*-2-cyanostilbene, m.p. 65–66.5°, isolated by chromatography on an alumina column using carbon tetrachloride as solvent. The compounds were identified by means of their infrared spectra.

---

[19] H. T. Clarke and R. R. Read, "Organic Syntheses," Coll. Vol. 1 John Wiley and Sons, Inc., New York, N. Y., 1941, p. 514.

COLUMBIA 1, S. C.

---

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE GEORGIA INSTITUTE OF TECHNOLOGY]

# Carbon Dihalides as Intermediates in the Basic Hydrolysis of Haloforms. IV. Relative Reactivities of Haloforms[1]

BY JACK HINE, ARTHUR M. DOWELL, JR., AND JOHN E. SINGLEY, JR.

RECEIVED JULY 13, 1955

The kinetics of the basic hydrolysis of six haloforms have been studied in 66²/₃% dioxane–water solution. All reactions were second order and the following order of reactivity was found: $CHBrClF \gg CHBrCl_2 > CHBr_2Cl \sim CHCl_2I > CHBr_3 > CHCl_3$. The reaction of fluoroform was too slow to measure. The reactions of all six are believed to involve the intermediate formation of a reactive *carbon dihalide*. As evidence for this, all are much more reactive toward alkali than would be expected from the SN2 mechanism. Furthermore, the reactions of $CHBr_3$, $CHBr_2Cl$, $CHBrCl_2$ and $CHCl_3$ with sodium *p*-thiocresolate are found to be strongly catalyzed by sodium hydroxide. While most of the heats and entropies of activation are within experimental error of each other, the great reactivity of CHBrClF is at least partly an entropy effect.

In earlier articles of this series[2,3] evidence has been presented that the alkaline hydrolysis of chloroform proceeds by the mechanism

$$\text{I}\qquad CHX_3 + OH^- \rightleftarrows CX_3^- + H_2O$$
$$CX_3^- \longrightarrow CX_2 + X^-$$
$$CX_2 \xrightarrow[\text{fast}]{OH^-,\ H_2O} CO \text{ and } HCO_2^-$$

In order to investigate the possibility that other haloforms react by this mechanism and to study the effect of structure on reactivity we have obtained data on some other haloforms.

**Reaction Mechanism.**—Each of the six haloforms studied underwent kinetically second-order alkaline hydrolysis in aqueous dioxane as required by mechanism I.[4] There are, of course, two other reasonable mechanisms that yield second-order kinetics.[2]

$$\text{II}\qquad CHX_3 + OH^- \rightleftarrows CX_3^- + H_2O$$
$$H_2O + CX_3^- \longrightarrow H_2\overset{+}{O}\text{–}\overset{-}{C}X_2 + X^-$$
$$H_2\overset{+}{O}\text{–}\overset{-}{C}X_2 \xrightarrow[\text{fast}]{OH^-,\ H_2O} CO \text{ and } HCO_2^-$$

$$\text{III}\qquad CHX_3 + OH^- \longrightarrow CHX_2OH + X^-$$
$$CHX_2OH \xrightarrow[\text{fast}]{OH^-,\ H_2O} CO \text{ and } HCO_2^-$$

Since III is simply an example of the SN2 mechanism[5] which has been rather well established for the reactions of many organic halides, and no such precedent exists for II, most of our attention has been directed at distinguishing between mechanisms I and III. Our arguments are of the same type already used in the case of chloroform.[2]

Doering and Hoffmann have used olefins as nucleophilic reagents in reaction with chloroform and bromoform.[6] They find the reaction to be accelerated by the base potassium *t*-butoxide. This rules out the SN2 mechanism (III) but does not distinguish between mechanisms I and II.

Bromoform, bromodichloromethane and dichlorofluoromethane, the only other haloforms which appear to have been studied, all undergo base-catalyzed deuterium exchange.[7] Apparently then, trihalomethylcarbanions are formed rather generally from haloforms and alkali.

Toward weakly basic nucleophilic reagents haloforms have been found to be less reactive than the analogous methylene halides in all of the cases studied. Examples of this may be seen in the

---

[1] From the Ph.D. thesis submitted by Arthur M. Dowell, Jr., in 1954, and the M.S. thesis submitted by John E. Singley, Jr., in 1952, to the Graduate School of the Georgia Institute of Technology. Presented in part before the Organic Section at the XIIth International Congress of Pure and Applied Chemistry, New York, N. Y., Sept. 13, 1951. For part III see ref. 3.

[2] J. Hine, THIS JOURNAL, **72**, 2438 (1950).

[3] J. Hine and A. M. Dowell, Jr., *ibid.*, **76**, 2688 (1954).

[4] The mass law effect,[3] by which halide ions slow the reaction by combining with carbon dihalide to regenerate trihalomethyl anions, was negligible under the conditions used.

[5] For the significance of the terms SN1 and SN2 see C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953, chap. VII.

[6] W. von E. Doering and A. K. Hoffmann, THIS JOURNAL, **76**, 6162 (1954).

[7] J. Hine, N. W. Burske and R. C. Peek, Jr., unpublished work from this Laboratory.

TABLE I

KINETIC CONSTANTS FOR THE BASIC HYDROLYSIS OF HALOFORMS AND RELATED COMPOUNDS IN $66^2/_3\%$ DIOXANE–WATER

| Compound | $k \times 10^4$, l. mole$^{-1}$ sec.$^{-1}$ 0° | 25.3° | 35.7° | $\Delta H^\ddagger$, kcal. | $\Delta S^\ddagger$, e.u. |
|---|---|---|---|---|---|
| $CHCl_3$[b] | 0.0104 ± 0.0008 | 0.602 ± 0.023 | 3.19 ± 0.05[c,d] | 26.3 ± 0.8 | +10.5 ± 3 |
| $CHBrCl_2$ | .352 ± .010 | 16.0 ± .6 | 86.5 ± 2.2 | 25.6 ± .8 | +14.8 ± 3 |
| $CHBr_2Cl$ | .137 ± .003 | 8.01 ± .22 | 39.8 ± 2.1 | 26.0 ± .8 | +14.4 ± 3 |
| $CHBr_3$ | 87.0 ± 3.1[e] | 3.20 ± .12 | 15.4 ± 0.3 | 25.0 ± 1.0 | + 9.4 ± 3 |
| $CHCl_2I$ | 0.118 ± .003 | | 39.9 ± 0.4[c,d] | 27.2 ± 1.0 | +18.8 ± 3 |
| CHBrClF | 191 ± 4 | 2150 ± 80[f] | | 25.8 ± 1.2 | +28.4 ± 4 |
| $CH_2Br_2$ | | | .0061 ± .0006 | | |
| $CH_2BrCl$ | | | .025 ± .003 | | |

[a] For carbon tetrabromide $k < 10^{-4}$ at 35.7°, for fluoroform $k < 10^{-6}$ at 50°. [b] At 49.9° $k = (20.8 \pm 0.8) \times 10^{-4}$. [c] At 35.0°. [d] This run was inadvertently carried out in 67% dioxane, but a preliminary study of the solvent effect shows that this should make little difference. [e] At 49.9°. [f] At 14.3°.

data of Petrenko-Kritschenko and Opotsky,[8] and in addition, bromodichloromethane has been found to be less than one-hundredth as reactive as bromochloromethane or methylene bromide toward sodium iodide in acetone.[9,10] Since the replacement of α-hydrogen atoms by halogen is known to decrease $S_N2$ reactivity,[10] this behavior is expected. Toward strongly *basic* nucleophilic reagents, Petrenko-Kritschenko and Opotsky found haloforms to be more reactive than the corresponding methylene halides. Our data (Table I) show that every bromine-containing haloform studied is at least six hundred times as reactive as bromochloromethane or methylene bromide toward hydroxide ions in aqueous dioxane. These data would not be expected for reaction by mechanism III, but are quite reasonable for the carbon dihalide mechanism.

Additional evidence against mechanism III was obtained by the use of *p*-thiocresolate anions[11] to capture the reactive carbon dihalide intermediates. For chloroform, bromodichloromethane, dibromochloromethane and bromoform, reaction with sodium *p*-thiocresolate is strongly accelerated by the presence of free hydroxide ions (see Table III). While this is quite unexplainable in terms of mechanism III, it is exactly what would be expected from mechanism I, since the strongly basic hydroxide ions are required to furnish the necessary intermediate trihalomethyl anions.

These arguments against mechanism III are based on evidence that the trihalomethyl anion is an intermediate in the reaction, and are therefore valueless in distinguishing between mechanism I and II. Nevertheless, mechanism II seems improbable for a number of reasons which already have been described.[2] Since this mechanism has now been disproven for the case of chloroform,[3] it seems unlikely that it operates for other haloforms. While the other haloforms (or at least those studied here) thus apparently undergo alkaline hydrolysis by the carbon dihalide mechanism, we cannot be sure that in all cases the equilibrium between haloform and trihalomethyl anions is established at a rate rapid compared to carbon dihalide formation. It may be that with some haloforms under some conditions the formation of the trihalomethyl anion is the rate-controlling step of the reaction.

**Relative Reactivities of Haloforms.**—As shown in Table I, we found the reactivity of the haloforms studied to vary in the order $CHBrClF >> CHBrCl_2 > CHBr_2Cl \sim CHCl_2I > CHBr_3 > CHCl_3 >> CHF_3$ under the conditions employed. We believe that the most reactive compound, bromochlorofluoromethane, still reacts by the carbon dihalide mechanism although we have not studied its reaction with sodium thiocresolate. The molecule is simply bromochloromethane with an α-hydrogen replaced by fluorine, and yet it is about 300,000 times as reactive (data extrapolated to 35.7°) as bromochloromethane. Its great reactivity is not reasonably explained by mechanism III since in reactions known to be $S_N2$ in character the replacement of α-hydrogen by fluorine decreases the reactivity.[10]

We plan to discuss the effect of structure on the reactivity of haloforms in connection with further experimental work in a subsequent article.

## Experimental

**Reagents.**—Dioxane and chloroform were purified by the methods described by Fieser.[12] Bromodichloromethane, methylene bromide, bromoform and dibromochloromethane were fractionally distilled at atmospheric pressure under nitrogen and stored under nitrogen in brown bottles. Refractive indices and boiling points of the first three compounds agree well with values reported in the literature. The boiling point of our dibromochloromethane agrees with that reported but we found no value for the refractive index or density in the literature. For our material, $n^{25}D$ 1.5450, $d^{32}_4$ 2.411. Since the bromoform obtained from the purification procedure described contained a small amount of acidic impurity, it was further purified by fractional freezing to give neutral material which was stored as a solid at 0°. Du Pont fluoroform and carbon tetrabromide (m.p. 90.4°) and bromochloromethane, both Eastman Kodak Co. white label products, were used without further purification. Dichloroiodomethane was prepared from iodoform and mercuric chloride by the method of Auger.[13] It was found desirable to add 1% of diphenylamine to inhibit iodine-forming decomposition reactions, even when the material was stored under nitrogen in the dark.

To prepare bromochlorofluoromethane, 200 g. of mercuric fluoride and 387 g. of dibromochloromethane were mixed in a three-necked flask equipped with a stirrer and a reflux condenser maintained at 40°. On top of the reflux condenser was a distilling head and 0° condenser leading to a Dry Ice

---

(8) P. Petrenko-Kritschenko and V. Opotsky, *Ber.*, **59B**, 2131 (1926).

(9) For the information that $k < 10^{-5}$ l. mole$^{-1}$ sec.$^{-1}$ for dichlorobromomethane at 50°, we are indebted to Dr. C. H. Thomas who obtained it by the method described for the methylene halides.[10]

(10) J. Hine, C. H. Thomas and S. J. Ehrenson, THIS JOURNAL, **77**, 3886 (1955).

(11) These are used instead of the thiophenolate ions employed previously[2] largely because the higher melting reaction product (tri-*p*-tolyl orthothioformate) is easier to isolate in a pure form.

(12) L. F. Fieser, "Experiments in Organic Chemistry," 2nd ed., D. C. Heath and Co., Inc., New York, N. Y., 1941, Part II, chap. III.

(13) M. V. Auger, *Compt. rend.*, **146**, 1037 (1908).

cooled receiver. The crude product was fractionated to yield 102 g. (37%) of material, b.p. 36.0–36.7°, $n^{25}D$ 1.4143. Berry and Sturtevant[14] report b.p. 36.11–36.18°, $n^{25}D$ 1.4144.

**Kinetic Runs.**—Kinetic runs at temperatures above 0° were made in constant temperature water-baths. The temperature variation was less than 0.05° and a Bureau of Standards calibrated thermometer showed the absolute temperature to be within 0.1° of that listed. When necessary, ice-water was circulated through the cooling coils of a bath. For runs at 0° insulated containers full of a water-ice slurry were used.

Runs were started by pipetting a thermostated standard solution of haloform in dioxane into a thermostated solution of sodium hydroxide in aqueous dioxane. At measured time intervals samples were withdrawn by pipet, added to an excess of cold standard acid and back-titrated with standard base. In runs at 0° the standard haloform was dissolved in aqueous dioxane since pure dioxane is a solid at this temperature. All runs were carried out under nitrogen and those with iodo- and polybromo- compounds in the dark. In most runs the initial concentrations of haloform and alkali were both between 0.02 and 0.04 $M$, except at 0° where higher concentrations were used in some cases. With the very reactive CHBrClF lower concentrations were used.

**Calculation of Rate Constants.**—Rate constants were calculated from each point by means of the integrated rate equation[2]

$$k = \frac{2.303}{t(a[3+f] - b)} \log \frac{b(a-x)}{a(b - [3+f]x)} \qquad (1)$$

where $a = [\mathrm{CHCl_3}]_0$, $b = [\mathrm{OH^-}]_0$, $x = \Delta[\mathrm{CHCl_3}]_t$, $t$ = time (in seconds), $k$ = rate constant (expressed in liters/moles of haloform × seconds) and $f$ = fraction of the haloform hydrolyzed which gives formate (the rest gives carbon monoxide).

In most cases $f$ was evaluated late in a kinetic run by measuring the concentration of halide ions formed as well as the concentration of hydroxide ions used up.

$$f = 3\,\frac{(\Delta[\mathrm{OH^-}] - [\mathrm{X^-}])}{[\mathrm{X^-}]}$$

In addition another method for determining $f$ was devised based on the direct titration of formate as a base in methanol solution. In this method the reaction solution was evaporated to dryness and titrated with standard *p*-toluenesulfonic acid in methanol to a *m*-cresolsulfonphthalein endpoint. By this method known samples of sodium formate were titrated with less than 0.5% error even in the presence of large quantities of sodium chloride. The more basic sodium fluoride was found to interfere with the titration, however. With 0.14 $N$ sodium hydroxide and 0.1 $M$ chloroform in water, three determinations by the methanolic *p*-toluenesulfonic acid method gave $f = 0.1451 \pm 0.0013$, while four determinations by the hydroxide–halide method gave $f = 0.184 \pm 0.012$. This observation shows that the hydroxide–halide method gives a value of $f$ in the correct general area but we are unable to account for the discrepancy between the values obtained by the two methods. Fortunately the value of $k$ is relatively insensitive to the value chosen for $f$, especially early in a kinetic run and in runs where the haloform is present in considerable excess over the base (as in almost all of ours). Since the method involving the direct titration of formate seemed more dependable, we used the value 0.15 for $f$ in all calculations of rate constants for chloroform. Values differing from this were obtained under different conditions but in no case did we feel sure that the difference was larger than our sometimes considerable experimental error. The same value was used for bromodichloromethane and dichloroiodomethane since the hydrolysis of these haloforms should proceed *via* the same intermediate (carbon dichloride) as does that of chloroform. For the other haloforms the value of $f$ determined (by the hydroxide–halide method) in a given run was used in calculating the $k$'s for that run. Values of $f$ for bromoform and dibromochloromethane ranged from 0.00 to 0.083 and those for bromochlorofluoromethane from 0.605 to 0.653. These determinations of $f$ also may be seen to constitute a product analysis. Thus with bromochlorofluoromethane about 3.63 moles of base was required per mole of haloform. The titration with silver nitrate showed that 2.0-moles of bromide plus chloride were formed so that 1.63 moles of the salts of other acids, presumably hydrofluoric and formic, were formed. In all runs, bubbles of gas, shown in several cases to be carbon monoxide, were formed.

Comparisons of the concentrations of halide ions formed with the concentration of alkali used up in the cases of methylene bromide and bromochloromethane show that about 2.5 hydroxide ions react per molecule of methylene halide. This is in agreement with a formaldehyde-forming displacement followed by a Cannizzaro reaction.

$$2\mathrm{CH_2Br_2} + 5\mathrm{OH^-} \longrightarrow 4\mathrm{Br^-} + \mathrm{HCO_2^-} + \mathrm{CH_3OH} + 2\mathrm{H_2O}$$

Therefore, for these compounds, the factor $[3 + f]$ in equation 1 was replaced by 2.5. The rate constants for carbon tetrabromide fell with all the rate equations tried. The value in Table I is calculated from equation 1 with $[3 + f]$ replaced by 5, since halide ion determinations showed about 5 or 6 hydroxide ions used up per molecule of carbon tetrabromide. In most cases about ten points were taken in the run(s) on a given compound at a given temperature and the reaction followed to 60–70% completion.

Data on a typical run are shown in Table II. Averaged rate constants and their average deviations are listed in Table I. Heats and entropies of activation were calculated from the absolute rate equation[15]

$$k = \frac{\mathrm{k}T}{h}\, e^{-\Delta H^{\ddagger}/RT} e^{\Delta S^{\ddagger}/R}$$

(by a least squares method when rate constants at more than two temperatures were obtained). The deviations listed here are based on our estimates of possible errors from all sources and were chosen to yield a confidence level of greater than 90%.

TABLE II

BASIC HYDROLYSIS OF BROMOCHLOROFLUOROMETHANE IN $66^2/_3$% DIOXANE-WATER AT 0.0°[a]

$[\mathrm{CHBrClF}]_0 = 0.007925$, $[\mathrm{NaOH}]_0 = 0.01713$

| Time, sec. | $[\mathrm{NaOH}]_t$ | $k \times 10^4$, l. mole$^{-1}$ sec.$^{-1}$ |
|---|---|---|
| 338 | 0.01429 | 198 |
| 568 | .01292 | 189 |
| 921 | .01112 | 186 |
| 1604 | .00822 | 196 |
| 2604 | .00577 | 195 |
| 3003 | .00507 | 195 |
| | Av. | 193 ± 4 |

[a] The data of this run were averaged with those from another to get the rate constant listed in Table I.

**Reaction of Haloforms with Sodium *p*-Thiocresolate.**—The reaction of haloforms with sodium *p*-thiocresolate was carried out in a manner similar to that used for kinetic runs in aqueous dioxane. In one set of runs sodium hydroxide, *p*-thiocresol and haloform were added to give a solution initially about 0.14 $M$ in sodium *p*-thiocresolate, about 0.11 $M$ in free sodium hydroxide and about 0.11 $M$ in haloform. The reaction was then allowed to proceed for a time calculated to be sufficient to bring about the reaction of almost all of the free base. The concentration of *p*-thiocresol used was determined by iodometric titrations. In a second set of experiments the same concentration of haloform and *p*-thiocresol was used, but only enough sodium hydroxide had been added to neutralize about 95% of the *p*-thiocresol. The reaction was allowed to proceed for the same length of time with a given haloform as the reaction in the presence of excess hydroxide had gone. The results of these experiments are summarized in Table III.

To learn whether the haloforms might be reacting with *p*-thiocresol in some way (such as oxidation to the disulfide) other than to form tri-*p*-tolyl orthothioformate, an isolation experiment was carried out on the reaction mixture from

---

(14) K. L. Berry and J. M. Sturtevant, THIS JOURNAL, **64**, 1599 (1942).

(15) S. Glasstone, K. J. Laidler and H. Eyring, "The Theory of Rate Processes," McGraw-Hill Book Co., Inc., New York, N. Y., 1941, p. 14.

TABLE III

EFFECT OF HYDROXIDE ION CONCENTRATION ON REACTION OF SODIUM $p$-THIOCRESOLATE WITH HALOFORMS[a]

| Haloform | $p$-$CH_3C_6H_4SNa$ reacted, % <br> $[OH^-]_0 = 0.00$ | <br> $[OH^-]_0 \sim 0.11$ |
|---|---|---|
| $CHCl_3$ | 0.23 | 23.0 |
| $CHBrCl_2$ | 2.5 | 23.0 |
| $CHBr_2Cl$ | 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 $\sim$ 0.1 $N$ base; $[CHX_3]_0 \sim 0.11\ M$, $[p\text{-}CH_3C_6H_4SNa] \sim 0.14$.

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).

ATLANTA, GEORGIA

---

[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-propanol(1)

BY GEORGE B. BUTLER

RECEIVED JANUARY 18, 1955

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 Wagner[2] 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 Johnson[3] 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 Henry[4] that reaction of two equivalents of an aliphatic secondary amine with one equivalent of formaldehyde at 60° produces the methylenediamine. Recent work by Ingwalson[5] 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 mixture 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

$$(R_2N)_2CH_2 + H_2O \rightleftarrows R_2NCH_2OH + R_2NH$$

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[7] 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 recrystalli-

---

(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. Communs.*, **6**, 549 (1934).

(7) V. Prelog and G. J. Driza, *Coll. Czechoslov. Chem. Commun.*, **5**, 497 (1933).