Trichloromethylation of Anhydrides. Ring–Chain Tautomerism[1a]

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The synthesis of trichloromethyl-substituted ketones, keto acids, and hydroxy lactones through the thermal decomposition of sodium trichloroacetate in the presence of anhydrides is described. Infrared evidence indicates that in solution the hydroxy lactones and keto acids exist in equilibrium with their tautomeric forms. The stability of the lactone ring, as shown by the infrared, ultraviolet, and pK_a, is a function of the degree of separation between the trichloroacetyl and the carboxyl groups.

Reactions of Sodium Trichloroacetate with Anhydrides.—In 1959 Wagner[2,3] reported the generation of dichlorocarbene by the thermal decomposition of sodium trichloroacetate in 1,2-dimethoxyethane solvent. During a study of the addition of carbenes to bicyclic olefins we found that, when the decomposition of sodium trichloroacetate is carried out in the presence of an olefinic anhydride, reaction occurs exclusively at the carbonyl group of the anhydride, apparently by the trichloromethyl anion precursor of the carbene, to give trichloromethyl addition products.[4] Thus, with *endo-cis*-bicyclo[2.2.1]-5-heptene-2,3-dicarboxylic anhydride the trichloromethylhydroxy lactone **1** was obtained in 75% yield. The cyclic structure **1**, rather than its tautomer, the open-chain keto acid, was consistent with the strong hydroxyl and lactone carbonyl bands in the infrared spectrum (Nujol), Table I. Treatment of **1** with base produced chloroform and the diacid salt of the parent anhydride.

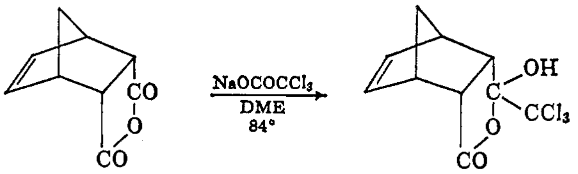

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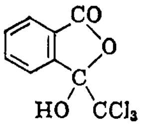
Table I

Infrared Absorption of Trichloromethyl Ketones and Hydroxy Lactones

Compd.	Phase	Absorption, μ OH	Lactone C═O	Ketone C═O	Acid C═O
CH_3COCCl_3	Neat			5.66	
$C_6H_5COCCl_3$	Neat			5.83	
1	Nujol	2.90	5.64	...	...
	CCl_4	2.79	5.54	...	...
	$CHCl_3$	2.80	5.57	...	...
2	Nujol	3.05	5.70	...	...
	CCl_4	2.79	5.54	...	...
	$CHCl_3$	2.79	5.59	5.7 sh	5.81 w
3	Nujol	3.07	5.70	...	...
	CCl_4	2.80	5.53	...	...
	$CHCl_3$	2.78	5.52	5.6 sh	5.83 w
4	Nujol	...	...	5.68	5.84
	CCl_4	2.80 w	5.51	5.67	5.81
	$CHCl_3$	2.79	5.53	5.66	5.80
5	Nujol	...	...	5.73	5.89
	CCl_4	2.79	5.50	5.71	5.84
	$CHCl_3$	2.81	5.55	5.75	5.85 w

The realization of high yields in the initial work indicated that this reaction might prove to be a useful synthetic method for introducing the trichloromethyl group into organic structures. In the past this has been done through the reaction of chloroform and base on aldehydes[5] and ketones[6] to give trichloromethyl-substituted alcohols, but the yields of product are often not high. In order to ascertain the usefulness of the method, the reaction was carried out with a variety of aliphatic and aromatic anhydrides. With acetic and benzoic anhydrides, yields of 19 and 13% of the α,α,α-trichloroacetone and trichloroacetophenone, respectively, were obtained. Reaction with phthalic anhydride afforded an 80% yield of 3-hydroxy-3-trichloromethylphthalide (**2**). Treatment of maleic anhydride with sodium trichloroacetate resulted in extensive decomposition with the production of tars. However, a 7.6% yield of the trichloromethyl addition product **3** was obtained. The lactone structure rather than the keto acid tautomer for both **2** and **3** was assigned on the basis of the strong hydroxyl and lactone carbonyl absorption in the infrared (Nujol), Table I. Succinic anhydride and *cis*-4-cyclohexene-1,2-dicarboxylic anhydride gave **4** and **5** in yields of 20 to 30%. In these cases the two carbonyl peaks in the infrared spectra (Nujol), one for the lactone and the other for the acid (Table I), clearly indicate the open-chain keto acid form. All of these compounds on reaction with



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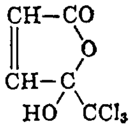

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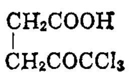

$$\begin{array}{l} CH_2COOH \\ | \\ CH_2COCCl_3 \end{array}$$

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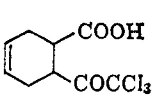

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(1) (a) Presented in part by A. Winston at the 37th Annual Meeting of the West Virginia Academy of Science, Morgantown, W. Va., April 1962; the 14th Southeastern Regional Meeting of the American Chemical Society, Gatlinburg, Tenn., Nov. 1962; the 148th National Meeting of the American Chemical Society, Chicago, Ill., Sept. 1964. (b) Taken in part from the M.S. Thesis of J. P. M. Bederka, West Virginia University, 1961. (c) West Virginia University Graduate Research Assistant. (d) National Science Foundation Undergraduate Research Participation Program, summer 1962. (e) Taken in part from the doctoral research of J. C. Sharp.

(2) W. M. Wagner, *Proc. Chem. Soc.*, 229 (1959).

(3) W. M. Wagner, H. Kloosterziel, and S. Van der Ven, *Rec. trav. chim.*, **80**, 740 (1961).

(4) (a) A. Winston and J. P. M. Bederka, *Proc. West Va. Acad. Sci.*, **34**, 84 (1962). (b) Abstracts of papers presented at the 14th Southeastern Regional Meeting of the American Chemical Society, Gatlinburg, Tenn., Nov. 1962; *Branched Chain*, **18**, No. 3, 70 (1962). (c) Abstracts of papers presented at the 148th Meeting of the American Chemical Society, Chicago, Ill., Sept. 1964, p. 78S.

(5) (a) J. Jocicz, *Chem. Zentr.*, **68I**, 1013 (1897); (b) J. W. Howard, *J. Am. Chem. Soc.*, **47**, 455 (1925); (c) J. W. Howard, *ibid.*, **57**, 2317 (1935); (d) J. W. Howard and G. N. Stephens, *ibid.*, **60**, 228 (1938); (e) E. D. Bergmann, D. Ginsburg, and D. Lavie, *ibid.*, **72**, 5012 (1950).

(6) (a) C. Willgerodt, *Ber.*, **14**, 2451 (1881); **15**, 2305 (1882); **16**, 1585 (1883); (b) M. Guedras, *Compt. rend.*, **133**, 1011 (1901); (c) C. Weizmann, E. Bergmann, and M. Sulzbacher, *J. Am. Chem. Soc.*, **70**, 1189 (1948).

dilute base yielded chloroform and the corresponding diacid salt.

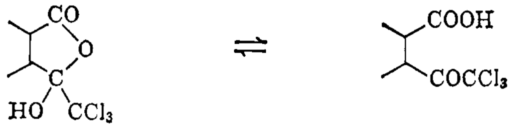
Several of these compounds have appeared in the literature. Compound **2** was first reported by Gabriel and Michael[7] in 1887, who prepared it and the corresponding tribromo analog by direct halogenation of phthalideneacetic acid. Compound **3** was reported in 1884 by Kekulé and Strecker[8] as the product of the oxidation of both benzene and benzoquinone with chlorous acid. The structure was given as the open-chain keto acid, but this was later corrected by Anschütz[9] to the cyclic tautomer.

Since our first report[4a] of the reaction between sodium trichloroacetate and anhydrides, Wagner, Kloosterziel, Van der Ven, and Bickel[10] have reported the preparation of α,α,α-trichloroacetone and compound **5**, and have suggested that the low yields of the ketones could be ascribed to the abstraction of Cl^+ from the already formed trichloride to give carbon tetrachloride and another anion. In several of our cases, particularly the reaction with phthalic and *endo-cis*-bicyclo[2.2.1]-5-heptene-2,3-dicarboxylic anhydrides, the sodium salt of the trichloromethylketo acid is extremely insoluble in the reaction medium and precipitates as a gelatinous mass. This removal of product from the site of reaction would prevent the chlorine abstraction reaction and thus favor higher yields.

The optimum reaction time seems to be about 1 hr. or less. In one experiment a 67% yield of **2** was obtained after only a 20-min. reaction time. Prolonged reaction times seem to lower the yield. Although the direct cause of this is not known, apparently some decomposition occurs, perhaps through chlorine abstraction. It may be significant that maleic anhydride afforded the lowest yield, since loss of Cl^+ from the product **3** would lead to elimination with the formation a more highly conjugated system.

Preliminary experiments have shown that anhydrides accelerate markedly the decomposition of sodium trichloroacetate in dimethoxyethane solvent. It is conceivable that the addition of the trichloromethyl group proceeds through a bimolecular reaction between the trichloroacetate ion and the anhydride accompanied by the elimination of carbon dioxide, rather than by the alternate path involving the initial decomposition of trichloroacetate to a trichloromethyl anion[11] which then adds to the carbonyl. Further experiments are being conducted along these lines.

Ring–Chain Tautomerism.—The establishment of an equilibrium between the ring and chain tautomeric forms **6**, which is characteristic of γ-keto acids,[12] is clearly indicated by the changes in the infrared spectra when these compounds are placed in solution (Table I). When compounds **2** and **3**, which in the crystalline state are entirely in the lactone form as indicated by the Nujol spectra, are dissolved in chloroform, weak infrared bands for the ketone and acid carbonyl groups appear in addition to the strong lactone and hydroxyl bands. The relative intensities of the bands associated with each tautomer indicates that the ring form is greatly favored. Compounds **4** and **5**, which are entirely in the keto acid form in the solid, give rise in both carbon tetrachloride and chloroform to hydroxyl and lactone carbonyl bands in addition to the keto acid bands, again indicating the establishment of the ring–chain equilibrium. In these cases the open-chain keto acid forms are favored. In the bicyclic analog **1** the ketone and acid carbonyl bands failed to appear in the solution spectra, indicating a high degree of stability for this lactone. The large shifts to shorter wave lengths for the hydroxyl and lactone carbonyl bands on dissolution of **1**, **2**, and **3** are characteristic of hydroxy lactones and may be attributed to the disruption of the strong intermolecular hydrogen bonds existing in the crystal.[13]



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The following order of lactone ring stability, as indicated by the infrared data, also corresponds to a decreasing distance between the acid and trichloromethyl groups in the open-chain forms.

$$\mathbf{4} \cong \mathbf{5} < \mathbf{2} \cong \mathbf{3} < \mathbf{1}$$

The groups of **4** can become widely separated through internal rotation, while those of **5** are directed out of coplanarity due to the conformation of the cyclohexene ring. For **2** and **3** the groups are of fixed coplanarity and are about the same distance apart. In compound **1** the groups are coplanar and have the least separation owing to the eclipsed nature of these groups in the boat conformation of the bridged cyclohexene system.

The ultraviolet absorption data, Table II, support the infrared interpretations. Only **4** and **5**, which exist primarily in the keto acid forms, and α,α,α-trichloroacetone show absorption at the proper wave length and intensity to be attributed to the trichloromethyl ketone. The spectra of lactones **1** and **3** do not show any absorption in this region, while the spectrum of **2** is difficult to compare owing to the strong aromatic absorption.

Table II

Ultraviolet[a] and Relative pK_a[b] Data

Compd.	λ_{max} mμ	ϵ	pK_a
1	...	...	7.01 ± 0.08
2	275 283	930 830	6.46 ± 0.07
3	...	...	6.36 ± 0.06
4	287	48	5.35 ± 0.05
5	287	86	5.54 ± 0.06
CCl_3COCH_3	286	28	...
n-Valeric acid	...	...	6.02 ± 0.11
Cyclohexane-carboxylic acid	...	...	6.32 ± 0.09
Benzoic acid	...	...	5.46 ± 0.08

[a] Determined in 95% ethanol solution. [b] Determined in 50% ethanol solution.

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(7) S. Gabriel and A. Michael, *Ber.*, **10**, 1551 (1877).

(8) A. Kekulé and O. Strecker, *Ann.*, **223**, 170 (1884).

(9) R. Anschütz, *ibid.*, **239**, 161 (1887).

(10) W. M. Wagner, H. Kloosterziel, S. Van der Ven, and A. F. Bickel, *Rec. trav. chim.*, **81**, 947 (1962).

(11) (a) F. H. Verhoek, *J. Am. Chem. Soc.*, **56**, 571 (1934); (b) *ibid.*, **67**, 1062 (1945); (c) G. A. Hall, Jr., and F. H. Verhoek, *ibid.*, **69**, 613 (1947).

(12) (a) R. E. Lutz, P. S. Bailey, C. Dien, and J. W. Rinker, *ibid.*, **75**, 5039 (1953); (b) R. E. Lutz, C. T. Clark, and J. P. Feifer, *J. Org. Chem.*, **25**, 346 (1960); (c) R. E. Lutz and H. Moncure, *ibid.*, **26**, 746 (1961).

(13) P. Wilder, Jr., and A. Winston, *J. Am. Chem. Soc.*, **77**, 5598 (1955).

Further information on the stability of the lactone ring is given by the relative apparent pK_a values.[12b] When compounds **1**–**5**, in 50% ethanol, were titrated potentiometrically by the general procedures described by Albert and Serjeant,[14] two equivalence points were observed, the first for the neutralization reaction and the second for the hydrolysis of the trichloromethyl group. In the first equivalence range, the pH values for lactones **1**, **2**, and **3** tended to drift slowly to lower values after each addition of base, while for keto acids **4** and **5**, the pH was essentially stable. This slow decrease in pH may be attributed to an increase in acidity caused by the re-establishment of the equilibrium through a slow ring opening of the lactone. For this reason the pK_a values were determined from titrations carried out fairly rapidly so that the effect of the ring opening on the pK_a would be minimized.

Between the first and second equivalence points the pH increased sharply on each addition of base and then slowly decreased as the base was consumed in the hydrolysis of the trichloromethyl group. This effect continued up to the second equivalence point, which was clearly indicated on the pH curve constructed from values measured 30 min. after each addition of base. As the second equivalence point was almost exactly twice that of the first, little hydrolysis could have occurred during the neutralization reaction from which the pK_a data were determined.

In Table II the apparent pK_a values for compounds **1**–**5**, *n*-valeric acid, cyclohexanecarboxylic acid, and benzoic acid are compared. The indicated range is the maximum scatter of six to eight points making up the average. For keto acids **4** and **5** the low values for the pK_a is consistent with the open-chain structure which was previously assigned on the basis of the infrared data. The inductive effect of the trichloromethyl ketone is operating to increase the acidity of **4** and **5** over that of the standards, *n*-valeric acid and cyclohexanecarboxylic acid. On the other hand, for bicyclic lactone **1**, the fact that the pK_a is greater than that of the two standard acids is evidence for a high degree of stability of the lactone ring. For compounds **2** and **3** the pK_a values are considerably above that of benzoic acid, which is in the opposite direction from that expected from the inductive effect of the trichloroacetyl group. Hence, **2** and **3** also possess a high order of ring stability.

Experimental[15]

Sodium Trichloroacetate.—A solution of trichloroacetic acid in absolute methanol was neutralized to the phenolphthalein end point with a freshly prepared solution of sodium methoxide while maintaining the temperature below 20°. The excess methanol was removed by a rotary evaporator at 20° leaving the white solid of sodium trichloroacetate. The solid was dried in a vacuum oven at 50° over P_2O_5 for 20 hr. A quantitative yield of sodium trichloroacetate was obtained.

Reaction of Sodium Trichloroacetate with *endo-cis*-Bicyclo[2.2.1]-5-heptene-2,3-dicarboxylic Anhydride.—To a solution of 125 g. (0.75 mole) of the anhydride in 500 ml. of anhydrous 1,2-dimethoxyethane, 166 g. (0.84 mole) of sodium trichloroacetate was added. The reaction mixture was refluxed for 15 min., whereupon a white solid appeared, and the reaction mixture became pasty. An additional 100 ml. of anhydrous 1,2-dimethoxyethane was added, and the mixture was refluxed for 1.5 hr. The solvent was evaporated *in vacuo*, and the tan solid salt which remained was dried in a vacuum oven at 50° for 5 hr. The dried salt was dissolved in water and upon acidification with hydrochloric acid, a solid precipitated. Recrystallization from ethyl ether–heptane gave 150 g. (75% yield) of tan crystals of **1**, micro m.p. 192°.

Anal. Calcd. for $C_{10}H_9Cl_3O_3$: C, 42.32; H, 3.19; Cl, 37.51. Found: C, 42.16; H, 3.27; Cl, 37.43.

Basic hydrolysis of the reaction product followed by acidification provided another solid, which from its melting point and infrared spectrum was identified as *endo-cis*-bicyclo[2.2.1]-5-heptene-2,3-dicarboxylic acid.

Reaction of Sodium Trichloroacetate with Acetic Anhydride.—A solution of 20.6 g. (0.11 mole) of sodium trichloroacetate and 10.2 g. (0.10 mole) of acetic anhydride in 50 ml. of 1,2-dimethoxyethane was heated under reflux for 4 hr. The reaction mixture was added to 100 ml. of water and extracted with ether. The ether was washed with sodium bicarbonate solution, then with ether. The ether was washed with sodium bicarbonate solution, then with water, and was dried over magnesium sulfate. Evaporation of the ether left an oily residue which on distillation under reduced pressure gave 3.08 g. (19% yield) of a clear oil: b.p. 56–58° (40 mm.), micro b.p. 134° (754 mm.), n^{20}D 1.4586; for 1,1,1-trichloro-2-propanone, lit. b.p. 57° (48 mm.),[16] 134° (atm.),[16,17] n^{20}D 1.462.[18]

Reaction of Sodium Trichloroacetate with Benzoic Anhydride.—Into a 100-ml. three-neck flask was placed 50 ml. of 1,2-dimethoxyethane and 22.5 g. (0.12 mole) of sodium trichloroacetate. The mixture was warmed to about 60° with stirring until the solid had dissolved. Into this solution was dissolved 22.6 g. (0.10 mole) of benzoic anhydride. The solution was then heated to the reflux temperature whereupon carbon dioxide was evolved. After about 5 min. of heating, a large volume of gelatinous solid separated to interfere with the stirring. After the addition of some solvent, the reaction mixture was heated under reflux for 6 hr. and was then cooled and poured into 100 ml. of water. The gelatinous solid dissolved. The water solution was extracted several times with ether. The ether was washed with aqueous sodium bicarbonate, then with water, and was dried over magnesium sulfate. Evaporation of the ether left a liquid residue which was distilled under reduced pressure to give 2.8 g. (12.6% yield) of a clear oil: b.p. 125–126° (13 mm.), n^{20}D 1.5658; for trichloroacetophenone, lit. b.p. 125° (14 mm.),[19] n^{20}D 1.5685.[20] Basic hydrolysis of the product followed by acidification yielded benzoic acid and chloroform.

Reaction of Sodium Trichloroacetate with Phthalic Anhydride.—Phthalic anhydride (1 mole, 148 g.) and 1 mole (184 g.) of sodium trichloroacetate were dissolved in 500 ml. of anhydrous 1,2-dimethoxyethane and heated under reflux with stirring. After 20 min. a white solid appeared and a thick paste formed. An additional 300 ml. of anhydrous 1,2-dimethoxyethane was added and heating was continued for 45 min. The solvent was removed under vacuum, and the yellow solid salt which remained was dried in a vacuum oven at 75° for 5 hr. This salt was then dissolved in water and filtered of any insoluble material. Upon acidification of the filtrate with hydrochloric acid, light yellow crystals were obtained. Recrystallization from benzene gave 205 g. (80% yield) of white crystals of **2**, micro m.p. 145.8–146.0°, lit.[7] m.p. 144°.

Anal. Calcd. for $C_9H_5Cl_3O_3$: C, 40.41; H, 1.88; Cl, 39.76. Found: C, 40.67; H, 1.85; Cl, 40.03.

Treatment of the product with dilute sodium hydroxide afforded phthalic acid and chloroform.

Reaction of Sodium Trichloroacetate with Maleic Anhydride.—To a solution of 49 g. (0.5 mole) of maleic anhydride in 300 ml. of 1,2-dimethoxyethane, 92.5 g. (0.5 mole) of sodium trichloro-

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(14) A. Albert and E. P. Serjeant, "Ionization Constants of Acids and Bases," John Wiley and Sons, Inc., New York, N. Y., 1962.

(15) Micro melting points were determined on a Kofler hot stage and are corrected. Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. Infrared spectra were recorded on the Perkin-Elmer, Model 21, infrared spectrophotometer. The ultraviolet measurements were made on a Beckman DU spectrophotometer with a hydrogen lamp source powered by a Beckman DU power supply. The pK_a values were determined by potentiometric titration in 50% ethanol using a Beckman Zeromatic pH meter. The solvent, 1,2-dimethoxyethane, was dried over calcium hydride and distilled. All equipment for the decomposition of sodium trichloroacetate was dried in an oven before use.

(16) E. E. Blaise, *Compt. rend.*, **155**, 1252 (1912).

(17) F. Arndt, J. Amende, and W. Ender, *Monatsh.*, **59**, 202 (1932).

(18) R. Jacob, *Bull. soc. chim. France*, **7**, 581 (1940).

(19) H. Staudinger and N. Kon, *Ann.*, **384**, 38 (1911).

(20) S. G. Cohen, H. T. Wolosinski, and P. J. Scheuer, *J. Am. Chem. Soc.*, **72**, 3952 (1950).

acetate was added over a period of 5 min. The reaction mixture, which turned black immediately upon adding sodium trichloroacetate, was heated under reflux for 30 min. The solvent was removed by evaporation under reduced pressure to leave a brown solid residue. The solid was extracted several times with ether. The ether extract was washed with dilute aqueous sodium bicarbonate, then with water, and was dried over anhydrous magnesium sulfate. After decolorizing with charcoal, the ether was evaporated, and a white solid was isolated. This solid was recrystallized from benzene to 8.3 g. (7.6% yield) of white crystals of **3**, micro m.p. 137–138°, lit.[8] m.p. 131–132°.

Anal. Calcd. for $C_5H_3Cl_3O_3$: C, 27.62; H, 1.39; Cl, 48.92. Found: C, 27.53; H, 1.16; Cl, 48.72.

Basic hydrolysis of the product, followed by acidification, yielded maleic acid and chloroform.

Reaction of Sodium Trichloroacetate with Succinic Anhydride.—To a solution of 30.0 g. (0.30 mole) of succinic anhydride in 150 ml. of 1,2-dimethoxyethane, heated under reflux, was added 60.1 g. (0.32 mole) of solid sodium trichloroacetate. The addition was carried out under a nitrogen atmosphere over a 45-min. period, the solid being added through a large rubber tube connecting the reaction flask to the addition flask. As carbon dioxide was evolved, the reaction mixture changed gradually from a pink to a brown-black color. After 1.5 hr., the rate of evolution of carbon dioxide had slowed considerably. The reaction mixture was then poured into 200 ml. of water. The aqueous solution was extracted with ether, and the dried ether solution was evaporated to yield a solid, which on crystallization from ligroin provided 3.5 g. of white crystals, micro m.p. 79.0–79.9°. The aqueous solution was acidified with dilute hydrochloric acid and again extracted with ether. Evaporation of the ether left a solid, which on crystallization from ligroin provided 11.5 g. of white crystals of **4**, micro m.p. 78.0–79.5°. The infrared spectra of the two batches of material were identical in every respect. The combined yield was 15.0 g. (23%).

Anal. Calcd. for $C_5H_5Cl_3O_3$: C, 27.36; H, 2.30; Cl, 48.47. Found: C, 27.34; H, 2.40; Cl, 48.38.

Reaction of Sodium Trichloroacetate with *cis*-4-Cyclohexene-1,2-dicarboxylic Anhydride.—To a solution of 15.2 g. (0.12 mole) of the anhydride in 75 ml. of 1,2-dimethoxyethane, heated under reflux with stirring in a nitrogen atmosphere, was added 22.3 g. (0.12 mole) of solid sodium trichloroacetate in small portions over a period of 0.5 hr. Carbon dioxide was evolved and a fine white precipitate separated. The reaction was allowed to continue until the evolution of CO_2 ceased, about 0.5 hr. after the addition of sodium trichloroacetate was complete. The reaction mixture was added to 200 ml. of water and extracted with ethyl ether. The ether solution was washed with water, dried, and evaporated to yield an oily brown residue which slowly crystallized. The product was recrystallized from benzene–petroleum ether to yield 8.4 g. (31.2%) of tan crystals of **5**, micro m.p. 121.5–122°, lit.[10] m.p. 126–126.5°.

Anal. Calcd. for $C_9H_7Cl_3O_3$: C, 40.11; H, 2.60; Cl, 39.47. Found: C, 40.29; H, 2.83; Cl, 39.19.

Basic hydrolysis of the product, followed by acidification, yielded *cis*-4-cyclohexene-1,2-dicarboxylic acid.

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Kinetics of the Reaction of Nitroalkanes with Methylenebispiperidine. A Study of the Mannich Reaction[1a]

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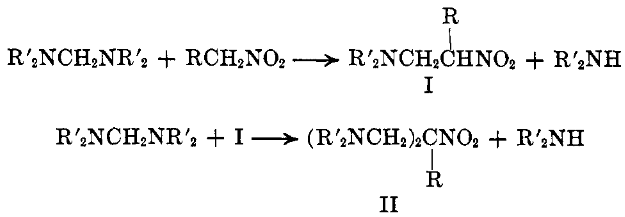
Pseudo-first-order kinetics are reported for the Mannich reaction of methylenebispiperidine with nitromethane, nitroethane, and 2-nitropropane in the solvents dioxane and dimethylformamide. Evidence presented supports the *aci* tautomer as the reactive form of the nitroalkane. A cyclic transition state is suggested for all three nitroalkanes in media of low dielectric constant, and for nitroethane and 2-nitropropane in media of moderately high (~25) dielectric constant. Under the latter conditions nitromethane probably reacts through a linear polar transition state. A rather large entropy of activation is found for the reaction of 2-nitropropane. While nitromethane and nitroethane fail to undergo a second alkylation with methylenebispiperidine in anhydrous media, the second alkylation occurs when water is present or when ethoxymethylpiperidine is used as reactant. These observations, along with rate studies employing 2-nitropropane and methylenebispiperidine in the presence of small amounts of water, point strongly to the N-hydroxymethylpiperidine as the intermediate in these Mannich reactions.

In a previous publication[2] we reported kinetics of he reaction of 2-nitropropane with methylenebis-iperidine and methylenebismorpholine in media of arying dielectric constant. We now wish to report n extension of that work to other nitroalkanes, *viz.*, itromethane and nitroethane, as part of the over-all roblem of the effects of structure on reactivity and nechanism in the Mannich reaction.

The present kinetic study involves pseudo-first-rder reactions of piperidine with nitromethane, nitro-thane, and 2-nitropropane, the effect of medium dielectric constant in the range 5–28, and the effect of small amounts of water on reaction rate.

Mannich bases, I (R = CH_3), of nitroethane have been reported along with the disubstitution products[3]



$$R'_2NCH_2NR'_2 + RCH_2NO_2 \longrightarrow \underset{\text{I}}{R'_2NCH_2\overset{\displaystyle R}{\overset{|}{C}}HNO_2} + R'_2NH$$

$$R'_2NCH_2NR'_2 + \text{I} \longrightarrow \underset{\text{II}}{(R'_2NCH_2)_2\underset{\displaystyle R}{\underset{|}{C}}NO_2} + R'_2NH$$

II (R = CH_3). Mannich bases, I (R = H), of nitromethane had not been reported, however, since all

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[1] (a) Presented at the 148th National Meeting of the American Chemi-al Society, Chicago, Ill., Sept. 1964. A preliminary communication of part f this work appeared in *Tetrahedron Letters*, 2889 (1964). (b) To whom ommunications concerning this paper should be addressed. (c) Student articipant sponsored by National Science Foundation Undergraduate cience Education Grant No. GE-1210.

[2] J. E. Fernandez and J. S. Fowler, *J. Org. Chem.*, **29**, 402 (1964). In-ludes several references to work on the mechanism of the Mannich reaction.

[3] (a) A. T. Blomquist and T. H. Shelley, Jr., *J. Am. Chem. Soc.*, **70**, 147 (1948); (b) W. D. Emmons, *et al.*, *ibid.*, **75**, 1993 (1953).