Reactions of Enamines. VII. The Reaction of Cyclic Enamines with Trichloroacetic Acid[1]

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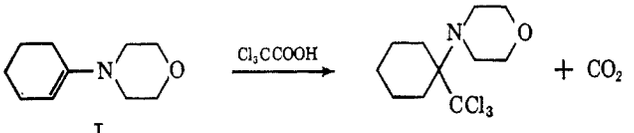
Trichloroacetic acid reacts with the cyclic enamines (I and VII) to form the somewhat unstable trichloromethyl derivatives (II and VIII). The latter undergo rearrangement to α-chloroamides (III and IX) *via* intermediate aziridinium salts. The formation of II and VIII demonstrates that trichloromethyl anion will react preferentially with an organic cationic species to form a neutral compound rather than undergo loss of chloride ion to dichlorocarbene.

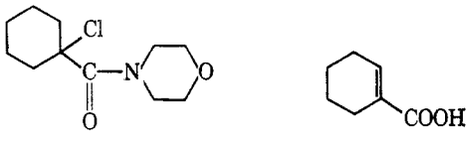
Recently there has been considerable interest and some confusion in the reaction of dichlorocarbene with cyclic enamines.[2-5] The course of reaction of dichlorocarbene generated from chloroform and potassium *t*-butoxide with enamines has recently been established.[5] There are some aspects of the reaction of dichlorocarbene generated by thermal decomposition of trichloroacetates with enamines, however, which need elaboration.

We have found that reaction of N-morpholinyl-1-cyclohexene (I) with trichloroacetic acid in refluxing benzene gave an unstable oil which on careful recrystallization from aqueous acetone afforded the crystalline trichloromethyl derivative II. II was identified by



I II

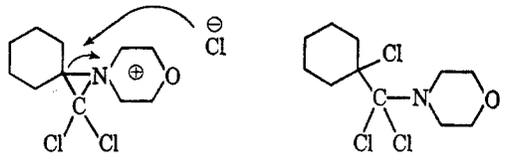
its elemental analysis, nmr spectrum, and by its subsequent reactions. It was found that prolonged heating during the recrystallization of II caused a vigorous reaction with evolution of hydrogen chloride. The amide III, isolated from the reaction of II with aqueous ethanol under similar conditions, was characterized by



III IV

elemental analysis and nmr spectrum, and could be hydrolyzed with ethanolic NaOH to the known acid IV[6] characterized as the amide and *p*-nitrobenzyl ester. IV was also obtained directly by alkaline hydrolysis of II.

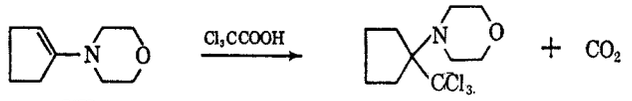
The formation of II and its subsequent reactions are easily rationalized. Protonation of I would give an iminium cation which readily adds the trichloromethyl anion[7] generated by decarboxylation of trichloroacetate to give II.[8] The conversion of II to III probably proceeds *via* the aziridinium salt V which can suffer opening[9] to VI. The latter is readily hydrolyzed to III.



V VI

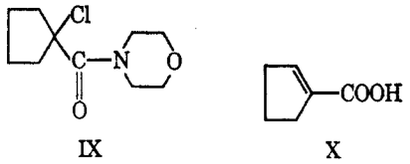
In view of the different reactions of cyclopentanone and cyclohexanone enamines with dichlorocarbene,[5] the reaction of N-morpholinyl-1-cyclopentene VII with trichloroacetic acid was also investigated.

The compound VII reacted smoothly with trichloroacetic acid in refluxing benzene to give VIII. Product



VII VIII

VIII was also unstable to prolonged heating in aqueous acetone and hydrolyzed to the amide IX identified by



IX X

elemental analysis, spectral data, and by its hydrolysis to the known acid X.[10] The acid X was also obtained directly from VIII by basic hydrolysis.

The reaction of trichloroacetic acid with 5,5-dimethyl-3-N-morpholinylcyclohex-2-en-1-one[11] in boiling benzene was also tried. Carbon dioxide was rapidly evolved but the starting enamino ketone was quantitatively recovered. Evidently protonation of the enamino ketone on oxygen[1] had occurred followed by decarboxylation of the trichloroacetate anion; however, instead of reacting with the cationic species, the trichloromethyl anion had abstracted the proton giving chloroform and unchanged enamino ketone.

(1) Part VI: G. H. Alt and A. J. Speziale, *J. Org. Chem.*, **30**, 1407 (1965).

(2) G. Stork, Abstracts, 140th National Meeting of the American Chemical Society, Chicago, Ill., Sept 1961, p 45Q.

(3) A. G. Cook and E. K. Fields, *J. Org. Chem.*, **27**, 3686 (1962).

(4) M. Ohno, *Tetrahedron Letters*, 1753 (1963).

(5) J. Wolinsky, D. Chan, and R. Novak, *Chem. Ind.* (London), 720 (1965).

(6) E. J. Boorman and R. P. Linstead, *J. Chem. Soc.*, 261 (1935).

(7) The reaction of ternary iminium salts with nucleophiles is well known: see (a) N. J. Leonard and A. S. Hay, *J. Am. Chem. Soc.*, **78**, 1984 (1956); (b) G. Opitz, A. Griesinger, and H. W. Schubert, *Ann.*, **665**, 91 (1963).

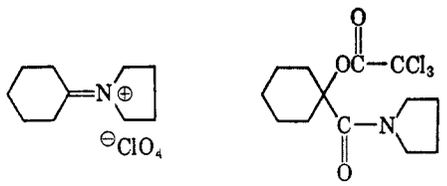
(8) A. Lukasiewicz [*Tetrahedron* **20**, 1 (1964)] has isolated α-trichloromethylamine derivatives from the reaction of trichloroacetic acid with Schiff's bases.

(9) N. J. Leonard and K. Jann [*J. Am. Chem. Soc.*, **84**, 4806 (1962)] have demonstrated the opening of aziridinium salts by nucleophiles.

(10) A. H. Cook and R. P. Linstead, *J. Chem. Soc.*, 956 (1934).

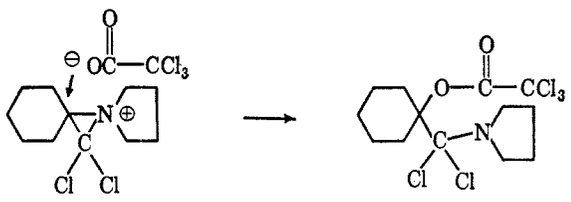
(11) G. H. Alt and A. J. Speziale, *J. Org. Chem.*, **29**, 794 (1964).

Cook and Fields[3] heated the iminium perchlorate XI with 2 moles of sodium trichloroacetate in ethylene chloride and obtained the trichloroacetoxy compound XII. They postulated a mechanism involving the



XI XII

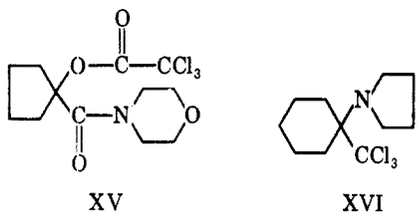
aziridinium salt XIII formed by the reaction of XI with dichlorocarbene as the intermediate. Opening of XIII by trichloroacetate to XIV and hydrolysis of the latter by residual water in the sodium trichloroacetate was then presumed to afford XII. It seemed to us



XIII XIV

that dichlorocarbene was probably not involved in this reaction. It was shown above that the trichloromethyl derivatives II and VIII are converted to the corresponding α-chloroamides III and IX by heating with aqueous solvent *via* the intermediate iminium salts which are opened by chloride. Hence, it seems reasonable that if the hydrolysis of the trichloromethyl derivatives is carried out in the presence of a nucleophile better than chloride ion such as trichloroacetate, the latter will open the aziridinium salt to give a trichloroacetoxy compound.

To test this hypothesis VIII was treated with 1 mole of sodium trichloroacetate in boiling aqueous acetone. From the neutral portion of the product the trichloroacetoxy compound XV was isolated. The α-chloro-



XV XVI

amide (IX) was recovered unchanged by similar treatment with sodium trichloroacetate, confirming that XV was not formed by displacement of the chlorine of IX by trichloroacetate.[3]

It would thus appear that in the work of Cook and Fields, dichlorocarbene is not involved and that the initial product is the trichloromethyl derivative XVI. The latter undergoes reaction with the second mole of trichloroacetate. Hence XIII is not the initial product but an intermediate in the conversion of XVI to XII.

In summary, it may be concluded that when trichloromethyl anion is generated in the presence of an organic cationic species with which it can react to form a neutral compound or from which an acidic proton may be abstracted, these reactions will take precedence over loss of chloride ion to form dichlorocarbene. In other words, loss of chloride from trichloromethyl anion occurs at a rate much slower than the addition of trichloromethyl anion to a cationic species or the abstraction of an acidic proton.

Experimental Section[12]

N-[1-(Trichloromethyl)cyclohexyl]morpholine (II).—To a solution of the enamine I (8.35 g, 0.05 mole) in refluxing benzene (70 ml) was added trichloroacetic acid (8.25 g, 0.05 mole) in benzene (40 ml) over a period of 30 min. Carbon dioxide was evolved during the addition and the reaction mixture was heated for a further 2 hr. Evaporation of the solvent under reduced pressure gave approximately 14 g of an oil which solidified on standing. Rapid recrystallization from aqueous acetone[13] afforded needles: mp 75–77°; ν_{max} 8.91 (s), 13.0 (s), 14.72 (s) μ. The nmr spectrum showed absorption at τ 8.42 (6H, complex multiplet), 7.92 (4H, complex multiplet), 6.95 (4H, multiplet $-CH_2-N-$), 6.42 (4H, multiplet $-CH_2-O$).

Anal. Calcd for $C_{11}H_{18}Cl_3NO$: C, 46.09; H, 6.33; Cl, 37.11; N, 4.92. Found: C, 46.19; H, 6.60; Cl, 37.42; N, 5.15.

N-(1-Chlorocyclohexylcarbonyl)morpholine (III).—A solution of II (7.2 g, 0.025 mole) in 90% ethanol was heated at reflux for 18 hr. During this time HCl was evolved and on cooling a small amount of a crystalline solid was separated which was identified as morpholine hydrochloride. The ethanol was removed by evaporation and the residue was taken up in benzene. After the benzene solution was washed with sodium bicarbonate solution and water, it was dried (Mg_2SO_4), filtered through alumina, and evaporated. The residue (*ca.* 4 g) was distilled through a 45 × 0.5 cm spinning-band column to give 2.8 g (48%) of III: bp 88–89° (0.05 mm); $n^{25}D$ 1.5185; ν_{max} 6.12, 8.96 μ. The nmr spectrum showed absorption at τ 8.36 (6H, complex multiplet CH_2), 7.98 (4H, complex multiplet $-CH_2-$), 6.43 (4H, CH_2-N-), 6.30 (4H, $-CH_2-O-$).

Anal. Calcd for $C_{11}H_{18}ClNO_2$: C, 57.01; H, 7.83; Cl, 15.30; N, 6.05. Found: C, 57.20; H, 7.84; Cl, 15.08; N, 6.21.

1-Cyclohexene-1-carboxylic Acid (IV). A. By Alkaline Hydrolysis of II.—A solution of II (14.3 g, 0.05 mole) in ethanol (100 ml) was heated with excess aqueous 20% sodium hydroxide for 18 hr. The reaction mixture was cooled, diluted with water, and extracted with chloroform to remove neutral and basic materials. The aqueous layer was acidified with concentrated hydrochloric acid and again extracted with chloroform. Evaporation of the chloroform extracts gave 5 g (79%) of IV: ν_{max} 3.40 (s), 5.93 (s), 6.10 (m) μ. The acid was characterized as the amide,[14] mp 126–128° (aqueous ethanol), lit.[15] mp 128°. The acid gave a *p*-nitrobenzyl ester:[14] bp 172–174° (0.4 mm); $n^{25}D$ 1.5578; mp 58–59° (from petroleum ether); ν_{max} 5.86 (s), 6.11 (w) μ.

Anal. Calcd for $C_{14}H_{15}NO_4$: C, 64.35; H, 5.79; N, 5.36. Found: C, 64.54; H, 5.93; N, 5.45.

B. By Alkaline Hydrolysis of III.—Subjecting the morpholide III to hydrolysis with aqueous ethanolic sodium hydroxide, followed by a work-up similar to that above, gave IV identified by infrared spectrum.

N-[1-(Trichloromethyl)cyclopentyl]morpholine (VIII).—To a solution of the enamine VII (7.7 g, 0.05 mole) in refluxing benzene (70 ml) was added trichloroacetic acid (8.25 g, 0.05 mole) in benzene (40 ml) over a period of 30 min. The reaction mixture was heated for 1 hr after the evolution of carbon dioxide ceased. Evaporation of the solvent under reduced pressure gave 13 g of oil which solidified on standing. Rapid recrystallization from

(12) Boiling point and melting points are uncorrected. Melting points were taken on a Mel-Temp capillary melting point apparatus. Infrared spectra were taken on a Beckman IR 5A instrument as capillary films or in chloroform solution. Nmr spectra were taken with a Varian A-60 instrument in deuteriochloroform solution using tetramethylsilane as internal standard.

(13) Aqueous methanol, ethanol, or acetone are suitable solvents for recrystallization. Prolonged heating must be avoided, as a reaction vigorous enough to boil the solvent without external heat takes place with formation of III.

(14) Prepared by the method of R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds," 4th ed, John Wiley and Sons, Inc., New York N. Y., 1956, p 200.

(15) A. Einhorn, *Ber.*, **26**, 457 (1893).

aqueous acetone afforded pure VIII as platelets: mp 64–65°; ν_{max} 8.92 (s), 12.95 (s), 14.78 (s) μ. The nmr spectrum showed absorption at τ 8.22 (4H, multiplet $-CH_2-$), 7.95 (4H, multiplet $-CH_2-$), 6.96 (4H, multiplet $-CH_2-N-$), 6.42 (4H, multiplet $-CH_2-O-$).

Anal. Calcd for $C_{10}H_{16}Cl_3Cl_3NO$: C, 44.06; H, 5.92; Cl, 39.02; N, 5.14. Found: C, 44.16; H, 5.94; Cl, 38.89; N, 5.11.

N-(1-Chlorocyclopentylcarbonyl)morpholine (IX).—A solution of VIII (6.8 g, 0.025 mole) in aqueous acetone was heated under reflux for 18 hr. Most of the acetone was removed by evaporation *in vacuo* and the residue taken up in chloroform. After washing the chloroform solution with water it was dried (Mg_2SO_4) and evaporated. The residual oil was distilled through a short-path distillation apparatus to give 2.5 g (46%): bp 107–110° (0.4 mm); $n^{25}D$ 1.5131; ν_{max} 6.12 (s), 8.96 (s) μ. The nmr spectrum showed absorption at τ 8.20 (4H, complex multiplet $-CH_2-$), 7.75 (4H, complex multiplet $-CH_2-$), 6.30 (8H, complex multiplet $-CH_2-$ of morpholine).

Anal. Calcd for $C_{10}H_{16}ClNO_2$: C, 55.17; H, 7.41; Cl, 16.29; N, 6.44. Found: C, 54.98; H, 7.19; Cl, 16.38; N, 6.49.

1-Cyclopentene-1-carboxylic Acid (X). A. By Hydrolysis of VIII.—A solution of VIII (5.4 g, 0.02 mole) in aqueous ethanol (50 ml) was heated with excess aqueous 20% sodium hydroxide for 18 hr. The reaction mixture was cooled, diluted with water, and extracted with chloroform to remove neutral and basic materials. The aqueous layer was acidified with concentrated hydrochloric acid and again extracted with chloroform. Evaporation of the chloroform afforded an oily solid which on recrystallization from methylcyclohexane gave 1.5 g (68%) of X: mp 120–121°; $\nu_{max}^{CHCl_3}$ 5.95 (s), 6.15 (m) μ; lit.[10] mp 121°. The acid X gave *p*-nitrobenzyl ester:[14] mp 74–76° (from methylcyclohexane); $\nu_{max}^{CHCl_3}$ 5.86 (s), 6.15 (w) μ.

Anal. Calcd for $C_{13}H_{13}NO_4$: C, 63.15; H, 5.30; N, 5.67. Found: C, 63.20; H, 5.38; N, 5.56.

B. By Hydrolysis of IX.—The morpholide IX was hydrolyzed with aqueous ethanolic sodium hydroxide at the reflux temperature for 18 hr. A work-up similar to that under A afforded X, mp and mmp 120–121°.

N-[1-(Trichloroacetoxy)cyclopentylcarbonyl]morpholine (XV).—Sodium trichloroacetate (1.85 g, 0.01 mole) and VIII (2.75 g, 0.01 mole) in 20% aqueous acetone (50 ml) was heated at the reflux temperature for 16 hr. The acetone was then evaporated, water was added, and the mixture was extracted with chloroform. The chloroform extract was dried (Mg_2SO_4) and evaporated *in vacuo*. The residue was recrystallized from methylcyclohexane to give 1.2 g (35%) XV: mp 112–114°; $\nu_{max}^{CHCl_3}$ 5.68 (s), 6.10 (s), 9.0 (s) μ. The nmr spectrum showed absorption at τ 8.20 (4H, complex multiplet $-CH_2-$), 7.72 (4H, complex multiplet $-CH_2-$), 6.35 (8H, multiplet $-CH_2-$ of morpholine).

Anal. Calcd for $C_{12}H_{16}Cl_3NO_4$: C, 41.82; H, 4.68, Cl, 30.86; N, 4.07. Found: C, 42.01; H, 4.77; Cl, 30.91; N, 4.02.

Attempted Conversion of IX to XV.—Treatment of IX (0.01 mole) with sodium trichloroacetate (0.01 mole) in aqueous acetone for 16 hr followed by a work-up as above gave a quantitative recovery of unchanged IX.

Attempted Reaction of 5,5-Dimethyl-3-N-morpholinylcyclohex-2-en-1-one with Trichloroacetic Acid.—5,5-Dimethyl-3-N-morpholinylcyclohex-2-en-1-one[11] (5.25 g, 0.025 mole) in refluxing benzene (70 ml) was treated with a solution of trichloroacetic acid (4.1 g, 0.025 mole) in benzene (25 ml). Carbon dioxide was rapidly evolved during the addition and heating was continued for a further 2 hr. Evaporation of the benzene *in vacuo* afforded 5.2 g (99%) of enamino ketone, mp 127–129°, not depressed on admixture with authentic starting material.

11-Amino Steroids. II. 11-Amino- and 11-Acetamido-3,20-dioxypregnanes[1]

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5β-Pregnane-3α,20β-diol-11-one was converted to its 11-oxime, and then to the 11α-amine (Na–PrOH reduction) or the 11β-amine (Pt–H_2–HOAc reduction). By standard reactions, these were then converted to the corresponding 11-acetamidoprogesterones and their 1-dehydro analogs.

The intense interest in steroids possessing nitrogen atoms is best exemplified by the long list of references to scientific articles in three recent reviews on this subject.[3] In an earlier communication we reported[2] on the relatively facile preparation of 11α- and 11β-aminopregnanes from readily available 11-ketopregnanes; this paper describes such work in detail, as well as the conversion of these amines to certain steroid hormone analogs.

The 11-keto group in steroids containing both angular methyl groups is relatively unreactive toward the usual ketonic reagents, although vigorous conditions can sometimes effect transformations.[4] Similar unreactivity had been noted for 21-acetoxy-20-keto steroids (*e.g.*, they do not readily form ketals,[5] semicarbazones,[6] or 2,4-dinitrophenylhydrazones[7] at C-20 if the C-21 acetate is not hydrolyzed first). However, our observation[8] that 21-acetoxy-20-keto steroids reacted *normally* with hydroxylamine or hydrazine prompted us to explore the reactivity of 11-ketones with such smaller ketonic reagents, although it was generally believed that 11-ketones would not react.[9] Indeed, refluxing 3α,20β-dihydroxy-5β-pregnan-11-one with hydroxylamine hydrochloride in aqueous pyridine for 18 hr produced an excellent yield of the 11-oxime

(1) A portion of this work has been published previously.[2]

(2) E. B. Hershberg, E. P. Oliveto, and R. Rausser, *Chem. Ind.* (London), 1477 (1958).

(3) (a) M. Alauddin and M. Martin-Smith, *J. Pharm. Pharmacol.*, **14**, 325 (1962); (b) *ibid.*, **14**, 469 (1962); (c) M. Martin-Smith and M. Sugrue, *ibid.*, **16**, 569 (1964).

(4) Some examples of such reactions are given in these references: (a) ketal formation, B. Magerlein and R. Levin, *J. Am. Chem. Soc.*, **77**, 1904 (1955); C. Engel, *Can. J. Chem.*, **35**, 131 (1957); (b) Wolff–Kishner reduction, R. Moffet and J. Hunter, *J. Am. Chem. Soc.*, **73**, 1973 (1951); H. Heusser, K. Eichenberger, P. Kurath, H. Dallenbach, and O. Jeger, *Helv. Chim. Acta*, **34**, 2106 (1951); L. F. Fieser, J. Herz, and W.-Y. Huang, *J. Am. Chem. Soc.*, **73**, 2397 (1951); L. F. Fieser, W.-Y. Huang, and J. Babcock, *ibid.*, **75**, 116 (1953); L. F. Fieser and W.-Y. Huang, *ibid.*, **75**, 5356 (1953); C. Djerassi and G. Thomas, *Chem. Ind.* (London), 1228 (1954); D. H. R. Barton, D. Ives, and B. Thomas, *J. Chem. Soc.*, 2056 (1955); C. Djerassi, A. Manson, and H. Bendas, *Tetrahedron*, **1**, 22 (1957); H. Osaka, *Chem. Pharm. Bull.* (Tokyo), **10**, 417 (1962); W. Nagata and H. Itazaki, *Chem. Ind.* (London), 1194 (1964); (c) alkyl- and aryllithium, H. Ringold, E. Batres, and J. Zderic, *Tetrahedron*, **2**, 164 (1958); G. Fonken and J. Hogg, *ibid.*, **2**, 365 (1958); G. Fonken, *J. Org. Chem.*, **23**, 1075 (1958); G. Fonken, J. Hogg, and A. McIntosh, *ibid.*, **24**, 1600 (1959); J. Elks, *J. Chem. Soc.*, 3333 (1960); G. Fonken, *J. Org. Chem.*, **30**, 2095 (1965).

(5) R. Antonucci, S. Bernstein, R. Lenhard, K. Sax, and J. Williams, *ibid.*, **17**, 1369 (1952); R. Antonucci, S. Bernstein, M. Heller, R. Lenhard, R. Littell, and J. Williams, *ibid.*, **18**, 70 (1953); J. von Euw, R. Neher, and T. Reichstein, *Helv. Chim. Acta*, **38**, 1423 (1955).

(6) N. L. Wendler, Huang-Minlon, and M. Tishler, *J. Am. Chem. Soc.*, **73**, 3818 (1951); O. Mancera, *ibid.*, **72**, 5752 (1960).

(7) G. Fleisher and E. C. Kendall, *J. Org. Chem.*, **16**, 556 (1951). See, however, H. Reich and B. Samuels, *ibid.*, **19**, 1041 (1954).

(8) E. P. Oliveto, R. Rausser, L. Weber, E. Shapiro, D. Gould, and E. B. Hershberg, *J. Am. Chem. Soc.*, **78**, 17 6 (1956).

(9) L. Fieser and M. Fieser, "Natural Products Related to Phenanthrene," 3rd ed, Reinhold Publishing Co., New York, N. Y., 1949, pp 409, 655. Also see, *e.g.*, J. Elks and G. Phillipps, *J. Chem. Soc.*, 4326 (1956); O. Schindler, *Helv. Chim. Acta*, **39**, 1698 (1956).