2-Trichloromethyl-4-methyl-1,3-dioxole (12).—Heating of 0.3 mol of **6** with 3.0 g of Linde Molecular Sieve Type 13X in nitrogen to 125° caused an exothermic reaction which raised the temperature to 250°. Cooling during 5 min to 180° and maintaining 180° for 30 min afforded 36 g of distillables consisting of 25% **6** and 75% **12**. Spinning-band distillation gave 15 g (24.5%) of 92% pure **12**: bp 66–68° (7.8 mm); $n^{25}D$ 1.4815; ir (neat) 5.82 (C=C), 8.15, 8.85 (COC), 11.95–12.45 μ (CCl_3); nmr (δ, $CDCl_3$), 1.90 (3 H, d, J = 1.5 Hz, H_a), 6.18 (1 H, 9, J = 1.5 Hz, H_b), 6.04 (1 H, s).

The elemental analysis of **12** was identical with that of **6**.

Registry No.—*cis* **1**, 20286-92-4; *trans* **1**, 20287-07-4; *cis* **2**, 20287-28-9; *trans* **2**, 20287-08-5; *cis* **3**, 20287-29-0; *trans* **3**, 20287-09-6; **4**, 16042-56-1; **5**, 16042-57-2; **6**, 16042-58-3; **7**, 17292-90-9; *trans* **10**, 20302-81-2; **12**, 20287-11-0.

Acknowledgments.—The authors are indebted to W. Harple, H. Hoberecht, and G. Vickers, of Olin Central Analytical Research Department, for determining and interpreting spectral data and to Dr. R. Rittner and his coworkers for performing instrumental and microanalytical work.

1,4-Bis(2-chloroethyl)-1,4-diazabicyclo[2.2.1]heptane Diperchlorate[1,2]

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Received February 4, 1969

Reaction between bis(2-chloroethyl)amine and formalin in ethanol solution was found to yield 1,4-bis(2-chloroethyl)-1,4-diazabicyclo[2.2.1]heptane (**1a**) dichloride, a novel quaternary ammonium salt. The condensation leading to diazabicyclo[2.2.1]heptane **1a** was found generally useful and substances **1b–1f** were easily obtained. Hydrogenolysis of, for example, salt **1e** was found to yield piperazine **8b**. Other pertinent aspects of the chemical and physical (principally proton magnetic resonance) evidence in support of the new ring system have been summarized.

Early in our study of bis(2-chloroethyl)amine in Mannich-type reactions,[3] formation of a water-soluble quaternary ammonium chloride was noted.[4] By allowing bis(2-chloroethyl)amine to react with formalin in ethanol solution followed by addition of perchloric acid, the new compound was conveniently obtained as the less soluble perchlorate salt.

While mass spectral analysis employing a variety of techniques did not give useful information, elemental analytical data and a cryoscopic formula weight determination indicated $C_9H_{18}Cl_4N_2O_8$ for the perchlorate salt. The molecular formula corresponded to combination of 2 mol of bis(2-chloroethyl)amine with 1 mol of formaldehyde. Based on the chemistry of 2-haloethylamines,[5] a number of possible structures (*cf.* **2**) were considered. All but a few could be firmly rejected. Of the remaining possibilities, bicyclic structure **1a** and aziridinium salts **3** and **4** seemed most reasonable. Examination of the chemical and physical (*e.g.*, nmr spectra) properties of the new quaternary ammonium salt led to its assignment as 1,4-bis(2-chloroethyl)-1,4-diazabicyclo[2.2.1]heptane diperchlorate (**1a**): a new heterocyclic system.[6]

The rapid alkylation of thiosulfate by aziridinium ring containing compounds and by 2-chloroethylamines capable of cyclizing to such intermediates serves as a means of distinguishing between a piperazinium or aziridinium structure.[7] Using a quantitative technique, salt **1a** was found not to alkylate thiosulfate. Under the same conditions, thiosulfate was consumed as expected by 1-methyl-1-(2-chloroethyl)aziridinium picrylsulfonate,[7a] N-methylbis(2-chloroethyl)amine hydrochloride,[8a] 1,4-bis(2-chloroethyl)piperazine diperchlorate,[5d] and 2,2-pentamethylene-1,1-tetramethyleneaziridinium perchlorate.[5b,8b] An aziridinium ring was thereby excluded. In addition, aziridinium structures **3** and **4** were eliminated by absence of nmr signals near δ 3.3 in the spectrum of salt **1a**.[9]

The condensation reaction leading to bicyclo[2.2.1]-heptane **1a** was found relatively general for N-alkyl and N-benzyl substituted 2-haloethylamines, and a number of analogous quaternary ammonium salts[10] were prepared. The nmr spectrum of each quaternary salt was easily interpreted in terms of structure **1**. For example, the spectrum of ethyl derivative **1b** displayed a sharp two-proton singlet at δ 5.3 (bridge methylene), an eight-proton singlet at δ 4.3 (piperazine ring), and the char-

(1) Antineoplastic Agents. XXIV. Part XXIII: G. R. Pettit, H. B. Wood, and J. A. Hartwell, *Cancer Res.*, **28**, 2186 (1968).

(2) (a) Based in part on the Ph.D. dissertations of J. A. Settepani, University of Maine, 1963, and D. C. Fessler, Arizona State University, 1968. (b) This investigation was aided in part by Grants T-79B and T-79G from the American Cancer Society and by PHS Research Grant CA-10115-02 from the National Cancer Institute.

(3) G. R. Pettit and J. A. Settepani, *J. Org. Chem.*, **27**, 1714 (1962).

(4) Preliminary communication: G. R. Pettit and J. A. Settepani, *Chem. Ind.* (London), 1805 (1964).

(5) (a) C. R. Dick, *J. Org. Chem.*, **32**, 72 (1967); (b) N. J. Leonard, *Rec. Chem. Progr.*, **26**, 211 (1966); (c) N. B. Chapman and D. J. Triggle, *J. Chem. Soc.*, 1385 (1963); (d) G. R. Pettit and J. A. Settepani, *J. Org. Chem.*, **27**, 2962 (1962); (e) M. F. Sartori, *Chem. Rev.*, **48**, 225 (1951).

(6) Prior examples of the 1,4-diazabicyclo[2.2.1]heptane system have not been confirmed. The 7-thione derivative of **1** has been briefly mentioned in two surveys of thioureas in respect to goitiogenic activity: D. A. McGinty and W. G. Bywater, *J. Pharmacol.*, **84**, 342 (1945) [*Chem. Abstr.*, **40**, 948 (1946)]; R. H. Williams, G. A. Kay and B. Solomon, *Am. J. Med. Sci.*, **213**, 198 (1947) [*Chem. Abstr.*, **41**, 4855 (1947)]. One study was performed at the Parke-Davis laboratories, and these investigators (H. Geer, personal communication, March 11, 1963) kindly identified Union Carbide Co. as their source of the bicyclic compound. Subsequently, it was learned (D. W. Johnson, personal communication, March 26, 1963) that the 1,4-diazabicyclo[2.2.1]heptane-7-thione structure was believed to be in error. For another pertinent report see M. L. Tomayo and R. Madronero, *Rev. Real Acad. Cienc. Exact., Fis. Nat.*, **53**, 1 (1959)

(7) (a) C. Golumbic, J. S. Frutow, and M. Bergmann, *J. Org. Chem.*, **11**, 518 (1946); (b) M. Beroza and A. B. Bofkovec, *J. Med. Chem.*, **7**, 44 (1964).

(8) (a) G. R. Pettit and J. A. Settepani, *J. Org. Chem.*, **27**, 1714 (1962); (b) We are grateful to Professor N. J. Leonard for providing this specimen.

(9) The nmr spectrum of compound **1a** was initially recorded at Varian Associates, Palo Alto, Calif., by Dr. N. S. Bhacca.

(10) A description of these bicyclo[2.2.1]heptanes has been reported in conjunction with a biological study: D. C. Fessler, G. R. Pettit, and J. A. Settepani, *J. Med. Chem.*, **12**, 542 (1969).

acteristic ethyl triplet and quartet. The two-proton methylene bridge singlet at δ 5.3–5.6 was common to all of the spectra, and a singlet corresponding to the remaining ring protons was observed in all examples of bicyclo[2.2.1]heptane **1** where R was alkyl. Where R was benzyl, the piperazine ring protons no longer appeared as a singlet, but instead appeared as a broad resonance. The broad signal seemed plausible in terms of different spatial relationships between the benzene ring and *exo* and *endo* protons of the bicyclic ring. The resulting chemical shift difference between *exo* and *endo* protons would lead to a signal broadened by coupling.

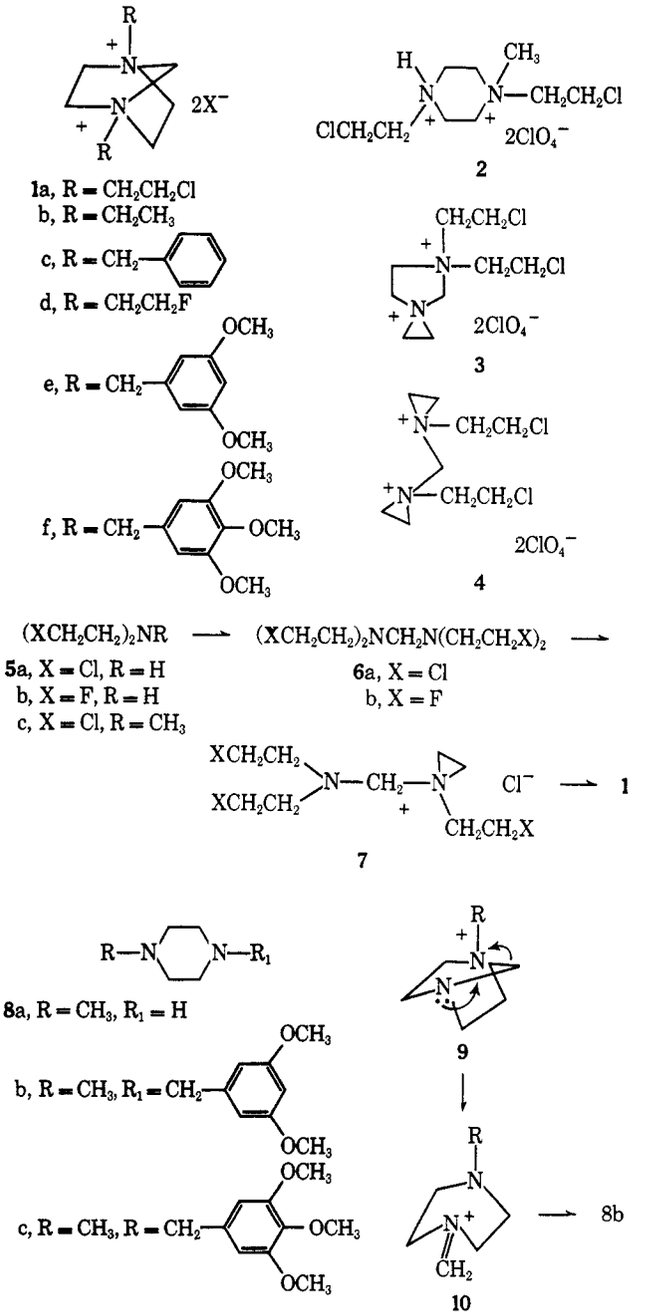
To provide additional support for structure **1**, both an unequivocal synthesis[11] and a degradation of salt **1a** were undertaken. Before a useful alternate synthesis could be developed, the combined spectral and chemical results, which now follow, provided sufficient evidence favoring proposal **1**. The synthetic attempts did, however, serve to emphasize utility of the 2-haloethylamine–formaldehyde route to **1**.

From a chemical standpoint, formation of salt **1a** was easily rationalized as outlined by **5** → **7** → **1**. The first step (**5a** → **6a**), formation of a bis(amino)methane from formaldehyde and a secondary amine, has been well documented.[11b] Conversion of tertiary amine **6a** to **1a** through aziridinium intermediates (**7**)[12a] seems consistent with the known propensity of tertiary nitrogen mustards and bis(2-chloroethyl)amine to form piperazine derivatives by self-condensation. Such a pathway, and hence structure **1**, was supported by isolation of tetrakis(2-fluoroethyl)methylenediamine (**6b**) as an intermediate in conversion of bis(2-fluoroethyl)amine (**5b**) to 1,4-bis(2-fluoroethyl)-1,4-diazabicyclo[2.2.1]-heptane (**1d**) diperchlorate.[10] Other[12b] but less important chemical evidence was obtained as noted below.

Basic hydrolysis of benzyl derivative **1c** was shown to yield dibenzylpiperazine and formaldehyde.[12b] Piperazine derivatives were also formed by hydrogenolysis. One attempt to prepare the parent ring system, 1,4-diazabicyclo[2.2.1]heptane, by catalytic debenzylation of **1c** resulted in formation of 1-methylpiperazine (**8a**) and piperazine. Trace quantities of a component resembling 1,4-dimethylpiperazine was detected but not conclusively identified. Analogous hydrogenolysis of 3,5-dimethoxybenzyl derivative **1e** resulted in absorption of only 2 mol of hydrogen, forming 1-methyl-4-(3′,5′-dimethoxybenzyl)piperazine (**8b**) dihydrochloride. Similarly, perchlorate salt **1f** gave 1-methyl-4-(3′,4′,5′-trimethoxybenzyl)piperazine (**8c**) diperchlorate as the only product of hydrogenolysis. Characterization of piperazine **8c** was completed by comparison with an authentic sample obtained by alternate synthesis.

The hydrogenolysis reaction just described may proceed by loss of a benzyl group to yield tertiary amine **9**, which undergoes ring opening to give an intermediate such as **10**, which rapidly undergoes reduction to, *e.g.*, methylpiperazine **8b**. That ring cleavage occurred only after loss of a benzyl group was suggested by failure of ethyl analog **1b** to undergo hydrogenolysis. The difference in hydrogenolysis products derived from quaternary salts **1c** and **1e,f** may be viewed in terms of some prior experiments[13] where a methoxyl substituent in any position of a benzyl ring was found to greatly retard the rate of hydrogenolysis.

The convenient preparation of bicyclo[2.2.1]heptanes herein described should facilitate entry into future synthetic and theoretical investigations of this interesting bicyclo-ring system.



Experimental Section

Catalytic hydrogenations were accomplished with a slight positive pressure of hydrogen. Melting points were recorded

(11) A number of unsuccessful attempts to construct a methylene bridge between the two nitrogen atoms of piperazine have been reported. Procedures employing cyanic acid (a), phosgene (b), carbon bisulfide (b, c) and formaldehyde (b) have all led to products other than 1,4-diazabicyclo-[2.2.1]heptane: (a) W. L. Mosby, "The Chemistry of Heterocyclic Compounds," A. Weissberger, Ed., Vol., XV-2, Interscience Publishers, Inc., New York, N. Y., 1961, pp 1283–1284; (b) W. Herz, *Ber.*, **30**, 1584 (1897); J. F. Walker, "Formaldehyde," 3rd Ed., Reinhold Publishing Corp., New York, N. Y., 1964, p 359, and W. V. Farrar, *Rec. Chem. Prog.*, **29**, 85 (1968); (c) A. Schmidt and G. Wichmann, *Ber.*, **24**, 3237 (1891).

(12) (a) For a related example refer to H. Böhme and H. Orth, *Chem. Ber.*, **99**, 2842 (1966); (b) see also H. Böhme and H. Orth, *Arch. Pharm.*, **300**, 148 (1967).

(13) R. Baltzly and P. B. Russell, *J. Amer. Chem. Soc.*, **72**, 3410 (1950).

employing a Kofler melting point apparatus and purity was confirmed by thin layer chromatography using silica gel HF_{254} (E. Merck, Darmstadt) on microscope slides. Unless otherwise noted, each chromatogram was prepared using the top layer of water–*n*-butanol–acetic acid (5:4:1) mixture as solvent and developed with iodine vapor. Each analytical sample was colorless.

Infrared spectra were determined in potassium bromide with a Beckman IR-12 by Miss K. Reimer. Nmr spectra were recorded in deuterium oxide (tetramethylsilane as external standard, Varian A-60). Elemental microanalytical data were provided by Dr. A. Bernhardt, Max Planck Institute, Mülheim, Germany.

1,4-Bis(2′-chloroethyl)-1,4-diazabicyclo[2.2.1]heptane Diperchlorate (1a).—A solution of bis(2-chloroethyl)amine (0.20 *M*), 37% formalin (33 ml), and 95% ethanol (66 ml) was left at room temperature for 10 hr. Treating the colorless solution with 70% perchloric acid (15 ml) followed by cooling (ice bath) gave a crystalline solid (32.3 g, 76%) decomposing at 210–211°. Repeated recrystallization from aqueous ethanol afforded a sample as colorless plates: mp 222–223° dec; ν_{max} 1450 (br), 1362, and 1100 cm^{-1}; nmr δ 4.4–3.9 (m, 8 H), 4.45 (s, 8 H), and 5.6 ppm (s, 2 H).

Anal. Calcd for $C_9H_{18}Cl_4N_2O_8$: C, 25.49; H, 4.27; Cl, 33.48; N, 6.60. Found: C, 25.54; H, 4.49; Cl, 33.65; N, 6.37.

The formula weight of 1,4-bis(2-chloroethyl)-1,4-diazabicyclo-[2.2.1]heptane diperchlorate (**1a**) was determined cryoscopically in water, using a procedure described by Daniels.[14] Both bis(2-chloroethyl)amine (**5a**) perchlorate (mol wt 242) and N-methylbis(2-chloroethyl)amine (**5c**) perchlorate (mol wt 256) were used as standards. The results shown in Table I were obtained and are consistent with a $(C_9H_{18}Cl_4N_2O_8)_1$ unit.[15]

TABLE I

	Wt of water, g	Wt of salt, g	Temp, °C	Mol wt	% deviation
Ia	17.72	0.170	0.111	472	+10
Ia	26.12	0.200	0.092	462	+8
5a	18.06	0.205	0.170	246	+1.6
5c	15.94	0.200	0.168	272	+6.2

Nuclear Magnetic Resonance Study of 1,4-Diazabicyclo[2.2.1]-heptanes.—**1b**, δ 1.5 (t, J = 7.5 cps, 6 H), 3.9 (q, J = 7.5 cps, 4 H), 4.3 (s, 8 H), and 5.3 ppm (s, 2 H); **1c**, δ 4.4 (br 8 H), 5.2 (s, 4 H), 5.65 (s, 2 H), and 7.85 ppm (s, 10 aromatic H); **1d**, δ 4.33–4.48 (m, 4 H), 4.73 (s, 8 H), 5.65–5.75 (m, 4 H), and 5.77 ppm (s, 2 H); **1e**, δ 4.0 (s, 12-OMe H), 4.4 (br, s, 8 H), 5.1 (s, 4 H), 5.65 (s, 2 H), and 7.0 ppm (s, 6 aromatic H); **1f**, δ 3.9 (s, 6-OMe H), 3.95 (s, 12-OMe H), 4.35 (br, 8 H), 5.05 (s, 4 H), 5.5 (s, 2 H), and 7.05 ppm (s, 4 aromatic H); 1, R = 3′-chlorobenzyl, δ 4.4 (br, 8 H), 5.25 (s, 4 H), 5.7 (s, 2 H), and 7.9 ppm (m, 8 aromatic H); 1, R = 2-cyclopentylethyl, δ 1.9 (m, 13 H), 3.9 (br, 4 H), 4.2 (s, 8 H), and 5.45 ppm (s, 2 H); 1, R = 2-phenylethyl, δ 3.4 (t, J = 15 cps, 4 H), 4.3 (*t*, J = 15 cps, 4 H), 4.5 (s, 8 H), 5.6 (s, 2 H), and 7.7 ppm (s, 10 aromatic H); 1, R = 2-(3′,4′,5′-trimethoxyphenyl)ethyl, δ 3.25 (br, 4 H), 3.71 (s, 6-OMe H), 3.88 (s, 12-OMe H), 4.25 (br, 4 H), 4.4 (s, 8 H), 5.5 (s, 2 H), and 6.7 (s, 4 aromatic H).

Tetrakis(2-fluoroethyl)methylenediamine (6b).—A solution of bis(2-fluoroethyl)amine (**5b**) hydrobromide[16] (1.9 g) in water was neutralized with aqueous sodium hydroxide (0.4 g in 2 ml). Addition of 37% formalin (1 ml) followed by cooling in an ice bath resulted in separation of an oil (0.20 g) which was chromatographed on basic alumina (10 g of Brockman activity I). Elution with diethyl ether gave a viscous oil (0.05 g) which was dried *in vacuo* at room temperature.

Anal. Calcd for $C_9H_{18}F_4N_2$: C, 46.96; H, 7.86; F, 33.01; N, 12.16. Found: C, 46.93; H, 8.24; F, 33.05; N, 12.25.

Hydrogenolysis of 1,4-Dibenzyl-1,4-diazabicyclo[2.2.1]heptane (1c) Diperchlorate.—The perchlorate salt (**1c**, 0.65 g) in water (200 ml) containing suspended 10% palladium on carbon (0.1 g) was hydrogenated at room temperature. After hydrogen (3 mol) uptake had ceased (18 hr), catalyst was removed by filtering the solution through Celite. The filtrate was washed with benzene (10 ml) and freeze dried, yielding a colorless solid (0.4 g) which showed only two singlets (3 H at δ 3.0 and 8 H at δ 3.6) in then mr spectrum. Three components with R_f's identical with those of 1,4-dimethylpiperazine, 1-methylpiperazine, and piperazine were detected on a thin layer chromatogram (chloroform–methanol–17% ammonium hydroxide, 2:2:1). The free bases were separated by preparative layer chromatography (1.5 mm silica gel HF_{254} plate) using the above solvent system. Each of the three bands was eluted with methanol. Treating the eluates of zones corresponding to piperazine and 1-methylpiperazine with methyl iodide led in both cases to a single component identical (by thin layer) with 1,1,4,4-tetramethylpiperazinium iodide. The third zone appeared to be a mixture, and similar treatment with methyl iodide gave inconclusive results.

Hydrogenolysis of 1,4-Bis(3′,5′-dimethoxybenzyl)-1,4-diazabicyclo[2.2.1]heptane (1e) Diperchlorate.—Perchlorate salt **1e** (0.6 g) in aqueous (200 ml) solution was hydrogenated for 18 hr at room temperature using 10% palladium on carbon (0.10 g) as catalyst. Isolation of product was accomplished as summarized for **1c** to yield **1-methyl-4-(3′,5′-dimethoxybenzyl)piperazine (8b)** diperchlorate (0.45 g, mp 165–168°). A pure specimen was obtained by three crystallizations from ethanol–diethyl ether: mp 190–191.5°; ir ν_{max} 3010, 2800, 1600 (d), 1470 (d), 1120 (br), and 640 cm^{-1}; nmr δ 3.1 (s, 3 methyl H), 3.7 (s, 8 H), 3.95 (s, 6 methoxyl H). 4.4 (s, 2 benzyl H), 6.8 (s, 4 aromatic H).

Anal. Calcd for $C_{14}H_{24}Cl_2N_2O_{10}$: C, 37.25; H, 5.37; Cl, 15.71; N, 6.21. Found: C, 37.18; H, 5.49; Cl, 15.60; N, 6.29.

Hydrogenolysis of 1,4-Bis(3′,4′,5′-trimethoxybenzyl)-1,4-diazabicyclo[2.2.1]heptane (1f) Dichloride.—Using 0.10 g of 5% palladium on carbon, chloride salt **1f**, (0.8 g) in water (50 ml) was hydrogenated (7.5 hr) at room temperature. Treatment as with **1c** yielded a colorless solid (0.5 g) homogeneous by thin layer chromatography. Three crystallizations from acetone–ethanol–hexane afforded a pure sample shown to be **1-methyl-4-(3′,4′,5′-trimethoxybenzyl)piperazine (8c)** dihydrochloride by infrared spectral comparison and mixture melting point determination with an authentic sample (see below): mp 181–183°; mmp 180–183°.

1-Methyl-4-(3′,4′,5′-trimethoxybenzyl)piperazinium (8c) Dihydrochloride.—A solution of 1-methyl-4-(3′,4′,5′-trimethoxybenzoyl)piperazine[17] (13.0 g) in tetrahydrofuran (50 ml) and a solution of diborane in tetrahydrofuran[18] (160 ml of 1 *M*) were combined at ice bath temperature and allowed to stand for 24 hr at room temperature. The solution was cooled (ice bath) and concentrated hydrochloric acid (20 ml) was added. After removal of tetrahydrofuran at reduced pressure, the resulting white slurry was diluted with ice water, made basic with 50% potassium hydroxide solution, and extracted with diethyl ether (100 ml). The ether layer was washed with water (50 ml) and saturated with hydrogen to yield crude **8c** dihydrochloride (2.35 g). Three crystallizations from the same solvent afforded a pure sample as needles: mp 184–185°; ν_{max} 3300 (br), 2610 (br), 1600, 1470, 1430, 1250, and 1130 cm^{-1}; nmr δ 3.1 (s, 3 methyl H), 3.7 (s, 8 H), 3.9 (s, 3 methoxyl H), 3.95 (s, 6 methoxyl H), 4.4 (s, 2 benzylic H), and 6.9 ppm (s, 2 aromatic H).

Anal. Calcd for $C_{15}H_{26}Cl_2N_2O_3$: C, 50.98; H, 7.43; Cl, 20.07; N, 7.93. Found: C, 50.91; H, 7.43; Cl, 19.96; N, 7.85.

Attempted Hydrogenolysis of 1,4-Diethyl-1,4-diazabicyclo-[2.2.1]heptane Diperchlorate (1b).—Perchlorate salt **1b** (0.5 g) in water (100 ml) was hydrogenated over 10% palladium on carbon. After 24 hr, no hydrogen had been absorbed. Treatment as for **1c** gave starting salt (0.4 g) as evidenced by a nmr spectrum.

Registry No.—**1** (R = 3′-chlorobenzyl), 20429-61-2; **1** (R = 2-cyclopentylethyl), 20445-46-9; **1** (R = 2-phenylethyl), 20429-54-3; **1** (R = 2(3′,4′,5′-trimethoxy-

(14) F. Daniels, J. H. Mathews, J. W. Williams, P. Bender, and R. A. Alberty, "Experimental Physical Chemistry," Fifth ed, McGraw-Hill Book Co., Inc., New York, N. Y., 1956, pp 68–71.

(15) While it would be possible to use the observed freezing point depression to arrive at a formula weight consistent with a dimer or higher polymer of $C_9H_{18}Cl_2N_2$ (by inserting the larger number of ions per gram formula weight into the van't Hoff equation), such experimental formula weights would be lower than calculated values (by 9% in the case of a dimer). For this reason, higher multiples of the 426 formula weights were considered unlikely.

(16) G. R. Pettit and R. L. Smith, *Can. J. Chem.*, **42**, 572 (1964).

(17) G. Gerbai, G. DiPaco, and G. Dell'Omadarme, *Boll. Chim. Farm.*, **101**, 211 (1962); *Chem. Abstr.*, **59**, 6403*h* (1963).

(18) Employed as received from Metal Hydrides Division, Ventron Corp.

phenylethyl), 20429-55-4; **1a** (diperchlorate), 1020-94-6; **1b** (diperchlorate), 20445-47-0; **1c** (diperchlorate), 15567-89-2; **1d** (diperchlorate), 1083-67-6; **1e** (diperchlorate), 20429-72-5; **1f** (dichloride), 20429-73-6; **8b** (2 $HClO_4$), 20429-60-1; **8c** (2HCl), 20429-59-8.

Novel Reactions of 3-Unsubstituted 3-Isoxazolin-5-ones

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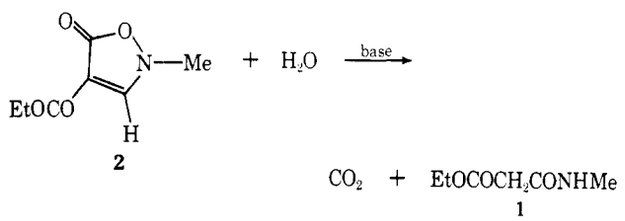
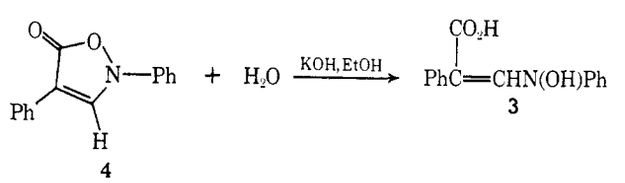
Received January 22, 1969

The reaction of 2,4-diphenyl-3-isoxazolin-5-one, **4**, and ethoxide gives ethyl 2-phenylmalonanilate, **7**, while that of 2-methyl-4-carbethoxy-3-isoxazolin-5-one, **2**, with acetate gives an enolic C-acyl derivative, **23** (R = Me). Both reactions may involve rearrangement of the normal ring-opening products.

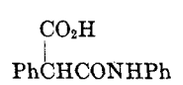
The base-catalyzed ring opening of 3-unsubstituted 3-isoxazolin-5-ones was shown to involve abstraction of the proton from the 3-position and rupture of the N–O bond by Ulrich, Tilley, and Sayigh,[1] who obtained ethyl N-methylmalonamate, **1**, from the treatment of 2-methyl-4-carbethoxy-3-isoxazolin-5-one, **2**, with aqueous base. An alternative pathway for ring



opening, cleavage of the ester function, had been proposed earlier by Rupe and Grünnolz,[2] who reported the isolation of 3-(N-hydroxy)anilinoatropic acid, **3**, from the reaction of 2,4-diphenyl-3-isoxazolin-5-one, **4**, with ethanolic potassium hydroxide. Fabbrini, Renzi, and

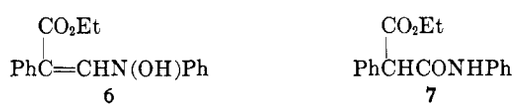


Speroni[3] accepted this latter pathway for the formulation of the products in a related case, but later DeSarlo and Renzi[4] demonstrated that, in fact, fission of the N–O bond is a general reaction and that the product assigned structure **3** is actually 2-phenylmalonanilic acid, **5**.



In the course of an independent study of isoxazolones, we also identified the product from **4** as **5**[5] and found, in addition, that the reactions of **4** and **2** with ethoxide and acetate ions, respectively, give ring-opening products of unexpected structure.

In support of the mode of ring opening they had proposed, Rupe and Grünholz[2] showed that the same compound, which they formulated as **6**, was obtained both from **4** and potassium hydroxide in ethanol and from esterification of the acid they thought to be **3**. In our reexamination of this work, we found, instead, that the product is ethyl 2-phenylmalonanilate, **7**, the ester of **5**.



The possibility that ethoxide actually might attack the 5 position of **4** to give **6** is ruled out by the nmr spectrum of the compound, which lacks the characteristic low-field signals expected for the olefinic and hydroxyl protons of the vinylogous hydroxamic acid function of **6**.[7] Similarly, while the spectral properties are in complete accord with **7**, the tautomers **8** and **9**, which might be obtained directly from the ring opening with N–O bond rupture, are excluded by the absence of any nmr signal or ir band in the regions indicative of the carboxylic acid proton.[9]

Our major interest in the 3-unsubstituted isoxazolones stemmed from the potential synthetic utility of the reaction with carboxylic acid anions. Specifically, the ring opening of **2** with carboxylate, followed by decarboxylation, would be expected to give **10** (or **11**) (Scheme I), which closely resembles the intermediates **12** (or **13**) in the isoxazolium salt method of peptide synthesis.[11]

Facile 6-center intramolecular acyl migrations are

(1) H. Ulrich, J. N. Tilley, and A. A. Sayigh, *J. Org. Chem.*, **27**, 2160 (1962).

(2) H. Rupe and J. Grünholz, *Helv. Chim. Acta*, **6**, 102 (1923).

(3) L. Fabbrini, G. Renzi, and G. Speroni, *Chim. Ind.* (Milan), **43**, 1195 (1961).

(4) F. DeSarlo and G. Renzi, *Tetrahedron*, **22**, 2995 (1966).

(5) J. D. Jacobsen and J. V. Van Ornum,[6] unpublished results.

(6) National Science Foundation Undergraduate Research Participant, 1967.

(7) Both signals appear downfield from the aromatic proton signal in the related compound 3-(N-hydroxy)anilinoacrylophenone.[8] The conceivable nitrone tautomer of **6** also would have a low-field aldehydic signal and would be inconsistent with the NH band in the infrared spectrum.

(8) R. B. Woodward, D. J. Woodman, and Y. Kobayashi, *J. Org. Chem.*, **32**, 388 (1967).

(9) The =NH—$^+$ ir band of the possible zwitterionic form of **9** also would appear at long wavelength, comparable with that of the carboxylic acid absorption.[10]

(10) K. Nakanishi, "Infrared Absorption Spectroscopy," Holden-Day, Inc., San Francisco, Calif., 1962, p 39.

(11) R. B. Woodward, R. A. Olofson, and H. Mayer, *J. Amer. Chem. Soc.*, **83**, 1010 (1961); *Tetrahedron Suppl.*, **8**, 321 (1966).