Studies in the Norbornane Series. I. A Simple Stereospecific Synthesis of *exo*-2-Norbornyl Methyl Ketone

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The first sterically unequivocal synthesis of *exo*-2-norbornyl methyl ketone has been described by Berson.[1] The procedure consists of five steps and is too lengthy for preparations on a larger scale. This prompted us to investigate a simpler synthesis whose concept is based on the combination of two already known facts: (1) the free-radical addition of aldehydes to olefins yields ketones,[2,3] (2) the first step of the addition of free radicals or ions to the double bond of norbornene almost exclusively follows the "*exo*" course.[4]

Heating the commercially available norbornene with acetaldehyde at 80° for 40 hr. in presence of 0.02 mole of azobisisobutyronitrile[5] yielded 80% *exo*-norbornyl methyl ketone. The *exo* configuration of the ketone was proven by checking its refractive index and the melting point and mixture melting point of its semicarbazone and also by converting the ketone into *exo*-norborneol by reaction with perbenzoic acid. It had been shown previously[6] that the Baeyer–Villiger oxidation proceeds without change of configuration.

The steric uniformity of the ketone was demonstrated by the fact that the semicarbazone of the correct melting point was formed in 96% yield.

Experimental[7]

***exo*-Norbornyl Methyl Ketone.**—Freshly distilled norbornene (47.0 g., 0.5 mole) was dissolved in 132 g. of freshly distilled acetaldehyde containing 0.01 mole of azobisisobutyronitrile. The mixture was heated in an autoclave at 80° for 40 hr. After removing most of the unchanged acetaldehyde at atmospheric pressure the remainder was distilled *in vacuo* to yield 56.7 g. of *exo*-norbornyl methyl ketone, b.p. 79–81° (15 mm.), lit.[1] b.p. 87° (19 mm.), and an unidentified high-boiling residue. The ketone which had $n^{24}D$ 1.4709, lit.[1] $n^{25}D$ 1.4710, formed a semicarbazone in 96% yield, m.p. 181.5–182.5°, lit.[1] m.p. 182–183°. The semicarbazone gave no melting point depression upon admixture with a semicarbazone, prepared from authentic *exo* ketone[1]; admixture with authentic *endo* semicarbazone,[1] m.p. 179–180°, resulted in a melting point depression of about 10°. Following the procedure already reported,[1] the *exo* ketone was converted into *exo*-norborneol, m.p. 126–127°; dinitrobenzoate, m.p. 104°.

Acknowledgment.—This author is indebted to Mr. R. W. Waite for performing some experiments and gratefully acknowledges a gift of norbornene from Enjay Chemical Company and Union Carbide Company.

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[1] J. A. Berson and S. Suzuki, *J. Am. Chem. Soc.*, **81**, 4088 (1959).

[2] M. S. Kharasch, W. H. Urry, and B. M. Kuderna, *J. Org. Chem.*, **14**, 248 (1949).

[3] K. Ziegler, *Brennstoff-Chem.*, **30**, 181 (1949).

[4] See among others: (a) K. Alder and K. Backendorf, *Ann.*, **535**, 106 (1938); (b) G. Stork, E. E. Van Tamelen, L. J. Friedman and A. W. Burgstahler, *J. Am. Chem. Soc.*, **75**, 384 (1953); (c) L. Kaplan, H. Kwart, and P. von R. Schleyer, *ibid.*, **82**, 2341 (1960); (d) W. Reusch, *J. Org. Chem.*, **27**, 1882 (1962).

[5] It should be noted that *replacement of this initiator by other free-radical sources of peroxidic nature drastically reduces the amount of ketone formed in the present case.* Some reasons for this are given in ref. 2 and 3.

[6] R. B. Turner, *J. Am. Chem. Soc.*, **72**, 878 (1950); *cf.* also ref. 1

[7] Melting points were determined using the Kofler hot-stage apparatus.

A 1,3,5-Dioxazine

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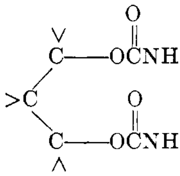
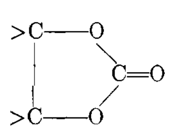
In a recent publication, we described an improved method of synthesis of carbamates of alcohols, thiols, phenols, and oximes using a procedure that involves simply stirring a mixture of the alcohol, thiol or oxime, sodium cyanate, trifluoroacetic acid, and a solvent for a brief period.[1] When this reaction was applied to 1,3-glycols, the biscarbamate (I) was formed; when applied to 1,2-glycols, the cyclic carbonate (II) was the major product.

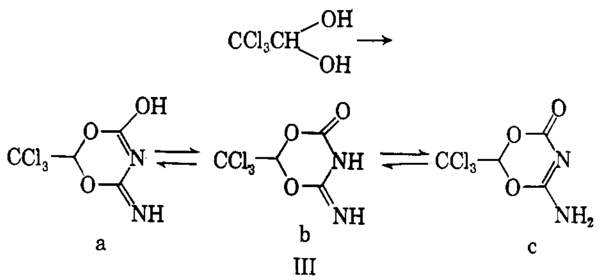


I



II

We now wish to report a novel product prepared by the reaction of a 1,1-glycol, chloral hydrate, under the same reaction conditions. This product, assigned the tautomeric substituted 1,3,5-dioxazine structures (III)



III

is a high-melting, water-insoluble, tasteless crystalline solid—in sharp contrast to the starting material, chloral hydrate, a low-melting, hygroscopic, bitter, amorphous solid. The compound is insoluble in aqueous acid, soluble in and decomposed by aqueous base, and insoluble in most of the ordinary organic solvents other than alcohols. It could not be catalytically reduced with platinum or palladium catalysts at 50 p.s.i.g.

The near-infrared absorption spectra[2] support the assigned structure and suggest that it is mainly in the form IIIb. The n.m.r.[2] shows only a single tertiary C–H; the compound does not absorb in the ultraviolet region (220 to 230 mμ).

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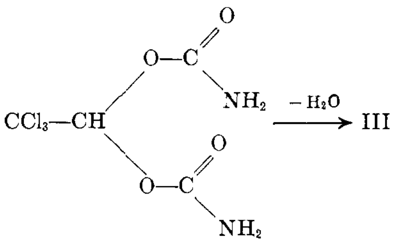
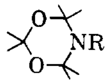
[1] B. Loev and M. F. Kormendy, *J. Org. Chem.*, **28**, 3421 (1963).

[2] We are indebted to Dr. W. Thompson and R. Warren for running these spectra for us. N.m.r. spectra were measured at 60 Mc. on a Varian Associates Model A-60 spectrophotometer, in perdeuteriomethanol solution. Chemical shifts are given with reference to tetramethylsilane. The near-infrared spectra were determined as a mineral oil mull on a Perkin-Elmer Model 137-G.

A possible mechanism for the reaction could be through dehydration of an intermediate biscarbamate.



The only other examples of 1,3,5-dioxazines that have been described previously are the dihydro derivatives (IV, R = H, CH_2COOH, CH_2COOEt, CH_2CONH_2, Cl, NO_2, NH_2).[3]



IV

Experimental

2-Trichloromethyl-4-keto-6-amino-4*H*-1,2,5-dioxazine.—To a solution of 16.6 g. (0.1 mole) of chloral hydrate in 250 ml. of tetrahydrofuran was added 26.0 g. (0.4 mole) of sodium cyanate. The mixture was chilled and 29.7 ml. (0.4 mole) of trifluoroacetic acid was added. The mixture was stirred for 2 hr. at room temperature and filtered to remove the sodium trifluoroacetate (more tetrahydrofuran may be added). The filtrate was evaporated at 25°, *in vacuo*, leaving an oil (35 g.). The infrared spectra of the oil showed no absorption at 4.4 μ (isocyanate). The oil solidified on standing, better on stirring with a little water; the solid was collected and dried in a desiccator. It was recrystallized twice from acetone–water or from tetrahydrofuran and petroleum ether (b.p. 60–70°), m.p. 240° dec.

Anal. Calcd. for $C_4H_3Cl_3N_2O_3$: C, 20.58; H, 1.30; Cl, 45.56; N, 12.00. Found: C, 20.88; H, 1.31; Cl, 45.58; N, 11.93.

The n.m.r. showed a single peak (—$\overset{|}{\underset{|}{\mathrm{C}}}$—H) at 348 c.p.s. (5.81 p.p.m.). The near-infrared showed an absorption (—$\overset{|}{\underset{|}{\mathrm{C}}}$—H) at 2.82 and a triplet at 5.55–5.78 μ from a tautomeric carbonyl. Attempts to determine the molecular weight by nonaqueous titration or cryoscopically gave inconsistent values ranging from 239 to 248 (theoretical, 233.45). The pK_a determined in 50% aqueous ethanol was 8.15.

When chloral was treated with sodium cyanate and trifluoroacetic acid under the same conditions described previously, *no reaction occurred*, and chloral was recovered.

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(3) (a) T. Curtius and R. Jay, *Ber.*, **23**, 740 (1890); M. Bergmann, M. Jacobsohn, and H. Schotte, *Z. Physiol. Chem.*, **131**, 20 (1923). (b) NOTE ADDED IN PROOF.—After this work had been submitted, we learned of an article by F. W. Hoover, H. B. Stevenson, and H. S. Rothrock, *J. Org. Chem.*, **28**, 1825 (1963), in which is described the reaction of chloral with free isocyanic acid to give $CCl_3CH(OH)NCO$.

A New Conversion of Isonitriles to Isocyanates

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An apparently new oxidation of isonitriles with dimethyl sulfoxide in the presence of small amounts of halogen has been encountered in these laboratories. Previously isonitriles have been converted to isocyanates by the action of mercuric oxide,[2] ozone,[3] and similar reagents. The reaction of isonitrile dihalides with water to yield an amine, presumably *via* the isocyanate, was reported.[4]

In the studies of the effect of solvent on the reaction of silver cyanide with alkyl halides, isopropyl iodide and silver cyanide were heated in dimethyl sulfoxide for 24 hr. Examination of the infrared spectrum indicated the presence of an isocyanate (maximum, 2220 cm.$^{-1}$).[5] Further study of the reaction showed that isopropyl isonitrile (prepared by the dehydration of isopropylformamide with *p*-toluenesulfonyl chloride in quinoline[6]) was stable to dimethyl sulfoxide at the same temperatures and times, thus indicating that a direct oxidation of the isonitrile was not involved. Addition of 5 mole % of bromine to an equimolar mixture of isopropyl isonitrile and dimethyl sulfoxide in chloroform solvent at refluxing temperatures led to smooth formation of isopropyl isocyanate and dimethyl sulfide, both identified by comparison with authentic samples. The yield of isocyanate was approximately equal (±10%) to that of dimethyl sulfide. The chloroform and dimethyl sulfoxide used in this study were dried with calcium hydride to obviate the possible hydrolysis of isonitrile dihalide.[4] A preliminary infrared study of the reaction showed that the isonitrile maximum (2120 cm.$^{-1}$) decreased steadily with time. No peak at 1690 cm.$^{-1}$ (isonitrile dihalide) was observed, and the spectrum could be described by the superposition of the maxima of the isonitrile, isocyanate, dimethyl sulfoxide, and the chloroform. Addition of dimethyl sulfoxide to preformed isonitrile dibromide in chloroform (infrared maximum, 1690 cm.$^{-1}$) gave isocyanate in a rapid exothermic reaction at room temperature. Dimethyl sulfide was again identified as the other product.

On the basis of the information presently available, the most probable course of the reaction appears to be that shown in eq. 1 and 2. A chain reaction (presumably ionic) is implied by the necessity for the halogen coupled with the fact that only 5 mole % is required for the conversion. Equation 1 indicates a well known reaction of isonitriles.[4]

$$\mathrm{R{-}NC} + X_2 \longrightarrow \mathrm{R{-}N{=}CX_2} \qquad (1)$$

$$\mathrm{R{-}N{=}CX_2} + (CH_3)_2SO \longrightarrow \mathrm{RNCO} + (CH_3)_2S + X_2 \qquad (2)$$

What is written as eq. 2 is probably a multistep process, and the halogen may never be formed *per se*, but may be transferred from some intermediate adduct of dimethyl sulfoxide and isonitrile dihalide directly to another mole of isonitrile (eq. 3). Further study of the reaction is required to settle these points. It is, however, apparent that process 1 is not greatly faster than process 2, otherwise the build-up of the 1690 cm.$^{-1}$ isonitrile dihalide maximum would have been observed.

$$\mathrm{R{-}N{=}CX_2}\cdot(CH_3)_2SO + \mathrm{RNC} \longrightarrow \mathrm{RNCO} + (CH_3)_2S + \mathrm{RNCX_2} \qquad (3)$$

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(1) National Science Foundation Undergraduate Research Participant.

(2) A. Gautier, *Ann. chim.* (Paris) [4] **17**, 229 (1869).

(3) H. Feuer, H. Rubinstein, and A. T. Nielsen, *J. Org. Chem.*, **23**, 1107 (1958).

(4) H. Guillemard, *Ann. chim.* (Paris), [8] **14**, 311 (1908); *Bull. Soc. Chem.*, (1904); J. J. Nef, *Ann.*, **270**, 257 (1892).

(5) H. Hoyer, *Ber.*, **89**, 2677 (1956).

(6) J. Casanova, Jr., R. E. Schuster, and N. D. Werner, *J. Chem. Soc.*, 4280 (1963). We thank Professor Casanova for a preprint of this paper.