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N-Aryl- and N-*t*-Butylisoxazolium Salts

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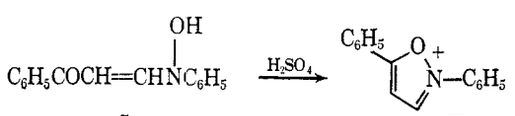
As part of an investigation[2] of the isoxazolium salt method of peptide synthesis,[3,4] we have found methods for preparing two new types of isoxazolium salts, those bearing aryl and *t*-butyl groups on the quaternary nitrogen atom.

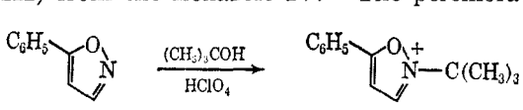
The route to N-arylisoxazolium salts, illustrated by the conversion of 3-(N-hydroxyanilino)acrylophenone (I)[5,6] to the N,5-diphenylisoxazolium cation (II), resembles the synthesis of 5-isoxazolones from β-keto esters and phenyl- or methylhydroxylamine,[7,8] in that the substituent is attached to nitrogen prior to ring formation. Cyclization of I is effected simply by dissolving the compound in concentrated sulfuric acid. The ultraviolet maximum of the solution is at



I II

328 mμ, in the range anticipated for II. On dilution of the reaction mixture with ice, the bisulfate salt of II precipitates in good yield. Alternatively, the less soluble perchlorate salt can be obtained by further dilution with enough water to redissolve the bisulfate of II and addition of sodium perchlorate solution.

N-*t*-Butylisoxazolium salts can be obtained by the usual tactic of alkylating the isoxazole ring. The *t*-butylation of isoxazoles is readily achieved with *t*-butyl alcohol and perchloric acid, as shown by the preparation of the N-*t*-butyl-5-phenylisoxazolium cation (III) from the isoxazole IV. The perchlorate of



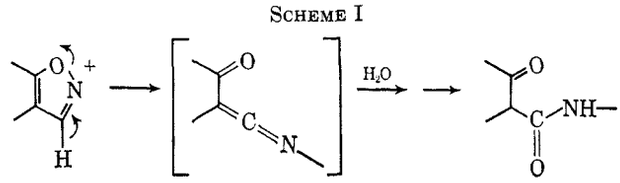
IV III

III precipitates in 90% yield from a mixture of IV and *t*-butyl alcohol with excess 70% perchloric acid.

Both preparative procedures should have broad applicability, in the former case because compounds of the type I are obtainable by condensation of various hydroxymethylene ketones with N-arylhydroxylamines (from reduction of the readily available aromatic nitro compounds). The generality of these reactions and use of the product isoxazolium salts in peptide synthesis are under investigation.

The N-*t*-butylisoxazolium cation III and related cations have been proposed by Eugster, Leichner, and Jenny as intermediates in the reaction of 3-unsubstituted isoxazoles with various carbonium ion precursors in concentrated sulfuric acid.[9] However, these authors isolated, rather than the isoxazolium salts, products that would be expected from the established[3] ring-opening mechanism for 3-unsubstituted isoxazolium salts, followed by hydration (Scheme I). These authors considered the established mecha-

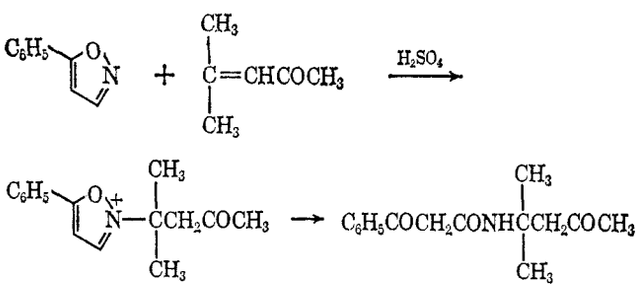
SCHEME I



nism, since it involves hydrogen abstraction by some base, unlikely in their acidic reaction media. Instead, they proposed an alternative ring-opening mechanism for 3-unsubstituted isoxazolium salts in concentrated sulfuric acid.

It seemed more likely to us that destruction of the isoxazolium salts occurred in the work-up method used by Eugster, Leichner, and Jenny, because the reported procedures include neutralization of the reaction mixtures, an operation fraught with peril for base-sensitive isoxazolium salts. To test this possibility we have repeated one such experiment, omitting the neutralization step.

Cautious neutralization with bicarbonate of a sulfuric acid solution of 5-phenylisoxazole and mesityl oxide, extraction with dichloromethane, and removal of the organic solvent was reported[9] to give an oil in 60% yield (based on IV), which afforded the keto amide VI on purification. However, when we merely diluted a similar reaction mixture with water, washed the solution with dichloromethane to remove any neutral organic impurities, and added sodium perchlorate solution, we obtained the perchlorate salt of the isoxazolium cation V. Isolation of the isoxazolium salt confirms the proposed alkylation of isoxazoles under these conditions and shows that the destruction of the isoxazolium cations took place



V VI

(1) Harvard Prize Fellow, 1960–1961; National Science Foundation Summer Assistant Fellow, 1961; National Institutes of Health Predoctoral Fellow, 1961–1964. This work was also supported by a grant from the National Institutes of Health.

(2) D. J. Woodman, Ph. D. Thesis, Harvard University, 1965.

(3) R. B. Woodward and R. A. Olofson, *J. Am. Chem. Soc.*, **83**, 1007 (1961).

(4) R. B. Woodward, R. A. Olofson, and H. Mayer, *ibid.*, **83**, 1010 (1961).

(5) L. Allesandri, *Atti Reale Accad. Lincei, Rend.*, **19**, 122 (1910).

(6) J. Thesing, A. Müller, and G. Michel, *Chem. Ber.*, **88**, 1027 (1955).

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

(8) A. J. Boulton and A. R. Katritzky, *Tetrahedron*, **12**, 41 (1961).

(9) C. H. Eugster, L. Leichner, and E. Jenny, *Helv. Chim. Acta*, **46**, 543 (1963).

during neutralization by the usual mechanism, rather than by a new ring-opening reaction in concentrated sulfuric acid.

Experimental Section

Melting points were taken on a Kofler hot-stage microscope, calibrated with melting point standards from Arthur H. Thomas Co. Ultraviolet spectra were run on a Cary 14 spectrophotometer and nmr spectra on a Varian A-60 spectrometer. The nmr data refers to deuteriochloroform solution, and chemical shifts are in τ values relative to tetramethylsilane as an internal standard (τ 10.00). Elemental analyses were performed by Scandinavian Microanalytical Laboratories and Dr. C. Daesslé of Montreal.

N,5-Diphenylisoxazolium (II) Bisulfate.—Concentrated sulfuric acid (12 ml) was stirred in an ice bath while 2.4 g (10 mmoles) of I was added. When the solid had all dissolved, the reaction mixture was poured over 50 g of ice. The precipitate was filtered with suction, washed three times with acetone, and air dried in the funnel, giving 3.0 g (94%) of yellow solid: mp 114–117°. The crude product was dissolved in 45 ml of absolute ethanol and precipitated with 180 ml of ether. The precipitated yellow needles of the bisulfate weighed 1.7 g (50%): mp 115–117°. The light-sensitive compound was stored in the dark.

Anal. Calcd for $C_{15}H_{13}NO_5S$: C, 56.41; H, 4.10; N, 4.39; S, 10.04. Found: C, 56.36; H, 4.29; N, 4.39; S, 10.00.

The ultraviolet spectrum of the bisulfate salt contained $\lambda_{max}^{0.1\ N\ HCl}$ 220 mμ (ϵ 7400) and 320 mμ (ϵ 22,500).

N,5-Diphenylisoxazolium (II) Perchlorate.—Concentrated sulfuric acid (60 ml) was stirred in an ice bath while 12 g (0.05 mole) of I was added. When the solid had all dissolved, the reaction mixture was poured over 250 g of ice. Addition of 1 l. of water and stirring redissolved the bisulfate of II, and the solution was filtered. Next, a solution of 14.0 g of sodium perchlorate monohydrate (0.10 mole) in 20 ml of water was added with stirring. The cream precipitate was filtered, washed three times with water, and air dried in the funnel, giving 15 g of crude product, decomposing to dark tar at 159–160°. Precipitation from 150 ml of acetonitrile with 450 ml of ether gave 14 g (88%) of pale yellow crystals: dec pt 159–160°. The perchlorate salt did not detonate when tiny samples were heated to 250°, pounded, or ground. When heated in an open flame, the compound burns with a flash, but the small samples used did not explode. The light-sensitive compound was stored in the dark.

Anal. Calcd for $C_{15}H_{12}ClNO_6$: C, 56.00; H, 3.76; Cl, 11.02; N, 4.35. Found: C, 56.03; H, 3.97; Cl, 10.71; N, 4.54.

The ultraviolet spectrum of the perchlorate salt contained $\lambda_{max}^{0.1\ N\ HCl}$ 222 mμ (ϵ 7400) and 320 mμ (ϵ 23,000).

N-*t*-Butyl-5-phenylisoxazolium (III) Perchlorate.—A mixture of 14.5 g (0.10 mole) of 5-phenylisoxazole (IV) and 7.4 g (0.10 mole) of *t*-butyl alcohol was stirred in an ice bath, and 42.3 g (0.30 mole) of 71% perchloric acid was added dropwise. A white precipitate formed during the addition. When all the acid had been added, the precipitate gradually thickened as stirring was continued. After 12 hr at room temperature, the mixture had solidified. About 100 ml of water was added, the suspension was stirred until homogeneous, and the solid was filtered. Washing with water, air drying, and washing with dichloromethane left 27 g (90%) of the crude perchlorate salt, decomposing at *ca.* 170° (turns yellow). Precipitation from 300 ml of acetonitrile with 600 ml of ether gave 24 g (80%) of colorless rods, decomposing to yellow oil at 170–175° on rapid heating. When heated above the melting point, the substance darkened to a black tar and bubbled, but did not detonate up to 250°. The light-sensitive compound was stored in the dark.

Anal. Calcd for $C_{13}H_{16}ClNO_5$: C, 51.75; H, 5.35; Cl, 11.75; N, 4.64. Found: C, 51.90; H, 5.49; Cl, 11.90; N, 4.52.

The ultraviolet spectrum of the perchlorate salt contained $\lambda_{max}^{CH_2Cl_2}$ 296 mμ (ϵ 21,800).

N-(2-Methyl-4-oxopent-2-yl)-5-phenylisoxazolium (V) Perchlorate.—A mixture of 7 g of 5-phenylisoxazole and 5 g of mesityl oxide was added dropwise very slowly to 20 ml of concentrated sulfuric acid, which was stirred in an ice–salt bath. The viscous orange solution was allowed to stand 2 days in a refrigerator, diluted with ice and water to 250 ml, washed with three 25-ml portions of dichloromethane, and filtered. Addition of a solution of 14 g of sodium perchlorate monohydrate to the aqueous phase precipitated a yellow oil. The oil was taken up in dichloromethane, and the aqueous solution was washed with more of the organic solvent. The organic extracts were washed with dilute hydrochloric acid, dried over sodium sulfate, and filtered. Removal of the solvent under reduced pressure left 14 g (80%) of a yellow–brown, viscous oil, which partly crystallized in the deep freeze. The crude material was mixed with 50 ml of ether, and acetone (*ca.* 50 ml) was added at the boiling point, until all but a few seed crystals had dissolved. Chilling in the deep freeze overnight gave 7 g of large, colorless crystals. A second crop, 3 g, was collected by saturating the mother liquor at the boiling point with more ether. The two crops were ground together: mp 81–83°. For further purification the product was dissolved in acetone (5 ml/g) and precipitated in an ice–salt bath by slowly adding ether (10 ml/g, crystallization induced by scratching at the cloud point): mp 82–83°.

Anal. Calcd for $C_{15}H_{18}ClNO_6$: C, 52.40; H, 5.28; Cl, 10.31; N, 4.08. Found: C, 52.33; H, 5.26; Cl, 10.37; N, 3.98.

The ultraviolet spectrum of the perchlorate salt contained $\lambda_{max}^{CH_2Cl_2}$ 298 mμ (ϵ 22,400).

The nmr spectrum contained signals at τ 8.10 (singlet, 6.1 H), τ 7.85 (singlet, 3.1 H), τ 6.53 (singlet, 1.9 H), τ 2.73 (doublet, J = 3 cps, 1.1 H), τ 2.66–2.00 (complex, 4.9 H), and τ 0.76 (doublet, J = 3 cps, 0.9 H).

Hydroxyl Coupling Constants in Conformational Analysis

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The conformational preference of the hydroxyl group in cyclohexanol and related compounds has been determined in many ways, including nmr spectroscopy. The nmr spectral parameters which have been used to diagnose conformational equilibria include the chemical shift of the α protons[2-4] (O–C–H), the chemical shift of the hydroxyl protons,[5] and vicinal, ring proton–proton coupling constants.[6] We would like to suggest that an additional parameter, the vicinal coupling constant between the hydroxyl proton and the α proton, J_{CHOH}, may be used as a conformational probe.[7]

The hydroxyl group in cyclohexanol can readily equilibrate among its possible rotomeric conformations within the lifetime of either of the two chair cyclohexanol conformations.[8] An equatorial hydroxyl group probably partitions itself among the three rotomeric conformations which may be identified by their average dihedral angle (θ) between the O–H/C–H bonds of 60, 180, and 300°. An axial hydroxyl group probably has only two important rotomeric conformations,

(1) National Science Foundation Undergraduate Research Participant.

(2) E. L. Eliel and M. H. Gianni, *Tetrahedron Letters*, 97 (1962).

(3) A. H. Lewin and S. Winstein, *J. Am. Chem. Soc.*, **84**, 2464 (1962).

(4) J. Reisse, J. C. Celotti, D. Zimmerman, and G. Chiurdoglu, *Tetrahedron Letters*, 2145 (1964).

(5) R. J. Ouellette, *J. Am. Chem. Soc.*, **86**, 4378 (1964).

(6) F. A. L. Anet, *ibid.*, **84**, 1053 (1962).

(7) This coupling can be observed in dimethyl sulfoxide because of a relatively slow hydroxyl proton exchange rate.[14]

(8) The activation energy for interconversion between chair conformations is about 10 kcal/mole, while the rotational energy barrier in methanol is about 1.1 kcal/mole; *cf.* E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience Publishers, New York, N. Y., 1965, pp 41, 140.