petroleum ether and chromatographed on alumina (Spence Type H). The first fraction eluted by petroleum ether gave an unidentified oil (47 mg.) which rapidly darkened in color on standing at room temperature. A second fraction (100 mg.) eluted by the same solvent (50 ml.) was unchanged cholestanone (m.p. 129°, identical infrared spectrum). The third fraction, eluted with the same solvent (35 ml.), was an oil which crystallized on standing. One recrystallization from ether–methanol gave **cholest-1-en-3-one (10)** as small needles (98 mg.): m.p. 97–98°, $[\alpha]_D$ +53° (*c* 1.3), λ^{EtOH} 232 mμ (ε 10,500); lit.[21] m.p. 98–100°, $[\alpha]_D$ +57.5°, λ 231 mμ (log ε 3.99).

The last fraction eluted by petroleum ether (35 ml.) gave an oil, which crystallized from ether–methanol to give **4-bromocholest-4-en-3-one (11)** as needles (84 mg.): m.p. 112–114°, $[\alpha]_D$ +104° (*c* 1.1), λ^{EtOH} 261 mμ (ε 10,500); lit.[22] m.p. 114–115°, $[\alpha]_D$ +107°.

Action of Triphenylphosphine Dibromide on Methyl Cholate (12, R = H).—Methyl cholate (250 mg.) was added to a solution of triphenylphosphine dibromide (253 mg.) in dimethylformamide (10 ml.) and the mixture was heated with stirring at 90° for 2 hr. under a nitrogen atmosphere. The crude product, isolated in the usual way, gave a positive Beilstein test and thin layer chromatography indicated the presence of one major product in addition to triphenylphosphine oxide and a small amount of starting material. The product was dissolved in benzene and chromatographed on silica gel. The benzene eluate (60 ml.) on evaporation gave a colorless oil, which yielded an amorphous solid (300 mg.) on attempted crystallization from ether–petroleum ether. This solid was dissolved in pyridine (10 ml.), acetic anhydride (1 ml.) was added, and the mixture was left overnight at room temperature, diluted with water, and extracted with ether. The washed and dried extract was evaporated and the residue was crystallized from aqueous methanol to give **methyl 3β-bromo-7α,12α-diacetoxycholanate (13, R = Ac)** as long needles (290 mg.), m.p. 176–177°, $[\alpha]_D$ +45° (*c* 0.9).

Anal. Calcd. for $C_{29}H_{45}BrO_6$: C, 61.15; H, 7.96; Br, 14.03. Found: C, 61.01; H, 8.13; Br, 13.97.

Methyl 7α,12α-Dihydroxycholanate (14, R = CH_3).—Amorphous methyl 3β-bromo-7α,12α-dihydroxycholanate (40 mg.) was dissolved in 95% ethanol (25 ml.) and Raney nickel (*ca.* 2 ml. of suspension) was added. The mixture was stirred vigorously for 24 hr. in a hydrogen atmosphere, filtered, and evaporated. Crystallization of the residue from aqueous methanol gave methyl 7α,12α-dihydroxycholanate as very small needles (30 mg.), m.p. 148–150°, $[\alpha]_D$ +22° (lit.[23] m.p. 151°).

7α,12α-Dihydroxycholanic Acid (14, R = H).—The methyl ester (15 mg.) was dissolved in 5% methanolic potassium hydroxide solution (5 ml.), left at room temperature overnight, acidified with 10% aqueous hydrochloric acid, diluted with water, and extracted with ether. Evaporation of the washed and dried extract gave an oil (10 mg.) which on crystallization from aqueous methanol gave 7α,12α-dihydroxycholanic acid as prisms, m.p. 206–208°, $[\alpha]_D$ +28° (lit.[23] m.p. 206–208°, $[\alpha]_D$ +27°).

Methyl 3α-Acetoxy-12α-hydroxychol-7-enate (16a).—Methyl 3α-acetoxy-7α,12α-dihydroxycholanate (15, 250 mg.) was added to a solution of triphenylphosphine dibromide (2.5 g.) in dimethylformamide (10 ml.) and the mixture was heated with stirring at 90° for 20 hr. It was worked up in the usual way, and a solution of the neutral product in benzene was chromatographed on silica gel. Crystallization of the benzene-eluted fraction from aqueous methanol gave methyl 3α-acetoxy-12α-hydroxychol-7-enate as needles (163 mg.), m.p. 172–173°, $[\alpha]_D$ +104° (*c* 1.1) (lit.[16] m.p. 172–174°, $[\alpha]_D$ +101°).

Hydrolysis of the ester with 5% ethanolic potassium hydroxide solution gave 3α,12α-dihydroxychol-7-enic acid (16b) as prisms, m.p. 208–210°, $[\alpha]_D$ +86° (*c* 1.3) (lit.[16] m.p. 210–212°, $[\alpha]_D$ +93°, dioxane).

Esterification of the acid with diazomethane gave methyl 3α,12α-dihydroxychol-7-enate (16c) as small needles, m.p. 64–66°, $[\alpha]_D$ +82° (*c* 1.2) (lit.[16] m.p. 64–67°, $[\alpha]_D$ +78°).

Methyl 3α,7α-Diacetoxychol-11-enate (18a).—Methyl 3α,7α-diacetoxy-12α-hydroxycholanate (260 mg.) was added to a solution of triphenylphosphine dibromide (5.5 g.) in dimethylformamide (15 ml.); the mixture was heated at 90° for 50 hr. with constant stirring, then worked up in the usual way. Purification of the product by silica gel chromatography and elution with benzene gave methyl 3α,7α-diacetoxy-chol-11-enate as needles (130 mg.), m.p. 138–139°, $[\alpha]_D$ +4° (*c* 1.3), after crystallization from aqueous methanol (lit.[17] m.p. 139–141°, $[\alpha]_D$ +9°).

Hydrolysis of the ester with 5% ethanolic potassium hydroxide solution gave 3α,7α-dihydroxychol-11-enic acid (18b) as small flat needles, m.p. 203–205°, $[\alpha]_D$ +5° (*c* 0.9) (lit.[17] m.p. 204–206°, $[\alpha]_D$ +9°, dioxane).

(21) C. Djerassi and C. R. Scholz, *J. Am. Chem. Soc.*, **69**, 2404 (1947).

(22) J. I. Shaw and R. Stevenson, *J. Chem. Soc.*, 3549 (1955).

(23) S. Kuwada and S. Morimoto, *Bull. Chem. Soc. Japan*, **17**, 147 (1942).

Proton Magnetic Resonance Spectra of Certain Methyltetrazoles

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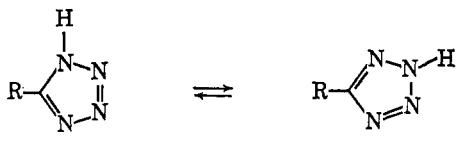
Proton n.m.r. spectra were used to study the tautomeric equilibrium of a 5-substituted tetrazole. The chemical shifts of the C-methyl resonances of the isomeric dimethyltetrazoles were insufficiently different to assign the composition of 5-methyltetrazole. From temperature and concentration dependence studies of the N–H resonance, it was concluded that in SO_2 solution 5-methyltetrazole exists in a dimeric, hydrogen-bonded species. A convenient synthesis of 5-methyltetrazole, its conversion to 2,5-dimethyltetrazole, and the characterization of the latter compound are also reported.

That a tautomeric equilibrium can exist for tetrazoles is well recognized. It has been difficult, however, to determine the relative amounts of tautomers or even to demonstrate their interconvertibility prior to nuclear magnetic resonance spectroscopy. The classical approach to such a problem, deriving the assignment of tautomeric structure from product composition, is inadequate.[2]



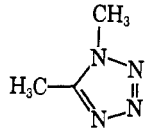
Ia Ib

(1) (a) Based in part on the Honors Thesis of W. T. B. (1962).

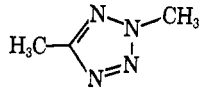
(2) For a discussion of the pitfalls inherent in such procedures, see A. R. Katritzky and J. M. Lagowski, "Advances in Heterocyclic Chemistry," Vol. 1, A. R. Katritzky, Ed., Academic Press Inc., New York, N. Y., 1963, pp. 321–324.

Our interest in the synthesis and decomposition of 5-aryltetrazoles[3,4] has led us to consider the tautomerism in 5-methyltetrazole (I, R = CH_3). The selection of this compound was based on the recent work of Moore and Whittaker who concluded from chemical shift data that tetrazole existed predominantly as the 1-protonated structure (I, R = H).[5] Similar studies also have been successful with unsymmetrically substituted pyrazoles.[6,7] The present study was therefore undertaken to determine if the tautomeric composition of 5-methyltetrazole could be deduced in an analogous manner from the chemical shift of the C-methyl group.

Although 5-methyltetrazole has been known for some time, the preparations have not been convenient ones.[8] We have found that the procedure of Herbst and Wilson[9] can be applied to acetonitrile; the convenience of this method compensates for the moderate yield of I (R = CH_3). The isomeric dimethyltetrazoles were selected for model compounds, but only 1,5-dimethyltetrazole (II) has been reported. The isomeric 2,5-



II



III

dimethyltetrazole (III) was secured by the methylation of I (R = CH_3) with diazomethane.[10,11] Characterization of the previously unknown III included the dipole moment, for which a value of 2.42 D. was determined. This compares favorably with a calculated value of 1.8 D.[13] These data are analogous to the observed and calculated moments for 2-ethyltetrazole of 2.7 and 1.8 D., respectively.[14]

Proton n.m.r. spectra were obtained for the isomeric dimethyltetrazoles in deuteriochloroform solution (tetramethylsilane internal standard) at 60 Mc. For both compounds only two sharp peaks in the ratio of 1:1 are observed: N-CH_3 resonance at δ = 4.05 and 4.30 p.p.m. and C-CH_3 resonance at δ = 2.58 and 2.53 p.p.m. for II and III, respectively. Assignment of tautomeric structures for 5-methyltetrazole is therefore impossible because the chemical shift between the C-5 methyl groups in II and III is only about 3 c.p.s.

(3) R. Huisgen, J. Sauer, M. Seidel, and J. H. Markgraf, *Chem. Ber.*, **93**, 2106 (1960).

(4) J. H. Markgraf, S. H. Brown, M. W. Kaplinsky, and R. G. Peterson, *J. Org. Chem.*, **29**, 2629 (1964).

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(6) J. A. Moore and C. L. Habraken, *ibid.*, **86**, 1456 (1964).

(7) J. K. Williams, *J. Org. Chem.*, **29**, 1377 (1964).

(8) (a) W. Oberhummer, *Monatsh.*, **63**, 285 (1933); (b) J. S. Mihina and R. M. Herbst, *J. Org. Chem.*, **15**, 1082 (1950); (c) E. Wiberg and H. Michaud, *Z. Naturforsch.*, **9**, 496 (1954); (d) W. P. Norris, *J. Org. Chem.*, **27**, 3248 (1962).

(9) R. M. Herbst and K. R. Wilson, *ibid.*, **22**, 1142 (1957).

(10) We thank Dr. R. A. Henry for suggesting the diazomethane method to avoid small amounts of N,N-dialkylureas, which he observed in similar alkylations with methyl iodide or methyl sulfate (unpublished results).

(11) Although the base-catalyzed methylation of 5-phenyltetrazole with methyl iodide or methyl sulfate gives predominantly the 2-methyl derivative,[12] we obtained only 1,5-dimethyltetrazole when this procedure was applied to 5-methyltetrazole.

(12) (a) R. A. Henry, *J. Am. Chem. Soc.*, **73**, 4470 (1951); (b) R. M. Herbst, *J. Org. Chem.*, **26**, 2372 (1961); (c) R. Huisgen, J. Sauer, and M. Seidel, *Chem. Ber.*, **94**, 2503 (1961).

(13) A. J. Owen, private communication.

(14) A. J. Owen, *Tetrahedron*, **14**, 237 (1961).

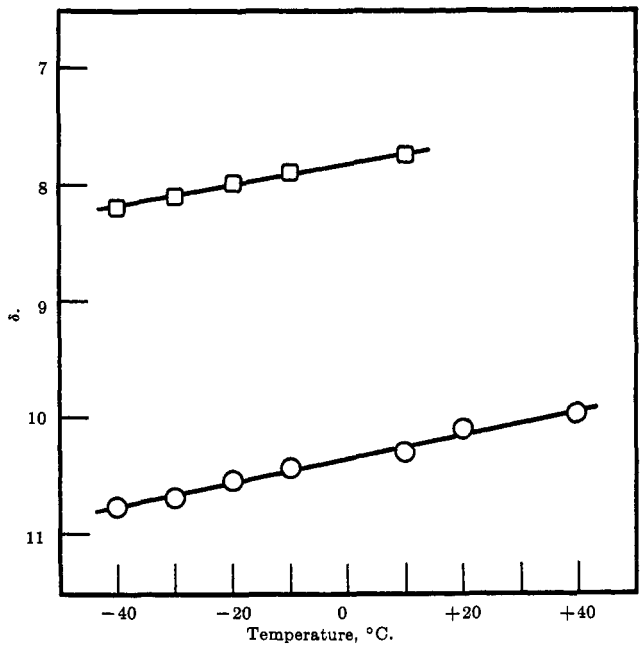


Figure 1.—Variation of the chemical shift with temperature for 5-methyltetrazole in SO_2: □, 0.12 *M*; ○, 0.25 *M*.

In addition to the methylated derivatives, it was of interest to examine the N–H resonance of 5-methyltetrazole. Variation of the chemical shift was measured over a range of temperatures and concentrations in sulfur dioxide solution; the absorption band was a single sharp peak. The results over a temperature range of −40 to +40° on two solutions are summarized in Figure 1; the observed behavior is that expected in both cases. Increasing temperature causes a shift of the N–H resonance toward higher field regardless of whether solute–solute or solvent–solute hydrogen bonding is occurring, since higher temperature shifts the equilibrium toward the nonhydrogen-bonded species which is well known to show resonance at higher field.[15a] A striking feature in the present case is the large upfield shift on dilution from 0.25 to 0.12 *M*. This seems to indicate quite clearly that 5-methyltetrazole self-associates more readily than it associates with SO_2. The dependence of the chemical shift on concentration was examined more extensively at −40°; the results are presented in Figure 2. Over the range of 0.045 to 0.42 *M* the chemical shift changes by 7.4 p.p.m. Such pronounced concentration dependence is compatible with solute–solute hydrogen-bonding effects which are reduced on dilution with concomitant shifts to higher field.[15b] Furthermore the value of δ at high dilution (4.9 p.p.m.) suggests that SO_2 and I (R = CH_3) do not hydrogen bond very strongly. Hence, it is concluded that dimerization (and/or higher association) of 5-methyltetrazole occurs in SO_2 solution.

The most reasonable form of such association is a dimeric, hydrogen-bonded species. Of the several structural variations which are possible for this species, two such forms are represented by IV and V; the former can account for the interconversion of tautomers (Ia and Ib, R = CH_3). Although the C-methyl resonance of a 0.4 *M* solution of 5-methyltetrazole in

(15) (a) J. A. Pople, W. G. Schneider, and H. J. Bernstein, "High-resolution Nuclear Magnetic Resonance," McGraw-Hill Book Co., Inc., New York, N. Y., 1959, pp. 419–421; (b) A. J. R. Bourn, D. G. Gillies, and E. W. Randall, *Tetrahedron*, **20**, 1811 (1964).

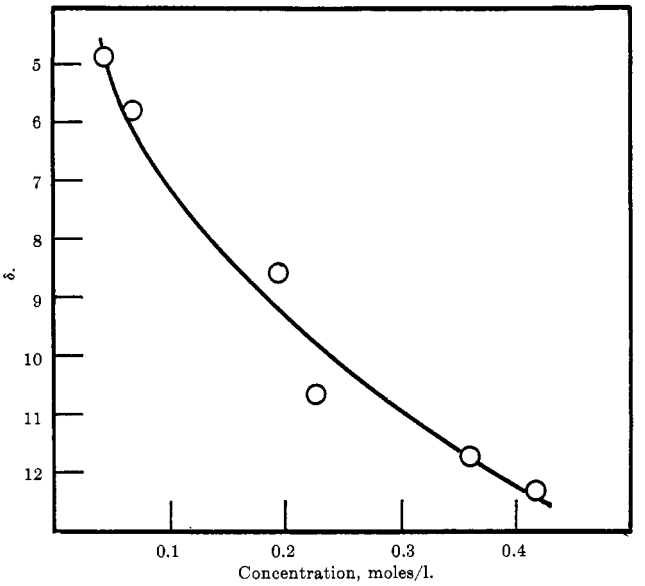
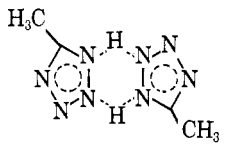
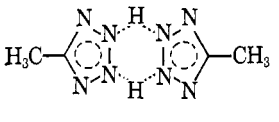


Figure 2.—Variation of the chemical shift with concentration for 5-methyltetrazole in SO_2 at −40°.

SO_2 at −40° was examined under high resolution, only a single sharp peak was observed. The absence of any doubling of the C–CH_3 bond probably indicates only that the rate of interchange between the possible forms is sufficiently fast to average the environment for the methyl group.



IV



V

Experimental Section[16]

5-Methyltetrazole.—Acetonitrile (41.1 g., 1.00 mole) was treated with sodium azide (107 g., 1.64 moles) and glacial acetic acid (124 g., 2.07 moles) in 1-butanol (440 ml.) by the method of Herbst and Wilson[9] to give 26.7 g. (31.8%) of 5-methyltetrazole, m.p. 145.2–145.7° after recrystallization from ethanol–ethyl acetate (lit.[8b] m.p. 148–148.5°).

1,5-Dimethyltetrazole.[17]—To a cold solution of acetoxime (26.0 g., 0.356 mole) in 342 ml. of 1 *N* sodium hydroxide was added dropwise with stirring benzenesulfonyl chloride (63.1 g., 0.357 mole) and then sodium azide (23.1 g., 0.355 mole). The heterogeneous mixture was refluxed for 6 hr. and then evaporated to dryness at reduced pressure. The residual solid was extracted overnight with 1 l. of chloroform in a Soxhlet apparatus, and the chloroform solution was evaporated to dryness at reduced pressure. The crude product was recrystallized twice from benzene–ethyl ether to give 19.7 g. (56.4%) of 1,5-dimethyltetrazole, m.p. 71.8–72.6° after vacuum sublimation (lit.[18] m.p. 73–74°).

2,5-Dimethyltetrazole.—To a magnetically stirred solution of 5-methyltetrazole (2.50 g., 0.0297 mole) in 40 ml. of 95% ethanol–ethyl ether (1:1 v./v.) was added dropwise an ethereal solution of diazomethane prepared from N-methyl-N-nitroso-*p*-toluenesulfonamide (10.75 g., 0.0502 mole; "Diazald" from Aldrich Chemical Co.). The reaction solution, which was maintained at 0° during the addition, was left overnight at room temperature and then concentrated under an air stream; residual traces of solvent were removed at reduced pressure. The residue (1.95 g. of yellow liquid and white solid) was dissolved in 10 ml. of dichloromethane, filtered to remove insoluble starting material (0.022 g.), and chromatographed on alumina (20 g.) with dichloromethane as eluent to give 0.27 g. (9.3%) of 1,5-dimethyltetrazole, m.p. 72.6–74.2°, and 1.39 g. (47.7%) of clear, colorless 2,5-dimethyltetrazole, b.p. 57.0–57.2° (13 mm.), $n^{25}D$ 1.4432.

Anal. Calcd. for $C_3H_6N_4$: C, 36.73; H, 6.16; N, 57.11. Found: C, 36.89; H, 6.36; N, 56.92.

The infrared spectra of both of the isomeric dimethyltetrazoles showed the absence of NH absorption at 7.89 μ and the presence of ring absorption between 9 and 10 μ.[19] The dimethyltetrazoles and 5-methyltetrazole exhibited no absorption in the ultraviolet region between 230 and 340 mμ.[20]

Dipole Moment.—A WTW Dipolmeter Model DM 01 with a DFL-2 cell with a capacity of 4 ml. was used. The cell was provided with a thermostatic jacket to maintain the temperature of the solutions at 30.00 ± 0.05°. Dielectric constants were determined for the pure solvent (benzene) and for a series of six solutions, the weight fraction of solute in which varied from 0.002 to 0.016. The density of the solvent and of each of the solutions was determined using a 8-ml. pycnometer.

The dipole moment was calculated using the Halverstadt–Kumler equation.[21] The electronic polarization was obtained from the values of Vogel, *et al.*[22]

N.m.r. Spectra.—All spectra were obtained on a Varian A-60 spectrometer equipped with standard variable-temperature apparatus. For spectra in SO_2 solution the sample tubes were sealed by a Teflon plug held in place by a special two-piece Teflon collet. The chemical shifts from internal tetramethylsilane are accurate to ±0.02 p.p.m. Temperatures are accurate within ±3°.

Acknowledgment.—The authors are indebted to Professor H. G. Mautner (Yale) for the dipole moment determination and to Dr. A. J. Owen (Ministry of Aviation, England) for correspondence regarding the calculated moment of 2,5-dimethyltetrazole.

(16) Melting points and boiling points are uncorrected. Infrared spectra were obtained as mineral oil mulls or chloroform solutions with a Perkin-Elmer Infracord spectrophotometer, Model 137. Ultraviolet spectra were obtained as methanol solutions with a Cary spectrophotometer, Model 11. Analyses were made by Galbraith Laboratories, Inc., Knoxville, Tenn.; nitrogen analyses were by the Dumas method.

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(22) A. I. Vogel, W. T. Cresswell, G. H. Jeffery, and J. Leicester, *J. Chem. Soc.*, 514 (1952).