Tautomerism of 2-Ethoxy-4-pyrimidinone

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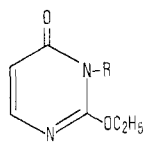
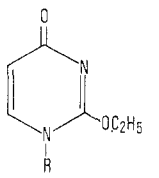
The fine structure of 2-ethoxy-4-pyrimidinone was studied by comparing its ultraviolet spectrum with that of its N-alkyl derivative. In aqueous solution, both *o*- (**1a**) and *p*-quinonoid (**2a**) forms are equally represented. In chloroform the *ortho* form predominates; this conclusion is further supported by the value of the stretching vibration of the NH bond.

The tautomeric equilibria involving *o*- and *p*-quinonoid forms (*e.g.*, **1a** and **2a**, respectively) are generally less one-sided than other tautomeric equilibria in heterocycles. In this work 2-ethoxy-4-pyrimidinone (**1a**–**2a**) was studied, and the results together with data from the literature are used for a modification of Mason's rule[1,2] covering ν_{NH} frequencies in similar compounds. The tautomerism of 2-ethoxy-4-pyrimidinone has been previously studied briefly by Shugar and Fox[3] and by Waring and Katritzky;[4] the compound is clearly in the oxo form[4] and the value of ν_{NH} in chloroform[4,5] indicates the predominance of the form **1a** by application of Mason's rule.

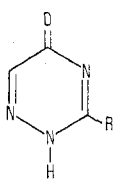
Derivatives with fixed and unequivocal *o*- and *p*-quinonoid structures were required for this study. The unsubstituted **1a**–**2a**, by reaction with diazomethane in ether, gave 2-ethoxy-3-methyl-4-pyrimidinone (**1b**), the structure of which was established by hydrolysis to 3-methyluracil. 2-Ethoxy-4-methoxypyrimidine is another product of the reaction; the structure follows from the methylation by methyl iodide, which gives 1-methyl-4-methoxy-2-pyrimidinone by the Hilbert–Johnson reaction.[6] So-called cyclouridines are compounds of type **2**, but apparently caution is necessary, as strains in these heterocycles change the uv spectrum considerably. Thus O^2:5′ cyclo derivatives of uridine have one band,[7,8] at *ca.* 237 mμ; O^2:2′ derivatives have two bands,[9,10] at *ca.* 250 and 225 mμ. These strains should be lower in O^2-alkyluridine derivatives. These absorb[9] at *ca.* 250 and 230 mμ. In our study we used 2′,3′-O-isopropylidine-O^2-ethyluridine (**2c**). We also tried to prepare simpler derivatives of type **2**, starting directly from the unsubstituted **1a**–**2a**. Alkylations under different conditions did not give the desired derivative, but led to substitution on the oxygen atom followed by nitrogen alkylation to give derivatives of 2-pyrimidinone; other products were of the *o*-quinonoid type **1**. Eventually we found that vinylation of **1a**–**2a** with vinyl acetate, catalyzed by mercuric acetate and sulfuric acid, gives 1-vinyl-2-ethoxy-4-pyrimidinone. The structure of this compound was established by hydrogenation and hydrolysis, which ultimately led to 1-ethyl-5,6-dihydrouracil. Partial hydrogenation of the vinyl compound then gave 1-ethyl-2-ethoxy-4-pyrimidinone (**2b**) with uv maxima at 256 and 225 mμ. Comparison of uv spectra of **1b** and **2b** confirms the observation that *o*-quinonoid compounds adsorb[11] at longer wavelengths than the *para* isomers.



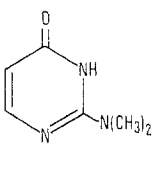
1 a, R=H
b, R=CH_3



2 a, R=H
b, R=C_2H_5
c, R=2′,3′-O-isopropylidene-1-β-D-ribofuranosil



3 a, R=SCH_3
b, R=$N(CH_3)_2$



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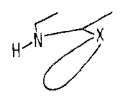

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Uv spectra of **1a**–**2a**, **1b**, and **2c** in chloroform[12] (Figure 1) show clearly that the *o*-quinonoid form **1a** predominates over **2a**. In the ir spectrum (same solvent), **1a**–**2a** has ν_{NH} as a singlet at 3387 cm^{-1}, indicating that only one form is present; variation of temperature (20–55°) failed to bring about the appearance of any new band which could be attributed to **2a**. The situation in neutral aqueous solutions is quite different. Compound **1a**–**2a** displays a large spectral shift from 273 mμ in chloroform to 258 mμ in water solution; comparison of the spectra in Figure 2 shows that both forms **1a** and **2a** are now present. Graphical matching (system **1** and **2**, **a** and **b**) suggests approximately equal proportions of **1a** and **2a**; the tautomeric constant is then *ca.* 1; if the temperature is raised the proportion of **1a** increases. The apparent explanation of this solvent dependence of the tautomeric equilibrium lies in

(1) A. R. Katritzky and L. M. Lagowski, *Advan. Heterocycl. Chem.*, **1**, 339 (1963).
(2) S. F. Mason, *J. Chem. Soc.*, 4874 (1957).
(3) D. Shugar and J. J. Fox, *Biochim. Biophys. Acta*, **9**, 199 (1952).
(4) A. R. Katritzky and A. J. Waring, *J. Chem. Soc.*, 1540 (1962).
(5) The value of ν_{NH} in the present paper is different by 42 cm^{-1} from the published[4] one.
(6) G. E. Hilbert and T. B. Johnson, *J. Amer. Chem. Soc.*, **52**, 2001 (1930).
(7) All spectral data given in this paper correspond to neutral forms.
(8) D. M. Brown, A. R. Todd, and S. Varadarajan, *J. Chem. Soc.*, 868 (1957).
(9) D. M. Brown, A. R. Todd, and S. Varadarajan, *ibid.*, 2388 (1956).
(10) J. J. Fox and I. Wempen, *Tetrahedron Lett.*, 643 (1965).
(11) J. A. Berson, *J. Amer. Chem. Soc.*, **75**, 3521 (1953).
(12) All data on chloroform solutions were measured under dilutions where intermolecular association is negligible, as checked by ir.

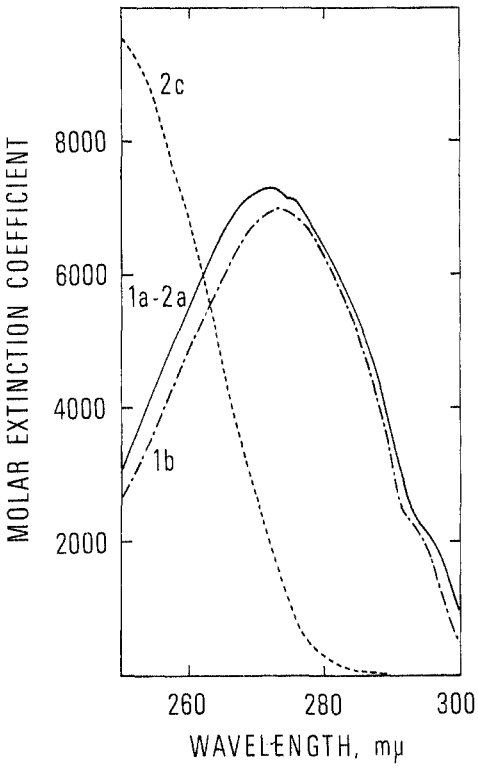

Figure 1.—Ultraviolet spectra in chloroform solution; each curve is labeled by the corresponding formula number.

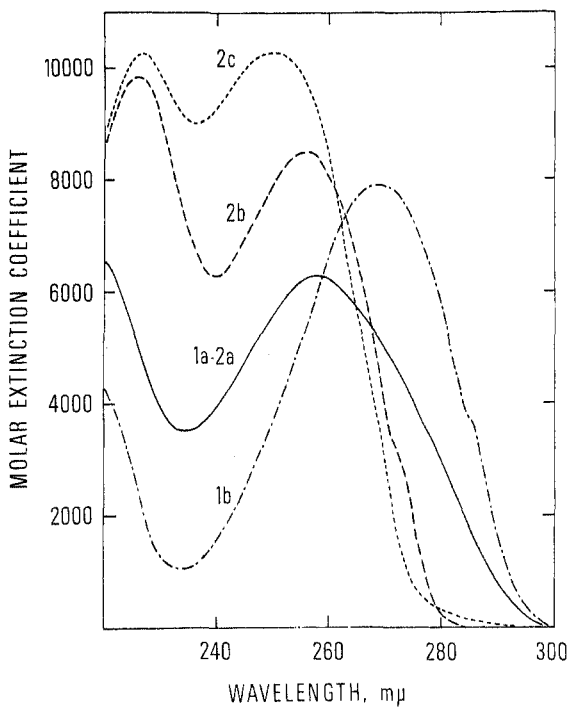

Figure 2.—Ultraviolet spectra of neutral molecules in aqueous buffer; each curve is labeled by formula numbers.

the different solvation energies; the more polar form **2a** is favored in the more polar solvent.

Our observations on the **1a–2a** tautomeric system both in water and nonpolar solvents are comparable with similar results[13–15] with 2-amino-4-pyrimidinone; the situation apparently is not changed by the difference in substitution of position 2. On the other hand, the low energetic difference between the *ortho* and *para* forms enables changes, similar to those induced by solvent, to be effected also by a proper ring substitution. Thus, in **3a** and **3b** the *ortho* form would have the hydrogen atom in the 3 position, which has a lower electron density and therefore a higher acidity in 6-aza analogs of pyrimidines; in both cases the *para* forms are predominant.[16–18]

For the study of *o–p*-quinonoid tautomerisms in nonpolar solutions, a useful rule was formulated by Mason.[1,2] He observed ν_{NH} of *o*-quinonoid forms to be generally lower (3360–3420 cm^{-1}) than ν_{NH} of *p*-quinonoid forms (3415–3445 cm^{-1}). 2-Ethoxy-4-pyrimidinone has ν_{NH} at 3387 cm^{-1}, indicating that only the *ortho* form **1a** is present in chloroform solutions and at 20–50°, the conditions under which the spectra were measured.

It is interesting to note that compounds **1a**, **3b**, and **4** have ν_{NH} values in accordance with the rule (3387, 3445, and 3405 cm^{-1}, respectively[19]), while the value for **3a** is clearly too low[16,17] (3401 cm^{-1}) and forms the only known exception to the rule. This unusual decrease could be explained by the proximity of the colinear lone electron pair to the NH bond, as illustrated in structure **5**; such a geometrical arrangement is known[20] to lower ν_{NH} considerably (10–30 cm^{-1}). In contrast, the closely similar **3b** absorbs as predicted by the rule; the only lone electron pair of the exocyclic nitrogen is conjugated with the ring and so, being in the perpendicular rather than colinear position, does not decrease the frequency of the NH bond.

(13) H. Morita and S. Nagakura, *Theor. Chim. Acta*, **11**, 279 (1968).
(14) C. Heléne and P. Douzou, *Compt. Rend.*, **259**, 4387, 4853 (1964).
(15) D. J. Brown and T. Teitei, *Aust. J. Chem.*, **18**, 559 (1965).
(16) J. Jonas and J. Gut, *Collect. Czech. Chem. Commun.*, **27**, 1886 (1962).
(17) M. Horak and J. Gut, *ibid.*, **28**, 3392(1963).
(18) J. Pitha, P. Fiedler, and J. Gut, *ibid.*, **31**, 1964 (1966).
(19) The spectrum of compound 4 was measured in chloroform solution; variation of temperature (20–50°) failed to cause appearance of a new band corresponding to the other tautomeric form. The value for **3b** was published previously.[18]

Experimental Section

Melting points were determined on a hot stage and are not corrected. Uv spectra were measured with a Cary 14 spectrophotometer. For aqueous solution, phosphate buffers and 10-mm cells were used; chloroform spectra were measured using spectro quality solvent and 2-mm cells. The temperature dependence of uv spectra was recorded on a Gilford Model 2400 recording spectrophotometer. Infrared spectra were measured with a Beckman IR-12 spectrophotometer. For identification purposes the potassium bromide technique was used. Stretching vibrations of NH bonds were studied in chloroform solutions as concentrations of *ca.* 1 mg/ml; 10-mm Infrasil cells with thermostated jackets were used.

2-Ethoxy-4-pyrimidinone.—For spectral study the compound[21] was recrystallized six times from water; the ir spectrum remained constant after the second recrystallization.

Reaction of 2-Ethoxy-4-pyrimidinone with Diazomethane.—2-Ethoxy-4-pyrimidinone (1 g) was dissolved in 50 ml of dry tetrahydrofuran; an excess of diazomethane in ether was then added and the solution was left for 4 days at 5°. The solvent was then evaporated *in vacuo*, the resulting crystals were dissolved in ether, and the solution was extracted with 1 *N* NaOH. The ethereal solution was dried with magnesium sulfate and evaporated; a mixture of crystals and oil resulted. The crystals were purified by three recrystallizations from cyclohexane, followed by sublimation *in vacuo* (0.05 mm). The final yield was 190 mg (15%), mp 59–60°.

Anal. Calcd for $C_7H_{10}N_2O_2$: C, 54.53; H, 6.54; N, 18.17. Found: C, 54.57; H, 6.56; N, 18.11.

(20) J. Pitha and S. Vasickova, *Collect. Czech. Chem. Commun.*, **30**, 1792 (1965).
(21) G. E. Hilbert and E. F. Jansen, *J. Amer. Chem. Soc.*, **57**, 552 (1935).

This substance is 2-ethoxy-3-methyl-4-pyrimidinone, as its hydrolysis (1 *N* hydrochloric acid, 1 hr boiling) gave 3-methyluracil; the identity was established by paper chromatography and ir spectra. The mother liquor from the recrystallizations from cyclohexane were evaporated, dissolved in ligroin, and left at 0° overnight. The crystals which formed were separated, the liquid was evaporated, the residue was distilled *in vacuo* (80° bath temperature, 10 mm); and 120 mg of oily distillate resulted, which remained as a liquid even after long standing at room temperature.

Anal. Calcd for $C_7H_{10}N_2O_2$: N, 18.17. Found: N, 17.88.

This substance is apparently 2-ethoxy-4-methoxypyrimidine, as reaction with excess methyl iodide at room temperature gave 1-methyl-4-methoxy-2-pyrimidinone. The identity of the product was established by the ir spectrum.

Preparation of 1-Vinyl-2-ethoxy-4-pyrimidinone.—A solution of 0.1 ml of concentrated sulfuric acid in 2 ml of ethyl acetate was added to a suspension of 0.5 g of mercuric acetate in 250 ml of vinyl acetate in a pressure flask. A clear solution resulted; 1.5 g of 2-ethoxy-4-pyrimidinone was then added. Nitrogen was bubbled through the solution and kept in a 50° bath for 2 days. Dry sodium acetate was then added, and the solution was stirred for 10 min and filtered. The filtrate was evaporated *in vacuo* and the residue was dissolved in chloroform. The chloroform solution was extracted five times with cold 1 *N* NaOH; the emulsion formed was separated by centrifugation. After drying, the chloroform fraction was evaporated *in vacuo;* yellow crystals and an oil remained. The crystals were first recrystallized from carbon tetrachloride and then from a large volume of cyclohexane, and sublimed *in vacuo* (0.05 mm). White crystals were obtained (200 mg, 10%): mp 97–99°; λ_{max} (0.05 *M* phosphate buffer, pH 7) 266 mμ (ε 12,800) and 240 (side band, 10,400); λ_{min} 222 mμ.

Anal. Calcd for $C_9H_{10}N_2O_2$: C, 57.82; H, 6.07; N, 16.86. Found: C, 57.81; H, 6.05; N, 16.88.

Hydrogenation of 1-Vinyl-2-ethoxy-4-pyrimidinone.—The vinyl compound (150 mg) was dissolved in 15 ml of ethanol and 15 ml of water, 75 mg of catalyst (5% Pd on carbon) was added, and the solution was hydrogenated at room temperature and atmospheric pressure. After 70 min, hydrogen corresponding approximately to one double bond had been consumed. The mixture was then filtered with Celite and the solution was evaporated, yielding crystals, mp 81–93° after recrystallization from a small volume of carbon tetrachloride and vacuum sublimation. Spectral properties indicated that 1-ethyl-2-ethoxy-4-pyrimidinone was the main component, but further purification was difficult. Attempted separation of impurities by extraction with alkali gave low yields, apparently owing to hydrolysis. Gas–liquid partition chromatography separation requires a high temperature (200°, Hewlett–Packard 700 laboratory chromatograph, 10% silicon fluid S-96 column), causing a partial isomerization. Finally, a pure compound was obtained through fractional vacuum sublimation. At 0.1-mm pressure and 65° (bath temperature) the sublimed fractions were monitored by disappearance of the ir band at 1680 cm^{-1}, which represents an impurity subliming before the desired compound. Fractions not having this absorption (60%), mp 94–97°, were recrystallized from tetrahydrofuran and resublimed, mp 99.5–100°; these operations did not change the ir spectrum.

Anal. Calcd for $C_8H_{12}N_2O_2$: N, 16.66. Found: N, 16.50.

Hydrogenation and Hydrolysis of 1-Vinyl-2-ethoxy-4-pyrimidinone.—The vinyl compound was hydrogenated in the same way as in the previous experiment. The residue after evaporation was dissolved in 10 ml of 1 *N* hydrochloric acid and left overnight. The solution was evaporated and the residue was resublimed *in vacuo* (0.05 mm), yielding 70 mg of white crystals, mp 130–140°, apparently a mixture. This product was dissolved in 80 ml of water, 40 mg of catalyst (5% Rh on Al_2O_3) was added, and the solution was hydrogenated in the same way as described earlier. After filtration, the solution was evaporated and the resulting crystals were sublimed *in vacuo*, giving 50 mg of sublimate which, according to the ir spectrum, is identical with 1-ethyl-5,6-dihydrouracil.

Registry No.—**1b**, 20541-38-2; **2b**, 23220-30-6; 2-ethoxy-4-methoxypyrimidine, 23220-28-2; 1-vinyl-2-ethoxy-4-pyrimidinone, 23220-29-3.

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Cycloaddition Reactions of Thiete 1,1-Dioxides. The Preparation of 2-Thiabicyclo[2.2.0]hexane Derivatives[1]

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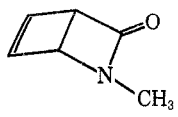
The reaction of thiete 1,1-dioxide and its 2,2-dimethyl derivative with typical enamines, ynamines, and dienamines has been studied. Cycloaddition resulted in the examples reported to give derivatives of the previously unknown 2-thiabicyclo[2.2.0]hexane system and of 7-thiabicyclo[4.2.0]oct-3-ene. Such condensations provide a ready synthetic entry to such molecules. The nmr spectra of the adducts are discussed.

In contrast with the recent surge of interest in bicyclo[2.2.0]hexane chemistry,[3] little attention has been paid to monoheteroatomic analogs of this strained bicyclic ring system. The only successful synthesis of a 2-azabicyclo[2.2.0]hexane derivative (**1**) was reported by Corey and Streith[4] in 1964. 1-Azabicyclo[2.2.0]-hexane (**2**) is recognized at this time only as a transitory intermediate.[5] Several 2-oxabicyclo[2.2.0]hexanes, such as **3**[4] and **4**,[6] are recognized to result from



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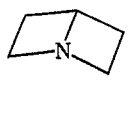

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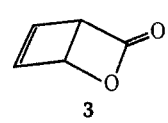

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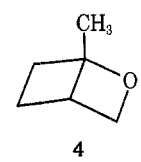

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(1) Unsaturated Heterocyclic Systems. LXVIII. For the previous paper in this series, see L. A. Paquette, T. Kakihana, and J. F. Hansen, *Tetrahedron Lett.*, in press.

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(3) K. B. Wiberg, *Advan. Alicycl. Chem.*, **2**, 185 (1968).

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(5) C. A. Grob and V. Krasnobajew, *Helv. Chim. Acta*, **47**, 2145 (1964); I. N. Nazarov, N. S. Postakov, N. N. Mikhelva, and N. A. Tradkina, *J. Gen. Chem. USSR*, **29**, 2573 (1959); V. Prelog, E. Cerkovnikov, and G. Ustricev, *Justus Jiebigs Ann. Chem.*, **535**, 37 (1938).

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