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Studies of Heteroaromatic Systems by Nuclear Magnetic Resonance Spectroscopy. 4-Pyrimidones and 4-Pyrimidthiones (1)

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Proton magnetic resonance spectral parameters of 4-pyrimidone, 1- and 3-alkyl-4-pyrimidones as well as some of their thione analogs are presented and are compared to those of 4-substituted pyrimidines. It was found that the *ortho*, *meta* and *para* coupling constants in each series were constant for 4-substituted pyrimidines, the 1-alkyl- and the 3-alkyl-4-pyrimidones. A particularly large *meta* ($J_{2,6}$) coupling constant was an outstanding feature found in 1-methyl-, 1-ethyl- and 1-benzyl-4-pyrimidones and also in 1-methyl-4-pyrimidthione but was virtually zero for the corresponding 3-alkyl-4-pyrimidones. These findings are interpreted in terms of the aromatic character of these 4-pyrimidones and thiones. During the synthetic aspects of this work, an interesting carbon-sulfur cleavage was discovered when it was observed that 2-benzylmercapto-4-pyrimidones were readily hydrolyzed by hot concentrated hydrochloric acid to the corresponding 2-thiouracils.

In continuing our proton magnetic resonance studies of potentially tautomeric heteroaromatic systems (2), we turned to examine the spectra of 4-pyrimidones and their thione analogs (I, II, X = O, S), with the aim to relate their n.m.r. parameters to their fine structure and aromatic character. Furthermore, it was of interest to ascertain if n.m.r. spectroscopy could be used to determine if 4-pyrimidone and its thione analog exist as a preferred tautomer in solution (structure I *vs.* II where R = H). It was essential to examine some representative 4-substituted aromatic pyrimidines first, and the models chosen for this study were 4-methoxy- and 4-methylmercaptopyrimidines (III, X = OCH_3, SCH_3), since these had the same heteroatom attached at position 4 as in 4-pyrimidone and the thione analog.

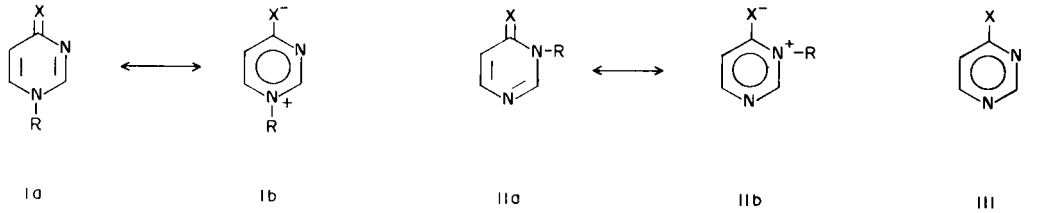
The n.m.r. data of the pyrimidine derivatives under discussion are assembled in Table I. The ring proton patterns of representative examples are shown in Figures I and II. Each of these 4-substituted pyrimidines presented an ABX pattern which could be analyzed by first order rules. The signal furthest downfield arose from H-2, being sandwiched between the two electronegative ring nitrogen atoms, and was always broad due to the electric quadrupole moment of the nitrogens. Its *meta* and *para* coupling constants were determined from the analysis of the absorption patterns of H-5 and H-6. The resonance just upfield from H-2 was attributed to H-6, being adjacent to a ring nitrogen atom, and consisted of a doublet (*ortho* coupling to H-5) which frequently exhibited considerable *meta* coupling. The doublet furthest upfield was associated with H-5 and was split, in most instances, due to a relatively large *para* coupling constant ($J_{2,5}$).

4-Substituted Pyrmidines.

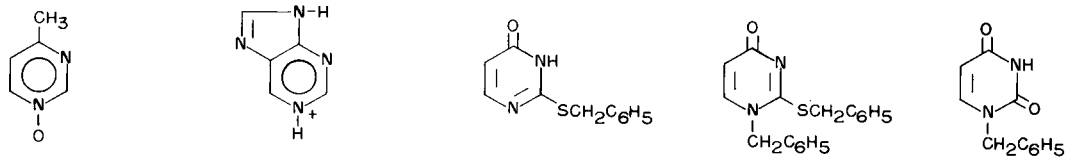
The resonances of the ring protons of 4-methoxy- and 4-methylmercaptopyrimidines (III) appeared according to the pattern described above as did those in previously reported spectra of 4-methyl-, (3,4) 4-amino- (4) and 4-acetamidopyrimidines (4). The major difference in the chemical shifts of 4-methoxy- and 4-methylmercaptopyrimidines was visible in the greater deshielding of H-5 due to the sulfide group at position 4, probably due to the d-orbital expansion of sulfur, thus accommodating a pair of π-electrons from the aromatic sextet of the ring, and, to a lesser degree, to the induced anisotropy of the ring current. In the 4-methoxy-, 4-methylmercapto-, 4-amino- and 4-acetamidopyrimidines *meta* coupling through one of the ring nitrogen atoms ($J_{2,6}$) was readily discernible (about 0.4 c.p.s.) but was not reported for 4-methylpyrimidine (3,4). In the latter it might have been obscured by long range coupling of the methyl protons to H-2 and H-6 which was estimated to be about 0.3 c.p.s. (3). *Meta* coupling through a "pyridine-like" nitrogen atom is seldom seen in pyridines (5) or in pyrimidine itself (3). At the same time, the para coupling constant ($J_{2,5}$) in 4-substituted pyrimidines was somewhat larger (1.1 to 1.4 c.p.s.) than expected when compared to benzene and pyridine derivatives (averaging 0.75 c.p.s.) but was of the same magnitude (1.5 c.p.s.) as that found in pyrimidine itself (3).

1- and 3-Alkyl-4-pyrimidones and Thiones (I and II, X = O,S).

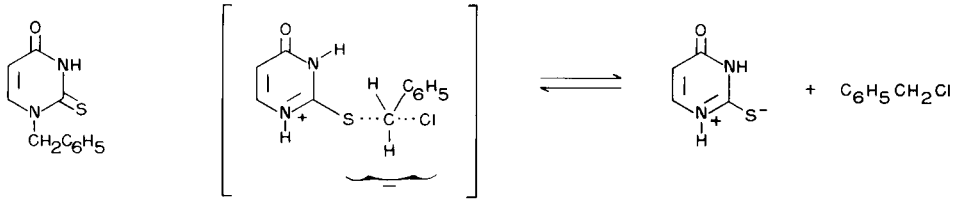
Three members in each series (I and II) were examined where R is methyl, ethyl and benzyl. The



Ia Ib IIa IIb III



IV V VI VII VIII



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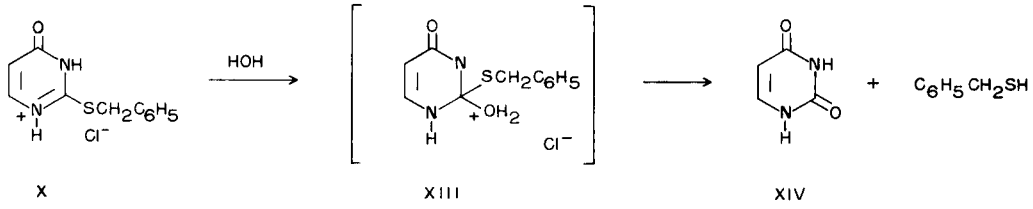
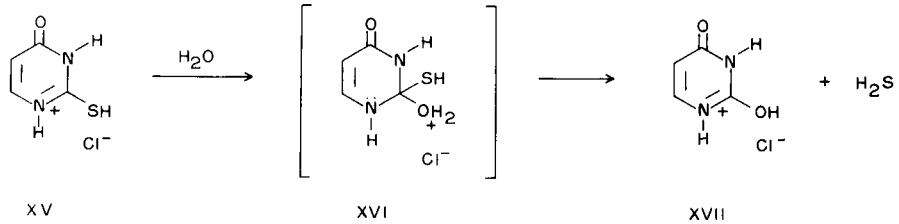


X XIII XIV



XV XVI XVII

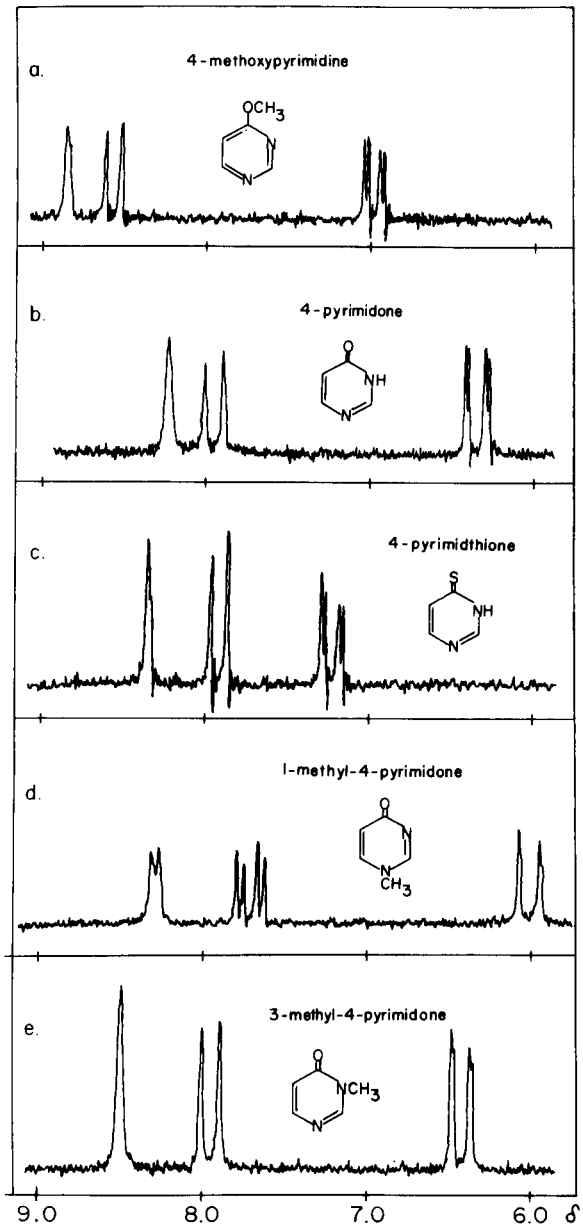


FIGURE I

N.m.r. spectra of some 4-substituted pyrimidines in dimethylsulfoxide between 6 and 9 parts per million (from tetramethylsilane).

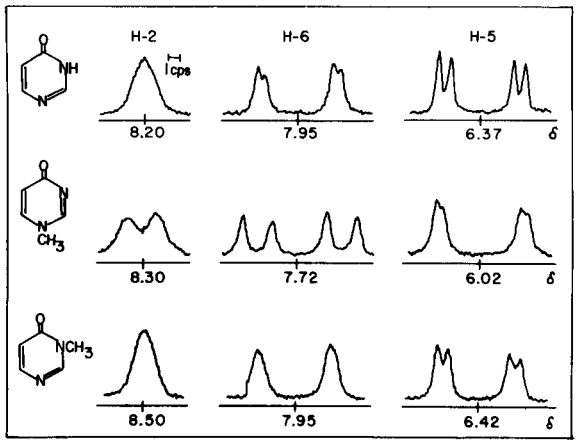


FIGURE II

Expanded n.m.r. spectra of some 4-substituted pyrimidines in dimethylsulfoxide (δ in parts per million from tetramethylsilane).

chemical shifts (going upfield) appeared in the order of H-2, H-6 and H-5 just like that observed in the aromatic counterparts (III), but each corresponding resonance was shifted somewhat further upfield. However, the resonances of H-5 in I and II (X = S) suffer much smaller upfield shifts, again due to d-orbital expansion of the sulfur group. The greater shielding of corresponding protons in I and II is attributed to lesser aromatic character (ability to sustain a ring current (6)) of the pyrimidones and thiones than the pyrimidines, and to π-electron density changes. This apparent localization of the π-electrons over some of the bonds is reflected in some of the coupling constants observed in these two series. In 1-alkyl-4-pyrimidones and thiones (I, X = O and S, respectively), the *ortho* coupling constant, $J_{5,6}$, is considerably larger than that for 4-substituted pyrimidines, perhaps indicative of more isolated double bond character of C_5-C_6. But what is even more astounding is the large *meta* coupling constant ($J_{2,6}$ ~ 2.0 to 2.5 c.p.s.) in I (X = O,S) through one of the ring nitrogen atoms. This can perhaps be rationalized if one assumes that the neutral resonance hybrid (Ia) contributes heavily towards the structure thus making N-1 almost like a "pyrrole-type" ring nitrogen atom. In several 3,4-disubstituted pyrroles, the *meta* coupling constant ($J_{2,5}$) was found to be of the order of 2 c.p.s. (7). In the same sense, 3-alkyl-4-pyrimidones and the thiones (II, X = O,S), show practically no *meta* coupling through N-1 ($J_{2,6}$ ~ 0-0.3 c.p.s.) and this is taken as an indication that the aromatic hybrid (IIb) contributes more heavily to the structure of II. For II this manifests itself also in smaller *ortho* but larger *para* coupling constants, approaching those found in the aromatic pyrimidines (III). An interesting corollary presents itself when comparing the *meta*-coupling constants of I, II and III. Apparently, when N-1 in pyrimidines is substituted, $J_{2,6}$ becomes very large. For example, 4-methylpyrimidine 1-oxide (IV) exhibits $J_{2,6}$ of 2.0 c.p.s. while it is negligible in the isomeric 4-methylpyrimidine 3-oxide (8). Equally interesting is the observation that $J_{2,6}$ in purine could not be observed but in the N-1 protonated species (V), $J_{2,6}$ is of the order of 1 c.p.s. (9,10). The property common to I, IV and V is the trisubstituted ring nitrogen (N-1) which possesses various degrees of a formal positive charge and is devoid of a pair of electrons available for bonding as in II and III.

4-Pyrimidone and 4-Pyrimidthione.

From ultraviolet studies (11,12), it was concluded that 4-pyrimidone exists in solution as the 1-H and 3-H forms, I and II (R = H), in a ratio of 1:2. Upon comparing the coupling constants of these two po-

TABLE I

N.M.R. Parameters of 4-Substituted Pyrimidines in Dimethyl Sulfoxide (a)

Compound	Chemical Shifts (p.p.m.) H_2	H_6	H_5	Other (Multiplicity) (b)	Coupling Constants (c.p.s.) $J_{5,6}$	$J_{2,6}$	$J_{2,5}$	Other
4-Methoxypyrimidine	8.83	8.55	6.97	OCH_3-3.93 (s)	5.4	0.4	1.1	
4-Methylmercaptopyrimidine	8.92	8.43	7.40	SCH_3-2.58 (s)	5.2	0.3	1.3	
1-Methyl-4-pyrimidone	8.30	7.72	6.02	CH_3-3.59 (s)	7.0	2.5	0.5	
1-Ethyl-4-pyrimidone	8.38	7.83	6.03	CH_3-1.30 (q) CH_2-3.92 (t)	7.0	2.6	-	$J_{CH_3-CH_2}$ 7.5
1-Benzyl-4-pyrimidone	8.58	7.82	6.07	CH_2-5.12 (s) C_6H_5-7.40 (s)	7.0	2.5	0.5	
3-Methyl-4-pyrimidone	8.50	7.95	6.42	CH_3-3.45 (s)	6.0	-	0.85	
3-Ethyl-4-pyrimidone	8.52	7.93	6.40	CH_3-1.25 (t) CH_2-3.95 (q)	6.1	0.3	0.85	$J_{CH_3-CH_2}$ 7.0
3-Benzyl-4-pyrimidone	8.70	7.97	6.45	CH_2-5.15 (s) C_6H_5-7.35 (s)	6.1	0.25	0.8	
4-Pyrimidone	8.20	7.95	6.37	NH-12.4 (bd)	6.3	0.5	1.0	
1-Methyl-4-pyrimidthione	8.32	7.55	7.10	CH_3-3.62 (s)	6.7	2.0	0.8	
3-Methyl-4-pyrimidthione	8.80	7.85	7.37	CH_3-3.78 (s)	5.6	-	0.85	
4-Pyrimidthione	8.32	7.90	7.20	NH-13.6 (bd)	5.7	-	1.1	

(a) Solutions were 15% (w/v) or saturated at room temperature. (b) s = singlet; t = triplet; q = quartet; bd = broad.

tentially tautomeric systems with those of the N-alkyl derivatives and taking cognizance of the relatively small values of $J_{2,6}$ exhibited by these compounds, one might conclude that the n.m.r. spectra indicate a predominance of the 3-H compounds in dimethyl sulfoxide solution.

Synthetic Methods.

Alkylation of 4-pyrimidone (12) furnished a mixture of 1- and 3-alkyl-4-pyrimidones which were separated on alumina. Although both 1- and 3-methyl-4-pyrimidones were known, it was imperative to establish the structures of the ethyl and benzyl analogs unequivocally. The structure of 1-ethyl-4-pyrimidone was proved readily by the Raney nickel desulfurization of 1-ethyl-2-thiouracil (13). Of the two N-benzyl-4-pyrimidones, we chose to determine the structure of the 1-benzyl isomer since known precursors were available from the literature. Alkylation of 2-benzylmercapto-4-pyrimidone (14) (VI) with benzyl chloride furnished only the known 1-benzyl-2-benzylmercapto-4-pyrimidone (14, 15) (VII) which was desulfurized to 1-benzyl-4-pyrimidone thus establishing the identity of that isomer. To ensure that VII did possess its assigned structure, we attempted to hydrolyze it to the corresponding uracil. Usually, acid hydrolysis of alkyl 2-pyrimidyl sulfides to the corresponding 2-pyrimidone proceeds with great ease (16a) and hence it was expected that hot hydrochloric acid would convert VII to the known 1-benzyluracil (17) (VIII). However, short exposure (15 minutes) of VII to boiling concentrated hydrochloric acid afforded 1-benzyl-2-thiouracil (IX), a reaction which involved an interesting carbon-sulfur cleavage. This cleavage had been reported previously (17) when it was stated that VII when warmed on a steam bath with concentrated hydrochloric acid and evaporated to dryness gave IX. Since 1- and 3-alkyl-2-alkylmercapto-4-pyrimidones (18) were hydrolyzed readily to the corresponding uracils by concentrated hydrochloric acid over a period of several hours, it was decided to apply a lengthier hydrolysis to VII. Heating VII with concentrated hydrochloric acid for 5 hours did indeed diminish the yield of IX and some 1-benzyluracil was formed. This suggested to us that under these conditions there exists the possibility that the thiouracil (IX) so formed initially was transformed further to the uracil (VIII). Since direct cleavage of the sp^3-carbon to sulfur bond in alkyl 2-pyrimidyl sulfides has been effected only by anhydrous hydrogen chloride at 170° (16b), we surmised that the facile conversion of VII to IX was due to the presence of the benzylmercapto group in VII. It is therefore proposed that benzyl 2-pyrimidyl thioethers undergo two different reactions, and to test such a theory, 2-benzylmercapto-4-pyrimidone (VI) was heated with concentrated hydrochloric acid at the reflux. After 0.5 hour the product consisted of an equal mixture of uracil (XIV) and thiouracil (XII). This ratio of XIV to XII was increased to 2:1 after 2 hours, to 4:1 after 6 hours and after 21 hours, XIV was the sole product. These experiments reinforced the idea that two competing reactions can take place with the protonated form of VI, *viz.*, X. It is suggested that a nucleophilic attack by chloride ion occurs readily at the benzyl carbon of VI, or even better at the protonated species, X, *via* a transition state XI to

form 2-thiouracil (XII) and benzyl chloride. The reverse nucleophilic displacement reaction of XII with benzyl chloride becomes equally possible and reforms X. The other reaction appears to be slower and is apparently irreversible. It is visualized that water attacks C-2 and in a typical aromatic nucleophilic displacement *via* an intermediate XIII, forms uracil (XIV) and benzyl mercaptan. This would account for the formation of uracil and 2-thiouracil from VI. Some uracil may arise, albeit slowly, by direct hydrolysis of 2-thiouracil (see below) although in general 2-pyrimidthiones are hydrolyzed reluctantly by hydrochloric acid to the corresponding 2-pyrimidone. However, the "hydrolysis" of 2-pyrimidthiones may be expedited by heating with an aqueous solution of chloroacetic acid. It has been suggested that chloroacetic acid converts the thione first to 2-(carboxymethylmercapto)pyrimidine hydrochloride, and in the acid medium it is the sulfide which is hydrolyzed readily (16a). It was now of interest to test if benzyl chloride could act as a convenient vehicle to effect this hydrolysis of 2-pyrimidthiones, presumably *via* a benzyl thioether.

The hydrolysis of 1-benzyl-2-thiouracil (IX) was studied with and without benzyl chloride. When IX was heated under reflux with concentrated hydrochloric acid for 70 hours, it was recovered unchanged; but under the same conditions in the presence of one equivalent of benzyl chloride the product was a mixture of IX and 1-benzyluracil (VIII) in a ratio of 1:2 (n.m.r. analysis) thus lending credence to the mechanism proposed above. It was then decided to ascertain if benzyl chloride could speed the hydrolysis of 2-thiouracil. Thus, when 2-thiouracil (XII) was boiled with concentrated hydrochloric acid, the mixture of solids so isolated was shown (by n.m.r. analysis of the ring protons in dimethylsulfoxide) to consist of starting material (XII) and uracil (XIV) in a ratio of 4:1 after 6 hours and of 1:5 after 65.5 hours. However, the hydrolysis of 2-thiouracil under identical conditions in the presence of one equivalent of benzyl chloride produced uracil faster, the ratio of XII to XIV being 1:2 after 6 hours and only uracil was present after 65.5 hours. It is evident, then, that benzyl chloride helped the hydrolysis of 2-thiouracil, and it is postulated that 2-benzylmercapto-4-pyrimidone is formed in this medium and it is this thioether which is hydrolyzed readily. However, cognizance must be taken of the experiment in which 2-thiouracil was hydrolyzed slowly to uracil in the absence of benzyl chloride. This reaction must take place by direct displacement of the sulfur function in a salt of type XV presumably *via* an intermediate XVI to form uracil (shown as the salt XVII). The direct hydrolysis of a thiol group at the 2- and 4-positions of pyrimidine has been reported rarely, examples being the hydrolysis of 6-methyl-2-thiouracil by concentrated hydrochloric acid in a sealed tube at 150-160° to 6-methyluracil (19a) and the conversion of 2,4-dithiouracil by concentrated hydrobromic acid to 2-thiouracil (24). It was also reported that prolonged hydrolysis of 2-ethylmercapto-4-pyrimidthione gave uracil (19b) whereas short hydrolysis caused displacement of the thioether group only to form 4-thiouracil.

EXPERIMENTAL (20)

Starting Materials.

4-Pyrimidone was prepared (21) in 86% yield by the Raney nickel (22) desulfurization of 2-thiouracil (23) and was purified by sublimation *in vacuo* or by recrystallization from ethanol, m.p. 163-164°, lit. (21) m.p. 163-165°. The 4-pyrimidthiones were synthesized from the corresponding 4-pyrimidones with phosphorus pentasulfide in redistilled pyridine: 4-pyrimidthione in 22% yield, m.p. 190-192° (from water) lit. (24) m.p. 190-192°; 1-methyl-4-pyrimidthione in 32%, m.p. 239-242° (from ethanol), lit. (25) m.p. 246°; 3-methyl-4-pyrimidthione in 55%, m.p. 95-97° (from petroleum ether, b.p. 60-75°) lit. (25) m.p. 97-98.5°. 4-Methoxypyrimidine was synthesized from 4-chloropyrimidine hydrochloride by a modified literature procedure (26). 4-Methylmercaptopyrimidine was obtained pure in 79% yield when 4-pyrimidthione was treated with methyl iodide, b.p. 105-106° at 10 mm., lit. (25) b.p. 86-87° at 12 mm. (27).

1-Methyl- and 3-methyl-4-pyrimidones.

Methyl iodide (31.2 g., 0.22 mole) was added to a solution of 4-pyrimidone (19.2 g., 0.2 mole) in ethanolic potassium hydroxide (13.2 g. of 85%; 0.2 mole, in 150 ml.) and the mixture boiled under gentle reflux for 0.5 hour, filtered, and evaporated to dryness *in vacuo*. The residue was boiled down twice with benzene to remove residual ethanol and then was dissolved in chloroform-benzene (1:1) and placed on alumina (475 g.; Woelm, neutral, grade 1). Elution with chloroform (1000 ml.) yielded 3-methyl-4-pyrimidone (7.1 g., m.p. in the range 120-126°) which crystallized from benzene (5.5 g., 25%), m.p. 124-126°, lit. (12) m.p. 125-126°. Further elution with chloroform-ethanol (1:1, 600 ml.) gave, after crystallization from acetone, 1-methyl-4-pyrimidone (1.0 g., 4.5%), m.p. 156-158°, lit. (12) m.p. 155-156°.

An alternate preparation of these isomers consisted of the Raney nickel desulfurization of 1- and 3-methyl-2-methylmercapto-4-pyrimidones (28). However, this method proved to have no particular advantage.

1-Ethyl- and 3-ethyl-4-pyrimidones.

4-Pyrimidone (8.64 g., 0.09 mole) was dissolved in ethanol (75 ml.) containing potassium hydroxide (5.93 g. of 85%, 0.09 mole). Ethyl iodide (15.6 g., 0.1 mole) was added and the mixture heated at the reflux for 1 hour and worked up as for the last experiment. The crude product (11.6 g.) was dissolved in chloroform and chromatographed on neutral alumina (Woelm, grade 1, 240 g.). Elution with chloroform (550 ml.) and subsequent crystallization from *n*-hexane yielded 2.87 g. (26%) of 3-ethyl-4-pyrimidone, m.p. 60-64°.

Anal. Calcd. for $C_6H_8N_2O$: C, 58.05; H, 6.50; N, 22.57. Found: C, 57.98; H, 6.48; N, 22.33.

Further elution with methanol (300 ml.) furnished 1-ethyl-4-pyrimidone as a dark oil, b.p. 224-226° at 0.3 mm. After standing for several days in a vacuum dessicator it set to a glass which was found to be extremely hygroscopic. Its hydrochloride was prepared by passing hydrogen chloride gas through an ethanol solution of the base. Crystallization from ethanol provided 1-ethyl-4-pyrimidone hydrochloride, m.p. 232-234°.

Anal. Calcd. for $C_6H_9ClN_2O$: C, 44.85; H, 5.65; N, 17.44. Found: C, 44.62; H, 5.67; N, 17.14.

Desulfurization of 1-ethyl-2-thiouracil (13).

1-Ethyl-2-thiouracil (0.15 g.) was boiled with Raney nickel (0.5 g., weighed wet) and concentrated ammonium hydroxide (1 ml.) in 5 ml. of water for 2 hours. The nickel was filtered off, washed with 10 ml. of hot water and the combined filtrates evaporated *in vacuo*. The residual oil was dried *in vacuo* and converted to its hydrochloride as in the last experiment. The salt (0.08 g., 52%) was identical to 1-ethyl-4-pyrimidone hydrochloride prepared above.

1-Benzyl- and 3-benzyl-4-pyrimidones.

A solution of 4-pyrimidone (8.64 g., 0.09 mole) in ethanol (75 ml.) containing potassium hydroxide (5.93 g. of 85%, 0.09 mole) and benzyl chloride (12.66 g., 0.1 mole) was heated at reflux for 0.5 hour and the reaction was worked up as described for the N-methyl pyrimidones. A benzene solution of the product was placed on alumina (Woelm, neutral, grade 1, 330 g.). Elution with methylene chloride (400 ml.)

followed by crystallization from 95% ethanol afforded 2.1 g. (13%) of 3-benzyl-4-pyrimidone, m.p. 102-105°.

Anal. Calcd. for $C_{11}H_{10}N_2O$: C, 70.95; H, 5.41; N, 15.04. Found: C, 71.06; H, 5.35; N, 14.93.

Elution with methanol (400 ml.) followed by crystallization from acetone gave 2.0 g. (12%) of 1-benzyl-4-pyrimidone, m.p. 142-144°.

Anal. Calcd. for $C_{11}H_{10}N_2O$: C, 70.95; H, 5.41; N, 15.04. Found: C, 71.13; H, 5.52; N, 15.18.

1-Benzyl-2-benzylmercapto-4-pyrimidone.

A solution of 2-benzylmercapto-4-pyrimidone (14) (19.8 g., 0.09 mole) and potassium hydroxide (6.6 g. of 85%, 0.1 mole) in ethanol (150 ml.) was treated with benzyl chloride (12.6 g., 0.10 mole) at reflux for 2 hours. The solvent was evaporated *in vacuo* and the residue treated with water (100 ml.) and extracted with methylene chloride (6-50 ml. portions). The extract was washed with 50 ml. of water, dried (sodium sulfate) and taken to dryness. The dry residue was crystallized from benzene to yield 1-benzyl-2-benzylmercapto-4-pyrimidone (7.1 g., 23%), m.p. 144-146°, lit. (15) m.p. 144-145°. Upon standing the solution yielded 2.95 g. of a solid, m.p. 145-185°, which was chromatographed on neutral alumina (60 g.). Elution with chloroform (400 ml.) gave an additional 0.75 g. (2.4%) of the product. Further elution with methylene chloride-ethanol (9:1, 600 ml.; 7.3, 100 ml.) and methanol (100 ml.) gave 1.9 g. (9.6%) of starting 2-benzylmercapto-4-pyrimidone.

1-Benzyl-4-pyrimidone.

A suspension of 1-benzyl-2-benzylmercapto-4-pyrimidone (3.0 g., 0.0097 mole) and Raney nickel (9 g., weighed wet) in water (40 ml.) containing concentrated ammonium hydroxide (5 ml.) was boiled under reflux for 2 hours. The precipitate was filtered off, washed with 20 ml. of boiling water and the combined filtrates evaporated *in vacuo* to yield a gummy solid. Crystallization (twice) from acetone gave 1-benzyl-4-pyrimidone, m.p. 142-144°, identical in all respects to the sample prepared above.

Hydrolysis of 1-benzyl-2-benzylmercapto-4-pyrimidone.

(A) 1-Benzyl-2-benzylmercapto-4-pyrimidone (1.0 g., 0.0332 mole) was heated on a steam bath with concentrated hydrochloric acid (50 ml.) for 0.25 hour. The product was filtered and dried to yield 0.6 g. (86%) of 1-benzyl-2-thiouracil, m.p. 230-233°, undepressed on admixture with an authentic sample (13) lit. (15) m.p. 231°.

(B) 1-Benzyl-2-benzylmercapto-4-pyrimidone (1.0 g., 0.0032 mole) was boiled under reflux with concentrated hydrochloric acid (50 ml.) for 5 hours. The precipitate from the hot solution was filtered off and consisted of 1-benzyl-2-thiouracil (0.35 g., 50%), m.p. 220-235°. Upon cooling, the solution yielded an additional 0.06 g. (8.6%) of 1-benzyl-2-thiouracil, m.p. 215-220°. The mother liquor was set aside for 4 days. 1-Benzyluracil separated, (0.14 g.) m.p. 173-175°, lit. (17) m.p. 173-174°.

REFERENCES

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(2) C. L. Bell, R. S. Egan and L. Bauer, *J. Heterocyclic Chem.*, 2, 420 (1965).

(3) G. S. Reddy, R. T. Hobgood and J. H. Goldstein, *J. Am. Chem. Soc.*, 84, 336 (1962).

(4) S. Gronowitz, B. Norman, B. Gestblom, B. Mathiasson and R. A. Hoffman, *Arkiv. Kemi*, 22, 65 (1964).

(5) W. Brügel, *Z. Elektrochem.*, 66, 159 (1962).

(6) D. W. Davies, *Chem. Comm.*, 258 (1965) and references quoted therein.

(7) S. Gronowitz, A. Hörnfeldt, B. Gestblom and R. A. Hoffman, *Arkiv Kemi*, 18, 133 (1961).

(8) M. Ogata, H. Watanabe, K. Tori, and H. Kano, *Tetrahedron Letters*, 19 (1964).

(9) W. C. Coburn, M. C. Thorpe, J. A. Montgomery and K. Hewson, *J. Org. Chem.*, 30, 1110 (1965).

(10) J. M. Read and J. H. Goldstein, *J. Am. Chem. Soc.*, 87, 3440 (1965).

(11) S. F. Mason, *J. Chem. Soc.*, 674 (1958).

(12) D. J. Brown, E. Hoerger and S. F. Mason, *ibid.*, 211 (1955).

(13) Kindly provided to us by Dr. R. N. Warrener; see R. N. Warrener and E. N. Cain, *Chem. and Ind.*, 1989 (1964).

(14) H. L. Wheeler and I. M. Liddle, *Am. Chem. J.*, 40, 547 (1908).

(15) T. B. Johnson and A. W. Joyce, *J. Am. Chem. Soc.*, 38, 1385 (1916).

(16a) D. J. Brown, "The Pyrimidines", Interscience, New York, N. Y., 1962, pp. 233, 283; (b) p. 274.

(17) T. B. Johnson and J. H. Derby, *Am. Chem. J.*, 40, 444 (1908).

(18) The hydrolysis of 1-benzyl-2-ethylmercapto-4-pyrimidone quantitatively to 1-benzyluracil with hot concentrated hydrochloric acid for 5-6 hours was reported (Reference 17). Also reported have been the hydrolyses of 1- and 3-methyl-2-methylmercapto-4-pyrimidones to the corresponding 1- and 3-methyluracils (only) when carried out for 2.5 and 1 hours, respectively. (Reference 12.)

(19a) R. List, *Ann.*, 236, 1 (1886); (b) H. L. Wheeler and T. B. Johnson, *Am. Chem. J.*, 42, 30 (1909).

(20) All melting and boiling points are uncorrected. Analyses were performed by Dr. Kurt Eder, Geneva, Switzerland. The n.m.r. spectra were determined on a Varian A-60 spectrometer using tetramethylsilane (TMS) as internal reference, all signals being recorded in p.p.m. (δ) downfield from TMS.

(21) D. J. Brown, *J. Soc. Chem. Ind.*, 69, 353 (1950).

(22) Purchased from Raney Catalyst Co., Chattanooga, Tennessee.

(23) Purchased from J. T. Baker Chemical Co. and Matheson Scientific Co.

(24) H. C. Koppel, R. H. Springer, R. K. Robins and C. C. Cheng, *J. Org. Chem.*, 26, 792 (1961).

(25) A. Albert and G. B. Barlin, *J. Chem. Soc.*, 3129 (1962).

(26) Made by J. Shoffner [Ph.D. Dissertation, University of Illinois at the Medical Center, June, 1965] by treating 4-chloropyrimidine hydrochloride with sodium methoxide in tetrahydrofuran. The use of methanol as solvent as reported previously [D. J. Brown and L. N. Short, *J. Chem. Soc.*, 331 (1953)] was not found satisfactory.

(27) When 4-chloropyrimidine hydrochloride was treated with thiourea, 4-pyrimidthione hydrochloride was obtained [M. P. V. Boarland and J. F. W. McOmie, *J. Chem. Soc.*, 1218 (1951)]. Methylation of this sample by the method of Albert and Barlin (Reference 25) furnished a mixture which was separated on alumina (Alcoa, Grade F) into two fractions. Elution with petroleum ether, b.p. 30-60°, yielded a liquid whose n.m.r. spectrum ($CDCl_3$) suggested it to be 4-ethoxypyrimidine. It showed a pattern typical of an ethoxy group [δ CH_3 at 1.41 (triplet), δ CH_2 at 4.66 (quartet), J = 7.5 c.p.s.] and the pyrimidine protons as follows: H-2 at 8.91, H-5 at 6.80 and H-6 at 8.55 δ, $J_{2,5}$ = 1 c.p.s. and $J_{5,6}$ = 6 c.p.s. Further elution with benzene yielded 4-methylmercaptopyrimidine whose n.m.r. spectrum was identical with that prepared from pure 4-pyrimidthione.

(28) These two isomers were prepared by the methylation of 2-thiouracil according to Brown's procedure (Reference 12) with the following modification. 3-Methyl-2-methylmercapto-4-pyrimidone which precipitated first when filtered off, and then the filtrate was extracted with methylene chloride (ten-50 ml. portions) to yield a mixture of 1- and 3-methyl-2-methylmercapto-4-pyrimidones. Chromatography on neutral alumina and elution with methylene chloride gave pure 3-methyl-2-methylmercapto-4-pyrimidone and with methylene chloride-ethanol, 19:1 and 9:1 furnished 1-methyl-2-methylmercapto-4-pyrimidone.

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