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# Nucleosides and Nucleotides. V.[1] Identification and Substitution Reaction of 1-Methyl-2,4-dialkoxypyrimidinium Salts: Model Studies on Hilbert-Johnson Pyrimidine Nucleoside Synthesis

Tohru Ueda and Hiroko Ohtsuka (née Nishino)

*Faculty of Pharmaceutical Sciences, Hokkaido University*[2]

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Methylation of 2,4-dialkoxypyrimidines with methyl iodide gave the reactive 1-methylpyrimidinium salts, the intermediates to 1-methyl-4-alkoxy-2-pyrimidinones. The isolation of the 1-methylpyrimidinium salt verifies the postulated mechanism of the Hilbert–Johnson reaction for pyrimidine nucleoside synthesis. The results of the substitution reaction of various 2,4-disubstituted 1-methylpyrimidinium salts are described, and the device of the extension of the Hilbert–Johnson procedure for the general method of the synthesis of 2-substituted pyrimidine nucleosides is discussed.

The Hilbert–Johnson procedure has been one of the excellent method for the synthesis of various 2-oxopyrimidine nucleosides which involves the condensation of a 2,4-dialkoxypyrimidine (I) with a protected glycosyl halide (II).[3-5] In this reaction the 1-glycosylpyrimidinium salt (III) has been postulated, though neither isolated or detected, as an intermediate leading to the 2-oxopyrimidine nucleoside (IV) by the fact that 4-amino-2-methoxypyrimidine (V) gave the 1-methylpyrimidinium salt (VI) which, in turn, was converted to 1-methylcytosine (VII).[6]

This paper describes the isolation and identification of 1-methyl-2,4-dialkoxypyrimidinium salts as an intermediate of 1-methyluracil from I and the studies on the substitution reaction of 2- and 4-position of various 1-methyl-2,4-disubstituted pyrimidinium halide as the model compounds of the Hilbert–Johnson reaction intermediate. The preliminary account of some of the results described herein has been appeared.[7]

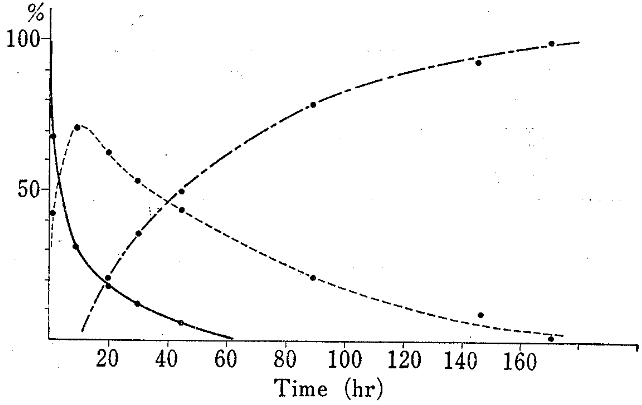

Fig. 1. Reaction of 2,4-Diethoxypyrimidine with Methyl Iodide in $d_6$-DMSO (See experimental for the reaction condition)

——: 2,4-diethoxypyrimidine
------: 2,4-diethoxy-1-methylpyrimidinium iodide (XII)
-----: 4-ethoxy-1-methyl-2-pyrimidinone

2,4-Diethoxy-5-methylpyrimidine (VIII) was brought into reaction with methyl iodide in acetonitrile at room temperature and the course of the reaction was followed by thin-layer chro-

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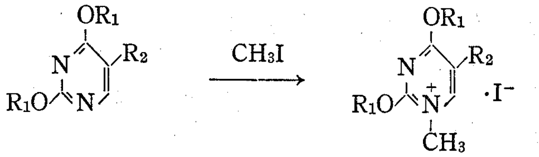
1) Following previous papers constitute this series: *a*) Part I: T. Ueda, Y. Iida, K. Ikeda and Y. Mizuno, *Chem. Pharm. Bull.* (Tokyo), **16**, 1788 (1968); *b*) Part II: T. Ueda and H. Nishino, *Chem. Pharm. Bull.* (Tokyo), **17**, 920 (1969); *c*) Part III: T. Ueda and I. Kawai, *Chem. Pharm. Bull.* (Tokyo), **18**, 2303 (1970); *d*) Part IV: K. Miura and T. Ueda, *Chem. Pharm. Bull.* (Tokyo), **19**, 2567 (1971).
2) Location, *Kita-12, Nishi-6, Kita-ku, Sapporo.*
3) G.E. Hilbert and T.B. Johnson, *J. Am. Chem. Soc.*, **52**, 2001, 4489 (1930). For the general reviews on the Hilbert–Johnson procedure for pyrimidine nucleoside synthesis see ref. 4 and 5.
4) J.J. Fox and I. Wempen, *Advan. Carbohydrate Chem.*, **14**, 283 (1958).
5) J. Priml and M. Prystas, *Advan. Heterocyclic Chem.*, **8**, 115 (1967).
6) G.E. Hilbert, *J. Am. Chem. Soc.*, **56**, 190 (1934).
7) T. Ueda and H. Nishino, *J. Am. Chem. Soc.*, **90**, 1678 (1968).

matography (silica gel, chloroform–ethanol as the solvent). A new spot tailing from the starting point appeared after 15 min and became predominant after 5 hr. On addition of excess of ether to the reaction solution furnished the white crystals, 2,4-diethoxy-1,5-dimethylpyrimidinium iodide (IX). The structure of IX was confirmed by elemental analysis and nuclear magnetic resonance (NMR) spectra, and by successive acid treatment to yield 1-methyl-4-ethoxy-2-pyrimidinone (X) and 1-methylthymine (XI). When the reaction was carried out in benzene IX could not be detected and X appeared on elongation of the reaction time. A prolonged reaction in acetonitrile also resulted in the formation of X as the major product. Similar phenomena were observed in the study of the time course of the reaction of 2,4-diethoxypyrimidine with methyl iodide in $d_6$-dimethylsulfoxide by NMR measurement (Fig. 1).

It is to be emphasized that the isolation of IX and XII was the direct proof of the postulated mechanism of the Hilbert–Johnson procedure,[6] since the synthesis of ribofuranosyluracil and -thymine starting from the respective diethoxypyrimidines are already known.[8]

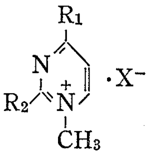
For the study of substitution reactions of the 1-alkylpyrimidinium salts several 2,4-dialkoxy- and 2,4-disubstituted-pyrimidines were converted to their 1-methyl derivatives (see Table I and II).

TABLE I. Synthesis of 1-Methyl-2,4-dialkoxypyrimidinium Iodides



| Product | $R_1$ | $R_2$ | $CH_3I$, eq. | Reaction time (hr) | Yield (%) | mp (decomp.) (°C) | UV $\lambda_{max}$, (nm) |
|---|---|---|---|---|---|---|---|
| IX | ethyl | $CH_3$ | 2 | 21 | 43 | 77.5— 78 | 268 |
| XII | ethyl | H | 2 | 5.5 | 35.3 | 56.5— 58.5 | 222, 260 |
| XIII | isopropyl | $CH_3$ | 2 | 6 | 9.7 | 79 — 81 | 269 |
| XIV | phenyl | H | 30 | 168 | 61.6 | 180 —186 | 264 |

TABLE II. 2,4-Disubstituted 1-Methylpyrimidinium Halides Synthesized



| Compound | $R_1$ | $R_2$ | X | Method[a] | UV $\lambda_{max}$, nm in $H_2O$ $(\varepsilon \times 10^{-3})$ |
|---|---|---|---|---|---|
| XV | OEt | $SCH_3$ | I | A | 227.5(31), 251sh(13.6), 275sh(7.6) |
| XVI | $SCH_3$ | OEt | I | A | 227.5(18.7), 258(4.8), 304(18.7) |
| XVII[1a] | $SCH_3$ | $SCH_3$ | I | A | 229, 265, 295, 310sh |
| XVIII | $OCH_3$ | $NH_2$ | Cl | A | 272(3.9), 1N NaOH 307(1.8) |
| XIX[6] | $NH_2$ | $OCH_3$ | Cl | A | 233(7.1), 266.5(7.6) |
| XX[9a] | $NH_2$ | $SCH_3$ | Cl | B | 242(28.1) |
| XXI | $SCH_3$ | $NH_2$ | I | B | 220.5(24.4), 278sh(9.6), 300.5(12.3), 310sh(10.3)<br>1N NaOH 276.5(9.4), 333(2.9) |
| XXII[9a,b] | $NH_2$ | $NH_2$ | Cl | B | pH 9 235(10.4), 270(6.8), 1N NaOH 297(2.8) |

*a)* Method A designates the N-methylation of parent pyrimidines and method B involves amination of the appropriate 1-methylpyrimidinium salt(s), see experimental.

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8) *a)* G.A. Howard, B. Lythgoe and A.R. Todd, *J. Chem. Soc.*, **1947**, 1052; *b)* M. Roberts and D.W. Visser, *J. Am. Chem. Soc.*, **74**, 668 (1952); *c)* J. Farkas, L. Kaplan and J.J. Fox, *J. Org. Chem.*, **29**, 1469 (1964).

Pyrimidinium salts having a 2-alkoxy group are generally unstable at room temperature and tend to form 1-alkyl-2-pyrimidinones, whereas those having 2-substituent other than alkoxy group, namely, methylthio, phenoxy and amino, gave rather stable 1-methylpyrimidinium salts. In the case of certain 2-amino and 2-methylthio-pyrimidines similar observations have been advanced by Brown and co-workers[9] and Curd and co-workers.[10] As revealed by the ultraviolet (UV) spectral examinations the 1-methylpyrimidinium salts are fairly stable under acidic condition while labile, except for 2-amino derivatives, in alkaline solution in which 2-pyrimidinone derivatives were formed almost instantly. The NMR spectral characteristics of the pyrimidinium salts are the down field shift of signals of 5-and 6-protons as compared with the parent pyrimidines.

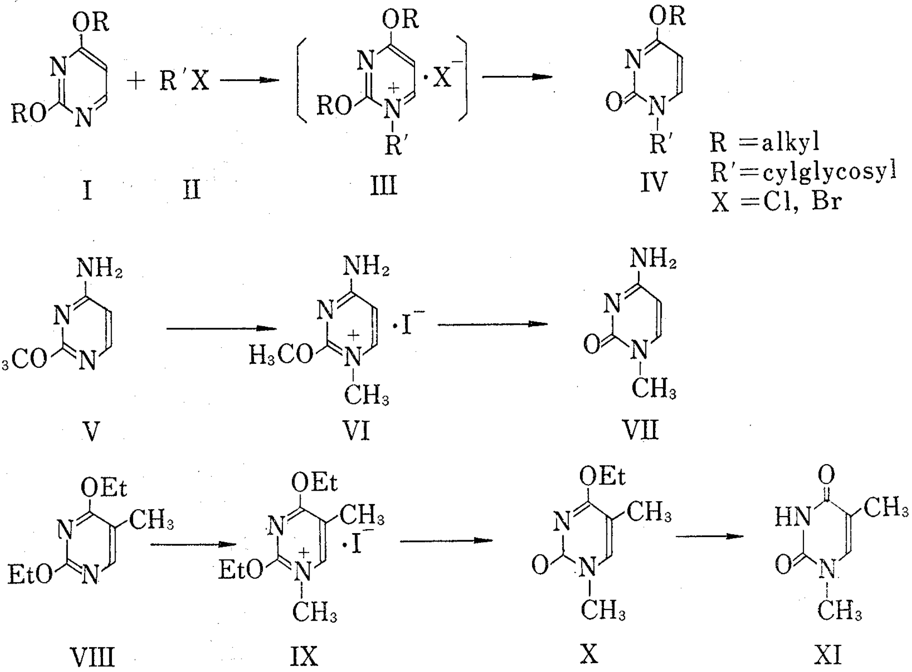

Chart 1

Studies of the substitution reaction of position-2 of the pyrimidinium salts are next undertaken. It was originally expected that the substitution of 2-alkoxy group in IX by hydrogen sulfide ion would give the 2-pyrimidinethione thus make use of the pyrimidinium intermediate for the preparation of various 2-thiopyrimidine nucleosides. Treatment of 1-methyl-2,4-dialkoxypyrimidinium iodide with sodium hydrogen sulfide in ethanol, however, resulted in a formation of 1-methyl-4-ethoxy-2-pyrimidinone as the sole product. The reaction of hydrogen sulfide in dimethylformamide with triethylamine, which was the condition used for the cleavage of $O^2$,5'-cyclouridine to a 2-thiouridine,[11] gave only trace amount of the 2-thio derivative. These results show that the alkyl-oxygen fission rather than aryl-oxygen was predominant under the reaction condition adopted.[12] On the other hand 2,4-diphenoxy

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[9] *a*) D.J. Brown and N.W. Jacobson, *J. Chem. Soc.*, **1962**, 3172; *b*) D.J. Brown and T. Teitei, *J. Chem. Soc.*, **1965**, 755.

[10] *a*) F.H.S. Curd and D.N. Richardson, *J. Chem. Soc.*, **1955**, 1850, 1853; *b*) H.C. Carrington, F.H.S. Curd and D.N. Richardson, *J. Chem. Soc.*, **1955**, 1858.

[11] D.M. Brown, D.B. Parihar, A.R. Todd and S. Varadarajan, *J. Chem. Soc.*, **1958**, 3028.

[12] Our recent studies disclosed that liquid hydrogen sulfide in pyridine cleaves the $O^2$,5'-cyclo linkage by almost selective aryl-O fission to give 2-thiouridines, see T. Ueda and S. Shibuya, *Chem. Pharm. Bull.* (Tokyo), **18**, 1076 (1970).

derivative (XIV) gave 2,4-dithio-1-methyluracil[13] in a good yield on treatment with hydrogen sulfide ion. 2-Methylthiopyrimidinium salts (XV, XVII, XX) afforded 2-pyrimidinones with alkaline treatment and 2-pyrimidinethiones with hydrogen sulfide ion treatment which suggests that the substitution occurs at position 2 with the aryl-thio fission predominating in these compounds.

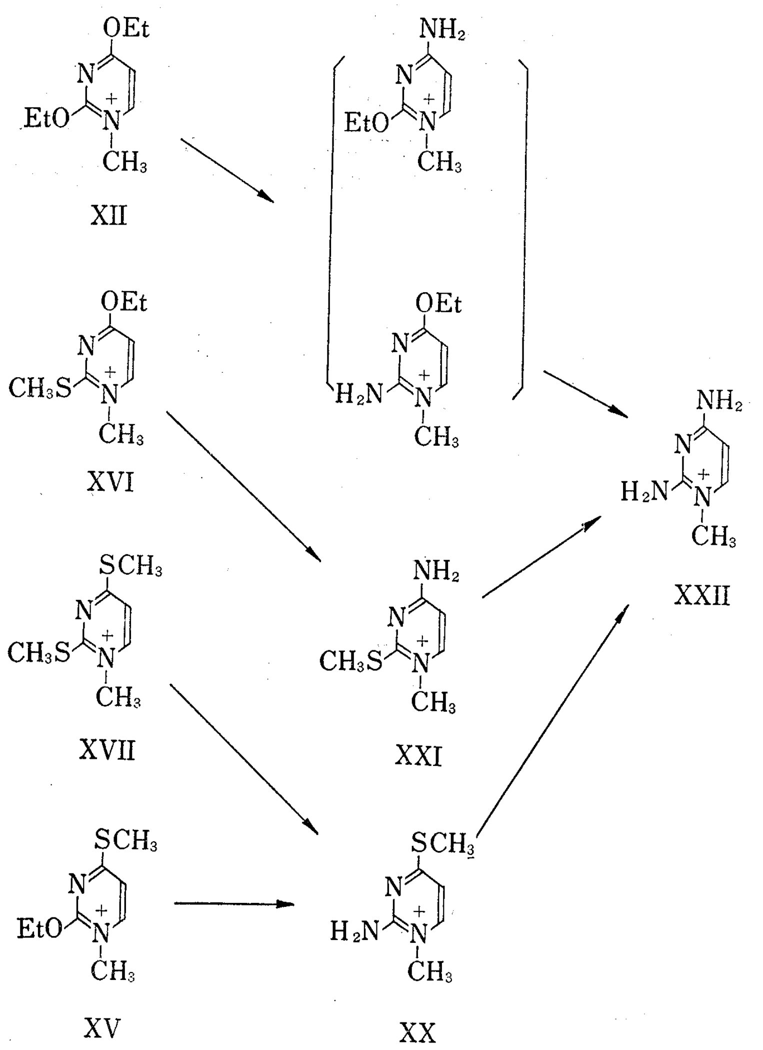

Chart 2

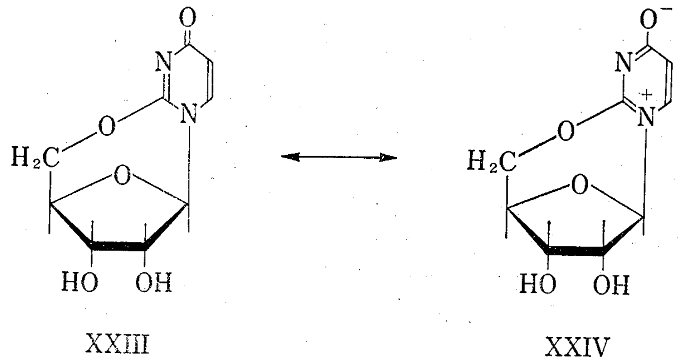

Chart 3

Considering the stability of derivatives of 2-methylthiopyrimidinium salts and the feasibility of replacement of the methylthio group it is very likely that methylthiopyrimidines rather than methoxypyrimidines would be the useful starting pyrimidines for the Hilbert–Johnson procedure.

The substitution reaction of the pyrimidinium salts with ammonia was undertaken. The action of methanolic ammonia with 1-methyl-2,4-dialkoxypyrimidinium salts (for example XII) at 0° rapidly gave 1-methyl-2,4-diaminopyrimidinium salt (XXII). On the other hand 2,4-dimethylthiopyrimidinium iodide (XVII) gave 2-amino-4-methylthio derivative (XX) as a stable intermediate at room temperature. Under forced reaction condition XX was converted to XXII. The amination of 1-methyl-4-ethoxy-2-methylthiopyrimidinium salt (XVI) afforded 4-amino derivative (XXI), which is further aminated to XXII under mild reaction condition. On the other hand 1-methyl-2-ethoxy-4-methylthiopyrimidinium salt (XV), the positional isomer of XVI, gave 2-amino-4-methylthio derivative XX which is rather resistant to further amination as described above. From these observations it is evident that in the amination reaction a) ethoxy group is more reactive to substitution reaction over methylthio group and b) the substituent at position 2 is more replaceable than that at position 4, c) the effect of the leaving ability of

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[13] D.J. Brown and J.S. Harper, *J. Chem. Soc.*, **1961**, 1298.

the substituent is overwhelming to the positional effect in the case of methylthio versus methoxy, which is in contrast with the result of the attack of hydroxide or sulfhydryl ion.

It is of some interest to correlate the reactivity of 1-methylpyrimidinium salt with that of the pyrimidine cyclonucleosides (for example, $O^2$,5′-cyclouridine (XXIII)). The cyclonucleosides are reported[14] to have the contribution of zwitterionic structure (XXIV) which is very likely the pyrimidinium structure. Therefore the mode of cleavage of the cyclolinkages[15] are fairly similar to those described here in 1-methylpyrimidinium salts.

In conclusion it seems reasonable that the mechanism of the Hilbert–Johnson procedure involves the formation of 1-ribosylpyrimidinium salt as the initial intermediate, which is very reactive and loses the 2-alkyl group with alkyl-oxygen fission by the attack of nucleophiles present. Therefore it may well be possible that the Hilbert–Johnson procedure can be extended to the general method for the synthesis of 2-substituted pyrimidine nucleosides, if one uses the proper 2-substituted pyrimidine which gives the stable pyrimidinium salt as the intermediate. The studies along these lines by the application of the model studies described here will be reported separately.

## Experimental

UV and NMR spectra were determined on a Hitachi Recording Spectrophotometer 3T and Hitachi H-60 Spectrometer, respectively.

**2,4-Diethoxy-1,5-dimethylpyrimidinium Iodide (IX)**——2,4-Diethoxy-5-methyl pyrimidine,[16] 300 mg, was dissolved in 4 ml of acetonitrile and 0.21 ml, 2 eq, of methyl iodide was added and kept for 21 hr at room temperature in the darkness. Excess of ether was added and the resulted white suspension was kept in a refrigerator and filtered, washed with ether, and dried to yield 230 mg, 43%, of IX. *Anal.* Calcd. for $C_{10}H_{17}O_2N_2I$: C, 37.05; H, 5.29; N, 8.64. Found: C, 37.17; H, 5.41; N, 8.61. NMR ($CDCl_3$) $\delta$ ppm: 1.16, 1.55 (t, $C\underline{H}_3$-$CH_2$-) 2.28 (5-$CH_3$), 4.7, 4.83 (q, $CH_3$-$C\underline{H}_2$-), 4.14 (N-$CH_3$), 9.3 (6-H). Signals of the starting pyrimidine are: 1.46 (t, $C\underline{H}_3$-$CH_2$-), 2.08 (5-$CH_3$), 4.45 (m, $CH_3$-$C\underline{H}_2$-), 8.11 (6-H). Paper electrophoretic mobility at pH 5.8 in acetate buffer, 700 V, 6 mA for 1.5 hr was −8.7 cm. Upon standing of IX in 1N NaOH for 1 hr it was converted to XI. Compound (IX) was stable in 1N HCl for 24 hr. Treatment of IX with NaSH in EtOH or DMF resulted in the formation of XI after the work-up. The time course of the methylation reaction was followed by TLC ($CHCl_3$: EtOH=10: 35). After 15 min the formation of a spot tailing from the starting point and strongly colorized by iodine vapor was noted. After 5 hr the spot (corresponding to IX) became major and another spot corresponding to X began to appear. When the reaction was carried out in benzene the spot for IX was not visible throughout the reaction and after 24 hr the spot of X appeared.

**2,4-Diethoxy-1-methylpyrimidinium iodide (XII)**——2,4-Diethoxypyrimidine,[3] 606 mg, in 2.5 ml of acetonitrile was treated with 0.44 ml, 2 eq, of methyl iodide at room temperature for 5 hr. Dry ether was added to the reaction mixture to afford crystals, 0.38 g, 35.3%. *Anal.* Calcd, for $C_9H_{15}O_2N_2I$: C, 34.85; H, 4.88; N, 9.03. Found: C, 35.02; H, 4.98; N, 8.73. NMR ($d_6$-DMSO) $\delta$ ppm: 3.80 (N-$CH_3$), 7.09 (d, 5-H), 8.74 (d, 6-H) $J_{5,6}=8$ Hz. Signals of the starting pyrimidine were 6.48 (d, 5-H, $J=6$ Hz), 8.24 (d, $J=6$ Hz). On standing XII decomposed gradually to 4-ethoxy-1-methyl-2-pyrimidinone.[3] NMR ($d_6$-DMSO) $\delta$ ppm: 3.39 (N-$CH_3$), 5.90 (d, 5-H), 7.97 (d, 6-H), $J_{5,6}=8$ Hz. Compound (XII) was stable in 1N HCl for 24 hr but was converted to 1-methyluracil in a week. The time course of the methylation reaction was followed by NMR spectroscopy. To 2,4-diethoxypyrimidine in $d_6$-DMSO was added excess methyl iodide and spectra were measured over the period of 200 hr. Due to the methylation of the solvent the kinetic study was not possible. The ratio of the product was calculated from the intensity of $C_5$- and $C_6$-protons. The results are shown in Fig. 1.

**2,4-Diisopropoxy-1,5-dimethylpyrimidinium Iodide (XIII)**——2,4-Diisopropoxy-5-methylpyrimidine, (prepared from 2,4-dichloro-5-methylpyrimidine and sodium isopropoxide,[17] $bp_3$ 76°, 500 mg) and methyl iodide, 0.3 ml in 3.0 ml of acetonitrile was kept for 6 hr at room temperature from which 83 mg, 9.7%, of XIII was obtained by the similar work-up as described above. *Anal.* Calcd. for $C_{12}H_{21}O_2N_2I$: C, 40.92; H, 6.01; N, 7.96. Found: C, 41.28; H, 6.01; N, 7.81.

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14) K.C. Murdock and R.B. Angier, *J. Am. Chem. Soc.*, **84**, 2748 (1962).

15) For the review of the chemistry of pyrimidine cyclonucleosides see J.J. Fox, "Pure and Applied Chemistry," Vol. 18, Butterworth, London, 1969, p. 223.

16) W.S. Nichols and T.B. Johnson, *J. Am. Chem. Soc.*, **52**, 4511 (1930).

17) M. Prystas and F. Sorm, *Collection Czech. Chem. Commun.*, **31**, 1035 (1966).

**2,4-Diphenoxy-1-methylpyrimidinium Iodide (XIV)**——*a*) 2,4-Diphenoxypyrimidine: 2,4-Dichloropyrimidine,[3)] 4.47 g, in abs. EtOH was added 30 ml of NaOEt in EtOH (1.5 g of Na) and 6.5 g of phenol. After stirring for 30 min NaCl was filtered off and the filtrate was concentrated *in vacuo* and the residue dissolved in benzene. The benzene layer was washed with 30% NaOH and water and dried over $Na_2SO_4$. The solvent was removed and the residue was crystallized from EtOH to yield 4.58 g, 58%, of 2,4-diphenoxypyrimidine[18)], mp 110—111.5°, UV $\lambda_{max}$ 260 nm, $\lambda_{min}$ 240 nm. *Anal.* Calcd. for $C_{16}H_{12}O_2N_2$: C, 72.71; H, 4.55; N, 10.60. Found: C, 72.72; H, 4.58; N, 10.39.

b) 2,4-Diphenoxypyrimidine, 862 mg, was dissolved in 5.94 ml of methyl iodide and kept in a sealed flask for 7 days and the resulting precipitate was recystallized from EtOH–*n*-hexane to yield 0.83 g, 61.6%, of XIV. *Anal.* Calcd. for $C_{17}H_{15}O_2N_2I$: C, 50.26; H, 3.72; N, 6.90. Found: C, 50.42; H, 3.77; N, 6.65. The compound is unstable in alkaline solution and converted to 1-methyluracil as evidenced by the UV spectral measurement.

**2,4-Dithio-1-methyluracil from XIV**——Compound XIV, 440 mg, was dissolved in NaSH–MeOH and $H_2S$ was bubbled through for 3 hr. The resulted precipitate was collected and recrystallized from benzene to give 145 mg, 84.7%, of 2,4-dithio-1-methyluracil.[1a,13)]

**4-Ethoxy-1-methyl-2-methylthiopyrimidinium Iodide (XV)**——a) 4-Ethoxy-2-methylthiopyrimidine: To a solution of 4-chloro-2-methylthiopyrimidine[19)], 9.5 g, in 30 ml of EtOH was added 30 ml of NaOEt–EtOH (prepared from 2 g of Na in 50 ml of EtOH) under stirring. After 30 min NaCl was filtered and the filtrate was concentrated under reduced pressure and the residue was taken up in $CHCl_3$. The solution was washed with 30% NaOH, water and dried over $Na_2SO_4$ overnight. After the removal of the solvent the residue was distilled to give viscous oil which solidifies in a refrigerator, 7.75 g, 78%, $bp_{10}$ 117°. UV $\lambda_{max}$ 249.5 nm, 275 nm (sh), $\lambda_{min}$ 228 nm.

b) 4-Ethoxy-2-methylthiopyrimidine, 173 mg, was dissolved in 3 ml of acetonitrile and 0.12 ml of methyl iodide was added and left to stand for 110hr. The product, XV, 250 mg, 78.3%, was obtained by the similar work-up. *Anal.* Calcd. for $C_8H_{13}ON_2SI$: C, 30.78; H, 4.20; N, 8.98. Found: C, 30.84; H, 4.28 N, 8.72. NMR ($CDCl_3$) $\delta$ ppm: 1.57 (t, EtO), 2.91 (s, $CH_3S$-), 4.29 (s, N-$CH_3$), 6.99 (d, 5-H, $J=7$ Hz), 9.45 (d, 6-H, $J=7$ Hz). On addition of NaOH solution into the ethanolic solution of XV the UV spectra gradually changed to those of 4-ethoxy-1-methyl-2-pyrimidinone with the release of methanethiol.

**Conversion of XV to 4-Ethoxy-1-methyl-2-pyrimidinethione**——To the ethanolic solution of 0.84 g of XV was added NaSH–EtOH (2 eq) and hydrogen sulfide was bubbled for 2 hr and the separated yellow needles were collected and recrystallized from EtOH to leave 0.35 g, 77.5%, of 4-ethoxy-1-methyl-2-pyrimidinethione, mp 134—135° (decomp.). *Anal.* Calcd. for $C_7H_{10}ON_2S$: C, 49.39; H, 5.92; N, 16.46. Found: C, 49.45; H, 5.96; N, 16.70. UV $\lambda_{max}$ ($\varepsilon$), 276 nm (9800), $\lambda_{min}$, 248.6 nm (1600), $\lambda_{max}^{1N\ HCl}$, 277 nm (10600), $\lambda_{mim}$, 252 nm (2300). The compound is converted to 1-methyl-2-thiouracil by treatment with 1N HCl at 100° for 30 min or at room temperature overnight, or with 1N NaOH overnight. Treatment of the 4-ethoxy-thione, 17 mg, in sat. $NH_3$–MeOH, 1.5 ml, at 110—120° for 9 hr in a sealed tube afforded 1-methyl-2-thiocytosine[1a)] in a good yield.

**2-Ethoxy-4-methylthio-1-methylpyrimidinium Iodide (XVI)**——2-Chloro-4-methylthiopyrimidine,[20)] 8.37 g, in 50 ml of abs. EtOH was added excess sodium ethoxide solution. After 30 min NaCl precipitated was removed and the solvent was distilled off and the residue was taken up in benzene. The benzene layer was washed with bicarbonate solution, water and dried over $Na_2SO_4$. After removal of benzene the residue was distilled, $bp_{1-3}$ 79—93°. This syrup contained some starting pyrimidine but used for the next step without further purification. The syrup, 0.5 g, in 5 ml of acetonitrile was added 0.6 ml of methyl iodide and kept for 12 hr at room temperature and ether was added to afford white crystals of XVI, 0.35 g. *Anal.* Calcd. for $C_8H_{13}ON_2SI$: C, 30.78; H, 4.20; N, 8.98. Found: C, 31.00; 4.29; N, 8.96. The UV spectra of XVI in alkaline solution gave those of 1-methyl-4-methylthio-2-pyrimidinone.[21)] NMR ($CDCl_3$), $\delta$ ppm: 2.72 ($CH_3S$-), 4.10 (N-$CH_3$), 9.11 (6-H), $J_{5,6}=7$ Hz.

**2-Amino-4-methoxy-1-methylpyrimidinium Chloride (XVIII)**——Methylation of 2-amino-4-methoxypyrimidine[6)] afforded XVIII in a crude form, UV $\lambda_{max}$, 223.5, 272 nm; $\lambda_{max}^{OH^-}$ 305 nm. This was converted to the chloride by treatment with silver chloride in EtOH. Acid or alkaline treatment of XVIII gave 1-methylisocytosine.[22)] Similarly, from the crude 2-amino-4-benzyloxypyrimidine its 1-methyl derivative was obtained. *Anal.* Calcd. for $C_{12}H_{14}ON_3I$: C, 42.00; H, 4.11; N, 12.25. Found: C, 41.96; H, 4.23; N, 12.20.

**Amination of XV to 4-Amino-2-methylthio-1-methylpyrimidinium Iodide (XX)**——Two hundred mg of XV was dissolved in 1.8 ml of abs. EtOH, 1.8 ml of sat. $NH_3$–EtOH was added at 0° and stirred. The separated precipitate (XX) was collected, ether was added to the mother liquor and kept in refrigerator to give more precipitate. The total precipitate weighed 142 mg, 78.3%, identical with the reported.[9a)]

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18) The IR spectra of the compound are reported in L.N. Short and H.W. Thompson, *J. Chem. Soc.*, **1952**, 168.

19) T. Matsukawa and B. Ohta, *Yakugaku Zasshi*, **69**, 491 (1949).

20) T. Ueda and J.J. Fox, *J. Med. Chem.*, **6**, 697 (1963).

21) M. Ikehara, T. Ueda and K. Ikeda, *Chem. Pharm. Bull.* (Tokyo), **10**, 767 (1962).

22) R.B. Angier and W.V. Curran, *J. Org. Chem.*, **26**, 1891 (1961).

NMR ($D_2O$) $\delta$ ppm: 2.69 ($CH_3S$-), 3.78 (N-$CH_3$), 6.75 (d, 5-H), 7.92 (d, 6-H), $J_{5,6}=7.9$ Hz. Compound (XX) was converted to 1-methylcytosine or 1-methyl-2-thiocytosine with alkali or NaSH treatment.

**Amination of XX to 2,4-Diamino-1-methylpyrimidinium Iodide (XXII)**——Compound (XX) was dissolved in ethanolic ammonia and kept for 3 hr at room temperature. After the work-up XXII[9a,b] was obtained in quantitative yield.

**Amination of XVI to 2-Amino-4-methylthio-1-methylpyrimidinium Iodide (XXI)**——Compound (XVI) was dissolved in 2 ml of sat. $NH_3$–EtOH and quickly evaporated to leave a mass which was recrystallized from EtOH–ether to give XXI, 87 mg, 68.5%, mp 151—153°. *Anal.* Calcd. for $C_6H_{10}N_3SI$: C, 25.45; H, 3.59; N, 14.85. Found: C, 25.08; H, 3.69; N, 14.81. NMR ($D_2O$) $\delta$ ppm: 2.65 (S-$CH_3$), 3.76 (N-$CH_3$), 6.95 (d, 5-H), 7.85 (d, 6-H), $J_{5,6}=7$ Hz. Compound (XXI) is stable in 1N HCl at 80—90° for 1—2 hr.

**Amination of XXI to XXII**——Compound (XXI) was dissolved in sat. $NH_3$–EtOH and heated for 3 hr at 100° in a sealed tube. The spectra of the reaction mixture changed to those of XXII.

**Amination of 2,4-Dimethylthio-1-methylpyrimidinium Iodide (XVII) to XXI**——To a solution of XVII,[1a] 100 mg in 2.5 ml of EtOH, was added 4 ml of sat. $NH_3$–EtOH and kept for 30 min at room temperature. After the removal of the solvent the residue was crystallized from EtOH to leave 67 mg of XXI, which is identical with that obtained from the amination of XVI.

**Amination of 2,4-Diethoxy-1-methylpyrimidinium Iodide (XII) to XXII**——When a small amount of XII was dissolved in sat. $NH_3$–EtOH at 0° XXII was obtained instantly and the possible amino/ethoxy intermediate (s) was not detected throughout the reaction.

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