Ten-π-Electron Nitrogen Heterocyclic Compounds. IV. The Synthesis, Bromination, and Nuclear Magnetic Resonance Spectra of Some Imidazo[1,2-a]pyrimidines

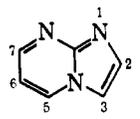
W. W. PAUDLER AND J. E. KUDER

Department of Chemistry, Ohio University, Athens, Ohio

Received September 13, 1965

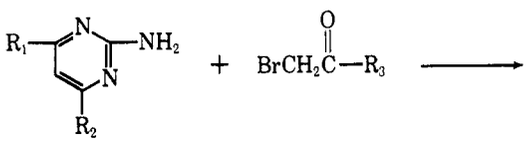
The synthesis of some imidazo[1,2-a]pyrimidines is described. Bromination has been shown to occur at position 3 of the compounds, while protonation and N-methylation occurs at N-1. These results are in agreement with the predictions based on the frontier electron densities. The chemical shifts of the protons have been calculated by a semiempirical method.

Our recent interest in imidazo[1,2-a]pyridines[1,2] prompted us to extend our investigations to some imidazo[1,2-a]pyrimidines (**1**), another so-called "ten-π-electron" nitrogen heterocyclic system.

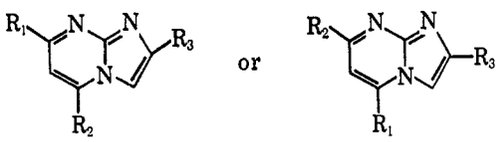


1

The syntheses of these compounds involve the condensation of properly substituted 2-aminopyrimidines with the appropriate α-halo carbonyl compounds. The structure of the products obtained from these condensations are unequivocal if the 2-aminopyrimidine used is either unsubstituted, monosubstituted at position 5, or symmetrically disubstituted at positions 4 and 6. Thus, the condensation of a 2-amino-4-substituted pyrimidine (**2**, R_1 or R_2 = H) with α-bromoacetaldehyde can yield either a 5-substituted or a 7-substituted imidazo[1,2-a]pyrimidine (**3**, R_1 = H; R_2 = alkyl; R_3 = H, or **4**, R_1 = H; R_2 = alkyl; R_3 = H, respectively). It became of interest to prepare a series of these imidazo[1,2-a]pyrimidines and to study their nmr spectra. An understanding of these spectra should permit unequivocal structural assignments of the compounds when two products can be expected.



2



3 **4**

The analysis of the spectrum of imidazo[1,2-a]pyrimidine is straightforward, except for the assignment of H-2 and H-3 of the AB pattern and the assignment of H-5 *vs.* H-7 (Figure 1 and Table I). In order to establish which "doublet" of the AB pattern is H-3 it is necessary to obtain the spectrum of a 5-substituted imidazo[1,2-a]pyrimidine. We chose the 5,7-dimethylimidazo[1,2-a]pyrimidine (**3**, R_1 = R_2 = CH_3; R_3 = H) since its structure is unequivocal. We would anticipate (in analogy with the imidazo[1,2-a]pyridines[1]) that H-3 would appear at a more shielded position than in the parent substance. This additional shielding of H-3 ($\Delta\tau$ 0.24) is clearly visible (Table I). Thus, we find that H-2 is the more deshielded "doublet" of the AB pattern owing to the five-membered ring protons.

A decision as to which member of the ABX system (H-5, H-7, and H-6) is H-7 and H-5 can be reached by an analysis of the spectrum of the imidazo[1,2-a]pyrimidine obtained from 2-amino-4-methylpyrimidine and α-bromoacetaldehyde. This compound is either the 5-methyl or the 7-methyl derivative, depending upon the direction of cyclization. If the compound is the 5-methyl derivative, we would expect H-3 to resonate at essentially the same frequency as is observed in the 5,7-dimethyl compound. This is not the case (*cf.* Table I); both H-2 and H-3 have essentially the same chemical shifts as in the parent compound. Hence, the cyclization of 2-amino-4-methylpyrimidine with α-bromoacetaldehyde yields 7-methylimidazo[1,2-a]pyrimidine (**3**, R_1 = CH_3; R_2 = R_3 = H). The cyclization occurs in the same sense when 2-amino-4-methylpyrimidine is condensed with 3-bromo-2-butanone; the resulting compound is the 2,3,7-trimethylimidazo[1,2-a]pyrimidine. The proton on C-5 is more shielded in this compound than in the parent, as well as in the 7-methyl compound ($\Delta\tau$ 0.58). One of the methyl groups in the 5,7-dimethyl compound appears as a doublet while H-6 appears as a quartet. Since the methyl group in the 7-methyl compound is a clear singlet, it must be the methyl group on C-5 which is coupled to H-6. The assignments of the methyl groups reported in Table I are therefore justified.[3]

These analyses can be utilized in establishing the structure of the previously reported imidazo[1,2-a]-pyrimidine resulting from the interaction of phenacyl bromide with 2-amino-4-methylpyrimidine.[4] This has been assigned the 2-phenyl-5-methyl structure. If this assignment is correct, we would anticipate that the methyl group protons appear as a doublet, and the coupling constants of the six-membered ring proton AB system to be 4.1–4.5 cps (Table I). Since this phenyl derivative is virtually insoluble in deuterio-

(1) W. W. Paudler and H. L. Blewitt, *Tetrahedron*, **21**, 353 (1965).

(2) W. W. Paudler and H. L. Blewitt, *J. Org. Chem.*, **30**, 4081 (1965).

(3) The various spin–spin coupling constants are of the same order of magnitude as the corresponding constants observed in other polyazaindenes [ref 1 and 2 and Y. Makisumi, H. Watanabe, and K. Tori, *Chem. Pharm. Bull.* (Tokyo), **12**, 204 (1964); L. M. Jackman, Q. N. Porter, and G. R. Underwood, *Australian J. Chem.*, **17**, 1128 (1964); J. P. Paolini and R. K. Robins, *J. Heterocyclic Chem.*, **2**, 53 (1965)] and consequently further confirm the assignments reported in Table I.

(4) E. Ochiai and M. Yanai, *J. Pharm. Soc. Japan*, **59**, 97 (1939).

TABLE I

NMR SPECTRA TABULATION OF SOME IMIDAZO[1,2-*a*]PYRIMIDINES

Compd[a]	Chemical shift, τ H-2	H-3	H-5	H-6	H-7	Substituent	Coupling constants, cps $J_{2,3}$	$J_{5,6}$	$J_{6,7}$	$J_{5,7}$	$J_{H\text{-}6\text{-}Me}$
Parent	2.23 (1.80 or 1.87)	2.34 (1.87 or 1.80)	1.28 (0.70)	3.09 (2.22)	1.40 (0.80)	Nil	1.4	6.9	4.1	2.0	...
7-Methyl	2.30 (1.92 or 2.02)	2.41 (2.02 or 1.92)	1.40 (1.02)	3.20 (2.40)	... ...	7.42 (7.12)	1.4	6.9	...	...	...
5,7-Dimethyl	2.21 (1.95 or 2.04)	2.58 (2.04 or 1.95)	... ...	3.35 (2.55)	... ...	7.42 (7-Me) 7.40 (5-Me) [7.07 (5-Me)] [7.18 (7-Me)]	1.4	...	...	...	1.0
2,3,7-Trimethyl	... ...	... ...	1.98 (1.20)	3.30 (2.40)	... ...	7.45 (7-Me) 7.62 (2-Me) 7.68 (3-Me) [7.42 (2- and 3-Me)] [7.14 (7-Me)]	...	6.9	...	...	...
2-Phenyl-7-methyl	...	2.35 (1.82)	1.78 (1.05)	3.40 (2.39)	... ...	7.42 (7-Me)[b] [7.10 (7-Me)]	...	6.9	...	...	...
3-Bromo	2.16	...	1.66	3.08	1.38	Nil	...	6.9	4.2	2.0	...
3-Bromo-5,7-dimethyl[c]	2.51	...	...	3.58	...	7.08 (5-Me) 7.58 (7-Me)	...	...	...	...	1.0
Parent methiodide[d]	1.85 or 1.78	1.78 or 1.85	0.74	2.27	0.87	5.83 (N–Me)	2.1	6.9	4.5	1.8	...
Parent hydrochloride[d]	1.72 or 1.69	1.69 or 1.72	0.62	2.22	0.80	Nil	2.1	6.9	4.5	1.8	...
5,7-Dimethyl methiodide[d]	1.83	1.83	...	2.39	...	5.86 (N–Me) 7.13 (5–Me) 7.21 (7–Me)	2.1	...	...	...	0.9
2,3,7-Trimethyl methiodide[d]	...	...	1.09	2.40	...	6.00 (N–Me) 7.13 (7–Me) 7.40 (2- and 3-Me)	...	6.9	...	...	...

[a] Solutions are in $CDCl_3$ (8%); numbers in parenthesis refer to 8% solution in deuteriotrifluoroacetic acid. [b] At 60° in $CDCl_3$ (concentration approximately 2%). [c] The larger shielding of H-2 is almost certainly due to steric crowding between the bromine atom and the 5-methyl grouping, and has been commented on before in related systems.[2,5] [d] Solutions are in D_2O (8%).

TABLE II

ELECTRON DENSITIES OF SOME IMIDAZO[1,2-*a*]PYRIMIDINES[a]

Compd	Type[b]	Electron density at position 1	2	3	4	5	6	7	8	9
Parent	A	1.439	1.033	1.102	1.472	0.854	1.019	0.866	1.267	0.949
	B	0.566	0.078	0.543	0.003	0.231	0.075	0.111	0.297	0.096
7-Methyl	A	1.446	1.039	1.105	1.482	0.853	1.047	0.766	1.323	0.949
	B	0.561	0.089	0.547	0.001	0.201	0.050	0.110	0.338	0.100
5-Methyl	A	1.443	1.038	1.102	1.487	0.749	1.068	0.865	1.309	0.949
	B	0.550	0.078	0.519	0.000	0.214	0.117	0.084	0.351	0.081
5,7-Dimethyl	A	1.449	1.044	1.105	1.495	0.750	1.100	0.767	1.361	0.949
	B	0.549	0.089	0.526	0.000	0.189	0.087	0.083	0.387	0.086

[a] The heteroatom model was used. [b] A, total π-electron density; B, frontier electron density.

chloroform, if became necessary to find another common solvent for these compounds in order to ascertain the structure of this material. Deuteriotrifluoroacetic acid was found to be a convenient solvent, and the various parameters in this solvent of the different compounds reported in this paper are listed in Table I.

Table I clearly shows that the structure assignment of the phenyl compound is in error. We observe that the coupling constant $J_{5,6}$ is 6.9 cps and is typical of the H-5–H-6 AB system of these compounds. Furthermore, the methyl group protons are not split by H-6, as would be expected if the methyl group were at C-5. The compound is, consequently, 2-phenyl-7-methylimidazo[1,2-*a*]pyrimidine (**3**, $R_1 = CH_3$; $R_2 = H$; $R_3 = C_6H_5$).

HMO Calculations.—In view of the success of the HMO frontier electron density calculations on imidazo[1,2-*a*]pyridines,[2] these calculations, using the same parameters, were employed in calculating the various electron densities in the imidazo[1,2-*a*]pyrimidines. The results are recorded in Table II. As is the case in the imidazo[1,2-*a*]pyridines, the frontier electron densities predict electrophilic substitution on carbon to occur at position 3, while protonation and N-methylation are predicted to occur at N-1. The total π-electron densities do not differentiate between substitution on C-2 and on C-3, while they predict N-methylation to occur at N-4.

Bromination of Some Imidazo[1,2-*a*]pyrimidines.—The bromination of the parent compound with N-bromosuccinimide (NBS) in chloroform yielded one halogen-containing compound which gave a correct analysis for $C_6H_4N_3Br$. The nmr spectrum of this compound (Figure 1, Table I) still exhibits the ABX spectrum ascribed to the protons on the six-membered ring. The AB pattern due to the five-membered ring protons is no longer present and has been replaced by a singlet. Thus, halogenation has occurred at

either C-2 or C-3. The chemical shifts of H-6 and H-7 are essentially the same in this monobromo compound as they are in the parent. The proton on C-5 is, however, more shielded in the bromo compound than in the parent. Consequently, bromination has occurred at the position predicted by the frontier electron density calculations and the compound is 3-bromoimidazo[1,2-*a*]pyrimidine (**5**). (A similar shielding of H-5 upon introduction of a bromine at C-3 has been observed in the imidazo[1,2-*a*]pyridines.[2])

Bromination of 5,7-dimethylimidazo[1,2-*a*]pyridine at C-3 causes a significant deshielding of the methyl group on C-5.[2] The monobromination product resulting from the action of NBS on 5,7-dimethylimidazo[1,2-*a*]pyrimidine shows a similarly deshielded methyl group on C-5. The protons on C-2 and C-6 are more shielded in the bromo compound than in the precursor. We can consequently conclude that bromination of 5,7-dimethylimidazo[1,2-*a*]pyrimidine also occurs at the predicted (by frontier electron densities) 3-position.

N-Methylation and Protonation of Imidazo[1,2-*a*]-pyrimidines.—A recent publication by Armarego[5] suggests that protonation of this ring system occurs at N-1. This conclusion was reached on the basis of some ultraviolet spectral studies. Our nmr data confirm this suggestion.

The nmr spectra of the parent hydrochloride and the parent methiodide are essentially superimposable upon each other (Figure 2 and Table I); thus, both protonation and N-methylation must occur at the same nitrogen atom. These spectra do not, however, permit an assignment of the site of N-methylation and protonation. If methylation occurred at N-8, one might anticipate that the resonance position of the N-methyl group be different in the methiodide of the 5,7-dimethylimidazo[1,2-*a*]pyrimidine than in the parent methiodide. Table I shows that this is not the case. If, on the other hand, methylation occurred at N-1, the chemical shift of the N-methyl group protons should certainly be effected if a substituent were present on C-2.

We do indeed find that the N-methyl group in the methiodide of the 2,3,7-trimethylimidazo[1,2-*a*]pyrimidine is at a more shielded position than in the parent methiodide and in the 7-methyl methiodide. Consequently, N-methylation and protonation occur at the predicted position, N-1.

Calculations of the Chemical Shifts.—The factors which contribute to the shielding of aromatic protons have been the subject of numerous papers.[6-13] While a semiquantitative evaluation of the effects of the ring current and changes in the π-electron charge densities upon shielding values of aromatic protons is now possible, the effects of the hybridization of the carbon atom bearing the proton under study, and the diamagnetic anisotropy of the σ framework, cannot as

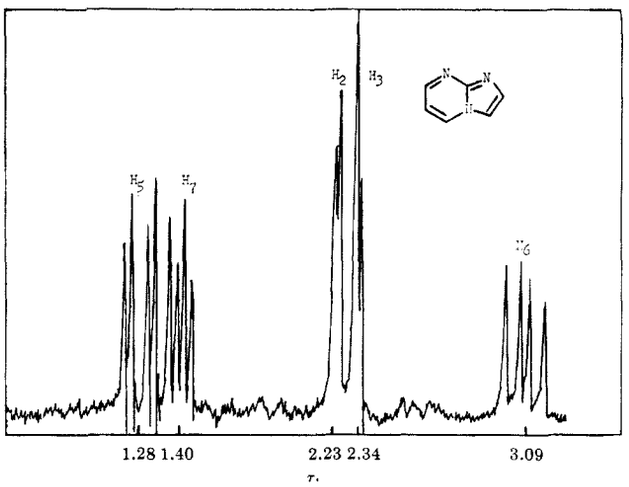


Figure 1.—The nmr spectrum of imidazo[1,2-*a*]pyrimidine.

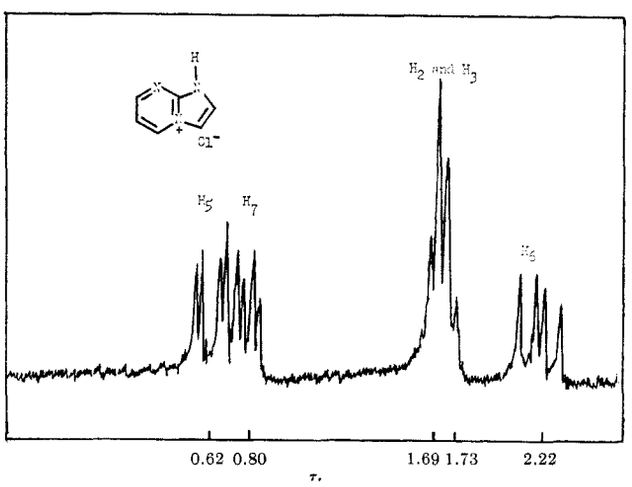


Figure 2.—The nmr spectrum of imidazo[1,2-*a*]pyrimidine hydrochloride.

yet be evaluated with any degree of certainty. The anisotropy effect of any heteroatom is best approximated by comparison with suitable reference compounds. This effect should diminish rapidly (R^{-3}) with the distance (R) between the proton under study and the heteroatom.[7]

If one compares two different chemical structures which possess essentially the same ring current and heteroatom anisotropy effects, while differing in the charge-density distribution on the various atoms in question, the chemical shifts should be predictable from the charge density–field effects only.

Two systems which fulfill these requirements for all but two protons are the imidazo[1,2-*a*]pyridines compared with the imidazo[1,2-*a*]pyrimidines (**1**).

It is a reasonable assumption that the ring currents in these two compounds are very similar. Furthermore, the effect of N-1 and that of N-4 is certainly the same in the two compounds. The effect of N-8 in the imidazo[1,2-*a*]pyrimidine might be expected to influence H-7 only.

It therefore should be possible to predict the chemical shifts of H-2, H-3, H-6, and H-5 of the imidazo-[1,2-*a*]pyrimidines from a consideration of the spectrum of imidazo[1,2-*a*]pyridine and the charge differences at the various atoms in the pyrimidine compound compared with those of the pyridine derivative.

(5) W. L. F. Armarego, *J. Chem. Soc.*, 2778 (1965).
(6) J. A. Pople, *Proc. Roy. Soc.* (London), **A239**, 541, 550 (1957).
(7) G. G. Hall, A. Hardisson, and L. M. Jackman, *Tetrahedron*, **19**, *Suppl.*, **2**, 101 (1963), and references therein.
(8) T. W. Marshall and J. A. Pople, *Mol. Phys.*, **1**, 199 (1958).
(9) T. Schaefer and W. G. Schneider, *Can. J. Chem.*, **41**, 966 (1963).
(10) M. P. Schweizer, S. I. Chan, G. K. Helmkamp, and P. O. P. Ts'o, *J. Am. Chem. Soc.*, **86**, 696 (1964).
(11) J. I. Musher, *J. Chem. Phys.*, **37**, 34 (1962).
(12) C. E. Johnson and F. A. Bovey, *ibid.*, **29**, 1012 (1958).
(13) R. McWeeny, *Mol. Phys.*, **1**, 311 (1958).

TABLE III
SEMIEMPIRICAL CALCULATION OF CHEMICAL SHIFTS (τ)

Imidazo[1,2-*a*]pyridine

	Position					
	2	3	5	6	7	8
Olefinic proton std (benzene, τ 2.73; ring-current contrib, 1.55)	4.28	4.28	4.28	4.28	4.28	4.28
Ring-current contrib	−2.02	−2.30	−2.38	−2.04	−2.04	−2.38
Charge density contrib	1.57	1.82	0.68	0.70	0.39	0.71
Total (calcd)	3.83	3.80	2.58	2.94	2.63	2.61
Obsd[a]	2.38	2.44	1.88	3.28	2.91	2.36
D (obsd − calcd)	−1.45	−1.36	−0.70	0.34	0.28	−0.25

Imidazo[1,2-*a*]pyrimidine

	Position				
	2	3	5	6	7
Olefinic proton std	4.28	4.28	4.28	4.28	4.28
Ring-current contrib	−2.02	−2.30	−2.38	−2.04	−2.04
Charge density contrib	1.46	1.81	−0.12	0.51	−0.34
D	−1.45	−1.36	−0.70	0.34	0.28
Calcd chemical shift	2.27	2.43	1.08	3.09	2.18
Obsd chemical shift	2.23	2.34	1.28	3.09	1.40

[a] These values are somewhat different from those reported in ref 1, since they represent the chemical shifts in 8% $CDCl_3$ solution.

If we assume that the chemical shifts of the protons in imidazo[1,2-*a*]pyridine are obtainable by the addition of the ring current and the field effects, then, any difference (*D*) between the observed and the calculated chemical shifts must be due to the anisotropy effects of the nitrogen atoms and any deviations due to the crudeness of the model in general. The results of these calculations are reported in Table III.

The spectrum of imidazo[1,2-*a*]pyrimidine can then be calculated by totaling the ring current and charge effects with the *D* parameters as obtained from the imidazo[1,2-*a*]pyridine.

The observed and calculated chemical shifts of the pyrimidine derivative are listed in Table III. It is clear that this approach gives satisfactory results for H-2, H-3, H-5, and H-6. The proton on C-7 of the imidazo[1,2-*a*]pyrimidine is subject to the anisotropy effect of N-8 as is evidenced by the discrepancy of the calculated and observed chemical shifts of H-7. This deviation (0.78 ppm) is of the same order of magnitude as that suggested for the N-anisotropy of a pyridine-type nitrogen atom.[14]

We wish to emphasize that these calculations represent a self-consistent set of data only, and any discrepancies in the calculations of the π-electron densities by the HMO method are largely cancelled, since the calculations for both systems were made using the same parameters.

Experimental Section[16]

Preparation of Imidazo[1,2-*a*]pyrimidines.—The imidazo[1,2-*a*]pyrimidines were prepared by condensing the appropriate 2-aminopyrimidines with the proper α-halocarbonyl compounds by the procedure described for the preparation of the imidazo-[1,2-*a*]pyridines.[2] This procedure is slightly different from that described by Ochiai[4] and affords higher yields. Purification was accomplished by chromatography on grade III neutral Woelm alumina. The imidazo[1,2-*a*]pyrimidines were eluted with ethyl acetate, and finally purified by vacuum sublimation.

Imidazo[1,2-*a*]pyrimidine, mp 217–218.5°, 69% yield.

Anal. Calcd for $C_6H_5N_3$: C, 60.49; H, 4.23; N, 35.28. Found: C, 60.26; H, 3.95; N, 35.35.

Imidazo[1,2-*a*]pyrimidine methiodide, mp 237–238.5°.

Anal. Calcd for $C_7H_8IN_3$: C, 32.20; H, 3.08; N, 16.10. Found: C, 32.46; H, 3.00; N, 16.34.

Imidazo[1,2-*a*]pyrimidine hydrochloride, mp 231–232°.

Anal. Calcd for $C_6H_6ClN_3$: C, 46.32; H, 3.89; N, 27.00. Found: C, 46.20; H, 3.85; N, 26.88.

7-Methylimidazo[1,2-*a*]pyrimidine (**3**, $R_1 = CH_3$; $R_2 = R_3 = H$), mp 167–169°, 86% yield.

Anal. Calcd for $C_7H_7N_3$: C, 63.14; H, 5.30; N, 31.56. Found: C, 63.04; H, 5.22; N, 31.38.

5,7-Dimethylimidazo[1,2-*a*]pyrimidine (**3**, $R_1 = R_2 = CH_3$; $R_3 = H$), mp 124–125°, 78% yield.

Anal. Calcd for $C_8H_9N_3$: C, 65.29; H, 6.16; N, 28.55. Found: C, 65.00; H, 6.02; N, 28.38.

5,7-Dimethylimidazo[1,2-*a*]pyrimidine, mp 255–255.5°.

Anal. Calcd for $C_9H_{12}IN_3$: C, 37.38; H, 4.18; N, 14.53. Found: C, 37.18; H, 4.00; N, 14.53.

2,3,7-Trimethylimidazo[1,2-*a*]pyrimidine (**3**, $R_1 = CH_3$; $R_2 = H$; $R_3 = R_4 = CH_3$), mp 214–215.5°, 86% yield.

Anal. Calcd for $C_9H_{11}N_3$: C, 67.05; H, 6.88; N, 26.07. Found: C, 67.25; H, 6.72; N, 26.28.

2,3,7-Trimethylimidazo[1,2-*a*]pyrimidine methiodide, mp 188–190°.

Anal. Calcd for $C_{10}H_{14}IN_3$: C, 39.61; H, 4.65; N, 13.86. Found: C, 39.47; H, 4.80; N, 13.86.

2-Phenyl-7-methylimidazo[1,2-*a*]pyrimidine (**3**, $R_1 = CH_3$; $R_2 = H$; $R_3 = C_6H_5$) was prepared by the procedure described by Ochiai and Yanai.[4] The melting points recorded by these authors for the free base, and the hydrochloride (mp 223–224 and 240–243° dec, respectively) are in agreement with the corresponding melting points (mp 224–224.5 and 242–244° dec) obtained in this investigation.

Bromination of Some Imidazo[1,2-*a*]pyrimidines.—An equal molar solution of the imidazo[1,2-*a*]pyrimidine and NBS was heated at reflux until thin layer chromatography (silica gel G, ethyl acetate–methanol 75:25) showed that all of the starting material had reacted. The bromo compounds were purified by chromatography on neutral grade III alumina by elution with ethyl acetate. The analytical samples were prepared by vacuum sublimation of the compounds from the chromatographic column.

3-Bromoimidazo[1,2-*a*]pyrimidine (**5**): reaction time, 4 hr; mp 157–158.5°; 76% yield.

Anal. Calcd for $C_6H_4BrN_3$: C, 36.39; H, 2.03; N, 21.22. Found: C, 35.97; H, 2.02; N, 21.00.

3-Bromo-5,7-dimethylimidazo[1,2-*a*]pyrimidine: reaction time, 2.5 hr; mp 247–248°; 87% yield.

(14) N. Nakagawa, Y. Kawazoe, H. Hofla, and M. Ilo, Symposium on Nuclear Magnetic Resonance, Tokyo, Nov 1961.[15]

(15) *Cf.* Makisumi, *et al.*, ref 3.

(16) The nmr spectra were obtained with a Varian A-60 instrument. Melting points are corrected. The elemental analyses were performed by Mrs. J. deBoer of this laboratory.

Anal. Calcd for $C_8H_8BrN_3$: C, 42.50; H, 3.57; N, 18.59. Found: C, 42.25; H, 3.50; N, 18.48.

Calculation of Chemical Shifts.—The ring-current calculations were done by the method of Pople.[17] The geometries of a regular hexagon and a regular pentagon were assumed for the six- and five-membered rings, respectively. The lengths of the sides were taken to be 1.08 A. Each ring was assumed to have six π electrons. Electron density field effects were calculated by the method of Schweizer and co-workers.[11] The electron densities used in these calculations are those obtained from a modified HMO calculation.[1]

(17) J. A. Pople, *J. Chem. Phys.*, **24**, 1111 (1956).

Synthesis of Purine and Pyrimidine Nucleosides of Thiopentoses[1]

BRANKO URBAS AND ROY L. WHISTLER

Department of Biochemistry, Purdue University, Lafayette, Indiana

Received October 8, 1965

Condensation of 2,3,5-tri-*O*-acetyl-4-thio-α,β-D-ribofuranosyl chloride (I) with 2,4-diethoxy-5-methylpyrimidine followed by methanolysis produces the α and β anomers of 1-(4-thio-D-ribofuranosyl)thymine (IIIa and b). When condensation was made with compound I and 2,4-diethoxypyrimidine the corresponding uracil (VIa and b) or cytosine (VIIa and b) nucleosides were produced, after methanolysis or ammonolysis. In all instances α-D and β-D anomers were formed in ratio of 1:2. A similar sequence of reactions was used for the preparation of nucleosides of 5-thio-D-xylose. A purine nucleoside of 5-thio-D-xylose was prepared by condensing compound VIII with 6-benzamido-9-chloromercuripurine. In the D-xylose series only one anomeric nucleoside was isolated.

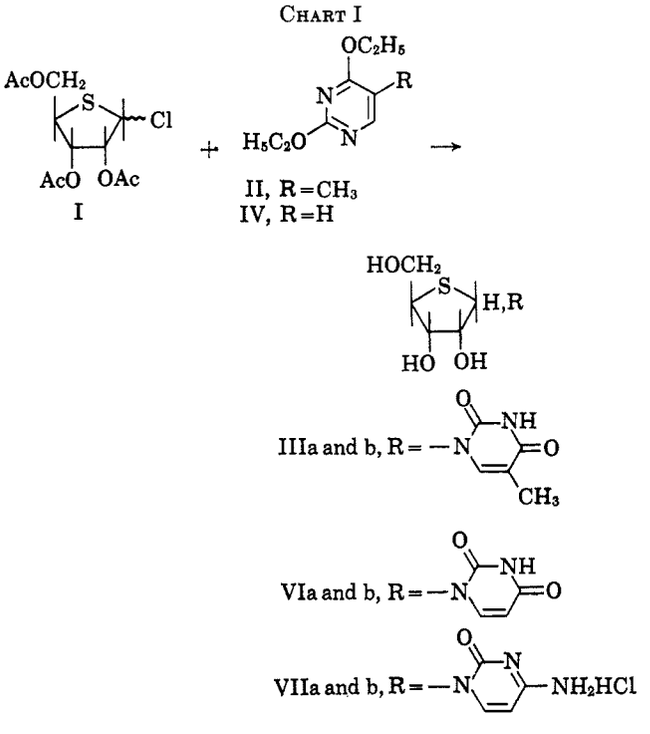
In recent years this laboratory has been active in the synthesis of aldoses in which the normal ring oxygen is replaced with a sulfur atom. Such so-called thio sugars or their derivatives represent a new class of compounds which may have unusual physiological properties.

The D and L isomers of 9-(4-thioribofuranosyl)-adenine nucleosides have been previously described.[2] We wish to report herein the synthesis of pyrimidine and purine nucleosides of 4-thio-D-ribofuranose[3] and 5-thio-D-xylopyranose.[4]

The most promising methods available for the synthesis of pyrimidine and purine nucleosides appeared to be the method of Hilbert–Johnson and the mercury salt procedure. These methods have been used here. Attempts to use the mercury procedure for the synthesis of pyrimidine nucleoside were repeatedly unsuccessful due presumably to the instability of the thio sugar.

The starting material for the synthesis of the 4-thio-D-ribofuranose nucleoside was methyl 4-deoxy-2,3-*O*-isopropylidene-4-thioacetyl-β-D-ribofuranoside. Treatment of this compound with aqueous acetic acid followed by acetolysis under the usual conditions[5] gave two anomeric 1,2,3,5-tetra-*O*-acetyl-4-thio-D-ribofuranoses. The anomeric mixture was converted to the syrupy 2,3,5-tri-*O*-acetyl-4-thio-D-ribofuranosyl chloride (I), which was further condensed with an excess of 2,4-diethoxy-5-methylpyrimidine[6] to yield the corresponding blocked pyrimidine nucleoside. In this condensation α-D and β-D anomers of 1-(2,3,5-tri-*O*-acetyl-4-thio-D-ribofuranosyl)-4-ethoxy-5-methyl-2(1H)-pyrimidinone were isolated as a syrup which was separated on a silica gel column. The first anomer had a rotation of $[\alpha]_D$ −14.9° and after methanolysis gave thymine nucleoside IIIa, $[\alpha]_D$ −44°, while the second blocked nucleoside with $[\alpha]_D$ +8° gave after methanolysis another anomer (IIIb) with a rotation of $[\alpha]_D$ +20°. (See Chart I.)

CHART I



When the sugar chloride I was condensed with 2,4-diethoxypyrimidine[7,8] under the same conditions, two anomeric forms of 1-(2,3,5-tri-*O*-acetyl-4-thio-D-ribofuranosyl)-4-ethoxy-2(1H)-pyrimidinone were isolated. The anomer Va, with a rotation of $[\alpha]_D$ +1.3°, after methanolysis gave uracil nucleoside VIa, $[\alpha]_D$ −22°, while the other anomer Vb, with a rotation of −7.4°, gave uracil nucleoside VIb, $[\alpha]_D$ +3.1°, after methanolysis. When either compound Va or Vb was treated with methanolic ammonia, the corresponding

(1) Journal Paper No. 2654 of Purdue Agricultural Experiment Station, Lafayette, Ind. Presented in part at the 149th National Meeting of the American Chemical Society, Detroit, Mich., April 1965.

(2) E. J. Reist, D. E. Gueffroy, and L. Goodman, *J. Am. Chem. Soc.*, **86**, 5658 (1964).

(3) R. L. Whistler, W. E. Dick, T. R. Ingle, R. M. Rowell, and B. Urbas, *J. Org. Chem.*, **29**, 3723 (1964).

(4) D. L. Ingles and R. L. Whistler, *ibid.*, **27**, 3896 (1962).

(5) M. S. Feather and R. L. Whistler, *Tetrahedron Letters*, **No. 15**, 667 (1962).

(6) W. Schmidt-Nickels and T. B. Johnson, *J. Am. Chem. Soc.*, **52**, 4511 (1930).

(7) G. E. Hilbert, *ibid.*, **59**, 330 (1937).

(8) G. E. Hilbert and E. F. Jansen, *ibid.*, **58**, 60 (1936).