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IDENTIFICATION BY NMR SPECTROSCOPY OF SOME ISOMERIC 1,2,4-TRIAZOLO[4,3-*a*] AND [1,5-*a*]PYRIMIDINES

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Abstract—The title compounds have been prepared with four known procedures. The mixtures of isomers obtained have been separated by countercurrent distribution and the single isomers identified by NMR spectroscopy.

The synthesis of the fused structures *s*-triazolo[4,3-*a*] and [1,5-*a*]pyrimidines has been known for a long time. The preparation has been described in several papers[2-7] and almost invariably mixtures of isomers have been obtained. The type, number and relative quantities of the reaction products appear to depend critically upon the reaction conditions (temp., acidity and time).

The identification of the various isomers, based mainly on their UV and IR spectra, is not straightforward and the published results are to a certain extent in disagreement with each other. Allen *et al.*[5] resorted to chemical evidence to ascertain the path of cyclization and the transposition reaction occurring in the course of the preparation. In the attempt to define the effect of the various reaction parameters (temp., time and acidity) on the reaction products and to provide a simple mean of identification, we have repeated several synthetic procedures in carefully controlled conditions. The different reactions are summarized in the scheme and are:

(a) reaction of 2-hydrazino-4-hydroxy-6-methylpyrimidine(1) with boiling ethylorthoformate.[4]

(b) reaction of 1 with formic acid at 50–60°.[4]

(c) reaction of 1 with boiling formic acid (2 hr reflux).[6]

(d) reaction of 1 with boiling formic acid (12 hr reflux).[2]

The NMR spectra of the isomeric mixtures thus obtained are reported in Fig. 1.

The reaction mixtures have been treated in a countercurrent apparatus and the single products isolated, purified and characterized by elemental analysis, m.p., IR and NMR spectra. The physico-chemical characteristics of the compounds are reported in the experimental part and the NMR spectral data are collected in Table 1, where the chemical shifts of the unsubstituted rings are also reported for comparison.

For the assignment of the NMR resonances, the starting assumption has been that the mild conditions of reaction (A) afford the non-transposed products 3 and 4, as reported by Allen[5] on the basis of chemical evidence. The two isomers have been separated and 4 identified through its physico-chemical properties, precisely determined by Allen.[4] Once assigned the signals of 4, those of 3 are immediately identified in the spectrum *a* of Fig. 1; at this point the other assignments are straightforward.

Once determined the resonance frequencies of the isolated isomers, it is trivial to establish the type and relative quantities of the products obtained with the four reaction procedures employed (see spectra in Fig. 1).

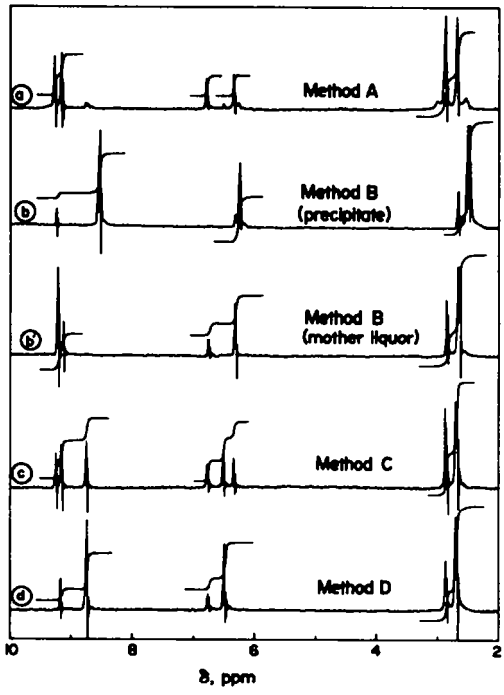


Fig. 1. NMR spectra of the mixtures of isomers at room temperature, in TFA (ν_0 = 90 MHz, TMS internal reference).

Procedure (A) yields 3 and 4 (50 and 50%) quantitatively after 12–15 hr. reflux. There is no need for an exceedingly long reaction time (72 hr) as suggested by Allen.[4] The reaction has been followed by NMR and no transposed product could be detected, even after 80 hr of reflux. Method (B) affords a mixture of 2 and 4 (87 and 13% *ca.*, respectively) and not only 4 as reported by Allen[4] (Fig. 1b).

The mother liquor of this preparation taken to dryness yields a mixture of 3 and 4 (*ca.* 29 and 71%, respectively) as shown by the NMR spectrum (Fig. 1b').

Procedure C affords a mixture of the three isomers 3, 4 and 5 (*ca.* 34, 29 and 37%, respectively) (Fig. 1c).

The longer reaction time of method D yields a mixture of 3 and 5 (*ca.* 24 and 76%, respectively) (Fig. 1d), whereas Shirakawa assigns structures 3 and 6 (reported m.ps: 300° dec and 227–229°, respectively) to these products. The very low m.p. reported by Shirakawa for 5 is very likely due to the presence of a certain amount of

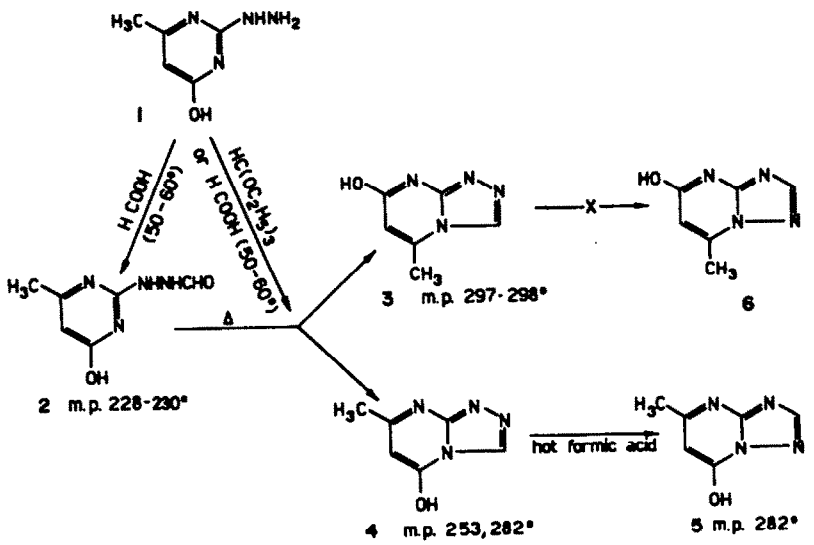
Table 1. NMR spectral data of some triazolopyrimidines (a)

	II	III	IV	(8)	V	(8)
H_2	——	——	——	——	8.74(8.18)	8.52[b](8.76)
H_3	——	9.16(8.82)	9.24(8.96)	(9.28)	——	——
H_5	6.26q(5.53)	——	——	(9.02)	——	9.00[b](9.52)
H_6	——	6.76q(5.98)	6.33q(5.66)	(7.15)	6.50q(5.82)	7.29[b](7.46)
H_7	——	——	——	(8.77)	——	8.87[b](8.98)
5-CH_3	——	2.86d(2.49)	——	——	——	——
6-CH_3	2.51d(2.04)	——	——	——	——	——
7-CH_3	——	——	2.67d(2.29)	——	2.69d(2.33)	——
2'-CHO	8.56(8.00)	——	——	——	——	——
$^4J_{allylic}$	0.8±0.1 Hz (0.8±0.1)	1.20±0.05 Hz	0.8±0.1 Hz (0.6±0.1)	——	0.8±0.1 Hz	——

(a) Chemical shifts are reported in δ units (ppm) from internal TMS, numbers in parentheses refer to DMSO-d_6 solutions; the others refer to solutions in TFA.

(b) In $CDCl_3$

(c) The δ values in DMSO-d_6 for the two NH of the side chain are 9.9 ± 0.5 and 10.6 ± 0.7 ppm; the signals are broadened by exchange with the solvent water.



Scheme 1

the other isomer, which greatly depresses the m.p. It is indeed extremely difficult to purify these products by crystallization as Shirakawa did. We could obtain the pure isomers only by countercurrent separation.

The absence of 6 among the products indicates that 3 does not undergo transposition even in the severe conditions of reaction D, while under the same conditions 4 is completely transposed to 5.

The intermediate 2-(2'-formylhydrazino)-4-hydroxy-6-methylpyrimidine(2), obtained by procedure (B), has not been previously described, and indeed Allen *et al.*[4] could not isolate it. The NMR spectrum in DMSO (Table 1) clearly shows the two NH signals of the formylhydrazino sidechain, thus ruling out the possibility of an hydrate of either 4 or 5. The isolation of this intermediate clarifies the route of cyclization which leads to the title compounds and the NMR parameters provide an easy and sure way for their identification.

EXPERIMENTAL

Chemicals and apparatus. All reagents were Merck PA products and were used without further purification.

The IR spectra were recorded with a Perkin-Elmer mod. 157 spectrometer, in Nujol mulls.

The NMR spectra were obtained with a Bruker HX90 spectrometer operating at 90 MHz; TMS was used as internal standard and for field-frequency lock.

M.ps were determined on a Büchi-Tottoli apparatus and are uncorrected.

Isolation and characterization of the products. The synthetic procedures used are described in the literature;[2,4,5] only the preparation of 2, not previously isolated, will be reported in detail.

The separation of the mixtures of isomers was conducted in a countercurrent distribution apparatus (H. O. Post, Scientific Instruments Co., 100 tubes), using water as lower phase and EtOAc as upper phase. The solvents were previously saturated with each other.

Table 2. UV absorption spectra of some triazolopyrimidines

Compound	$\lambda_a^{(a)}$	$\lambda_b^{(a)}$	$\lambda_c^{(a)}$	ref.
2-(2'-formylhydrazino)-4-hydroxy-6-methylpyrimidine (II)	209(13.7) 225(11.2) sh		282(6.6)	this work
5-Methyl-7-hydroxy-1,2,4-triazolo 4,3-a pyrimidine (III)	210(22.7)	248(7.0)		5,9
5-Hydroxy-7-methyl-1,2,4-triazolo 4,3-a pyrimidine (IV)	210(17.7)	246(4.8)	294(6.8)	5,9
5-Hydroxy-7-methyl-1,2,4-triazolo 1,5-a pyrimidine (V)		256(6.4)	278(10.8)	5,9

(a) wavelength is in mμ; the extinction, in parentheses, is $\varepsilon \times 10^{-3}$, solvent is methanol.

2-(2'-formylhydrazino)-4-hydroxy-6-methylpyrimidine 2

An heterogeneous mixture of 1 (5 g) and 98% formic acid (7.5 ml) was kept, with occasional stirring, on a steam bath at 55° for 1 hr (method B). The heterogeneous system was then cooled to room temp and the white ppt separated by filtration and desiccated under vacuum at 40° (yield 2.8 g). The solid mixture obtained was treated in the countercurrent apparatus described and 2 thus isolated dissolved in the minimum amount of water. Twice this amount of anhydrous EtOH was then added, and the soln kept for 2 days in a deep-freezer. A white amorphous ppt was then isolated (m.p. 228–230°; IR (Nujol): 705, 765, 838, 862, 919, 960, 982, 1005, 1018, 1053, 1082, 1195, 1244, 1299, 1364, 1399, 1510, 1580–1715, 3289). (Found: C, 42.69; H, 4.61; N, 33.17. Calc. for $C_6H_8N_4O_2$: C, 42.86; H, 4.79; N, 33.32%).

5-Methyl-7-hydroxy-1,2,4triazolo[4,3-a]pyrimidine (3). The isolated isomer was recrystallized from anhydrous EtOH (m.p. 297–298, dec.; IR (Nujol): 743, 866, 955, 972, 1013, 1024, 1037, 1218, 1279, 1416, 1506, 1590, 1661, 1689, 2720, 3420). (Found: C, 47.99; H, 4.05; N, 37.44. Calc. for $C_6H_6N_4O$: C, 48.00; H, 4.02; N, 37.32%).

5-Hydroxy-7-methyl-1,2,4triazolo[4,3-a]pyrimidine (4) was recrystallized from water (m.p. 253, 282; the two successive m.ps, originally observed by Shirakawa, correspond to the transposition of 4 to 5 and melting of 5, respectively, as confirmed by recording the NMR spectrum of the product obtained after the first softening, which is identical to that of 5; IR (Nujol): 708, 755, 835, 881, 961, 991, 1009, 1033, 1136, 1176, 1200, 1244, 1408, 1568, 1631, 1715, 3125). Found: C, 47.87; H, 3.97; N37.47%.

5-Hydroxy-7-methyl-1,2,4triazolo[1,5-a]pyrimidine (5) was recrystallized from anhyd. EtOH (m.p. 282–283; IR (Nujol): 708, 750, 813, 822, 848, 921, 958, 1017, 1057, 1140, 1153, 1190, 1208, 1250, 1309, 1406, 1570, 1618, 1669, 1706). Found: C, 47.84; H, 3.96; N, 37.09%.

The NMR and UV spectral data for 2, 3, 4 and 5 are reported in the Tables 1 and 2. The UV spectra have been divided, for convenience, into three regions, *a*, *b*, and *c*, according to the scheme followed by Allen *et al.*[5,9] For the intermediate 2 no *b* band could be detected, but the *a* band shows a shoulder (Table 2); this behaviour could be related to the open structure of 2 as compared with the fused ring structures of the other compounds examined.

REFERENCES

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[2]K. Shirakawa, *Yakugaku Zasshi* **78**, 1395 (1960); *Chem. Abstr.* **53**, 8150e (1958).

[3]K. Shirakawa, *Ibid.* **80**, 1542 (1960); *Chem. Abstr.* **55**, 10450e (1960).

[4]C. F. H. Allen, H. R. Beilfuss, D. M. Burness, G. A. Reynolds, J. F. Tinker and J. A. Van Allan, *J. Org. Chem.* **24**, 787 (1959).

[5]C. F. H. Allen, G. A. Reynolds, J. F. Tinker, and L. A. Williams. *Ibid.* **25**, 361 (1960), and earlier papers in the series.

[6]B. Camerino and T. La Noce, *Fr. Pat.* 1 220, 810 (11 Jan. 1959); (Filed 24 Oct. 1956).

[7]B. Camerino and T. La Noce, *Ger. Pat.* 1 071, 088 (17 Dec. 1959); (Claims priority, application Italy, 18 Jan. 1957); *Chem. Abstr.* **55**, 16576f (1961).

[8]W. W. Paudler and L. S. Helmick, *J. Heterocyclic Chem.* **3**, 269 (1966).

[9]C. F. H. Allen, H. R. Beilfuss, D. M. Burness, G. A. Reynolds, J. F. Tinker and J. A. Van Allan, *J. Org. Chem.* **24**, 779 (1959).