New Polyazaheterocycles. 9-Methyl-di-*s*-triazolo[4,3-*a*:4,3-*c*]pyrimidine and 9-Methyl-*s*-triazolo[4,3-*c*]tetrazolo[1,5-*a*]pyrimidine

T. La Noce and A. M. Giuliani

Consiglio Nazionale delle Ricerche, Rome, Italy

Received November 15, 1974

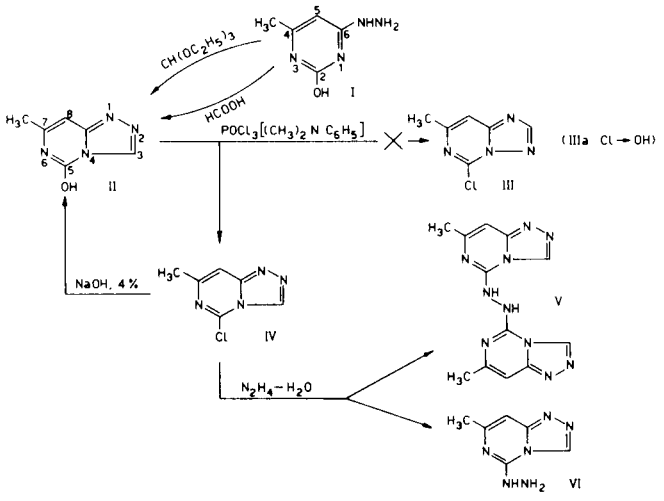
9-Methyl-di-*s*-triazolo[4,3-*a*:4,3-*c*]pyrimidine and 9-methyl-*s*-triazolo[4,3-*c*]tetrazolo[1,5-*a*]-pyrimidine have been synthetized from 4-hydrazino-7-methyl-*s*-triazolo[4,3-*c*]pyrimidine. Structural assignments based on nmr, ir and chemical manipulations are discussed.

The characteristic tautomerism of the hydrazine groups *ortho* to heterocyclic nitrogen atoms, has been exploited to condense an *s*-triazole ring on the N_3-C_4 bond of a pyrimidine ring and then an *s*-triazole ring, or alternatively a tetrazole ring, on the N_1-C_2 bond of the same pyrimidine ring.

The resulting new polyazatricyclic compounds 9-methyl-di-*s*-triazolo[4,3-*a*:4,3-*c*]pyrimidine and 9-methyl-*s*-triazolo[4,3-*c*]tetrazolo[1,5-*a*]pyrimidine, are the subject of the present paper.

In the course of previous research aimed at the synthesis of new heterocyclic structures similar to purines, one of us (1) obtained 5-hydroxy-7-methyl-*s*-triazolo[4,3-*c*]pyrimidine (II) by reaction of 2-hydroxy-4-methyl-6-hydrazinopyrimidine (I) with formic acid. Compound II, by reacting for a long time with phosphorus oxychloride in the presence of *N,N'*-dimethylaniline, affords the 5-chloro derivative IV

Scheme I



(2). Compound IV, when treated with hydrazine, yields 5-hydrazino-7-methyl-*s*-triazolo[4,3-*c*]pyrimidine (VI), which can be considered the starting material for the present work.

The course of the reactions and the structures of the compounds have been determined essentially by ir and nmr spectroscopy.

Scheme I shows the transpositions which could have taken place in our bicyclic systems (3a-b). The mechanisms proposed for this type of rearrangements have recently been reviewed by M. Tišler (3c).

It has been shown by Camerino and co-workers (4) that in the step I → II no transposition occurs in the bicyclic system II. This conclusion was based on the fact that the same product II had been obtained by cyclization both with formic acid and with a non-acidic formylating agent (triethyl orthoformate). Their proof, however, is not conclusive considering the results reported by Paudler and Helmick (5), who obtained two isomeric trimethyl-*s*-triazolopyrimidines by reaction of 4,6-dimethyl-2-hydrazinopyrimidine with ethyl orthoacetate. We have repeated the cyclization reaction of I with ethyl orthoformate and followed it by ir and nmr spectroscopy. Samples of the reaction mixture taken at different times indicate that only one isomer is slowly formed from I (from the nmr spectra: 30% after 5 hours, 55% after 12 hours and 100% after 25 hours). Given the conditions of the reaction (cyclization by orthoformate) and the presence of only one product, we assume that II is the exclusive reaction product, without simultaneous formation of 5-hydroxy-7-methyl-*s*-triazolo-[2,3-*c*]pyrimidine (IIIa).

The long time required for the cyclization of the hydrazinopyrimidine with ethyl orthoformate is not surprising, since Allen *et al.* (3a) refluxed for 72 hours the 2-hydrazino-4-methyl-6-hydroxypyrimidine in ethyl orthoformate in order to obtain the *s*-triazolo[4,3-*a*]pyrimidines.

TABLE I

Chemical Shifts of Some Polyazaheterocycles (a)

Compound	Position of substituent (b,c)									J (Hz) (c)
	2	3	4	5	6	7	8	9	10	
I			2.49d	6.19q						1.1
2-Mercaptomethyl-4-methyl-6-hydrazinopyrimidine	2.83s		2.60d	6.83q						0.7
2-Mercaptomethyl-4-methyl-6-chloropyrimidine (d)	2.86s		2.76d	7.46q						0.6
2-Mercaptomethyl-4-methyl-6-formylhydrazinopyrimidine	2.73s (2.42s)		2.54d (2.22d)	6.61q (6.14q)	9.45NH; 8.49CHO (9.97 and 9.16NH; 8.12CHO)					0.6 (0.6)
II		8.93s				2.74d	7.10q			0.8
IV		9.08s (8.68s)				2.90d (2.56d)	8.01q (7.80q)			0.8 (0.90 ± 0.05)
V		8.96s (8.52s)		(10.50)		2.69d (2.27d)	6.92q (6.91q)			0.8
VI		8.90s (8.39s)		(9.21NH; 4.62NH_2)		2.80d (2.40d)	7.50q (6.85q)			0.6 (0.75 ± 0.05)
VII		9.08s (8.61s)				9.82s (9.37s)		3.12d (2.71d)	7.85q (7.30q)	1.0 (1.20 ± 0.05)
VIII		9.01s						3.48d	7.29q	1.1
IX		8.98s				3.03s		3.23d	7.60q	1.1
X		8.97s						2.82d	7.66q	0.7
7,9-Dimethyl-di-*s*-triazolo-[4,3-*a*:4,3-*c*]pyrimidine		8.88s				2.41s		2.77d	7.41q	0.65 ± 0.05

(a) Chemical shifts are reported in δ units from TMS as internal reference; numbers in parentheses refer to spectra in DMSO-d_6 solutions, others refer to TFA solutions; t = 28 ± 1°. (b) As from scheme 1 and 2. (c) Reading accuracy ± 0.02 ppm on δ and ± 0.1 Hz on J, unless otherwise indicated in the table. (d) Varian Cat. 126, spectrum at 60 MHz in chloroform: δ_{H_5} 6.85; δ_{CH_3} 2.55 and 2.45 ppm.

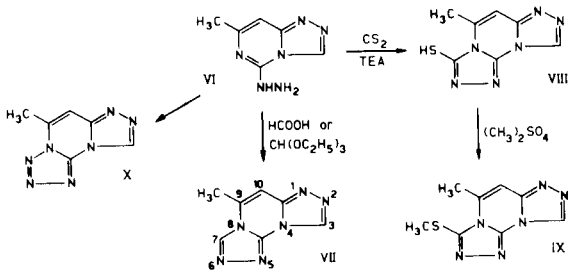
Compound II, when heated for 15 minutes at 80-90° in 1*N* sodium hydroxide solution, under the conditions indicated by Miller and Rose (3b), remained unchanged. This result supports the stability of the bicyclic system II. Not even treatment with phosporus oxychloride induced the transposition; indeed IV yielded starting material II when refluxed for 15 minutes with a 4% aqueous solution of sodium hydroxide.

As no transposition is observed following treatment with a strong alkali like sodium hydroxide, such a reaction should also be ruled out when IV is treated with hydrazine hydrate to give VI.

The comparison of the nmr spectra of II and VI (Table I) in TFA shows that the chemical shift of the proton in 3 is almost identical for the two compounds (8.93 and 8.90 ppm for II and VI respectively), thus supporting the preceding conclusion. No direct comparison is possible with the spectrum of IV since the halogen substituent on the aromatic bond system shifts all the resonances downfield (Table I). Inefficient stirring during the reaction led to simultaneous formation of VI and 1,2-bis-(7-methyl-5-*s*-triazolo[4,3-*c*]pyrimidinyl)hydrazine (V) in the approximate ratio of 5 to 1.

The third heterocyclic ring was formed (Scheme 2) by cyclization of VI both with formic acid and ethyl orthoformate.

Scheme 2



The same compound, 9-methyl-di-*s*-triazolo[4,3-*a*:4,3-*c*]-pyrimidine (VII), was obtained with both reactants. We assume that no transposition took place since a single compound was obtained and the reaction with the orthoformate occurred in a very short time (1 hour reflux); these arguments however are not completely unquestionable (5).

The use of a non-acidic condensing agent (ethyl orthoformate) is to be preferred because, as observed by Shiho and Tagami (6), it does not lead to pigment formation.

The cyclization of VI with carbon disulphide, under the conditions suggested by Broadbent *et al.* (7) for similar bicyclic compounds, yielded 7-mercapto-9-methyl-di-*s*-triazolo[4,3-*a*:4,3-*c*]pyrimidine (VIII). This product was also methylated at the thiol group with dimethylsulphate to give IX.

To prepare the second tricyclic structure, where one triazole ring is substituted by a tetrazole ring (Scheme 2), compound VI was reacted with nitrous acid. The 9-methyl-*s*-triazolo[4,3-*c*]tetrazolo[1,5-*a*]pyrimidine (X) was obtained.

Work is now in progress to assess the microbiological activity and the pharmacological properties of all the new compounds.

EXPERIMENTAL

Instruments.

All melting points were determined on a Büchi-Tottoli apparatus and are uncorrected. The infrared spectra were recorded on a Perkin-Elmer, Model 137 spectrophotometer.

For the nmr spectra, a Bruker HX90 instrument, operating at 90 MHz, was used. TMS was added to each sample as reference and for field stabilization.

Preparation.

We consider it useful to describe here also the syntheses of some compounds already known and covered by patent (1,2), giving the experimental details of the preparations and the physicochemical characteristics not reported in the patent.

5-Hydroxy-7-methyl-*s*-triazolo[4,3-*c*]pyrimidine (II) (1).

Method A.

A solution of 10 g. of 2-hydroxy-4-methyl-6-hydrazino pyrimidine (I) in 100 ml. of 98-100% formic acid was refluxed for 2 hours in an oil bath (125°). The excess acid was removed under reduced pressure (12-15 mm Hg) and the pale yellow residue was warmed for 1 hour at 90° under vacuum. The crude product was treated with decolorizing charcoal and crystallized from water. Compound II was obtained as white flakes (7 g.). An additional 0.8 g. of useful product was obtained from the mother liquor, total yield 7.8 g. (73%), m.p. 271-272°; ir (nujol mull): 1770, 1640, 1550, 1375, 1215, 1190, 1040, 1000, 970, 920, 815, 760 cm^{-1}.

Method B.

Compound I (1.4 g.) and 25 ml. of ethyl orthoformate were refluxed for 25 hours. During this time, the hydrazine derivative, only slightly soluble, was slowly transformed into the bicyclic compound II, which too has a low solubility in the reaction solvent. The yield was almost quantitative. The physical properties of this compound (ir, nmr, mixed m.p.) were identical to those reported for the same substance as obtained with method A.

Method C.

5-Chloro-7-methyl-*s*-triazolo[4,3-*c*]pyrimidine (IV) (0.337 g.) was refluxed for 15 minutes with 5 ml. of a 4% aqueous sodium hydroxide solution. The resulting orange-yellow solution, after cooling, was neutralized with glacial acetic acid. The precipitate, in the form of thin plates, was collected and crystallized from water, yield 0.185 g. (62%). This compound was identical with that obtained by method A.

5-Chloro-7-methyl-*s*-triazolo[4,3-*c*]pyrimidine (IV) (2).

Compound II (24 g.), 720 ml. of phosphorus oxychloride and 60 ml. of *N,N*-dimethylaniline was refluxed for 5 hours in an oil bath (130°). The excess solvent was removed under reduced pressure and the residue was poured into *ca.* 1 kg. of an ice-water

mixture. The mixture was stirred for about 15 minutes and the golden yellow flakes were separated and washed with ice-cooled water. After drying at 80° under reduced pressure, 18.2 g. of IV was obtained (67.5%), m.p. 152-154°. The product, of adequate purity for use in the next synthetic steps, could be recrystallized from ethanol (after treatment with decolorizing carbon) and obtained as white translucent thin plates with the same melting point; ir (nujol mull): 1620, 1460, 1280, 1245, 1180, 1035, 995, 938, 873, 808, 758 cm^{-1}.

5-Hydrazino-7-methyl-*s*-triazolo[4,3-*c*]pyrimidine (VI) and 1,2-bis-(7-methyl-5-*s*-triazolo[4,3-*c*]pyrimidinyl)hydrazine (V).

A solution of 27 g. of 85% hydrazine hydrate diluted with 60 ml. of anhydrous ethanol was added slowly and with precaution to a suspension of 18 g. of IV in 225 ml. of anhydrous ethanol. After addition of one third of the hydrazine solution a white abundant precipitate started forming. When all of the hydrazine had been added, the solution was warmed on a steam bath for 30 minutes. The mixture was then cooled in an ice-water bath, the precipitate was separated and washed 2-3 times with small amounts of ice water, and 14.2 g. of the product, m.p. 200°, (a mixture of V and VI) was collected after drying *in vacuo* at 80°. Crystallization from water (650 ml.) afforded, abundantly, pure VI as white thin plates (10 g.), m.p. 220-221°; ir (nujol mull): 3350, 1645, 1610, 1325, 1265, 1230, 1200, 1140, 932, 820, 766, 747 cm^{-1}.

The fraction not soluble in water (V) (2.6 g., m.p. 263-265°) was recrystallized from ethanol (1 g. in 400 ml. of ethanol) as white needles, m.p. 294-295° dec.; ir (nujol mull): 3400, 1550, 1300, 1265, 1185, 1120, 1010, 970, 895, 838, 728, 710 cm^{-1}.

Anal. Calcd. for $C_{12}H_{12}N_{10}$: C, 48.64; H, 4.08; N, 47.28. Found: C, 48.64; H, 4.25; N, 47.10.

9-Methyl-di-*s*-triazolo[4,3-*a*:4,3-*c*]pyrimidine (VII).

Method A.

Compound VI (0.656 g.) suspended in 10 ml. of ethyl orthoformate was refluxed for 1 hour. During heating the solid residue assumed different colours from red to dark yellow. The reaction mixture was cooled to room temperature and the precipitate filtered off. After drying 0.632 g. of VII was obtained (90.8%). Crystallization from methanol afforded pale green prismatic needles, m.p. 291-292° dec.; ir (nujol mull): 3050, 1660, 1590, 1335, 1300, 1280, 1255, 1215, 1170, 1115, 965, 945, 930, 850, 838, 795, 740, 698 cm^{-1}.

Anal. Calcd. for $C_7H_6N_6$: C, 48.27; H, 3.47; N, 48.26. Found: C, 48.55; H, 3.57; N, 48.22.

Method B.

Compound VI (0.656 g.) was refluxed for 2 hours in 98-100% formic acid (10 ml.). The resulting bright yellow solution was evaporated to dryness under reduced pressure (15 mm Hg). The residue was slurried with ethyl ether, collected and dried at 80°, yield 0.686 g. (98.5%); m.p. 289-291°. The product has the same ir and nmr characteristics as the substance obtained by method A; its melting point was not depressed by A.

7-Mercapto-9-methyl-di-*s*-triazolo[4,3-*a*:4,3-*c*]pyrimidine (VIII).

Compound VI (2.46 g.), 9 ml. of carbon disulphide, 18 ml. of 1-butanol and 5.6 ml. of triethylamine were refluxed together for 8 hours. During the first hour of reaction lively evolution of hydrogen sulphide was observed together with foam formation. The mixture was allowed to stand overnight and the precipitate which formed was then collected and washed twice with butanol. After drying, 2.76 g. of ivory white product was obtained (89.6%). A sample for the elemental analysis was recrystallized from DMF; no melting was observed up to 300°; ir (nujol mull): 2720-2550, 1675, 1615, 1540, 1345, 1290, 1250, 1225, 1170, 1135, 1070, 1045, 1015, 957, 890, 855, 738 cm^{-1}.

Anal. Calcd. for $C_7H_6N_6S$: C, 41.06; H, 2.96; N, 40.87; S, 15.52. Found: C, 40.76; H, 2.93; N, 40.76; S, 15.58.

7-Methylmercapto-9-methyl-di-*s*-triazolo[4,3-*a*:4,3-*c*]pyrimidine (IX).

One g. of VIII was added to a solution of 7.1 g. of sodium carbonate in 15 ml. of water. Dimethyl sulphate (0.5 ml.) was added, with stirring and dropwise, to the resulting suspension, at room temperature. Stirring was continued for 1 hour at room temperature and then for 30 minutes at 60°. The mixture was allowed to stand for two days. The product IX, also, is only slightly soluble in the aqueous solvent. The precipitate was collected and washed with water to neutrality. Yield 0.9 g. (84.9%). The product was recrystallized from methylcellosolve to yield white translucent leaflets, m.p. 255-256°; ir (nujol mull): 3070, 1660, 1600, 1535, 1360, 1330, 1280, 1230, 1180, 1140, 970, 925, 857, 804, 740, 698 cm^{-1}.

Anal. Calcd. for $C_8H_8N_6S$: C, 43.62; H, 3.66; N, 38.16. Found: C, 43.89; H, 3.65; N, 38.14.

9-Methyl-*s*-triazolo[4,3-*c*]tetrazolo[1,5-*a*]pyrimidine (X).

A solution of 0.207 g. of sodium nitrite in 2.5 ml. of water was added dropwise to a suspension of 0.492 g. of VI in 20 ml. of a 12% aqueous solution of acetic acid, maintained at 0-5°. The precipitation of an abundant orange-yellow compound began at once. When all the nitrite solution had been added, the mixture was stirred for 1 hour at room temperature. During this time the precipitate became bright red and changed from amorphous to a crystalline form. After drying *in vacuo* at 60°, 0.350 g. (66.7%) of X was obtained. Recrystallization from methanol yielded the compound X as translucent bright red plates, m.p. 192-193° dec.; ir (nujol mull): 3050, 1660, 1570, 1535, 1320, 1265, 1320, 1265, 1230, 1175, 1160, 1140, 1110, 1075, 1045, 970, 955, 930, 870, 790, 748 cm^{-1}.

Anal. Calcd. for $C_6H_5N_7$: C, 41.26; H, 3.03; N, 55.92. Found: C, 41.14; H, 2.88; N, 55.98.

Nmr Spectra.

All the pertinent data are collected in Table I, together with those of similar systems, reported for comparison. A long distance coupling (allylic) was observed between the methyl on the pyrimidine ring and the *ortho* proton, for all the substances under study.

Acknowledgments.

We wish to thank Profs. F. Pocchiari and A. Tonolo for the kind hospitality in the laboratories of Istituto Superiore di Sanità (Rome) and Dr. A. Mazzeo Farina of the analytical chemistry division of the same Institute for elemental analyses. We thank also Prof. R. Passino of Istituto di Ricerca sulle Acque (National Research Council - Italy) for his assistance.

REFERENCES

(1) B. Camerino and T. La Noce, German Patent 1,074,589 (Feb. 4, 1960); *Chem. Abstr.*, 55, 19967e (1961).

(2) B. Camerino and T. La Noce, French Patent 1,205,144 (Jan. 29, 1960).

(3a) C. F. H. Allen, H. R. Beilfuss, D. M. Burness, G. A. Reynolds, J. F. Tinker, and J. A. VanAllan, *J. Org. Chem.*, **24**, 787 (1959). (b) G. W. Miller and F. L. Rose, *J. Chem. Soc.*, 5642 (1963). (c) M. Tišler, Chim. Ind. (Milan), **55**, 39 (1973).

(4) B. Camerino, G. Palamidessi and R. Sciaky, *Gazz. Chim. Ital.*, **90**, 1821, 1830 (1960).

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

(6) D. I. Shiho and S. Tagami, *J. Am. Chem. Soc.*, **82**, 4044 (1960).

(7) W. Broadbent, G. W. Miller and F. L. Rose, *J. Chem. Soc.*, 3369 (1965).