Tetrahedron Vol. 43, No. 11, pp. 2497 to 2504, 1987
Printed in Great Britain.

0040–4020/87 $3.00 + .00
Pergamon Journals Ltd.

ON TRIAZOLES XI[1]. STRUCTURE ELUCIDATION OF ISOMERIC 1,2,4-TRIAZOLOPYRIMIDINONES[2].

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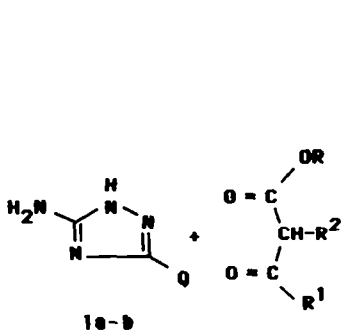
(*Received in UK* 9 *April* 1987)

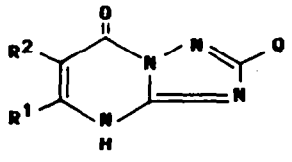
Abstract - The structure of isomeric 3 - 6 type triazolo-pyrimidinones and their N-methylated and N-benzylated derivatives was elucidated. In spite of the good agreement between the carbonyl bands of derivatives 3 - 6 (R^1= CH_3, R= H, Q=SCH_3) and their structure the IR method did not prove to be characteristic in general for the above structures. In contrast to the results reported previously it was found that the 3 - 6 type derivatives are well characterised by their UV spectra taken in neutral solution.

The ^{13}C-NMR spectra gave an unequivocal proof of the above structures corroborating the conclusions drawn from the UV measurements.

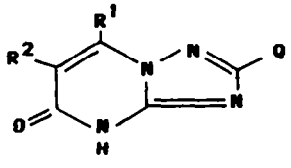
The reaction of 3-substituted-5-amino-1,2,4-triazoles (1) with beta-keto-esters (2) is ambiguous often giving the mixture of 3 - 6 type 1,2,4-triazolo-pyrimidinones (Scheme 1). As it was shown previously[3] the structure determination of products isolated is a major problem in this field. For this reason the structure-elucidation of the novel condensed ring systems[4] prepared by the reaction of 1 type triazoles with different cyclic beta-keto-esters [2, R^1 and R^2 form together with the -CH-CO- moiety a homo-, or heterocyclic ring (Scheme 1)] required - as models - the spectral data of all possible (3 - 6 type) triazolo-pyrimidinone isomers of unambiguously proved isomeric and tautomeric structure.



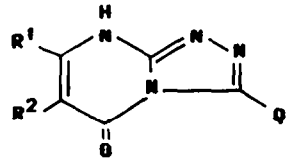
1a-b



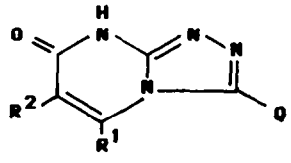
3a-b



4a-b



5a-b



6a-b

a Q= SCH_3, R^1 = CH_3, R^2= H

b Q= morpholino, R^1 = CH_3, R^2= H

Scheme 1

As model compounds representing the 3 - 6 type triazolo-pyrimidinones the four possible isomers 3a - 6a (Q= SCH_3, R^1= CH_3, R^2= H) derived from the reaction of 3-methylthio-5-amino-1*H*-1,2,4-triazole (1, Q= SCH_3) and acetoacetic acid esters

Table 1

Compound	M.p. (C°) our data (Lit. data)	IR (cm^{-1}) our	IR (cm^{-1}) Lit.[6] data	IR (cm^{-1}) our	IR (cm^{-1}) Lit.[6]	UV λ_{max} ($\varepsilon .10^{-3}$) our data EtOH	10 % EtOH +90 % 0.1 N HCl	10 % EtOH +90 % 0.1 N NaOH	Lit. data (MeOH)	Lit. data[3a] given for the Q= H analogues (H_2O) pH=2	pH=10
3a	290-291.5 (285-286[5])	1740 1720 1645 1595 1525 1460	1667 1626 1563	1410 1385 1355w 1320wsh 1295 1270	1325	228 (24.6) 265 (9.6)	227 (23.0) 265 (12.6)	228 (25.4) 281 (9.9)	229 (24.7)[5] 267 (10.2)	238(3.8) 275(8.8)	255(6.2) 285 (11.9) 295sh(8.2)
4a	286-288 (280-281[6])	1705 1585 1515 1460 1425	1695 1582	1385 1315wsh 1295 1250	1325	209 (20.4) 290 (8.8)	287 (10.6)	285 (7.5)	292 (9.4)[6']	269 (5.9)	239sh(4.5) 281 (3.8)
5a	305-307 (280-281[5])	1720 1641 1528 1468 1418 1395	1709 1639 1575	1375 1350 1310 1290 1275		200 (9.3) 231 (9.6) 260 (4.3) 309 (4.9)	231 (9.5) 258 (4.3) 303 (4.7)	231 (10.0) 271 (5.0) 314 (5.7)	231 (14.2)[5] 260 (7.0) 309 (7.1)	236 (4.5) 293 (10.8)	255 (5.2) 265sh(4.3) 309 (14.0) 320sh (11.4)
6a	276-278 (254[5])	1690 1597 1475 1433 1408	1685 1600	1379 1315wsh 1288wsh		230 (17.3) 252sh(8.4)	228 (16.6) 252sh(7.5)	231 (20.2) 252sh(8.2)	229(22.4)[5] ≈300sh(1.2)	246(2.5)	261sh(2.3) 282 (5.7)
3b	336-338	1700w 1663 1628 1583 1543 1508		1445 1402 1381 1327 1273		228 (26.1) 270 (10.0)	226 (26.7) 270 (11.3)	232 (32.9) 281 (9.5)			
4b	248-250	1676 1634 1583 1564 1499		1452 1412 1371 1337 1275		208 (33.2) 294 (8.1)	203 (27.1) 293 (9.7)	221 (27.2) 297 (7.9)			
3c	213-215 (160-170[5])*	1705 1690 1610 1560		1470 1331 1294 1271		232 (25.0) 270 (12.1)	230 (24.5) 271 (13.7)	231 (23.2) 271 (12.8)	231 (22.0) 270 (9.8)		
4c	180-182	1680 1630w 1550 1480		1435 1395 1365 1270		206 (26.5) 289 (10.2)	205 (31.0) 286 (10.6)	220 (21.9) 284 (10.3)			

(2, $R^1 = CH_3$, $R^2 = H$) were chosen. Derivatives 3a, 5a and 6a (Q= SCH_3, $R^1 = CH_3$, $R^2 = H$) were prepared by known methods[5]. Derivative 4a (Q= SCH_3, $R^1 = CH_3$, $R^2 = H$) described by a different synthetical route previously[6] was obtained from the reaction mixture of 3-methylthio-5-amino-1*H*-1,2,4-triazole (1, Q= SCH_3) and ethyl β-ethoxy-crotonate.

The UV spectra of derivatives 3a–6a (Q= SCH_3, $R^1 = CH_3$, $R^2 = H$) obtained were in good agreement with those of given in the literature (Table 1). In contrast their IR data recorded in solid state (KBr pellets) differed significantly from those of reported previously[6] (Table 1).

Our IR data well followed the rule formulated by Allen and coworkers[7] in the course of their study of derivatives 3, 5 and 6 (Q= H or CH_3, $R^1 = CH_3$ and $R^2 = H$) according to which the higher √C=O frequency is expected in case of the "ring acylated" i.e.

Table 1 - Continued

Compound	M.p. (C°) our data (Lit. data)	IR (cm^{-1}) our	Lit.[6] data	our	Lit[6]	UV λ_{max} ($\varepsilon.10^{-3}$) EtOH	our data 10 % EtOH +90 % 0.1 N HCl	10 % EtOH +90 % 0.1 N NaOH	Lit. data (MeOH)	Lit. data[3a] given for the Q= H analogues (H_2O) pH=2	pH=10
5c	197-199 (195-196[5])	1700 1682 1589 1545 1460		1414 1394 1323w 1300w		202 (16.2)	201 (16.0) 235 (7.9) 233 (9.4) 263 (9.4) 261 (7.9) 313 (10.4)	306 (7.9)	234 (9.0) 235 (8.0) 262 (8.1) 263 (9.0) 312 (10.3) 314 (10.4)		
6c	218-220 (218[5])	1682 1570 1485 1447		1421 1400 1268 1254		228 (18.5)	226 (18.3) 238sh(15.4) 268sh(2.0)	226 (18.6) 238sh(15.3) 264sh(2.5)	229 (19.4) 238sh(15.5) 264sh(2.3)		
3d	264-265	1674 1616 1587 1556 1458		1429 1402 1371 1331 1273			230 (27.7) 274 (11.5)	230 (29.0) 274 (12.3)	230 (29.0) 274 (12.3)		
3e	145-147	1709 1686 1610 1564 1466		1452 1373wsh 1358wsh 1296 1273			232 (26.3) 273 (14.6)	231 (24.8) 271 (14.8)	232 (21.4) 271 (12.4)		
4e	136-137	1660 1540 1485 1440w		1360wsh 1315wsh 1265 1245			209 (18.2) 291 (7.9)	206 (22.0) 287 (9.3)	220 (20.9) 288 (9.1)		
3f	165-167	1703 1618 1574 1541		1445 1427 1352 1273			231 (26.5) 273 (12.5)	230 (29.7) 274 (13.9)	229 (29.0) 273 (13.4)		
4f	196-198	1670 1547 1487 1452 1425		1375 1354 1339 1277			209 (23.0) 294 (8.7)	205 (25.1) 292 (9.6)	221 (23.9) 297 (9.2)		

w = weak; wsh = weak sharp; [a]in[4] given as logε; [b]deduced from the Figures 2, 3, 4 and 5 of [3]; [c]no method of its preparation given in[5].

a: Q= SCH_3, R^1= CH_3, R^2= H; b: Q= morpholino, R^1= CH_3, R^2= H;

c: Q= SCH_3, R^1= R^3= CH_3, R^2= H; d: Q= morpholino, R^1= R^3= CH_3, R^2= H;

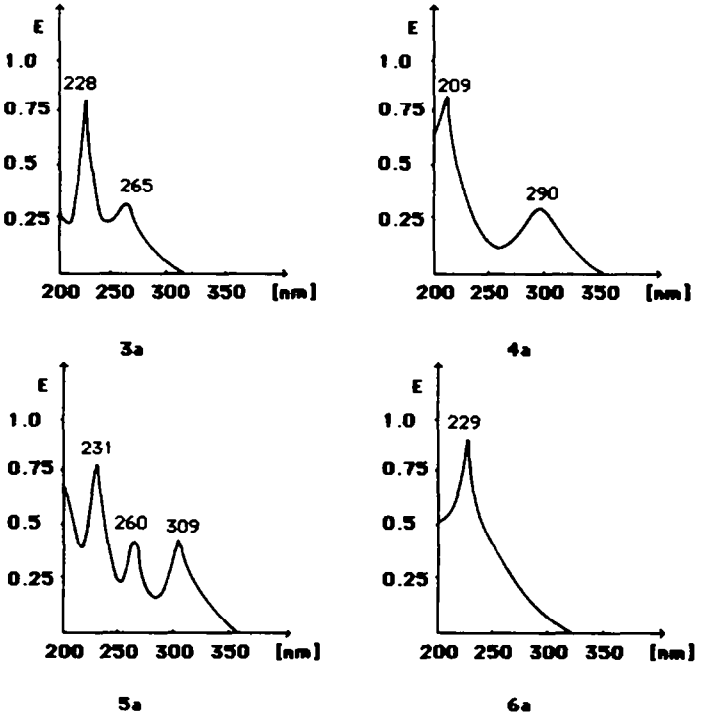
e: Q= SCH_3, R^1= CH_3, R^2= H; R^3= benzyl; f: Q= morpholino, R^1= CH_3, R^2= H, R^3= benzyl.

the "5-one" derivatives 3 and 5, respectively (Table 1). In addition to we found good agreement between the √C=O frequencies and the anellation of the 1,2,4-triazole and the pyrimidinone ring. Namely the √C=O frequencies of the 1,2,4-triazolo[1,5-a]-pyrimidinone derivatives 3a and 4a proved to be by 10-20 cm^{-1} higher than those of the corresponding 1,2,4-triazolo-[4,3-a]pyrimidinones 5a and 6a, respectively (Table 1). However, as shown from the √C=O frequencies of our further 3 - 6 type derivatives prepared as models to control the validity of the above rules (Table 1), the influence of the substituents of the triazole-pyrimidinone moiety to the √C=O frequencies was greater than the difference arising from the Allen's rule.

Consequently the √C=O frequencies could not be used in general for the structure elucidation of the 3 - 6 type isomers. It is worth to mention that we did not recognise either the strong absorption band at 1325 cm^{-1} proposed by Williams[6] for the characterisation of the 1,2,4-triazolo[1.5-a]pyrimidinones 3 and 4, which had to be absent in the 1,2,4-triazolo[4,3-a]pyrimidinone isomeric analogues 5 and 6, respectively, or the extra absorption bands between 1575 and 1563 cm^{-1} proposed by the same author for the characterisation of the "5-one" structures 3 and 5, respectively (Table 1). Consequently the above bands could not be characteristic for any of these structures.

The UV spectra of derivatives 3a - 6a (Q= SCH_3, R^1= CH_3, R^2= H) and those of their N-methyl analogues 3c, 5c and 6c taken in ethanolic solution were in good agreement with those of reported in the literature (Table 1). The slight difference between the shoulders of derivatives 6a and 6c observed by us and those of reported in the literature[6] is probably due to the different solvents used and different recording conditions.

The highest UV maxima of derivatives 3a and 5a (Q= SCH_3, R^1= CH_3, R^2= H) taken in alkaline conditions were shifted towards the higher wavelengths as compared with those of taken in acidic media (Table 1) in good agreement with the observation of Beckat and coworkers[3] made during the study of derivatives 3 - 6 (Q= H, R^1= CH_3, R^2= H). On the other hand we did not observe the increase of the intensity of these maxima in alkaline solution as compared with those of measured in acidic conditions thought to be characteristic[3] for structures 3a and 5a. To the contrary of the Beckat and coworkers' observation[3], who stated that the UV spectra of derivatives 4 and 6 taken in acidic media were characterised with one absorbtion band only which underwent batochromic shift in alkaline condition being accompanied with the decrease of intensity, the maximum of 4a (Q= SCH_3, R^1= CH_3, R^2= H) taken in alkaline condition was not shifted towards the higher but rather towards the lower wavelenghts as compared with that of taken in acidic media. In case of 6a (Q= SCH_3, R^1= CH_3, R^2= H) we did not observe the proposed decrease of the intensity of the above absorption band (Table 1).



Scheme 2

To our experience derivatives 3 - 6 are the best characterised by their UV spectra taken in neutral i.e. in ethanolic or methanolic solutions where the shape of their spectra (see. e.g. the spectra of derivatives 3a - 6a (Q= SCH_3, R^1= CH_3, R^2= H, Scheme 2) as well as the position of their maxima and minima differs significantly. Thus

a/ the spectra of derivatives 3 are characterised with two absorption bands appearing at about 230 and 270 nm,

b/ the spectra of derivatives 4 are characterised with two absorption bands appearing at about 280 and 290 nm,

c/ the spectra of derivatives 5 are characterised with three absorption bands appearing at about 230, 260 and 310 nm and

d/ the spectra of derivatives 6 are characterised with one absoption band only appearing at about 230 nm.

To prove unequivocally the tautomeric structures of derivatives 3a - 6a (Q= SCH_3, R^1= CH_3, R^2= H) and 3b - 4b (Q= morpholino, R^1= CH_3, R^2= H) their N-methyl- [3c - 6c (Q= SCH_3, R^1= CH_3, R^2= H), 3d (Q= morpholino, R^1= CH_3, R^2=H)] and N-benzyl- [3e - 4e (Q= SCH_3, R^1= CH_3, R^2= H), 3f - 4f (Q= morpholino, R^1= CH_3, R^2= H)] derivatives were synthesised either by the alkylation of derivatives 3a - 6a (Q= SCH_3, R^1= CH_3, R^2= H) and 3b - 4b (Q= morpholino, R^1= CH_3, R^2= H) or by direct synthesis (see Schemes 3-5).

The UV spectra of derivatives 3a - 6a (Q= SCH_3, R^1= CH_3, R^2= H) were fully analogous with those of the methyl derivatives 3c - 6c (Q= SCH_3, R^1= CH_3, R^2= H), respectively, giving proof that the same chromophore systems were present in methanolic or ethanolic solution, i.e. to the tautomeric structures of derivatives 3a - 6a (Q= SCH_3, R^1= CH_3, R^2= H) shown on

Table 2
^{1}H-NMR and ^{13}C-NMR data of derivatives 3–6 taken in DMSO-d_6

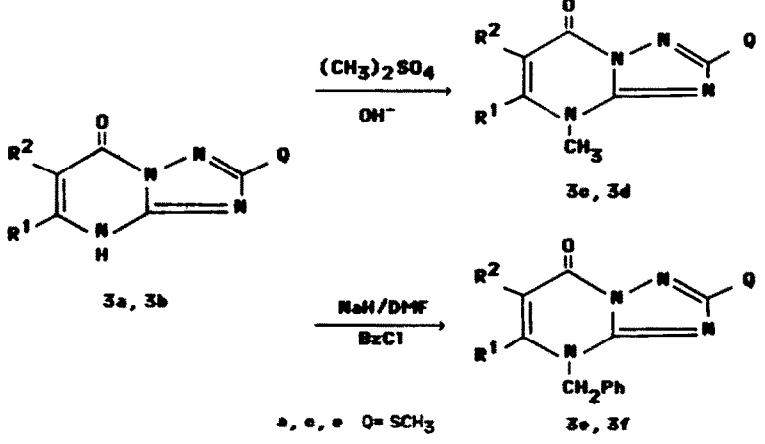
Compound	^{1}H-NMR δ, ppm						^{13}C-NMR δ, ppm									
	SCH_3	NCH_2	OCH_2	CH	CCH_3	NCH_3	$C_2(C_3)$	C_5	C_6	C_7	C_{8a}	SCH_3	CCH_3	NCH_3	NCH_2	OCH_2
3a	2.64			5.82	2.35		163.2q	154.9d	98.4dq	150.6qd	151.3s	13.5	18.5			
4a	2.56			6.00	2.47		162.8q	146.9qd	104.3dq	160.6s	150.7s	13.4	16.0			
5a	2.58			5.50	2.26		143.2q	156.7d	95.3dq	158.3m	150.4s	13.3	20.2			
6a	2.67			5.90	2.61		142.7q	145.0qd	107.9dq	160.3s	150.2s	16.0	18.5			
3b		3.39	3.70	5.69	2.26		164.2	155.0	98.4	148.9	150.3		18.2		45.8	65.4
4b		3.34	3.68	5.86	2.39		164.8	146.9	102.0	160.7	150.1		16.0		45.7	65.4
3c	2.60			5.93	2.40	3.70	162.9	153.9	99.8	152.7[x]	152.3[x]	13.4	18.4	34.2		
4c	2.59			6.12	2.45	3.44	162.4	145.7	103.6	158.9	151.2	13.3	17.6	29.6		
5c	2.53			5.63	2.23	3.72	142.1q	156.4d	97.1dq	167.0m	149.8q	13.0	23.8	33.5		
6c	2.67			6.05	2.62	3.31	143.9	146.2	107.2	158.7	150.9	16.1	18.3	28.2		
3d		3.42	3.71	5.88	2.40	3.69	164.4m'	155.1d'	101.3dq'	149.0m'	151.8q'		20.2'	34.1'	46.1'	66.4'
3e	2.70	5.48		5.85	2.38		162.9	153.6	98.4	152.9	151.4	13.3	18.1		50.1	
4e	2.58	5.20		6.17	2.46		162.6	146.4	103.9	158.7	151.1	13.4	15.9		45.9	
3f		5.42		5.82	2.29		164.3	154.6	101.5	148.8	152.1		18.5		50.5	
		3.58	3.77												45.8	66.0
4f		5.18		6.01	2.40		164.4	146.8	101.9	158.7	150.3		16.0		45.7	
		3.36	3.68												45.7	65.5

[x]may be exchanged ; 'taken in $CDCl_3$ solution

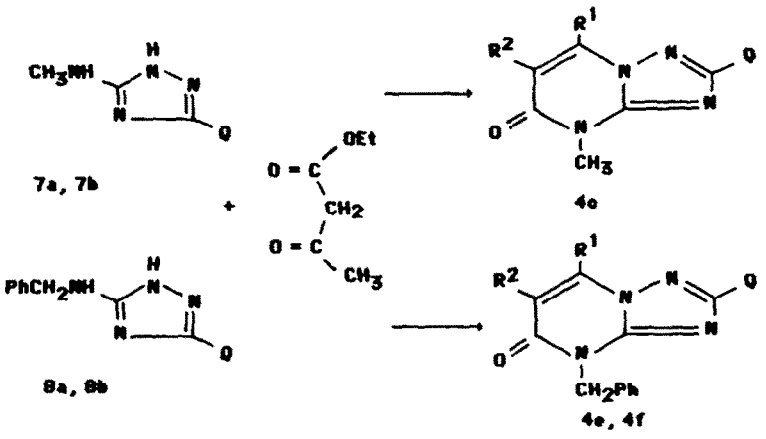
Scheme 1. The same was observed with the spectra of the methyl derivatives 3c – 6c (Q= SCH_3, R^1= CH_3, R^2 = H) and all other derivatives 3b – 4b (Q= morpholino, R^1= CH_3, R^2 = H), 3d (Q= morpholino, R^1 = CH_3, R^2= H), 3e – 4e (Q= SCH_3, R^1= CH_3, R^2= H) and 3f – 4f (Q= morpholino, R^1= CH_3, R^2= H), respectively, proving unequivocally the tautomeric structures of the morpholino derivatives 3b – 4b (Q= morpholino, R^1= CH_3, R^2 = H) shown on Scheme 1. These spectral data were used in the structure elucidation of the novel condensed ring systems[4], too.

The ^{1}H-NMR spectra of derivatives 3 – 6, were in good agreement with the proposed structures (Table 2), but – in accordance with a previous observation[3] – the differencies between the signals were not large enough to formulate any general rule for their characterisation.

On the other hand the ^{13}C-NMR spectra taken in DMSO-d_6 solution (the correct assignement of which was checked by recording the gated spectra) were fully characteristic for all 3 – 6 type derivatives giving a further, unequivocal proof of their structure (Table 2).



Scheme 3



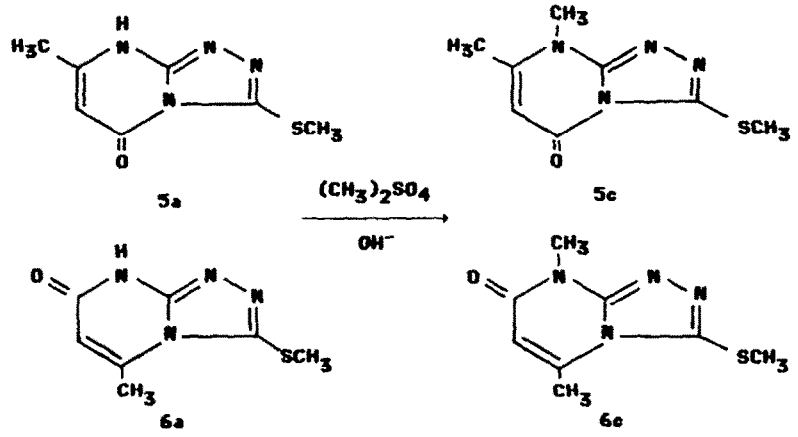
a, c, e Q= SCH_3

b, d, f Q= morpholino

Scheme 4

Thus the [1,5-a] type 1,2,4-triazolo-pyrimidinone derivatives 3 and 4, respectively, were characterised by the triazole carbon atom (2) appearing with the chemical shift of approximately 163 ppm being very different from those of the analogues triazole carbon atom (3) of the [4,3-a] type 1,2,4-triazolo-pyrimidinone derivatives 5 and 6, respectively, appearing at about 143 ppm.

The differentiation between the "ring-acylated" 1,2,4-triazolo-pyrimidinone derivatives 3 and 5 and their "acylamine" analogues 4 and 6, respectively made possible the chemical shift of the carbonyl carbon atoms (5) and (7) appearing at about 154 and 160 ppm, respectively.



Scheme 5

To summarise:

It can be stated that in spite of the good agreement between the √C=O frequencies and the structure of derivatives 3a - 6a (Q= SCH_3, R^1= CH_3, R^2= H) the IR spectra are not characteristic in general for structures 3 - 6.

The 3 - 6 type derivatives are well characterised by their **UV spectra taken in neutral solution** which differ significantly.

The ^{13}C-NMR **spectra offers a method giving unequivocal proof** of structures 3 - 6 corroborating the conclusions drawn from the UV measurements.

EXPERIMENTAL

Melting points were determined on a Koffler-Boëtius micro apparatus and are uncorrected. The infrared spectra were obtained as potassium bromide pellets using Perkin-Elmer 577 spectrophotometer. The ultraviolet spectra were obtained by a Varian Cary 118 and a Pye Unicam SP 8-150 instrument. The ^1H-NMR and the ^{13}C-NMR measurements were performed using Varian XL-100, Brucker WH-250 and Brucker WP-80 SY instruments. The IR, NMR and UV data are summarised in Tables 1 and 2.

The preparation of the compounds apart from the following has been reported previously[5]

5-Methyl-2-methylthio-1,2,4-triazolo[1,5-a]*pyrimidine-7(8H)-one* (4a)
To the solution of sodium ethylate in ethanol (prepared from 1.15 g (0.05 mole) of sodium and 50 ml of absolute ethanol) 6.5 g (0.05 mole) of 5-amino-3-methylthio-1*H*-1,2,4-triazole (1, R= methylthio)[8] and 7.9 g (0.05 mole) of ethyl β-ethoxy-crotonate[10] was added and the mixture was refluxed with stirring for 24 hours. After cooling the mixture was decomposed with 200 ml of water and acidified with acetic acid. The crystals precipitated were filtered off and washed with water to yield 5.2 g (53 %) of the title *product* which after recrystallisation from butanol melted at 266–268°C. Anal. Calcd. for $C_7H_8N_4OS$ (MW. 196.23): C, 42.84, H, 4.11, N, 28.55, S, 16.34. Found: C, 42.97, H, 4.34, N, 28.52, S, 16.42.

7-Methyl-2-morpholino-1,2,4-triazolo[1,5-a]*pyrimidine-5(8H)-one* (3b)
To the solution of 16.9 g (0.1 mole) of 5-amino-3-morpholino-1*H*-1,2,4-triazole (1, R= morpholine)[8] in 40 ml of glacial acetic acid 10.8 ml (11.6 g, 0.1 mole) of methyl acetoacetate was added and refluxed for 2 hours. The solution crystallised while hot. After cooling the crystals precipitated were filtered off and re-crystallised from dimethylformamide to yield 16.5 g (70.1 %) of the title *product*, m.p. 336–338°C. Anal. Calcd. for $C_{10}H_{13}N_5O_2$ (MW. 235.24): C, 51.05, H, 5.57, N, 29.77. Found: C, 51.12, H, 5.73, N, 29.65.

5-Methyl-2-morpholino-1,2,4-triazolo[1,5-a]*pyrimidin-7(8H)-one* (4b)
The mixture of 0.34 g (0.002 mole) of 5-amino-3-morpholino-1*H*-1,2,4-triazole (1b)[8] and 0.35 g (0.0022 mole) of ethyl β-ethoxy-crotonate[10] was heated to 150°C for 10 minutes. The melt obtained crystallised after cooling. It was re-crystallised from dimethylformamide to yield 0.31 g (66.0 %) of the title *product*, m.p. 248–250°C. Anal. Calcd. for $C_{10}H_{13}N_5O_2$ (MW. 235.24): C, 51.05, H, 5.57, N, 29.77. Found: C, 51.00, H, 5.63, N, 29.91.

7,8-Dimethyl-2-methylthio-1,2,4-triazolo[1,5-a]*pyrimidin-5(8H)-one* (3c)
To the solution obtained by dissolving of 5.5 g (0.028 mole) of 7-methyl-2-methylthio-1,2,4-triazolo[1,5-a]pyrimidin-5(8*H*)-one (3a)[5] in the solution of 1.7 g (0.0425 mole) of sodium hydroxyde in 150 ml of water 3.0 ml (3.99 g, 0.0316 mole) of dimethyl sulfate was added by dropping it at 40–45°C with stirring during 1/2 hour. After cooling the solution crystallised. The crystals were filtered off and re-crystallised from methanol to yield 3.1 g (70.1 %) of the title *product*, m.p. 213–215°C (Lit.[5] m.p. 160–170°C). Anal. Calcd. for $C_8H_{10}N_4OS$ (MW. 210.26): C, 45.70, H, 4.79, N, 26.65, S, 15.25. Found: C, 45.58, H, 4.88, N, 26.55, S, 15.21.

5,8-Dimethyl-2-methylthio-1,2,4-triazolo[1,5-a]*pyrimidin-7(8H)-one* (4c) by alkylation of 4a.
To the solution of 0.73 g (0.004 mole) of 5-methyl-2-methylthio-1,2,4-triazolo[1,5-a]pyrimidin-7(8*H*)-one (4a) in 15 ml of absolute dimethylformamide 0.22 g (0.007 mole) of sodium hydride (80 % in toluene) was added and the reaction mixture heated to 40°C for 10 minutes. The solution obtained was cooled to 18°C and 0.63 ml (1.41 g, 0.01 mole) of methyl iodide was added by dropping it to the reaction mixture with stirring. The stirring was continued at the laboratory temperature for 4 hours. The reaction mixture was decomposed with 50 ml of water extracted with 2x50 ml of chloroform, the combined chloroform layers were washed with water, dried over sodium sulfate and evaporated to dryness to yield 0.78 g (92.7 %) of the title *product* which after re-crystallisation from isopropanol melted at 180–182°C. Anal. Calcd. for $C_8H_{10}N_4OS$ (MW. 210.26): C, 45.70, H, 4.79, N, 26.65, S, 15.25. Found: C, 45.68, H, 4,86, N, 26,57, S, 15.18.

5,8-Dimethyl-2-methylthio-1,2,4-triazolo[1,5-a]*pyrimidin-7(8H)-one* (4c) by ring closure of 7a.
The mixture of 1.44 g (0.01 mole) of 5-methylamino-3-methylthio-1*H*-1,2,4-triazole (7a)[9] and 3 ml of ethyl acetoacetate was refluxed for 30 minutes. The solution obtained crystallised upon cooling. The crystals precipitated were filtered off and washed with isopropanol to yield 1.5 g (71.4 %) of white crystals which after re-crystallisation from isopropanol melted at 168–171°C. The product obtained is a 2:1 mixture (on the basis of ^{1}H-NMR) of 7,8-dimethyl-2-methylthio-1,2,4-triazolo[1,5-a]pyrimidin-5(8*H*)-one (3c) and 5,8-dimethyl-2-methylthio-1,2,4-triazolo[1,5-a]pyrimidin-7(8*H*)-one (4c).

6,8-Dimethyl-3-methylthio-1,2,4-triazolo[4,3-a]*pyrimidin-5(8H)-one* (5c)
To the mixture of 2.18 g (0.01 mole) 6-methyl-3-methylthio-1,2,4-triazolo[1,5-a]pyrimidin-5(8*H*)-one sodium salt (5a - Na) (prepared by dissolving 8.0 g of 5a[5] in 200 ml of hot 5 % sodium hydroxide, leaving the solution to crystallise and filtering off the crystals precipitated to yield 7.0 g of the corresponding sodium salt, m.p. > 350°C) and 10 ml of dry dimethylformamide 1.26 ml (2.82 g = 0.02 mole) of methyl iodide was added in one portion with stirring at room temperature. The crystals of the starting material were dissolved within a few minutes and the solum iodide precipitated. After 15 minutes of stirring 25 ml of water was added to the reaction mixture, the crystals precipitated were filtered off, washed with water and re-crystallised from dimethylformamide to yield 1.1 g (52.3 %) of the title *product* m.p. 197–199°C (Lit.[5] m.p. 195–196°C).

7,8-Dimethyl-2-morpholino-1,2,4-triazolo[1,5-a]*pyrimidin-5(8H)-one* (3d)
To the mixture of 4.7 g (0.02 mole) of 7-methyl-2-morpholino-1,2,4-triazolo[1,5-a]pyrimidin-5(8*H*)-one (3b) and 25 ml of dry dimethylformamide 0.66 g (0.022 mole) of sodium hydride (80 % in toluene) was added is small portions with stirring. The mixture was heated to 100°C for 30 minutes during which the starting materials had dissolved. The reaction mixture was then cooled to 0°C and 1.86 ml (4.25 g, 0.03 mole) of methyl iodide was added to it with stirring during a period of 10 minutes. After 2 hours of stirring at room temperature 50 ml of water was added to the reaction mixture, the crystals precipitated were filtered off, washed with water and re-crystallised from dimethylformamide to yield 4.0 g (80.3 %) of the title *product*, m.p. 264–265.5°C. Anal. Calcd. for $C_{11}H_{15}N_5O_2$ (MW. 249.27): C, 53.00, H, 6.07, N, 28.10. Found: C, 52.88, H, 6.15, N, 28.13.

8-Benzyl-7-methyl-2-methylthio-1,2,4-triazolo[1,5-a]*pyrimidin-5(8H)-one* (3e)
To the mixture of 4.9 g (0.025 mole) of 7-methyl-2-methylthio-1,2,4-triazolo[1,5-a]pyrimidine-5(8*H*)-one (3a)[5] and 30 ml of absolute dimethylformamide 1.31 g (0.03 mole) of sodium hydride (55 % in toluene) was added with stirring. The mixture was heated to 80°C for 50 minutes during which the starting materials had dissolved. After cooling to 45°C 4.0 g (0.031 mole) of benzyl chloride was added and the reaction was completed by heating the solution to 85°C for 1 hour. After cooling 100 ml of water was added to the reaction mixture, the crystals precipitated were filtered off and washed with water to yield 4.1 g (63.1 %) of the title *product*, which after re-crystallisation from ethanol melted at 145–147°C. Anal. Calcd. for $C_{14}H_{14}N_4OS$ (MW. 286.35): C, 58.72, H, 4.93, N, 19.57, S, 11.20. Found: C, 58.56, H, 5.00, N, 19.62, S, 11.08.

8-Benzyl-5-methyl-2-methylthio-1,2,4-triazolo[1,5-a]*pyrimidin-7(8H)-one* (4a)

The mixture of 2.2 g (0.01 mole) of 5-benzylamino-3-methylthio-1*H*-1,2,4-triazole (6a)[9] and 6 ml of ethyl acetoacetate was refluxed for 15 minutes. The solution obtained crystallised while hot. After cooling the crystals precipitated were filtered off, washed with hexane and re-crystallised from ethanol to yield 1.15 g (40.2 %) of the title *product*, m.p. 136-137.5°C. Anal. Calcd. for $C_{14}H_{14}N_4OS$ (MW. 286.35): C, 58.72, H, 4.93, N, 19.57, S, 11.20. Found: C, 58.80, H, 5.12, N, 19.55, S, 11.18.

8-Benzyl-7-methyl-2-morpholino-1,2,4-triazolo[1,5-a]*pyrimidin-5(8H)-one* (3f)

The solution of 2.57 g (0.01 mole) of 7-methyl-2-morpholino-1,2,4-triazolo[1,5-a]pyrimidin-5(8*H*)- one sodium salt (3b-Na) (prepared by dissolving 10 g of 3b in 30 ml of 1*N* warm sodium hydroxyde, leaving the solution to cool and filtering off the crystals precipitated to yield 7.05 g of the sodium salt, m.p. 335°C) in 15 ml of dimethylformamide 1.26 ml (1.39 g, 0.011 mole) of benzyl chloride was added and refluxed with stirring for 1 hour. After cooling 100 ml of water was added to the reaction mixture, the solution obtained was extracted twice with 100 ml portions of benzene, the combined benzene layers were dried over anhydrous sodium sulfate and evaporated to dryness. The crystalline residue was re-crystallised from 2-propanol to yield 1.82 g (56.0 %) of the title *product*, m.p. 165-167°C. Anal. Calcd. for $C_{17}H_{19}N_5O_2$ (MW. 325.36): C, 62.75, H, 5.89, N, 21.53. Found: C, 62.68, H, 5.95, N, 21.57.

8-Benzyl-5-methyl-2-morpholino-1,2,4-triazolo[1,5-a]*pyrimidin-7(8H)-one* (4f)

The mixture of 0.26 g (0.001 mole) of 5-benzylamino-3-morpholino-1*H*-1,2,4-triazole (8b) [preparation: 5-amino-3-morpholino-1*H*-1,2,4-triazole (1b)[8] was converted with benzaldehyde to 5-benzalimino-3-morpholino-1*H*-1,2,4-triazole, m.p. 171°C (EtOAc), and then reduced with lithium-aluminium-hydride in tetrahydrofurane to 8b, m.p. 224°C (MeOH)] and 2 ml of ethyl acetoacetate was refluxed for 10 minutes. The solution obtained was evaporated to dryness and the residue re-crystallised from ethanol to yield 0.23 g (70.1 %) of the title product, m.p. 196-198°C. Anal. Calcd. for $C_{17}H_{19}N_5O_2$ (MW. 325.36): C, 62.75, H, 5.89, N, 21.53. Found: C, 62.77, H, 6.03, N, 21.44.

Acknowledgement : The authors wish to express their thanks to Miss. Ilona Sztruhár and Mrs. Erzsébet Varhol-Tóth for recording the UV spectra, to Mrs. Zsoltné Bíró and Miss Mónika Sipos for recording the IR spectra, to Mr. István Parragi and Mr. Attila Fürjes for recording of some NMR spectra to Dr. Pál Sohár for helpful NMR disscussions, to Mrs. Lászlóné Bodrogai, Mrs. Lászlóné Zalavári, Miss. Viktória Fuchs and Mr. Béla Kasszán for performing the elemental analysises and to Mrs. Lászlóné Nyikos and Mrs. Miklosné Marczis, for technical assistance.

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