Nitrogen Bridgehead Compounds. Part 77. Addition Reaction of 9-Methylene-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones

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Addition of bromine or thioacetic acid onto 6-methyl-9-methylenetetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones is stereoselective and gives the *cis* 6-Me,9-CH substituted products. Addition is also stereoselective in respect to the C(9) and C(10) centers, and gives as the primary product the *erythro* diastereomer, which may then undergo epimerization to the *threo* isomer. Relative configuration and predominant conformation of the products were determined by 1D and 2D nmr methods.

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In a recent series of papers [1-16] we discussed electrophilic reactions at the C(9) methylene group of 6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones which resulted in the preparation of some promising pharmacones [17-22]. Among others we found that reaction of ethyl 6-methyl-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one-3-carboxylate (**1**) with aldehydes yielded condensation products **2** with an exocyclic C(9)=C(10) double bond of *E* configuration [1].

Scheme 1

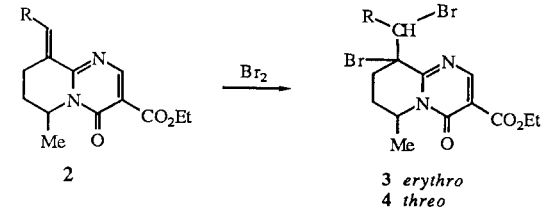
1 **2**

Since in compounds **2** the exocyclic double bond is part of an α,β-unsaturated cyclic amidine system it can be expected that it can be further reacted both in electrophylic and nucleophylic reactions whereupon products with two additional chiral centers are formed. In this communication we describe the addition of bromine and thiols to compounds **2** along with the determination of the relative configuration and conformation of the products.

Addition of bromine to 6-methyl-9-methylene-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one-3-carboxylate.

In chlorinated solvents compounds **2** readily add bromine at room temperature giving the dibromo compounds **3** and **4** in good yield.

Scheme 2



2

3 *erythro*
4 *threo*

R
a, C_6H_5
b, 4'-Cl-C_6H_4
c, 4'-Meo-C_6H_4
d, CO_2H

The products are stable at room temperature and lose bromine only on boiling or prolonged storage. Although even after recrystallization the products still contained some of the starting material, the crude products were already sufficiently pure for structural studies. Since the starting materials **2** contain at C(6) a center of chirality not only the formation of *erythro* **3** and *thero* **4** dibromides can be anticipated, but the relative disposition of the C(6) methyl group and the bromine atom at C(9) may be either *cis* or *trans*. When starting from compounds **2a-2c**, however, the formation of only one isomer was experienced, as shown by the ^1H nad ^{13}C nmr spectra of the crude products which exhibited a single series of signals. Similar stereoselectivity was found earlier in the bromination of α,β-unsaturated ketones, *e.g.* with 3-benzylideneflavanone and its thio analogue [23]. In the bromination of **2d**, in turn, the nmr spectra of the crude product showed two series of signals of about equal intensity, suggesting the formation of two isomers.

Assignment of configuration and conformation to com-

Table 1
Characteristics ^{1}H Chemical Shifts of Compounds **2-6**

	H-2	H-6	Heq-7	Hax-7	Heq-8	Hax-8	H-9	H-10	Me-6
2a [a]	8.67	5.20	2.03	1.86	2.80	3.05	-	8.36 (*E*) 6.98 (*Z*)	1.36
3a [a]	8.70	5.08	1.96	2.39	2.17	3.24	-	6.47	1.47
3b [a]	8.65	5.03	1.93	2.35	2.08	3.17	-	6.42	1.43
3c [a]	8.71	5.07	1.96	2.38	2.17	3.21	-	6.44	1.46
3d [a]	8.71	5.12	2.05	2.5	2.90	3.02	-	5.98	1.40
4d [a]	8.61	5.12	2.05	2.5	2.5	2.9	-	5.78 [g]	1.40
5a [b]	8.69	4.90	1.7		2.2		3.45 [c]	5.83	1.32
6a [b]	8.79	4.90	1.7		2.2		3.55 [d]	5.99	0.65
5d [b]	8.46	4.77	1.8		2.1		3.44 [e]	5.25	1.29
6d [b]	8.45	4.77	1.8		2.1		3.40 [f]	4.99	1.29

[a] Measured at 400 MHz. [b] Measured at 250 MHz. [c] J (9,10) = 3.4 Hz. [d] J (9,10) = 4.1 Hz. [e] J (9,10) = 3.7 Hz. [f] J (9,10) = 3.0 Hz. [g] Broad.

Table 2
^{13}C Chemical Shifts of Compounds **2-6** (δ TMS = 0.0 ppm)

	2a (*E*) [a]	**2a** (*Z*) [a]	**2d** (*E*) [a]	**3a** [a]	**3b** [a]	**3c** [a]	**3d** [b]	**4d** [b]	**5a** [b]	**6a** [b]	**5d** [b]	**6d** [b]
2	156.4	156.0	157.2	157.2	157.0	157.2	157.0	157.0	157.0	157.0	156.1	156.3
3	111.3	113.2	115.2	115.0	115.0	114.9	115.0	115.2	114.0	113.9	113.5	113.9
4	156.9	156.6	157.3	157.6	157.3	157.6	158.0	157.7	158.1	158.1	157.1	156.9
6	45.5	45.5	47.2	48.4	48.2	48.4	48.6	49.5	48.2	48.0	48.3	48.5
7	25.2	26.1	25.9	24.0	23.8	24.0	24.0	24.8	27.1	26.9	26.4	26.4
8	20.0	25.6	21.0	26.5	26.4	26.5	26.3	29.4	18.9	16.5	18.1	20.0
9	126.8	126.9	126.5	65.7	65.4	66.3	60.3	60.3	47.8	47.0	48.0	48.0
9a	158.3	158.9	158.1	162.7	162.3	162.8	160.9	162.6	163.8	164.1	165.3	166.6
10	138.7	138.0	144.0	58.7	57.5	58.7	53.4	53.4	50.6	50.1	43.4	43.7
1'	134.4	134.8	-	135.1	133.7	127.1	-	-	139.6	137.1	-	-
2',6'	129.5	127.8	-	131.2	132.4	132.4	-	-	128.2	128.3	-	-
3',5'	127.5	126.8	-	127.9	128.0	113.2	-	-	128.4	128.8	-	-
4'	128.1	127.4	-	129.2	135.1	160.1	-	-	127.5	127.7	-	-
CO_2Et	163.0	162.6	163.9	163.6	163.4	163.6	163.3	163.0	163.8	163.8	163.5	163.5
	59.6	59.7	61.4	61.3	61.2	61.3	61.6	61.7	60.9	60.9	60.5	60.6
	13.3	13.3	14.3	14.2	14.1	14.2	14.1	14.1	14.2	14.2	14.1	14.1
Me-6	16.3	17.4	17.4	19.1	19.0	19.0	19.1	18.4	18.5	17.9	18.1	18.3
COOH	-	-	168.1	-	-	-	168.4	168.4	-	-	170.8	171.0
SCOMe	-	-	-	-	-	-	-	-	193.2 30.4	193.2 30.4	193.1 30.0	193.1 29.1

[a] Measured at 100 MHz. [b] Measured at 67.2 MHz.

Table 3
Results of NOE Measurements for Compounds **2-5**

	Proton Irradiated	NOE Observed
2a [a]	H-8	H-2', 6' (10%)
3a [a]	Hax-8	Me-6 (7.2%), Heq-7 (2.3%), Heq-8 (20.6%), H-2', 6' (6.9%)
	Heq-8	Hax-7 (2.3%), Hax-8 (22.7%), H-2', 6' (3.6%)
	H-10	H-2 (1.3%), H-8 (0%!), H-2', 6' (11.6%)
3b [a]	Hax-8	Me-6 (7.6%), Heq-7 (2.1%), Heq-8 (22.3%), H-2', 6' (7.4%)
	Heq-8	Hax-7 (3.8%), Hax-8 (21.6%), H-2', 6' (3.5%)
	H-10	H-8 (0%!), H-2', 6' (9.9%)
3c [a]	Hax-8	Me-6 (7.6%), Heq-7 (2.4%), Heq-8 (18.4%), H-2', 6' (7.2%)
	Heq-8	Hax-7 (1%), Heq-7 (2%), Hax-8 (17.3%), H-2', 6' (2.4%)
	H-10	H-8 (0%!), H-2', 6' (8.4%)
	H-2', 6'	Hax-8 (5.4%), Heq-8 (2.8%), H-10 (10.9%), H-3', 5' (17.5%)
	Me-6	Heq-7 (3.2%), Hax-8 (6.5%)
3d [b]	H-10	H-8 (0%!)
4d [b]	H-10	H-8 (0%!)
5a [b]	H-9	Heq-8, Hax-7 (6.6%), H-10 (7.8%), H-2', 6' (3.0%)
	H-10	H-8 (0%!), H-9 (8.4%), H-2', 6' (10.1%)
	H-2', 6'	H-8 (4.4%), H-9 (3.9%), H-10 (9.8%)
5d [b]	H-10	H-8 (0%!), H-9 (6.0%)

[a] Measured at 400 MHz. [b] Measured at 250 MHz.

Table 4
Observed ^{13}C-^{1}H Long-range Correlation of Quaternary Carbons for Compounds **2a** and **3b**

	2a		**3b**	
C	^{2}J	^{3}J	^{2}J	^{3}J
3	H-2			
4		H-2	H-2	H-2
6	Me-6, Hax-7	H-8		Heq-8
9	H-8, H-10	Heq-7	Heq-8	Heq-7
9a		H-2, H-8, H-10		H-2, Heq-8
10		H-8, H-2', 6'		Hax-8, H-2', 6'
COO-		H-2		H-2

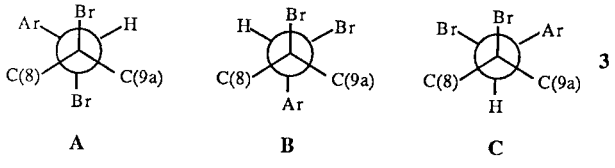
pounds **3** and **4** was accomplished by detailed nmr analysis involving, among others, the recording of two-dimensional heterocorrelation and 1D proton-proton nOe difference spectra. Characteristic spectral parameters were compiled in Tables 1-4.

In the course of our studies on 9-mono- and 9,9-disubstitued 6-methyl-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones we have demonstrated that of the two possible half-chair conformations of the tetrahydropyrimidine ring always that one is preferred in which the methyl group is axially oriented [8]. The equatorial disposition of H-6 is in accord with its large chemical shift due to deshielding by the *peri*-positioned C(4)=O group, as well as with the value of vicinal $J(6,7_{ax})$ and $J(6,7_{eq})$ couplings (both 3 Hz) [24]. Irradiation of the Me-6 protons in **3c** induced a characteristic increase in the intensity of the signal of the 1,3-*syn*-diaxially oriented H_{ax}-8 proton. Steric interaction between Me-6 and $H_2C(8)$ (γ-gauche effect) is also reflected by the chemical shift of the respective carbon atoms [8,24]. Based on the above facts the structural problems with compounds **3** and **4** are narrowed to the determination of the relative configuration of the center C(9). A quasi-axial orientation of the substituent at C(9) involves unfavour-

able γ-gauche type steric interaction with the C(7) methylene group, while in case of a quasi-equatorial disposition of this substituent 1,3-allylic strain [25] is generated by interaction with the C(9a)=N double bond [6,8]. We have shown that for the C(9)-halogeno derivatives the quasi-axial orientation of the halogen atom is favoured, since the quasi-equatorial position is further destabilized by dipole-dipole repulsion with the C(9a)=N double bond, while in case of a quasi-axial orientation of the halogen atom stabilizing orbital interaction may be established between this atom and the C(9)=N double bond [5,8]. When the C(9) substituent is a carbamoyl group it is unequivocally in an equatorial orientation [6], while for the corresponding methyl and benzyl derivatives the energy of the two conformers is about equal [1,26]. With 9-bromo-6,9-dimethyl-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones *cis* and *trans* isomers can be distinguished by characteristic differences in the shifts of C(7) (26.9 and 24.9 respectively), since the γ-anti effect of a quasi-equatorial bromine atom is about 2 ppm higher than that of a similarly oriented methyl group [8].

On bromination of compounds **2a-2c** only one isomer was obtained, for which the chemical shift of the C(7) indicated quasi-axial orientation of bromine. The 1D nOe spectra permitted the assignment of configuration and conformation to the products. Possible rotamers of the *erythro* isomer **3** obtainable by rotation around the C(9)-C(10) bond are shown below:

Scheme 3



Observation of nOe between the *ortho* protons of the phenyl ring and the C(8) methylene protons support the proximity of these protons. Since, in turn, there could be no nOe observed between H_2-8 and H-10, the conformational equilibrium is shifted in favour of rotamer **A**. To support this assumption and to obtain some quantitative data about this equilibrium molecular mechanics calculations were carried out to obtain heats of formation for the three rotamers [27,28]. Results are shown in Table 5 and indicate that for compounds **3** actually only rotamer **A** is present in the equilibrium. Note that for all three rotamers the energy content was substantially higher for the corresponding *threo* isomer than for the *erythro* one **4**. Assuming an *anti*-type mechanism of bromination it could be anticipated that inversion of the configuration of the *exo* double bond in our substrates would lead to the *threo* dibromides. In the case of 9-arylaminomethylene-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones isomerization of the *exo* double bond could be effected by proton catalysis [29,30]. Now when we added a trace of trifluoracetic acid to a chloroform solution of (*E*)-**2a** after standing for one week at room temperature a new set of signals could be observed in the nmr spectra. The ^1H and ^{13}C shifts suggested that an equilibrium mixture containing 5% of the *Z* isomer was formed. The ratio of isomers was determined with the aid of the H-10 and H-2 signals. Compared with that in the *E* isomer the H-10 signal suffered a significant upfield shift (from 8.36 to 6.98). In the *Z* isomer, namely the paramagnetic effect on the C(9a)=N double bond was not operative anymore [29]. The C(8) signal, in turn, was shifted downfield by 5.6 ppm due to the absence of the γ-gauche effect in the *Z* isomer, since here C(8) and the phenyl group were not close to each other anymore. We exploited this characteristic difference in the shift of C(8) in the *Z*/*E* isomers for configurational assignment of the analogous 9-aminomethylene- and 9-phenylhydrazonotetrahydropyridopyrimidines [29,11].

Table 5

Strainenergy *E* (calculated from MM_2 including π-calculation) of Rotamers *A*, *B*, *C*, and Equilibrial Rotamerpopulation p of Compounds **3a**, **3d**, and **4d**

Compounds	E_A kJ/mol	E_B kJ/mol	E_C kJ/mol	P_A %	P_B %	P_C %
3a	127	150	144	100	0	0
3d	106	113	126	96	4	0
4d	105	125	117	99	0	1

Owing to extended delocalization of electrons, *E*/*Z* isomerism is affecting conjugation. This is reflected as characteristic changes in the chemical shifts of relatively remote carbon atoms. Thus in the *Z* isomer upfield shifts can be observed for C(2), C(4), and the ester-CO being at 3 and 5 bonds distance respectively from the *exo* double bond, while the C(3) signal at a distance of 4 bonds suffers a downfield shift of 1.9 ppm. Whereas carbon-proton correlation [31] studies permitted a clear assignment of proton bearing carbons, identification of the closely spaced signals of quaternary C(4) and C(9a) was only possible by COLOC [32] measurement optimized for the long range coupling J(C,H) = 7 Hz. Characteristic ^2J and ^3J correlations are compiled in Table 4. The values of the vicinal couplings $^3J_{C(9a),H\text{-}10}$ and $^3J_{C(9a),H\text{-}8}$ respectively prove the assignment of C(9a) in the spectra of compounds **2** and **3**.

When a *Z*/*E* mixture of **2a** was brominated we could only detect the *erythro* product *i.e.* **3a**. Probably the minor *threo* (**4**) product was lost during work-up. Compounds **3** remain unchanged on standing in chloroform solution for 1 week at room temperature and do not incorporate deuterium when deuterium oxide was added. High stereoselectivity of bromine addition can be attributed to steric

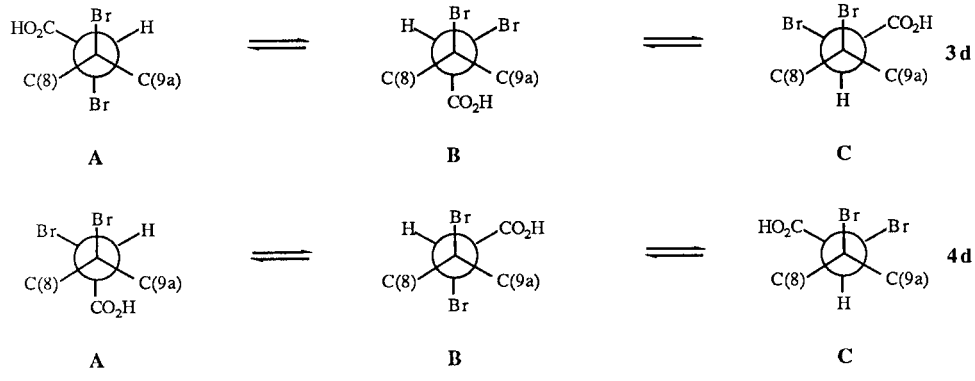
shielding of one face of the ring by the quasi-axial 6-Me group coupled by the known *anti* mechanism of bromine addition. It was therefore surprising that bromination of the pure *E* isomer of **2d** gave rise to two isomers, **3d** and **4d**. As shown by the C(7) signals (24.0 and 24.8 ppm), the product was not a mixture of *cis* and *trans* isomers, further the 6-Me group and C(9)-Br atom were *trans* diaxially disposed. Since the mechanism of bromine addition excludes the simultaneous formation of *erythro* and *threo* isomers the reaction was next directly monitored by nmr. This revealed that the primary product was **3d** which was then transformed to **4d** to give finally an equilibrium mixture containing 55% of **4d**. Conformational equilibria of **3d** and **4d** are shown below.

According to molecular mechanics calculation conformer **A** should predominate for both steroisomers. Also heats of formation of their most favoured conformers are nearly equal with a slight preference for **4d**, which is in good agreement with the ratio found experimentally. Preference for rotamer **A** was further supported by 1D nOe difference studies, since no effect was observed between H-8 and H-10, *i.e.* participation of rotamers **B** and **C** in the equilibrium is negligible. It is of interest that the H-10 signal is broad at room temperature but becomes sharp at 50°, indicating hindered rotation around the C(9)-C(10) bond. The reason for the tendency for epimerization of **3d**, in contrast to **3a-3c**, which are configurationally stable, may be that electron attraction by the CO_2H group is much stronger than by the phenyl group. Epimerization is thus a proton catalyzed process introduced by deprotonation at C(10) as indicated by proton-deuterium exchange at this atom on treatment with deuterium oxide. Addition of thiols to 6-methyl-9-methylene-6,7,8,9-tetrahydro-4*H*-[1,2-*a*]pyrimidin-4-ones.

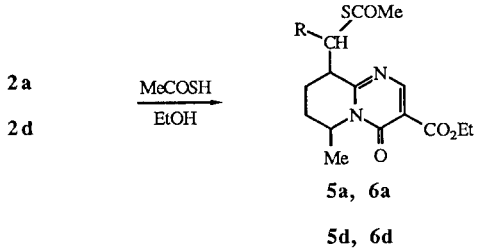
Among various O, N, and S nucleophiles only thiols reacted with **2**. Thus, thioacetic acid added readily both onto **2a** and **2d** at room temperature. The attack is regioselective at C(10), while the formation of stereoisomers can be anticipated.

The ^1H and ^{13}C nmr spectra of the recrystallized product exhibited two sets of signals relative intensity of which changed in time and converged to 60%/40%. After one day reversion to the starting materials could also be observed. Shift of the H-9 signals and the value of the $J_{H\text{-}9,Hax\text{-}8}$ coupling (9 Hz) indicated the quasi-equatorial orientation of the C(9) substituent, *i.e.* its *cis* configuration relative to the quasi-axial 6-Me group. This was further supported by the nearly equal chemical shifts of C(7) in both isomers proving that there is no steric interaction between C(7) and C(9) in none of them. In other words, the isomers are C(10) epimers. Another feature of the ^1H nmr spectra of of **5** and **6** is that the H-10 signal is a doublet with 3-4 Hz splitting, *i.e.* the preferred rotamer in respect of the C(9)-C(10) bond is the one in which the attached protons are in gauche disposition. Lack of nOe effect between the respective protons proved that C(8) and H-10 are antiperiplanar. Assignment of the relative configuration at C(9) and C(10) was permitted by a nOe experiment involving H-9 and the *ortho* protons of the phenyl group. It is of interest that immediately after dissolution the crude product showed only one set of signals and by irradiating H-9 gave a positive nOe effect at the *ortho* proton signals, *i.e.* the primary product was of *erythro* configuration. After

Scheme 4

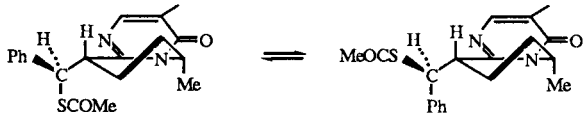


Scheme 5



standing for a few hours in chloroform at room temperature an equilibrium with two isomers was established. Most characteristic for the ^1H nmr spectrum of the new isomer **6b** was an upfield shift by 0.67 ppm of the 6-Me signal. This clearly indicated that in the *threo* isomer that rotamer was predominant in which the methyl and phenyl groups were close to each other whereby the well-known diamagnetic effect of the aromatic ring became operative.

Scheme 6

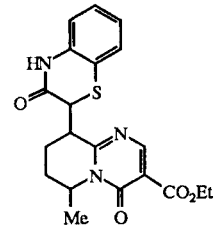


5a *erythro* **6a** *threo*

Addition of thioacetic acid onto **2d** gave also a single primary product **5d** which epimerized on standing in solution. For both **5d** and **6d** the predominant conformer is the one in which C(8) and H-10 are in antiperiplanar orientation. Distinction between *erythro* and *thero* configuration was based on the value of $^3J_{H\text{-}9,CO}$ coupling. For **5d**, in which H-9 and CO_2H are antiperiplanar this was 7 Hz, while in **6d**, due to gauche orientation of these groups, only a broadening of the CO signal could be observed. After standing for 1 day in chloroform solution a satellite doublet with approximately 3 Hz splitting and of about 1-2% intensity appeared near the H-10 signals. This may have originated from *trans* isomers generated by epimerization at C(9), but the unambiguous identification of further signals was precluded by their low percentage.

In the reaction of **2d** with 2-aminophenol nucleophilic addition was followed by spontaneous cyclization to a benzo-1,4-thiazin-3-one. The isolated product was sufficiently soluble only in DMSO and the nmr spectrum indicated an *erythro*/*threo* ratio of 1:1.

Scheme 7



7, 8

EXPERIMENTAL

The nmr spectra were obtained on Bruker AM-400, AC-250 and Jeol FX-100 spectrometers at room temperature. Chemical shifts are given on the δ scale. The homonuclear nOe difference and two-dimensional correlations spectra were run using the Bruker software package. In the 2D experiments 1K x 1K data matrixes were transformed.

Table 6

Physical and Analytical Data of Compounds **3a-d**, **5a-d** and **7**

Compounds	Mp °C	Formula	Mw	Analysis C	Calcd./Found % H	N	Yield %
3a	215-218	$C_{19}H_{20}Br_2N_2O_3$	484.18	47.13 47.02	4.16 4.19	5.79 5.70	86
3b	156-158	$C_{19}H_{19}Br_2ClN_2O_3$	518.62	44.00 43.92	3.69 3.60	5.40 5.43	89
3c	213-215	$C_{20}H_{22}Br_2N_2O_4$	514.21	46.72 46.61	4.31 4.37	5.45 5.51	82
3d	112-114	$C_{14}H_{16}Br_2N_2O_5$	452.09	37.19 37.00	3.57 3.51	6.20 6.12	91
5a	110-111	$C_{21}H_{24}N_2O_4S$	400.49	62.98 63.10	6.04 6.00	6.99 6.90	79
5d	154-157	$C_{16}H_{20}N_2O_6S$	368.41	52.16 52.01	5.47 5.51	7.60 7.52	81
7	194-196	$C_{20}H_{21}N_3O_4S$	399.47	60.13 60.00	5.30 5.25	10.52 10.46	92

Bromination of Compounds **2a,b,c,d**.

Bromine (0.01 mole, 1.62 g, 0.54 ml) dissolved in 5 ml of methylene chloride was added to 0.01 mole of compounds **2** in 30 ml of the same solvent at room temperature. After 2-3 hours stirring the homogenous reaction mixture was evaporated *in vacuo*, the residue was triturated with ethanol (**3a,b,c**) or hexane (**3d**) and filtered.

Thiol Addition of Compounds **2a,d**.

The mixture of 0.01 mole of **2a,d** and 0.015 mole of thiol in 20 ml of ethanol was stirred 6 hours at room temperature. In 0.5-1 hour the suspension became clear solution and slowly white crystals began to separate. The product was filtered, washed with ethanol and dried on air.

Melting points, yields and analytical data are given in Table 6. The ^{1}H nmr data of compound **7** (*threo/erithro* isomer mixture) δ (DMSO-d_6): EtO 1.26 t (3), 4.22 q (2), $CH_3CHCH_2CH_2$ 1.26 d (1.39 d) (3), 4.85 m (1), 1.7-2.2 m (4), H-9 3.5 m (1), SCH 4.67 d (4.58 d) (1) (J = 3 Hz), ArH 6.8-7.4 m (4), H-2 8.30 s (1).

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