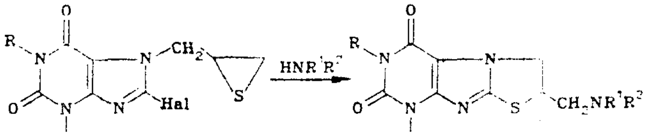
SYNTHESIS OF 2-AMINOMETHYL DERIVATIVES OF DIHYDROTHIAZOLO[2,3-f]XANTHINE

F. A. Khaliullin, Yu. V. Strokin, and V. A. Kataev

UDC 547.857.4'789.6.07:543.51

2-Aminomethyl derivatives of dihydrothiazolo[2,3-f]xanthine were obtained by the reaction of 8-halo-7-(2,3-epithiopropyl)xanthines with amines.

Methods for the synthesis of unsubstituted 2,3-dihydro-6,8-dimethylthiazolo[2,3-f]xanthine [1, 2] and 2-(7-xanthinyl)methyl-substituted 2,3-dihydrothiazolo[2,3-f]xanthine [3] are known. We have developed a general method for the synthesis of 2-substituted dihydrothiazolo[2,3-f]xanthines by the reaction of 8-halo-7-(2,3-epithiopropyl)xanthines Ia, b with nucleophilic reagents. In the present communication we describe the production of 2-aminomethyl derivatives of dihydrothiazolo[2,3-f]xanthine derivatives IIa-i, which are of interest as potential biologically active compounds (see Tables 1 and 2).



I a,b IIa-i

Ia, IIa–f R=CH_3, Ib, IIg–i R=H; IIa–c R^1=H, d, g $R^1+R^2=(CH_2)_2O(CH_2)_2$, e, h $R^1=R^2=C_2H_5$, f, i, $R^1+R^2=(CH_2)_6$, a $R^2=CH_2C_6H_5$, b $R^2=C(CH_3)_3$, c R^2=cyclohexyl; Ia Hal=Br, b Hal=Cl

Compounds IIa-i were synthesized by heating thiiranes Ia, b with an excess (1:3-10 moles) of the amines in alcohol. The reaction probably proceeds through nucleophilic opening of the thiirane ring attached to the most hydrogenated carbon atom to give a thiolate anion, which replaces the halogen atom intramolecularly. The absence of the polymeric transformations that are characteristic for the reaction of thiiranes with amines [4] constitutes evidence for the effective stabilization of the thiolate anion.

Singlets of xanthine N-methyl groups and signals of protons of residues of the corresponding amines are present in the PMR spectra of IIa-e, h, i. The protons of a dihydrothiazole ring are recorded in the form of a multiplet at 4.1-4.8 ppm, the complexity of which is due to the magnetic nonequivalence of the ring methylene protons. The PMR spectra of IIb-e in $CDCl_3$ contain signals of protons of a $2\text{-}CH_2N$ group in the form of a doublet with spin-spin coupling constant (SSCC) $^3J \approx 7$ Hz (for IId, e) or in the form of two AB systems with SSCC $^2J \approx 10$ Hz (for IIb, c). In the PMR spectra of IIa, h, i in CF_3COOH the signal of the protons of the $2\text{-}CH_2N$ group is shifted ≈0.5 ppm to the weak-field region and is recorded in the form of a multiplet; this is explained by protonation of the nitrogen atom of the aminomethyl group and retardation of the exchange of NH protons in acidic media [5].

In the ^{13}C NMR spectra of IIe-g the carbon atoms of the dihydrothiazole ring are recorded in the form of a triple [$C_{(3)}$] and a doublet [$C_{(2)}$] at 49-50 and 51-54 ppm, respectively.

EXPERIMENTAL

The PMR spectra of solutions of the compounds in $CDCl_3$ were recorded with a Tesla BS-567 spectrometer (100 MHz) with hexamethyldisiloxane (HMDS) as the internal standard, while the ^{13}C NMR spectra were obtained with a Jeol FX spectrometer (22.4 MHz) with tetramethylsilane (TMS) as the internal standard. The individuality of the compounds was monitored by TLC on Silufol UV-254 plates in an n-butanol—acetic acid—water (4:1:2) system with development by iodine vapors.

Fifteenth Anniversary of the All-Union Lenin Young Communist League Bashkir State Medical Institute, Ufa 450000. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 6, pp. 840-842, June, 1991. Original article submitted August 10, 1989; revision submitted October 22, 1990.

0009-3122/91/2706-0663$12.50 ©1991 Plenum Publishing Corporation

TABLE 1. Characteristics of the Synthesized IIa-i

Compound	Empirical formula	mp, °C (from ethanol)	PMR spectrum, δ, ppm*					Yield, %
			6-CH_3, s	8-CH_3, s	2-CH_2N	2-H and 3-H, m	other protons	
IIa	$C_{17}H_{19}N_5O_2S$	148...149	3,08	3,25	3,25...3,62	3,94...4,80**	7,00 (5H, brs, , 5CH arom)	89
IIb	$C_{14}H_{21}N_5O_2S$	179...180	3,20	3,36	2,74...3,08	4,10...4,64	1,00 (9H, s, 3CCH_3)	69
IIc	$C_{16}H_{23}N_5O_2S$	171...172	3,25	3,42	2,78...3,12	4,10...4,60	0,84...1,40 (6H, m, 3CCH_3); 1,40...1,96 (4H, m, 2CCH_2); 2,20...2,52 (1H, m, NCH)	78
IId	$C_{14}H_{19}N_5O_3S$	213...215	3,34	3,51	2,76	4,18...4,80	2,51 (4H, m, $N(CH_2)_2$); 3,70 (4H, m, $O(CH_2)_2$)	78
IIe	$C_{14}H_{21}N_5O_2S$	175...177	3,30	3,45	2,87	4,14...4,77	1,05 (6H, t, 2CCH_3); 2,62 (4H, q, $N(CH_2)_2$)	81
IIf	$C_{16}H_{23}N_5O_2S$	172...174	...	...	...	...	...	86
IIg	$C_{13}H_{17}N_5O_3S$	192...194	...	...	...	...	...	79
IIh	$C_{13}H_{19}N_5O_2S$	192...194	—	3,20	3,30...3,52	4,14...4,82	1,04 (6H, t, 2CCH_3); 2,87...3,20 (4H, m, $N(CH_2)_2$)	61
IIi	$C_{15}H_{21}N_5O_2S$	206...208	—	3,20	...***	4,12...4,84	1,26...1,70 (8H, m, 4CCH_2); 3,20...3,64 (6H, m, $N(CH_2)_2$ and 2-CH_2N)	65

---

*The spectra of IIb-e were recorded in $CDCl_3$, while the spectra of IIa, h, i were recorded in CF_3COOH.

**The signals of the protons of the dihydrothiazole ring are overlapped with the signals of the NCH_2 protons, forming a multiplet with an intensity of 5H.

***The signals of the 2-CH_2N protons are overlapped with the signals of the $N(CH_2)_2$ protons.

TABLE 2. ^{13}C NMR Spectra of IIe-f

Compound	Chemical shifts, δ, ppm					
	$N_{(6)}-CH_3$, q	$N_{(8)}-CH_3$, q	$C_{(3)}$, t	$C_{(2)}$, d	2-CH_2N, t	other carbon atoms*
IIe	27,83	29,82	49,50	53,44	56,82	12,01 (q, $2CCH_3$); 47,38 (t, $N(CH_2)_2$)
IIf	27,78	29,78	49,28	53,62	60,98	29,96 (t, $2CCH_2$); 28,48 (t, $2CCH_2$); 55,48 (t, $N(CH_2)_2$)
IIg	—	29,18	49,61	51,37	61,69	53,69 (t, $N(CH_2)_2$); 66,65 (t, $O(CH_2)_2$)

---

*The singlets of the carbon atoms of the xanthine ring are not presented in the table.

The results of elementary analysis for C, H, N, and S were in agreement with the calculated values.

2-Aminomethyl Derivatives (IIa-i) of 2,3-Dihydrothiazolo[2,3f]xanthine. A. The corresponding amine (30 mmole) was added to a solution of 3.31 g (10 mmole) of 8-bromo-1,3-dimethyl-7-(2,3-epithiopropyl)xanthine (Ia) in 50 ml of ethanol, and the mixture was refluxed for 3 h. It was then cooled, and the resulting precipitate was removed by filtration, washed with 20 ml of ethanol and water, and dried. This method was used to obtain IIa-d.

B. The corresponding amine (30 mmole) was added to a solution of 2.73 g (10 mmole) of 3-methyl-8-chloro-7-(2,3-epithiopropyl)xanthine (Ib) in 100 ml of isobutyl alcohol, after which the mixture was refluxed for 5 h and worked up as in method A. This procedure was used to obtain IIf, g, i.

C. A 10.4-ml (100 mmole) sample of diethylamine was added to a solution of 10 mmole of thiirane Ia or Ib in 75 ml of ethanol, and the mixture was heated for 5 h in a steel autoclave at 120°C. The mixture was then worked up as in method A. This method was used to obtain IIe, h.

LITERATURE CITED

1. F. Cacace and R. Masironi, *Ann. Chim. (Roma)*, **46**, 806 (1956).
2. B. V. Kurmaz, V. A. Grin', M. I. Yurchenko, V. I. Kalaida, V. A. Shumeiko, and P. M. Kochergin, Summaries of Papers Presented at the 2nd Conference of Pharmacists of the Ukrainian SSR on Current Problems of Pharmaceutical Science and Practice [in Russian], Kiev (1972), p. 393.
3. Yu. V. Strokin and F. A. Khaliullin, *Khim. Geterotsikl. Soedin.*, No. 9, 1284 (1988).
4. A. V. Fokin and A. F. Kolomiets, *The Chemistry of Thiiranes* [in Russian], Nauka, Moscow (1978).
5. B. I. Ionin, B. A. Ershov, and A. I. Kol'tsov, *NMR Spectroscopy in Organic Chemistry* [in Russian], Khimiya, Leningrad (1983).