SYNTHESIS OF 1H-[1]BENZOTHIOPYRANO[3,4-d]IMIDAZOL-4-ONES

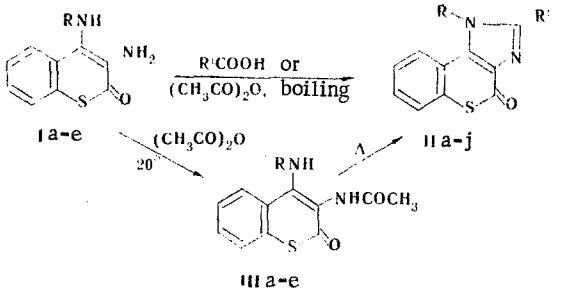
V. L. Savel'ev, T. G. Afanas'eva, S. M. Klyuev, and V. A. Zagorevskii

UDC 547.785.5'818.5.07

By the condensation of 3,4-diaminothiocoumarins containing primary or secondary amino groups in position 4, with formic and acetic acids (or acetic anhydrides), a number of 1H-[1]benzothiopyrano[3,4-d]imidazol-4-ones and their 2-methyl derivatives have been synthesized; the latter have also been obtained from the corresponding 3-monoacetylamino-4-aminothiocoumarins. By the acetylation of 3-4-diaminothiocoumarins with tertiary amino groups in positions 4 their 3-diacetyl derivative has been obtained, and these, under the action of bases, have been converted into 3-N-acetyl derivatives. The structures of the compounds synthesized have been confirmed by IR, PMR, and mass spectroscopy.

The synthesis of benzimidazoles by condensing o-arylenediamines with carboxylic acids and their derivatives is well known (see, e.g., the reviews [1-3]). The same reaction using heterocyclic ortho-diamines has been considerably less widely studied. In this connection we have investigated the reaction of the 3,4-diaminothiocoumarins (Ia-d) obtained previously [4] with formic and acetic acids, and also with acetic anhydride, at the boil and, as a result we have synthesized a new condensed heterocyclic system — that of 1H-[1]-benzothiopyrano[3,4-d]imidazol-4-one (IIa-j).

By the action of acetic anhydride on the diamines (Ia-e) (20°C, 30 min-1 h) we succeeded in obtaining the corresponding intermediate 4-(R-amino)-3-acetylaminothiocoumarins (IIIa-e), which it was possible by boiling in acetic anhydride or by simple heating to cyclize into the imidazolones (IIf-j).



Ia IIa,f IIIa R=H; Ib IIb,g, IIIb R=CH_3; Ic IIc,h IIIc R=n-C_4H_9; Id IId,i IIId R=$CH_2C_6H_5$; Ie, IIe, j, IIIe R=C_6H_5; for IIa-e R'=H; for IIf j R'=CH_3

Because of their ready cyclization to the imidazoles (IIf-j), the acetyl derivatives (IIIa-e) have no sharp melting points (the presence of compounds (IIf-j) in melts of substances (IIIa-e) was shown by TLC).

It was interesting to note that, as in the case of the 3,4-diaminocoumarins [5], the acetylation of a 3,4-diaminothiocoumarin with a teritiary amino group in position 4 takes place considerably more slowly than that of one of compounds (Ia-e). Thus, under the action of acetic anhydride at 20°C the 3,4-diaminothiocoumarins (IVa-c) remained unchanged for 1 h, and only increasing the reaction time to 15 h [for the case of the diamine (IVb)] led to the 3-acetylamino derivative (V). This difference in case of acetylation can probably be explained by the assumption that in a diamine with a tertiary amino group in position 4 additional steric hindrance is created around the nitrogen atoms on the C_3 atom, which can easily

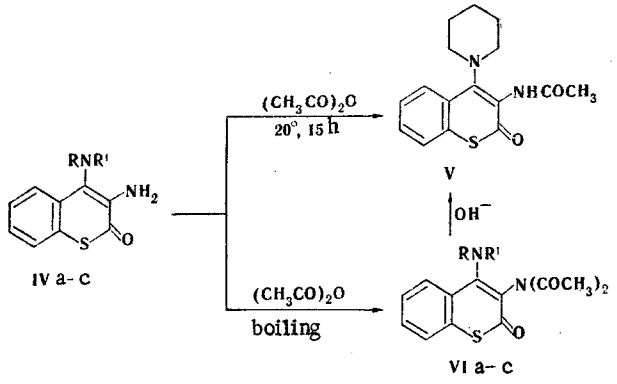
Scientific-Research Institute of Pharmacology, Academy of Medical Sciences of the USSR, Moscow. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 4, pp. 479-483, April, 1980. Original article submitted June 20, 1979.

0009-3122/80/1604-0363$07.50

TABLE 1. Characteristic Peaks of the Ions in the Mass Spectra of Compounds (IIa-j)

Compound	m/e (% of the maximum ion)
IIa	203 (12,7), 202 (100), 174 (51,7), 147 (23,8), 146 (21,8), 120 (25,3), 108 (3,0), 98 (6,1)
IIb	217 (13,6), 216 (100), 188 (56,3), 187 (13,6), 173 (6,2), 161 (3,0), 160 (9,6), 146 (13,1), 134 (6,3), 108 (4,1), 98 (3,0)
IIc	259 (17,4), 258 (100), 230 (21,1), 229 (15,7), 173 (3,0), 202 (3,7), 146 (10,7), 134 (4,1), 120 (5,3), 108 (3,6), 98 (3,1)
IId	293 (5,2), 292 (23), 264 (2,9), 263 (3,0), 173 (3,0), 146 (6,2), 121 (4,1), 120 (3,1), 108 (3,1), 98 (54,4), 91 (100)
IIe	279 (18,7), 278 (100), 250 (66,6), 249 (10,5), 223 (10,3), 222 (3,0), 146 (13,7), 121 (12,7), 108 (3,3), 98 (12,7)
IIf	217 (13,5), 216 (100), 188 (55,7), 187 (14,1), 147 (33,1), 146 (23,6), 120 (3,0), 108 (5,7), 98 (8,0)
IIg	231 (16,0), 230 (100), 202 (52,0), 201 (16,6), 187 (12,3), 161 (3,0), 160 (8,0), 134 (5,6), 120 (4,3), 98 (3,6)
IIh	273 (20,0), 272 (100), 244 (39,1), 243 (10,5), 203 (5,0), 202 (29,0), 187 (32,5), 176 (3,0), 134 (7,1), 120 (5,1), 108 (2,9), 98 (29,8)
IIi	307 (6,0), 306 (25,9), 278 (3,0), 277 (3,1), 187 (3,2), 134 (4,0), 120 (3,0), 98 (27,5), 91 (100)
IIj	293 (20,5), 292 (100), 264 (62,3), 263 (16,6), 223 (7,4), 222 (16,2), 120 (7,8), 98 (22,4)

be seen in a consideration of molecular models. If the reaction of the diamines (IVa-c) with acetic anhydride was performed at the boil, the corresponding diacetyl derivatives (VIa-c) were formed, and these were converted partially during TLC on alumina or completely under the action of ammonium hydroxide in ethanol into the monoacetyl derivatives [in the case of compound (VIb) for example].



IVa, VIa $R=R^1=C_2H_5$; IVb, VIb $R+R^1=-(CH_2)_5-$; IVc, VIc $R+R^1=-CH_2CH_2OCH_2CH_2-$

The structures of the compounds obtained were confirmed by spectroscopic methods. The IR spectra of the imidazoles (IIa-j) show strong absorption bands at 1615-1645 cm^{-1} due to the dependent vibrations of the carbonyl group; the stretching vibrations of the NH groups of compounds (IIa) and (IIf) appear at 3140 cm^{-1} in the form of a broad band. In the PMR spectrum of substance (IIc) there is an unresolved signal at 0.8-2.3 ppm ($-CH_2CH_2CH_3$), a triplet signal (J = 7 Hz) at 4.5 ppm ($-CH_2N-$), and a series of signals in the 7-8 ppm region (5 H, C_6H_4 and 2-H); the singlet signal of the $2-CH_3$ group of substance (IIh) appears at 2.5 ppm.

The mass spectra of the imidazoles (IIa-j) (Table 1) in each case show the peak of the molecular ion (M^+) which, as a rule, has the maximum intensity. Exceptions are compounds (IId) and (IIi), in which the positive charge is localized in the phenyl radical, which is extremely specific for all benzyl-substituted hetaryls. This fact explains the usual β-decomposition relative to the phenyl residue, which leads to the formation of a stable ion with a tropylium structure (m/e 91). In the first stage of the fragmentation of compounds (IIa-j) the carbonyl group is split out with the formation of a pseudomolecular ion of a substituted imidazolo[4,5-b]benzothiophene (A).

TABLE 2. 1H-[1]Benzothiopyrano[3,4-d]imidazol-4-ones (IIa-j)

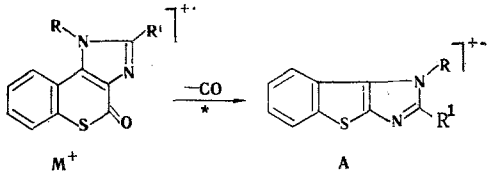
Compound	mp, °C[a]	R_f	Found, %		Empirical formula	Calculated, %		Yield, %
			N	S		N	S	
IIa	320[b]	0	13,8	16,0	$C_{10}H_6N_2OS$	13,9	15,8	93
IIb	260—261[c]	0,15	13,0	15,0	$C_{11}H_8N_2OS$	13,0	14,8	81
IIc	158—159[c]	0,37	10,8	12,2	$C_{14}H_{14}N_2OS$	10,8	12,4	88
IId	270—271[b]	0,37	9,6	10,9	$C_{17}H_{12}N_2OS$	9,6	11,0	93
IIe	206—207 c	0,54	9,8	11,6	$C_{16}H_{10}N_2OS$	10,1	11,5	92
IIf	311—312[d]	0,27	13,0	14,9	$C_{11}H_8N_2OS$	13,0	14,8	83[e] (76[f])
IIg[g]	209—210[h] 226—228[i]	0,55	12,1	13,7	$C_{12}H_{10}N_2OS$	12,2	14,0	78[e] (100[f])
IIh	181—182[i]	0,67	10,2	11,5	$C_{15}H_{16}N_2OS$	10,3	11,8	73[e] (96[f])
IIi[g]	183—184[j,k] 193—194[h]	0,78	9,3	10,5	$C_{18}H_{14}N_2OS$	9,2	10,5	99[e] (93[f])
IIj	240—241[j]	0,80	9,6	11,0	$C_{17}H_{12}N_2OS$	9,6	11,0	91[e] (100[f])

[a]Compounds (IIa, b, d-g, and j) melted with sublimation. [b]From n-butanol. [c]From 70% ethanol. [d]From ethanol. [e]Method A. [f]Method. [g]The compound exists in two crystalline modifications which have identical TLC mobilities and give identical IR (in solutions) and mass spectra. [h]From 50% ethanol. [i]From benzene. [j]From ethyl acetate. [k]On remelting, the solidified substance had mp 192-193°C.

TABLE 3. 3-Acetylamino-4-aminothiocoumarins (IIIa-e) and (V)

Compound	mp, °C[a]	R_f	IR spectrum, cm^{-1}	m/e (M^+)	Found, %		Empirical formula	Calculated, %		Yield, %
					N	S		N	S	
IIIa	250—263[b]	0	3420, 3320, 3250, 1660, 1630	234	12,0	13,7	$C_{11}H_{10}N_2O_2S$	12,0	13,7	81
IIIb	170—212[b]	0,13	3320, 3230, 1650, 1590	248	11,3	13,1	$C_{12}H_{12}N_2O_2S$	11,3	13,0	54[c]
IIIc	164—182[d]	0,43	3310, 3260, 1650, 1580	290	9,8	11,1	$C_{15}H_{18}N_2O_2S$	9,7	11,0	90
IIId	155—192	0,39	3360, 3290, 1660, 1626	324	8,7	9,7	$C_{18}H_{16}N_2O_2S$	8,6	9,9	95
IIIe	165—197[b]	0,82	3240 (broad) 1668 1596 (broad)	310	8,8	10,3	$C_{17}H_{14}N_2O_2S$	9,0	10,3	92
V	215—225[d]	0,62	3200, 1650, 1610	302	9,2	10,7	$C_{16}H_{18}N_2O_2S$	9,3	10,6	85

[a]Compound (IIIa) was recrystallized from n-butanol, compound (V) from 50% ethanol, and the other substances from ethanol. [b]On further heating, the substance solidified and remelted at the melting point of the corresponding imidazole (IIf, g, or j) (Table 2). [c]From the filtrate after the separation of the compound (IIIb) chloroform extracted the imidazole (IIg), yield 30%, mp 226-228°C (from ethyl acetate). [d]The melt that had hardened after cooling, on subsequent heating melted at 152-154°C, and an authentic mixture of compound (IIa) and (IIIa) had mp 154-156°C. [e]After three recrystallizations.



M^+ A

The further course of fragmentation of ion A (elimination of HCN or R^1CN, and also H or R) is typical for 1- and 2-substituted imidazoles [6, 7].

While in the mass spectra of the monoacetyl derivatives (IIa-e) and (V) the M^+ peak is observed, in the mass spectra of the diacetyl derivatives (VIa-c) the M^+ peak is absent, but there are the peaks of the pseudomolecular ions of the corresponding monoacetyl derivatives.

TABLE 4. 4-Amino 3-Diacetylaminothiocoumarins (VIa-c)

Compound	mp, °C[a]	R_f[b]	IR spectrum, cm^{-1}	Found, %		Empirical formula	Calculated, %		Yield, %
				N	S		N	S	
VIa	156—158	0,69	1705, 1596, 1586	8,1	9,3	$C_{17}H_{20}N_2O_3S$	8,4	9,6	79
VIb	192—194	0,71	1705, 1593, 1580	8,2	9,6	$C_{18}H_{20}N_2O_3S$	8,1	9,3	80
VIc	221—223[c]	0,35	1710, 1612, 1588	8,2	9,2	$C_{17}H_{18}N_2O_4S$	8,1	9,2	77

[a]From ethanol. [b]TLC on Silufol; solvent, ether. [c]With decomposition.

EXPERIMENTAL

The melting points were determined on a Boëtius micro heating instrument. IR spectra were taken on a Perkin-Elmer 457 instrument in paraffin oil, and PMR spectra on a Varian T-60 instrument in deuterochloroform. Mass spectra were obtained on a Varian MAT-112 chromatomass spectrometer with a system for the direct introduction of the sample into the ion source at a temperature of 100-120°C and an ionizing energy of 70 eV, the temperature of the ionization chamber being 250°C. The course of the reactions and the purity of the products were monitored with the aid of TLC on Alufol (type T) using chloroform as the solvent.

1H-[1]Benzothiopyrano[3,4-d]imidazol-4-ones (IIa-e). A solution of 5 mmole of a diamine (Ia-e) in 25 ml of 98% formic acid was boiled for 5-6 h and was then cooled and diluted with water. The precipitate that deposited was filtered off, washed with water, and dried, giving the corresponding compound (IIa-e) (Table 2).

2-Methyl-1H-[1]benzothiopyrano[3,4-d]imidazole-4-ones (IIf-j). A. A solution of 5 mmole of a diamine (Ia-e) in 25 ml of acetic anhydride was boiled for 1-2 h, cooled, diluted with water, stirred for 1 h, and left in the refrigerator for 2-3 h. The precipitate was filtered off, washed with water, and dried, to give the corresponding compound (IIf-j) (Table 2).

B. A solution of 2.5 mmole of one of the diamines (Ia) and (Ib) in 10 ml of glacial acid was boiled for 8 h, and it was then cooled and was diluted with water. The precipitate that deposited was filtered off, washed with water, and dried. In this way, substances (IIf) and (IIh) were obtained with yields of 98 and 81%, respectively.

C. One of the acetyl derivatives (IIIa-e) (1 mmole) was heated in a sublimation apparatus for 1 h (substance IIIa) or for 3 h at the melting point of the corresponding compound (IIf-j) and it was then cooled; in the case of the thermolysis of compound (IIIa) the sublimate was collected and in the other cases the solidifying mass was dissolved in chloroform, and the solution was filtered and evaporated. This gave substances (IIf-j) (the yields are shown in Table 2).

D. A suspension of 0.23 g (1 mmole) of compound (IIIa) in 5 ml of acetic anhydride was boiled for 2 h and was then worked up as in method A, giving a substance (IIf) with a yield of 83%.

3-Acetylamino-4-aminothiocoumarins (IIIa-e). A mixture of 2 mmole of a diamine (Ia-e) and 10 ml of acetic anhydride was stirred at 20°C for 30 min to 1 h, diluted with water, stirred for another 1 h, and left in the refrigerator for 1-2 h. The precipitate that deposited was filtered off, washed with water, and dried. This gave compounds (IIIa-e).

3-Acetylamino-4-piperidinothiocoumarin (V). A. A solution of 0.26 g (1 mmole) of the diamine (IV) in 5 ml of acetic anhydride was left at 20°C for 15 h and was then worked up as in the preceding experiment, giving compound (V).

B. A solution of 0.1 g (0.3 mmole) of substance (VIb) in 10 ml of ethanol was treated with 1 ml of concentrated ammonia solution and the mixture was stirred at 20°C for 2 h and was then evaporated, and the residue was triturated with petroleum ether, after which 0.09 g (99%) of compound (V) was filtered off. Information on compounds (IIIa-e) and (V) is given in Table 3.

4-Amino-3-diacetylaminothiocoumarins (VIa-c). A solution of 2 mmole of one of the diamines (IVa-c) in 10 ml of acetic anhydride was boiled for 3 h, cooled, and worked up as described above, giving the corresponding compound (VIa-c) (Table 4).

LITERATURE CITED

1. E. S. Schipper and A. R. Day, in: Heterocyclic Compounds, R. C. Elderfield (ed.), Vol. 5, Wiley, New York (1957), Chap. 4.
2. A. F. Pozharskii, A. D. Garnovskii, and A. M. Simonov, Usp. Khim., 35, 261 (1966).
3. P. N. Preston, Chem. Rev., 74, 279 (1974).
4. V. L. Savel'ev, T. G. Afanas'eva, and V. A. Zagorevskii, Khim. Geterotsikl. Soedin., No. 1, 43 (1978).
5. V. L. Savel'ev, O. S. Artamonova, and V. A. Zagorevskii, Khim. Geterotsikl. Soedin., No. 3, 316 (1976).
6. R. A. Khmel'nitskii, A. N. Kost, K. Kondal Reddi, and V. I. Vysotskii, Zh. Or. Khim., 5, 1153 (1969).
7. A. Magnestia, J. van Haverbeke, and R. Flammang, Org. Mass Spectrom., 10, 313 (1975).