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SYNTHESIS AND STRUCTURE OF 5,5-DIALKYL-3-ARYLAMINO-2-THIOHYDANTOINS

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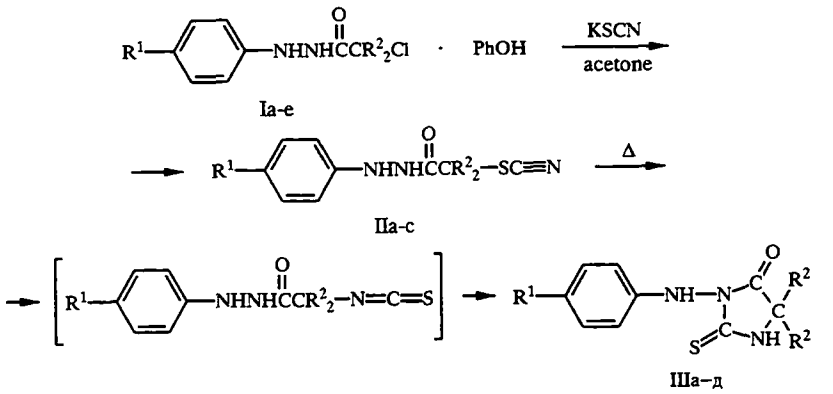
The reaction of arylhydrazides of α-alkyl-α-chlorocarboxylic acids with thiocyanate ions gave intermediate thiocyanates which rearranged to isothiocyanates on heating and the latter cyclized to 5,5-dialkyl-3-arylamino-2-thiohydantoins.

It is known that 5-substituted 3-amino-2-thiohydantoins can be obtained from the hydrazides of α-chlorocarboxylic acids and thiocyanates [1]. 5,5-Disubstituted hydantoins and thiohydantoins with antispasmodic and neurotropic properties are of medical interest [2-4]. We have developed a method for the synthesis of 5,5-dialkyl-3-arylamino-2-thiohydantoins from arylhydrazides of α-alkyl-α-chlorocarboxylic acids (Ia-e) and thiocyanate salts (see Scheme) in order to study their biological activity:



I, II, III a $R^1 = H, R^2 = Et$; б $R^1 = H, R^2 = Pr$; c $R^1 = H, R^2 = Bu$; d $R^1 = Me, R^2 = Bu$; e $R^1 = Br, R^2 = Bu$

The reaction occurs readily in 0.5-12 h at room temperature in aqueous acetone; either sodium or potassium thiocyanate can be used as the source of thiocyanate ion. Compounds Ia-e were added to the reaction mixture as their H-complexes with phenol which are readily purified and are stable on storage [5]. The characteristics of the products (IIa and IIb, IIIa-e) and their elemental analyses are given in Table 1, their spectroscopic characteristics in Table 2.

It is known that α-halogenocarbonyl compounds react with thiocyanate ion in acetone to give the thiocyanate initially by an S_{N2} substitution [1]. Formation of isothiocyanates was observed in the reaction of α-bromophenoxyacetic acids with ammonium thiocyanate in DMF [6] apparently via an S_{N1} mechanism in which the phenoxy group stabilized the partial (or complete) positive charge and the α-C. In our case one would expect that the tertiary chlorides I would readily undergo solvolysis to form a carbocation which would give an isothiocyanate according to Kornblum's rule. However, as a result of the strong destabilizing effect of the α-carbonyl group on the formation of a carbocation, the reaction occurred by a bimolecular nucleophilic substitution to give thiocyanates II. We believe that the route via aziridinones, formed from α-halogenoamines under the influence of bases [7, 8] is unlikely since the products of attack on $C_{(2)}$ of the aziridinone were not observed [9].

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TABLE 1. Characteristics of Compounds II and III

Compound	Molecular formula	(Found, %) / (Calculated, %)				M.p., °C (ethanol)	Yield, %
		C	H	N	S		
IIa	$C_{13}H_{17}N_3OS$	59.40 59,29	6.90 6,51	15.77 15,96	12.33 12,17	127...128	75
IIb	$C_{15}H_{21}N_3OS$	61.77 61,82	7.29 7,26	14.38 14,42	11.08 11,00	130...135*	47
IIIa	$C_{13}H_{17}N_3OS$	59.03 59,29	6.77 6,51	16.12 15,96	12.25 12,17	151...152	88
IIIb	$C_{15}H_{21}N_3OS$	61.55 61,82	7.03 7,26	14.71 14,42	10.99 11,00	174...177	75
IIIc	$C_{17}H_{25}N_3OS$	63.78 63,92	8.03 7,89	13.33 13,15	9.90 10,04	147...148	81
IIId	$C_{18}H_{27}N_3OS$	65.03 64,83	7.99 8,16	12.41 12,40	9.46 9,61	172...174	90
IIIe	$C_{17}H_{24}BrN_3OS$	51.44 51,46	6.18 6,07	10.50 10,55	7.96 8,05	182...183	73

*Cyclized to compound IIIb on melting.

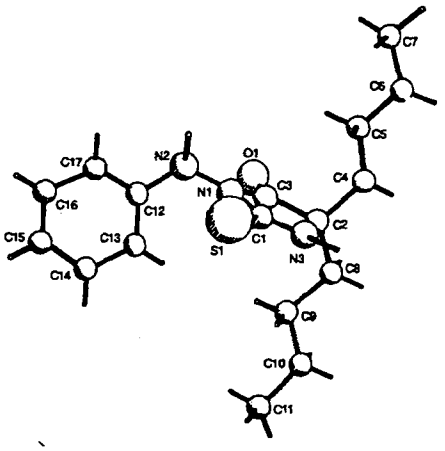

Fig. 1. Structure of compound IIIc.

Thiocyanates IIa and IIb can be purified by rapid recrystallization from ethanol, but prolonged (more than 10 min) heating at 70°C in ethanol, dioxane or toluene led to rearrangement to the thiocyanates which could not be isolated because of their rapid cyclization to the corresponding thiohydantoins (IIIa and IIIb). Thiocyanates IIc-e are viscous oily substances which rearrange very readily to the isothiocyanates which subsequently cyclize to the thiohydantoins IIIc-e (consequently the thiocyanates were not characterized, see Experimental section). The experimental plan for rearrangement with cyclization (conversion II → III) was successfully carried out by boiling compounds II in DMF for 0.5-1 h.

The IR spectra of the thiocyanates IIa and IIb contain bands for the S−C≡N group at 2120-2135 cm^{-1} (in the crystal) [10] which are absent from the spectra of products III; the bands of the carbonyl group in compounds IIa and IIb appear in the range 1650-1655 cm^{-1} while those for compounds IIIa-e appear at 1740-1765 cm^{-1}.

The ^1H NMR spectra (Table 2) and mass spectra (Experimental section) of compounds II and III agree well with their structures. The most intense peak in the spectrum of compound IIIe at *m/z* 142 arises from rupture of the thiohydantoin ring at the $C_{(2)}-N_{(1)}$ and $C_{(4)}-C_{(5)}$ bonds.

The structure of thiohydantoin IIIc was confirmed by single crystal x-ray crystallography (Fig. 1). The coordinates of the atoms, the bond lengths and bond angles are given in Tables 3, 4, and 5. The geometric parameters are very close to those found previously for 2-thiohydantoin [11].

The imidazolidone ring of IIIc is planar to 0.012 Å and the plane is conjugated with the oxygen atom. The sulfur atom is only 0.06 Å out of the plane, which indicates π-conjugation between this atom and the imidazolidine ring. This is also indicated by the C−N and C−C bond lengths in the heterocycle: they are all uniformly short.

TABLE 2. Spectroscopic Characteristics of Compounds II and III

Compound	IR spectra, ν, cm^{-1} *			^1H NMR spectrum, δ, ppm †			
	C=O	N—H	other bands	β-NH (br. s)	α-NH or NHC(S) (s)	H_{arom}	R^2 and other protons
IIa	1650	3260, 3340	1595, 1540, 1300, 1240, 1170, 1090, 960	‡	10,20	6,71...7,11 (6H, m, H_{arom} and β-NH)	0,97 (6H, t, $2CH_3$), 1,94 (2H, q, CH_2), 2,16 (2H, q, CH_2)
IIb	1655	3225, 3300	1600, 1560, 1420, 1245, 1130, 1105, 1100, 1070, 1020, 900	‡	10,28	6,33...7,23 (6H, m, H_{arom} and β-NH)	0,94 (6H, t, $2CH_3$), 2,29 (8H, m, $4CH_2$)
IIIa	1755	3180, 3280	1595, 1520, 1485, 1335, 1230, 1160	6,44	7,59	6,81...7,10 (5H, m)	0,88 (6H, t, $2CH_3$), 1,74 (4H, q, $2CH_2$)
IIIb	1740	3240 (sh)	1600, 1505, 1490, 1270, 1220, 1150	6,26	7,88	6,52...7,20 (5H, m)	0,90 (6H, t, $2CH_3$), 1,13...2,10 (8H, m, $4CH_2$)
IIIc	1755	3280 (sh)	1620, 1540, 1505, 1310, 1290, 1260, 1230	5,88	8,43	6,30...6,95 (5H, m)	0,50 (6H, t, $2CH_3$), 0,88 (8H, m, $4CH_2$), 1,52 (4H, t, $2CH_2$)
IIId	1760	3280 (sh)	1630, 1535, 1500, 1315, 1260, 1225, 1160	6,33	8,19	6,56 (2H, d, 2'- and 6'-H), 6,86 (2H, d, 3'- and 5'-H)	0,86 (6H, t, $2CH_3$), 1,21 (8H, m, $4CH_2$), 1,68 (4H, t, $2CH_2$), 2,20 (3H, s, CH_3 in Ar)
IIIe	1765	3230 (sh)	1610, 1535, 1515, 1250, 1240, 1215, 1160, 1080	6,05	8,16	6,36 (2H, m, 2'- and 6'-H), 7,40 (2H, m, 3'- and 5'-H)	0,62 (6H, t, $2CH_3$), 1,19 (8H, m, $4CH_2$), 1,71 (4H, t, $2CH_2$)

*For the $S-C\equiv N$ groups, ν = 2120 (IIa) and 2135 cm^{-1} (IIb).

†The spectra of IIa and IIb were recorded in DMSO-D_6, the rest in $CDCl_3$.

‡The signal was overlapped by the aromatic multiplet.

TABLE 3. Atomic Coordinates (fractions of the axes of the unit cell) and Thermal Parameters $B_{(iso)}$ and $B_{(eq)}$ for Molecule IIIc

Atom	x	y	z	$B_{(iso)}/B_{(eq)}$
S(1)	0,1183(1)	0,1272(1)	0,9800(0)	6,07(5)
O(1)	0,0901(2)	-0,2119(2)	0,7458(1)	5,9(1)
N(1)	0,1149(2)	-0,0710(2)	0,8676(1)	4,7(1)
N(2)	0,1418(2)	-0,1498(2)	0,9452(2)	5,1(1)
N(3)	0,0568(2)	0,0911(2)	0,7883(2)	5,2(1)
C(1)	0,0952(2)	0,0516(3)	0,8775(2)	3,9(1)
C(2)	0,0413(2)	-0,0027(2)	0,7137(2)	4,3(1)
C(3)	0,0840(2)	-0,1107(3)	0,7739(2)	3,8(1)
C(4)	-0,0833(2)	-0,0208(3)	0,6733(2)	4,7(2)
C(5)	-0,1585(3)	-0,0529(3)	0,7492(2)	4,6(2)
C(6)	-0,2792(3)	-0,0682(4)	0,7107(3)	5,7(2)
C(7)	-0,3498(3)	-0,1062(4)	0,7857(3)	5,5(2)
C(8)	0,1109(3)	0,0213(3)	0,6316(2)	5,4(2)
C(9)	0,2363(3)	0,0341(3)	0,6628(2)	5,2(2)
C(10)	0,3005(3)	0,0607(4)	0,5786(2)	5,9(2)
C(11)	0,4248(3)	0,0696(4)	0,6076(3)	6,7(2)
C(12)	0,2546(3)	-0,1570(3)	0,9886(2)	4,9(2)
C(13)	0,3437(3)	-0,1287(3)	0,9406(2)	5,4(2)
C(14)	0,4519(3)	-0,1451(4)	0,9865(3)	5,0(2)
C(15)	0,4722(4)	-0,1886(4)	1,0792(3)	5,9(2)
C(16)	0,3842(4)	-0,2154(4)	1,1267(3)	7,6(3)
C(17)	0,2760(3)	-0,2004(3)	1,0828(2)	6,4(2)
H(1N2)	0,082(2)	-0,139	0,998	6,5(3)
H(1N3)	0,024(2)	0,169	0,774	5,9(3)

TABLE 4. Bond Lengths in the Molecule of Compound IIIc

Bond	d, Å	Bond	d, Å
S(1)—C(1)	1,641(3)	O(1)—C(3)	1,202(4)
N(1)—N(2)	1,391(3)	N(1)—C(1)	1,401(4)
N(1)—C(3)	1,369(3)	N(2)—H(1N2)	1,093(3)
N(2)—C(12)	1,404(4)	N(3)—H(1N3)	0,966(3)
N(3)—C(1)	1,329(3)	N(3)—C(2)	1,465(3)
C(2)—C(3)	1,515(4)	C(2)—C(4)	1,535(4)
C(2)—C(8)	1,525(4)	C(4)—C(5)	1,520(4)
C(5)—C(6)	1,480(5)	C(6)—C(7)	1,491(5)
C(8)—C(9)	1,512(4)	C(9)—C(10)	1,512(5)
C(10)—C(11)	1,492(5)	C(12)—C(13)	1,372(5)
C(12)—C(17)	1,380(4)	C(13)—C(14)	1,374(5)
C(14)—C(15)	1,362(6)	C(15)—C(16)	1,353(6)
C(16)—C(17)	1,363(6)		

Atom $N_{(2)}$ is conjugated with the phenyl ring from which it is only 0.082 Å out of plane, whereas it is 0.185 Å from the plane of the heterocycle. The two rings, phenyl and thiohydantoin, are almost perpendicular to one another in compound IIIc: the angle between them is 87°.

All of the carbon atoms of both butyl groups are in a single plane with a precision of 0.046 Å, and this plane is parallel to the phenyl ring (the angle between the planes is 10°) and perpendicular to the plane of the thiohydantoin ring (90.4°). The IIIc molecules in the crystal are linked by O...N hydrogen bonds between the oxygen atom and the $N_{(3)}$ atoms in neighboring heterocycles. The O...$N_{(3)}$ distance is 2.819(5) Å and the angle at the hydrogen atom is 157.2°.

Compounds IIIa and IIIc showed no analgesic, anti-inflammatory or antitubercular activity.

EXPERIMENTAL

IR spectra of Nujol mulls were recorded on a UR-20 machine. ^{1}H NMR spectra were recorded with a Tesla BS-587A spectrometer at 80 MHz with HMDS as internal standard. Mass spectra of compounds IIa, IIIa, and IIIe were recorded with

TABLE 5. Bond Angles in the Molecule of Compound IIIc

Angle	ω, deg	Angle	ω, deg
N(2)—N(1)—C(1)	124,7(2)	N(2)—N(1)—C(3)	121,7(2)
C(1)—N(1)—C(3)	112,5(2)	N(1)—N(2)—H(1N2)	110,1(2)
N(1)—N(2)—C(12)	118,1(2)	H(1N2)—N(2)—C(12)	113,5(3)
H(1N3)—N(3)—C(1)	124,3(3)	H(1N3)—N(3)—C(2)	120,1(3)
C(1)—N(3)—C(2)	114,1(2)	S(1)—C(1)—N(1)	125,4(2)
S(1)—C(1)—N(3)	128,6(2)	N(1)—C(1)—N(3)	106,0(2)
N(3)—C(2)—C(3)	100,6(2)	N(3)—C(2)—C(4)	111,8(2)
N(3)—C(2)—C(8)	111,7(2)	C(3)—C(2)—C(4)	109,4(2)
C(3)—C(2)—C(8)	111,8(2)	C(4)—C(2)—C(8)	111,1(2)
O(1)—C(3)—N(1)	126,2(3)	O(1)—C(3)—C(2)	127,1(3)
N(1)—C(3)—C(2)	106,7(2)	C(2)—C(4)—C(5)	115,0(3)
C(4)—C(5)—C(6)	115,1(3)	C(5)—C(6)—C(7)	113,9(3)
C(2)—C(8)—C(9)	115,5(3)	C(8)—C(9)—C(10)	113,2(3)
C(9)—C(10)—C(11)	113,9(3)	N(2)—C(12)—C(13)	123,4(3)
N(2)—C(12)—C(17)	117,6(3)	C(13)—C(12)—C(17)	118,9(3)
C(12)—C(13)—C(14)	119,8(3)	C(13)—C(14)—C(15)	120,9(4)
C(14)—C(15)—C(16)	119,2(4)	C(15)—C(16)—C(17)	121,0(4)
C(12)—C(17)—C(16)	120,2(3)		

a Hitachi M-80 machine with direct insertion of the sample into the ion source and an ionizing voltage of 70 eV. The course of reactions and the purity of products were monitored by TLC on silufol with benzene–ether (3:2) as eluent and development with iodine vapor.

X-Ray Crystallographic Study of Compound IIIc. Compound IIIc crystallizes in the monoclinic system: a = 11.998(4), b = 11.184(3), c = 13.827(8) Å, β = 98.08(4)°, Z = 4, sp. gp. $P2_1/c$, V = 1837(1) Å^3. Unit cell parameters and 4424 reflections were measured on an Enraf Nonius CAD4 automatic diffractometer with the sample enclosed in transparent plastic (MoK_α, graphite monochromator, $\omega/2\theta$ scanning with $2\theta_{max}$ = 60° without accounting for absorption). The structure was solved by direct methods using the SHELX suite of programs and refined by full matrix least squares in the isotropic and then the anisotropic approximation. The hydrogen atoms on atoms $N_{(1)}$ and $N_{(3)}$ were found by Fourier difference syntheses and then their positional and thermal parameters were refined isotropically. The positions of the remaining hydrogen atoms were calculated geometrically and were not refined. The final confidence limit was R = 0.036.

Phenylhydrazides of α-alkyl-α-Thiocyanatocarboxylic Acids (IIa and b). NaSCN (0.19 g, 2.4 mmol) in water (3 cm^3) was added to a solution of hydrazine Ia (0.90 g, 2.3 mmol) in acetone (10 cm^3) at 25°C. After 24 h the product was filtered off, washed with water and crystallized to give IIa (0.45 g, 75%). Mass spectrum, m/z (I_{rel}, %): M^+ 263(38); [M^+ −HNCS, M^+ −2C_2H_5] 204(55); 176(8), 150(8), [$C_6H_5NHNCO^+$] 134(100), [$C_6H_5NHNH_2^+$]: 108 (75).

Compound IIb was obtained analogously. Its relatively small yield (47%) is explained by its partial conversion into the thiohydantoin IIIb during purification.

3-Phenylamino-5,5-diethyl-2-thiohydantoin (IIIa). Thiocyanate IIa (0.5 g, 1.9 mmol) was boiled in DMF (3 cm^3) for 0.5 h. The reaction mixture was cooled, poured onto ice, and the precipitate was crystallized from ethanol to give IIIa (0.44 g, 88%). Mass spectrum, m/z (I_{rel}, %): M^+ 263 (100); 235(5), 206(35), 150(40), 134(52), 109(19).

Compound IIIb was obtained analogously from thiocyanate IIb.

3-Arylamino-5,5-dibutyl-2-thiohydantoins (IIIc to IIIe). NaSCN (0.46 g, 5.7 mmol) in water (3 cm^3) was added dropwise with stirring to a solution of the complex of a hydrazide Ic-e with phenol (5 mmol) in acetone (20 cm^3). After 12 h the reaction mixture was poured over ice (100 g) and the aqueous layer was decanted. The oily residue was dissolved in ether (20 cm^3) and the solution was washed with water and dried over $MgSO_4$. The residue after removal of the ether was boiled for 0.5 h in DMF (4 cm^3), cooled and poured over ice. The crystalline product III was separated, washed with water and crystallized from ethanol.

Compound IIIa, mass spectrum, m/z (I_{rel}, %): [M^+ + 1] 399(27); M^+ 398(6); 397(25), 340(5), 338(5), 314(13), 312(13), 214 (7), 199(8), 173(5), 172(8), 171(6), 170(5), 153(20), 142(100).

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