SOME TRANSFORMATIONS OF AMINES OF THE DIHYDROPYRAN SERIES

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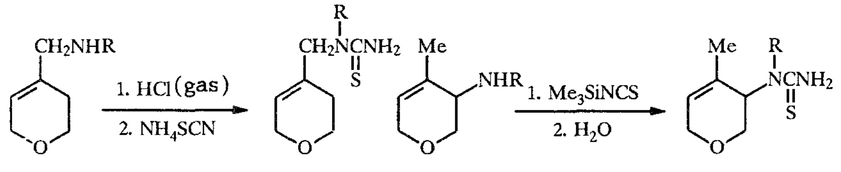
Thioureas, chloroacetamides, and 4-thiazolinone and 2-aminothiazole derivatives were obtained from 4-methyl-5-(R-amino)-5,6-dihydro-2H-pyrans and 4-(R-aminomethyl)-5,6-dihydro-2H-pyrans.

It is known [1] that the corresponding secondary amines of the dihydropyran series, which are convenient starting compounds for obtaining active substances that display antimicrobial and hypotensive properties and ease bronchial spasms, are formed in the reaction of 3,4-dibromo-4-methyl- and 3-bromo-4-(bromomethyl)tetrahydropyrans with alkyl- or arylamines. In the present research we have accomplished the conversion of amines of this sort to thioureas, chloroaceto derivatives, thiazolines, and thiazoles.

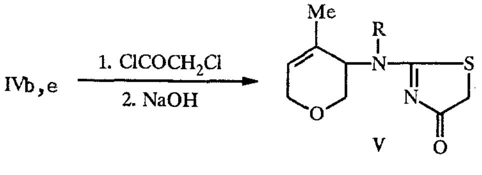
Refluxing the hydrochlorides of amines Ia, b with ammonium thiocyanate in chlorobenzene gave thioureas IIa, b [2]. The yields of the latter were only 36% and 20%, respectively, based on the starting amines, since hydrochlorination of the amines is accompanied by pronounced resinification even at low temperatures. We were able to synthesize the corresponding thioureas IVa-e in higher yields (58-75%, Table 1) by the reaction of trimethylsilyl thiocyanate with amines IIIa-e by the method in [3].



Ia,b II a,b III a-e IVa-e

I—IV a R=c-C_6H_{11}; c R=Ph; c R=o-MeC_6H_4; d R=m-MeC_6H_4; eR=p-MeC_6H_4

It is known that one method for the synthesis of thiazoline derivatives is the action of chloroacetylating agents on thioureas [4]. In fact, the chloroacetylation of IVb, e in dry $CHCl_3$ with chloroacetyl chloride led to the corresponding hydrochlorides, which were converted to thiazolinones Va, b by treatment with 20% NaOH.



V

Va R=Ph; b R=p-MeC_6H_4

The final products are crystalline substances with lower melting points than the starting thioureas (see Table 1).

We have previously [5] obtained pyridinium salts by the successive treatment of dihydropyranylamines with chloroacetyl chloride and pyridine. The intermediate chloroacetamides in this synthesis are convenient starting reagents for obtaining new

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TABLE 1. Characteristics of the Synthesized Compounds

Compound	Empirical formula	mp, °C	IR spectrum, cm^{-1}	PMR spectrum,* ppm	Yield, %
IIa	$C_{13}H_{16}N_2OS$	207	1225 (C=S), 3450, 3300 (NH_2), 1040 (C—O—C)	1,75 (2H, s CH_2); 3,5...4,1 (4H, m, CH_2—OCH_2); 5,8 (1H, s CH=C); 6,5...6,9 (7H, m NH_2, C_6H_5)	36
IIb	$C_{14}H_{18}N_2OS$	183	1228 (C=S), 3460, 3270 (NH_2), 1040 (C—O—C)	1,8 (2H, s, CH_2); 2,0 (3H, s, o-CH_3—C_6H_4); 3,7...4,1 (4H, m, CH_2OCH_2); 5,8 (1H, s CH=C); 6,4...6,8 (6H, m NH_2, C_6H_4)	20
IVa	$C_{13}H_{22}N_2OS$	151	1228 (C=S), 3500, 3310 (NH_2), 1040 (C—O—C)	1,0...2,2 (11H, m, cyclo C_6H_{11}); 1,8 (3H, s 4-CH_3); 3,3...4,5 (5H, m, CH_2OCH_2, CHN); 5,4 (1H, s, CH=C); 6,4 (2H, s NH_2)	58
IVb	$C_{13}H_{16}N_2OS$	138	1226 (C=S), 3510, 3320 (NH_2), 1030 (C—O—C)	2,5 (3H, s 4-CH_3); 4,0...4,3 (5H, m CH_2OCH_2 & CHN); 6,2 (1H, s, CH=C); 7,5 (2H, s NH_2); 7,6...8,1 (5H, m C_6H_5)	62
IVc	$C_{14}H_{18}N_2OS$	118	1230 (C=S), 3450, 3310 (NH_2), 1040 (C—O—C)	1,8 (3H, s 4-CH_3); 2,3 (3H, s, o-$\underline{C}H_3C_6H_4$); 3,5...4,0 (5H, m, CH_2OCH_2, CHN); 5,5 (1H, s CH=C); 7,2...7,8 (6H, m NH_2, C_6H_4)	75
IVd	$C_{14}H_{18}N_2OS$	127	1229 (C=S), 3510, 3320 (NH_2), 1035 (C—O—C)	2,0 (3H, s 4-CH_3); 2,3 (3H, s m-$\underline{C}H_3$—C_6H_4); 3,5...4,2 (5H, m CH_2OCH_2, CHN); 5,8 (1H, s CH=C); 7,2...7,8 (6H, m NH_2, C_6H_4)	68
IVe	$C_{14}H_{18}N_2OS$	122	1225 (C=N), 3510, 3300 (NH_2), 1050 (C—O—C)	1,7 (3H, s 4-CH_3), 2,3 (3H, s, p-$\underline{CH}_3C_6H_4$); 3,8...4,5 (5H, m CH_2OCH_2, CHN); 5,8 (1H, s CH=C); 7,1...7,7 (6H, m NH_2, C_6H_4)	70
Va	$C_{15}H_{16}N_2O_2S$	78	1650 (C=N), 1720 (C=O)	1,8 (3H, s 4-CH_3); 3,2...4,0 (7H, m. CH_2OCH_2, CH_2, CHN); 5,5 (1H, s CH=C); 6,3...7,1 (5H, m, C_6H_5)	35
Vb	$C_{16}H_{18}N_2O_2S$	71	1640 (C=N), 1735 (C=O)	1,7 (3H, s, 4-CH_3); 2,2 (3H, s, p-$\underline{CH}_3C_6H_4$); 3,5...4,0 (7H, m CH_2OCH_2, CH_2, CHN); 5,5 (1H, s CH=C), 6,8...7,8 (4H, m C_6H_4)	32
VIa	$C_{14}H_{22}NO_2Cl$	63	730 (C—Cl), 1790 (C=O)	1,2...2,2 (11H, m, cyclo C_6H_{11}); 1,7 (3H, s 4-CH_3); 3,5...4,0 (7H, m CH_2OCH_2, CH_2Cl, CHN); 5,5 (1H, s, CH=C)	91
VIb	$C_{14}H_{16}NO_2Cl$	83	720 (C—Cl), 1790 (C=O)	1,7 (3H, s, 4-CH_3); 3,5...4,1 (7H, m, CH_2—O—CH_2, CH_2—Cl, CHN); 5,5 (1H, s CH=C); 6,7...7,5 (5H, m, C_6H_5)	70
VIc	$C_{15}H_{18}NO_2Cl$	58	725 (C—Cl), 1785 (C=O)	1,65 (3H, s 4-CH_3); 2,1 (3H, s o-$\underline{CH}_3C_6H_4$); 3,5...4,1 (7H, m CH_2OCH_2, CH_2—Cl, CHN); 5,4 (1H, CH=C); 6,2...6,9 (4H, m C_6H_4)	80
VIIa	$C_{15}H_{23}N_3OS$	74	1630 (C=N), 1575 (CH=C), 3530, 3300 (NH_2)	1,0...1,9 (11H, m, cyclo C_6H_{11}); 1,8 (3H, s 4-CH_3); 3,5...4,1 (5H, m CH_2OCH_2, CHN); 5,5 (1H, s, CH=C); 5,7 (1H, s, CH=C); 6,5 (2H, s, NH_2)	18
VIIb	$C_{15}H_{17}N_3OS$	41	1625 (C=N), 1570 (CH=C), 3520, 3250 (NH_2)	1,7 (3H, s 4-CH_3); 3,5...4,1 (5H, m CH_2OCH_2, CHN); 5,5 (1H, s, CH=C); 5,7 (1H, s, CH=C); 6,5...7,5 (7H, m. NH_2, C_6H_5)	36

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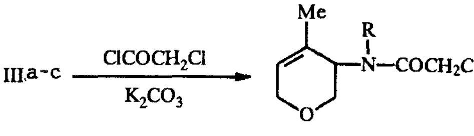
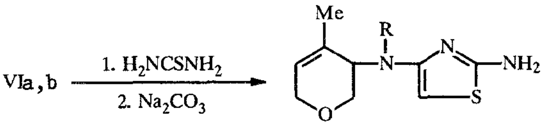
*The following solvents were used to record the spectra of the indicated compounds: DMSO for IIa, CCl_4—d_5-pyridine for IVa, d_7-DMF—CCl_4—d_5-pyridine for IVd, d_6-acetone for IVe, $CDCl_3$ for VIa-c, and CCl_4 for the remaining compounds.

heterocycles, particularly aminothiazoles. In this connection, the corresponding amides VIa-c were synthesized in good yields (58-90%) from substituted amines IIIa-c.



VI a-c

A crystalline substance, which was identified as 2,4-[N-cyclohexyl-(4-methyl-5,6-dihydro-2H-pyran-5-yl)]diaminothiazole (VIIa) from the PMR spectrum, was isolated when chloroacetamide VIa and thiourea were heated in absolute alcohol for 5 h. The low yield (18%) of the product can be explained by the donor properties of the amino group in the starting chloroacetamide, since the yields of 2-aminothiazoles from chloro ketones via a similar method range from 90% to 95% [6]. One therefore might have expected that decreasing the basicity of the nitrogen atom would lead to an improvement in the results. In fact, 2-aminothiazole VIIb is obtained in higher yield when N-phenyl derivative VIb is used in this reaction.



VII a,b

The structures of the synthesized compounds are confirmed by the spectral data presented in Table 1.

EXPERIMENTAL

The IR spectra of suspensions of the compounds in mineral oil were recorded with a Perkin—Elmer 457 spectrometer. The PMR spectra were obtained with a Tesla BS-487 C spectrometer (80 MHz) with hexamethyldisiloxane (HMDS) as the internal standard. The individuality of the substances obtained was verified by TLC on Silufol-254 plates in benzene—alcohol (6:1) and hexane—ethyl acetate (3:1) systems.

Starting amines Ia-b and IIIa-e were synthesized by a previously developed method [1].

Thioureas IIa-b and IVa-e were obtained by the methods in [2] and [3], respectively. The characteristics of the synthesized compounds are presented in Table 1. The results of elementary analysis of the compounds for C, H, and N were in agreement with the calculated values.

2-[N-Aryl-N-(4-methyl-5,6-dihydro-2H-pyran-5-yl)amino]-2-thiazolin-4-ones Va, b. A 2.37-g (21 mmole) sample of chloroacetyl chloride was added dropwise to a solution of 4.92 g (20 mmole) of thiourea IVb in 30 ml of dry $CHCl_3$, and the mixture was heated up to the boiling point. Heating was then discontinued, and the mixture was allowed to stand for 24 h. The precipitated hydrochloride of thiazolinone Va was removed by filtration, washed with acetone, and treated with 20% NaOH. The resulting precipitate was removed by filtration, washed with water until the washings were neutral, and recrystallized from alcohol to give 2 g of product Va. Thiazolinone Vb was similarly synthesized from thiourea IVe.

N-R-N-(4-Methyl-5,6-dihydro-2H-pyran-5-yl)chloroacetamides VIa-c. A 6.2-g (55 mmole) sample of chloroacetyl chloride was added dropwise to a mixture of 10.2 g (50 mmole) of amine IIIc and 13.8 g (100 mmole) of K_2CO_3 in 50 ml of absolute ether. After CO_2 evolution ceased, the precipitate was removed by filtration, washed with water, and dried to give 8.4 g of chloroacetamide VIc. Chloroacetamides VIa, b, respectively, were similarly synthesized from amines IIIa, b.

2,4-[N-R-N-(4-Methyl-5,6-dihydro-2H-pyran-5-yl)]diaminothiazoles VIIa, b. A mixture of 5.9 g (20 mmole) of chloroacetamide VIa and 16.7 g (22 mmole) of thiourea in 50 ml of absolute alcohol was refluxed for 5 h, after which the alcohol was removed, and the residue was washed with absolute ether. The precipitated crystals of the hydrochloride of diaminothiazole VIIa were treated with 20 Na_2CO_3 solution, and the resulting crystalline product was removed by filtration and washed with water to give 1.15 g (3.9 mmole) of product VIIa. Diaminothiazole VIIb was similarly synthesized from amide VIb.

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SYNTHESIS AND INVESTIGATION OF THE MESOMORPHIC PROPERTIES OF PYRAN DERIVATIVES

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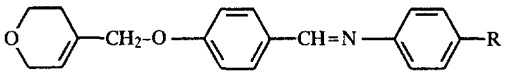
4′-[(5,6-Dihydro-2H-pyran-4-yl)methoxy]benzylidene-4″-alkoxyanilines, which have the properties of smectic liquid crystals, were synthesized. The effect of the pyran ring in the benzylidene component and the length of the aliphatic radical in the aniline component on the type and thermal stability of the meso phase was ascertained.

Continuing our investigation of the effect of the molecular structure on mesomorphism in azomethines [1] we synthesized 4′-[(5,6-dihydro-2H-pyran-4-yl)methoxy]benzylidene-4″-alkoxyanilines.



I - XI

I R=H, II R=OCH_3, III R=OC_2H_5, IV R=OC_3H_7; V R=OC_4H_9, VI R=OC_5H_{11}, VII R=OC_6H_{13}, VIII R=OC_7H_{15}, IX R=OC_8H_{17}, X R=OC_9H_{19}, XI R=$OC_{10}H_{21}$

4-Methylenetetrahydropyran (XII), which is a high-tonnage waste product in the manufacture of isoprene via the dioxane method [2], was used as the starting compound. Compound XII reacts quantitatively with bromine in CCl_4, and the resulting 4-bromo-4-bromomethyltetrahydropyran (XIII) reacts with p-hydroxybenzaldehyde in methyl ethyl ketone in the presence of potassium carbonate to give 4′-[(5,6-dihydro-2H-pyran-4-yl)methoxy]benzaldehyde (XIV). Condensation of XIV with p-alkoxyanilines gave I-XI.

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