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α-DIMETHYLAMINOMETHYLENE-γ-THIOBUTYROLACTONE AND SYNTHESIS OF HETEROCYCLIC DERIVATIVES

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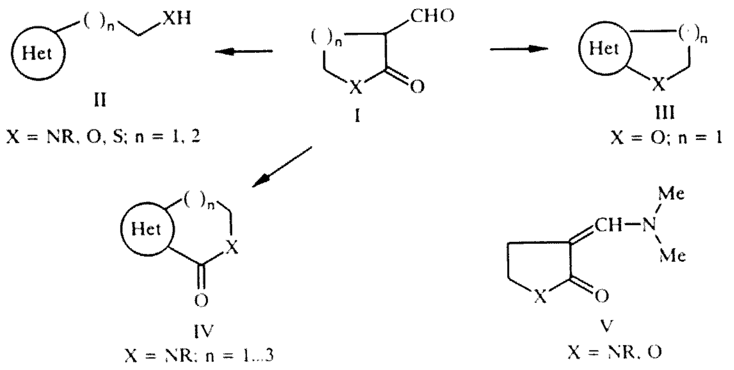
By the interaction of γ-thiobutyrolactone with bis(dimethylamino)-tert-butoxymethane, α-dimethylamino-methylene-γ-thiobutyrolactone has been obtained. Its reactions with arylhydrazines have been investigated. With phenylhydrazine, 4-(2-mercaptoethyl)-1-phenylpyrazolone-5 is formed; but with α-substituted phenylhydrazines, as a result of the Fischer reaction and expansion of the thiolactone ring, 9-substituted 4,9-dihydrothiopyrano[3,4-b]indol-1(3H)-ones are formed. Analogous reactions with 1-amino derivatives of tetrahydroquinoline and tetrahydroquinaldine lead to the formation of 5,6,10,11-tetrahydro-4H,8H-thio-pyrano[4',3':4,5]pyrrolo[3,2,1-ij]quinolin-8-ones, representatives of a new heterocyclic system.

α-Formyl derivatives of lactams, lactones, and thiolactones I, together with other α-acyl derivatives, are valuable synthons for the preparation of various heterocyclic compounds. A common feature of these interesting β-dicarboxylic compounds is their capability for ring opening in the course of a reaction, to form heterocyclic compounds of the type of II with ω-aminoalkyl, ω-hydroxyalkyl, or ω-mercaptoalkyl substituents [1, 2]. Moreover, it is possible to obtain condensed heterocycles of the type of III [3] and IV [4, 5].



II
X = NR, O, S; n = 1, 2

I

III
X = O; n = 1

IV
X = NR; n = 1...3

V
X = NR, O

Unfortunately, the aldehydes I, particularly α-formyl-γ-thiobutyrolactone (I, with X = S, n = 1) are not readily accessible. This compound has been obtained by Claisen condensation of thiobutyrolactone with ethyl formate, in a yield of only 26%, by the use of the diisopropyl amide of magnesium bromide as a condensing agent [6]. At the same time, for the lactams [7] and lactones [8], rather effective methods have been reported for the synthesis of α-dimethylaminomethylene derivatives V, which are the enamines of the corresponding aldehydes. It has also been shown that these enamines can be used successfully as the equivalents of the corresponding aldehydes in reactions with hydrazines [4, 5, 9]. Moreover, the enamines V, in contrast to the aldehydes I, are not subject to dimerization and trimerization processes.

The work reported here was aimed at synthesizing α-dimethylaminomethylene-γ-thiobutyrolactone (VIII) and investigating the possibility of its use in synthesizing sulfur-containing heterocycles in reactions with arylhydrazines.

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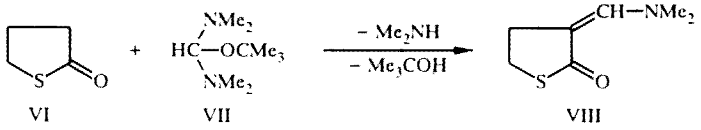
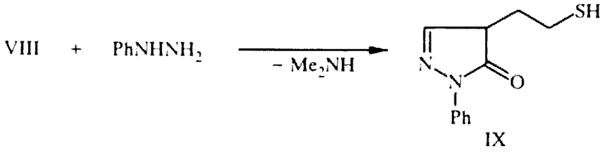
As a reagent for the formylation of γ-thiobutyrolactone (VI), we selected bis(dimethylamino)-tert-butoxymethane (VII), which had given good results in the formylation of γ-butyrolactone [8]. The aminalether VII also proved to be effective in the reaction with the thiolactone. As a result of this interaction, we obtained the enamine VIII in a 75% yield.

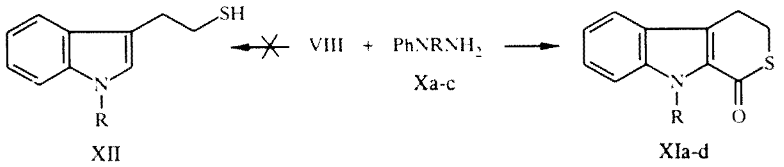


Interaction of the enamine VIII with phenylhydrazine leads to the formation of the pyrazolone IX. In this case, the enamine VIII was completely analogous to the enamine of formyllactone V (X = O) [10]. At the same time, we could expect the formation of the thiopyranoindole XIa by analogy with the reactions of the N-alkyllactams V (X = NAlk) [4]; however, we did not find any XIa in the reaction mixture.



In the interaction of the enamine VIII with α-substituted phenylhydrazines Xa-c, pyrazolone formation is impossible, and Fischer indolization takes place. With the aim of preventing hydrolytic cleavage of the thiolactone ring, we first carried out the reaction in an anhydrous acidic medium (absolute dioxane in the presence of trifluoroacetic acid). Under these conditions, the same as in reactions with the lactone V (X = 0) [9], indolization is accompanied by a rearrangement with expansion of the thiolactone ring. The reaction results in the formation of 9-substituted 4,9-dihydrothiopyrano[3,4-b]indol-1(3H)-ones (XIa-c).

We had hoped that when the reaction is carried out in an acidic water-alcohol solution, we would also obtain 3-(2-mercaptoethyl)indoles (thiotryptophols) XII as a result of hydrolysis of the thiolactone ring and subsequent decarboxylation, as did take place in the synthesis of tryptophols from α-formyl-γ-butyrolactone [2]. However, we found that the thiolactone ring does not undergo hydrolysis under acidic conditions, and that the reaction products are the same thiopyranoindoles XIa-c, in very nearly the same yields. We did not find any thiotryptophols XII in the reaction mixtures. Thus, it proved to be unnecessary to use absolute solvents in the synthesis of the thiopyranoindoles XI, in contrast to their oxygen analogs.

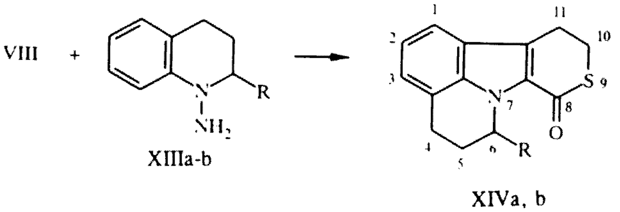


X,XI: a) R = $PhCH_2$; b) R = Ph; c) R = Me; d) R = H

From these results it can be seen that the thiolactone VIII in its reaction with phenylhydrazine behaves in the same manner as the lactone V (X = O), i.e., the ring is opened to form the pyrazolone IX; but in reactions with α-substituted phenylhydrazines in an acidic water-alcohol medium, it behaves in the same manner as the N-alkyllactams V (X = NAlk), i.e., it resists acid hydrolysis and forms the tricyclic compounds XI.

It should be noted that in the chromatographic purification of the thiopyranoindole XIc, along with the principal substance, the 9-unsubstituted thiopyranoindole XId was recovered with a yield of 9%. Similar processes of dealkylation in the course of the reaction had been observed previously in the interaction of α-substituted phenylhydrazines with enamines of formyllactams V (X = NR) [4, 5].

As α-substituted arylhydrazines in the reaction with the enamine VIII, we also introduced 1-amino derivatives of tetrahydroquinoline XIIIa and of tetrahydroquinaldine XIIIb. The reaction yielded 5,6,10,11-tetrahydro-4H,8H-thiopyrano[4',3':4,5]pyrrolo[3,2,1-ij]quinolin-8-ones XIVa,b, which are derivatives of a new heterocyclic system.



XIII,XIV: a) R = H; b) R = Me

The mechanism through which compounds XIa-c and XIVa,b are formed is most likely no different from that of their nitrogen analogs, derivatives of β-carboline [4]. The IR spectra of these compounds exhibit an intense band of vibrations of the thiolactone carbonyl in the 1600-1635 cm^{-1} region. A characteristic feature of the PMR spectra of compounds XI and XIV is the closeness of the chemical shifts of signals from the two methylene groups of the thiolactone ring, which are observed in the 3.25-3.50 ppm interval. When the spectra are recorded on an instrument with a low working frequency (60 MHz), the signals from the protons of these groups appear in the form of a singlet. With a spectrometer frequency of 250 MHz, this part of the spectrum takes on a form that is typical for an AA'BB' system; i.e., it consists of two multiplets of nine lines each, symmetric relative to their common center. For compound XIVb, the form of the spectrum is more complicated, since all of the protons of the thiolactone ring in this case are nonequivalent, forming an ABCD system. Nonetheless, an increase of the working frequency of the instrument to 400 MHz does not make it possible to obtain a first-order spectrum for these protons.

EXPERIMENTAL

The UV spectra were taken on a Hitachi EPS-3T instrument in isopropyl alcohol, the IR spectra on a Jasco IR-S instrument in KBr tablets. The PMR spectra were recorded on Tesla BS-467 (60 MHz) or Bruker WM-250 instruments in $CDCl_3$ or on a Varian XL-400 instrument in DMSO-d_6, internal standard TMS. Mass spectra were obtained on a Varian MAT-311-A instrument with direct introduction of the sample into the ion source, with an ionizing electron energy of 70 eV. Only the peaks with intensities above 10% are reported here. The course of the reaction and the purity of the compounds was monitored by means of TLC on Silufol UV-254 plates, with development in UV light or in iodine vapor.

Elemental analyses of the synthesized compounds for C and H matched the calculated values.

The phenylhydrazine and the α-substituted phenylhydrazines X were obtained in the form of ready-prepared salts (hydrochlorides, or the sulfate in the case of Xc) without additional purification.

1-Amino-1,2,3,4-tetrahydroquinoline(XIIIa) and 1-amino-1,2,3,4-tetrahydroquinaldine (XIIIb) were prepared by a method given in [11].

γ-Thiobutyrolactone VI was obtained by generally known methods, with the following scheme: γ-Butyrolactone, under the action of $SOCl_2$ in the presence of $ZnCl_2$, is cleaved to form γ-chlorobutyryl chloride; by reaction with thiourea, this is converted to γ-mercaptobutyric acid, by analogy with a method given in [13]. The mercapto acid is subsequently dehydrated to the thiolactone VI [13]. Overall yield 51%.

Bis(dimethylamino)-tert-butoxymethane VII was obtained by a method given in [14].

α-Dimethylaminomethylene-γ-thiobutyrolactone (VIII, $C_7H_{11}NOS$). A mixture of 1 g (10 mmoles) of the thiolactone VI and 2 g (11.5 mmoles) of the aminalether VII was heated on an oil bath for 2 h at 105-115°C, while excluding atmospheric moisture; then, the tert-butyl alcohol and the dimethylamine that had been formed were removed under vacuum, and the mixture was heated for another 30 min at 115°C. After cooling, 7 ml of absolute ether was added, and the reaction mixture was left overnight in a refrigerator. The precipitated crystals were filtered off and washed with ether. Obtained 1.02 g of light yellow crystals of the enamine VIII. An additional 0.16 g was recovered from the ether filtrate. Yield 75%, mp 83-85°C (from cyclohexane). R_f 0.21 (benzene–ether, 3:1). IR spectrum, cm^{-1}: 1647 (C=O), 1579 (C=C). UV spectrum, λ_{max}, nm (and log ε): 248 (3.52), 328 (4.50). PMR spectrum (60 MHz), ppm: 3.03 (6H, s, $2CH_3$), 3.18 (4H, s, CH_2CH_2), 7.06 (1H, s, CH). Product gives a dark green color with $FeCl_3$.

4-(2-Mercaptoethyl)-1-phenylhydrazolone-5 (IX, $C_{11}H_{12}N_2OS$). To a suspension of 300 mg (2.1 mmoles) of phenylhydrazine hydrochloride in 20 ml of absolute dioxane, there was added a solution of 300 mg (1.9 mmoles) of the ena-

TABLE 1. Data from Elemental Analyses

Compound	Found, %		Empirical formula	Calculated, %	
	C	H		C	H
VIII	53,82	7,26	$C_7H_{11}NOS$	53,47	7,05
IX	59,92	5,36	$C_{11}H_{12}N_2OS$	59,98	5,49
XIa	73,66	5,14	$C_{18}H_{15}NOS$	73,69	5,15
XIb	73,30	4,72	$C_{17}H_{13}NOS$	73,09	4,69
XIc	66,27	5,18	$C_{12}H_{11}NOS$	66,33	5,10
XId	65,42	4,80	$C_{11}H_9NOS$	65,00	4,46
XIVa	69,13	5,35	$C_{14}H_{13}NOS$	69,10	5,39
XIVd	69,85	5,80	$C_{15}H_{15}NOS$	70,00	5,88

mine VIII in 10 ml of absolute dioxane and 2.5 ml of trifluoroacetic acid. The reaction mixture was refluxed for 8 h; after cooling, the dioxane was removed under vacuum. The residue was dissolved in 30 ml of chloroform, the solution was washed with water to neutral reaction and dried with $MgSO_4$, and the solvent was removed under vacuum. The solid residue was triturated with benzene, and the residue was filtered off. After recrystallizing from a mixture of benzene and acetone, obtained 180 mg (43%) of the pyrazolone IX, mp 149-151°C. R_f 0.13 (benzene–ether, 3:1). IR spectrum, cm^{-1}: 1613, 1577. UV spectrum, λ_{max}, nm (and log ε): 245 (4.14), 274 shoulder (3.85). Mass spectrum, *m/z* (and I, %): 220 (48, M^+), 174 (15), 173 (100), 93 (13), 78 (15), 77 (46). Calculated: M 220.29.

9-Benzyl-4,9-dihydrothiopyrano[3,4,b]indol-1(3H)-one (XIa, $C_{18}H_{15}NOS$). Method A. A solution of 450 mg (1.9 mmoles) of α-benzylphenylhydrazine hydrochloride (Xa), 300 mg (1.9 mmoles) of the enamine VIII, and 3 ml of trifluoroacetic acid in 35 ml of absolute dioxane was refluxed for 8 h. The solvent was removed under vacuum, benzene and water were added to the residue up to 20 ml, the mixture was shaken, and the organic layer was separated, washed with water (2 × 20 ml), and dried with Na_2SO_4. The benzene solution was filtered through a layer of silica gel and evaporated under vacuum. The residue was recrystallized from isopropyl alcohol, obtaining 430 mg (77%) of compound XIa, mp 159-160°C (from acetone). R_f 0.64 (benzene). IR spectrum, cm^{-1}: 1615 (C=O). UV spectrum, λ_{max}, nm (and log ε): 241 (4.20), 283 (3.72), 322 (4.29). PMR spectrum (60 MHz), ppm: 3.30 (4H, s, CH_2CH_2), 5.73 (2H, s, $N-CH_2$), 6.95-7.40 (8H, m, H_{arom}), 7.63 (1H, d, J = 7 Hz, 5-H). Mass spectrum, *m/z* (I, %): 293 (100, M^+), 218 (21), 147 (12), 92 (21), 91 (98). Calculated: M 293.39.

Method B. A solution of 300 mg (1.3 mmoles) of the hydrazine hydrochloride Xa and 200 mg (1.3 mmoles) of the enamine VIII in 10 ml of isopropyl alcohol, 3 ml of water, and 0.4 ml of concentrated HCl was refluxed for 3.5 h; the reaction mixture was cooled, and the precipitate was filtered off. Obtained 280 mg (75%) of compound XIa, mp 158-160°C (from acetone). A mixture of samples obtained by methods A and B did not show any melting point depression.

9-Phenyl-4,9-dihydrothiopyrano[3,4-b]indol-1(3H)-one (XIb, $C_{17}H_{13}NOS$), obtained from the enamine VIII and the hydrochloride of 1,1-diphenylhydrazine Xb, by a procedure analogous to that used for compound XIa, method B. After cooling the reaction mixture, the solvent was removed under vacuum. The residue was dissolved in benzene; the solution was washed with water to neutral reaction and dried with Na_2SO_4, and the solvent was removed under vacuum. The residue was purified chromatographically in an 18 × 1.2 cm column with 100-160 μm silica gel, with a 7:3 benzene–hexane system as eluent. The yield of compound XIb was 57%, mp 124-126°C (from methyl alcohol). R_f 0.40 (benzene). IR spectrum, cm^{-1}: 1635 (C=O). UV spectrum, λ_{max}, nm (and log ε): 241 (4.22), 251 shoulder (4.12), 2.86 (3.84), 320 (4.30), 345 shoulder (3.97). PMR spectrum (60 MHz), ppm: 3.28 (4H, s, CH_2CH_2), 6.87-7.65 (9H, m, H_{arom}).

9-Methyl-4,9-dihydrothiopyrano[3,4-b]indol-1(3H)-one (XIc, $C_{12}H_{11}NOS$) and 4,9-dihydrothiopyrano[3,4-b]indol-1(3H)-one (XId, $C_{11}H_9NOS$) was obtained from the enamine VIII and the sulfate of α-methylphenylhydrazine Xc in the same manner as for compound XIb. Compound XIc was eluted from the column with benzene; yield 49%, mp 108-109.5°C (from cyclohexane). R_f 0.37 (benzene). IR spectrum, cm^{-1}: 1625 (C=O). UV spectrum, λ_{max}, nm (and log ε): 240 (4.28), 271 (3.74), 282 (3.74), 325 (4.32). PMR spectrum (25 MHz), ppm: 3.26-3.32 and 3.37-3.43 (4H, two m, CH_2CH_2); 4.04 (3H, s, CH_3); 7.17 (1H, ddd, J_{56} = 8.1 Hz, J_{67} = 6.8 Hz, J_{68} = 1.3 Hz, 6-H); 7.34 (1H, ddd, J_{78} = 8.3 Hz, J_{68} = 1.3 Hz, J_{58} = 0.9 Hz, 8-H); 7.42 (1H, ddd, J_{78} = 8.3 Hz, J_{67} = 6.8 Hz, J_{57} = 1.3 Hz, 7-H); 7.63 (1H, ddd, J_{56} = 8.1 Hz, J_{57} = 1.3 Hz, J_{58} = 0.9 Hz, 5-H).

Upon further elution with a 7:1 benzene–ether system, compound XId was recovered, yield 9%, mp 181-182°C (from benzene). R_f 0.40 (10:1 benzene–ether). IR spectrum, cm^{-1}: 3220 (NH), 1607 (C=O). UV spectrum, λ_{max}, nm (and log ε): 239 (4.24), 267 (3.79), 277 (3.75), 325 (4.38). PMR spectrum (250 MHz), ppm: 3.25-3.35 and 3.42-3.52 (4H, two m, CH_2CH_2); 7.17 (1H, ddd, J_{56} = 8.2 Hz, J_{67} = 6.8 Hz, J_{68} = 1.2 Hz, 6-H); 7.38 (1H, ddd, J_{78} = 8.2 Hz, J_{67} = 6.8 Hz, J_{78} = 1.0 Hz, 7-H); 7.46 (1H, br.d, J = 8.2 Hz, 8-H); 7.63 (1H, br.d, J = 8.2 Hz, 5-H); 9.36 (1H, br.s, NH). Mass spectrum, *m/z* (and I, %): 203 (100, M^+), 175 (43), 174 (40), 170 (26), 157 (28), 130 (36), 129 (99), 128 (21), 115 (23), 102 (23), 101 (13), 88 (18), 77 (15). Calculated: M 203.26.

5,6,10,11-Tetrahydro-4H,8H-thiopyrano[4',3':4,5]pyrrolo[3,2,1-ij]quinolin-8-one (XIVa, $C_{14}H_{13}NOS$), obtained from the enamine VIII and 1-amino-1,2,3,4-tetrahydroquinoline (XIIIa) in the same manner as for compound XIa, method B, with the exception that instead of water, 2 ml of concentrated HCl was added to the reaction mixture. After cooling the reaction mixture, the solvent was removed under vacuum. The residue was extracted with hot hexane, and the hexane was driven off. The remaining substance was crystallized from isopropyl alcohol with the addition of activated carbon. Yield 60%, mp 126-127°C. R_f 0.71 (10:1 benzene – acetone). IR spectrum, ppm: 1623 (C=O). UV spectrum, λ_{max}, nm (and log ε): 248 (4.30), 2.71 shoulder (3.69), 283 (3.65), 324 (4.29), 360 shoulder (3.74). PMR spectrum (250 MHz), ppm: 2.21 (2H, m, 5-CH_2); 2.96 (2H, m, AA' part of AA'XX' system, 4-CH_2); 3.27-3.34 and 3.37-3.44 (2H and 2H, two m, CH_2CH_2S); 4.53 (2H, m, AA' part of AA'XX' system, 6-CH_2); 7.03-7.10 (2H, m, 2-H and 3-H); 740-7.47 (1H, m, 1-H).

6-Methyl-5,6,10,11-tetrahydro-4H,8H-thiopyrano[4',3':4,5]pyrrolo[3,2,1-ij]quinolin-8-one (XIVb, $C_{15}H_{15}NOS$), obtained from the enamine VIII and 1-amino-1,2,3,4-tetrahydroquinaldine (XIb), in the same manner as for compound XIVa. Crystallized from a mixture of hexane and benzene, yield 59%, mp 107-109°C. R_f 0.74 (10:1 benzene – acetone). IR spectrum, cm^{-1}: 1632 (C=O). UV spectrum, λ_{max}, nm (and log ε): 248 (4.46), 271 shoulder (3.84), 283 (3.83), 324 (4.44), 360 shoulder (3.92). PMR spectrum (400 MHz, DMSO-d_6): 1.38 (3H, d, 6-CH_3); 2.10-2.20 (2H, m, 5-CH_2); 2.90 (1H, dt, J_{gem} = 16.5 Hz, $J_{4\text{-}e,5\text{-}a}$ = $J_{4\text{-}e,5\text{-}e}$ = 3.5 Hz, 4-H_e); 3.07 (1H, ddd, J_{gem} = 16.5 Hz, $J_{4\text{-}a,5\text{-}a}$ = 11.5 Hz, $J_{4\text{-}a,5\text{-}e}$ = 7.0 Hz, 4-H_a); 3.26-3.35 and 3.38-3.48 (2H and 2H, two m, CH_2CH_2S); 5.43 (1H, m, 6-H); 6.97-7.04 (2H, m, 2-H and 3-H); 7.39 (1H, d, J = 8.0 Hz, 1-H).

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