SYNTHESIS AND SOME TRANSFORMATIONS OF 1,2,3,4-TETRAHYDROPHENOTHIAZINE DERIVATIVES

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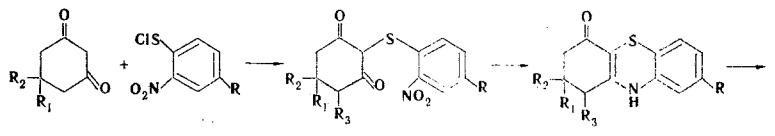
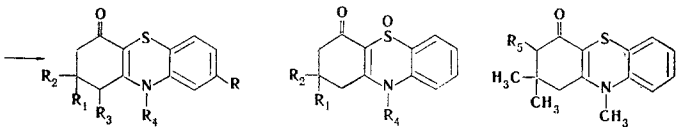
1,2,3,4-Tetrahydrophenothiazine derivatives were obtained from cyclic monoketones and 1,3-diketones and o-nitroarenesulfenyl chlorides. The alkylation, aminomethylation, and oxidation of the compounds obtained were studied.

Despite the enormous interest in the synthesis of various phenothiazine derivatives [1], hydrogenated derivatives of phenothiazine that contain a carbonyl group in the hydrogenated benzene ring have remained unknown up until now. 4-Oxotetrahydrophenothiazine and its derivatives are of doubtless interest. These compounds are the structural analogs of 4-oxotetrahydroindoles and carbazoles, which have affect on the central nervous system.

Hydrogenated phenothiazine derivatives can be obtained by the reaction of o-aminothiophenols and substituted α-halocyclohexanones. However, there is also another presently virtually unused route to the synthesis of hydrogenated phenothiazines, the possibility of which was indicated by Zincke, who used the products of the condensation of ketones with o-nitrobenzenesulfenyl chloride for the synthesis of benzothiazines [2].

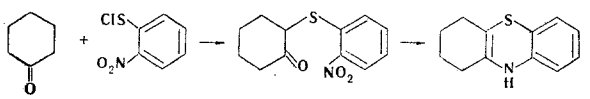


I-VI VII-XIII



XIV-XIX XXI-XXIV XXV, XXVI

I, VII $R=R_1=R_2=R_3=H$; II, VIII $R=Br$, $R_1=R_2=R_3=H$; III, IX $R=R_3=H$, $R_1=R_2=CH_3$; IV, X $R=Br$, $R_1=R_2=CH_3$, $R_3=H$; V, XI $R=R_2=R_3=H$, $R_1=C_6H_5$; VI, XII $R=Br$, $R_1=C_6H_5$, $R_2=H$, $R_3=COOC_2H_5$; XIII $R=R_2=H$, $R_1=C_6H_5$, $R_3=COOC_2H_5$; XIV $R=R_1=R_2=R_3=H$, $R_4=CH_3$; XV $R=R_3=H$, $R_1=R_2=R_4=CH_3$; XVI $R=R_1=R_3=H$, $R_2=C_6H_5$, $R_4=CH_3$; XVII $R=R_1=R_2=R_3=H$, $R_4=CH_2CH_2N(C_2H_5)_2$; XVIII $R=R_3=H$, $R_1=R_2=CH_3$, $R_4=CH_2CH_2N(CH_3)_2$; XIX $R=R_3=H$, $R_1=R_2=CH_3$, $R=CH_2N(CH_2)_4O$; XXI $R_1=R_2=R_4=H$; XXII $R_4=H$, $R_1=R_2=CH_3$; XXIII $R_1=R_2=R_4=CH_3$; XXIV $R_1=H$, $R_2=C_6H_5$, $R_4=CH_3$; XXV $R_5=CH_2N(CH_2)_4O$; XXVI $R_5=CH_2OH$



XXVII XXVIII

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TABLE 1. 1,3-Diketones (I-VI) and 1-Oxo-1,2,3,4-tetrahydrophenothiazines (VIII-XIII)

Comp.	R	R_1	R_2	R_3	mp, °C	Empirical formula	Found, %				Calculated, %				Yield, %
							C	H	N	S	C	H	N	S	
I	H	H	H	H	203—204	$C_{12}H_{11}NO_4S$	54,2	4,2	5,2	12,0	54,3	4,2	5,3	12,1	92
II	Br	H	H	H	192—193[a]	$C_{12}H_{10}BrNO_4S$	41,9	3,1	4,1	9,5	41,9	2,9	4,1	9,3	70
III	H	CH_3	CH_3	H	177—178[a]	$C_{14}H_{15}NO_4S$	57,4	5,2	4,8	11,0	57,3	5,2	4,8	10,9	90
IV	Br	CH_3	CH_3	H	225—226[a]	$C_{14}H_{13}BrNO_4S$	45,0	3,7	3,8	8,5	45,3	3,5	3,8	8,6	70
V	H	C_6H_5	H	H	226—227[b]	$C_{18}H_{15}NO_4S$	63,1	4,3	4,1	9,6	63,3	4,4	4,1	9,4	53
VI	Br	C_6H_5	H	H	207—208[b]	$C_{21}H_{18}BrNO_6S$	50,9	3,7	2,9	6,2	51,2	3,7	2,8	6,5	65
VII	Br	H	H	$COOC_2H_5$	266—267[b]	$C_{12}H_{10}BrNOS$	48,7	3,8	4,7	10,5	48,7	3,4	4,7	10,8	94
VIII	H	CH_3	CH_3	H	264—265[b]	$C_{14}H_{15}NOS$	68,7	6,1	5,7	13,1	68,5	6,2	5,7	13,1	82
IX	Br	CH_3	CH_3	H	265—266[b]	$C_{14}H_{14}BrNOS$	51,6	4,3	4,1	9,7	51,8	4,3	4,3	9,9	99
X	H	C_6H_5	H	H	194—195[b]	$C_{18}H_{15}NOS$	73,9	5,0	4,6	10,6	73,7	5,1	4,8	10,2	56
XII	Br	C_6H_5	H	$COOC_2H_5$	250—251[b]	$C_{21}H_{18}BrNO_3S$	—	—	3,2	7,3	—	—	3,2	7,2	50
XIII	H	C_6H_5	H	$COOC_2H_5$	230—231[a]	$C_{21}H_{19}NO_3S$	69,1	5,3	3,8	8,9	69,0	5,2	3,8	8,8	30

[a]From acetone. [b]From acetic acid.

In the present study, 1,3-diketones substituted with an o-nitroarylthio group (I-VI) were obtained in high yields by the action of o-nitroarenesulfenyl chlorides on cyclic monoketones and 1,3-diketones. The reaction readily proceeds identically both when the reagents are fused and when they are heated in a solution of an appropriate solvent. Diketones I-VI are converted to 1-oxo-1,2,3,4-tetrahydrophenothiazines (VII-XIII) in 60-80% yields when they are reduced with zinc dust in acetic acid.

The reaction with cyclohexanone proceeds similarly. Reduction of 2-(o-nitrophenylthio)cyclohexanone (XXVII) with zinc dust in acetic acid gives tetrahydrophenothiazine (XXVIII). The use of zinc dust for the reduction makes it possible to immediately obtain phenothiazine derivatives, while reductive cyclization of similar compounds by the action of stannous chloride leads to double tin salts of benzothiazines [2].

The oxotetrahydrophenothiazines (VII-XIII) are bright-red crystalline compounds that are rather sparingly soluble in most organic solvents. Their major properties are manifested weakly. Their salts can be obtained only in absolute solvents, since they are hydrolyzed by water to the bases.

The IR spectra of VII-XIII in mineral oil suspensions demonstrate that the compounds exist in the NH form (ν_{NH} = 3280 cm^{-1}). The absorption caused by the valence vibrations of the carbonyl group ($\nu_{C=O}$) is expressed considerably more weakly, apparently as a consequence of the existence of a strong intermolecular hydrogen bond. The absorption of the NH group appears at 3315 cm^{-1} in the spectrum of tetrahydrophenothiazine XXVIII.

We were unable to obtain any keto group derivatives of the 1-oxotetrahydrophenothiazines. The presence of a hydrogen bond makes the keto group extremely inert. Replacement of the hydrogen attached to the nitrogen atom by a methyl group restores the reactivity of the carbonyl group. Thus oxime XX was obtained by the action of hydroxylamine on XV in alkaline media. N-Methyl derivatives XIV-XVI are formed by the action of methyl iodide on the sodium derivatives of the oxotetrahydrophenothiazines. Dialkylaminoalkyl derivatives XVII and XVIII were obtained in low yield by the action of chloroalkyldialkylamines on the N-sodio derivatives. The Mannich reaction also gives low yields of products. The reaction of IX with methylolmorpholine proceeds with substitution of the hydrogen attached to nitrogen to give XIX, while aminomethylation of N-methyl derivative XV by the same method gives amino ketone XXV. When the Mannich reaction is carried out with formaldehyde and a secondary amine, only hydroxymethyl derivative XXVI is isolated. The oxidation of VII, IX, XV, and XVI with hydrogen peroxide gives water-soluble sulfoxides (XXI-XXIV).

EXPERIMENTAL

2-(o-Nitrophenylthio)cyclohexane-1,3-dione (I). A mixture of 11.2 (0.1 mole) of dihydroresorcinol and 19.0 g (0.1 mole) of o-nitrobenzenesulfenyl chloride in 10 ml of dry dioxane was heated on a water bath for 1 h. The resulting pre-

TABLE 2. 1-Oxo-1,2,3,4-tetrahydrophenothiazine Derivatives

Comp.	R	R_1	R_2	R_3	R_4	mp, °C (crystallization solvent)
XV	H	CH_3	CH_3	H	CH_3	181—182 (acetone)
XVI	H	H	C_6H_5	H	CH_3	175—176 (acetone)
XVIII · $C_4H_6O_6$	H	CH_3	CH_3	H	$CH_2CH_2N(CH_3)_2$	85—87 (methanol—ether)

TABLE 2 (continued)

Comp.	Empirical formula	Found, %				Calculated, %				Yield, %
		C	H	N	S	C	H	N	S	
XV	$C_{15}H_{17}NOS$	69,2	6,6	5,3	12,2	69,4	6,6	5,4	12,3	82
XVI	$C_{19}H_{17}NOS$	74,3	5,8	4,4	10,4	74,2	5,6	4,6	10,4	90
XVIII · $C_4H_6O_6$	$C_{18}H_{24}N_2OS \cdot C_4H_6O_6$	—	—	6,0	6,4	—	—	6,0	6,9	50

cipitate was removed by filtration and washed with ether to give 24.1 g of I. Compounds II-VI were similarly obtained (Table 1).

2-(o-Nitrophenylthio)cyclohexanone (XXVII). A mixture of 38 g (0.2 mole) of o-nitrobenzenesulfenyl chloride and 19.6 g (0.2 mole) of cyclohexanone was heated on a boiling-water bath until hydrogen chloride evolution ceased. The mixture was cooled, 20 ml of alcohol was added, and the resulting crystals were removed by filtration to give 37 g (73%) of XXVII with mp 110-111° (from alcohol). Found, %: C 57.3; H 5.2; N 5.6; S 12.7. $C_{12}H_{13}NO_3S$. Calculated, %: C 57.3; H 5.2; N 5.6; S 12.7.

1-Oxo-1,2,3,4-tetrahydrophenothiazine (VII). A 26-g (0.1 mole) sample of I, 10 g of fused sodium acetate, and 200 ml of acetic acid were placed in a three-necked flask equipped with a stirrer and reflux condenser, and the mixture was heated to 60°. A total of 40 g of zinc dust was then added to it in portions in the course of 15 min. The mixture was stirred and refluxed for 1 h, and the solution was decanted. The sludge was washed with five 15-ml portions of hot acetic acid, and the combined acetic acid solutions were diluted with cold water. The resulting precipitate was removed by filtration, washed with cold water, and dried to give 19 g (87%) of VII with mp 232-233° (from alcohol). Found, %: C 66.2; H 5.2; N 6.4; S 14.7. $C_{12}H_{11}NOS$. Calculated, %: C 66.4; H 5.1; N 6.4; S 14.8.

Compounds VIII-XIII (Table 1) were similarly obtained. In the synthesis of XIII, the intermediate was reduced, without isolation, with zinc dust in acetic acid.

Tetrahydrophenothiazine (XXVIII). This compound was similarly obtained in 40% yield and had mp 100-101° (from petroleum ether). Found, %: C 70.5; H 6.4; N 6.8; S 16.1. $C_{12}H_{13}NS$. Calculated, %: C 70.9; H 6.4; N 6.9; S 15.8.

1-Oxo-5-methyl-1,2,3,4-tetrahydrophenothiazine (XIV). Sodium alkoxide, prepared from 0.46 g (0.02 g-atom) of sodium, was added to a suspension of 4.35 g (0.02 mole) of VII in 10 ml of dry dioxane, and the solvents were removed by vacuum distillation. A 40-ml sample of methyl iodide was added to the resulting sodium derivative, and the mixture was refluxed for 1 h on a water bath. The methyl iodide was removed by distillation, the residue was treated with water, and the resulting crystals were removed by filtration to give 4.3 g (94%) of XIV with mp 155-156° (from aqueous alcohol). Found, %: C 67.3; H 5.6; N 6.2; S 14.0. $C_{13}H_{13}NOS$. Calculated, %: C 67.5; H 5.7; N 6.0; S 13.9.

Compounds XV and XVI (Table 2) were similarly obtained.

1-Oxo-3,3,5-trimethyl-1,2,3,4-tetrahydrophenothiazine Oxime (XX). A 2-g sample of sodium hydroxide was dissolved in 30 ml of boiling ethanol. The solution was cooled, 2.6 g (0.01 mole) of XV and 1.4 g (0.02 mole) of hydroxylamine hydrochloride were added, and the mixture was refluxed for 2 h. The reaction solution was poured into water, and the precipitate was removed by filtration to give 1.4 g (50%) of XX with mp 218-220° (from acetone). Found, %: C 66.0; H 6.7; N 10.2; S 11.4. $C_{15}H_{18}N_2OS$. Calculated, %: C 66.0; H 6.7; N 10.2; S 11.7.

Dihydrochloride of 1-Oxo-3,3-dimethyl-5-diethylaminoethyl-1,2,3,4-tetrahydrophenothiazine (XVII). A 2.1-g (0.015 mole) sample of diethylaminoethyl chloride and two drops of dry dimethylformamide were added to the sodium derivative prepared, under the conditions used to obtain XIV, from 3.6 g (0.015 mole) of IX and 0.35 g (0.015 g-atom) of sodium. The reaction mass was heated at 150° for 1 h and diluted with water. The resulting oil was extracted with benzene, and the benzene solution was dried by azeotropic distillation of the water with a Dean–Stark adapter. The benzene was removed by distillation, and the residual oil was dissolved in absolute ether. The ether solution was treated with hydrogen chloride to give 3.2 g (50%) of XVII with mp 98-100° (dec.). Found, %: C 57.6; H 7.3; N 7.1; S 7.6. $C_{20}H_{28}N_2OS \cdot 2HCl$. Calculated, %: C 57.5; H 7.2; N 6.7; S 7.7. Compound XVIII (Table 2) was similarly obtained.

1-Oxo-1,2,3,4-tetrahydro-3,3-dimethyl-5-morpholinomethylphenothiazine (XIX). A 1.8-g (0.015 mole) sample of N-methylolmorpholine was added dropwise with stirring to a suspension of 2.17 g (0.01 mole) of IX in 20 ml of glacial acetic acid at 60°, and the mixture was then stirred at the same temperature for 2 h. The mass was diluted with water, and the unchanged starting compound was removed by filtration. The filtrate was cooled and made alkaline with ammonium hydroxide, and the resulting precipitate was removed by filtration to give 1.1 g (55%) of a product with mp 253-254° (from alcohol). Found, %: C 66.2; H 7.0; N 8.1; S 9.3. $C_{19}H_{24}N_2O_2S$. Calculated, %: C 66.2; H 7.0; N 8.1; S 9.3.

1-Oxo-2-morpholinomethyl-3,3,5-trimethyl-1,2,3,4-tetrahydrophenothiazine (XXV) Dihydrochloride. This compound was obtained in 20% yield from XV via the method used to prepare XIX and had mp 139-140° (from alcohol). Found, %: N 6.4; S 7.4. $C_{20}H_{26}N_2O_2S \cdot 2HCl$. Calculated, %: N 6.5; S 7.4.

1-Oxo-1,2,3,4-tetrahydrophenothiazine S-Oxide (XXI). A 2.5-ml sample of 30% hydrogen peroxide was added dropwise with stirring to a suspension of 2.17 g (0.01 mole) of VII in 20 ml of acetic acid heated to 50°, and the resulting solution was stirred at room temperature for 1 h and poured into water. The aqueous solution was cooled to precipitate 1.9 g (80%) of grayish crystals with mp 222-223° (from alcohol). Found, %: C 61.8; H 4.9; N 5.8; S 13.9. $C_{12}H_{11}NO_2S$. Calculated, %: C 61.8; H 4.8; N 6.0; S 13.7.

1-Oxo-3,3-dimethyl-1,2,3,4-tetrahydrophenothiazine S-Oxide (XXII). This compound was similarly obtained in 95% yield and had mp 220-222° (dec., from methanol). Found, %: C 64.0; H 5.7; N 5.3; S 12.0. $C_{14}H_{15}NO_2S$. Calculated, %: C 64.3; H 5.8; N 5.3; S 12.3.

1-Oxo-3,3,5-trimethyl-1,2,3,4-tetrahydrophenothiazine S-Oxide (XXIII). This compound was similarly obtained in 92% yield and had mp 185-186° (from benzene). Found, %: C 65.5; H 6.0; N 5.2; S 11.5. $C_{15}H_{17}NO_2S$. Calculated, %: C 65.4; H 6.2; N 5.1; S 11.6.

1-Oxo-3-phenyl-5-methyl-1,2,3,4-tetrahydrophenothiazine S-Oxide (XXIV). This compound was similarly obtained in 80% yield and had mp 225-226° (from alcohol). Found, %: C 70.3; H 5.6; S 9.8. $C_{19}H_{17}NO_2S$. Calculated, %: C 70.6; H 5.3; S 9.9.

1-Oxo-2-hydroxymethyl-3,3,5-trimethyl-1,2,3,4-tetrahydrophenothiazine (XXVI). A mixture of 2.45 g (0.01 mole) of XV, 25 ml of acetic acid, 1 ml of formalin, and 1 g (0.01 mole) of N-methylpiperazine was refluxed for 2 h. The solution was cooled, and a small amount of crystals were separated. The mother liquor was diluted with 50 ml of water, and the precipitate was removed by filtration to give 10% of a product with mp 205-206° (from isopropyl alcohol). Found, %: C 66.4; H 6.4; N 4.8; S 11.6. $C_{16}H_{19}NO_2S$. Calculated, %: C 66.6; H 6.3; N 4.8; S 11.2.

LITERATURE CITED

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