SYNTHESIS OF 1,3,4,6,7,11b-HEXAHYDRO[1,4]THIAZINO[3,4,-a]-ISOQUINOLIN-4-ONE, AN ANALOG OF PRASIQUANTEL

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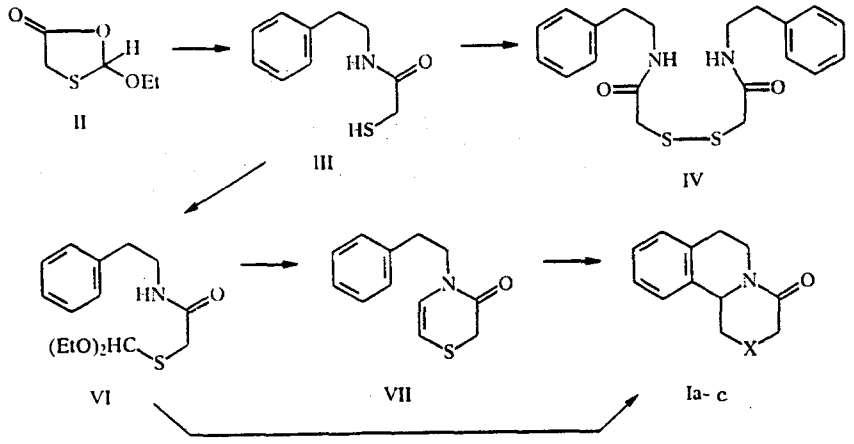
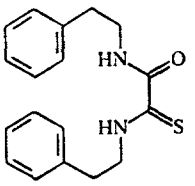
The derivatives of benzo[a]quinolizine and pyrazinoisoquinoline with the general formula Ia,b are interesting as key compounds in the synthesis of ipecacuanha alkaloids [1] and as biologically active compounds [2]. One of these compounds (prasiquantel Ib) is a highly effective antihelminthic with a broad-spectrum action [3]. In order to study its biological activity we have synthesized thiazinoisoquinoline Ic.



II III IV VI VII Ia-c

I a X=CH_2, b X=$NHCOC_6H_{11}$, c X=S



V

The reaction of thiolane II with 2-phenylethylamine leads to the formation of the amide of mercaptoacetic acid III (compare with [4]). The reaction proceeds ambiguously, because the amide III is easily oxidized with air oxygen to the disulfide IV (see Experimental). Besides this, the diamide of thiooxalic acid V is formed in the course of the reaction which is difficult to separate. The structure of compounds IV and V has been confirmed by IR and mass-spectrometric data. Analogous results were obtained when studying the reaction of the ethyl ester of thioglycolic acid with substituted 2-phenylethylamine [5]. Experiments showed that the freshly prepared amide III contains less than 10% of compounds IV and V, so that it can be used in further synthesis without additional purification.

The alkylation of the amide III with the diethylacetal of bromoacetic aldehyde gives compound VI with a high yield. When heated in the presence of a catalytic amount of p-toluenesulfonic acid, the latter undergoes cyclization to the

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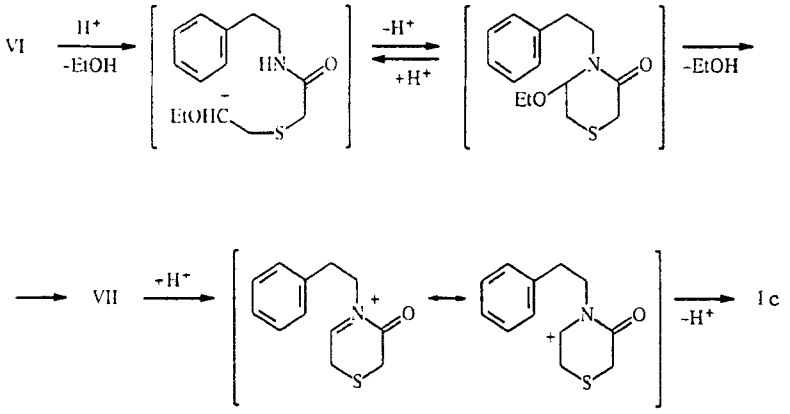
dihydrothiazinone VII, which by the action of conc. H_2SO_4 at 20°C is transformed to the final product Ic. It must be pointed out that the compound Ic can be obtained by the direct action of sulfuric acid on compound VI, however at a low yield (10-15%).

The transformation of compound VI or VII to the thiazinoisoquinoline Ic at the conditions of acid catalysis is an interesting example for the cyclization of ω-acylimmonium ions (see the review [6]) and probably proceeds by the following mechanism



This mechanism is supported by the fact that donor substituents in the aromatic ring enhance the ring formation by permitting it to be carried out at milder conditions [5], while the cyclization of the dihydrothiazinone VII takes place only in the presence of conc. H_2SO_4.

EXPERIMENTAL

The IR spectra were taken on a UR-20 spectrometer in KBr tablets, the PMR spectra on a Bruker WP-80 (80 MHz) spectrometer in $CDCl_3$, with HMDS as the internal standard. The mass spectra were obtained on a Varian MAT 311 A spectrometer at an energy of the ionizing electrons of 70 eV, with direct introduction of the sample into the ion source. The course of the reactions and the purity of the compounds obtained was checked by TLC on Silufol UV-254 sheets with ether–acetone (4:1) as the mobile phase. The elemental analysis data of the synthesized compounds correspond to the calculated values.

2-Phenylethyl Amide of Thioglycolic Acid (III, $C_{10}H_{13}NOS$). The solution of 13.45 g (95 mmole) 2-phenylethylamine in 100 ml anhydrous ethyl acetate is treated at 20°C (water cooling) with a solution of 14.06 g (95 mmole) thioxolane II [5] in 25 ml ethyl acetate. The mixture is allowed to stand overnight and the solvent stripped in vacuum; 19.1 g (98%) of a pale-yellow oil is obtained, which is quickly used in the next stage. According to TLC, the substance contains less than 10% of compounds IV and V (R_f of compounds III, IV, and V 0.4, 0.8, and 0.2 respectively).

Bis-2-phenylethyl Amide of Dithioacetic Acid (IV, $C_{20}H_{24}N_2O_2S_2$) and Bis-2-phenylethyl Amide of Monothiooxalic Acid (V, $C_{18}H_{20}N_2OS$). A solution of 4.92 g (40 mmole) 2-phenylethylamine in 60 ml ethyl acetate is treated with a solution of 5.29 g (40 mmole) thioxolane II in 10 ml ethyl acetate at 20°C and the mixture allowed to stand overnight. The solvent is evaporated in vacuum and the mixture allowed to stand for 48 h in a open flask. The solidified residue is recrystallized from benzene to give 5.8 g (74%) compound IV in the form of colorless crystals with mp 132-134°C. IR spectrum: 1656 (CO), 3302 cm^{-1} (NH). Mass spectrum, *m/z*: 388 (M^+), 297 (M — $PhCH_2$), 268 (M — $PhCH_2CH_2NH$), 240 (M — $PhCH_2CH_2NHCO$), 195 (M — $PhCH_2CH_2NHCOCH_2$).

The benzene filtrate is evaporated in vacuum and passed through a chromatographic column (3 × 60 cm) packed with silica gel 100/250 μm, with chloroform as the eluent. Obtained 1.12 g (9%) compound V in the form of pale-yellow crystals, mp 124-126°C. IR spectrum: 1676 (CO), 3262 cm^{-1} (NH). Mass spectrum, *m/z*: 312 (M^+), 279 (M — SH), 221 (M — $PhCH_2$), 208 (M — $PhCH_2CH_2$), 192 (M — $PhCH_2CH_2NH$).

2-Phenylethyl Amide of 2,2-Diethoxyethylthioacetic Acid (VI, $C_{16}H_{25}NO_3S$). A solution of sodium ethylate, prepared from 2.3 g (0.1 mole) sodium and 40 ml absolute ethanol, cooled to 0-5°C in a nitrogen atmosphere, is treated

consecutively with 18.5 g (0.095 mole) of amide III and 17.8 g (0.095 mole) of the diethylacetal of bromoacetic aldehyde. The reaction mixture is refluxed for 1 h, cooled, and the alcohol removed in vacuum. The residue is dissolved in 100 ml methylene chloride, the solution obtained is washed with water (2 × 40 ml), and dried over Na_2SO_4. After stripping of the solvent 22.15 g (75%) of substance VI is obtained in the form of a yellowish oil, which is used in the further stage without additional purification. The analytical sample of VI represented a light-yellow oil which was separated on a chromatographic column (3 × 15 cm), with silica gel 100/250 μm, by using chloroform as the eluent. R_f 0.6; IR spectrum: 1640 (CO), 3310 cm^{-1} (NH).

4-(2-Phenylethyl)dihydrothiazin-3-one (VII, $C_{12}H_{13}$ NOS). A solution of 7.30 g (23 mmole) of compound VI in 70 ml toluene is treated with 0.38 g (2 mmole) of p-toluenesulfonic acid monohydrate and the mixture refluxed for 2 h with a Dean and Stark packing. The reaction mixture is cooled and washed with water (3 × 20 ml); the organic layer is separated and dried over Na_2SO_4. The solvent is stripped off in vacuum, the residue is treated with 40 ml ethyl acetate, and the solution obtained filtered through a layer of silica gel; the solvent is again stripped in vacuum to give 3.51 g (70%) of virtually pure compound VII. The analytical sample is isolated by chromatography on a column (3 × 15 cm) packed with silica gel 100/250 μm, with chloroform as the eluent. Pale-yellow crystals with mp 45-47°. IR spectrum: 1670 cm^{-1} (CO). PMR spectrum: 2.92 (2H, triplet, α-CH_2); 3.26 (1H, singlet, $C_{(2)}$); 3.78 (2H, triplet, β-CH_2); 5.56 (1H, doublet, J = 2 Hz, $C_{4(5)}$); 6.16 (1H, doublet, J = 2 Hz, $C_{5(4)}$); 7.18-7.34 ppm (5H, multiplet, arom.).

1,3,4,6,7,11b-Hexahydro[1,4]thiazino[3,4-a]isoquinolin-4-one (Ic, $C_{12}H_{13}$NOS). A. To 1.5 ml conc. H_2SO_4 is added 1.1 g (5 mmole) of compound VII at 0-5°C with stirring and the mixture allowed to stand overnight at 20°C. The solution is treated with 10 g finely crushed ice and extracted with methylene chloride (3 × 20 ml); the extract is washed with water to pH 7 and dried over Na_2SO_4. The solvent is stripped off, the residue is chromatographed on a column (3 × 60 cm) packed with silica gel 100/250 μm, using a mixture of chloroform and methanol (10:1) as the eluent. Yield 0.34 g (31%) of compound Ic in the form of colorless crystals, mp 74-76°C (from ethyl acetate). IR spectrum: 1640 cm^{-1} (CO). PMR spectrum: 2.45-3.15 (5H, multiplet); 3.25-3.40 (2H, multiplet); 4.5-5.0 (2H, multiplet); 4.5-5.0 (2H multiplet); 7.18 ppm (4H, singlet, arom.).

B. To 1.5 ml conc. H_2SO_4 is added 1 g (3.2 mmole) of compound VI at 0-5°C with stirring and the mixture allowed to stand overnight at 20°C. Proceed as described under **A**. Yield 0.1 g (15%).

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