SYNTHESIS IN THE PHENOTHIAZINE SERIES

XXXIX.* DIMETHYLPYRIDOPHENOTHIAZINES

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Ketovinylaminophenylthiazines, which are cyclized in acidic media to dimethylpyridophenylthiazines – new four-ring compounds – were obtained by the action of acetylacetone on aminophenylthiazines.

The four-ring pyridothiazine system seems of definite interest, inasmuch as it includes a phenothiazine ring and a disubstituted quinoline fragment, which are the precursors of many biologically active preparations.

The corresponding aminovinyl ketones (IV-VI) were obtained when 2-amino- (I), 4-amino- (II), and 2-bromo-4-aminophenothiazines (III) were heated with acetylacetone; the condensation conditions differ and depend on the basicities of the above amines. The reaction of 2-aminophenothiazine with acetylacetone proceeds readily in xylene, and 4-aminophenothiazine reacts in the absence of a solvent in a large excess of acetylacetone, whereas 2-bromo-4-aminophenothiazine also requires, in addition, a longer heating period.

According to the data in [2], aminovinyl ketones can exist in three tautomeric forms, although most authors assume that the equilibrium is shifted to favor the ketoenamine form as the more stable of the two forms.

Shifting of the NH vibrational bands from 3310, 3210, and 3130 to 2440, 2380-2403, and 2290 and from 1555 to 1195 cm^{-1} was observed in a comparison of the IR spectra of crystalline IV and its deuterated derivative.

From a comparison of the IR spectra in the crystalline state and in chloroform, dioxane, and acetonitrile solutions of IV, the band at 1605 cm^{-1} can be assigned to $\nu_{C=O}$ absorption, inasmuch as in the spectra of these solutions it undergoes a shift to higher frequencies (1608, 1615, and 1612 cm^{-1}, respectively), whereas the band at 1590 cm^{-1} remains almost unshifted. The low frequency of the carbonyl group [3] can be explained by participation of the latter in the formation of an intramolecular hydrogen bond with NH, inasmuch as two bands at 3290 and 3420 cm^{-1}, which are retained on dilution from 0.1 to $1 \cdot 10^{-3}$ M, are observed in the spectra of chloroform and CCl_4 solutions. We assigned the bands at 3430 cm^{-1} to ν_{NH} of phenothiazine and the band at 3290 cm^{-1} to ν_{NH} of the aminovinyl ketone fragment with an intramolecular hydrogen bond.

The spectra of V and VI are similar to the spectrum of IV both in the region of the stretching vibrations of N–H and C–H bonds (2800-3450 cm^{-1}) and in the multiple-bond region (1400-1620 cm^{-1}), the similarity in the relative intensities of which makes it possible to conclude that the aminovinylcarbonyl fragments have the same type of structure. The UV spectra of IV and V are also similar and have two maxima.

* See [1] for communication XXXVIII.

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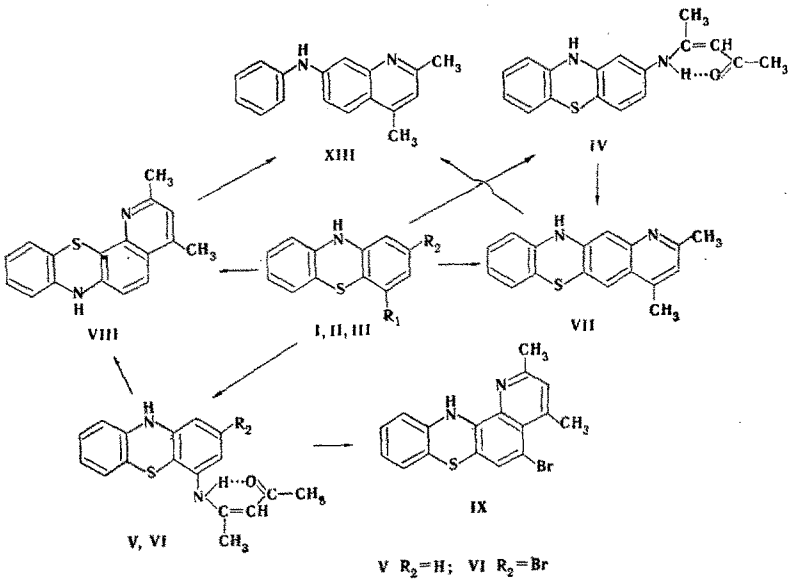
Broad singlets at 12.4 (N–H) and 5.2 ppm, and two singlets of methyl groups (1.9 and 2.4) with an intensity ratio of 1:1:3:3 are observed in the PMR spectrum of IV; this confirms the above assignment and constitutes additional evidence in favor of ketoenamine form IV.

Under the conditions of the Bischler–Napieralski reaction, IV-VI are cyclized to the corresponding pyridophenothiazines (VII-IX). In analogy with [4], VII and VIII were obtained by heating 2-amino- and 4-aminophenothiazine hydrochloride with acetylacetone in the presence of pyridine without isolation of the intermediate IV and V. We were unable to synthesize IX under the conditions described above. In this case, the reaction is complicated by the presence of a bromine atom, which lowers the basicity of the amine. As a result of this reaction, we isolated aminovinyl ketone VI.

Dimethylpyridophenothiazines VII-IX are high-melting (200-350°) colored compounds that are photostable and resistant to acidic and alkaline hydrolysis; they form bright-red hydrochlorides and quaternary salts (X-XII) and give N-acetyl derivatives.

Methylsulfonates XI and XII were reduced in aqueous alcohol with potassium borohydride to the corresponding N-methyl-1,2-dihydropyridophenothiazines, which proved to be extremely unstable compounds similar to dihydroquinolines [5]. During the reaction they decomposed with the liberation of methane and were converted to VII and VIII, respectively; this was confirmed by the analytical and physicochemical data.

The IR spectra of pyridothiazines VII and VIII contain a lower frequency (3250-3280 cm^{-1}) than the IR spectrum of phenothiazine (3340 cm^{-1}); this can apparently be explained by the formation of stronger intermolecular hydrogen bonds. The presence of a proton-acceptor center (the pyridine nitrogen atom) in VII and VIII may evidently serve as a reason for the reinforcement of these bonds and also for the increase in the melting points (see the Experimental section). More profound changes in the spectrum are observed on passing from phenothiazine to angular isomer VIII. For example, whereas the spectrum of VIII contains intense bands at 1565 and 1530 cm^{-1}, the spectrum of VII, like the spectrum of phenothiazine, does not contain appreciable absorption in this region; these changes are apparently due to the lower "psuedo-symmetry" of isomer VIII as compared with VII.



Although the formation of either a linear or an angular isomer is possible in the cyclization of IV, only one compound was isolated as a result of the reaction; a linear structure was assigned conjecturally to this product on the basis of the fact that electrophilic reactions proceed at the 3 and 7 positions in the phenothiazine ring. Subsequent studies confirmed our assumption.

One substance was isolated from the reductive desulfuration of VII and VIII; from the lack of a melting-point depression for a mixture of this product with an authentic sample and the identical R_f values and IR spectra, the product was 2,4-dimethyl-7-anilinoquinoline(XIII). Thisis possible only in the case of cyclization of IV in the 3 position of the phenothiazine ring to give a linear isomer. Compound XIII was also obtained by cyclization of N-(1-methyl-3-oxo-1-buten-1-yl)-3-anilinoaniline (XIV) in PPA or by heating the 3-anilinoaniline hydrochloride with acetylacetone in pyridine.

The dimethylpyridophenothiazines and their quaternary salts that we synthesized were subjected to pharmacological study, which showed that these compounds have hypotensive activity without manifestation of cataleptic and myorelaxant effects.

EXPERIMENTAL

The IR spectra of KBr pellets, mineral oil suspensions, or chloroform solutions of the compounds were recorded with a UR-10 spectrometer. The UV spectra of alcohol solutions were recorded with a Perkin–Elmer 402 spectrophotometer. The PMR spectra were obtained with a Varian T-60 spectrometer. Thin-layer chromatography (TLC) was performed on a loose layer of activity IV aluminum oxide in chloroform.

2-(1-Methyl-3-oxo-1-buten-1-yl)aminophenothiazine (IV). A 6.4-g (0.03 mole) sample of I and 10 g (0.1 mole) of acetylacetone were refluxed in xylene for 5 h. The solution was cooled, and the precipitate was removed by filtration to give 7.5 g (89%) of a light-yellow substance with mp 182-183° (from aqueous isopropyl alcohol) and R_f 0.43. UV spectrum: λ_{max} 265, 325 nm (log ε 4.41, 4.31). Found: C 69.2; H 5.4%. $C_{17}H_{16}N_2OS$. Calculated: C 68.9; H 5.5%.

4-(1-Methyl-3-oxo-1-buten-1-yl)aminophenylthiazine (V). A 0.64-g (0.003 mole) sample of II and 3 g (0.03 mole) of acetylacetone were refluxed for 5 h, after which the mixture was cooled and poured into water. The resulting oil began to crystallize, and the crystals were removed by filtration and washed with water to give 0.5 g (62.5%) of V with mp 143-144° (from aqueous isopropyl alcohol) and R_f 0.50. UV spectrum (in chloroform): λ_{max} 257, 318 nm (log ε 4.40, 4.25). Found: N 9.4; S 11.1%. $C_{17}H_{16}N_2OS$. Calculated: N 9.4; S 10.8%.

2-Bromo-4-(1-methyl-3-oxo-1-buten-1-yl)aminophenothiazine (VI). A 2.93-g (0.01 mole) sample of III and 10 g (0.1 mole) of acetylacetone were refluxed for 10 h, after which the mixture was worked up as in the case of V to give 2.5 g (66%) of a product with mp 184-185° (from aqueous isopropyl alcohol) and R_f 0.60. Found: Br 21.8; S 8.6%. $C_{17}H_{15}BrN_2OS$. Calculated: Br 21.9; S 8.5%.

N-(1-Methyl-3-oxo-1-buten-1-yl)-3-anilinoaniline (XIV). As in the preparation of IV, 6.4 g (0.035 mole) of 3-anilinoaniline and 10 g (0.1 mole) of acetylacetone gave 7 g (88%) of a substance with mp 70-71° (from aqueous ethanol). UV spectrum: λ_{max} 292-322 nm (log ε 4.19). Found: N 10.7%. $C_{17}H_{18}N_2O$. Calculated: N 10.5%.

2,4-Dimethylpyrido[2,3-b]phenothiazine (VII). A) A 4.2-g (0.015 mole) sample of IV was added in portions with stirring at 40-50° to polyphosphoric acid (from 25 ml of orthophosphoric acid and 40 g of phosphorus pentoxide), after which the temperature was raised to 100-110°, and the mixture was stirred for 3 h. It was then cooled to room temperature and poured into water, and the resulting red precipitate was removed by filtration and washed with water. A suspension of the phosphate in water was treated with sodium hydroxide solution until the mixture was alkaline. The crystalline base was removed by filtration, washed with water, and dried to give 2.3 g (60%) of VII with mp 303-305° (from toluene–DMFA) and R_f 0.26. UV spectrum (in chloroform): λ_{max} 255, 277, 287, and 385 nm (log ε 4.64, 4.53, and 3.86); 0.1 M HCl in alcohol: λ_{max} 450-460, 258-264 nm (log ε 3.34, 5.06). IR spectrum: ν_{NH} 3270 cm^{-1}. Found: C 73.7; H 5.2%. $C_{17}H_{14}N_2S$. Calculated: C 73.4; H 5.0%. The hydrochloride had mp 300° (from ethanol). Found: Cl 11.0%. $C_{17}H_{14}N_2S \cdot HCl$. Calculated: Cl 11.2%. The methylsulfonate (XI) of VII was prepared as follows. A 0.54-g (0.002 mole) sample of VII was dissolved in DMFA–ether (60 and 30 ml, respectively), 1.5 ml (0.016 mole) of dimethyl sulfate was added, and the mixture was allowed to stand for several days. The resulting red precipitate was removed by filtration to give 0.64 g (80%) of a product with mp > 300° (from ethanol). Found: N 6.7; S 15.6%. $C_{19}H_{20}N_2O_4S_2$. Calculated: N 6.9; S 15.8%. The reaction of methyl iodide with 0.54 g (0.002 mole) of VII gave the methiodide (X) with mp > 300° (from ethanol). The product was only slightly soluble in water. Found: I 30.6%. $C_{18}H_{17}IN_2S$. Calculated: I 30.7%.

B) A mixture of 2.5 g (0.01 mole) of the hydrochloride of I, 5 g (0.05 mole) of acetylacetone, and 3 ml of pyridine was refluxed for 6 h. The reaction mixture was worked up in accordance with method A to give 1.2 g (50%) of VII with mp 303-305°. No melting-point depression was observed for a mixture of this product with the product obtained by method A.

C) A 2-g (0.005 mole) sample of methylsulfonate XI was dissolved in aqueous ethanol (50%) and a solution of 1 g (0.02 mole) of potassium borohydride in water was added in small portions with stirring. During the reaction, the solution became colorless, and a yellowish precipitate began to form. Workup

gave 1 g (70%) of VII with mp 303-305° (from toluene–DMFA) and R_f 0.26. No melting-point depression was observed for a mixture of this product with the product obtained by method A.

2,4-Dimethylpyrido[3,2-c]phenothiazine (VIII). A) As in the preparation of VII by means of method A, 0.88 g (0.003 mole) of V gave 0.56 g (65%) of VIII with mp 212-214° (from toluene). The light-orange crystals were soluble in alcohols and chloroform and had R_f 0.76. UV spectrum (in chloroform): λ_{max} 245, 287, and 350 nm (log ε 4.40, 4.50, and 3.42). IR spectrum: ν_{NH} 3280 cm^{-1}. Found: N 10.3; S 11.2%. $C_{17}H_{14}N_2S$. Calculated: N 10.1; S 11.5%.

B) Under the conditions used to prepare VII by method B, 1.25 g (0.005 mole) of the hydrochloride of II gave 0.75 g (63%) of VIII with mp 213-214° (from toluene). The compounds obtained by methods A and B were identical. The methylsulfonate (XII) of VIII was obtained in 72% yield by the action of 2.5 ml of dimethyl sulfate on 1.08 g (0.004 mole) of VIII in chloroform. The dark-red product was soluble in water and had mp > 250° (from ethanol). Found: S 15.7%. $C_{19}H_{20}N_2O_4S_2$. Calculated: S 15.9%.

2,4-Dimethyl-5-bromopyrido[3,2-c]phenothiazine (IX). A 1.5-g (0.004 mole) sample of VI was heated in PPA under the conditions of cyclization of VII by method A. Workup gave 0.9 g (64%) of IX with mp 208-210° (from toluene) and R_f 0.83. Found: Br 22.0; N 7.6; S 8.8%. $C_{17}H_{13}BrN_2S$. Calculated: Br 22.3; N 7.8; S 9.0%.

2,4-Dimethyl-7-anilinoquinoline (XIII). A) A 2-g sample of Raney nickel catalyst was added to a solution of 0.28 g (0.001 mole) of VII in 15 ml of ethanol, and the mixture was refluxed and stirred for 5 h. The catalyst was removed by filtration, and the filtrate was diluted with water and cooled. The resulting yellow precipitate was removed by filtration to give XIII with mp 145-146° (from CCl_4) and R_f 0.4. UV spectrum: λ_{max} 276, 299, 308, 370 nm (log ε 4.43, 3.20, 4.17, 3.92). Found: C 82.3; H 6.6%. $C_{17}H_{16}N_2$. Calculated: C 82.2; H 6.5%.

B) Desulfuration by method A of 0.28 g (0.001 mole) of VIII gave a substance that, after crystallization from carbon tetrachloride, had mp 145-146°, R_f 0.4, and did not depress the melting point of the sample obtained by method A.

C) Under the conditions of cyclization of VII by method A, 3.99 g (0.015 mole) of aminovinyl ketone XIV gave 2.5 g (70%) of XIII with mp 144-145°.

D) Under the conditions used to prepare VII by method B, 1.1 g (0.005 mole) of hydrochloride XV gave 0.8 g of XIII with mp 144-145°. No melting-point depressions were observed for mixtures of the compounds obtained by methods A, C, and D.

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