Tetracyclic Phenothiazines. VI (1). Attempted Pummerer Cyclization of 10-(2-Keto-3-methylsulfinylpropyl)phenothiazine

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The title compound (**3**), a β-ketosulfoxide prepared by a Claisen-type condensation of ethyl 2-(10-phenothiazino)acetate (**4**) with dimsyl carbanion, was subjected to a variety of catalysts in attempts to achieve a Pummerer cyclization to 1,2-dihydro-3-methylthio-2-oxo-3*H*-pyrido[3,2,1-*kl*]phenothiazine (**2**). Although the Pummerer rearrangement product, 10-(2-oxo-3-hydroxy-3-methylthiopropyl)phenothiazine (**5**), could be obtained in excellent yield under mild conditions, neither it nor the β-ketosulfoxide could be successfully cyclized under any of the conditions attempted. Instead, phenothiazine, 2-hyroxy-3-(10-phenothiazinyl)-2-propen-1-al (**7**), 3-(10-phenothiazinyl)-1,1-di(methylthio)propan-2-one (**8**), 3-(10-phenothiazinyl)-1-methylthiopropan-2-one (**9**) and 10-phenothiazinylformamide (**10**) were variously obtained.

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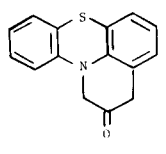
As a part of our program directed toward the synthesis of conformationally restricted phenothiazine tranquilizers (1,2), we required 2-oxo-3*H*-pyrido[3,2,1-*kl*]phenothiazine (**1**) as a key intermediate from which a variety of *N,N*-dialkylamino derivatives could readily be prepared by reductive amination with different amines. Since the phenothiazine ring system is known to be sufficiently electron rich to undergo other acid catalyzed cyclizations at the 1-position (3-5), our expectation was that the 3-methylthio derivative **2**, which should readily undergo selective reduction to **1** under appropriately chosen conditions (6), could be prepared by the Pummerer cyclization (6-8) of the β-ketosulfoxide **3**. This report describes the preparation of **3**, its facile rearrangment to **5**, and the reaction products formed during several unsuccessful attempts to cyclize both **3** and **5**.

Under conditions described to be optimal for the Pummerer cyclization in other systems (7), treatment of **3** with two mole equivalents of *para*-toluenesulfonic acid monohydrate in tetrahydrofuran at 65° for 15 minutes afforded excellent yield of **5** (90-95%) and trace amounts of **7**, **8** and **9**. The Pummerer rearrangment product **5** is sufficiently stable to be isolated and purified by recrystallization from ethyl acetate or triturating with ether-petroleum ether, but it readily eliminates methanethiol when heated under vacuum (2mm Hg) at 110° to form **7**. This compound, which can be considered to be the enol form of a β-amino-α-ketoaldehyde (**9**), was also obtained when **5** was subjected to attempted purification by column chromatography on silica gel. The existence of **7** in the enol form was evidenced by an exchangeable proton in the nmr spectrum (δ 6.0), the mass spectrum of its *N,O*-bis-trimethylsilyl derivative (m/e 341), the coincidence of experimental and calculated (10) absorption maxima (λ max 344 vs 340 nm)



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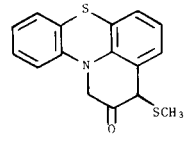

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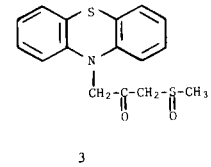

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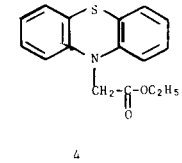

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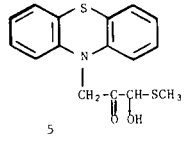

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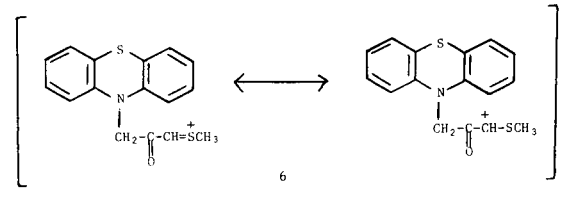

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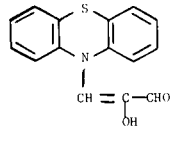

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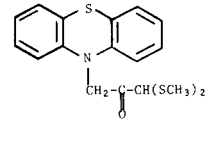

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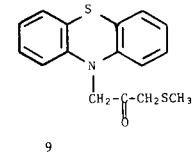

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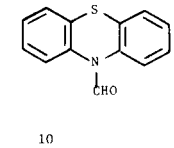

10

in the uv spectrum, and a characteristic ir absorption band 1618 cm^{-1}.

The formation of the dimethyl thioacetal **8** can be rationalized on the basis of addition of methanethiol (eliminated in the formation of **7** from **5**) to the cationic intermediate **6**. This intermediate, which is postulated to lie on the reaction coordinate for the Pummerer cyclization (7), apparently also abstracts a hydride from some source (possibly methanethiol) to undergo reduction to **9**.

When **3** was subjected to the longer reflux time of 3 hours under the reaction conditions described earlier, none of the desired cyclization product **2** could be detected. Instead, a complex mixture containing phenothiazine, **5**, **7**, **8**, **9** and 10-formylphenothiazine **10** was obtained. Treatment of the hemimercaptal **5** under these same conditions gave the same mixture of products. The mechanism by which phenothiazine and **10**, the major products of the reaction, are formed is not known. It is probable that protonation of the nitrogen atom of **5** followed by fragmentation of the side chain to give phenothiazine occurs. However, the formation of **10** in these reactions has not yet been explained.

Other acid catalysts and conditions (phosphorus pentoxide in tetrahydrofuran, Linde 5 Å molecular sieves in tetrahydrofuran, trifluoroacetic anhydride in benzene or tetrahydrofuran, anhydrous hydrogen fluoride, polyphosphoric acid, phosphorus pentoxide dissolved in methanesulfonic acid) likewise failed to cyclize either **3** or **5**, giving instead varying amounts of phenothiazine, compounds **7-10** and tar depending on the severity of the reaction conditions. Alternative procedures for the synthesis of **2** are currently under investigation.

EXPERIMENTAL

Melting points were determined on an Electrothermal melting point apparatus and are uncorrected. Infrared Spectra were recorded on a Beckman IR-33 Spectrophotometer as potassium bromide pellets and data are reported in cm^{-1} units. The nmr spectra were recorded in deuteriochloroform on a Varian EM360L Spectrometer using tetramethylsilane as an internal standard and chemical shifts are reported in δ units. Mass spectra were recorded on a Varian MAT 311 A double focusing mass spectrometer at 70eV. Microanalyses were performed by the University Analytical Center, Tucson, Arizona. The uv spectra were recorded on a Cary 15W visible spectrophotometer and data are reported as nm (log ϵ).

10-(2-Keto-3-methylsulfinylpropyl)phenothiazine (**3**).

This compound was synthesized following the procedure of Corey and Chaykovsky (11). Ethyl 10-(Phenothiazino)acetate (12) **4** (13.15 g, 0.046 mole) dissolved in 70 ml of freshly distilled tetrahydrofuran was added *via* syringe all at once to the dimsyl anion generated by reaction of oil-free sodium hydride (5.6 g, 0.233 mole) with 70 ml of dry dimethylsulfoxide. The reaction mixture was heated at 75° under magnetic stirring for 12 hours, then cooled down to room temperature. The dark-brown reaction mixture was poured into one liter of ice-cold brine solution while stirring with a glass rod. The *p*H was brought to 3-4 by concentrated hydrochloric acid. The light brown precipitate was filtered on Büchner-funnel, washed generously with distilled water and dried as much as possible. This slightly wet material was dissolved in 700 ml chloroform, transferred to a separatory funnel, washed with 100 ml of saturated sodium chloride solution. The organic layer was dried (anhydrous sodium sulfate), filtered and solvent removed on a rotary evaporator. The light brown solid residue was triturated with anhydrous ether. Almost colorless light microcrystalline material was filtered, washed with ether and dried, yield 12.23 g (84%), one spot on tlc (acetone), mp 176-177°; ir: ν 1715 (ketone, C=O), 1020 (>S→O); nmr: δ 2.68 (s, 3H, CH_3-SO-), 3.55-4.20 (a pair of doublets, AB pattern, 2H, -CH_2-SO-, J = 12 Hz), 4.68 (s, 2H, -NCH_2CO), 6.6-7.6 (m, 8H, aromatic).

Anal. Calcd. for $C_{16}H_{15}NO_2S_2$: C, 60.57; H, 4.73; N, 4.42. Found: C, 60.80; H, 4.80; N, 4.30.

10-(2-Oxo-3-hydroxy-3-methylthiopropyl)phenothiazine (**6**).

A slurry of **3** (6.34 g, 0.02 mole) and *p*-toluenesulfonic acid monohydrate (7.6 g, 0.04 mole) in 80 ml of freshly distilled tetrahydrofuran was refluxed for 15 minutes in an oil-bath under and argon gas atmosphere while stirring magnetically. The reaction flask was cooled in an ice-bath and *p*-toluenesulfonic acid was neutralized with 35 ml of aqueous sodium bicarbonate (3.40 g, 0.045 mole). Tetrahydrofuran was removed on a rotary evaporator. The precipitated material was extracted with 500 ml of chloroform, washed with brine (3 × 100 ml) and dried (anhydrous sodium sulfate). Filtration and removal of solvent afforded 6.0 g (94%) of light brown solid material, mp 140-142° containing trace amounts of **7**, **8**, and **9**. This was purified by triturating with a mixture of petroleum ether-ether (10:1), mp of purified product 153-154°; ir: ν 3390, 3300 (OH), 1715 (ketone C=O); nmr: δ 2.06 (s, 3H, CH_3S), 3.4-4.0 (broad hump, 1H, OH, exchangeable), 4.91 (s, 2H, N-CH_2CO), 5.52 (broad singlet, 1H, methine, becomes sharp singlet after deuterium oxide exchangeable), 6.5-7.4 (m, 8H, aromatic).

Anal. Calcd. for $C_{16}H_{15}NO_2S_2$: C, 60.58; H, 4.73; N, 4.42. Found: C, 60.60; H, 4.80; N, 4.30.

2-Hydroxy-3-(10-phenothiazinyl)-2-propen-1-al **7**.

When an attempt was made to purify 1.0 g of **5** on silica gel column by gradient elution with a mixture of hexane and ethyl acetate, 0.65 g of compound was obtained as a pale yellow solid, mp 189-190°; ir: ν 3440, 3320 (OH), 1618 (>N-CH=C(OH)-CHO); nmr: δ 6.0 (s, 1H, OH, exchangeable), 6.69 (s, 1H, olefinic), 7.1-7.4 (m, 8H, aromatic), 8.9 (s, 1H, CHO, characteristic absorption for enamino aldehyde): uv (methanol): λ max 205 (4.33), 232 (4.16), 254 (4.39), 316 (3.91) and 344 nm (4.17). According to Woodward's rules (10), calcd. λ max for unit R_2N-CH=C(OH)-CHO: 340 nm; experimental: 344 nm; ms: m/e (%) 269 (100, M^+), 271 (5.66, M+2, represents one sulfur), 212 (39.88), 199 (17.55), 198 (16.24), 167 (17.02); N,O-*bis*-trimethylsilylacetamide (TMS) derivatives: 341 (39.42) indicates incorporation of one trimethylsilyl function, 326 (44.73) due to loss of one methyl group, 73 (87.22), 52 (100).

Anal. Calcd. for $C_{15}H_{11}NO_2S$: C, 66.91; H, 4.09; N, 5.21. Found: C, 66.80; H, 4.00; N, 5.20.

3-(10-Phenothiazinyl)-1,1-di(methylthio)propan-2-one (**8**).

A mixture of **3** (1.05 g, 0.0033 mole), phosphorus pentoxide (0.0035 mole) and *p*-toluenesulfonic acid monohydrate (0.02 g, 0.0001 mole) in 100 ml of dry tetrahydrofuran was refluxed for three hours and worked up as for compound **5**. The dark gummy material was coated on 5 g silica gel and column chromatographed eluting with a mixture of hexane and toluene (1:1). The first fraction was phenothiazine. The second fraction afforded 0.06 g of the product **8** as a light green solid, mp 121-122°; ir: ν 1710 (ketone C=O); nmr δ 2.07 (s, 6H, two CH_3S), 4.65 (s, 1H, methine), 4.82 (s, 2H, NCH_2CO), 6.30-7.50 (m, 8H, aromatic); ms: m/e (%) 347 (32.39M^+), 349 (5.09, M+2), 212 (100), 180 (41.65).

Anal. Calcd. for $C_{17}H_{17}NOS_3$: C, 58.79; H, 4.90; N, 4.03. Found: C, 59.00; H, 4.60; N, 3.70.

3-(10-Phenothiazinyl)-1-methylthiopropan-2-one (**9**).

In the above mentioned experiment, the third fraction from the column chromatography afforded 0.12 g of the product **9** as a light green solid,

mp 119-120°; ir: ν 1710 (ketone C=O); nmr: δ 2.10 (s, 3H, CH_3S), 3.29 (s, 2H, -CH_2-S-), 4.72 (s, 2H, NCH_2CO), 6.32-7.50 (m, 8H, aromatic); ms: m/e (%) 301 (42.31, M^+), 303 (4.62, M+2), 212 (100), 180 (61.13).

Anal. Calcd. for $C_{16}H_{15}NOS_2$: C, 63.79; H, 4.98; N, 4.65. Found: C, 63.24; H, 4.80; N, 4.70.

N-Phenothiazinylformamide (**10**).

Phosphorus pentoxide (1.0 g, 0.007 mole) was dissolved in 10 g of methanesulfonic acid and to this colorless reagent **5** (0.317 g, 0.001 mole) was added all at once, and reaction mixture was magnetically stirred at room temperature for one hour. The dark-brown reaction mixture was poured into 250 ml ice-water. The red homogenous solution obtained was neutralized with aqueous sodium bicarbonate, extracted with chloroform, dried (sodium sulfate), filtered and solvent removed. The dark gummy residue (0.28 g) was purified on preparative plate (PLC) developing with a mixture of toluene and chloroform (1:1) which yielded 0.11 g of pale yellow solid material, mp 135-136° [lit (13) mp 139-140°]; ir: ν 1680 (>N-CHO); nmr: δ 7.19-7.40 (m, 7H, aromatic), 7.5 (d, 1H, aromatic, one of the two peri hydrogen atoms, J = 10 Hz), 8.66 (s, 1H, CHO).

Anal. Calcd. for $C_{13}H_9NOS$: C, 68.72; H, 3.96; N, 6.17. Found: C, 68.67; H, 3.90; N, 6.17.

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