Tetracyclic Phenothiazines IV (1). Synthesis of 1,2,3,4-Tetrahydroazepino[3,2,1-*kl*]phenothiazin-4-one

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The synthesis of 1,2,3,4-tetrahydroazepine[3,2,1-*kl*]phenothiazin-4-one was accomplished by cyclization of phenothiazine-10-butanoic acid using phosphorus pentoxide and absolute ethanol. The title compound represents the first reported example of the azepino[3,2,1-*kl*]phenothiazine ring system. A vastly improved malonic ester-type synthesis of the precursor acid has also been developed.

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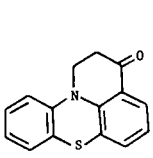
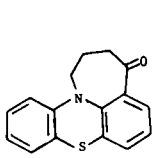
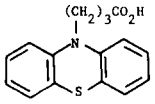
In connection with our investigation of potential ring expansion reactions of 1,2-dihydro-3-keto-3*H*-pyrido-[3,2,1-*kl*]phenothiazine (I) we sought an unequivocal synthesis of the title compound (II) as one of the possible products. This report describes details of the synthesis of II and a substantially improved synthesis of its immediate precursor, phenothiazine-10-butanoic acid (III) (3). The azepino[3,2,1-*kl*]phenothiazine ring system, of which II is an example, has not previously been reported.



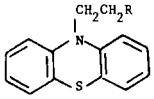
I



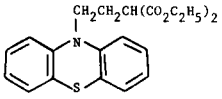
II



III



IV (a) R = Cl
(b) R = SO_3CH_3



V

Cyclization of III, as the acid chloride, was accomplished under Friedel-Crafts conditions (stannic chloride or aluminum chloride in methylene chloride at 0°, then allowed to warm to 25° for 12 hours), but the yields were low (20-25%) and the product thus obtained was difficult to purify. After several direct attempts to cyclize III (utilizing phosphorus pentoxide in benzene, trifluoroacetic anhydride (4), hydrogen fluoride, or polyphosphoric acid) all failed, success was finally achieved using phosphorus pentoxide and ethanol in sulfolane (5,6). Again the yield was low (25-30%), but the product was easily purified by column chromatography.

A side product obtained in the cyclization of III was phenothiazine (16%). Thus, dealkylation of the butyric acid side chain is an important competing process that occurred under the reaction conditions employed. It appears likely that an intramolecular reaction, possibly involving ethyl polyphosphate mixed anhydrides of III, must occur. In support of such a dealkylation mechanism we have, after repetition of the cyclization, detected γ-butyrolactone in the infrared spectrum (ν 1770 cm^{-1}) of the crude, benzene-soluble extract obtained during workup. Although the presence of the solvent (sulfolane) prevented quantitative isolation of the γ-butyrolactone (which is miscible in all proportions with water), inspection of the infrared spectrum of the crude reaction mixture indicated that approximately equal quantities of phenothiazine and γ-butyrolactone were formed.

The synthesis of III had been accomplished in 1960 by French chemists (3), who alkylated diethyl sodiomalonate with 10-(β-chloroethyl)phenothiazine (IVa) (7,8) to give V, followed by hydrolysis and decarboxylation to obtain (III). Because of the extremely low yield of III resulting from this procedure (which we repeated with similar results) we sought an improved synthesis.

Although an earlier attempt to obtain III by direct alkylation of phenothiazine was unsuccessful, we had hoped that such a reaction might be possible under appropriate conditions. However, attempts to react phenothiazine with either: ethyl γ-bromobutyrate (or ethyl γ-iodobutyrate) in the presence of sodium hydride in tetrahydrofuran or hexamethylphosphoramide (HMPA) (9); γ-butyrolactone and potassium hydroxide (10); or ethylmagnesium bromide and then *t*-butyl γ-bromobutyrate, all failed. Reexamination of the literature synthesis revealed that the low yield step (15-16%) was the alkylation reaction. We therefore decided to use the more reactive 10-(β-methanesulfonylethyl)phenothiazine (IVb) in the alkylation reaction and were rewarded with a 76% yield of V. Since IVb was obtained in 83% yield, using a two step procedure involving the alkylation of 10-lithiophenothiazine with ethyleneoxide (3), followed by esterification of the 10-(β-hydroxyethyl)phenothiazine thus formed with

methanesulfonylchloride in triethylamine, the overall yield of V with our procedure was 63% as compared with the 7.2% reported in the literature (3).

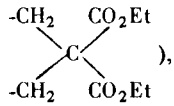
EXPERIMENTAL (11)

10-(β-Methanesulfonylethyl)phenothiazine (IVb).

To a solution of 10-(β-hydroxyethyl)phenothiazine (3), 38 g., in 300 ml. of dry dichloromethane containing 35 ml. of dry triethylamine and cooled to -10°, was added dropwise 15 ml. of freshly distilled methanesulfonyl chloride in 50 ml. of dichloromethane. The reaction mixture was then slowly raised to 25° over a 15 minute period. It was then diluted with 500 ml. of chloroform, washed successively with cold water (200 ml.), cold 5% hydrochloric acid solution (200 ml.), cold 5% sodium bicarbonate solution (200 ml.) and again with cold water (200 ml.) and dried over anhydrous sodium sulfate. Evaporation of the solvent *in vacuo* (water aspirator) afforded 45 g. (90%) of IVb as a white crystalline solid, m.p. 111-113; ir (chloroform): ν 1170, 1210, 1355 (-SO_2-); nmr (deuteriochloroform): δ 4.53 (s, 3H, CH_3), 4.0-4.68 (m, 4H, NCH_2CH_2O), 6.7-7.5 (m, 12H, aromatic). Because of its instability, IVb was not purified further (12), but was employed directly for the synthesis of V.

Diethyl [β-(10-Phenothiazinyl)ethyl]malonate (V).

Redistilled diethylmalonate (4.7 ml.) was added dropwise to a stirred suspension of 57% sodium hydride (1.18 g.) in 50 ml. of 1,2-dimethoxyethane. When the evolution of hydrogen gas ceased, 9.0 g. of dry pulverized IVb was added portionwise and the reaction was then refluxed for 20 hours. It was then cooled to 25°, diluted with 200 ml. of ether, washed with water and the ether extract dried over anhydrous sodium sulfate. The solvent and excess diethylmalonate were removed *in vacuo* to afford a pale brown oily residue which was subjected column chromatography on silica gel with benzene and then benzene-chloroform (1:1) as eluting solvents. Earlier fractions (benzene) afforded 0.9 g. (7%) of a viscous oil assumed to be the dialkylation product, diethyl bis[(10-phenothiazinyl)ethyl]malonate, from its nmr spectrum; nmr (deuteriochloroform): δ 1.17 (2t, 6H, CH_3), 2.31 (bt, 4H,



), 3.4-4.33 (bt and 2q overlapping, 8H, NCH_2 and OCH_2), 6.2-7.2 (m, 16H, aromatic). Later fractions (benzene-chloroform) gave 8.2 g. of V as a viscous oil which slowly crystallized, m.p. 65° [lit. (3) m.p. 65°]; ir (neat): ν 1725, 1740 (ester C=O); nmr (deuteriochloroform): δ 1.15 (t, 3H, CH_3), 2.41 (m, 2H, CCH_2C), 3.56 (t, 1H, CH), 4.03 (q, 2H, OCH_2), 6.66-7.33 (m, 8H, aromatic).

1,2,3,4-Tetrahydroazipino[3,2,1-*kl*]phenothiazin-4-one (I).

To 1.45 g. of phosphorous pentoxide in a 50 ml. flask cooled to 0° was added 1 ml. of absolute ethanol under anhydrous conditions. The viscous reaction mixture was then heated on a steam bath until it became homogeneous. Sulfolane (2 ml.) and 1 g. of phenothiazinyl-10-butanoic acid (III) were then added and the dark brown reaction mixture was heated at 90-95° for 3 hours. It was then poured slowly onto cracked ice (100 g.), and the mixture extracted with benzene. The yellow benzene layer was washed with saturated sodium chloride solution (100 ml.) and dried over anhydrous sodium sulfate. Evaporation of the solvent (water aspirator) afforded a brown oily residue; ir (neat): ν 3330 (phenothiazine NH), 1770 (butyrolactone C=O), 1680 [(II), C=O]. After the residue was taken up in benzene and washed with water to remove the sulfolane and γ-butyrolactone, it was subjected to column chromatography on silica gle with benzene as an eluting solvent. Earlier fractions were collected and concentrated to give 110 mg. (16%) of a yellow solid shown to be phenothiazine (ir and nmr). Later fractions afforded 230 mg. (25%) of II as a viscous yellow oil which formed a foam when the solvent was evaporated; ir (neat): ν 1680 (C=O); nmr (deuteriochloroform): 2.4 (m, 2H, CCH_2C), 2.6 (bt, 2H, CH_2CO), 3.7 (bt, 2H, NCH_2), 6.3-7.4 (m, 7H, aromatic).

Anal. Calcd. for $C_{16}H_{13}NOS$: C, 71.88; H, 4.90; N, 5.24; S, 11.99. Found: C, 71.62; H, 5.03; N, 5.13; S, 11.76.

Acknowledgment

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(11) Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are corrected. Infrared spectra were recorded on a Beckman IR-33 spectrophotometer and data are reported in cm^{-1} units. Nmr spectra were recorded on a Varian T-60 spectrometer using tetramethylsilane (TMS) as an internal standard and deuterated chloroform as a solvent and data are reported in δ (parts per million). Microanalyses were conducted by Galbraith Laboratories, Knoxville, Tennessee 37921.

(12) Freshly prepared IVb gave a single major spot on tlc (rf 0.45 on silica gel G with benzene as a solvent). However, after sotrage for 18 hours at 25° the material gave an additional spot on tlc (rf 0.80 under the same conditions). Elemental analysis of the reaction product (obtained 7 days after purification to one spot material), together with its nmr spectrum, suggests that the decomposition product is probably 2-vinylphenothiazine (vinyl protons centered at δ ≃ 5.6 ppm).