Tetracyclic Phenothiazines V (1). Construction of the Azepino[3,2,1-*kl*]-phenothiazine Ring System by Regioselective Ring Expansion

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Solvolysis of 1,2-dihydro-3-hydroxy-3-(*p*-toluenesolfonyloxymethyl)3*H*-pyrido[3,2,1-*kl*]-phenothiazine gave 1,2,3,4-tetrahydroazepino[3,2,1-*kl*]phenothiazin-3-one.

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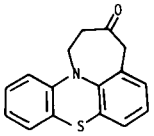
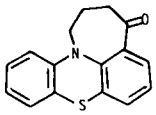
In connection with our efforts to synthesize phenothiazine derivatives with conformationally restricted basic side chains as potential neuroleptic agents, it was necessary to prepare 1,2,3,4-tetrahydroazepino[3,2,1-*kl*]phenothiazin-3-one (I) as a key intermediate. There appeared to be two general approaches that could feasibly be employed toward the synthesis of I, namely the transcarbonylation of the isomeric 1,2,3,4-tetrahydroazepino[3,2,1-*kl*]phenothiazin-4-one (II), the synthesis of which we had earlier reported (3), or the ring expansion of the known 1,2-dihydropyrido[3,2,1-*kl*]phenothiazine-3-one (III) (4). Since the conversion of II to I from available starting materials seemed destined to be a very lengthy (as well as a low yield) process, we decided to concentrate our efforts on the ring expansion of III.

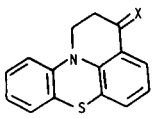
Only starting material was recovered from attempts to ring expand (III) directly using diazomethane in the presence of various catalysts (*e.g.*, lithium chloride in methanol, boron trifluoride etherate, *etc.*). Furthermore, two modifications (5,6) of the Tiffeneau-Demjanov ring



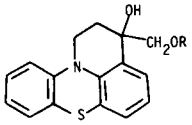
I



II



III X = O
IV X = CH_2



V (a) R = H
(b) R = $SO_2C_6H_4CH_3$

expansion of cycloalkanes (7), failed either because of the instability of the β-isocyanido (5) or β-aminoalcohol intermediates under acidic conditions, or the unusual reactivity of the phenothiazine ring system to electrophilic substitution. We then turned to the exocyclic olefin (IV) obtained in 44% yield by the Wittig reaction of III. The cyanogen azide ring expansion procedure of McMurry and Coppolino (8), when applied to IV gave neither the desired ketones I or II; nor was unreacted IV recovered, presumably owing to its instability to the reaction conditions (cyanogen azide, silver tetrafluoroborate, 25° 2-7 days) employed. The regioselective ring expansion procedure of cyclic aralkyl ketones using thallium(III) nitrate (TTN) recently reported by Taylor, *et al.* (9), seemed particularly suited to our needs since it had been successfully carried out on compounds containing a thioether linkage without oxidation of the sulfur atom. Unfortunately, only unidentified mixtures of polar compounds (tlc) were obtained from several attempts to react TTN with IV in methanol.

The desired ketone (I) was finally obtained as the sole product of the solvolytic ring expansion of the glycol monotosylate (Vb), using a modification of a procedure described by Corey, *et al.* (10). Thus, IV was reacted with osmium tetroxide in pyridine and the mixture treated with pyridine-sodium bisulfite (11) to afford Va. The glycol (Va) was then converted to the unstable monotosylate Vb, which was not purified (10), but rearranged to give I in 60-65% overall yields from IV after chromatography on neutral alumina. Glc analysis of the crude reaction mixture gave a single product peak for I, with a retention time considerably different from that of an authentic sample of the α-ketone (II) prepared by an unequivocal synthesis reported previously (3).

EXPERIMENTAL (12)

1,2-Dihydro-3-methylidenyl-3*H*-pyrido[3,2,1-*kl*]phenothiazine (IV).

To a suspension of dried methyltriphenylphosphonium bromide (2.0 g., 5.6 mmoles) in 30 ml. of ether dried over sodium was added dropwise a solution of 0.6*M* phenyllithium (3.1 ml.) in ether-benzene under a nitrogen atmosphere and the yellow-orange mixture was stirred at 25° for 3 hours. The solution of 1,2-dihydro-3-keto-3*H*-pyrido[3,2,1-*kl*]phenothiazine (III) (1.0 g., 3.9 mmoles) in 20 ml. of dry tetrahydrofuran was added dropwise to it. The mixture was stirred at 25° for 30 minutes and then refluxed for 14 hours. The mixture was cooled, diluted with ether (100 ml.), and filtered. The filtrate was washed with water, dried over anhydrous sodium sulfate, and the solvent removed *in vacuo* (aspirator) to give a brown oily residue. The residue was subjected to silica gel column chromatography using 1:1 benzene-hexane as the eluent to give a yellow oil, which was triturated with methanol to afford 440 mg. (44%), m.p. 85-86°; ir (Nujol): ν 1628 (olefinic C=C); nmr (deuteriochloroform): δ

2.7 (t, 2H, CCH_2), 3.7 (t, 2H, NCH_2), 4.9, 5.4 (2s, 2H, $=CH_2$).

Anal. Calcd. for $C_{16}H_{13}NS$: C, 76.45; H, 5.21; N, 5.55; S, 12.75. Found: C, 76.28; H, 5.18; N, 5.45; S, 12.55.

1,2-Dihydro-3-hydroxy-3-hydroxymethyl-3*H*-pyrido[3,2,1-*kl*]-phenothiazine (Va).

To an ice cold solution of IV (1 g., 3.97 mmoles) in 30 ml. of ether containing 1 ml. of pyridine was added dropwise a solution of 1 g. of osmium tetroxide in 5 ml. of ether and the mixture stirred at 25° in the dark for 40 hours. The brown precipitate which formed was collected on a filter and treated with a solution of 3.6 g. of sodium bisulfite in 9 ml. of water and 11.5 ml. of pyridine at 25° for 30 minutes. The clear orange solution which resulted was extracted several times with chloroform and the colorless chloroform extracts were combined, washed with saturated sodium chloride solution and dried over anhydrous sodium sulfate. Evaporation of the solvent *in vacuo* (aspirator) afforded a pale pink oily residue, which was triturated with hexane to give (1 g., 88%) of Va as colorless rhombic crystals, m.p. 163-164°; ir (Nujol): ν 3380, 3260 (OH); nmr (DMSO-d_6): δ 3.31 (CH_2C), 3.6 (m, 4H, NCH_2 or CH_2OH), 4.67, 5.00 (m, s, 2H, OHs), 6.75-7.50 (m, 7, aromatic).

Anal. Calcd. for $C_{16}H_{15}NO_2S$: C, 67.34; H, 5.29; N, 4.90. Found: C, 67.35; H, 5.33; N, 4.79.

1,2,3,4-Tetrahydroazepino[3,2,1-*kl*]phenothiazin-3-one.

A cold solution of freshly recrystallized *p*-toluenesulfonyl chloride (1.34 g., 2 mmoles) in 1 ml. of dry pyridine and 10 ml. of dry methylene chloride was added to a solution of 1 g. of Va in 2 ml. of dry pyridine and 50 ml. of dry methylene chloride cooled to 0° and the mixture maintained at 0-5° for 24 hours. Excess *p*-toluenesulfonyl chloride was hydrolyzed by the additon of 10 ml. of ice water with vigorous stirring for 30 minutes. The mixture was washed thoroughly with cold water and the methylene chloride layers separated and dried over anhydrous sodium sulfate. Evaporation of the solvents *in vacuo* at 25° afforded a pale yellow foam; ir (Neat): ν 1175, 1190 ($-SO_3$); which was used for the next reaction without further purification.

A solution of the crude monotosylate (Vb) in 20 ml. of dry tetrahydrofuran was added dropwise under a nitrogen atmosphere to a stirred suspension of 10 g. of lithium perchlorate (13) and 2 g. of anhydrous calcium carbonate in 50 ml. of dry tetrahydrofuran and the mixture heated at 50-60° for 19 hours. The mixture was cooled, diluted with 250 ml. of ether and filtered. The filtrate was washed several times with cold water and dried over anhydrous sodium sulfate. The solvent was evaporated *in vacuo* to leave a pink viscous oil, a sample of which was subjected to glc analysis (Hewlett-Packard Model 5740, OV-17/3% column, 230° column temperature) and exhibited a single peak with a retention time of 18.8 minutes. Glc of the α-ketone (II) prepared by an unequivocal independent synthesis (3) exhibited a retention time of 24.4 minutes under the same conditions. The crude residue (above) was then subjected to column chromatography on deactivated neutral alumina (grade III) using benzene as the eluting solvent to give 660 mg. (62% from IV), as a pale yellow solid, m.p. 128-130° (from 95% ethanol); ir (potassium bromide): ν 1723 (aliphatic C=O); nmr (deuteriochloroform): δ 2.8 (t, 2H, CH_2CH_2CO), 3.7 (s, 2H, Ar-CH_2CO), 4.0 (t, 2H, NCH_2), 6.6-7.4 (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, 72.09; H, 5.03; N, 5.06; S, 11.77.

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(12) 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^{-11} units. Nmr spectra were recorded on a Varian T-60 spectrometer using tetramethylsilane (TMS) as an internal standard in deuterated chloroform as a solvent (unless otherwise indicated) and data are reported in δ (parts per million) values. Microanalyses were performed by Galbraith Laboratories, Knoxville, Tennessee 37921.

(13) Lithium perchlorate was used to prevent ion pairing of the intermedaite carbonium ion (S. Winstein, S. Smith and D. Darwish, *J. Am. Chem. Soc.*, 81, 5511 (1959) with possible subsequent epoxide formation. No sulfur oxidation occurred under the anhydrous reaction conditions employed.