observed rotation is the sum of the above at the same wavelength

$$\alpha = \alpha_{HA} + \alpha_A = KC_{HA}[\alpha]_{HA} + KC_A[\alpha]_A \quad \text{(Eq. 1)}$$

$$\alpha = KC[\alpha] = K(C_{HA} + C_A)[\alpha] \quad \text{(Eq. 2)}$$

where C is the total concentration of the compound and $[\alpha]$ its specific rotation. Combining Eqs. 1 and 2 gives

$$\frac{C_A}{C_{HA}} = \frac{[\alpha] - [\alpha]_{HA}}{[\alpha]_A - [\alpha]}$$

In any pKa′ determination the concentration of the compound is kept constant and observed rotations can be substituted for specific rotations and the pKa″s are given by (6).

$$\text{pKa}' = \text{pH} - \log\left(\frac{[\alpha] - [\alpha]_{HA}}{[\alpha]_A - [\alpha]}\right)$$

Measurements were made in at least eight buffers and the pKa″s were calculated from the rotations at several wavelengths. The results are summarized below.

Betaine	pKa′ (μ = 0.10)
L chloride	1.75 ± 0.02
L bromide	1.75 ± 0.02
D chloride	1.76 ± 0.03
D bromide	1.73 ± 0.02

The results show the pKa′ to be independent of the configuration of the betaine and the nature of the anions investigated.

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Keyphrases

Betaine salts
Dissociation constants—betaine salts
Spectropolarimetry—dissociation constants

Improved Method for Preparing 3-Azabicyclo[3.2.1]octane Hydrochloride and the Synthesis of its Phenothiazine Derivatives

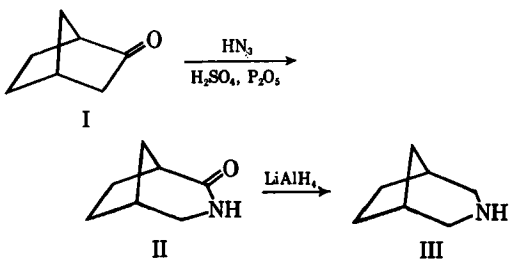
By N. D. POTTI and W. LEWIS NOBLES

Hydrazoic acid in the presence of concentrated sulfuric acid and phosphorus pentoxide has improved the yield of the lactam in the Schmidt reaction of norcamphor. Reduction of the lactam with lithium aluminum hydride gives 3-azabicyclo[3.2.1]-octane in good yields. The synthesis of two new phenothiazine derivatives of this complex amine is reported.

SEVERAL COMPOUNDS derived from azabicyclic amines were reported to possess useful and interesting pharmacodynamic and chemotherapeutic properties (1–3). The primary purpose of this study was to elaborate an easier method for the preparation of 3-azabicyclo[3.2.1]octane (III). A few methods have been reported in the literature (2, 4–7) for the synthesis of this compound or its derivatives; however, these methods either are time-consuming and laborious or they make use of special equipment. The synthesis of two new phenothiazine derivatives of this complex amine is also reported.

The Schmidt reaction of norcamphor (I) was reported (7) to yield 10–28% of the lactam (II), which on reduction gave the desired amine (III). (Scheme I.)

The reaction was repeated under different conditions in order to account for the unusually low yield of the lactam (II). It was noted that by using sodium azide at a temperature of −10°, approximately 40% of the norcamphor remained unreacted. Furthermore, the presence of unused sodium azide was noted. On repeating the reaction with hydrazoic acid instead of sodium azide, the yield of the lactam was found to increase up to 34%. Several attempted changes in the reaction conditions did not noticeably improve the yield. Nevertheless, an overall yield of 40–45% of the lactam (II) was obtained when the reaction was carried out in the presence of phosphorus pentoxide. The method of Blicke and Doorenbos



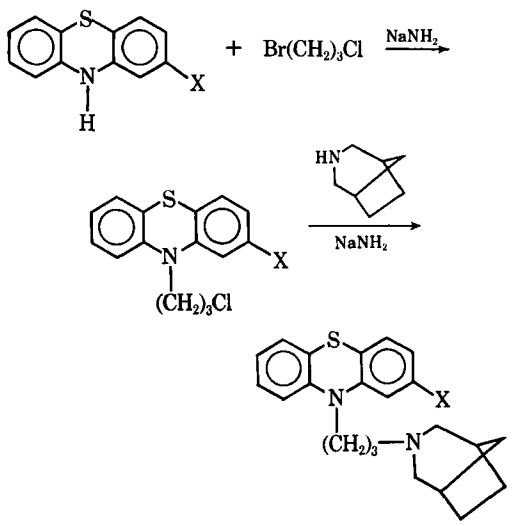
Scheme I

Received March 4, 1968, from the University of Mississippi, University, MS 38677
Accepted for publication June 11, 1968.

(8) gave about 16% of the lactam. The reduction of the lactam with lithium aluminum hydride proceeded smoothly to yield the amine (III) in almost quantitative yields.

Cyclic ketones, in general, undergo the Schmidt reaction to give the respective cyclic lactam in very good yields (8–10). The bicyclic ketone norcamphor differs considerably in this respect. It may be noted that a good percentage of cyclopentene-3-acetonitrile has been formed as a minor product (7). This is to be expected when one considers norcamphor as a branched aliphatic ketone, since such ketones are reported (11) to give nitriles as by-products in the Schmidt reaction.

Several aliphatic and alicyclic amine derivatives of phenothiazine were reported (12), but only a few compounds derived from azabicyclic amines were reported (13,14). These compounds were found to possess chlorpromazine-like activity. The compounds described herein were synthesized by Scheme II and were isolated as the oxalate, since other salts offered difficulty in crystallization.



X = H, OCH_3

Scheme II

EXPERIMENTAL[1]

3-Azabicyclo[3.2.1]octane-2-one (II)—*Method A*—In a 2-l., three-neck flask equipped with a stirrer, a thermometer, and a dropping funnel, a paste of 45 g. (0.7 mole) of sodium azide in 45 ml. of warm water was made. Five-hundred milliliters of chloroform was added and stirred while the temperature was maintained between 0–5°, with the help of an ice-salt bath. Forty-five milliliters of concentrated sulfuric acid was added dropwise, while the temperature was kept in the temperature range mentioned above. Stirring was continued for another 0.5 hr. after the completion of the addition of the acid. The temperature was not allowed to rise above 5° throughout this addition. The chloroform solution of hydrazoic acid was decanted into a 1-l. conical flask. The residue was washed with 100 ml. of chloroform, and the washings were added to the main bulk of the solution. The solution was kept cooled in an ice bath and dried with anhydrous sodium sulfate.

In a 2-l., three-neck flask equipped with a stirrer, a thermometer, and a dropping funnel, 90 ml. of concentrated sulfuric acid was placed. To this, 15 g. of phosphorus pentoxide was added and stirred while 55 g. (0.5 mole) of norcamphor[2] was added slowly, keeping the temperature of the mixture below 30° by occasional cooling with an ice-salt bath. Stirring was continued for another 15–30 min., and 250 ml. of dry chloroform was added. The temperature was maintained between 0–8°, using an ice-salt bath, while the hydrazoic acid solution was added dropwise with vigorous stirring. Stirring was continued for another 4 hr. after the addition, during which time the temperature of the reaction mixture was allowed to come to room temperature. It was made alkaline with 20% sodium hydroxide solution (about 750 ml.) with cooling, so that the temperature was kept below 30°. The chloroform layer was separated; the aqueous layer was extracted with two 250-ml. portions of chloroform and added to the main bulk of the chloroform solution. This chloroform solution was washed with 50 ml. of distilled water and dried over anhydrous sodium sulfate; it was then filtered into a 2-l. distilling flask. The chloroform was removed using a water aspirator. The residue (47 g.) was distilled under vacuum, using an oil bath whose temperature was kept between 130–150°. Twenty-seven grams (43.2%) of the lactam (II) boiling between 110–125° (5 mm.) was collected; this soon solidified into a white mass, which was recrystallized from petroleum ether (b.p. 60–90°); m.p. 93–94°.

Method B—Following the method of Blicke and Doorenbos (8), the Schmidt reaction with norcamphor was performed. In a three-neck, round-bottom flask, fitted with a stirrer and thermometer, 22 g. (0.2 mole) of norcamphor was dissolved in 200 ml. of concentrated hydrochloric acid. The reaction mixture was kept at about 5° and 21 g. (0.32 mole) of sodium azide was added with stirring, which was continued for 5 hr. Solid sodium carbonate was added gradually with stirring until the reaction mixture was alkaline. The organic material was extracted with chloroform, and the extract was dried over anhydrous sodium sulfate. Removal of the solvent left 16.5 g. of a yellow oil, which was distilled under vacuum to yield 4 g. (16%) of a lactam boiling between 110–125° (5 mm.). About 6 g. of a low boiling fraction containing mostly cyclopentene-3-aceto nitrile was also collected.

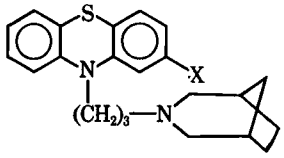
3-Azabicyclo[3.2.1]octane Hydrochloride (III)—The reduction of the lactam was effected essentially by following the method of Elderfield and Losin (7).

In a 3-l., three-neck flask fitted with an efficient condenser, stirrer, and dropping funnel was placed 1.5 l. of absolute ether. With stirring, 16 g. (0.16 mole) of lithium aluminum hydride was added

[1] All melting points are uncorrected. Melting points were determined on a Thomas-Hoover capillary melting point apparatus. Infrared spectra were determined on a Perkin-Elmer model 137 G Infracord spectrophotometer. As sodium azide and hydrazoic acid are highly toxic, the reaction must be carried out in a well-ventilated hood.

[2] Norcamphor was purchased from Aldrich Chemical Company, Inc., Milwaukee, Wisc.

TABLE I—PHENOTHIAZINE DERIVATIVES OF 3-AZABICYCLO[3.2.1]OCTANE



No.[a]	X	Formula	M.p., °C.[b]	Anal., %[c]	Calcd.	Found
1	H	$C_{22}H_{26}N_2S \cdot C_2H_2O_4$	204–205	C	65.48	65.32
				H	6.37	6.76
				N	6.37	6.26
2	OCH_3	$C_{23}H_{28}N_2OS \cdot C_2H_2O_4$	155–156	C	63.91	63.75
				H	6.39	6.44
				N	5.97	5.86

[a] Recrystallized from ethanol. [b] Melting points are uncorrected. [c] Microanalysis through Dr. Alfred Bernhardt, West Germany.

slowly. A solution of 25 g. (0.2 mole) of 3-azabicyclo[3.2.1]octane-2-one (II) in 750 ml. of absolute ether was added to the above, the addition being made in such a way that the reaction mixture refluxed gently. Stirring was continued for another 4–6 hr., and the reaction mixture stood overnight. A minimum quantity of ice was carefully added in small portions to break the complex (the color changed from gray to milky) and allowed to stand for 2 hr. The ether layer was separated from the inorganic material by filtration, and the residue was washed with two 200-ml. portions of ether. The ether solution was dried with anhydrous sodium sulfate. Twenty-two milliliters of concentrated hydrochloric acid (36%) in 100 ml. of ethanol was added with stirring to the above. The ether was removed by evaporation. The yellow viscous liquid was transferred to a 250-ml. round-bottom flask and evaporated to dryness under water vacuum. The crude hydrochloride was recrystallized from an ethanol–acetone mixture. The yield of the pure product was 21.8 g. (70%). The pure amine hydrochloride melted with decomposition above 298°. [Lit. (7) darkened at 240° and decomposed above 300°.] By further treatment of the mother liquor one may isolate 10–15% more of the compound.

The phenothiazine derivatives were prepared by following the method of Yale and Sowinski (15) with some modifications.

3-(10-Phenothiazinyl)-1-{N-(3-azabicyclo-[3.2.1]octyl)}propane Oxalate (Compound 1, Table I)—A mixture of 5.97 g. (0.03 mole) of phenothiazine and 1.4 g. (0.035 mole) of sodamide was refluxed in 100 ml. of dry toluene for 2 hr. To this 16.0 g. (0.12 mole) of 1-bromo-3-chloropropane was added. The refluxing was continued for 18 hr. The solvent and the excess 1-bromo-3-chloropropane were removed by distillation under water vacuum, and the residue was treated with 10 ml. of water and was extracted with 75 ml. of ether. The ether solution was dried with anhydrous sodium sulfate. The ether was removed under vacuum. The residue was dissolved in 100 ml. of dry toluene and dried with anhydrous sodium sulfate. The solution was decanted into a 200-ml. round-bottom flask and refluxed with 1.4 g. (0.035 mole) of sodamide and 3.3 g. (0.03 mole) of 3-azabicyclo[3.2.1]octane for 20 hr. The toluene solution was decanted into a separator and was extracted with dilute hydrochloric acid. The free base was precipitated from the acid solution by sodium carbonate and was extracted with 100 ml. ether. After drying, the ether was removed by evaporation. The residue was dissolved in 20 ml. of ethanol and 2 g. of oxalic acid in 20 ml. of ethanol was added. On cooling, the oxalate separated; on recrystallization from ethanol, this gave 3.60 g. (28%) of product, m.p. 204–205°.

3-[10-(2-Methoxy) Phenothiazinyl]-1-{N-(3-azabicyclo [3.2.1]octyl)}propane Oxalate (Compound 2, Table I)—This compound was prepared by the same procedure as described above, using 6.9 g. (0.03 mole) of 2-methoxy phenothiazine, which yielded 2.8 g. (25%) of the pure oxalate, m.p. 155–156°.

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Keyphrases

3-Azabicyclo[3.2.1]octane HCl—improved synthesis
Phenothiazine derivatives—3-azabicyclo-[3.2.1]octane HCl
Ir spectrophotometry—structure