oxidation of the base during hydrolysis. That this is plausible was shown by the following experiment. An electrolysis of a saturated lithium chloride–pyridine solution between aluminum electrodes for 20 hr. at an initial current of 0.010 amp. and a cell voltage of 130 V. was carried out. The V_t of the aluminum entering solution was 2.94. If it is assumed that some of the conjugate base of tetrahydro-4,4′-dipyridyl is formed by reduction of the solvent by lower valent aluminum anodically generated, calculation shows that only 18 mg. of dipyridyl should have been formed; actually 58 mg. was isolated.

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LAWRENCE, KAN.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF TENNESSEE]

Metalation of 12H-Benzo[a]phenothiazine with *n*-Butyllithium

DAVID A. SHIRLEY AND JEVONS C. LIU

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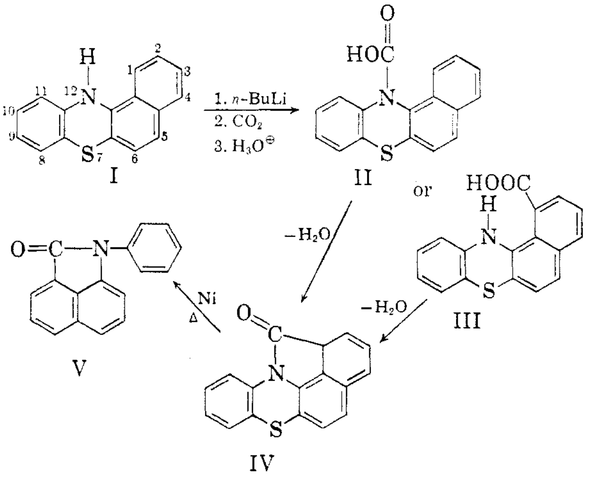
The metalation of 12H-benzo[a]phenothiazine with *n*-butyllithium followed by treatment with carbon dioxide produces 12H-benzo[a]phenothiazine-1-carboxylic acid in 94% yield. The structure of this acid is proved by its dehydration to a lactam and desulfurization to the known *N*-phenylnaphthastyril.

The metalation of a variety of heterocyclic molecules with organolithium reagents has demonstrated that this reaction is often characterized by 1) introduction of the lithium atom at positions adjacent to heteroatoms, 2) good yields, and 3) rapid reaction under mild conditions. As the positions adjacent to heteroatoms are often not the positions involved in other common substitution reactions, the metalation reaction offers a useful and convenient synthetic technique.

As a part of recent investigations[1] of the chemistry of 12H-benzo[a]phenothiazine and derivatives thereof, we have examined the metalation of this polynuclear heterocyclic type with *n*-butyllithium. Relatively few heterocyclic molecules containing >N—H bonds metalate well. The active hydrogen is rapidly replaced by metal and the resulting heterocyclic anion $>N:^-$ resists metalation. Examples of this from our work are the failures of C-metalation with pyrrole,[2] indole,[3] and imidazole,[4] although the *N*-alkyl and *N*-aryl types metalate smoothly. Carbazole[5] and pyrazole[6] metalate only in poor yield. Phenothiazine is an exception, however, as it metalates readily in 52% yield in the 1-position.[7]

Treatment of 12H-benzo[a]phenothiazine (I) with a three-fold excess of *n*-butyllithium in ether produced subsequent to carbonation a 94% yield of a deep red monocarboxylic acid derivative of I. The carboxylic acid was rather unstable and could not be purified by crystallization although it had a correct analysis and melted sharply at 136–137° with loss of water vapor. Heating the carboxylic acid above its melting point caused its conversion, by loss of a molecule of water, to a bright orange-red neutral compound. These results suggested either structure II or III for the monocarboxylic and the lactam IV for the dehydration product.



Structure II was eliminated as a possibility, as no carboxylic acid was isolated from an experiment comparable to the first metalation in which equimolar amounts of organolithium and benzophenothiazine were used.

The structure of IV was proved by its desulfurization with Raney nickel to *N*-phenylnaphthastyril (V). The latter compound was identical with a synthetic sample prepared *via* the route indicated.

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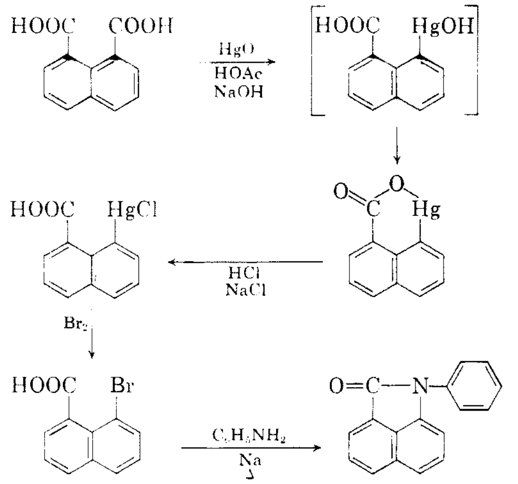

The metalation of 12H-benzo[a]phenothiazine in high yield and with remarkable selectivity of position is a further example of the effectiveness of organolithium reagents in substitution of heterocyclic systems. Polynuclear systems are generally difficult to substitute in good yield at single positions. Metalation of 12H-benzo[a]phenothiazine at the 1-position was not anticipated, as the 11-position should be quite susceptible to metalation on the basis of the results with phenothiazine.[7]

EXPERIMENTAL[8]

Metalation of 12H-benzo[a]phenothiazine (I). A solution of 5.0 g. (0.020 mole) of 12H-benzo[a]phenothiazine[1] in 75 ml. of ether was stirred under a dry nitrogen atmosphere while 78 ml. of a 0.77 molar solution of *n*-butyllithium in ether (0.060 mole of *n*-butyllithium) was added (5 min.). The now bright red solution was stirred for 90 min. after which an excess of solid carbon dioxide was added slowly. Hydrolysis with excess water, separation of the aqueous layer, washing the ether layer with water, and acidification of the combined aqueous layers yielded a red-brown crystalline solid. This was removed by filtration, washed with water, and dried. The product weighed 5.5 g. (94% yield) and melted at 136–137° with loss of water vapor but no apparent further decomposition. The product could not be recrystallized from common solvents, as it seemed to undergo decomposition. The acid could be reprecipitated from 5% aqueous sodium bicarbonate solution, but loss of acidic property seemed to occur on long standing of the solid at room temperature or more rapidly upon treatment with acid. An infrared spectrum of the product showed a carbonyl stretching band at 6.01 μ in accord with a carbonyl group conjugated to a naphthalene ring. On the basis of this data and the analyses below, the product is assigned the structure of a monocarboxylic acid derivative of 12H-benzo[a]phenothiazine.

Anal. Calcd. for $C_{17}H_{11}NO_2S$: C, 69.6; H, 3.75; N, 4.78. Found: C, 69.5, 69.7; H, 3.73, 3.71; N, 3.32, 4.60.

Ring closure of the monocarboxy-12H-benzo[a]phenothiazine to lactam IV. A 0.5-g. sample of the carboxylic acid isolated above was placed in a small test tube and heated at a bath temperature of 165° for several minutes. During this time the compound gave off water vapor but no carbon dioxide. The red-brown crystalline residue was recrystallized twice from ethanol to produce in good yield a bright orange-red neutral compound, m.p. 167–168°. Further crystallization from ligroin (b.p. 90–120°) raised the melting point to 169–170°. The product is insoluble in aqueous acid and base but becomes water soluble after several minutes heating with alcoholic potassium hydroxide solution. A similar solubility behavior has been reported for phenanthridone.[9] Acidification of the aqueous solution after the latter treatment precipitated black, crude carboxylic acid. The lactam IV showed a carbonyl stretching band at 5.90 μ representing an expected[10] shift to lower wave length upon closure of the 5-membered lactam ring from the starting carboxylic acid (III).

Anal. Calcd. for $C_{17}H_9NOS$: C, 74.1; H, 3.28; N, 5.10. Found: C, 74.1, 74.6; H, 3.54, 3.33; N, 4.84, 5.15.

Desulfurization of lactam IV. About 3 to 4 g. of Raney nickel in 40–50 ml. of absolute ethanol was added to a solution of 0.25 g. of the lactam IV in 40 ml. of 95% ethanol. The mixture was heated under reflux for 30 min., filtered and the filtrate added to an ice water slurry. The precipitated light yellow needles weighed 0.20 g. and melted at 90–95°. Two recrystallizations from petroleum ether (b.p. 60–90°) raised the melting point to 102–103°.

Desulfurization of monocarboxy-12H-benzo[a]phenothiazine (III). A sample of the monocarboxylic acid from the metalation experiment was treated generally as in the preceeding experiment except that the gummy solid formed on pouring the reaction mixture into excess ice, and water was extracted with warm aqueous 5% sodium bicarbonate solution and the remaining solid recrystallized from petroleum ether (b.p. 60–90°). The product melted at 103–104° and was identical in infrared spectrum with the sample above from desulfurization of the lactam.

Both of the above samples from desulfurization experiments were identical (infrared spectra) with a synthetic sample of *N*-phenylnaphthastyril[11] (V), m.p. 103–104° (lit., 104–105°). The synthesis of *N*-phenylnaphthastyril was accomplished by the sequence (see earlier formulas) naphthalic acid ⟶ anhydro-8-hydroxymercuric-1-naphthoic acid[12] ⟶ 8-chloromercuri-1-naphthoic acid[13] ⟶ 8-bromo-1-naphthoic acid[14] ⟶ N-phenylnaphthastyril.[11]

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[8] All elemental analyses were performed by Drs. Weiler and Strauss of Oxford, England. Infrared absorption bands were observed by the potassium bromide disc technique with a Perkin-Elmer Model 21 infrared spectrophotometer.

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