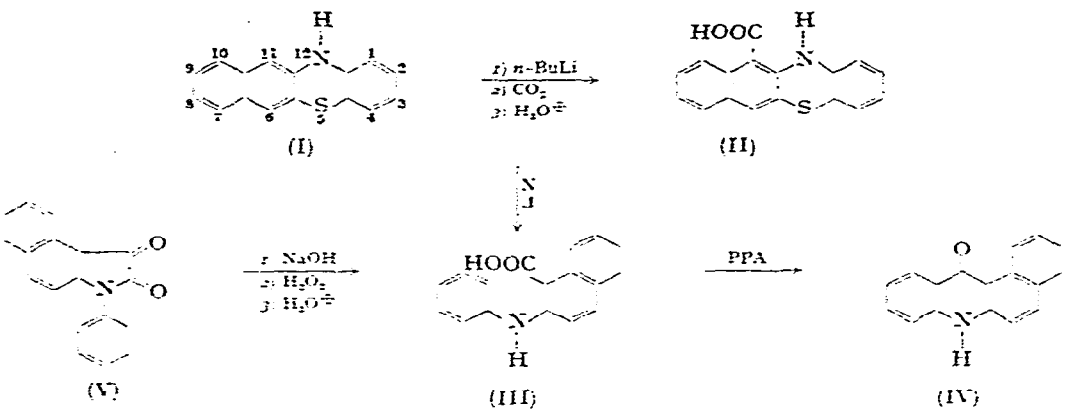
The metalation of 12*H*-benzo[*b*]phenothiazine with *n*-butyllithium

Earlier work from this laboratory has demonstrated that a variety of benzo- and dibenzophenothiazines may be monometalated in high yield and at single positions by the use of *n*-butyllithium[1–3]. This paper reports a study of the metalation of 12*H*-benzo[*b*]phenothiazine (I).

Metalation of one equivalent of (I) with 2.5 equivalents of *n*-butyllithium followed by reaction with carbon dioxide leads to formation of a monocarboxylic acid derivative (II) in 82% yield. The position of introduction of the lithium atom was determined by desulfurization of (II) with excess Raney nickel catalyst to 2-(phenylamino)-1-naphthoic acid (III). Ring closure of (III) to the known[4] benzo[*a*]acridone (IV) with polyphosphoric acid indicated that metalation had occurred in either the 1- or 11-position of benzo[*b*]phenothiazine. Metalation in the 11-position was proved



(I) (II) (III) (IV) (V)

by synthesis of a sample of 1-phenylbenzo[*e*]isatin[5] (V) from *N*-phenyl-2-naphthylamine and oxalyl chloride and the conversion of (V) to 2-(phenylamino)-1-naphthoic acid[5] (III) identical with a sample of (III) obtained by desulfurization of the metalation acid.

The metalation of benzo[*b*]phenothiazine in the 11-position is in line with the findings in the metalations of benzo[*a*]phenothiazine[3] and benzo[*c*]phenothiazine[2] in that (1) the naphthalene rather than the benzene ring is metalated and (2) the position nearest the nitrogen atom is substituted preferentially.

*Experimental**

Metalation of 12H-benzo[b]phenothiazine (I). A solution of 10 g (0.04 mole) of 12*H*-benzo[*b*]phenothiazine[6] in 200 ml of anhydrous ether was treated with 0.10 mole of *n*-butyllithium** in hexane. The deep orange solution was stirred under dry

* Microanalyses were by Weiler and Strauss, Oxford England. Melting points were determined on a Mel-Temp melting point block. Infrared spectra were made by the potassium bromide disk method on a Perkin Elmer Infracord spectrophotometer.

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nitrogen at reflux temperature for 24 h. An excess of crushed solid carbon dioxide was slowly added and the mixture allowed to warm to room temperature. The dark suspension was extracted several times with water. Acidification of the combined aqueous extracts with concentrated hydrochloric acid yielded 9.9 g of yellow-orange solid. The product was reprecipitated from 5 % aqueous sodium carbonate and recrystallized from a 80:20 mixture of ligroin (b.p. 60–90°) and tetrahydrofuran to yield 9.7 g (82 %) of yellow solid melting at 250–252°. The infrared spectrum showed a strong band at 6.10 μ somewhat higher than most carboxyl carbonyl conjugated to an aromatic system. (Found: C, 69.67, 69.42; H, 4.00, 3.94; N, 5.06, 5.00; Neut. eq., 292. $C_{17}H_{11}NO_2S$ calcd.: C, 69.60; H, 3.78; N, 4.80 %; Neut. eq., 293.)

11-Methoxycarbonyl-12H-benzo[b]phenothiazine. A suspension of 1.0 g (3.4 mmole) of the carboxylic acid from the metalation reaction in 25 ml of ether was treated with an ethereal solution containing an excess of diazomethane[7] and the mixture allowed to stand overnight in a hood. A yellow-orange oil was obtained which was taken into solution in ligroin (b.p. 60–90°) and treated with charcoal. Upon concentration 0.95 g (91 %) of a yellow-orange solid, m.p. 96–98°, was obtained. An infrared spectrum showed a carbonyl band at 5.97 μ. (Found: C, 70.49, 70.07; H, 4.26, 4.21; N, 4.46, 4.47. $C_{18}H_{13}NO_2S$ calcd.: C, 70.33; H, 4.26; N, 4.56 %.)

Desulfurization of 12H-benzo[b]phenothiazine-11-carboxylic acid. About 6 g of Raney nickel catalyst[8] was added to a solution of 0.5 g (1.7 mmole) of the acid (II) in 150 ml of benzene. After stirring under reflux for 15 min the color of the solution had changed from deep orange to yellow, but stirring under reflux was continued for another 1.5 h. The catalyst was removed by filtration and the filtrate concentrated to about 15 ml and ligroin (b.p. 30–60°) was added. Upon cooling 0.3 g of yellow solid, m.p. 120–132°, was obtained. Recrystallization from 30:70 benzene and ligroin (b.p. 30–60°) gave 0.2 g (45 %) of acid, m.p. 145–146°.

The melting point of the above product was identical with that of an authentic sample of 2-(phenylamino)-1-naphthoic acid (see below). A mixture melting point showed no depression and the infrared spectra of the two compounds were identical.

Benzo[a]acridone (IV). A mixture of 100 mg of 2-(phenylamino)-1-naphthoic acid, from the desulfurization reaction, and about 20 ml of polyphosphoric acid was heated on the steam bath to 90° for 1 h with occasional stirring. The solution was cooled and excess water added. A yellow solid precipitated and this was recrystallized from 95 % ethanol to yield 30 mg (32 %) of yellow crystals, m.p. 372–378°, with decomposition. The melting point of this material was identical with that of a sample of benzo[a]-acridone prepared by the method of Rosetti[4].

1-Phenylbenzo[e]isatin (V). This and the following procedure are modified from work reported by Stollé[5]. To a solution of 11 g (50 mmole) of *N*-phenyl-2-naphthylamine in 200 ml of dry ether was added, dropwise, 6.3 g (50 mmole) of oxalyl chloride[9]. The mixture was stirred at ice bath temperature and allowed to warm slowly to room temperature. The solution was stirred at room temperature for 3 days during which time 8.2 g (60 %) of the deep red 1-phenylbenzo[e]isatin, m.p. 230–230.5°, precipitated from the ether. The reported[5] value is 229°.

2-(Phenylamino)-1-naphthoic acid (III)[9]. A mixture of 1.0 g (4.4 mmole) of 1-phenylbenzo[e]isatin, 20 ml of water and 0.50 g (12.3 mmole) of solid sodium hydroxide was heated at 60–70° with occasional stirring. After 10 min 2 ml of hydrogen peroxide (30 %) was added and heating was continued for 1 h. Filtration and acidifica-

tion of the filtrate with concentrated hydrochloric acid yielded a yellow-brown solid. This was recrystallized from benzene and ligroin (b.p. 30–60°) to yield 0.40 g (38 %) of 2-(phenylamino)-1-naphthoic acid, m.p. 146°.

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Use of the bromoethyl leaving group for the synthesis of an ethoxyacetyleneboronic ester*

The elimination of ethylene from dibutyl 2-bromoethaneboronate has been found to occur with extreme ease in the presence of mild bases[1]. It was postulated that the base, Z^-, initially attacked the boron atom.

$$BrCH_2CH_2B(OBu)_2 + Z^- \longrightarrow BrCH_2CH_2B^-(OBu)_2 \longrightarrow Br^- + C_2H_4 + ZB(OBu)_2$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\quad |$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\quad Z$$

With the bases used in our original study, the product $ZB(OBu)_2$ was unstable toward disproportionation. However, reaction of *B*-tris(β-bromoethyl)-*N*-triphenylborazine with phenyl- or ethylmagnesium bromide has been reported to replace the bromoethyl group with phenyl or ethyl, respectively[2]. It occurred to us that replacement of the bromoethyl group in the boronic ester series might be a particularly useful route to moderately labile carbon–boron bonds that resist synthesis by other methods.

To test the feasibility of this method, we began with the preparation of dibutyl acetyleneboronate from dibutyl 2-bromoethaneboronate and ethynylmagnesium bromide.

$$BrCH_2CH_2B(OBu)_2 + HC{\equiv}CMgBr \longrightarrow HC{\equiv}CB(OBu)_2 + MgBr_2 + C_2H_4$$

As anticipated, ethylene was evolved, magnesium bromide (as the tetrahydrofuran or ether complex) crystallized, and a good yield of dibutyl acetyleneboronate was obtained on distillation of the solution.

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