[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF IOWA STATE COLLEGE]

The Metalation of 10-Phenylphenothiazine and of 10-Ethylphenothiazine[1]

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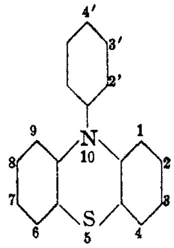
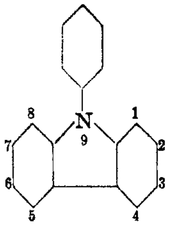
In connection with studies on the biological action of some phenothiazine derivatives, an examination has been made of the metalation by *n*-butyllithium of 10-phenylphenothiazine and of 10-ethylphenothiazine. The 10-phenylphenothiazine (I) undergoes mono-metalation to give, subsequent to carbonation, a · carboxy-10-phenylphenothiazine. There are seven isomeric carboxy-10-phenylphenothiazines, and five of them merit particular consideration in providing an answer to the structure of the acid formed by metalation.



(I)



(II)

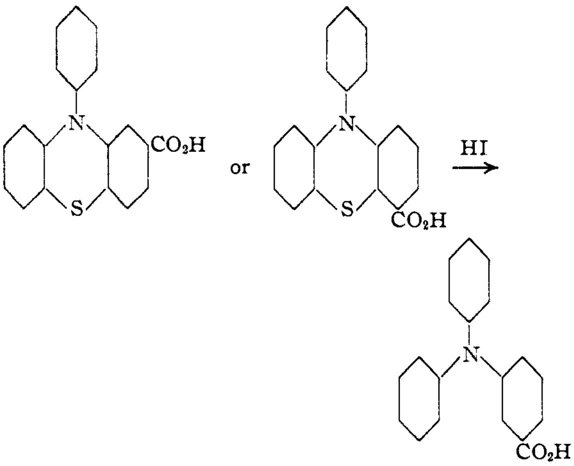
On the basis of earlier work which showed that triphenylamine underwent metalation by *n*-butyllithium in the *meta*-position,[2] one might have predicted that the *meta*- or 3′-position in the 10-phenyl group was involved. However, the 3′-carboxy-10-phenylphenothiazine was synthesized and shown to be unlike the acid obtained by metalation.

The 2′-position seemed to be probable not only because of a general tendency of metalation to occur *ortho* to a hetero element, but especially because the related 9-phenylcarbazole (II) was shown[3] to metalate in the *ortho*-position of the 9-phenyl group. This probability of the 2′-position was ruled out because of the non-identity of the metalation-acid with the very recently described 2′-carboxy-10-phenylphenothiazine.[4] Incidentally, it was shown that the 10-phenyl group was not involved in any way, for the *para*- or 4′-acid (4′-carboxy-10-phenylphenothiazine) was prepared and shown to be different from the metalation-acid.

The 1-position in the parent cycle had plausibility: first, it was *ortho* to a hetero element; and second, phenothiazine itself undergoes metalation by *n*-butyllithium in the 1-position.[4] However, the probability of the 1-position being involved was eliminated by comparison of the metalation-acid with the recently synthesized 1-carboxy-10-phenylphenothiazine.[4]

There remained, then, positions 2, 3 and 4. The 3-position was considered highly unlikely because this would involve both *para* metalation to nitrogen and *meta*-metalation to sulfur, and there is no supporting evidence for either type of metalation by an organolithium compound.

The synthesis of either the 2- or the 4-acid should establish the structure of the metalation-acid; but, unfortunately, there is no convenient approach to the preparation of authentic specimens of these isomers. We did, however, establish by a degradation reaction that the 2- or the 4-position is involved. Concentrated hydriodic acid desulfurizes the metalation-acid to give 3-carboxytriphenylamine.



It appears highly probable that the metalation-acid is 4-carboxy-10-phenylphenothiazine for two reasons. First, the 4-position is favored by the orienting influences of both sulfur and nitrogen—the sulfur always orienting *ortho* in polynuclear systems where the hetero elements are sulfur,[5a] and the nitrogen frequently orienting *meta* when three aryl groups are attached to the nitrogen. Second, sulfur generally has a stronger orienting influence than nitrogen. For example, in competitive reactions for an insufficient quantity of *n*-butyllithium, dibenzothiophene is metalated much more rapidly than N-ethylcarbazole.[5b]

10-Ethylphenothiazine.—Like the phenyl analog, 10-ethylphenothiazine undergoes mono-metalation by *n*-butyllithium to give, subsequent to carbonation, a carboxy-10-ethylphenothiazine. This metalation was carried out prior to the experiments with 10-phenylphenothiazine, and at that time the 3-position was considered very

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(1) Paper LV in the series: "The relative reactivities of organometallic compounds"; the preceding paper is in THIS JOURNAL, 66, 625 (1944).

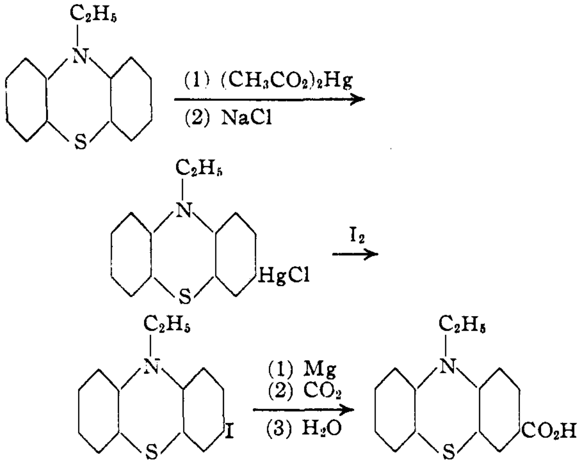
(2) Gilman and Brown, THIS JOURNAL, 62, 3208 (1940).

(3) Gilman, Stuckwisch and Kendall, *ibid.*, 63, 1758 (1941).

(4) Gilman, Shirley and Van Ess, *ibid.*, 66, 625 (1944).

(5) (a) See Gilman and Jacoby, *J. Org. Chem.*, 3, 108 (1938), for the metalation of dibenzothiophene, and Gilman and Stuckwisch, THIS JOURNAL, 65, 1461 (1943), for the metalation of thianthrene. (b) Unpublished studies by C. G. Stuckwisch.

probable. This was based on earlier studies by Finzi,[6] who showed that 10-ethylphenothiazine was mercurated in the 3-position. Accordingly, 3-carboxy-10-ethylphenothiazine was prepared by the reactions



This acid was shown to be unlike the metalation-acid. The structure of the acid obtained by metalation was established as either 2 or 4 by hydrogen iodide degradation or reduction which yielded 3-carboxydiphenylamine. Here, also, it seems most likely that the metalation took place *ortho* to sulfur to give 4-carboxy-10-ethylphenothiazine. It is interesting to note that whereas dibenzofuran undergoes mercuration with difficulty and metalation by *n*-butyllithium with ease, 10-ethylphenothiazine is mercurated with great ease and metalated by *n*-butyllithium with difficulty.

Experimental

Preparation of 10-Ethylphenothiazine.—An attempt to apply the method of Stevens and Tucker[7] for alkylation of carbazole by diethyl sulfate, gave negative results with phenothiazine. However, ethylation was effected in essential accordance with the procedure of Bernthsen.[8] A mixture of 100 g. (0.5 mole) of crude phenothiazine, 200 ml. of absolute ethanol, and 80 g. (0.75 mole) of ethyl bromide was heated at 120–130° for 15 hours in a steel bomb. The yield of 10-ethylphenothiazine melting at 101–103° after crystallization from ethanol was 65 g. (56%).

Metalation of 10-Ethylphenothiazine.—A solution made up of 13.62 g. (0.06 mole) of 10-ethylphenothiazine in 100 ml. of ether and filtered *n*-butyllithium (prepared from 0.1 mole of *n*-butyl bromide in 175 ml. of ether) was refluxed with stirring for 20 hours in a dry nitrogen atmosphere. Subsequent to carbonation by conventional procedures there were obtained, in addition to some *n*-valeric acid, 6 g. of a gummy acid and 8 g. (59%) of 10-ethylphenothiazine. From the crude acid, after extraction with a mixture of petroleum ether (b. p. 60–68°) and toluene, there was isolated 2.6 g. of solid melting over the range 156–165°. Recrystallization, first from a 1:1 solution of chloroform and petroleum ether (b. p. 60–68°), and then from dilute ethanol gave 0.95 g. (6%) of yellow prisms melting at 178–179°. This carboxy-10-ethylphenothiazine is soluble in concd. hydrochloric acid.

Anal. Calcd. for $C_{15}H_{13}O_2NS$: N, 5.17; neut. equiv., 271. Found: N, 5.37 and 5.23; neut. equiv., 273.

The **carbomethoxy-10-ethylphenothiazine** was prepared from the acid and diazomethane in a 57% yield. The ester melted at 111–112° after crystallization, as light yellow prisms, from dilute methanol followed by crystallization from petroleum ether (b. p. 60–68°).

Anal. Calcd. for $C_{16}H_{15}O_2NS$: C, 67.32; H, 5.30; N, 4.91. Found: C, 66.87; H, 5.20; N, 5.05 and 5.06.

3-Iodo-10-ethylphenothiazine.—First, 3-acetoxymercuri-10-ethylphenothiazine was prepared in essential accordance with the procedure of Finzi.[6] The yield of white platelets, melting at 151–153° after crystallization from ethanol, was 37%. Second, the 3-acetoxymercuri-10-ethylphenothiazine (4.5 g.) was converted to the 3-chloromercuri compound by treatment with an excess of 10% sodium chloride solution. Then the filtered 3-chloromercuri-10-ethylphenothiazine was suspended in 25 ml. of a molar solution of potassium iodide, and 50 ml. of carbon tetrachloride was added. Finally, 20 ml. of a 0.05 molar solution of iodine in potassium iodide was added slowly with stirring, and after removing the excess of iodine by dilute sodium sulfite, there was obtained (subsequent to crystallization from ethanol) 2.7 g. (80%) of colorless needles melting at 126–127°. In an attempted analysis by the Carius method some polynitro compound was obtained. Also, decomposition in a Parr bomb was unsatisfactory, the analyses being about 15% low. Successful analysis was effected by the method of Baubigny and Chavanne.[9]

Anal. Calcd. for $C_{14}H_{12}NIS$: I, 35.95. Found: I, 36.39 and 36.23.

3-Carboxy-10-ethylphenothiazine.—The Grignard reagent from 3-iodo-10-ethylphenothiazine was prepared in a customary manner by reaction of 3.53 g. (0.01 mole) of the iodide (dissolved in a mixture of 30 ml. ether and 30 ml. of benzene), 0.5 g. of magnesium turnings, several drops of *n*-butylmagnesium bromide, and a crystal of iodine. Carbonation by solid carbon dioxide gave 2.08 g. (76%) of acid melting at 194–196°; recrystallization from dilute ethanol followed by crystallization from chloroform gave yellow plates melting at 197.5–198.5°.

Anal. Calcd. for $C_{15}H_{13}O_2NS$: N, 5.17; neut. equiv., 271. Found: N, 5.27 and 5.31; neut. equiv., 272.

Preparation of 10-Phenylphenothiazine.—10-Phenylphenothiazine was first prepared by Barnett and Smiles,[10] and this method of preparation was later modified by Finzi.[6] The method of preparation used here presents several further modifications.

Two hundred grams (1.0 mole) of Eastman Kodak Co. "practical" grade phenothiazine, 306 g. (1.50 mole) of iodobenzene, 120 g. of anhydrous sodium carbonate, and 10 g. of copper powder were stirred and refluxed for twelve hours. The mixture was steam distilled, and 40 g. of iodobenzene was recovered in the distillate. The solid residue from steam distillation was filtered off and washed with 10% hydrochloric acid followed by water. The material was then distilled at 220–223° (1 mm.). The distillate weighed 176 g. (64%) and solidified to a light yellow-brown solid which melted at 92–93°. The compound was recrystallized from glacial acetic acid to give white prisms melting at 94.5°. The earlier workers[6,10] had reported the melting point of 10-phenylphenothiazine as 89–90°.

Metalation of 10-Phenylphenothiazine.—To 800 ml. of an ethereal solution containing 0.275 mole of *n*-butyllithium was added 55 g. (0.2 mole) of 10-phenylphenothiazine, and the mixture was stirred at room temperature for twenty-two hours and then allowed to stand for another twelve hours. The resulting yellow solution was carbonated by solid carbon dioxide. The crude acidic metalation product was isolated as previously described[4] in the metalation of phenothiazine; recrystallization from acetic acid gave 6 g. (9.5%) of yellow powder melting at 258–258.5°.

Anal. Calcd. for $C_{19}H_{13}O_2NS$: N, 4.38; neut. equiv., 319. Found: N, 4.62; neut. equiv., 324 and 327.

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(6) Finzi, *Gazz. chim. ital.*, **62**, 175 (1932) [*C. A.*, **26**, 4338 (1932)].

(7) Stevens and Tucker, *J. Chem. Soc.*, **123**, 2145 (1923).

(8) Bernthsen, *Ann.*, **230**, 88 (1885).

(9) Hans Meyer, "Analyse und Konstitutionsermittlung organischer Verbindungen," Julius Springer, Berlin, 1931, p. 140.

(10) Barnett and Smiles, *J. Chem. Soc.*, **97**, 364 (1910).

Methyl Ester of the Metalation Acid of 10-Phenylphenothiazine.—The monocarboxy acid from the metalation of 10-phenylphenothiazine was esterified with methyl alcohol and dry hydrogen chloride in 37% yield. The product was a yellow solid and melted at 133–134° after recrystallization from a mixture of benzene and petroleum ether (b. p. 80–110°).

Anal. Calcd. for $C_{20}H_{15}O_2NS$: N, 4.20. Found: N, 4.24.

10-(4'-Carbomethoxy)-phenylphenothiazine.—A mixture of 10 g. (0.038 mole) of methyl *p*-iodobenzoate, 7.5 g. (0.038 mole) of phenothiazine, 5 g. of anhydrous potassium carbonate, 0.5 g. of copper powder, and 60 ml. of a high boiling petroleum fraction (b. p. 200–230°) was stirred and refluxed for eighteen hours. The mixture was filtered hot and allowed to cool. An equal volume of petroleum ether (b. p. 80–110°) was added to the filtrate, and the solution was decanted from some precipitated tar. The volume of the solution was reduced to 15 ml. by distillation, and upon cooling 7.0 g. of brown crystalline solid precipitated. Two recrystallizations from glacial acetic acid gave 5.0 g. (39%) of small brown prisms which melted at 140.5–141.5°.

Anal. Calcd. for $C_{20}H_{15}O_2NS$: N, 4.20. Found: N, 4.32.

10-(4'-Carboxy)-phenylphenothiazine.—The saponification of 10-(4'-carbomethoxy)-phenylphenothiazine was accomplished in 77% yield by refluxing for two and one-half hours with 10% aqueous sodium hydroxide. The acid was recrystallized twice from glacial acetic acid and melted at 221–221.5°.

Anal. Calcd. for $C_{19}H_{13}O_2NS$: N, 4.38; neut. equiv., 319. Found: N, 4.56; neut. equiv., 326.

10-(3'-Carboxy)-phenylphenothiazine.—Eight grams (0.031 mole) of methyl *m*-iodobenzoate, 6.1 g. (0.031 mole) of phenothiazine, 5 g. of potassium carbonate, 1.5 g. of copper bronze, and 2 ml. of xylene were stirred and refluxed for twenty-four hours according to the procedure used for the preparation of *m*-carbomethoxytriphenylamine.[2] The mixture was extracted several times with hot ether and with hot benzene, but nothing could be isolated from the extracts. The residue from this treatment was boiled with water to remove potassium carbonate, and the hot mixture was filtered. Acidification of the aqueous filtrate gave a light green solid which, upon removal and two recrystallizations from glacial acetic acid, gave 0.075 g. of yellow powder which melted at 254–255°. Analysis and a neutralization equivalent indicated that this acidic material was 10-(3'-carboxy)-phenylphenothiazine. The ester group had apparently been hydrolyzed, and no evidence of unhydrolyzed reaction product was found. The yield of 10-(3'-carboxy)-phenylphenothiazine was only 0.8%.

Anal. Calcd. for $C_{19}H_{13}O_2NS$: N, 4.38; neut. equiv., 319. Found: N, 4.32; neut. equiv., 315.

10-(3'-Carbomethoxy)-phenylphenothiazine.—Refluxing 0.050 g. (0.00016 mole) of 10-(3'-carboxy)-phenylphenothiazine dissolved in a saturated solution of dry hydrogen chloride in absolute methanol for one hour yielded, upon evaporation of the solution, 0.020 g. (38%) of gray-green ester melting at 98–99°.

Anal. Calcd. for $C_{20}H_{15}O_2NS$: N, 4.20. Found: N, 4.30.

Action of Concentrated Hydriodic Acid on the Metalation Acid of 10-Phenylphenothiazine.—Two grams (0.0063 mole) of the metalation acid of 10-phenylphenothiazine and 30 ml. of concentrated hydriodic acid were refluxed for three days. Hydrogen sulfide was evolved during the reaction. The cold solution was filtered to collect the precipitated solid. The solid was recrystallized once from a mixture of benzene and petroleum ether (b. p. 80–110°) and once more from pure benzene to yield 0.20 g. of yellow powder melting at 184–185°. A mixed melting point of this compound and an authentic sample[2] of 3-carboxytriphenylamine established the identity of the two compounds.

Action of Concentrated Hydriodic Acid on the Metalation Acid of 10-Ethylphenothiazine.—Two grams (0.0074 mole) of the metalation acid of 10-ethylphenothiazine was refluxed with 20 ml. of concentrated hydriodic acid for twenty hours. The product was a yellow powder which was recrystallized from benzene–petroleum ether (b. p. 80–110°) to give 0.5 g. of light yellow powder melting at 138–139°. This material was shown to be identical (mixed melting point) with a sample of 3-carboxydiphenylamine.

Preparation of 3-Carboxydiphenylamine.—Five grams (0.019 mole) of methyl *m*-iodobenzoate, 30 ml. of aniline, 5 g. of potassium carbonate, and 0.5 g. of copper bronze were stirred and refluxed for four hours. The mixture was steam distilled to remove excess aniline, and the residue was refluxed with 75 ml. of 15% alcoholic potassium hydroxide solution for five hours. The resulting solution was poured into water, filtered and acidified. The precipitated black solid was reprecipitated from alkaline solution, treated with charcoal and recrystallized from a mixture of benzene–petroleum ether (b. p. 80–110°). The product weighed 0.1 g. (2.5%) and was a yellow powder melting at 140°.

The patent literature[11] mentions 3-carboxydiphenylamine, but there is given no method of preparation or a description of properties of the compound.

Anal. Calcd. for $C_{13}H_{11}O_2N$: N, 6.58; neut. equiv., 213. Found: N, 6.65; neut. equiv., 219 and 221.

Summary

10-Phenylphenothiazine and 10-ethylphenothiazine have been metalated by *n*-butyllithium. Hydrogen iodide cleavage, supplemented by the syntheses of some alternative structures, has shown that metalation occurs in either the 2- or the 4-position, with the latter position made more probable by certain analogies.

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[11] French Patent 824,480 (1937) [*Chem. Zentr.*, **109**, II, 185 (1938)].