Cleavage Studies in the Carbazole and Phenothiazine Systems

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Received September 13, 1956

In connection with general studies of carbazole and phenothiazine derivatives, methods were sought for determining the position taken by the entering substituent in various substitution reactions. The reports on the lithium[1] and Raney nickel[2] cleavage of dibenzofuran and dibenzothiophene, and those on the action of Raney nickel on phenothiazine[3] and 2-phenothiazinecarboxylic acid[4] prompted us to extend the cleavage studies to carbazole, phenothiazine, and their N-ethyl derivatives. Copper, which has been used to convert phenothiazine to carbazole,[5,6] and Raney nickel have not as yet been reacted with 9-ethylcarbazole or 10-ethylphenothiazine.

The reaction between metallic lithium and phenothiazine in refluxing dioxane followed by hydrolysis yielded *o*-mercaptodiphenylamine and diphenylamine. Termination of the reaction by carbonation gave only *o*-mercaptodiphenylamine. When the reaction was carried out in anhydrous ether, the only material isolated was phenothiazine. 10-Ethylphenothiazine and lithium in refluxing dioxane yielded a yellow-brown oil which was assumed to be *o*-mercaptodiphenylethylamine. In contrast to the phenothiazine system, neither carbazole nor 9-ethylcarbazole underwent cleavage. Earlier Signaigo[7] found that phenothiazine in dioxane with hydrogen and a cobalt sulfide catalyst at elevated temperature and pressure gave diphenylamine and *o*-mercaptodiphenylamine. These are the same products which we obtained using lithium metal.

The results obtained indicate that under the conditions employed the carbon-nitrogen bonds within the carbazole and phenothiazine systems are not cleaved. That this inertness is not due to any influence of the sulfur atom is shown by the almost complete recovery of starting material when carbazole or 9-ethylcarbazole is used as a reactant. It would be interesting to determine the extent of cleavage with phenoxazine and, particularly, 5,10-dihydrophenazine.

The isolation of both *o*-mercaptodiphenylamine and diphenylamine from the reaction with phenothiazine can be explained by the mechanism previously proposed[1] which involves cleavage of one or both carbon-sulfur bonds to give carbon-lithium bonds. The failure to obtain a positive Color Test I[8] and to isolate any carboxylic acid on carbonation leads to the conclusion that any intermediate organometallic compound is immediately destroyed by the refluxing dioxane.

The possible use of refluxing hydriodic acid, successfully employed in determining the position of metalation of 10-ethyl- and 10-phenylphenothiazine,[9] appeared to warrant investigation as a cleavage reagent. As with lithium, 9-ethylcarbazole was unaffected by the reagent while 10-ethylphenothiazine yielded mainly the parent heterocycle, phenothiazine. Although a portion of the phenothiazine derivative was desulfurized, as evidenced by the odor of H_2S, the isolation of such a substantial amount of phenothiazine is in marked contrast to the results reported previously; it was found that the 10-ethyl- and 10-phenylphenothiazinecarboxylic acids formed by metalation and carbonation decomposed to give *m*-carboxydiphenylamine and *m*-carboxytriphenylamine, respectively.[9] Thus, desulfurization occurred with both carboxylic acids, but only the N-ethyl group was removed. The desulfurization probably involves the carboxyl group, but additional information must be obtained before the mechanism can be elucidated.

EXPERIMENTAL[10]

Lithium cleavage of phenothiazine. Run I. To 200 ml. of purified dioxane[11] under a nitrogen atmosphere in a three-necked flask equipped with a condenser and mechanical stirrer were added 19.9 g. (0.1 mole) of phenothiazine and 2.22 g. (0.32 g. atom) of lithium. The mixture was stirred and heated to reflux temperature and there maintained for 15 hr. The odor of hydrogen sulfide was evident and a lead acetate test for this substance was positive soon after heating was begun. Color Test I,[8] taken intermittently during the reaction, was negative. After 15 hr. the reaction mixture was cooled and slowly hydrolyzed with a water-dioxane solution. The solvent was distilled off at reduced pressure leaving a light brown, gummy solid. The residue was extracted with two 50 ml. portions of 5% sodium hydroxide, washed with water, extracted with two 50 ml. portions of 5% hydrochloric acid, and then with two 25 ml. portions of methanol. Two recrystallizations from toluene of the residual material gave 7.2 g. (36% recovery) of phenothiazine; a mixed melting point was not depressed. Neutralization of the alkaline extract gave a yellow-brown oil with a mercaptan odor. The oil was dissolved in ether. Ex-

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[1] H. Gilman and D. L. Esmay, *J. Am. Chem. Soc.* **75**, 2947 (1953).

[2] F. F. Blicke and D. G. Sheets, *J. Am. Chem. Soc.* **70**, 3768 (1948).

[3] K. H. Shah, B. D. Tilak, and K. Venkataraman, *Proc. Indian Acad. Sci.*, **28A**, 142 (1948) [*C. A.*, **44**, 3958 (1950)].

[4] R. Baltzly, M. Harfenist, and F. J. Webb, *J. Am. Chem. Soc.*, **68**, 2673 (1946).

[5] A. Goske, *Ber.*, **20**, 232 (1887).

[6] P. Charpentier, *Compt. rend.*, **225**, 306 (1947).

[7] F. K. Signaigo, U. S. Patent **2,402,686** [*Chem. Abstr.*, **40**, 5767 (1946)].

[8] H. Gilman and F. Schulze, *J. Am. Chem. Soc.*, **47**, 2002 (1925).

[9] H. Gilman, P. R. Van Ess, and D. A. Shirley, *J. Am. Chem. Soc.*, **66**, 1214 (1944).

[10] All melting points are uncorrected.

[11] L. F. Fieser, *Experiments in Organic Chemistry*, D. C. Heath and Co., New York, N. Y., 1941, p. 368.

traction of the ethereal solution with 5% sodium hydroxide and careful neutralization of the extract of 0–5° gave 5.8 g. (29%) of a yellow solid, melting at 35–37°. The solid changed to an oil again on standing, probably due to some oxidation to the disulfide. The mercaptan was dissolved in dilute sodium hydroxide and treated with an alcoholic solution of iodine until coloration due to iodine was evident. Filtration gave the disulfide of *o*-mercaptodiphenylamine; m.p. 161–162° (lit.,[12] 162°).

Anal. Calcd. for $C_{24}H_{20}N_2S_2$: S, 16.02. Found: S, 15.92, 15.81.

Neutralization of the hydrochloric acid extract gave no insoluble material.

Water dilution of the methanolic extract gave a light yellow solid which melted from 45–50°. Recrystallization from dilute ethanol gave 0.74 g. (4.4%) of diphenylamine melting at 51–52°; a mixed melting point with an authentic specimen showed no depression.

Run II. Run I was repeated, except that the reaction mixture was carbonated rather than hydrolyzed. Following the evaporation of the carbon dioxide the residue was extracted with sodium bicarbonate solution, then with dilute sodium hydroxide. No acid was obtained from the bicarbonate solution. Neutralization of the sodium hydroxide extract gave 6.7 g. (33.5%) of *o*-mercaptodiphenylamine, melting at 35–37°C; a mixed melting point with a sample from Run I was not depressed. No diphenylamine was isolated, but a 37.2% recovery of phenothiazine was obtained.

Run III. Run I was repeated employing anhydrous ether as a solvent rather than dioxane. The only material isolated was 16.0 g. (80.5% recovery) of phenothiazine.

Lithium cleavage of 10-ethylphenothiazine. Run I. 10-Ethylphenothiazine (11.2 g., 0.05 mole) and 0.8 g. (0.115 g. atom) of lithium were refluxed with 100 ml. of purified dioxane for 15 hr. as described above. Color Test I[3] was negative throughout the reaction. The reaction mixture was cooled and carbonated. The resulting mixture was acidified with 5% hydrochloric acid and the layers separated. The ether layer was extracted with an 8% sodium bicarbonate solution. Careful acidification of the cooled extract gave no solid product. The ethereal solution was then extracted with 10% sodium hydroxide solution. Neutralization gave 2.7 g. of a yellow-brown oil (24% if the product was *o*-mercaptodiphenylethylamine). Attempts to prepare the disulfide yielded a tan, gummy material which defied purification. The residual ether solution was evaporated and the residue recrystallized thrice from ethanol to give 3.5 g. (30.7% recovery) of 10-ethylphenothiazine; m.p. and mixed m.p. 100–102°. Neutralization of the original hydrochloric acid layer gave no precipitate.

Run II. Run I was repeated using 0.23 g. atom of lithium rather than 0.115 g. atom. A 33% yield of the mercaptan and a 28.6% recovery of 10-ethylphenothiazine were obtained. Again no diphenylethylamine was obtained.

Attempted lithium cleavage of carbazole. Run I. A mixture of 16.7 g. (0.1 mole) of carbazole and 4.0 g. (0.57 g. atom) of lithium in 200 ml. of purified dioxane was stirred and refluxed for 24 hr. The mixture was cooled and then poured over cracked ice. The resulting white solid (15.5 g., 93% recovery) was found to be carbazole; m.p. 239–243°. A mixed melting point determination with an authentic sample showed no depression.

Run II. Run I was repeated except that only 0.32 g. atom of lithium was employed and that the reaction mixture was carbonated instead of being hydrolyzed. Intermittent Color Test I[3] was negative. The reaction mixture was worked up as described above for the reaction with 10-ethylphenothiazine. The only product isolated was carbazole (88% recovery); m.p. and mixed m.p. 239–242°.

Attempted lithium cleavage of 9-ethylcarbazole. Run I. 9-Ethylcarbazole (19.5 g., 0.1 mole) and 2.0 g. (0.29 g. atom) of lithium were refluxed with 200 ml. of purified dioxane for 14 hr. The mixture was filtered through a glass wool plug into another flask and carefully hydrolyzed with a 1:1 water-dioxane solution. The addition of more water precipitated 16.0 g. (82% recovery) of 9-ethylcarbazole, melting at 63–66°. A mixed melting point determination with an authentic sample showed no depression.

Run II. Run I was repeated using 3.2 g. (0.46 g. atom) of lithium and a reflux time of 24 hr. Hydrolysis of the cooled reaction mixture gave a 95% recovery of 9-ethylcarbazole; m.p. and mixed m.p. 69–70°.

Run III. Run II was repeated except that the reaction mixture was carbonated instead of being hydrolyzed. The only product was 19.0 g. (97% recovery) of 9-ethylcarbazole; m.p. and mixed m.p. 69–70°.

Hydriodic acid cleavage of 10-ethylphenothiazine. To 11.35 g. (0.05 mole) of 10-ethylphenothiazine was added 50 ml. (0.275 mole) of 47% hydriodic acid. The mixture was heated to a moderate reflux and there maintained for 72 hr. with occasional shaking. The odor of hydrogen sulfide was evident throughout the reaction. After cooling, the yellowish solid was filtered off. Recrystallization from dilute ethanol gave 8.5 g. (85.9%) of phenothiazine; m.p. and mixed m.p. 186–187.5°. The original filtrate was extracted with ether and the extract evaporated to give only a very small amount of dark tar. The residual aqueous layer was made alkaline with sodium hydroxide to give 0.2 g. of white solid which did not melt at temperatures up to 365°. The material was insoluble in acetone, but soluble in cold 6*N* hydrochloric acid.

Attempted hydriodic acid cleavage of 9-ethylcarbazole. A mixture of 9.75 g. (0.05 mole) of 9-ethylcarbazole and 50 ml. (0.275 mole) of 47% hydriodic acid was refluxed gently for 72 hr. The only product isolated was 9.7 g. (99% recovery) of 9-ethylcarbazole; m.p. and mixed m.p. 68–70°.

A second experiment gave almost identical results.

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[12] A. I. Kiprianov and I. K. Ushenko, *J. Gen. Chem.* (*U.S.S.R.*), **17**, 2201 (1947) [*Chem. Abstr.*, **42**, 5016 (1948)].

Thermal Rearrangement of Benzoylmeconic Acid

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Received August 10, 1956

The chemistry of meconic acid, 3-hydroxy-4-pyrone-2,6-dicarboxylic acid (I), is very obscure and no reactions are recorded in which nuclear substitution of the compound has been effected.

There are reports, however, of the nuclear substitution of its partially decarboxylated derivative, comenic acid. Verkade[1] has described the partial decarboxylation of meconic acid with hydrochloric acid and has proven that the carboxyl lost during the reaction is from the position adjacent to the hydroxyl since the resulting comenic acid reacts with diazobenzene acetate. This indicates the presence in the compound of a methylene group which could only be located in the 2 position. The bromination of meconic acid also results

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[1] P. E. Verkade, *Rec. trav. chim.*, **43**, 879 (1924).