From the above mechanism it will be seen that the split of the molecule to yield carbonium ion and aldehyde occurs at the position beta to the position of electron deficiency. The electrons in this particular position are the most accessible to the oxygen atom. The position of the split, as well as the extent of splitting, is in complete harmony with the findings of Whitmore and Stahly[5] and Whitmore and Mosher.[6] This "beta-effect," discussed by Dean Whitmore[7] in 1944, has its physical basis in the fact that the beta electrons are the closest electrons to the deficient atom in which the deficient atom does not already have a part interest.

This work was possible through a Frederick G. Cottrell Grant from the Research Corporation, which we gratefully acknowledge.

Experimental

Preparation of Alcohols.—Methyl-*n*-amylcarbinol was obtained from Carbide and Carbon Chemical Corporation. Ethyl-*s*-butylcarbinol and *n*-propyl-*t*-butylcarbinol were prepared by the Grignard reaction from the appropriate starting materials. Materials were purified by fractionation through a Whitmore–Lux[8] total condensation, partial take-off type column packed with single turn glass helices,[9] and equivalent to 20 theoretical plates.

Oxidation.—(a) All secondary alcohols were oxidized in the following manner exemplified with ethyl-*s*-butylcarbinol: a solution of 80 g. (0.8 mole) of chromic anhydride in 50 ml. of water and 125 ml. of glacial acetic acid was added dropwise to a stirred solution of 168 g. (1.4 mole) of the carbinol in 100 ml. of glacial acetic acid over a period of 5.75 hours. The temperature was kept below 30° at all times. The oil layer formed on dilution of the reaction mixture was separated, washed with bicarbonate solution, and then with water. The aqueous layer was steam distilled and the oil layer, after washing as before, was combined with the main portion. The dried oil layers were fractionated through a column of 20 theoretical plates. From the distillation charge of 133 g. the following cuts were obtained: I (1.5 g., 0.9%), 2,4-dinitrophenylhydrazone, m. p. and mixed m. p. with an authentic derivative of methyl ethyl ketone 116–117°; II (1.4 g., 0.8%), phenylurethan, m. p. and mixed m. p. with a derivative of *s*-butyl alcohol 64–65°; III (100.1 g., 63%), ethyl *s*-butyl ketone, 2,4-dinitrophenylhydrazone m. p. 78°. Unchanged carbinol (11.0 g., 7%) was recovered. Still residue, 8.1 g., was a dark viscous liquid.

(b) Methyl-*n*-amylcarbinol distillation charge 220 g. The corresponding ketone and *n*-amyl acetate boil very close together. The acetate was isolated from the proper fractions by removing the ketone as the bisulfite addition compound and the final traces as the semicarbazone. After drying over anhydrous sodium sulfate a trace (0.08 g., 0.03%) of *n*-amyl acetate, $n^{20}D$ 1.4039, characteristic odor, was isolated; 192 g. (83.2%) of methyl *n*-amyl ketone, 2,4-dinitrophenylhydrazone m. p. and mixed m. p. 74°, was obtained; 7.6 g. (3.4%) unoxidized carbinol was recovered. Still residue was 14.3 g.

(c) *n*-Propyl-*t*-butylcarbinol: No glacial acetic acid was used in order to facilitate isolation of any aldehydes or acids. The carbinol was added dropwise to a vigorously stirred aqueous solution of chromic anhydride. Distillation charge 180 g.; 6.8 g. (4%) of *n*-butyraldehyde, 2,4-dinitrophenylhydrazone m. p. and mixed 122–123°, and a corresponding amount of *t*-butyl alcohol, isolated as the chloride, were obtained. The main fraction (67.3 g., 40.8%), 2,4-dinitrophenylhydrazone m. p. 123–124°, consisted of the corresponding ketone; 50 g. (30.3%) of unoxidized carbinol, phenylurethan m. p. 70–71°, was recovered. Still residue amounted to 21.6 g.

Summary

1. The chromic acid oxidation of ethyl-*s*-butylcarbinol yields the expected ketone, but also small amounts of *s*-butyl alcohol and methyl ethyl ketone.

2. Methyl-*n*-amylcarbinol in acetic acid solution gives a trace of *n*-amyl acetate.

3. Oxidation of *n*-propyl-*t*-butylcarbinol gives small amounts of *t*-butyl alcohol and *n*-butyraldehyde in addition to the expected ketone.

NEWARK, DELAWARE RECEIVED JULY 6, 1948

(5) Whitmore and Stahly, THIS JOURNAL, **55**, 4153 (1933); **67**, 2158 (1945).

(6) Whitmore and Mosher, *ibid.*, **68**, 281 (1946).

(7) Whitmore, Organic Division, American Chemical Society, New York, N. Y., September, 1944.

(8) Whitmore and Lux, THIS JOURNAL, **54**, 3448 (1932).

(9) Wilson, Parker and Laughlin, *ibid.*, **55**, 2795 (1933).

[CONTRIBUTION FROM THE DEPARTMENT OF BIOLOGICAL AND COLLOIDAL CHEMISTRY, THE HEBREW UNIVERSITY]

A Reaction between Resorcinol and Glycine

BY N. LICHTENSTEIN, J. DOBKIN AND EVA HEIMANN-HOLLAENDER

Glycine dissolves with the evolution of carbon dioxide when heated in melted resorcinol at 175–185°. A colorless, crystalline substance can be isolated from the product which remains after the excess resorcinol is removed with ether. The elementary composition and chemical properties of this substance correspond to those to be expected of N-(*m*-hydroxyphenyl)-glycine anhydride (I).

The substance is insoluble in sodium bicarbonate solution, but dissolves readily in dilute sodium hydroxide. It gives positive color reactions with Millon reagent, with 2,6-dichloroquinonechlorimide,[1] and with diazotized sulfanilic acid. The picric acid reaction for diketopiperazines[2] is positive, whereas the fluorescein reaction for resorcinol and the ninhydrin color reaction give negative results. Van Slyke amino determination and titration in acetone according to Linderstrøm–Lang failed to reveal the presence of a free amino group.

Benzoylation of our substance converted it into a corresponding monobenzoyl derivative which was insoluble in dilute sodium hydroxide and gave no color reaction with Millon reagent.

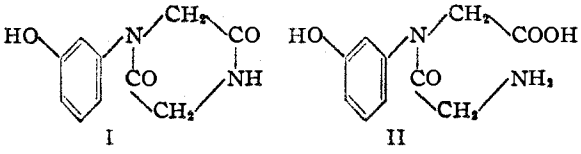
The substance was hydrolyzed with hydrochlo-

(1) H. D. Gibbs, *J. Biol. Chem.*, **72**, 649 (1927).

(2) E. Abderhalden and E. Komm, *Z. physiol. Chem.*, **139**, 181 (1924).

ric acid. When the hydrolysate was evaporated to dryness, dissolved in absolute alcohol and saturated with hydrogen chloride, glycine ethyl ester hydrochloride crystallized out.

It is known that the glycine anhydride ring can easily be opened by treatment with sodium hydroxide to form glycylglycine. In a similar manner, we succeeded in opening the substituted diketopiperazine ring of our substance by treating it with sodium hydroxide and we were able to isolate in good yield a product whose C, H, N and amino N content correspond to the values theoretically expected of glycyl-N-(*m*-hydroxyphenyl)-glycine (II)

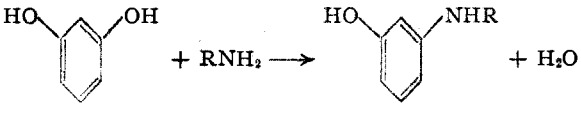


I II

Finally, the same substance as that obtained from glycine was isolated after treating glycylglycine with hot resorcinol under similar conditions.

On heating with resorcinol at 175–185°, glycine anhydride could be recovered unchanged.

The formation of N-(*m*-hydroxyphenyl)-glycine anhydride from glycine and resorcinol may be explained as follows. It is known[3] that resorcinol reacts on heating with ammonia or with amines according to the equation



In a similar manner glycine may be assumed to react with resorcinol, yielding N-(*m*-hydroxyphenyl)-glycine. Heating would lead to the decomposition of a considerable part of this substance into carbon dioxide and *m*-methylaminophenol and the latter is thereafter removed with ether. An analogous decarboxylation of N-phenylglycine "on rapid distillation" is described by Bischoff and Hausdörfer.[4] A portion of the N-(*m*-hydroxyphenyl)-glycine, however, reacts with a second molecule of glycine to yield our substance (I). Similarly, glycylglycine would react primarily with resorcinol to give N-(*m*-hydroxyphenyl)-glycylglycine, which then forms the corresponding substituted diketopiperazine (I) by losing one molecule of water. However, we have not yet succeeded in isolating any of the hypothetical intermediary products mentioned above.

Experimental

Preparation of N-(*m*-Hydroxyphenyl)-glycine Anhydride (I).—One hundred grams of resorcinol was heated in an oil-bath at a bath temperature of 175°. Twenty grams of glycine was added to the melted resorcinol, and the mixture was heated for an hour at 175–185° (bath temperature) with occasional stirring. The glycine soon dissolved with the evolution of gas bubbles. When the evolved gas was introduced into an aqueous solution of barium hydroxide, a precipitate was formed which was free of organic matter and which dissolved in diluted acids with the formation of gas bubbles. The clear hot solution was poured into a porcelain mortar. The solidified mass was treated with dry ether, the ether drawn off by suction and the residue washed with ether and dried; yield, 16 g. This material was repeatedly boiled with several portions of absolute alcohol, using the total volume of 1600 cc. of alcohol. The pooled filtered alcoholic extracts were concentrated to about 100 cc. and allowed to stand overnight. The brownish precipitate was filtered by suction, washed with a little absolute alcohol and dried; yield, 9 g. This substance was boiled with about 40 parts of water and filtered through a hot water funnel. The filtrate was boiled with *carbo animalis* and refiltered. On cooling, a precipitate in the form of yellowish needles appeared. It was filtered by suction, washed with water and dried. On recrystallization of the substance from 100 parts of 70% alcohol 3 g. of a colorless, crystalline substance was obtained in the form of glittering needles. The substance gives a red color reaction when boiled with Millon reagent. A deep orange color appears when diazotized sulfanilic acid and soda are added to its aqueous solution. With dichloroquinone chlorimide[1] and borate buffer (*p*H 9.2) a blue color is formed. The diketopiperazine reaction of Abderhalden and Komm[2] is positive. The ninhydrin color reaction and the fluorescein test for resorcinol are negative. The Linderstrøm–Lang titration value and the amino value according to Van Slyke are 0. The substance is insoluble in cold aqueous sodium bicarbonate but dissolves readily in dilute sodium hydroxide.

For analysis, the substance was twice recrystallized from 70% alcohol and dried *in vacuo* over phosphorus pentoxide at 100°.

Anal. Calcd. for $C_{10}H_{10}N_2O_3$: C, 58.2; H, 4.9; N, 13.6. Found: C, 58.5; H, 4.7; N, 13.5.

The substance has no definite melting point. It decomposes at 265–270° after previous darkening.

N-(*m*-Benzoyloxyphenyl)-glycine Anhydride.—One gram of N-(*m*-hydroxyphenyl)-glycine anhydride was treated with 45 cc. of 0.1 *N* sodium hydroxide (about 0.9 mole) and filtered. The filtrate was cooled in a mixture of ice and water and 0.6 g. of benzoyl chloride was added drop by drop with constant stirring. The colorless precipitate was filtered by suction, repeatedly washed with cold water and dried; yield, 900 mg. For analysis, the substance was recrystallized twice from a small amount of absolute alcohol, m. p. 171° (uncor.). *Anal.* Calcd. for $C_{17}H_{14}N_2O_4$: N, 9.03. Found: N, 9.08. The substance is insoluble in dilute sodium hydroxide and gives no color reaction with Millon reagent.

Acid Hydrolysis of N-(*m*-Hydroxyphenyl)-glycine Anhydride.—One gram of N-(*m*-hydroxyphenyl)-glycine anhydride was boiled with 15 cc. of hydrochloric acid (1:1) for fifteen to twenty hours. The hydrolyzate was evaporated to dryness in a vacuum desiccator over sulfuric acid and soda lime. α-Amino carboxyl determination (Van Slyke's ninhydrin method) showed that at least the greatest part of the substance was completely hydrolyzed. The evaporated hydrolyzate was dissolved in a small amount of absolute alcohol and saturated with dry hydrogen chloride. On standing, about 200 mg. of glycine ethyl ester hydrochloride crystallized out. *Anal.* Calcd.: N, 10.0; Cl, 25.4. Found: N, 10.1; Cl, 25.5.

Glycyl-N-(*m*-hydroxyphenyl)-glycine (II).—Two grams of N-(*m*-hydroxyphenyl)-glycine anhydride was dissolved in 40 cc. of *N* sodium hydroxide and allowed to stand for three days at 30°. Forty cc. of *N* hydrogen chloride was added, and the solution was evaporated to dryness *in vacuo*. The substance obtained was treated with 100 cc. of absolute alcohol and filtered the next day. The remaining product was dissolved in 4 parts of hot water, and the precipitate which formed on cooling was again recrystallized from water. Eight hundred and fifty mg. of a

(3) Beilstein's "Handbuch der organ. Chemie," **6**, 799, 806, 807 (1923).

(4) C. A. Bischoff and A. Hausdörfer, *Ber.*, **25**, 2270 (1892).

reddish, crystalline substance free of chlorine were obtained in this manner. The substance was dried *in vacuo* at 100° over phosphorus pentoxide. It gives positive color reactions with ninhydrin, with diazotized sulfanilic acid and with dichloroquinone chlorimide.

Anal. Calcd. for $C_{18}H_{18}N_2O_4$: C, 53.6; H, 5.6; N, 12.5; amino-N, 6.3. Found: C, 53.4; H, 5.6; N, 12.6; amino-N, 6.3 (Linderstrøm-Lang titration).

The substance has no definite melting point.

Formation of N-(*m*-Hydroxyphenyl)-glycine Anhydride from Glycylglycine and Resorcinol.—To 25 g. of melted resorcinol was added 5 g. of glycylglycine. The mixture was heated for three hours in an oil-bath at a bath temperature of 175–185°. The limpid, hot solution was poured into a porcelain mortar and the solidified material was treated with ether. (No gas formation was observed on heating the dipeptide with resorcinol). After removing the ether by suction the remaining substance was washed with ether and dried; yield, 7.4 g. Five grams of this product was extracted with ethyl acetate for twenty-four hours in a Soxhlet apparatus. The yellowish product which appeared in the extract was filtered by suction, washed with ethyl acetate and dried. The substance (1.1 g.) was recrystallized from 30 cc. of water to which *carbo animalis* was added. On cooling, 250 mg. of a colorless substance was obtained in the form of glittering needles. The Millon reaction was positive. *Anal.* Found: N, 13.2. On benzoylation of 200 mg. under the conditions previously described and on recrystallization from alcohol 170 mg. of a product was obtained whose melting point (171°) was identical with the melting point of the product obtained by benzoylation of N-(*m*-hydroxyphenyl)-glycine anhydride. The m. p. of a mixture of the two substances was also 171°.

Anal. Calcd. N, 9.0. Found: N, 9.2.

Treatment of Glycine Anhydride with Hot Resorcinol.—Glycine anhydride was heated for three hours with 5 parts of resorcinol at 175–185° in a similar manner to the treatment of glycine or glycylglycine. It dissolved in a short time. After solidification, the reaction mixture was treated with ether. The material obtained after drawing off the ether was boiled with 96% alcohol, filtered, washed with alcohol and dried. The product so obtained (80% of the original material) gave no color reaction with Millon reagent. It was recrystallized from water. *Anal.* Calcd. for glycine anhydride: N, 24.6. Found: N, 24.5.

Summary

N-(*m*-Hydroxyphenyl)-glycine anhydride was isolated after treating glycine with hot resorcinol at 175–185°. The same product is formed when glycylglycine is heated with resorcinol.

Treating with sodium hydroxide converts N-(*m*-hydroxyphenyl)-glycine anhydride into glycyl-N-(*m*-hydroxyphenyl)-glycine.

JERUSALEM, PALESTINE RECEIVED FEBRUARY 25, 1948

[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

The Preparation of 3,3'-Dibromobiphenyl and its Conversion to Organometallic Compounds

BY H. R. SNYDER, CLAY WEAVER[1,2] AND CLIFFORD D. MARSHALL

Although the reactions of various dibromobiphenyls with magnesium[3,4] and with an alkyllithium[5] have been reported, 3,3'-dibromobiphenyl appears to have escaped such investigation. Since symmetrical difunctional organometallic compounds related to biphenyl have been of interest to us as possible intermediates[6] in the synthesis of biphenyldiboronic acids,[7,8,9] the behavior of 3,3'-dibromobiphenyl toward magnesium, lithium and *n*-butyllithium has been examined.

3,3'-Dibromobiphenyl was prepared from *o*-nitrobromobenzene by reduction to the hydrazo compound, rearrangement to the benzidine, and deamination of the tetrazonium salt with hypophosphorous acid.[10] The hydrazo compound and the benzidine thus prepared were found to have melting points quite different from those observed on samples, obtained by processes involving the bromination of azobenzene[11] and of N,N'-diacetylbenzidine,[12] which have been considered[13] to have the structures of 2,2'-dibromohydrazobenzene and 3,3'-dibromobenzidine, respectively. The bromination of N,N'-diacetylbenzene was repeated, and a dibromobenzidine identical with our sample was the only product isolated in a pure state from the reaction mixture. In a Sandmeyer reaction with cuprous bromide the tetrazonium salt from our dibromobenzidine gave a product possessing the same melting point as the tetrabromobiphenyl[14] prepared by van Roosmalen from a dibromobenzidine obtained by the direct bromination method. Furthermore, our compounds had the expected compositions and yielded 3,3'-dibromobiphenyl of the correct properties.[15]

3,3'-Dibromobiphenyl did not react with magnesium under the usual conditions of Grignard preparations, but it did react in the presence of ethylmagnesium bromide. The difunctional Gri-

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(2) Present address: Experimental Station, E. I. du Pont de Nemours and Company, Incorporated, Wilmington, Delaware.

(3) Case, THIS JOURNAL, **58**, 1246 (1936).

(4) Malinovskii and Pokrovskii, *Trudy Gor'kov. Gosudarst. Pedagog. Inst.*, No. 5, 51–53 (1940) [*C. A.*, **37**, 3077 (1943)].

(5) Gilman, Langham and Moore, THIS JOURNAL, **62**, 2332 (1940).

(6) Khotinsky and Melamed [*Ber.*, **42**, 3094 (1909)] first prepared boronic acids from alkyl borates and Grignard reagents.

(7) Snyder and Weaver, THIS JOURNAL, **70**, 232 (1948).

(8) Snyder, Weaver and Parmerter, *ibid.*, **70**, 773 (1948).

(9) Snyder and Meisel, *ibid.*, **70**, 774 (1948).

(10) "Organic Reactions," Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1944, p. 262.

(11) Janowsky and Erb, *Ber.*, **20**, 364 (1887).

(12) Levenstein, German Patent 97,101, *Chem. Zentr.*, **69**, II, 522 (1898); see *Frdl.*, **5**, 75 (1901).

(13) Heilbron, "Dictionary of Organic Compounds," Vol. I, Oxford University Press, Oxford, 1934, pp. 429, 440.

(14) van Roosmalen, *Rec. trav. chim.*, **53**, 371 (1934).

(15) Ullmann, *Ann.*, **332**, 57 (1904).