generacies by asymmetry and by an external electric field, of centrifugal distortion, of the presence of excited vibrational states, of internal rotation, of isotopic varieties of the molecule, of nuclear quadrupole coupling, and of other allowed asymmetric rotor transitions are calculated. There is good general agreement between the theoretical and observed spectra for CH_3NCS. The spectrum of CH_3SCN was too weak for detailed analysis but values of the average rotational constant $^1/_2 (B + C)$ are presented.

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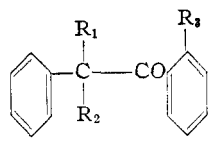
[CONTRIBUTION FROM THE CHEMISTRY LABORATORY OF THE OHIO STATE UNIVERSITY]

Steric Hindrance in the Stobbe Condensation[1]

BY MELVIN S. NEWMAN AND JACK LINSK[2]

The first step in the recently reported method for the synthesis of 1,2-benzanthracene[3] involves the Stobbe condensation (in 60% yield) of desoxybenzoin, I ($R_1 = R_2 = R_3 = H$), and methyl succinate. In order to apply this method to the synthesis of 1′,9-dimethyl-1,2-benzanthracene,



we prepared, o,α-dimethyldesoxybenzoin, II ($R_1 = R_3 = CH_3$, $R_2 = H$) and attempted to condense it with ethyl succinate. In spite of numerous attempts including the use of potassium *t*-butoxide[4] in place of sodium ethoxide and the substitution of methyl succinate, succinic anhydride, and *n*-methylsuccinimide for ethyl succinate, we were entirely unsuccessful. To test the suggestion that enolization of the ketone[5] might be responsible for this failure to condense, we prepared o,α,α-trimethyl-desoxybenzoin, III ($R_1 = R_2 = R_3 = CH_3$), and attempted the reaction, but without success. Hence it appeared that steric factors were involved.

Accordingly we prepared α-methyldesoxybenzoin, IV ($R_1 = R_3 = H$, $R_2 = CH_3$), α,α-dimethyldesoxybenzoin, V ($R_1 = R_2 = CH_3$, $R_3 = H$), and 2,5-dimethylphenyl benzyl ketone, VI (a compound analogous to *o*-methyldesoxybenzoin [$R_1 = R_2 = H$, $R_3 = CH_3$] but easier to prepare) and have tested these under similar conditions in the Stobbe reaction. All of these attempts failed except that with IV, which gave the expected product in about 60% yield. Thus, from a comparison of the reactions involving ketones IV and VI, it appears that the substitution of one methyl group in the ortho position of the phenyl group adjacent to the carbonyl is more effective in hindering reaction than the substitution of a methyl group in the methylene group. Substitution of a second methyl group in the methylene group (ketone V) effectively hinders reaction.

Experimental[6]

2-Phenyl-1-*o*-tolyl-1-propanol.—A solution of 386 g. (2.87 mole) of hydratropaldehyde[7] in 600 cc. of dry ether was added dropwise during two hours to a well stirred solution containing the Grignard reagent prepared from 835 g. (3.83 mole) of *o*-iodotoluene in two liters of dry ether. After decomposition of the reaction mixture with iced hydrochloric acid, the alcohol was obtained as a colorless oil, b. p. 149–150° at 2 mm., in 65% yield. The *p*-nitrobenzoate melted at 112.1–113.4° after three recrystallizations from methanol.

Anal.[a] Calcd. for $C_{16}H_{18}O$: C, 84.9; H, 8.0. Found: C, 85.0; H, 8.1. Calcd. for $C_{23}H_{21}O_4N$: N, 4.0. Found: N, 4.2, 4.0.

o,α-Dimethyldesoxybenzoin, II.—In all attempts to oxidize the above alcohol using chromic oxide, potassium dichromate and sulfuric acid, or nitric acid, considerable cleavage into acetophenone and *o*-toluic acid occurred. In the best experiment 220 g. (0.98 mole) of the alcohol was added during ten minutes to a well-stirred two phase system composed of 100 cc. of benzene and a solution of 200 g. of potassium dichromate in 900 cc. of water and 90 cc. of concentrated sulfuric acid. The temperature slowly rose to 54° but did not go higher. After stirring for twelve hours, during which time the temperature fell to room, the reaction products were taken into ether. The acid was removed by an alkaline wash and the ketone was obtained in 65% yield as a colorless oil, b. p. 120–124° at 1 mm., which soon crystallized. A sample crystallized from methanol melted at 54.4–55.5°. The 2,4-dinitrophenylhydrazone formed small yellow needles, m. p. 136.0–137.0° after several crystallizations from ethyl acetate and from chloroform–alcohol. In all attempts to effect a Stobbe condensation, the ketone was recovered in high yield.

Anal. Calcd. for $C_{16}H_{16}O$: C, 85.7; H, 7.2. Found[a]: C, 85.7; H, 7.3. Calcd. for $C_{22}H_{20}O_4N_4$: C, 65.3; H, 5.0; N, 13.9. Found[c]: C, 65.2; H, 4.7; N, 13.5.

o,α,α-Trimethyldesoxybenzoin, III.—Ketone II was methylated with potassium *t*-butoxide and methyl iodide[8] to yield III as a solid, m. p. 37–38°, in 92% yield. A sample recrystallized for analysis melted at 38.6–39.6°. We were unable to prepare a 2,4-dinitrophenylhydrazone, semicarbazone, or oxime of this ketone, or to secure any acidic material after attempted Stobbe condensations.[4]

(1) The material herein presented is taken from the Ph.D. thesis of Jack Linsk, Ohio State University, June, 1948. Present address: Standard Oil Company of Indiana, Whiting, Indiana.

(2) Abbott Laboratories Fellow, 1947–1948.

(3) Newman and Hart, THIS JOURNAL, **69**, 298 (1947).

(4) W. S. Johnson, A. Goldman and W. P. Schneider, *ibid.*, **67** 1367 (1945).

(5) Private communication from Dr. W. S. Johnson, University of Wisconsin.

(6) All melting points corrected. Analyses marked [a] by the Oakwold Laboratories, Alexandria, Va., [b] by James Polglase, Ohio State University, and [c] by Mrs. Edith Klotz, Ohio State University.

(7) Obtained from the Van Ameringen-Haebler Co., 417 Rosehill Place, Elizabeth, New Jersey.

(8) W. S. Johnson, THIS JOURNAL, **65**, 1317 (1943).

Anal.[a] Calcd. for $C_{17}H_{18}O$: C, 85.6; H, 7.6. Found: C, 85.3; H, 7.4.

α-Methyldesoxybenzoin, IV.—To a solution of the Grignard reagent prepared from 157 g. (1 mole) of bromobenzene and 30 g. of magnesium in 400 cc. of ether was added dropwise during one hour a solution of 63 g. (0.48 mole) of hydratropanitrile[9] in 100 cc. of benzene. After replacing 200 cc. of ether, which was allowed to distil, with an equal volume of benzene, the mixture was refluxed for five hours. The complex was decomposed with dilute hydrochloric acid, 200 cc. of concentrated hydrochloric acid was added, and the mixture refluxed for two hours to hydrolyze the imine hydrochloride. The ketone, IV, was finally isolated in 57% yield as a colorless oil, b. p. 136–137° at 2 mm., which soon crystallized to a solid. On recrystallization this ketone was obtained as feathery needles, m. p. 52–53°.[10]

3-Carboxy-4,5-diphenyl-4-hexenoic Acid.[11]—A solution of 10.3 g. (0.05 mole) of IV and 15.5 g. (0.09 mole) of ethyl succinate in 30 cc. of *t*-butyl alcohol was added to a cooled stirred solution of 2.2 g. (0.055 mole) of potassium in 30 cc. of *t*-butyl alcohol maintained under nitrogen. After refluxing for one and three-quarters hours, the mixture was cooled and treated with 12 cc. of 6 *N* hydrochloric acid. Since the crude half ester did not crystallize, it was saponified and the acid obtained in 42% yield as colorless needles, m. p. 174–176°. More acid was present, but no attempt to isolate the maximum amount was made. The pure acid, obtained on recrystallization from aqueous methanol, melted at 174.6–175.7°. From the neutral reaction products, 19% of IV was recovered.

Anal.[c] Calcd. for $C_{19}H_{18}O_4$: C, 73.8; H, 6.0. Found: C, 74.0; H, 6.2.

α,α-Dimethyldesoxybenzoin, V.—On methylation[8] IV was converted into V in 84% yield. The product boiled at 137–138° at 2 mm. and crystallized on standing to give thin rods, m. p. 45–47°.[12] The attempted Stobbe condensation failed, 79% of V being recovered.

2,5-Dimethylphenyl Benzyl Ketone, VI.—To a stirred cooled solution of 77.3 g. (0.5 mole) of phenylacetyl chloride and 90 g. of pure *p*-xylene[1] in one pound of carbon disulfide was added 110 g. of aluminum chloride during one hour. After heating to reflux during one hour and stirring at room temperature for two more, the mixture was decomposed with ice and hydrochloric acid. The ketone, VI, obtained in 86% yield, boiled at 147–148° at 2 mm. and melted at 30.5–32.0°. The Stobbe reaction failed, an 82% yield of VI being recovered from the reaction mixture.

Anal.[c] Calcd. for $C_{16}H_{16}O$: C, 85.7; H, 7.2. Found: C, 85.8; H, 7.4.

(9) Newman and Closson, THIS JOURNAL, **66**, 1553 (1944).

(10) Kayser, *Ann. Chim.*, (11) **6**, 188 (1936).

(11) The position of the double bond in this acid is assumed.

(12) Bruzan, *Ann. chim.*, [11] **1**, 335 (1934), reports m. p. 46–47°.

COLUMBUS, OHIO RECEIVED OCTOBER 25, 1948

Summary

Steric hindrance in the Stobbe condensation of several methylated desoxybenzoins has been observed. A methyl group ortho to the carbonyl effectively hinders the reaction as do two methyl groups in any positions adjacent to the carbonyl group.

[CONTRIBUTION FROM THE SMITH, KLINE AND FRENCH LABORATORIES]

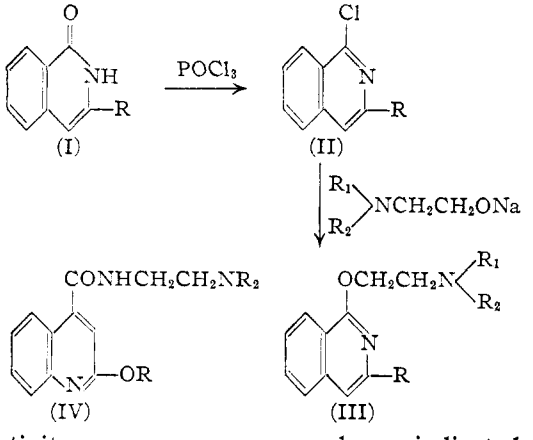
Local Anesthetics. Aminoalkoxyisoquinoline Derivatives

BY JAMES W. WILSON, III, NORMAN D. DAWSON,[1] WALTER BROOKS[2] AND GLENN E. ULLYOT

Aminoalkyl ethers of phenols have been reported to possess local anesthetic activity.[3,4]

As far as we can find, however, no one has investigated the pharmacological properties of aminoalkoxy derivatives of isoquinolines. Previous work in this Laboratory[5] provided an excellent method for preparing a group of isocarbostyrils (I) from which a series of aminoalkoxy derivatives (III) has been obtained according to the procedure outlined by formulas I–III.

In order to be able to study the effect of modifying the lipophylic and hydrophylic character of the terminal groups of the molecule (III) on the pharmacological properties, we have varied the nature of the R, R_1 and R_2 groups as shown in Table I. That such factors play a role is demonstrated by the effect of varying the R groups in the known local anesthetics of the quinoline type (IV),[6] and by gradations in the local anesthetic activity among our compounds, as indicated in the last column of Table I.



The 1-chloroisoquinolines which are intermediates in our syntheses are listed in Table II.

Experimental

Preparation of 1-Chloroisoquinolines.—All of these compounds were prepared from the corresponding isocarbostyrils by the action of phosphorus oxychloride[7] using essentially the same procedure in each case.

(1) Present address: Department of Chemistry, University of Virginia, University, Virginia.

(2) Present address: University of Pennsylvania, Philadelphia, Pennsylvania.

(3) Merck, German Patent 184,968 (1907).

(4) I. G. Farbenindustrie, Swiss Patents 135,890 (1929), 136,186 (1930).

(5) To be reported in a forthcoming paper.

(6) Miescher, *Helv. Chim. Acta*, **15**, 163 (1932).

(7) See Footnote [a], Table II.