NOTES

Some Derivatives of 4'-Hydroxydiphenylamine-4-carboxylic Acid

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In the course of studying various structural analogs of the thyroid hormones, a few diphenylamine derivatives were prepared with the hope that they might compete with oxidations of the hormones to quinonoid structures.[2] Their synthesis is reported below.

Experimental[3]

4-Benzoyloxydiphenylamine.—All attempts to prepare this compound with benzoyl chloride[4] furnished only the dibenzoyl derivative. Consequently, 260 g. (1.4 moles) of 4-hydroxydiphenylamine, 375 g. (1.65 moles) of benzoic anhydride and 250 ml. of dry pyridine were heated on a steam-bath for 6 hours, the cooled mixture was acidified with cold 50% sulfuric acid and filtered. The brownish residue was washed with 2% sodium hydroxide solution and water, excess benzoic anhydride was ethanolized, and the ethanolic solution was diluted with water. The resulting precipitate crystallized from dilute ethanol as pale-yellow leaflets, m.p. 112–114°. The yield was 330 g. (81%).

Anal. Calcd. for $C_{19}H_{15}NO_2$: C, 78.87; H, 5.26. Found: C, 78.73; H, 5.11.

4-Benzoyloxy-4'-cyanodiphenylamine.—A suspension of 40 g. (0.108 mole) of 4-benzoyloxy-4'-bromodiphenylamine[5] and 16 g. (0.172 mole) of cuprous cyanide in 240 ml. of dry quinoline was refluxed for 6 hours, the red solution was cooled and poured with rapid stirring into 200 ml. of ice-cold 37% hydrochloric acid. The precipitate was filtered, washed and recrystallized from benzene–ligroin. The almost colorless needles (17.5 g., 51%) had m.p. 178.5–180.5°.

Anal. Calcd. for $C_{20}H_{14}N_2O_2$: C, 76.41; H, 4.49. Found: C, 76.51; H, 4.50.

Hydrolysis with hot 5% ethanolic potassium hydroxide solution for 30 minutes gave a 71% yield of **4-cyano-4'-hydroxydiphenylamine**, m.p. 193–194.5° after recrystallization from dilute ethanol.

Anal. Calcd. for $C_{13}H_{10}N_2O$: C, 74.27; H, 4.79. Found: C, 74.37; H, 4.71.

4-Cyano-4'-methoxydiphenylamine, obtained with diazomethane, crystallized from aqueous acetone, m.p. 99–100°.

Anal. Calcd. for $C_{14}H_{12}N_2O$: C, 74.98; H, 5.40. Found: C, 74.82; H, 5.27.

4-Methoxydiphenylamine-4'-carboxylic acid was prepared in 43% yield by boiling the nitrile with 15% ethanolic potassium hydroxide for 20 hours. It crystallized from methanol, m.p. 165–167°. It was also obtained by hydrolysis of methyl 4-methoxydiphenylamine-4'-carboxylate with 10% sodium hydroxide solution.

Anal. Calcd. for $C_{14}H_{13}NO_3$: C, 69.12; H, 5.39. Found: C, 68.78; H, 5.78.

4-Hydroxydiphenylamine-4'-carboxylic Acid.—A solution of 5 g. of 4-cyano-4'-hydroxydiphenylamine in 40 ml. of ethylene glycol containing 6 g. of potassium hydroxide was refluxed for 3 hours, cooled and acidified. A brown precipitate was filtered and recrystallized from methanol with the aid of Darco. The colorless product weighed 3.56 g. (65%), m.p. 229–230° dec.[6] It turned pink in the air.

Anal. Calcd. for $C_{13}H_{11}NO_3$: C, 68.11; H, 4.83. Found: C, 67.81; H, 4.90.

Methylation with diazomethane gave **methyl 4-methoxydiphenylamine-4'-carboxylate**, which crystallized from ether–ligroin, m.p. 91.5–93.5°.

Anal. Calcd. for $C_{15}H_{15}NO_3$: C, 70.02; H, 5.88. Found: C, 69.76; H, 5.94.

3,5-Dichloro-4-hydroxy-4'-cyanodiphenylamine.—When 0.1 mole of 4-hydroxy-4'-cyanodiphenylamine was treated with 0.4 mole of iodine monochloride according to the general procedure of Willgerodt and Arnold,[7] a pink powder was obtained which turned blue in the air. Repeated crystallization from ether–ligroin gave a 30% yield of almost transparent colorless needles, m.p. 215–216°.

Anal. Calcd. for $C_{13}H_8Cl_2NO$: C, 55.93; H, 2.89; Cl, 25.41. Found: C, 55.64; H, 3.00; Cl, 25.25.

This unexpected chlorination with iodine chloride has its counterpart in the chlorination of 2,6-dinitro-4-methyl-4'-hydroxydiphenylamine with the same reagent.[6]

(1) National Institutes of Health Fellow, 1952–1953.

(2) C. Niemann and C. E. Redeman, This Journal, **63**, 1549 (1941); C. Niemann and J. F. Mead, *ibid.*, **63**, 2683 (1941).

(3) All melting points are corrected. All hydrolyses were carried out in an inert atmosphere.

(4) A. E. Smith and K. J. P. Orton, *J. Chem. Soc.*, **93**, 314 (1908).

(5) A. E. Bradfield, L. H. N. Cooper and K. J. P. Orton, *ibid.*, 2854 (1927).

(6) This acid had been prepared by R. C. Cookson, *ibid.*, 643 (1953), by a different route.

(7) C. Willgerodt and E. Arnold, *Ber.*, **34**, 3343 (1901).

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The Evaluation of the Kinetic Constants of Enzyme-catalyzed Reactions by Procedures Based upon Integrated Rate Equations. II[1]

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Enzyme-catalyzed reactions that can be represented by equations 1, 2 and 3 are of sufficient

$$E_f + S_f \underset{k_2}{\overset{k_1}{\rightleftharpoons}} ES \xrightarrow{k_3} E_f + P_{1f} + P_{2f} \cdots \quad (1)$$

$$E_f + P_{1f} \underset{k_5}{\overset{k_4}{\rightleftharpoons}} EP_1 \quad (2)$$

$$E_f + P_{2f} \underset{k_7}{\overset{k_6}{\rightleftharpoons}} EP_2 \quad (3)$$

general interest as to encourage the continued development of more reliable and convenient methods for the evaluation of the kinetic constants of such reactions.

For zone A conditions[3–5] a reaction represented by equations 1, 2 and 3 can be formulated in terms of equation 4 where $k_3' = k_3K_P/(K_P - K_S)$,

$$-d[S]/dt = k_3'[E][S]/(K_S' + [S]) \quad (4)$$

$K_S' = K_S(K_P + [S]_0)/(K_P - K_S, K_S = (k_2 + k_3)/k_1, K_P = 1\Big/\sum_{j=1}^{n} 1/K_{Pj}, K_{P1} = k_5/k_4$ and $K_{P2} = k_7/k_6$.

Definite integration of equation 4 to time t followed by rearrangement gives equation 5. It is seen from equation 5 that a

$$\left(\int_0^t [S]dt\right)\Big/([S]_0 - [S]_t) = ((2K_S' + [S]_0)/2k_3'[E]) + ([S]_t/2k_3'[E]) \quad (5)$$

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(2) To whom inquiries regarding this article should be sent.

(3) O. H. Straus and A. Goldstein, *J. Gen. Physiol.*, **26**, 559 (1943).

(4) A. Goldstein, *ibid.*, **27**, 529 (1944).

(5) R. J. Foster and C. Niemann, This Journal, **77**, 1886 (1955).