tion.) The interpretation of these results ought therefore to follow lines similar to the interpretation of the protein diffraction pattern. Either melanins must be considered as "anisotropic amorphous solid substances" according to Freundlich[7] or as non-amorphous crystalline substances according to Astbury.[4]

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(7) H. Freundlich, "Kapillarchemie," Akad. Verlagsgesellschaft Leipzig, 1922, p. 999.

Summary

X-Ray diffraction patterns of photosynthetic melanins as well as of the corresponding amino acids and of various tumor melanins and sepia are described. Slight differences observed in the diffraction patterns of the genuine melanins (from 9.8–10.6 Å. and from 3.86–4.66 Å.) run parallel with observed differences in the optical absorption power of the same substances.

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

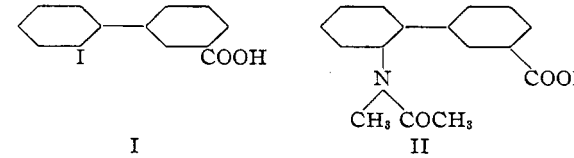
Stereochemistry of Biphenyls. XLVI.[1] 2-Substituted Biphenyls

BY ROGER ADAMS AND T. L. CAIRNS[2]

The prediction of restricted rotation in biphenyls by means of calculated interferences based on atomic radii has proved very helpful. In 2,2′-disubstituted biphenyls, however, the actual stability of the optically active forms is less than would be anticipated from the stability of closely related 2,2′,6- and 2,2′,6,6′-tri- and tetra-substituted compounds. On these grounds, biphenyls monosubstituted in the 2-position should show even greater instability than atomic radii calculations would indicate. The published results of Meisenheimer[3] and Lesslie and Turner[4] confirm this. These latter investigators found it impossible to resolve the 3′-bromobiphenyl-2-tetramethylammonium iodide but obtained the corresponding tetramethylarsonium iodide as a mutarotating compound. In the same paper they mention that 2-iodo-3′-carboxybiphenyl was prepared and could not be resolved. However, this latter compound and its method of preparation were not described. The fact that 2,2′-diiodo-4,4′-dicarboxybiphenyl has been separated into two optically active forms[5] indicates beyond a doubt that an iodine atom is sufficiently large to interfere with a hydrogen and consequently that, unless some mobility greater than that found in 2,2′-disubstituted biphenyls is present in monosubstituted compounds, 2-iodo-3′-carboxybiphenyl should be resolvable.

The syntheses of biphenyls with a substituent in the 2-position and, in addition, a salt-forming group are difficult. 2-Amino-3′-carbethoxybiphenyl offers an attractive starting point for the preparation of such biphenyls since the amino group should be converted readily into or replaced by groups of large radii without difficulty. The details have now been determined by which this compound can be made from the condensation of *o*-bromonitrobenzene and ethyl *m*-iodobenzoate followed by reduction of the nitro group. This synthesis, which appears simple, required much experimentation before a satisfactory procedure was found.

In this communication the preparation of 2-iodo-3′-carboxybiphenyl (I) and N-acetyl-N-methyl-2-amino-3′-carboxybiphenyl (II) from 2-amino-3′-carbethoxybiphenyl is described. The



I II

work of Lesslie and Turner was confirmed in that the iodo compound could not be resolved.

In view of the success of Mills and Kelham[6] in

(1) For previous paper see Adams and Joyce, THIS JOURNAL, **60**, 1491 (1938).

(2) Solvay Process Company Fellow, 1938–1939. An abstract of a thesis submitted in partial fulfilment of the requirements for the degree of Doctor of Philosophy in chemistry.

(3) Meisenheimer and Beitswenger, *Ber.*, **65B**, 32 (1932).

(4) Lesslie and Turner, *J. Chem. Soc.*, 1588 (1933).

(5) Searle and Adams, THIS JOURNAL, **55**, 1649 (1933).

(6) Mills and Kelham, *J. Chem. Soc.*, 274 (1937).

resolving N-acetyl-N-methyl-2-amino-8-naphthalene sulfonic acid and N-acetyl-N-methyl-2-amino-4-methylbenzene sulfonic acid, the N-acetylmethylamino group was introduced into the 2-position as shown in compound II. The sphere of influence assumed by Mills for this group should result in restricted rotation in molecule II. This might occur not only between the phenyl groups but also between the nitrogen atom and the carbon atom of the ring. If in both places, two diastereoisomeric forms should result. Careful fractionation of this product from methanol indicated the presence merely of a single compound.

When resolution of II was attempted through the quinine salt by fractionation from acetone, two salt fractions were obtained. They had different specific rotations (−125 and −140°) and different solubilities. They were not interconvertible, however, and did not mutarotate. Upon hydrolysis, both gave the original acid in the inactive form. Although the explanation of the two salt fractions is not clear, the results indicate that resolution was not accomplished.

The replacement of the amino group in 2-amino-3′-carboxybiphenyl by other groups of large radius is now being studied.

Experimental

2-Nitro-3′-carboxybiphenyl.—A mixture of 25.8 g. of *o*-bromonitrobenzene and 28 g. of ethyl *m*-iodobenzoate was heated under reflux, with mechanical stirring, to a temperature of 215°. In small quantities at a time, 48 g. of activated copper-bronze[7] was added. The temperature was then raised to 235–250° and maintained for forty-five minutes. After cooling, the mixture was extracted with acetone (500–600 cc.) and the copper and copper salts removed by filtration. The acetone solution was concentrated to about 50 cc., 100 cc. of ethanol was added, and the distillation continued until all the acetone was removed. A mixture of 500 cc. of ethanol and 160 cc. of 10% aqueous sodium hydroxide was then added and the solution refluxed for one hour. The alcohol was removed by distillation and 500 cc. of water added to the residue. After filtration, the filtrate was cooled and was extracted with ether to remove alkali-insoluble products. After warming the aqueous solution to evaporate the residual ether it was cooled in an ice-bath and acidified with dilute hydrochloric acid. The brownish mass which separated became hard on standing. This was dissolved in a minimum quantity of glacial acetic acid (150–200 cc.) and on cooling a crystalline product separated. It was recrystallized from ethanol with the use of norite: yellow crystals, m. p. 207–208° (corr.); yield, 7.6 g. (31%).

Anal. Calcd. for $C_{13}H_9O_4N$: C, 64.19; H, 3.70. Found: C, 64.46; H, 3.97.

(7) Kleiderer and Adams, THIS JOURNAL, **55**, 4219 (1933).

2-Nitro-3′-carbethoxybiphenyl.—A mixture of 7.5 g. of 2-nitro-3′-carboxybiphenyl and 30 cc. of thionyl chloride was refluxed gently for twenty to thirty minutes. The excess thionyl chloride was removed under reduced pressure and 50 cc. of ethanol was added drop by drop at first and then faster after the exothermic reaction subsided. The mixture was then refluxed until all the ester was in solution, cooled and poured onto 200 cc. of cracked ice. The pale yellow oil which separated solidified on standing. It was purified by distillation *in vacuo*, b. p. 215° (11 mm.), and then recrystallization from ethanol: white crystals, m. p. 63–65° (corr.); yield, 8 g. (84%).

Anal. Calcd. for $C_{15}H_{13}O_4N$: C, 66.42; H, 4.80. Found: C, 66.90; H, 4.78.

2-Amino-3′-carbethoxybiphenyl.—A solution of 16.5 g. of 2-nitro-3′-carbethoxybiphenyl in 150 cc. of 95% ethanol was refluxed for one hour and fifteen minutes with a teaspoonful of Raney nickel. This procedure was used to remove impurities which interfered with the normal reduction of the nitro to the amino group. After filtration, 0.22 g. of platinum oxide was added and reduction was carried out at 3–3.5 atmospheres (about thirty minutes). After filtration of the platinum, the solution was concentrated to 50 cc. and then poured into 400 cc. of ice water. The pale yellow oil which separated was extracted with 300 cc. of ether and the ether solution, in turn, extracted several times with dilute hydrochloric acid. The hydrochloric acid extract was warmed to remove the ether, filtered, cooled, and neutralized with a slight excess of aqueous ammonia. The oil which separated, rapidly solidified and was recrystallized from ethanol: white crystals, m. p. 75–76° (corr.); yield, 11.5 g. (80%).

Anal. Calcd. for $C_{15}H_{15}O_2N$: N, 5.81. Found: N, 5.86.

2-Iodo-3′-carboxybiphenyl.—In the replacement of the amino group by the iodine, crude 2-amino-3′-carbethoxybiphenyl was often used. Consequently, it was desirable to add 1 g. of the amino compound to a boiling mixture of 100 cc. of concentrated hydrochloric acid and 25 cc. of water and any insoluble material removed by filtration through glass wool. The solution was then cooled to below 5° and, over a period of two hours, 6 cc. of aqueous 10% sodium nitrite solution was added drop by drop. A saturated aqueous solution of 0.5 g. of potassium iodide was added and the mixture allowed to stand overnight at room temperature. The temperature was then raised to 80–85° and sufficient sodium bisulfite added to remove the free iodine. After cooling to room temperature and filtering, the product was washed and recrystallized from dilute dioxane (3:1 water to dioxane, by volume). Very pale pink crystals were obtained, m. p. 168–170° (corr.); yield, 0.9 g. (69%).

Anal. Calcd. for $C_{13}H_9O_2I$: C, 48.14; H, 2.78. Found: C, 48.05; H, 2.80.

Attempted Resolution of 2-Iodo-3′-carboxybiphenyl.—A solution of 0.504 g. of quinine in 25 cc. of anhydrous acetone was added to a solution of 0.504 g. of 2-iodo-3′-carboxybiphenyl in 10 cc. of anhydrous acetone. About 5 cc. of acetone was used to wash out the flask. The mixture was brought to boiling, filtered and the filter paper washed with 5 cc. more of acetone. After standing

overnight, 0.64 g. of pinkish crystals separated, m. p. 184–187° (corr.).

Upon concentration of the filtrate, other fractions were obtained which gave essentially the same melting point as the first fraction. Upon recrystallization of the various fractions from dilute methanol (5:1 methanol to water, by volume), the samples of salt obtained in every instance appeared to be identical, and within experimental error to give a constant rotation and no mutarotation.

Rotation. 0.0488 g. made up to 10 cc. in methanol, $\alpha^{0-2}D$ −0.516; $l = 1$; $[\alpha]^{0-2}D$ −106.

Anal. Calcd. for $C_{33}H_{33}O_4N_2I$: N, 4.32. Found: N, 4.11.

N-Acetyl-2-amino-3′-carbethoxybiphenyl.—A solution of 6 g. of 2-amino-3′-carbethoxybiphenyl in 40 cc. of glacial acetic acid was warmed almost to boiling and 2.4 g. of acetic anhydride and one drop of concentrated sulfuric acid were added. After heating for thirty minutes, the mixture was allowed to stand at room temperature for one hour and was then poured into 500 cc. of ice water. The oil which separated rapidly solidified and was purified by crystallization from petroleum ether (b. p. 60–110°): white crystals, m. p. 111–111.5° (corr.); yield, 6.5 g. (90%).

Anal. Calcd. for $C_{17}H_{17}O_3N$: C, 72.10; H, 6.01. Found: C, 71.87; H, 6.05.

N-Acetyl-N-methyl-2-amino-3′-carboxybiphenyl.—The general procedure followed was that described by Mills and Kelham.[6] To a solution of 4.5 g. of N-acetyl-2-amino-3′-carbethoxybiphenyl in 100 cc. of dry benzene was added 0.5 g. of powdered sodium and the mixture was refluxed for five hours. A solution of 3 g. of dimethyl sulfate in 20 cc. of dry benzene was now added and refluxing was continued for one hour and thirty minutes. The remaining sodium was decomposed by the addition of a small amount of ethanol and then a solution of 5 g. of potassium hydroxide in 100 cc. of 50% ethanol was added. After steam distillation to remove all the benzene, the alkaline solution was refluxed for two hours, treated with norite, filtered and, while still hot, acidified with dilute hydrochloric acid. The yellow precipitate was filtered and purified by solution in essentially the calculated amount of 1–2% aqueous potassium hydroxide, treatment with norite, filtration and acidification. It may be recrystallized from methanol: white crystals, m. p. 228–239° (corr.); yield, 3 g. (70%).

Anal. Calcd. for $C_{16}H_{15}O_3N$: C, 71.36; H, 5.57. Found: C, 71.46; H, 5.62.

From the filtrate a small quantity of N-acetyl-2-amino-3′-carboxybiphenyl was isolated. This was purified by recrystallization from water; white crystals, m. p. 183–188° (corr.).

Anal. Calcd. for $C_{15}H_{13}O_3N$: C, 70.60; H, 5.10. Found: C, 70.52; H, 4.85.

Fractionation of N-Acetyl-N-methyl-2-amino-3′-carboxybiphenyl.—A careful fractionation of the N-acetyl-N-methyl-2-amino compound from methanol gave no indication of the presence of more than a single compound. Practically every fraction had similar melting points and solubilities.

Attempted Resolution of N-Acetyl-N-methyl-2-amino-3′-carboxybiphenyl.—A solution of 0.94 g. of quinine in 20 cc. of methanol was added to a solution of 0.83 g. of N-acetyl-N-methyl-2-amino-3′-carboxybiphenyl in 60 cc. of methanol. The mixture was boiled and filtered and the filter washed with 20 cc. of methanol. The solution thus obtained deposited no crystals after many hours at 5°. It was evaporated, therefore, to dryness at room temperature and a pale yellow oil resulted. This was dissolved in 40 cc. of boiling dilute acetone (4:1 water to acetone, by volume) and after standing for thirty-six hours at 5–7°, 1.2 g. of white crystals separated, m. p. 170.5–173.5° (corr.).

Rotation. 0.0733 g. made up to 10 cc. in chloroform. $\alpha^{26}D$ −1.031; $l = 1$; $[\alpha]^{26}D$ −140.

This product was dissolved in 120 cc. of dry boiling acetone and filtered. After standing for four hours at 5–7°, 0.77 g. of white crystals separated: (Fraction A) m. p. 173–182° (corr.).

Rotation. 0.0691 made up to 10 cc. in chloroform $\alpha^{27}D$ −0.89; $l = 1$; $[\alpha]^{27}D$ −129.

Anal. Calcd. for $C_{36}H_{39}O_5N_3$: C, 72.85; H, 6.58; N, 7.08. Found: C, 72.46; H, 6.86; N, 6.90.

The filtrate from this material was evaporated to dryness and yielded a pale yellow oil. This was dissolved in boiling water (about 50 cc.), filtered and cooled. About 0.2 g. of white crystals (Fraction B), m. p. 172.5–173.5° (corr.).

Rotation. 0.0778 g. made up to 10 cc. in chloroform. $\alpha^{28}D$ −1.088; $l = 1$; $[\alpha]^{28}D$ −140.

Anal. Calcd. for $C_{36}H_{39}O_5N_3$: C, 72.85; H, 6.58; N, 7.08. Found: C, 73.17; H, 6.81; N, 6.90.

Fraction A was recrystallized from acetone and fraction B from water. In the case of fraction B cooling must be carried out slowly to avoid separation as an oil. The melting points and rotations of the fractions were essentially unchanged.

Upon decomposition of these two fractions with hydrochloric acid at 0°, the free acids were obtained which showed no optical activity.

The two fractions also showed no mutarotation upon heating in chloroform solution.

Summary

1. A satisfactory method for the preparation of 2-amino-3′-carbethoxybiphenyl has been developed.

2. 2-Iodo-3′-carboxybiphenyl and N-acetyl-N-methyl-2-amino-3′-carboxybiphenyl could not be resolved by fractionation of the quinine salts.

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