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The Synthesis of 2,2′-Biquinolyls and Related Compounds by Catalytic Dehydrogenation

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Received September 30, 1959

Heating a number of quinolines with 5% palladium-on-carbon has led to 2,2′-biquinolyl formation in 11–21% conversions, with most of the unchanged quinolines being recovered. This method for joining two nitrogen-heterocycles at the 2-positions also has been extended to 1,5-naphthyridine and two pyridines. The reaction is quite sensitive to steric factors, as 3-methylquinoline, benzo[h]quinoline, and isoquinoline fail to react.

Quinoline occasionally has been used as a solvent in dehydrogenation reactions. In a recent instance of such a use, we observed the formation of a crystalline compound in too high a yield to have arisen from the material being dehydrogenated. It appeared to result from the reaction of the quinoline with the palladium-on-carbon catalyst. This was confirmed by a parallel reaction employing only quinoline and the catalyst and by identification of the crystalline material as 2,2′-biquinolyl. Neither an impurity in the quinoline nor special activity in the particular catalyst sample were responsible, as the reaction occurred equally well with highly purified quinoline, quinoline recovered from a reaction with palladium-on-carbon, and various samples of commercial catalyst. The facility and high yield with which 2,2′-biquinolyl formation had taken place induced us to examine this reaction for its synthetic possibilities.

There has been considerable interest in 2,2′-biquinolyls because of their specificity as complexing agents for cuprous ion and their sensitivity,[1] which permits detection of copper in one part in 10^8. However, the methods of preparation have been poor and, in some cases, limiting. Condensation of an *o*-aminobenzaldehyde or an *o*-aminophenone with a 2-acylquinoline requires the laborious preparation of intermediates and still gives poor yields.[2] For unsymmetrical 2,2′-biquinolyls, this remains the only reliable method. However, for symmetrical 2,2′-biquinolyls, the best synthesis appeared to be the reductive coupling of Ueda,[3] employing the 2-bromoquinoline, palladium-on-calcium carbonate, hydrazine, and alcoholic potassium hydroxide. Although the yields are poor and vary widely,[4] the product is reliably the 2,2′-compound. A recent application of this method has reported more consistent results.[5] However, the preparation of the intermediate 2-bromoquinoline and the poor yields are still definite drawbacks. The same may be said for the Ullmann-type condensation, in which the yields are extremely poor.[2,4,6] Catalytic dehydrogenation has been invoked for the preparation of 2,2′-biquinolyls with nickel-alumina in a sealed tube[1,6,7] and with a specially prepared pyrophoric nickel catalyst.[8] In these cases, although starting materials are much simpler and are recovered to a large extent, conversions to biquinolyl were 4–5%, and this decreased rapidly with substituted quinolines.

In comparison with the above procedures, the simplicity of the palladium-on-carbon method and the improved yield were quite attractive. A brief study was made of the effect of time of heating, presence or absence of oxygen, and amount of catalyst. There was very little advantage to continue heating beyond 24 hr; the yield was the same in an oxygen or carbon dioxide atmosphere; and 10% by weight of a 5% palladium-on-carbon catalyst was sufficient. These conditions were incorporated into a general procedure which is presented in the experimental section, and which was applied to eleven quinolines and related compounds.

Seven of these compounds formed the corresponding 2,2′-biaryls in the per cent conversions shown in Table I. The actual yields are much higher, as in

TABLE I

2,2′-BIQUINOLYLS AND RELATED COMPOUNDS PREPARED BY CATALYTIC DEHYDROGENATION

Compound	M.P., °	Conversion, %
2,2′-Biquinolyl	196[a]	17
8,8′-Dimethyl-2,2′-biquinolyl	210–211[b]	12
4,4′-Diphenyl-2,2′-biquinolyl	358–360[c]	11
6,6′-Dimethoxy-2,2′-biquinolyl	280–281	21
2,2′-Bi-1,5-naphthyridyl	282–284	8
2,2′-Bipyridyl	70–71[d]	2
4,4′,6,6′-Tetramethyl-2,2′-bipyridyl	144–145	8

[a] Lit.[8] m.p., 193–194°. [b] Lit.[4] m.p., 203–204°. [c] Lit.[2] m.p., 362°. [d] Lit.[8] m.p., 70.5–71.5°.

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(1) J. G. Breckenridge, R. W. J. Lewis, and L. A. Quick, *Can. J. Res.*, **17B**, 258 (1939).

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(3) K. Ueda, *J. Pharm. Soc. Japan*, **57**, 180 (1937).

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(5) S. Nakano, *J. Pharm. Soc. Japan*, **79**, 310, 314 (1959).

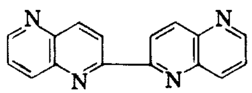
(6) J. G. Breckenridge, *Can. J. Res.*, **28B**, 593 (1950).

(7) J. P. Wibaut, H. D. T. Willink, Jr., and W. E. Nieuwenhuis, *Rec. trav. chim.*, **54**, 804 (1935).

(8) G. M. Badger and W. H. F. Sasse, *J. Chem. Soc.*, 616 (1956).

every case practically all of the uncondensed starting material was recovered, and the material balance was well over 90%. The products were established as the 2,2′-biaryls by elemental analyses and molecular weight determinations, by comparison of ultraviolet spectra and melting points with known compounds, and by complexing with cuprous ion. Complexing occurred in each case except with the sterically-hindered 8,8′-dimethyl-2,2′-biquinolyl and 4,4′,6,6′-tetramethyl-2,2′-bipyridyl.

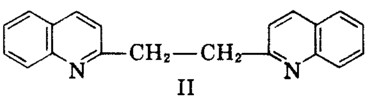
Of interest is the biaryl (I) which was formed


I

from 1,5-naphthyridine, and which gave a copper complex with $\lambda_{\max}$ at 550 mμ. The fact that bipyridyls are formed by this procedure and the possibility that higher temperatures may lead to better conversions are of interest in view of difficulties with present syntheses of bipyridyls.[8,9,10,11]

Three compounds gave no biaryls: 3-methylquinoline, benzo[h]quinoline, and isoquinoline. Each compound presents some steric interference either to complexing with the palladium catalyst or to formation of the biaryl. This absence of reaction indicates the sensitivity of the present method to steric factors.

2-Methylquinoline was subjected to the general procedure to see if coupling would occur to give the 4,4′-biquinolyl. None of this was obtained. However, a very small amount of a crystalline substance was isolated. Its molecular formula was that of a coupled product, and it has been assigned the structure 1,2-di-(2-quinolyl)ethane (II) on the basis of


II

its ultraviolet and infrared absorption. Its ultraviolet absorption maxima were almost identical with those of 2-methylquinoline, except for the absence of some short wavelength fine structure, and the extinction coefficients which were about doubled. In the infrared, 2-methylquinoline, 2,2′-biquinolyl, and compound II all showed bands at 745 cm.$^{-1}$ and 820 cm.$^{-1}$. These are characteristic of four and two adjacent aromatic hydrogens, respectively. There was no absorption in the 900–860 cm.$^{-1}$ range that could be attributed to an isolated aromatic hydrogen.[12]

EXPERIMENTAL[13]

General procedure for the preparation of heterocyclic biaryls. A stirred mixture of the quinoline (or related compound) and 10% by weight of a commercial 5% palladium-on-carbon catalyst was heated under reflux for 24 hr. In all cases, heating was at the boiling point of the compound, except for the following: 4-phenylquinoline was heated at 360°; 6-methoxyquinoline was heated at 265°; and 1,5-naphthyridine was heated at 220°. The mixture was then cooled, 10 parts by volume of chloroform was added, and this mixture was heated to boiling and filtered. Three digests with boiling chloroform (or benzene) were sufficient to remove all adsorbed material from the catalyst. The combined chloroform solutions were then distilled to remove chloroform and to recover unchanged starting material. Chromatography of the residue on alumina (Merck) gave the pure heterocyclic biaryl. Elution was usually accomplished with benzene to which increasing amounts of chloroform were added. In those instances where the starting heterocycle was not sufficiently volatile to be recovered by distillation, it was separated from the bis-compound by sublimation or by chromatography on alumina. The new biaryls prepared by this procedure are:

6,6′-Dimethoxy-2,2′-biquinolyl, m.p. 280–281°; ultraviolet absorption, $\lambda_{\max}^{\mathrm{MeOH}}$ 266 mμ (ϵ 50,000), 309 (12,600), 337 (23,000), 352 (32,000).

Anal. Calcd. for $C_{20}H_{16}N_2O_2$: C, 76.0, H, 5.1, N, 8.9, OCH_3, 19.6. Found: C, 75.9; H, 5.0; N, 9.1; OCH_3, 19.5.

2,2′-Bi-1,5-naphthyridyl, m.p. 282–284°; ultraviolet absorption, $\lambda_{\max}^{\mathrm{MeOH}}$ 233 mμ (ϵ 52,500), 265 (12,000), 275 (13,500) 286 (16,500), 321 (25,000), 333 (25,100).

Anal. Calcd. for $C_{16}H_{10}N_4$: C, 74.4; H, 3.9; N, 21.7; mol. wt., 258. Found: C, 74.7; H, 3.7; N, 21.8; mol. wt.. 238.

4,4′,6,6′-Tetramethyl-2,2′-bipyridyl, m.p. 144–145°.

Anal. Calcd. for $C_{14}H_{16}N_2$: C, 79.3; H, 7.5; N, 13.2; mol. wt., 212. Found: C, 79.3; H, 7.5; N, 13.2; mol. wt. (Rast), 202.

3-Methylquinoline (heated at its boiling point), isoquinoline (heated at its boiling point), and benzo[h]quinoline (heated at 370°) gave no evidence of biaryl formation and were recovered quantitatively when subjected to the above procedure.

1,2-Di-2-quinolylethane. When 20 g. of 2-methylquinoline was heated with palladium-on-carbon as described in the general procedure above, 18 g. was recovered. Chromatography of the residue on alumina gave crystalline material in the fractions eluted with benzene, and this was recrystallized from methanol. Following sublimation (155°/75 μ), 57 mg. were obtained, melting at 166–167°[14]; ultraviolet absorption,[15] $\lambda_{\max}^{\mathrm{MeOH}}$ 314 (ϵ 7200), 306 (4250), 301 (5500), 294 (4000), 233 (49,500).

Anal. Calcd. for $C_{20}H_{16}N_2$: C, 84.4; H, 5.6; N, 9.9. Found: C, 84.4; H, 5.6; N, 9.9.

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(13) All melting points are corrected. Microanalyses were performed by V. Tashinian, Microchemical Laboratory, University of California, Berkeley.

(14) It is possible that this is the same as the unidentified substance, $C_{20}H_{16}N_2 \cdot H_2O$, melting at 160–162°, obtained from the reaction of 2-methylquinoline and sulfur by W. V. Miller [*Ber.*, 21, 1827 (1888)].

(15) *Cf.* the ultraviolet absorption of 2-methylquinoline, $\lambda_{\max}^{\mathrm{MeOH}}$ 314 mμ (ϵ 4250), 308 (2500), 301 (3000), 295 (2250), 232 (25,200), 228 (27,500), 224 (27,300).