[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF TEMPLE UNIVERSITY]

The Synthesis of Certain Alkyl- and Phenyl-substituted 2,2′-Biquinolines[1]

BY FRANCIS H. CASE AND GERHARD MAERKER

RECEIVED MAY 2, 1953

The following derivatives of 2,2′-biquinoline have been synthesized in an effort to improve upon its properties as an analytical reagent for Cu(I): 3-ethyl, 3-*n*-propyl, 3-phenyl, 3-carboethoxy, 4-methyl, 4-phenyl and 4,4′-diphenyl.

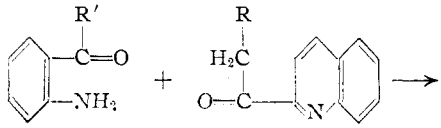
It has been known for some time[2,3] that 2,2′-biquinoline is an excellent reagent for the detection of Cu(I), yielding a purple complex of molecular extinction coefficient 5490, which is quantitatively extractable by isoamyl alcohol. Attempts to introduce alkyl substituents into the heterocyclic portion of the 2,2′-biquinoline nucleus have been limited to the synthesis of 3-methyl-[4] and 4,4′-dimethyl-2,2′-biquinoline.[4] By analogy with substituted 1,10-phenanthrolines this type of substitution, particularly in the 4-position, should result in increased sensitivity of the reagent, and extractability of the copper complex.[5]

In this paper are described syntheses of 3-ethyl- (I), 3-*n*-propyl- (II), 3-phenyl- (III), 3-carboethoxy- (IV), 4-methyl- (V), 4-phenyl- (VI), and 4,4′-diphenyl-2,2′-biquinoline. The first four of the above mentioned compounds were prepared by the action of *o*-aminobenzaldehyde in presence of dilute alkali on *n*-propyl, *n*-butyl and benzyl 2-quinolyl ketone and on ethyl quinaldoylacetate, respectively.

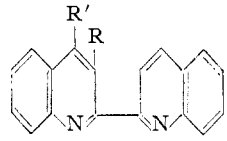
The *n*-propyl and *n*-butyl 2-quinolyl ketones, hitherto undescribed, were prepared by the method of Kaufman and Dändliker[6] from 2-cyanoquinoline. A similar procedure applied to the preparation of benzyl 2-quinolyl ketone was found by the above authors to be unsatisfactory. The results of their second method, involving the use of ethyl quinaldate, sodium amide and phenylacetontirile could not be duplicated by us. The most satisfactory method was found to be the procedure of Lorz and Baltzly[7] for 4-quinolyl ketone, using 2-cyanoquinoline (instead of the 4-isomer), phenylacetonitrile, and bromomagnesium di-*n*-butylamine, followed by acid hydrolysis of the resulting product.

It was found that it is much more difficult to condense *o*-aminoaceto- or benzophenone with 2-acetylquinoline than *o*-aminobenzaldehyde. The yields in the former reaction were found to be very low. 4-Methyl-2,2′-biquinoline was obtained in poor yield on long heating of *o*-aminoacetophenone and 2-acetylquinoline with concentrated alkali. The use of piperidine as condensing agent did not improve the yield. With *o*-aminobenzophenone and 2-acetylquinoline however, a somewhat better yield of 4-phenyl-2,2′-biquinoline was obtained in presence of the latter reagent.

The synthesis of 4,4′-diphenyl-2,2′-biquinoline involved the action of copper at a high temperature on 2-bromo-4-phenylquinoline.



I, R = C_2H_5–, R′ = H
II, R = *n*-C_3H_7–, R′ = H
III, R = C_6H_5–, R′ = H



IV, R = C_2H_5OC=O, R′ = H
V, R = H, R′ = –CH_3
VI, R = H, R′ = –C_6H_5

The authors are indebted to the Monsanto Chemical Company for a supply of *o*-nitroethylbenzene.

Experimental Part

***n*-Butyl 2-Quinolyl Ketone.**—Fifteen grams (0.096 mole) of 2-cyanoquinoline, prepared by the method of Kaufman and Dändliker, dissolved in a mixture of 125 ml. of benzene and 100 ml. of ether (both previously dried over calcium hydride), was treated with 0.24 mole of *n*-butylmagnesium bromide (prepared from 15 g. of magnesium turnings and 34 ml. of *n*-butyl bromide) under the conditions of an inverse Grignard reaction. The resulting brown precipitate was removed by filtration and hydrolyzed in 1500 ml. of a mixture of aqueous ammonium chloride and ice. After removal of the solvent, the resulting oil boiled at 178–182° at 10–11 mm. pressure, yielding 12.5 g. of brown crystals. Recrystallization from petroleum ether produced 11.0 g. of pale yellow crystals, m.p. 42–44°; yield 35%.

Anal. Calcd. for $C_{14}H_{15}NO$: C, 78.84; H, 7.09. Found: C, 78.54; H, 7.20.

***n*-Propyl 2-Quinolyl Ketone.**—This was prepared by a procedure similar to that above from 20.3 g. (0.13 mole) of 2-cyanoquinoline and 0.33 mole of *n*-propylmagnesium bromide. From the crude product a brown oil boiling at 146–150° at 3 mm. was separated. This crystallized on cooling and was recrystallized from petroleum ether producing pale yellow crystals, m.p. 41–42°, yield 24.8%.

Anal. Calcd. for $C_{13}H_{13}NO$: C, 78.36; H, 6.58. Found: C, 78.30; H, 6.54.

Benzyl 2-Quinolyl Ketone.—The directions of Lorz and Baltzly[7] for the preparation of benzyl 4-quinolyl ketone were used, starting with 2-cyanoquinoline instead of the 4-isomer. The yield of α-phenyl-β-(2-quinolyl)-β-iminopropionitrile (m.p. 147–149°) was 60.8%. On refluxing with 1–1 sulfuric acid, benzyl 2-quinolyl ketone (m.p. 81–83°) was obtained in 31.9% yield.

Ethyl Quinaldoylacetate.—The method of Campbell, Helbing and Kerwin[8] was used.

3-Ethyl-2,2′-biquinoline.—A solution of 1.82 g. (0.015 mole) of freshly prepared *o*-aminobenzaldehyde, 3 g. (0.015 mole) of *n*-propyl 2-quinolyl ketone and 3.8 ml. of normal potassium hydroxide in 50 ml. of ethanol was refluxed for 2 hr. The ethanol was partly removed by distillation and the remaining solution was poured into ice-water. The thick oil which separated solidified on prolonged cooling. The solid was crystallized from dilute methanol; yield 2.6 g. of white crystals, m.p. 96–97°, or 60%.

Anal. Calcd. for $C_{20}H_{16}N_2$: C, 84.47; H, 5.67. Found: C, 84.50; H, 5.69.

(1) This work was supported by a grant from the Committee on Research and Publications of Temple University.

(2) J. G. Breckenridge, W. J. Lewis and L. A. Quick, *Can. J. Research*, **B17**, 258 (1939).

(3) J. Hoste, *Anal. Chim. Acta*, **4**, 23 (1950).

(4) J. G. Breckenridge, *Can. J. Research*, **28B**, 593 (1950).

(5) W. H. McCurdy and G. F. Smith, *The Analyst*, **77**, 846 (1952).

(6) A. Kaufman and P. Dändliker, *Ber.*, **46**, 2924 (1913).

(7) E. Lorz and R. Baltzly, THIS JOURNAL, **70**, 1904 (1948).

(8) K. N. Campbell, C. H. Helbing and J. F. Kerwin, *ibid.*, **68**, 1840 (1946).

3-*n*-Propyl-2,2'-biquinoline.—This was prepared in a manner similar to the above procedure using the same molar quantities of *o*-aminobenzaldehyde and *n*-butyl 2-quinolyl ketone. The yield of pure product crystallizing from petroleum ether and melting at 49–50° was 1.5 g. or 33.5%.

Anal. Calcd. for $C_{21}H_{18}N_2$: C, 84.53; H, 6.08. Found: C, 84.65; H, 6.00.

3-Phenyl-2,2'-biquinoline.—Using the same molar quantities of *o*-aminobenzaldehyde and benzyl 2-quinolyl ketone as above, 3 g. of pure product was obtained, crystallizing from dilute methanol and melting at 147–148°, yield 60.2%.

Anal. Calcd. for $C_{24}H_{16}N_2$: C, 86.72; H, 4.85. Found: C, 86.42; H, 4.89.

3-Carboethoxy-2,2'-biquinoline.—The procedure was the same as in the previous case, using the same molar quantities of *o*-aminobenzaldehyde and ethyl quinaldoylacetate. The pure product (3.4 g.), crystallizing from dilute ethanol, melted at 109–110°; yield 69.1%.

Anal. Calcd. for $C_{21}H_{16}N_2O_2$: C, 76.81; H, 4.91. Found: C, 76.60; H, 4.89.

***o*-Aminoacetophenone.**—This was prepared by the catalytic reduction of *o*-nitroacetophenone, resulting from the air-oxidation of *o*-nitroethylbenzene.[9]

4-Methyl-2,2'-biquinoline.—A mixture of 2 g. of *o*-aminoacetophenone, 2.6 g. of 2-acetylquinoline, 25 ml. of ethanol, 1.2 g. of sodium hydroxide and 150 ml. of water was refluxed for 24 hr. The residue from the ether extraction of the reaction mixture was extracted with petroleum ether. After removal of the solvent, the residue was recrystallized from ethanol; yield 0.2 g., m.p. 171–172°, or 5.0%.

Anal. Calcd. for $C_{19}H_{14}N_2$: C, 84.41; H, 5.22. Found: C, 84.40; H, 5.33.

(9) W. S. Emerson, *et al.*, *ibid.*, **69**, 706 (1947).

4-Phenyl-2,2'-biquinoline.—A mixture of 3 g. of *o*-aminobenzophenone (prepared by the method of Hewett, *et al.*),[10] 3 g. of 2-acetylquinoline and 3 ml. of piperidine was heated for 24 hr. at 160°. The reaction mixture was treated with cold methanol, and the resulting precipitate crystallized from benzene–petroleum ether; yield 1 g. (17.2%) of pure product melting at 203°.

Anal. Calcd. for $C_{24}H_{16}N_2$: C, 86.72: H, 4.85. Found: C, 86.89; H, 4.95.

4-Phenyl-2-bromoquinoline.—A mixture of 10 g. of 4-phenylcarbostyril (prepared by the method of Hauser and Reynolds,[11] 20 g. of PBr_3 and 13 g. of $POBr_3$ was heated for 5 hr. at 140–150°. The reaction mixture was poured on ice and made alkaline with sodium hydroxide solution. The resulting precipitate was removed by filtration and crystallized from methanol; yield 8.5 g., m.p. 94–95°.

Anal. Calcd. for $C_{15}H_{10}NBr$: Br, 28.13. Found: Br, 28.09.

4,4'-Diphenyl-2,2'-biquinoline.—A mixture of 11.3 g. of 4-phenyl-2-bromoquinoline and 15 g. of Cu powder was heated at 260–280° for 2 hr. The reaction mixture was then finely powdered, and repeatedly extracted with concentrated hydrochloric acid. The solution was made alkaline, and the resulting precipitate removed by filtration, dried and extracted with benzene. The yield of pure product, crystallizing from benzene, was 0.5 g. or 3.1%, m.p. 362°.

Anal. Calcd. for $C_{30}H_{20}N_2$: C, 88.20; H, 4.94. Found: C, 87.85; H, 4.82.

(10) C. L. Hewett, *et al.*, *J. Chem. Soc.*, 293 (1948).

(11) C. R. Hauser and G. A. Reynolds, THIS JOURNAL, **70**, 2402 (1948).

PHILADELPHIA, PA.

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

The Synthesis of 6-*n*-Amylindole and 6-*n*-Amyltryptophan

BY H. R. SNYDER AND HARRY R. BEILFUSS[1]

RECEIVED MAY 4, 1953

The Reissert method has been utilized for the preparation of 6-*n*-amylindole from 2-nitro-4-(1-pentenyl)-toluene. 6-*n*-Amyltryptophan was prepared by saponification, decarboxylation and deacetylation of diethyl 6-*n*-amylskatylacetamidomalonate, obtained by the alkylation of diethyl acetamidomalonate with 6-*n*-amylgramine.

In a search for a useful synthetic route to 6-*n*-amyltryptophan it was necessary to investigate the preparation of 6-*n*-amylindole. Although this substance could be obtained by an application of the Tyson[2] ring closure to 2-methyl-5-*n*-amylformanilide, the yield was not high and attention was turned to a reaction sequence, outlined in formulas I–IX, utilizing a Reissert[3] indole cyclization.

n-Valeryl chloride was distilled from a mixture of benzoyl chloride and *n*-valeric acid according to the procedure of Brown[4] or prepared by the action of thionyl chloride on *n*-valeric acid. Nitration of the mixture obtained from the Friedel–Crafts reaction of *n*-valeryl chloride and toluene yielded two isomeric nitro compounds from which I was separated by recrystallization from low-boiling petroleum ether. A Meerwein–Ponndorf–Verley reduction of I provided the carbinol II in excellent yields. The unsaturated compound III was obtained when II was distilled from a trace of *p*-toluenesulfonic acid. The condensation of III with diethyl oxalate in the presence of potassium ethoxide gave good yields of an unidentified compound X when the procedure described by Blaikie and Perkin[5] was suitably modified. Acidification of an aqueous solution of V brought about the precipitation of crude X.

The anomalous solubility of X in chloroform and sharp melting point of the purified material led initially to the belief that X was the pyruvic acid derivative VI. However, an alkaline hygroscopic residue remained after ignition of an analytical sample of X and a platinum-wire flame test indicated the presence of potassium in the sample. The analytical results approached values which would be expected if X is assumed to be an equimolar mixture of V and VI. Further evidence for this assumption was established when it was found that VI was isolated quantitatively by ether extraction from a dilute hydrochloric acid slurry of X.

Ferrous sulfate in dilute ammonium hydroxide has been used by a number of authors[6–8] for the reductive cyclization of various substituted *o*-nitro-

(1) Procter and Gamble Fellow, 1951–1952.

(2) F. Tyson, THIS JOURNAL, **63**, 2024 (1941); **72**, 2801 (1950).

(3) A. Reissert, *Ber.*, **30**, 1030 (1897).

(4) H. Brown, THIS JOURNAL, **60**, 1325 (1938).

(5) K. Blaikie and W. Perkin, *J. Chem. Soc.*, **125**, 296 (1924).

(6) F. Mayer and E. Alken, *Ber.*, **55**, 2278 (1922).

(7) W. Kermack, W. Perkin and R. Robinson, *J. Chem. Soc.*, **119**, 1602 (1921).

(8) F. Bergel and A. Morrison, *ibid.*, 49 (1943).