TABLE IV

ENERGY TERMS (RELATIVE TO BENZOIC ESTERS) FOR 1-NAPHTHOIC ESTER FORMATION AND HYDROLYSIS

Reaction	$\Delta\Delta H\ddagger$[a]	$-2.303\ RT\ \sigma^*\rho^*$[b]	$-T\Delta\Delta S\ddagger$[c]	$-2.303\ RT\ E_s$[d]	$\Delta\Delta H\ddagger + 2.303\ RT\sigma^*\rho^*$[e]
Formation of methyl ester	0.14 ± 0.11	-0.01	0.41	0.54	0.15
Hydrolysis of methyl ester	0.11 ± 0.04	0.06	0.49	0.54	0.05
Hydrolysis of ethyl ester	0.02 ± 0.06	0.06	0.62	0.54	-0.04

[a] Relative heat of activation (ΔE). [b] Relative polar energy of activation ($\Delta\Delta E_0\ddagger$). [c] $2.303\ RT\ \Delta \log B$. [d] Nonpolar contribution to the relative free energy of activation. [e] Nonpolar contribution to the relative heat of activation ($\Delta\Delta H\ddagger - \Delta\Delta E_\sigma\ddagger$).

transition state in the hydrolysis of ethyl benzoate, relative to a simple aliphatic ester, is 6 *k*cal. mole^{-1}.[6] If resonance between the ring and side-chain in a 1-naphthoic ester were completely inhibited owing to the steric effect of the fused ring, then the 1-naphthoate would resemble an aliphatic ester in giving a $\Delta\Delta E\psi\ddagger$ value of -6 *k*cal. mole^{-1}. A lower limit for $\Delta\Delta E\psi\ddagger$ may be estimated from relative pK_a values for benzoic (4.20) and 1-naphthoic (3.69) acids. Resonance interaction between ring and side chain is less in the anion than in the parent acid. Some steric inhibition of such resonance in the case of naphthoic acid leads to a smaller decrease in resonance energy for 1-naphthoic acid ionization than for benzoic acid ionization. If this were the sole reason why 1-naphthoic acid is a stronger acid than benzoic acid, then $\Delta\Delta E\psi\ddagger$ for the ionization of 1-naphthoic acid (relative to benzoic) would be -0.7 *k*cal. mole^{-1} (*cf.* ref. 7). This may be accepted as a lower limit for $\Delta\Delta E\psi\ddagger$ for the ester hydrolysis because in this reaction all resonance interaction is frozen out in the transition state. Thus, the strain in the transition states, for hydrolysis and esterification involving simple 1-naphthoic esters, lies between 0.7 and 6 *k*cal. mole^{-1}.

In view of the small value for σ^* (Table III) it would appear that the relative reactivities of 1-naphthyl and phenyl derivatives will usually be governed more by steric than by polar factors.

DEPARTMENT OF CHEMISTRY
UNIVERSITY OF CANTERBURY
CHRISTCHURCH, NEW ZEALAND

(6) M. M. Kreevoy and R. W. Taft, *J. Am. Chem. Soc.*, 79, 4016 (1957).
(7) Ref. 3, p. 581.

Synthesis of Some New 8,8′-Disubstituted 2,2′-Biquinolines

FRANCIS H. CASE AND JOHN J. LAFFERTY

Received February 10, 1958

It has been shown[1] that when 2,2′-biquinoline is substituted in the 3-position with a methyl or ethyl group the molar absorptivity of the copper (I) complex is greatly reduced. However, substitution of a phenyl group in this position increases the value of the molar absorptivity. It has been proposed that the molar absorptivity and the stability of the complex are a function of the planarity of the biquinoline molecule and the electron density about the nitrogen atoms of the quinoline nuclei. Substitution of any of these substituents in the 3-position introduces a steric factor that causes distortion from planarity of the 2,2′-biquinoline molecule by rotation of the quinoline moieties about the bond between the 2,2′-positions. The stability of the complex and the molar absorptivity should then decrease. The anomalous behavior of 3-phenyl-2,2′-biquinoline was attributed to increased electron density about the nitrogen atoms of the quinoline nuclei by electron donation of the phenyl group. The resulting increased stability of the copper (I) complex would account for the increase in the value of the molar absorptivity of the complex.

To further test this proposal it was decided to prepare 2,2′-biquinolines substituted in the 8,8′-positions with the methyl, ethyl, and phenyl groups. Spatial models of these compounds indicate that formation of the copper (I) complex would require a similar rotation of the quinoline moieties about the bond between the 2,2′-positions of the biquinoline.

The preparation of 8,8′-dimethyl-2,2′-biquinoline from the reaction of 8-methylquinoline with sodium is claimed in the literature.[2] However, it has since been shown[3] that the application of this method to quinoline yields 2,3′-biquinoline and not the expected 2,2′-biquinoline. Although the yields vary widely when the method of Ueda[4] (reductive coupling using palladium and hydrazine) or the Ullmann reaction[5-7] is applied to the corresponding haloquinolines or haloisoquinolines for the preparation of biquinolines or biisoquinolines products of predictable structure are obtained. Application of the method of Ueda to 2-bromo-8-methylquinoline gave a product indicated by analysis to be 8,8′-

(1) G. F. Smith and D. H. Wilkins, *Anal. Chim. Acta*, 10, 139 (1954).
(2) E. Conolly, *J. Chem. Soc.*, 2083 (1925).
(3) K. Ueda, *J. Pharm. Soc. Japan*, 57, 817 (1937); *Chem. Abstr.*, 32, 1265 (1938).
(4) K. Ueda, *J. Pharm. Soc. Japan*, 57, 180 (1937); *Chem. Abstr.*, 33, 608 (1939).
(5) J. G. Breckenridge, *Can. J. Research B*, 28, 593 (1950).
(6) F. H. Case and G. Maerker, *J. Am. Chem. Soc.*, 75, 4920 (1953).
(7) F. H. Case, *J. Org. Chem.*, 17, 471 (1952).

TABLE I

INTERMEDIATE SUBSTITUTED QUINOLINES

	M.P., °C.	B.P., °C.	MM.	Yield, %	Calcd. C	Calcd. H	Calcd. Br	Found C	Found H	Found Br
2-Amino-8-methyl-[a]	84–85	150–155	0.1	41	—	—	—	—	—	—
2-Amino-8-ethyl-	118–119	100–105	0.15	66	76.71	7.02	—	76.90	6.89	—
2-Amino-8-phenyl-[a]	167–168	—	—	63	—	—	—	—	—	—
2-Hydroxy-8-methyl-[a]	218–219	—	—	79	—	—	—	—	—	—
2-Hydroxy-8-ethyl-	137–137.5	—	—	44	76.27	6.40	—	76.25	6.35	—
2-Hydroxy-8-phenyl	127–128	—	—	33	81.45	5.01	—	81.51	5.06	—
2-Bromo-8-methyl-	78–79	140–143	0.3	65	54.08	3.63	—	53.87	3.57	—
2-Bromo-8-ethyl-	26–27	172–175	0.2	80	—	—	33.85	—	—	33.36
2-Bromo-8-phenyl-	—	172–175	0.2	81	63.40	3.55	—	63.40	3.31	—

[a] Preparation previously reported in literature by another method.

dimethyl-2,2′-biquinoline, which melts 56° higher than that reported previously.[2]

The preparation of 8-methyl,[8] 8-ethyl,[9] and 8-phenyl[10] quinolines was effected by variation of the Skraup reaction as described in the literature.

From these, the required 2-aminoquinolines were conveniently prepared by the action of sodamide on solutions of the quinolines in dimethylaniline. This method of preparation was found to be superior to those described in the literature for the methyl[11] and phenyl[12] aminoquinolines.

Attempts to prepare the bromoquinolines from the corresponding aminoquinolines by variations of the Sandmeyer or Craig[13] reaction failed. It was found that the 2-aminoquinolines can be easily diazotized by the methods of Schoutissen[14] or Hodgson and Walker[15] but attempts to prepare the bromo derivatives by the diazonium method were unsuccessful. For this reason the diazonium salts prepared as above were converted to the respective carbostyrils. Of these only the 8-methyl derivative has been previously reported.[16]

From the carbostyrils the three requisite bromoquinolines, previously unreported, were prepared by the method of Kaslow and Lawton.[17]

Application of the Ullmann reaction to 8-ethyl-2-bromoquinoline gave 8,8′-diethyl-2,2′-biquinoline when the copper catalyst was pretreated by the method of Kleider and Adams.[18] With an untreated catalyst none of the desired products could be isolated from the reaction mixture. Application of the Ullmann reaction to 2-bromo-8-methyl and 8-phenylquinoline failed to yield the desired biquinolines. These were obtained in very small yield by the method of Ueda.[4]

These compounds are now being tested and the results will appear in a later publication.

EXPERIMENTAL

2-Amino-8-alkyl and 8-phenylquinolines. A mixture of 0.5 mole of the quinoline, 0.6 mole of sodamide, and 500 ml. of dimethylaniline was stirred and heated at 120–125° for 8–10 hr. The mixture was cooled and treated with 300 ml. of water. The dimethylaniline layer was washed several times with 100-ml. portions of water. The 2-amino-8-phenylquinoline was precipitated by addition of excess petroleum ether (b.p. 30–60°). It was purified by crystallization from benzene.

The 2-amino-8-methyl and 2-amino-8-ethyl quinolines were isolated by vacuum distillation following the removal of the dimethylaniline *in vacuo*. Crystallization of the distillates from benzene-hexane mixtures yielded the pure amines.

8-Alkyl and 8-phenylcarbostyrils. A solution of 0.24 mole of the aminoquinoline in 900 ml. of 85% phosphoric acid was cooled to 0° and diazotized with nitrosylsulfuric acid prepared from 18.6 g. of sodium nitrite in 450 ml. of concentrated sulfuric acid. The temperature was kept below 5° during the addition of the nitrosylsulfuric acid. Stirring was continued for 30 min. after the addition. The diazonium solution was slowly poured into 8 l. of hot water. The solution was heated on the steam bath for 1 hr. and allowed to stand for 15 hr. The *p*H of the solution was adjusted to approximately 5 with aqueous sodium hydroxide solution. The crude carbostyrils separated as semisolid masses which were dissolved in benzene. The benzene solutions were washed with water and evaporated to dryness. The carbostyrils were purified by crystallization from benzene-hexane.

2-Bromo-8-alkyl and 8-phenylquinolines. A mixture of 0.07 mole of the respective carbostyril, 40 g. of phosphorus tribromide, and 26 g. of phosphorus oxybromide was heated at 150–155° for 4 hr. The reaction mixture was poured on ice, made alkaline with aqueous sodium hydroxide solution, and extracted with benzene. The benzene was evaporated and the residual oil distilled *in vacuo*. The final purification of the 8-methyl and 8-ethyl-2-bromoquinolines was accomplished by recrystallization from hexane.

8,8′-Dimethyl-2,2′-biquinoline. A mixture of 10 g. of 8-methyl-2-bromoquinoline, 39.6 g. of 85% hydrazine hydrate in water, 4.5 g. of Pd on calcium carbonate (5% Baker Catalyst), and 300 ml. of 5% ethanolic potassium hydroxide was stirred at reflux for 2 hr. The reaction mixture was

(8) R. Adams and J. Johnson, *Elementary Laboratory Experiments in Organic Chemistry*, Third Ed., Macmillan Co., New York (1945), 351.

(9) R. A. Glenn and J. R. Bailey, *J. Am. Chem. Soc.*, **63**, 640 (1941).

(10) C. E. Kaslow and M. Hayek, *J. Am. Chem. Soc.*, **73**, 4986 (1951).

(11) F. W. Bergstrom, *J. Org. Chem.*, **3**, 233 (1938).

(12) F. W. Bergstrom, *J. Org. Chem.*, **3**, 424 (1938).

(13) L. Craig, *J. Am. Chem. Soc.*, **56**, 231 (1934).

(14) H. A. Schoutissen, *J. Am. Chem. Soc.*, **55**, 4531 (1933).

(15) H. H. Hodgson and J. Walker, *J. Chem. Soc.*, 530 (1935).

(16) O. Fischer, *Ber.*, **35**, 3678 (1902).

(17) C. E. Kaslow and W. R. Lawton, *J. Am. Chem. Soc.*, **72**, 1723 (1950).

(18) E. C. Kleider and R. Adams, *J. Am. Chem. Soc.*, **55**, 4225 (1933).

filtered. The spent catalyst was boiled in benzene and the benzene solution added to the filtrate. After evaporation of the solvent the residue was crystallized from benzene. The yield was 52 mg. (0.8%), m.p. 203–204°.

Anal. Calcd. for $C_{20}H_{16}N_2$: C, 84.47; H, 5.67. Found: C, 84.12; H, 5.76.

8,8'-Diphenyl-2,2'-biquinoline. The method of preparation was similar to that used for 8,8'-dimethyl-2,2'-biquinoline. From 6 g. of 8-phenyl-2-bromoquinoline, 71 mg. (1.7%) of purified product was obtained. After crystallization from benzene it melted at 247–248°.

Anal. Calcd. for $C_{30}H_{20}N_2$: C, 88.21; H, 4.94. Found: C, 88.37; H, 4.94.

8,8'-Diethyl-2,2'-biquinoline. A mixture of 7.5 g. of 8-ethyl-2-bromoquinoline and 10 g. of copper powder pretreated by the method of Kleider and Adams[18] was heated for 3 hr. at 210–220°. The reaction mixture was pulverized and extracted with hot concentrated hydrochloric acid. The acid extracts were cautiously neutralized with aqueous sodium hydroxide and then made strongly alkaline with ammonium hydroxide. The mixture was extracted with benzene and the extracts were concentrated to a small volume. The solution was adsorbed on an alumina column. Hexane and hexane-chloroform mixtures were used as eluents with fractions taken at every 20 ml. The residue from evaporation of the solvents was crystallized from benzene yielding 0.156 g. (3.1%) melting at 122–123°.

Anal. Calcd. for $C_{22}H_{20}N_2$: C, 84.58; H, 6.45. Found: C, 84.51; H, 6.41.

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

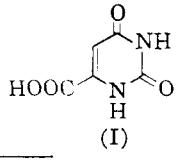
DEPARTMENT OF CHEMISTRY
TEMPLE UNIVERSITY
PHILADELPHIA, PA.

5-Bromoörotic Acid

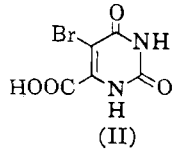
DONALD G. CROSBY AND ROBERT V. BERTHOLD

Received February 11, 1958

In the past few years, increased interest in the physiological properties of orotic acid (I) and its derivatives has been apparent. A variety of 5-substituted orotic acids have been investigated, including 5-halogenated derivatives; 5-chloroörotic acid was described by Johnson[1] in 1943, 5-iodoorotic acid has been synthesized and used to elucidate aspects of nucleic acid metabolism,[2] and the effect of 5-fluoroörotic acid on tumor growth has recently been studied.[3] However, no reliable synthesis or description of 5-bromoörotic acid (II) has been available.



(I)



(II)

Several reported attempts to brominate orotic acid directly in aqueous solution resulted in the formation of 5,5-dibromobarbituric acid.[4,5] Behrend[6] suggested that oxidation of 5-bromo-6-methyluracil with hot, fuming nitric acid gave 5-bromoörotic acid, but the yield was very poor and the product was not clearly described.

Although uracil[7] and 6-methyluracil[8] have been brominated in the 5-position in high yield by reaction with bromine in carbon disulfide, we recovered only unchanged starting material when orotic acid was treated with bromine in carbon tetrachloride at 70°. However, reaction with a mixture of aqueous hydrogen peroxide and hydrobromic acid led to a 73% yield of bromoörotic acid. The dihydrate crystallized from aqueous solution, and was converted to the anhydrous compound by heating at 80° *in vacuo* over phosphorus pentoxide. It was recovered unchanged after being boiled with aqueous sodium hydroxide solution, which indicates the stability of the C—Br bond and proves it to be at the 5-position as expected.

Potentiometric titration showed 5-bromoörotic acid to be dibasic, the $-\log$ of the apparent acidic ionization constants being 2.21 and 7.59. The corresponding values for orotic acid itself are 2.40[5,9] (2.8[10,11]) and 9.45,[10,11] while the value for o-bromobenzoic acid is 2.85.[9,12]

Upon heating above its melting point, the acid was smoothly decarboxylated to give a nearly quantitative yield of 5-bromouracil. Conversely, orotic acid itself has only recently been decarboxylated successfully, under drastic conditions, and the yield of the resulting uracil was low.[13]

EXPERIMENTAL[14]

Attempted direct bromination of orotic acid. Orotic acid monohydrate (25.0 g., 0.144 mole) was slurried with 100 ml. dry carbon tetrachloride, and bromine (23 g., 0.144 mole) was added dropwise with stirring. The red mixture was then boiled under reflux for several hours, cooled, and the solid filtered off and washed with carbon tetrachloride. After drying in air, the residue was recrystallized from water to give a quantitative recovery of orotic acid, m.p. 342° (decomp.) (immersed at 340°).

(1) T. B. Johnson, *J. Am. Chem. Soc.*, **65**, 1218 (1943).
(2) W. H. Prusoff, W. L. Holmes, and A. D. Welch, *Cancer Research*, **13**, 221 (1953).
(3) C. Heidelberger, N. K. Chadhuri, P. Danneberg, D. Mooren, L. Griesbach, R. Duschinsky, R. J. Schnitzer, E. Pleven, and J. Scheiner, *Nature*, **179**, 663 (1957); R. Duschinsky, E. Pleven, and C. Heidelberger, *J. Am. Chem. Soc.*, **79**, 4559 (1957).
(4) H. L. Wheeler, *Am. Chem. J.*, **38**, 358 (1908).
(5) M. Bachstez, *Ber.*, **63**, 1000 (1930).
(6) R. Behrend, *Ann.*, **240**, 1 (1888).
(7) H. L. Wheeler and H. F. Merriam, *Am. Chem. J.*, **31**, 603 (1904).
(8) R. Behrend, *Ann.*, **231**, 248 (1885).
(9) Determined by conductivity.
(10) Determined spectrophotometrically.
(11) D. Shugar and J. J. Fox, *Biochim. et Biophys. Acta*, **9**, 199 (1952).
(12) J. F. J. Dippy, *Chem. Revs.*, **25**, 151 (1939).
(13) M. R. Atkinson, M. H. Maguire, R. K. Ralph, G. Shaw, and R. N. Warrener, *J. Chem. Soc.*, 2363 (1957).
(14) All melting points were measured in a Vanderkamp block, and are corrected.