

Syntheses of 5*H*-Benzoxazolo[3,2-*a*]quinolin-5-ones

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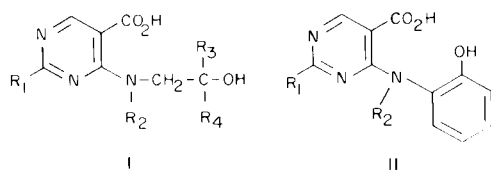
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Treatment of *N*-(2-hydroxyphenyl)anthranilic acid with acetic anhydride, under refluxing conditions provided a simple method for the synthesis of 5*H*-benzoxazolo[3,2-*a*]quinolin-5-one (IVa), a heretofore unreported ring system. When propionic anhydride was used in the above reaction, 6-methyl-5*H*-benzoxazolo[3,2-*a*]quinolin-5-one (Va) was obtained. Other examples prepared in this fashion were IVb, IVc and Vb. Treatment of IVa with methoxyethylamine afforded 1,2-dihydro-1-(2-hydroxyphenyl)-2-(methoxyethylimino)-4-quinolinol (VII). A possible mechanism for the cyclization reaction is discussed.

Recently, we reported on the ring closure reactions of various 4-(2-hydroxyethylamino)-5-pyrimidinecarboxylic acids (I) and 4-(2-hydroxyanilino)-5-pyrimidinecarboxylic acids (II) by the treatment with boiling acetic anhydride (1,2). The course of cyclization of these compounds was found to be markedly dependent upon the nature of substituents R_2 , R_3 and R_4 . Thus a number of different heterocyclic ring systems, *i.e.*, pyrimido[4,5-*e*] [1,4]oxazepine (1), oxazolo[2,3-*b*]pyrimido[4,5-*d*] [1,3]oxazine (1), oxazolo[2',3':6,1]pyrido[2,3-*d*]pyrimidine (1), and pyrimido[5,4-*c*] [1,5]benzoxazepine (2), have been prepared by variation of the side chain at the 4-position in I and II.

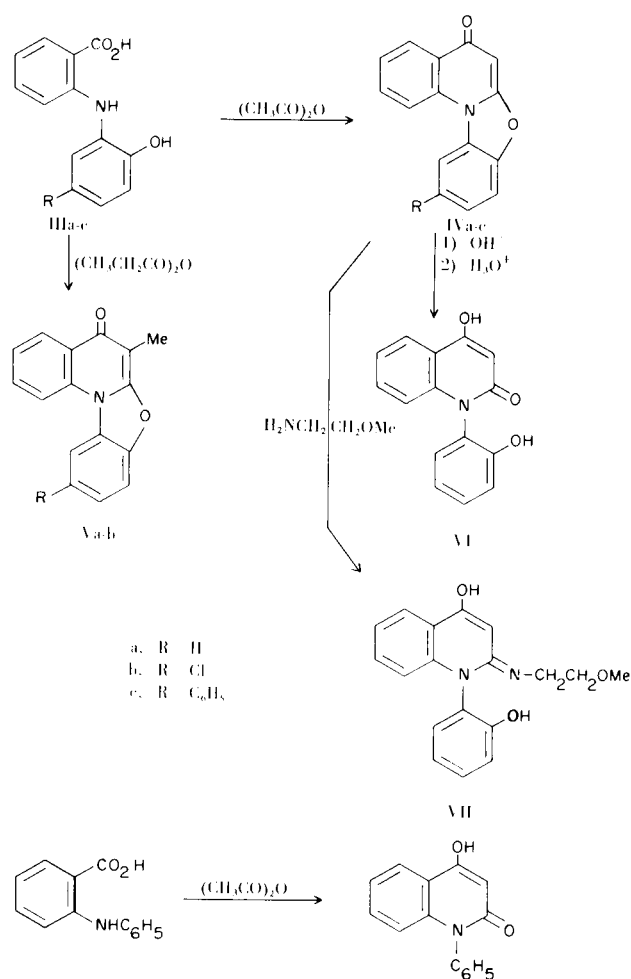
Work along these lines has now been extended to the synthesis of analogous compounds in which the pyrimidine nucleus (1) is replaced by a benzene ring in an effort to obtain biologically active agents. Compounds thus obtained were expected to be not only less basic, but also more



lipophilic than pyrimidine derivatives, and it was hoped that this structural change would bring a favorable physiological effect. As a result of this effort, examples of the heretofore unreported benzoxazolo[3,2-*a*]quinoline ring system were obtained.

This paper describes a simple method for the synthesis of otherwise difficultly accessible 5*H*-benzoxazolo[3,2-*a*]quinolin-5-ones from the reaction of *N*-(2-hydroxyphenyl)anthranilic acids and boiling carboxylic acid anhydrides (Scheme I).

Scheme I



The *N*-(2-hydroxyphenyl)anthranilic acids (IIIa-c) used in this work were prepared from 2-bromobenzoic acid and appropriately substituted 2-aminophenols under Ullmann condensation reaction conditions by the method described by Gurien, *et al.* (3,4). When the sodium salt of IIIa was allowed to react with methyl iodide in DMF at room temperature, *N*-(2-methoxyphenyl)anthranilic acid was obtained. Formation of the methyl ether of IIIa proved, therefore, that the displacement of the bromo group was made by the amino nucleophile rather than by the phenol oxygen of the 2-aminophenol.

Treatment of IIIa with acetic anhydride for 2.5 hours under refluxing conditions afforded a crystalline product with m.p. 209-211°. The assignment of the 5*H*-benzoxazolo[3,2-*a*]quinolin-5-one (IVa) structure was based on spectral and combustion analytical data. The infrared spectrum showed a band at 6.05 μ indicating the presence of a highly conjugated carbonyl group joined to a benzene ring. The uv spectrum of this compound obtained in 95% ethanol solution resembled closely that of 1,4-dihydro-1-methyl-4-oxoquinoline (5), showing absorption bands at $m\mu$ (ϵ) 216 (2.73×10^4), 241 (2.59×10^4), 248 shoulder (2.30×10^4), 256 shoulder (1.75×10^4), 273 (0.62×10^4), 283 (0.58×10^4), 328 (2.50×10^4) and 342 (2.22×10^4). The nmr spectrum (DMF) exhibited, apart from aromatic proton signals, one proton signal at δ 6.16 ppm as a singlet.

Study of the alkaline hydrolysis product of IVa afforded additional evidence in support of the tetracyclic structure. Thus, the treatment of IVa with aqueous sodium hydroxide solution for 1 hour under refluxing conditions followed by acidification afforded a product, 4-hydroxy-1-(2-hydroxyphenyl)carbostyryl (VI) the uv spectrum of which is almost superimposable with that of known 4-hydroxy-1-phenylcarbostyryl (6). The other spectral data were also conso-

nant with structure VI for the hydrolysis product, thus demonstrating the presence of a quinoline substructure in IVa.

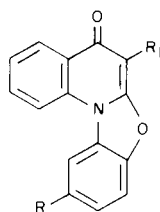
Cleavage of the C-O bond at the 7-position of IVa by a nucleophile was further demonstrated. When IVa was treated with methoxyethylamine under refluxing conditions, there was obtained 1,2-dihydro-1-(2-hydroxyphenyl)-2-(methoxyethylimino)-4-quinolinol (VII). Since compound VII exhibited a strong broad band centered at 4.0 μ in its ir spectrum, it probably exists as an inner salt formed *via* a protonation of the basic imino nitrogen by the phenolic proton.

Substitution of propionic for acetic anhydride in the above reaction afforded the 6-methyl derivatives Va and Vb. The nmr spectrum of these compounds exhibited a 3-proton methyl singlet at δ 2.17 ppm and aromatic peaks. Table I lists the benzoxazolo[3,2-*a*]quinolin-5-ones prepared in this fashion. In most cases the products were readily isolable by the addition of water or chilling of the reaction mixture.

A possible reaction mechanism for the formation of IV and V is suggested in Scheme II. The initial step presumably involves the acetylation of all three functional groups to form an intermediate such as VIII. Abstraction of a proton α to the carbonyl group of the carboxamide moiety by acetate ion creates a nucleophilic center. The latter carbanion thus formed then displaces the neighboring acetate group of the mixed anhydride, with resultant formation of the quinoline IX. In fact, when *N*-phenylanthranilic acid was treated with acetic anhydride under conditions similar to those used for the preparation of IV, 4-hydroxy-1-phenylcarbostyryl was obtained (7). The migration of the acetate group, initiated by the abstraction of the acidic methylene proton by the acetate ion, results in the forma-

TABLE I
5*H*-Benzoxazolo[3,2-*a*]quinolin-5-ones

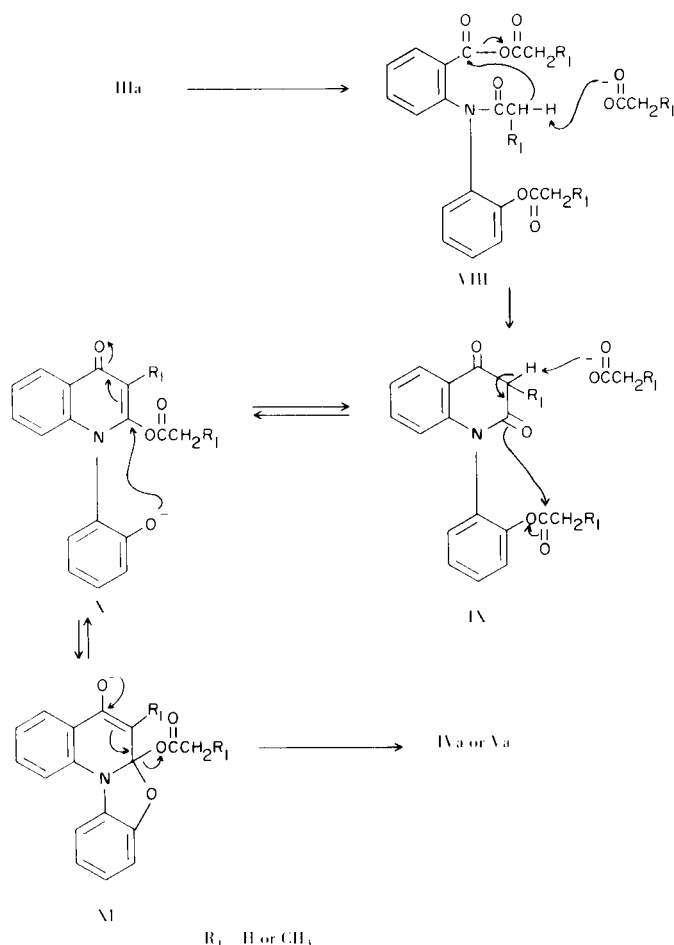
Cpd	R	R ₁	M.p., °C	Formula	C	Elemental analyses			Found, %	
						Calcd., %	H	N	C	H
IVa	H	H	209-211	C ₁₅ H ₉ NO ₂	76.58	3.86	5.96	76.62	4.08	5.95
IVb	Cl	H	233-235	C ₁₅ H ₈ ClNO ₂	66.80	2.99	5.19	66.49	3.18	5.12
IVc	C ₆ H ₅	H	242-244	C ₂₁ H ₁₃ NO ₂	81.01	4.21	4.50	81.34	4.06	4.52
Va	H	Me	217-219	C ₁₆ H ₁₁ NO ₂	77.09	4.45	5.62	77.39	4.56	5.66
Vb	Cl	Me	205-207	C ₁₆ H ₁₀ ClNO ₂	67.74	3.55	4.94	67.62	3.46	4.86



tion of the intermediate X. The acetate group at the 2-position of X then becomes susceptible to a nucleophilic displacement reaction. Intramolecular displacement of the acetate group by the phenoxide nucleophile *via* a species such as XI leads to the formation of the isolated product IV. The formation of the 6-methyl derivatives Va,b when propionic anhydride is used in the above reaction is in agreement with the proposed reaction mechanism.

It is interesting to note that 4-(2-hydroxyanilino)-2-phenyl-5-pyrimidine carboxylic acid (II: $R_1 = C_6H_5$, $R_2 = H$) is reported to cyclize under similar conditions to 11-acetyl-2-phenylpyrimido[5,4-*c*][1,5]benzoxazepin-5(11*H*)-one (2). The difference in the mode of cyclization between II ($R_1 = C_6H_5$, $R_2 = H$) and its phenyl analog IIIa may possibly be due to the difference in the basicities of the amino groups. The amino group in IIIa is sufficiently basic to form an intermediate such as VIII under the reaction conditions. In case of II ($R_1 = C_6H_5$, $R_2 = H$), however, the diminished basicity of the C₄-amino group makes the *N*-acetylation difficult, and the cyclization to the 7-membered ring compound is favored.

Scheme II



EXPERIMENTAL

Melting points were taken in capillary tubes (Thomas-Hoover melting point apparatus) and are uncorrected. Ir spectra were obtained in potassium bromide pellets using a Perkin-Elmer 21 spectrophotometer. Uv absorption spectra were obtained with a Perkin-Elmer Model 450-uv-visible NIR spectrophotometer. Nmr spectra were determined on a Varian A-60 spectrometer using tetramethylsilane as the internal reference. Combustion elemental analyses were performed by the Analytical Section of these Laboratories. The reported yields may be improved under optimal reaction conditions. No effort was made to improve them.

N-(2-Hydroxyphenyl)anthranilic Acid (IIIa).

To a hot mixture of potassium *o*-bromobenzoate (23.2 g.) and *o*-aminophenol (21.5 g.) in 60 ml. of 1-butanol was added 0.1 g. of copper powder. The resulting mixture was heated under reflux for 0.5 hour. The reaction mixture was cooled and treated with 2.5 g. of sodium bicarbonate and then with 25 ml. of a saturated aqueous solution of sodium bicarbonate. The organic solvent was removed by steam distillation. The dark residual material was filtered and the filtrate was acidified with dilute hydrochloric acid causing separation of a precipitate. The crude product was collected on a filter, dissolved in hot ethanol, treated with charcoal, and filtered. Removal of ethanol under reduced pressure afforded 9.2 g. of product, m.p. 187°. Recrystallization of the crude product from ethanol-water raised the m.p. to 189-191° [lit. (4) m.p. 190-191°].

N-(5-Chloro-2-hydroxyphenyl)anthranilic acid (IIIb) was prepared from potassium *o*-bromobenzoate and 2-hydroxy-5-chloroaniline by a method similar to that used for IIIa. After purification by dissolving in dilute aqueous sodium hydroxide solution and reprecipitating by addition of dilute hydrochloric acid, the compound melted at 217-220°; ir: μ 2.90 (OH), 3.02 (NH), 5.92 (C=O).

Anal. Calcd. for $C_{13}H_{10}ClNO_3$: C, 59.22; H, 3.82; N, 5.31; Cl, 13.44. Found: C, 59.10; H, 3.95; N, 5.32; Cl, 13.74.

N-(2-Hydroxy-5-biphenyl)anthranilic Acid (IIIc).

This compound was prepared similarly and purified by base-acid treatment, m.p. 167-171°.

Anal. Calcd. for $C_{19}H_{15}NO_3$: C, 74.74; H, 4.95; N, 4.59. Found: C, 74.76; H, 4.65; N, 4.95.

5*H*-Benzoxazolo[3,2-*a*]quinolin-5-one (IVa).

A mixture of 7.0 g. of IIIa and 70 ml. of acetic anhydride was heated under reflux for 2.5 hours, then concentrated on a rotary evaporator under reduced pressure to *ca.* a half of its original volume. Chilling of the concentrated solution in ice caused separation of a precipitate, which was collected on a filter and washed with ethanol several times. The product weighed 4.9 g. (68%) and melted at 205-207°. Analytical sample (m.p. 209-211°) was obtained by recrystallization from acetic anhydride.

10-Chloro-5*H*-benzoxazolo[3,2-*a*]quinolin-5-one (IVb).

A solution obtained by adding 0.55 g. of IIIb in 15 ml. of acetic anhydride was heated under reflux for 1 hour. The reaction mixture was concentrated under reduced pressure and chilled in ice. The precipitate thus separated was collected on a filter and washed with ether, giving 0.3 g. of product. Recrystallization from acetic anhydride afforded an analytical sample, m.p. 233-235°; ir μ 6.05 (C=O); uv λ max (95% ethanol): $m\mu$ (ϵ) 220 (2.63×10^4), 241 (2.37×10^4), 258 (1.59×10^4), 277 (0.44×10^4), 286 (0.42×10^4), 329 (2.69×10^4), 3.42 (2.84×10^4), nmr (deuteriochloroform): δ 6.33 ppm (s, 1H).

10-Phenyl-5*H*-benzoxazolo[3,2-*a*]quinolin-5-one (IVc).

A mixture of IIIc (7 g.) and acetic anhydride (100 ml.) was heated under reflux for 2 hours and the excess acetic anhydride was removed under reduced pressure. Trituration of the remaining solid with anhydrous ether afforded a brown solid which amounted to 6.2 g. and melted at 239.5-242°. Recrystallization of the product from acetic anhydride improved the m.p. to 242-244°; $\text{ir } \mu$ 6.08 (C=O); $\text{uv } \lambda$ max (95% ethanol): $m\mu$ (ϵ) 240 (3.74×10^4), 282 (0.54×10^4), 332 (2.60×10^4), 344 (2.60×10^4).

6-Methyl-5*H*-benzoxazolo[3,2-*a*]quinolin-5-one (Va).

A mixture of IIIa (3.5 g.) and propionic anhydride (50 ml.) was heated under reflux for 1 hour. The reaction mixture was cooled and poured into a large amount of cold water. The solid material that separated was collected on a filter and recrystallized from ethanol, giving 1.9 g. of product, m.p. 217-219°; ir : μ 3.30 (CH₃), 6.00 (C=O); $\text{uv } \lambda$ max (95% ethanol): $m\mu$ (ϵ) 217 (2.70×10^4), 242 (2.26×10^4), 248 (2.18×10^4), 350 (2.31×10^4); nmr (DMSO-d₆ + TFA): δ 2.17 (s, 3H, Me).

10-Chloro-6-methyl-5*H*-benzoxazolo[3,2-*a*]quinolin-5-one (Vb).

A mixture of IIIb (4.0 g.) and propionic anhydride (80 ml.) was refluxed for 1 hour and then allowed to stand over a weekend. The precipitate which separated was collected on a filter and recrystallized from DMF-water, giving 0.9 g. of product, m.p. 205-207°; $\text{ir } \mu$ 3.28 (CH₃), 6.00 (C=O); nmr (deuteriochloroform): δ 2.17 ppm (s, 3H, Me).

4-Hydroxy-1-(2-hydroxyphenyl)carbostyryl (VI).

A mixture of IVa (0.5 g.), 20% aqueous sodium hydroxide solution (16 ml.) and ethanol (3 ml.) was heated under reflux for 1 hour. The clear reaction mixture was cooled and acidified, first with concentrated hydrochloric acid and then with dilute hydrochloric acid, to pH \sim 3. The precipitate thus formed was collected on a filter and washed with water several times, giving 0.5 g. of product, m.p. 297-299° dec.; $\text{ir } \mu$ 2.95, 3.30, 6.10; $\text{uv } \lambda$ max (95% ethanol): $m\mu$ (ϵ) 225 (4.43×10^4), 273 (0.95×10^4), 282 (1.00×10^4), 315 (0.60×10^4).

Anal. Calcd. for C₁₅H₁₁NO₃·H₂O: C, 66.41; H, 4.83; N, 5.16. Found: C, 66.49; H, 4.39; N, 5.25.

4-Hydroxy-1-phenylcarbostyryl (7).

A mixture of *N*-phenylanthranilic acid (5.0 g.) and acetic anhydride (20 ml.) was heated in an oil bath, maintaining the temperature at $110 \pm 5^\circ$ for 4 hours. The reaction mixture was poured into ca. 100 g. of crushed ice in small portions, under stirring, then kept in a refrigerator overnight. It was made alkaline by addition of aqueous sodium hydroxide solution and filtered.

Much of the material remained as a resin. Acidification of the filtrate by addition of dilute hydrochloric acid to pH \sim 5 caused separation of a precipitate, which was collected on a filter and washed with water several times. The crude product was then recrystallized from ethanol; yield 0.3 g., m.p. 296-297.5° [lit. (6) m.p. 295-296°]; $\text{uv } \lambda$ max (95% ethanol): $m\mu$ (ϵ) 228 (4.21×10^4), 272 (0.31×10^4), 282 (0.77×10^4), 313 (0.60×10^4).

1,2-Dihydro-1-(2-hydroxyphenyl)-2-(2-methoxyethylimino)-4-quinolinol (VII).

A mixture of IVa (3.0 g.) and methoxyethylamine (60 ml.) was refluxed for 5 hours, allowed to stand over a weekend, and chilled in ice. The precipitate which formed was separated by filtration and washed with ethanol, giving 3.3 g. of product, m.p. 278-280° dec. An analytical sample was obtained by recrystallization from DMF; m.p. 278-280° dec.; ir : μ 3.01, 3.50, 4.00, 6.25; $\text{uv } \lambda$ max (95% ethanol): $m\mu$ (ϵ) 223 (3.88×10^4), 232 (3.38×10^4), 244 (2.48×10^4), 302 (1.86×10^4), 318 shoulder (1.21×10^4).

Anal. Calcd. for C₁₈H₁₈N₂O₃: C, 69.66; H, 5.85; N, 9.03. Found: C, 69.85; H, 6.02; N, 9.21.

N-(2-Methoxyphenyl)anthranilic Acid.

N-(2-Hydroxyphenyl)anthranilic acid (1.0 g.) was dissolved in a freshly prepared sodium methoxide-methanol solution obtained by dissolving 0.20 g. of sodium metal in 20 ml. of methanol. The solution was evaporated to dryness under reduced pressure and the residue was dissolved in DMF. To this solution was added 0.62 g. of methyl iodide. The reaction mixture was stirred at room temperature for 1 hour and was then poured into a large amount of water. The resulting mixture was acidified with dilute hydrochloric acid. The precipitate was collected on a filter and recrystallized from toluene; m.p. 172-175° [lit. (4) m.p. 175-176.5°]; ir : μ 2.95 (NH), 5.95 (C=O); nmr (deuteriochloroform): δ 4.07 (s, 3H, Me).

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