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Received May 18, 1981

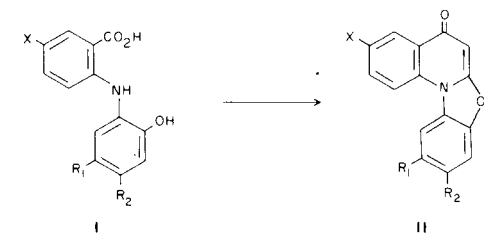
Reaction of *N*-(2-hydroxyphenyl)anthranilic acids (I) with acetic anhydride was investigated further. Treatment of Ia with refluxing acetic anhydride for 3 hours afforded two minor products, IIIa and IV, in addition to the previously reported IIa. Under similar conditions, the reaction of Ib with acetic anhydride afforded IIb as reported previously, and IIb and IXb in small quantities. Treatment of IIb with hydrazine gave X, and treatment of IXb with methoxyethylamine gave XI. When Ic was allowed to react with refluxing acetic anhydride, there were obtained three minor products, IIIc, IXc and XIII, in addition to IIc. Reaction of Id with acetic anhydride gave IId, and two minor products IXc and XIV. The formation of these minor products in the reaction of Ia-d with acetic anhydride are discussed based on the reaction mechanism proposed previously for the formation of II.

*J. Heterocyclic Chem.*, **18**, 1389 (1981).

Acetic anhydride is a versatile reagent especially useful in a wide variety of heterocyclic ring closure reactions (1). We have previously reported that the action of acetic anhydride in *N*-(2-hydroxyphenyl)anthranilic acids (Ia,b) results in the formation of 5*H*-benzoxazolo[3,2-*a*]quinolin-5-ones (IIa,b) (2). From the limited study at the time, it appeared that these products may be useful synthons for the preparation of novel quinoline derivatives of potential pharmacological interests. The novelty of the cyclization reaction of I to form II coupled with the potential usefulness of II led us to study the reaction further.

proton of IIa shown at  $\delta$  6.16. These spectral data and combustion elemental analyses indicated the compound to be 6-acetyl-5*H*-benzoxazolo-[3,2-*a*]quinolin-5-one (IIIa). The formation of IIIa may be envisioned from the reaction mechanism proposed previously for the formation of IIa (2): The acetylation at the 3-position of VII to give VIII and the subsequent elimination of acetic acid from VIII would give IIIa, as depicted in Scheme II. The third pro-

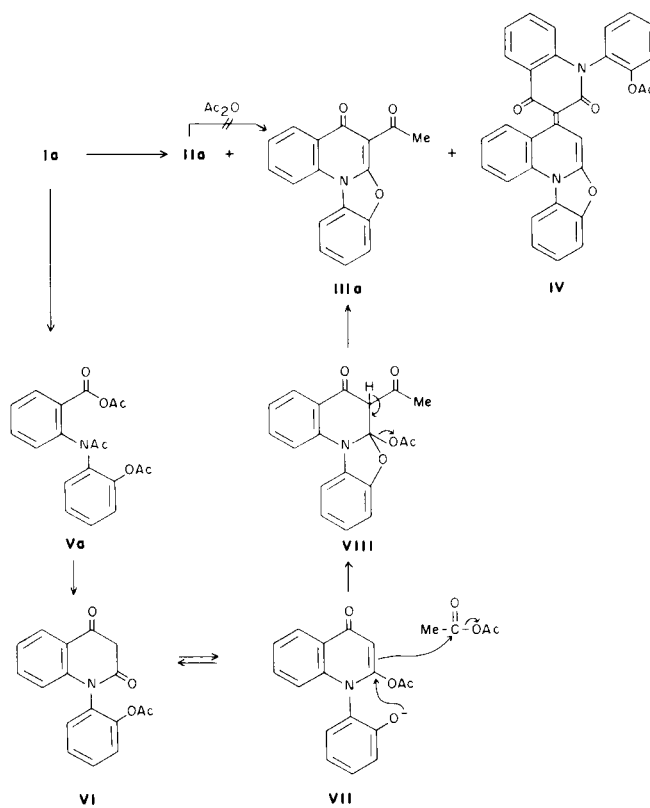
Scheme I



- a**, X = H, R<sub>1</sub> = H, R<sub>2</sub> = H  
**b**, X = H, R<sub>1</sub> = Cl, R<sub>2</sub> = H  
**c**, X = NO<sub>2</sub>, R<sub>1</sub> = H, R<sub>2</sub> = Me  
**d**, X = NO<sub>2</sub>, R<sub>1</sub> = Me, R<sub>2</sub> = H

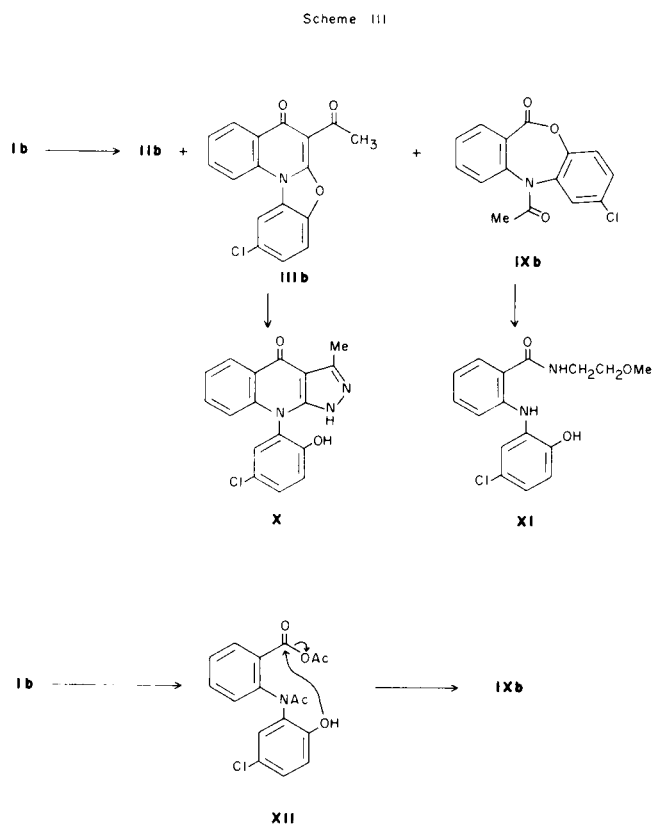
Previously, it was reported that the reaction of Ia with acetic anhydride under refluxing conditions affords IIa. The reaction was repeated in the presence of a small amount of pyridine as a catalyst. The modification did not improve the yield of IIa, but afforded two additional minor products (Scheme II). The product isolated from the acetic anhydride filtrate of IIa showed infrared carbonyl absorption bands at 1667 cm<sup>-1</sup> and 1626 cm<sup>-1</sup>. The nmr spectrum of the minor product exhibited a methyl proton signal at  $\delta$  2.67 ppm as a singlet at the expense of the C<sub>6</sub>

Scheme II



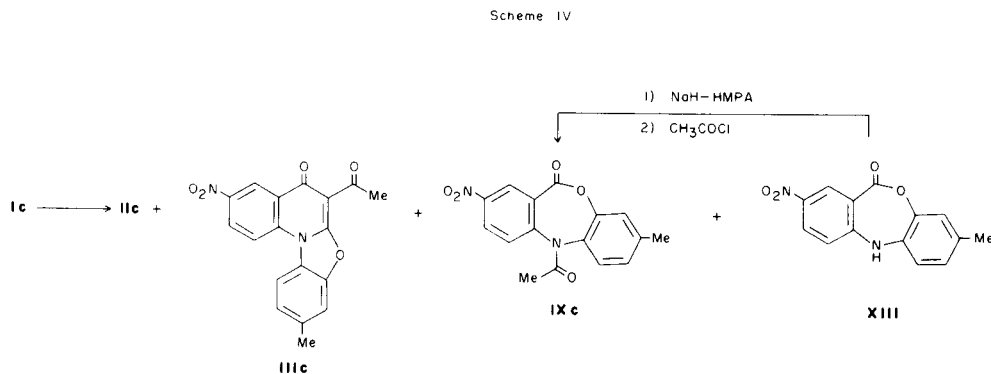
duct was isolated in 1.5% yield during the recrystallization of IIa as an ethanol insoluble high melting (349-350°) material. The following spectral and elemental analytical data supported structure IV, a compound formed by the condensation of IIa with intermediate VI, for the product: The elemental analysis of the product indicated the formula  $C_{32}H_{20}N_2O_5$ , which was ascertained by the mass spectrometry showing fragmentation peaks at  $m/e$  512( $M^+$ ), 470( $MH^+Ac$ ), 453 and 235. The infrared spectrum of the compound showed absorption bands at  $1776\text{ cm}^{-1}$  and  $1634\text{ cm}^{-1}$ . The former was attributed to the phenolic acetate carbonyl, and the latter was to the conjugated ketonic carbonyl group.

Upon heating a mixture of Ib and acetic anhydride under reflux for 3 hours, there were also isolated two minor products in addition to IIb (Scheme III). 6-Acetyl-10-chloro-5H-benzoxazolo[3,2-a]quinolin-5-one (IIIb) was isolated in 1.7% yield. The third product isolated in 6.2% yield (4) was characterized as 5-acetyl-7-chlorodibenz[*b,e*][1,4]oxazepin-11-(5H)one (IXb) based on the following spectral data: The infrared spectrum showed two carbonyl absorption bands at  $1739\text{ cm}^{-1}$  and  $1675\text{ cm}^{-1}$ , and the uv spectrum was distinctively different from those of IIb and IIIb but similar to that (5) of 7-chlorodibenz[*b,e*][1,4]oxazepin-11-(5H)one (6), showing absorption maxima at  $m\mu$  205 ( $\epsilon$ , 48200) and 280 ( $\epsilon$ , 2860). The cyclization of diacetylated Ib such as XII would explain the formation of IXb (Scheme III). The treatment of IXb with 2-methoxyethylamine gave 2-[(5-chloro-2-hydroxyphenyl)amino]-N-(2-methoxyethyl)benzamide (XI) in support of the structural assignment. When IIIb was treated with hydrazine hydrate in a mixture of ethanol and dimethylformamide, a linear tricycle, 9-(5-chloro-2-hydroxyphenyl)-1,9-dihydro-3-methyl-4H-pyrazolo[3,4-*b*]quinolin-4-one (X) was obtained in 75% yield. In consonance with the structure (X), the nmr spectrum of the new compound showed two broad exchangeable singlet proton signals at  $\delta$  10.85 and 13.50, and a methyl proton signal at  $\delta$  2.65 as a singlet. The formation of X is not unexpected, for it was shown previously



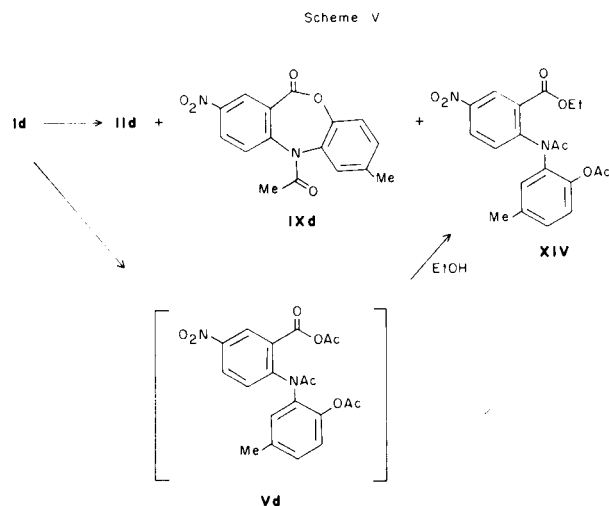
(2) that an electrophilic reaction of benzoxazolo[3,2-*a*]quinolin-5-ones take place exclusively at the 7-position with resultant cleavage of C-O bond (Scheme III).

In order to study the effect of the reduced basicity of the amino group on the distribution of products, *N*-(2-hydroxy-4-methylphenyl)-5-nitroanthranilic acid (Ic) was allowed to react with acetic anhydride. In this case, there were isolated four products, three of which are those formed in a fashion analogous to the reaction of Ib with acetic anhydride (Scheme IV). The fourth product isolated in 2.8% yield was proven to be 8-methyl-2-nitrodibenz[*b,e*][1,4]oxazepin-11-(5H)one (XIII) by comparison with



the authentic sample described in the literature (7). An attempt at *N*-acetylation of XIII with acetic anhydride to form IXc under the conditions similar to those used for the reaction of Ic with acetic anhydride failed, suggesting the improbability of XIII being an intermediate for the formation of IXc in the reaction. Although the direct acetylation of XIII with acetic anhydride failed, the reaction of XIII with acetyl chloride in the presence of sodium hydride in hexamethylphosphoramide gave IXc.

The reaction of Id with acetic anhydride was interesting since an additional product not encountered in previous examples was isolated. Thus, from this reaction no acetylated benzoxazolo[3,2-*a*]quinolin-5-one was isolated, but instead 2-[acetyl-[2-(acetyloxy)-5-methylphenyl]amino]-5-nitrobenzoic acid ethyl ester (XIV) was obtained in 3.6% yield. The latter was presumably formed, during the workup with ethanol, from Vd which was thought to be an intermediate in the reaction of Id with acetic anhydride to form IId (Scheme V).



The present study affirms that the reaction of *N*-(2-hydroxyphenyl)anthranilic acids with acetic anhydride proceed smoothly, giving 5*H*-benzoxazolo[3,2-*a*]quinolin-5-ones as major products in moderate to good yields. Common side reactions are formations of 5-acetyldibenz[*b,e*]1,4-oxazepin-11-(5*H*)ones and 6-acetylbenzoxazolo[3,2-*a*]quinolin-5-ones. The formation of these by-products can be envisioned from the previously proposed reaction mechanism (2).

#### EXPERIMENTAL

Melting points were taken in capillary tubes (Thomas-Hoover melting points apparatus) and are uncorrected. Ir spectra were obtained in potassium bromide pellets using a Perkin-Elmer 21 spectrophotometer. Uv absorption spectra were obtained in ethanol solution using a Perkin-Elmer Model 450-uv-visible NIR spectrophotometer. Nmr spectra were determined on a Joelco Model C-60HL nmr spectrometer using tetramethylsilane as the internal reference. Combustion elemental analyses were performed by the Analytical Section of these Laboratories

using a Perkin-Elmer Model 240 elemental analyzer. Mass spectra were obtained with an Associated Electrical Industries MS-9 high resolution mass spectrometer.

#### Reaction of *N*-(5-Chloro-2-hydroxyphenyl)anthranilic Acid (Ib) with Acetic Anhydride

A mixture of Ib (30 g) and acetic anhydride (400 ml) was refluxed for 3 hours, then concentrated on a rotary evaporator under reduced pressure to approximately 100 ml, then was allowed to set at room temperature overnight. A precipitate was collected on a filter and washed with acetic anhydride, then with ethanol to give 10-chloro-5*H*-benzoxazolo[3,2-*a*]quinolin-5-one (IIb) (18 g, 59%), mp 233-234°, lit mp (2), 233-235°. The acetic anhydride filtrate was concentrated on a rotary evaporator under reduced pressure to approximately 30 ml. The residue was diluted with hot absolute ethanol (50 ml), and allowed to set at room temperature for 5 days. The precipitate that separated was collected on a filter, washed with ethanol, and recrystallized from ethanol, giving 6-acetyl-10-chloro-5*H*-benzoxazolo[3,2-*a*]quinolin-5-one (IIIb) (0.6 g, 1.7%), mp 238-240°, mixture mp with IIb was depressed; ir: 1680 and 1637  $\text{cm}^{-1}$ ; uv: max  $m\mu$  ( $\epsilon$ ) 235 (3390), 271 (9700) and 326 (28000); ms: (E. I.) *m/e* 311 ( $M^+$ ), 296, 269 and 241.

Anal. Calcd. for  $C_{17}H_{10}ClNO_3$ : C, 65.50; H, 3.23; N, 4.49. Found: C, 65.22; H, 3.14; N, 4.43.

When the mother liquor (ethanol) from the above recrystallization was allowed to set at room temperature overnight, there was separated a crystalline product. After chilling the mixture in ice, the precipitate was collected on a filter and washed with cold ethanol, giving 5-acetyl-7-chlorodibenz[*b,e*]1,4-oxazepin-11-(5*H*)one (IXb) (1.5 g, 6.2%) which melted at 163-165°. The analytical sample obtained by recrystallization from ethanol melted at 165-167°; ir: 1739 and 1675  $\text{cm}^{-1}$ ; nmr (DMSO- $d_6$ ):  $\delta$  2.13 (3H,  $\text{CH}_3$ , s) and 7.54-8.03 (7H, aromatic, m).

Anal. Calcd. for  $C_{15}H_{10}ClNO_3$ : C, 62.62; H, 3.50; N, 4.87. Found: C, 62.81; H, 3.66; N, 4.86.

#### 9-(5-Chloro-2-hydroxyphenyl)-1,9-dihydro-3-methyl-4*H*-pyrazolo[3,4-*b*]quinolin-4-one (X)

6-Acetyl-10-chloro-5*H*-benzoxazolo[3,2-*a*]quinolin-5-one (IIIb, 1.4 g) was dissolved in a mixture of absolute ethanol (70 ml) and dimethylformamide (30 ml) with warming. To the warm solution was added hydrazine hydrate (95%, 0.6 g) dissolved in dimethylformamide (3 ml). The resulting mixture was heated under reflux for 2 hours, then chilled in ice. A precipitate was collected on a filter and washed with ethanol. The filter residue was triturated with dilute acetic acid, then with water, giving the product (1.1 g, 75%) which did not melt below 340°; ir: 3390, 3030 and 1626  $\text{cm}^{-1}$ ; ms: (C. I.) *m/e* 326( $MH^+$ ).

Anal. Calcd. for  $C_{17}H_{12}ClN_2O_2$ : C, 62.68; H, 3.71; N, 13.03. Found: C, 62.48; H, 3.64; N, 13.03.

#### 2-[(5-Chloro-2-hydroxyphenyl)amino]-*N*-(2-methoxyethyl)benzamide (XI)

A mixture of IXb (2.6 g), 2-methoxyethylamine (2.0 g), and ethanol (70 ml) was heated under reflux for 2.5 hours, then evaporated on a rotary evaporator under reduced pressure to give a resinous material. The residue was dissolved in water. The aqueous solution was acidified with dilute hydrochloric acid and extracted with ether. The combined ether extracts were dried over magnesium sulfate and evaporated on a rotary evaporator to give a resinous material. The residue was dissolved in anhydrous ether (ca. 40 ml) and the ether solution was diluted with petroleum ether until it becomes cloudy. Chilling of the mixture caused separation of a precipitate which was collected on a filter and washed with cold ether, giving the product (1.0 g, 31%), mp 126-128°; ir: 1715  $\text{cm}^{-1}$ .

Anal. Calcd. for  $C_{16}H_{17}ClN_2O_3$ : C, 59.90; H, 5.34; N, 8.74. Found: C, 59.95; H, 5.33; N, 8.70.

#### Reaction of *N*-(2-Hydroxyphenyl)anthranilic Acid (Ia) with Acetic Anhydride.

A mixture of Ia (7.0 g), acetic anhydride (70 ml) and pyridine (0.5 ml)

was heated under reflux for 3 hours, then evaporated on a rotary evaporator under reduced pressure to give a slurry residue. The residue was chilled and filtered. The filter residue was washed with ethanol repeatedly, and recrystallized from ethanol, giving 5*H*-benzoxazolo[3,2-*a*]quinolin-5-one (IIa) (4.9 g, 68%), mp 206-208°, lit. mp (2), 205-207°. The combined filtrate and washings were evaporated on a rotary evaporator and the residue was recrystallized from ethanol, giving 6-acetyl-5*H*-benzoxazolo[3,2-*a*]quinolin-5-one (IIIa) (0.5 g, 6%), mp 254-255°; ir: 1667 and 1626 cm<sup>-1</sup>; uv: max  $\mu$  ( $\epsilon$ ) 233 (31700), 247 (shoulder, 2400), 264 (10800), 273 (12800), 273 (12800) and 321 (24000); ms: (E. I.): m/e 277 (M<sup>+</sup>), 262 and 234.

*Anal.* Calcd. for C<sub>17</sub>H<sub>11</sub>NO<sub>3</sub>: C, 73.64; H, 4.00; N, 5.05. Found: C, 73.26; H, 4.03; N, 5.02.

During the recrystallization of crude IIa from ethanol there was obtained 0.23 g (1.5%) of 1-[2-(acetyloxy)phenyl]-3-(5*H*-benzoxazolo[3,2-*a*]quinolin-5-ylidene)-2, 4-(1*H*,3*H*)quinolinedione (IV) which was insoluble in hot ethanol. Recrystallization from acetic anhydride gave analytical sample, mp 349-350°; ir: 1776 and 1634 cm<sup>-1</sup>; ms: m/e 512 (M<sup>+</sup>), 470 (M<sup>+</sup>-H-Ac), 453 and 235.

*Anal.* Calcd. for C<sub>23</sub>H<sub>20</sub>N<sub>2</sub>O<sub>5</sub>: C, 74.99; H, 3.93; N, 5.47. Found: C, 74.75; H, 3.88; N, 5.39.

Reaction of *N*-(2-Hydroxy-4-methylphenyl)-5-nitroanthranilic Acids (Ic) with Acetic Anhydride.

A mixture of Ic (20 g) and acetic anhydride (500 ml) was heated under reflux for 4.5 hours, then chilled in a freezer for 2 days. The precipitate that separated was collected on a filter and washed with acetic anhydride, giving 9-methyl-3-nitro-5*H*-benzoxazolo[3,2-*a*]quinolin-5-one (IIc) (6.9 g, 34%), mp above 350°; ir: 1639 cm<sup>-1</sup>.

*Anal.* Calcd. for C<sub>16</sub>H<sub>10</sub>N<sub>2</sub>O<sub>4</sub>: C, 65.30; H, 3.43; N, 9.52. Found: C, 65.22; H, 3.43; N, 9.37.

The combined filtrate and washing were concentrated on a rotary evaporator under reduced pressure to about 20 ml, then chilled in ice. The precipitate that separated was collected on a filter and washed with acetic anhydride. Fractional recrystallization of the filter residue from ethanol separated the crude product into two fractions: hot ethanol soluble and hot ethanol insoluble fractions. Another recrystallization of the hot ethanol soluble fraction from ethanol gave 8-methyl-2-nitro-dibenz[*b,e*]1,4]oxazepin-11-(5*H*)one (XIII) (0.6 g, 2.8%), mp 267-269°, lit mp (7) 275-277°; mixture mp with authentic sample described by Kim (7) was not depressed; ir: 1700 cm<sup>-1</sup>; uv: max  $\mu$  ( $\epsilon$ ) 229 (27400) and 365 (14500). The hot ethanol insoluble fraction was recrystallized from dimethylformamide, giving 6-acetyl-9-methyl-3-nitro-5*H*-benzoxazolo[3,2-*a*]quinolin-5-one (IIIc) (0.6 g, 2.6%), mp 289-290°; ir: 1649 and 1667 cm<sup>-1</sup>.

*Anal.* Calcd. for C<sub>18</sub>H<sub>12</sub>N<sub>2</sub>O<sub>3</sub>: C, 64.28; H, 3.60; N, 8.33. Found: C, 64.24; H, 3.58; N, 8.70.

The dimethylformamide mother liquor from the recrystallization of IIIc was diluted with ethanol and allowed to set at room temperature for several days. The precipitate that separated was collected on a filter, washed with ethanol and recrystallized from ethanol, giving 5-acetyl-8-methyl-2-nitrodibenz[*b,e*]1,4]oxazepin-11-(5*H*)one (IXc) (2.0 g, 9.2%), mp 192-194°; ir: 1754 and 1704 cm<sup>-1</sup>; uv: max  $\mu$  ( $\epsilon$ ) 224 (23700) and 270 (8500); nmr(DMSO-*d*<sub>6</sub>):  $\delta$  2.15 (3H, CH<sub>3</sub>, s), 2.35 (3H, CH<sub>3</sub>, s), 7.10-8.70 (6H, aromatic, m).

*Anal.* Calcd. for C<sub>16</sub>H<sub>12</sub>N<sub>2</sub>O<sub>5</sub>: C, 61.54; H, 3.87; N, 8.97. Found: C, 61.68; H, 3.92; N, 8.95.

5-Acetyl-8-methyl-2-nitrodibenz[*b,e*]1,4]oxazepin-11-(5*H*)one (IXc) from XIII.

Sodium hydride (50% oil dispersion, 0.24 g) was washed with pentane

3 times, then suspended in hexamethylphosphoramide (30 ml). 8-Methyl-2-nitrodibenz[*b,e*]1,4]oxazepin-11-(5*H*)one (XIII, 1.25 g) was added to the mixture. A purple colored salt was formed with generation of hydrogen gas. The mixture was chilled in ice. Acetyl chloride (0.5 g) dissolved hexamethylphosphoramide (5 ml) was added dropwise with stirring. After 15 minutes at 0°, the reaction mixture was stirred at room temperature until the purple color disappeared. The mixture was poured into about 150 ml. of ice water and the precipitate that separated was collected on a filter. The filter residue was recrystallized from ethanol giving the unreacted starting material. The mother liquor was evaporated on a rotary evaporator under reduced pressure to give a resinous material. The residue was recrystallized from a small amount of ethanol giving 0.4 g (28%) of crude IXc. Recrystallization from ethanol with charcoal treatment gave the product, mp 178-180°. Mixture mp with that obtained from the reaction of Ic with acetic anhydride was not depressed.

Reaction of *N*-(2-Hydroxy-5-methylphenyl)-5-nitroanthranilic Acid (Id) with Acetic Anhydride.

A mixture of Id (10 g), acetic anhydride (250 ml) and pyridine (3.0 g) was heated under reflux for 4 hours, then chilled in a freezer overnight. The precipitate that separated was collected on a filter, and washed with acetic anhydride, then with ethanol, giving 10-methyl-3-nitro-5*H*-benzoxazolo[3,2-*a*]quinolin-5-one (IIId) (5.6 g, 55%), mp 287-293° dec. Analytical sample obtained by recrystallization from dimethylformamide melted at 313-315° dec; ir: 1645 cm<sup>-1</sup>.

*Anal.* Calcd. for C<sub>16</sub>H<sub>10</sub>N<sub>2</sub>O<sub>4</sub>: C, 65.30; H, 3.43; N, 9.52. Found: C, 65.05; H, 3.57; N, 9.25.

The filtrate (acetic anhydride) was evaporated on a rotary evaporator under reduced pressure and the residue was dissolved in a small amount of ethanol. When the ethanol solution was allowed to set at room temperature for 2 days there was separated a crystalline product which was collected on a filter and recrystallized from ethanol, giving 5-acetyl-7-methyl-2-nitrodibenz[*b,e*]1,4]oxazepin-11-(5*H*)one (IXd) (0.9 g, 8.3%), mp 143-146°. Another recrystallization from ethanol improved the mp to 146-149°; ir: 1715 and 1626 cm<sup>-1</sup>.

*Anal.* Calcd. for C<sub>16</sub>H<sub>12</sub>N<sub>2</sub>O<sub>5</sub>: C, 61.54; H, 3.87; N, 8.97. Found: C, 61.68; H, 3.95; N, 8.98.

When the mother liquor from recrystallization of IXd was allowed to set at room temperature for several weeks, a crystalline product was separated. The precipitate was collected on a filter and washed with ethanol, giving 2-[acetyl[2-(acetyloxy)-5-methylphenyl]amino]-5-nitrobenzoic acid ethyl ester (XIV), (0.5 g, 3.6%), mp 197.5-200° dec; ir: 1770 and 1742 cm<sup>-1</sup>; ms: (C.I.) m/e 401 (MH<sup>+</sup>) and 313.

*Anal.* Calcd. for C<sub>20</sub>H<sub>20</sub>N<sub>2</sub>O<sub>6</sub>: C, 59.99; H, 5.01; N, 7.00. Found: C, 59.99; H, 5.04; N, 7.00.

## REFERENCES AND NOTES

- (1) D. H. Kim, *J. Heterocyclic Chem.*, **13**, 179 (1976).
- (2) D. H. Kim, R. A. Fieber, A. A. Santilli and S. C. Bell, *ibid.*, **11**, 703 (1974).
- (3) The effect of pyridine on the reaction is not clear since it was later found that the reaction carried out in the absence of pyridine gave a similar result.
- (4) In one experiment the yield of IXb was as high as 27%.
- (5) Uv: max  $\mu$  ( $\epsilon$ ) 217 (28500), 227 (shoulder, 27400) and 265 (8300).
- (6) S. Raines, C. A. Kovacs, S. Goldstien and F. P. Palopoli, *J. Med. Chem.*, **11**, 896 (1968).
- (7) D. H. Kim, *J. Heterocyclic Chem.*, **18**, 855 (1981).