2-Aryl-5-hydroxy-3-methyl-6(2*H*)-cyclohepta[c]pyrazolones: The Cyclization Products of 5-Arylazo-4-ethyltropolone and Its Related Compounds

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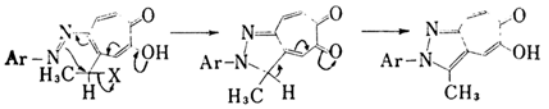
In our laboratory, a process has recently been developed for the preparation of 4-ethyltropolone[1] and 4-(1-hydroxyethyl)tropolone[2] from 4-acetyltropolone (I),[3] and the reactions of these tropolones have been investigated.[1,2] During these studies it has been observed that the 5-arylazo derivatives of these tropolones undergo a facile change upon heating, especially in the presence of a mineral acid; thus, 4-ethyl-5-(*p*-tolylazo)tropolone (II) afforded a pale yellow compound (III) with a m. p. of 203°C when heated in an alcoholic solution in the presence of hydrochloric acid.[1] 4-(1-Hydroxyethyl)-5-(*p*-tolylazo)tropolone (IV) also gave the same product (III) when merely heated over its melting point or when heated in an alcoholic solution in the presence of hydrochloric acid.[2] The present authors have prepared 4-(1-acetamidoethyl)-5-(*p*-tolylazo)-tropolone (V) from 4-acetyltropolone (I) and found that this azo compound also afforded the same product (III) when heated in alcohol. The rather curious behavior of these

1) T. Nozoe, K. Takase and K. Umino, This Bulletin, **38**, 358 (1965).
2) T. Nozoe, K. Takase, K. Shimizu and M. Yasunami, to be published.
3) T. Nozoe, K. Takase and M. Ogata, *Chem. & Ind.*, **1957**, 1070.

azo compounds prompted us to examine the structure of III. The account of the structural elucidation of III will be described herein, together with the record of some reactions of 4-(1-acetamidoethyl)tropolone.

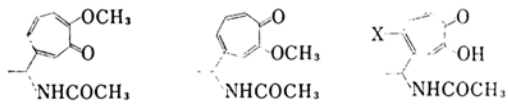
The catalytic reduction of 4-(1-hydroxyiminoethyl)tropolone (VI)[3] in the presence of palladized charcoal gave an amino compound (VII). The acetylation of VII afforded 4-(1-acetamidoethyl)tropolone (VIII), the structure of which was clear from the positive ferric chloride coloration and from the presence of the amide band at 1667 cm^{-1} in its infrared absorption spectrum. The tosylation of the amine (VII) with *p*-toluenesulfonyl chloride also gave the corresponding sulfonamide (IX).

The treatment of VIII with *p*-toluenediazonium chloride gave a *p*-tolylazo compound (V), the position of the azo group being assumed to be at the 5-position by analogy with the other azotropolones.[4] The heating of the azo compound (V) in ethanol gave pale yellow crystals with a m. p. of 203°C, which was found to be identical with the compound (III) obtained earlier from the azo compound (II and IV). The compound (III), whose elemental analysis corresponds to the formula $C_{16}H_{11}O_2N_2$, gives an orange sodium salt, and, in its ultraviolet absorption spectrum, shows a bathochromic shift of the absorption maxima in an alkaline solution, as is shown in Fig. 1. These results indicate that III is an acidic compound. The presence of the α-enolone system was suggested by the positive ferric chloride coloration and by the formation of an orange copper chelate, as well as by the presence of ν_{OH} at 3350 cm^{-1} in its infrared absorption spectrum. No hydroxyl group was observed in the infrared absorption spectra of its acetyl and



X=OH or $NHCOCH_3$ (IIIa) III

Chart 1. The reaction mechanism of the ring closure of the 5-arylazo derivatives of 4-(1-hydroxyethyl)- and 4-(1-acetamidoethyl)tropolone.



XVI$_a$ XVI$_b$ XVII: X=NH_2; XVIII: X=Cl; XIX: X=Br

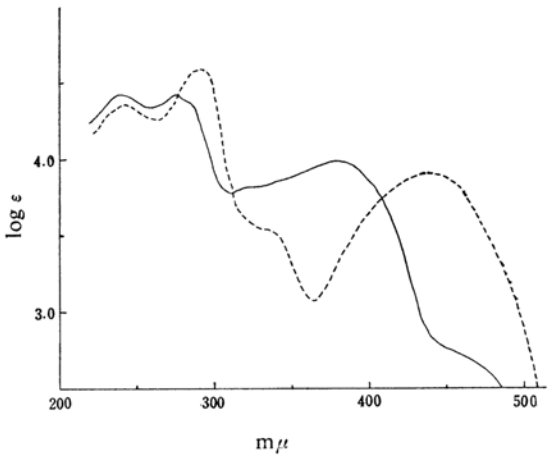


Fig. 1. The ultraviolet absorption of III in methanol (——) and in 0.1 N sodium hydroxide solution (- - -).

tosyl derivatives, which were neutral and lacked the ferric chloride coloration.

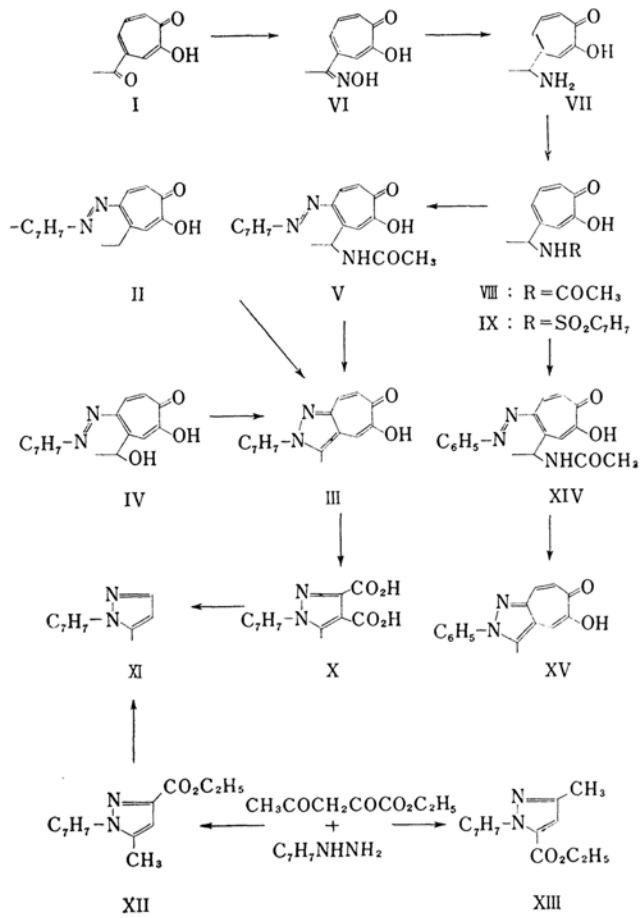
The alkaline permanganate oxidation of III gave a dicarboxylic acid (X). The decarboxylation of X by heating gave an oily substance, which was identified with 5-methyl-1-(*p*-tolyl)-pyrazole (XI)[5] by a direct comparison of their infrared absorption spectra and by an admixture of their picrates. An authentic specimen of XI was synthesized by a modified Finar and Hurlock method[6] as follows: The reaction of ethyl acetopyruvate and *p*-tolylhydrazine gave two isomeric condensation products, ethyl 5-methyl-1-(*p*-tolyl)pyrazole-3-carboxylate (XII) and ethyl 3-methyl-1-(*p*-tolyl)pyrazole-5-carboxylate (XIII). The alkaline hydrolysis of XII, followed by decarboxylation, gave XI. This result shows that the dicarboxylic acid (X) is 5-methyl-1-(*p*-tolyl)pyrazole-3, 4-dicarboxylic acid;[5] therefore, the compound (III) contains a pyrazole ring. From the above-mentioned evidence, only one structure, 5-hydroxy-3-methyl-2-(*p*-tolyl)-6(2*H*)-cyclohepta-[c]pyrazolone, is deduced for the compound (III).

4-(1-Acetamidoethyl)-5-phenylazotropolone (XIV), which was obtained by treating VIII with benzenediazonium chloride, also gave a pale yellow compound (XV) when heated in an alcoholic solution. From the elemental analysis, the positive ferric chloride coloration and the ultraviolet absorption spectrum, which are similar to those of III, it seems that the structure of XV is best represented by 5-hydroxy-3-methyl-2-phenyl-6(2*H*)-cyclohepta[c]pyrazolone. The infrared absorption spectrum also supported this structure.

4) T. Nozoe, *Nature*, **167**, 1055 (1951); *Fortschr. Chem. org. Naturstoffe.*, **13**, 233 (1956).

5) C. Bulow and A. Schlesinger, *Ber.*, **33**, 3365 (1900).

6) I. L. Finar and R. J. Hurlock, *J. Chem. Soc.*, **1958**, 3260.



The formation of the cyclohepta[c]pyrazolone derivatives (III and XV) from the azo compounds (V and XIV) is mechanistically conceivable, as Chart 1 shows. The formation of the same product (III) from the azo compound (IV) can also be explained by the same mechanism. This mechanism is apparently different from the mechanism of the formation of III from 4-ethyl-5-(*p*-tolylazo)tropolone (II), in which the inevitable dehydrogenation process accompanies the ring closure.[1] In the present case, the yield of the cyclization product showed no change upon the addition of the oxidant.[1,7] The reaction path, therefore, is the initial elimination of the acetamido or hydroxyl group, followed by the ring closure to afford the diketone (IIIa), which then enolizes to III.

The methylation of the acetamido compound (VIII) with diazomethane gave two isomeric methyl ethers, XVIa and XVIb. The structures of these ethers were determined by an examination of their infrared absorption spectra, in which the characteristic absorptions appeared at 791 cm^{-1} and at 828 cm^{-1} respectively.[8] These ethers are of interest in that they possess partial structures of colchicine and isocolchicine[9] respectively. The catalytic reduction of the azo compound (V) gave 4-(1-acetamidoethyl)-5-aminotropolone (XVII), from which 5-chloro (XVIII) and 5-bromo (XIX) derivatives were prepared by a Sandmeyer reaction.

Experimental[10]

4-(1-Aminoethyl)tropolone (VII).—To a suspension of 4-(1-hydroxyiminoethyl)tropolone (VI) (1.58 g.) in methanol (25 ml.), concentrated hydrochloric acid (5 ml.) was added. The mixture was then shaken with hydrogen, in the presence of 5% palladium on carbon (300 mg.), at room temperature and at atmospheric pressure; after 4 hr., 430 ml. of hydrogen was absorbed. The catalyst was removed, the

7) T. Nozoe, T. Ikemi and T. Ozeki, *Proc. Japan Acad.*, **27**, 110 (1951).

8) 2,4- and 2,6-Disubstituted tropones show the characteristic absorption in the 810—840 cm^{-1} and 770—800 cm^{-1} ranges respectively; T. Nozoe, K. Takase and M. Yasunami, to be published.

9) E. J. Forbes, *Chem. & Ind.*, **1956**, 192.

10) All melting points are uncorrected.

solution was concentrated to a small volume and adjusted to pH 5 with potassium hydroxide solution, and the potassium chloride thereby precipitated was filtered off. The filtrate was adjusted to pH 7, and the crystals thereby formed were collected by filtration and recrystallized from methanol to give the monohydrate of VII (1.35 g.) as yellow needles, m. p. 220°C (decomp.).

Found: C, 59.10; H, 6.86; N, 7.54. Calcd. for $C_9H_{11}O_2N \cdot H_2O$: C, 59.00; H, 7.15; N, 7.65%. λ_{max}^{MeOH} mμ (log ε); 243 (4.39), 335 (3.97), 395 (3.68).

4-(1-Acetamidoethyl)tropolone (VIII).—A mixture of VII (8.2 g.) and acetic anhydride (9 ml.) was allowed to stand for 1 hr. at room temperature. Water (9 ml.) was then added, and the crystals thereby formed were collected by filtration to give VIII (5.6 g.), m. p. 156°C. From the filtrate, further crops (2.64 g.) of VIII were obtained by extraction with ethyl acetate. Recrystallization from ethanol gave colorless prisms, m. p. 166°C. VIII is green in water or ethanol and red in chloroform with a ferric chloride solution.

Found: C, 63.83; H, 6.00; N, 6.63. Calcd. for $C_{11}H_{13}O_3N$: C, 63.75; H, 6.32; N, 6.76%. λ_{max}^{MeOH} mμ (log ε); 241 (4.43), 324 (3.89).

4-[1-(*p*-Toluenesulfonamido)ethyl]tropolone (IX).—To stirred solution of VII (170 mg.) in a 0.5 N sodidum hydroxide solution (5.5 ml.), *p*-toluenesulfonyl chloride (210 mg.) was added at room temperature. After being stirred for 4 hr., the mixture was acidified with 6 N hydrochloric acid, and the brown gummy material thereby formed was triturated in order to crystallize it. Recrystallization from ethanol gave IX (90 mg.) as colorless prisms, m. p. 176—177°C.

Found: C, 60.18; H, 5.37; N, 4.39. Calcd. for $C_{16}H_{17}O_4NS$: C, 59.69; H, 5.34; N, 4.61%. λ_{max}^{MeOH} mμ (log ε); 230 (4.47), 325—330 (3.88).

4-(1-Acetamidoethyl)-5-(*p*-tolylazo)tropolone (V).—To a stirred solution of VIII (2.10 g.) in pyridine (20 ml.), a *p*-toluenediazonium chloride solution prepared from *p*-toluidine (1.10 g.) was added with the mixture was being cooled in an ice bath; orage red crystals were separated out during stirring. After 30 min., water (100 ml.) was added and the crystals were collected by filtration and washed with water to give V (2.90 g.); m. p. 153—155°C. Recrystallization from benzene gave orange red needles, m. p. 167°C (decomp.).

Found: C, 66.13; H, 5.61; N, 12.77. Calcd. for $C_{18}H_{19}O_3N_3$: C, 66.44; H, 5.89; N, 12.97%. λ_{max}^{MeOH} mμ (log ε); 235 (4.33), 291 (3.95), 404 (4.36).

5-Hydroxy-3-methyl-2-(*p*-tolyl)-6(2*H*)-cyclohepta[c]pyrazolone (III).—A solution of V (1.00 g.) in ethanol (30 ml.) was heated under reflux for 3 hr. On cooling, III (700 mg.) was obtained as pale yellow needles, m. p. 203°C, which showed no depression on admixture with the specimen obtained from 4-ethyl-5-(*p*-tolylazo)tropolone (II)[1] or 4-(1-hydroxyethyl)-5-(*p*-tolylazo)tropolone (IV).[2] Their infrared spectra were also identical.

Found: C, 71.83; H, 5.26; N, 10.59. Calcd. for $C_{16}H_{14}O_2N_2$: C, 72.16; H, 5.30; N, 10.52%. λ_{max}^{MeOH} mμ (log ε); 239 (4.43), 275 (4.44), 379 (3.99). $\lambda_{max}^{0.1N\ NaOH}$ mμ (log ε); 242 (4.36), 292 (4.58), 435—440 (3.09).

Acetate: Obtained by treatment with acetic anhydride in the presence of sulfuric acid; colorless needles (from ethanol); m. p. 205—206°C.

Found: C, 69.98; H, 4.89; N, 9.35. Calcd. for $C_{18}H_{16}O_3N_2$: C, 70.11; H, 5.23; N, 9.35%. λ_{max}^{MeOH} mμ (log ε); 235 (4.42), 263 (4.47), 335—340 (4.20).

Tosylate: Obtained by treatment with *p*-toluenesulfonyl chloride in pyridine; pale yellow prisms (from benzene), m. p. 195—196°C.

Found: C, 66.42; H, 4.82; N, 6.76. Calcd. for $C_{23}H_{20}O_4N_2S$: C, 65.69; H, 4.79; N, 6.66%.

The Permanganate Oxidation of III.—To a stirred suspention of III (1.06 g.) in a mixture of a N potassium hydroxide solution of (8 ml.) and water (30 ml.), powdered potassium permanganate was added in small portions at room temperature; 3.2 g. of permanganate was consumed during 3 hr. After decomposing an excess of permanganate by the addition of methanol, manganese dioxide was filtered off and washed with water. The combined filtrate and washing were acidified with 6 N sulfuric acid, and the crystals thereby formed were collected by filtration and recrystallized from aqueous ethanol to give *5-methyl-1-(p-tolyl)pyrazole-3, 4-dicarboxylic acid (X)* (600 mg.) as colorless prisms, m. p. 243°C (decomp.).

Found: C, 59.84; H, 4.38; N, 10.59. Calcd. for $C_{13}H_{12}O_4N_2$: C, 59.99; H, 4.65; N, 10.59%.

5-Methyl-1-(*p*-tolyl)pyrazole (XI).—*a) From Ethyl 5-Methyl-1-(p-tolyl)pyrazole-3-carboxylate (XII).*—A mixture of XII (8.0 g.), a 2 N potassium hydroxide solution (25 ml.) and ethanol (15 ml.) was heated under reflux for 30 min. The reaction mixture was concentrated to a small volume and acidified with concentrated hydrochloric acid to give *5-methyl-1-(p-tolyl)pyrazole-3-carboxylic acid.* Recrystallization from aqueous ethanol afforded colorless rods of monohydrate (7.2 g.), m. p. 170°C.

Found: C, 61.88; H, 5.86; N, 12.04. Calcd. for $C_{12}H_{12}O_2N_2 \cdot H_2O$: C, 61.52; H, 6.02; N, 11.96%.

This acid (3.0 g.) was heated at 240—260°C for 10 min., and the oily substance thereby formed was distilled to give XI (1.1 g.) as a colorless oil, b. p. 137°C/5 mmHg, b. p. 272°C, reported[5] b. p. 270—280°C.

Found: C, 76.43; H, 6.93; N, 16.10. Calcd. for $C_{11}H_{12}N_2$: C, 76.71; H, 7.02; N, 16.27%.

Picrate: m. p. 121°C, yellow needles (from ethanol).

Found: C, 50.91; H, 3.55; N, 17.61. Calcd. for $C_{17}H_{15}O_7N_5$: C, 50.87; H, 3.77; N, 17.45%.

b) From 5-Methyl-1-(p-tolyl)pyrazole-3, 4-dicarboxylic Acid (X).—X (250 mg.) was heated at 250—255°C for 15 min., and the oily substance thereby formed was distilled to give a colorless oil. The infrared spectrum of this oil was identical with that of XI, and the picrate of this oil, m. p. 121°C, showed no depression on admixture with the picrate of XI.

Ethyl 5-Methyl-1-(*p*-tolyl)pyrazole-3-carboxylate (XII) and Ethyl 3-Methyl-1-(*p*-tolyl)pyrazole-5-carboxylate (XIII).—To a stirred solution of ethyl

acetopyruvate (28 g.) in glacial acetic acid (45 ml.), a solution of *p*-tolylhydrazine (21.6 g.) in the same solvent (20 ml.) was added at room temperature, and the mixture was heated under reflux for 2 hr. After it had been cooled, the mixture was poured into water (270 ml.) and extracted 4 times with ether, and the combined extract was washed with a 10% sodium carbonate solution (30 ml.×3). The solvent was evaporated, and the residue was fractionally recrystallized from ethanol. The sparingly soluble part gave XII (21.7 g.) as colorless scales, m. p. 77°C.

Found: C, 68.68; H, 6.36; N, 11.54. Calcd. for $C_{14}H_{16}O_2N_2$: C, 68.83; H, 6.60; N, 11.47%.

The more soluble part gave XIII (5.2 g.) as colorless needles, m. p. 65°C.

Found: C, 69.01; H, 6.50; N, 11.40. Calcd. for $C_{14}H_{16}O_2N_2$: C, 68.83; H, 6.60; N, 11.47%.

The heating of XIII with potassium hydroxide in aqueous ethanol gave *3-Methyl-1-(p-tolyl)pyrazole-5-carboxylic acid* as colorless needles, m. p. 203°C (decomp.) (from aqueous ethanol).

Found: C, 66.65; H, 5.59; N, 12.96. Calcd. for $C_{12}H_{12}O_2N_2$: C, 66.61; H, 5.34; N, 12.97%.

4-(1-Acetamidoethyl)-5-phenylazotropolone (XIV).—To a stirred solution of VIII (420 mg.) in pyridine (5 ml.), a benzene-diazonium chloride solution prepared from aniline (190 mg.) was added while the mixture was being cooled in an ice bath. After being stirred for 1 hr., the mixture was diluted with water and the crystals thereby formed were collected by filtration and recrystallized from benzene to give XIV (540 mg.) as orange red needles, m. p. 141°C.

Found: C, 66.05; H, 5.46; N, 13.53. Calcd. for $C_{17}H_{17}O_3N_3$: C, 65.58; H, 5.50; N, 13.50%. λ_{max}^{MeOH} mμ (log ε); 232 (4.35), 288 (4.03), 392 (4.35).

5-Hydroxy-3-methyl-2-phenyl-6(2*H*)-cyclohepta[c]pyrazolone (XV).—A solution of XIV (100 mg.) in ethanol (3 ml.) was heated under reflux for 1.5 hr. and allowed to cool. The crystals thereby formed were recrystallized from ethanol to give XV (50 mg.) as pale yellow prisms, m. p. 230—231°C.

Found: C, 71.26; H, 4.75; N, 10.90. Calcd. for $C_{15}H_{12}O_2N_2$: C, 71.41; H, 4.80; N, 11.11%. λ_{max}^{MeOH} mμ (log ε); 241 (4.37), 275 (4.43), 378—381 (3.95).

The Methylation of VIII.—To a stirred solution of VIII (560 mg.) in methanol (20 ml.), an ethereal solution of diazomethane was added while the mixture was being cooled in an ice bath; the mixture was then stirred for an additional 3 hr. The evaporation of the solvent left an oily substance, which was dissolved in ethyl acetate and chromatographed through an alumina column. The crystal obtained by evaporation of the solvent from the effluent were fractionallized from ethyl acetate to give *6-(1-acetamidoethyl)-2-methoxytropone (XVIa)* (100 mg.) as colorless prisms, m. p. 153.5°C.

Found: C, 65.08; H, 6.85; N, 6.33. Calcd. for $C_{12}H_{15}O_3N$: C, 65.14; H, 6.83; N, 6.33%. λ_{max}^{MeOH} mμ (log ε); 240 (4.41), 322 (3.88).

The more soluble part gave *4-(1-acetamidoethyl)-2-methoxytropone (XVIb)* (90 mg.) as colorless prisms, m. p. 162—163°C.

Found: C, 64.91; H, 6.73; N, 6.23. Calcd. for $C_{12}H_{15}O_3N$: C, 65.14; H, 6.83; N, 6.33%. λ_{max}^{MeOH} mμ (log ε); 240 (4.39), 346 (3.87).

4-(1-Acetamidoethyl)-5-aminotropolone (XVII).—A suspension of V (1.0 g.) in methanol (15 ml.) was shaken with hydrogen in the presence of platinum oxide (50 mg) at room temperature and at atmospheric pressure; 124 ml. of hydrogen was absorbed. After the removal of the catalyst, the solvent was evaporated and the residue was washed with a small amount of benzene and recrystallized from ethanol to give XVII (590 mg.) as yellow needles, m. p. 203°C (decomp.).

Found: C, 59.60; H, 6.15; N, 12.75. Calcd. for $C_{11}H_{14}O_3N_2$: C, 59.45; H, 6.35; N, 12.60%. λ_{max}^{MeOH} mμ (log ε); 239 (4.36), 359 (4.11), 388 (4.10).

4-(1-Acetamidoethyl)-5-chlorotropolone (XVIII).—To a stirred solution of XVII (220 mg.) in a mixture of dioxane (1 ml.) and 12% sulfuric acid (1.4 ml.), a solution of sodium nitrite (70 mg.) in water (0.4 ml.) was added while the mixture was being cooled in an ice bath. After being stirred for 30 min., the mixture was poured into a solution of cuprous chloride (250 mg.) in concentrated hydrochloric acid (2 ml.); the stirring was then continued for 4 hr. The reaction mixture was diluted with water (15 ml.) and extracted with chloroform, and the chloroform solution was saturated with hydrogen sulfide gas. The copper sulfide thereby formed was filtered off and the solvent was evaporated to give crystals. Recrystallization from methanol gave XVIII (30 mg.) as yellow microneedles, m. p. 227°C.

Found: C, 55.00; H, 5.11; N, 5.79. Calcd. for $C_{11}H_{12}O_3N_2Cl$: C, 54.66; H, 5.01; N, 5.80%. λ_{max}^{MeOH} mμ (log ε); 244 (4.37), 330 (3.99).

4-(1-Acetamidoethyl)-5-bromotropolone (XIX).—A diazotized solution of XVII (100 mg.) prepared as in the above experiment was poured into a solution of cuprous bromide (150 mg.) in concentrated hydrobromic acid (1 ml.). After being stirred for 5 hr., the mixture was treated with hydrogen sulfide gas as in the above experiment, and the crystals thereby obtained were recrystallized from methanol to give XIX (30 mg.) as yellow needles, m. p. 201°C (decomp.).

Found: C, 46.99; H, 4.28; N, 4.78. Calcd. for $C_{11}H_{12}O_3NBr$: C, 46.17; H, 4.23; N, 4.90%. λ_{max}^{MeOH} mμ (log ε); 244 (4.36), 330 (4.03).

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