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NITROANTHRAPYRIDONES

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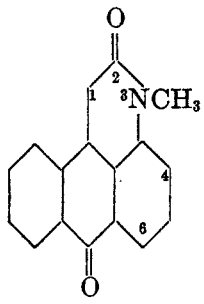
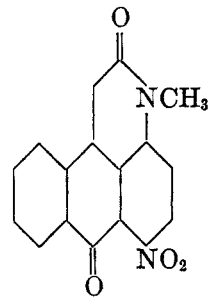
Certain α-toluidinoanthraquinones, when treated with dilute nitric acid, were oxidatively degraded to hydroxyanthraquinones (1). When an acetic acid solution of the dye, Alizarin Rubinol R (2), was treated with a few drops of nitric acid, a reddish solid separated quickly. Upon analysis, this new substance gave values which indicated that the sulfonic acid group had been replaced by a nitro group. The red compound is, thus, a nitroanthrapyridone.

A survey of the literature revealed but one nitroanthrapyridone. Seka (3) described a mononitroanthrapyridone, obtained by treating anthrapyridone with fuming nitric acid. The position of the nitro group was not determined, but he concluded that it must be in the heterocyclic ring, since it was easily replaced by aromatic amines—a conclusion which, as it will appear, was not entirely justified. Owing to the paucity of information in this field, the preparation of nitroanthrapyridones, together with a study of their behavior in chemical reactions, was undertaken.

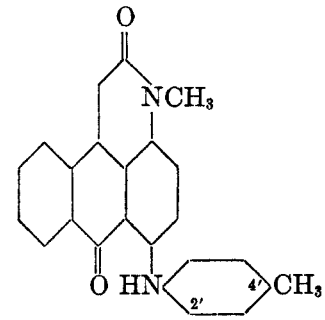
3-Methylanthrapyridone, I, gives the 6-nitro derivative, II, when treated with fuming nitric acid. The nitro group is replaced very easily by a toluidine residue when the substance is heated with *p*-toluidine. The 3-methyl-6-*p*-toluidinoanthrapyridone, III, is a known compound (4, 10); the specimen secured from the nitroanthrapyridone was identical with one prepared in the usual way from 3-methyl-6-bromoanthrapyridone. It was also sulfonated to give the dye, Alizarin Rubinol R, which was identical with an authentic specimen. Two conclusions are obvious: (a) upon nitration, the nitro group enters the 6-position, and (b) the nitro group is replaced very easily by a weakly basic group, such as toluidine.



I



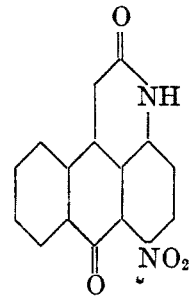
II



III

These observations suggest that Seka's mononitro derivative is, in fact, 6-nitroanthrapyridone, IV; unfortunately, none was available for comparison. All attempts to repeat Seka's nitration have been unsuccessful; either the starting material was recovered unchanged, or it was converted to a mixture

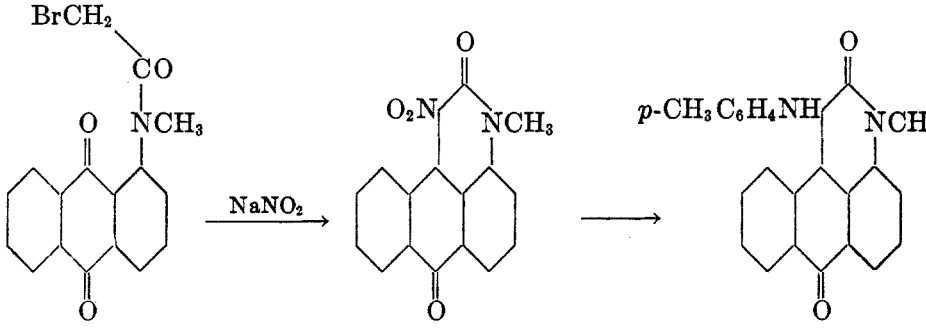
of low-melting products. Attempts to form IV by ring closure of 1-acetamino-4-nitroanthraquinone resulted in hydrolysis only.



IV

With the object of securing an anthrapyridone having the nitro group in the heterocyclic ring, 3-methyl-6-bromoanthrapyridone, V, was treated with fuming nitric acid, but it was recovered unchanged. That is, direct nitration does not occur in the heterocyclic ring system when the other position, susceptible to substitution, is blocked.

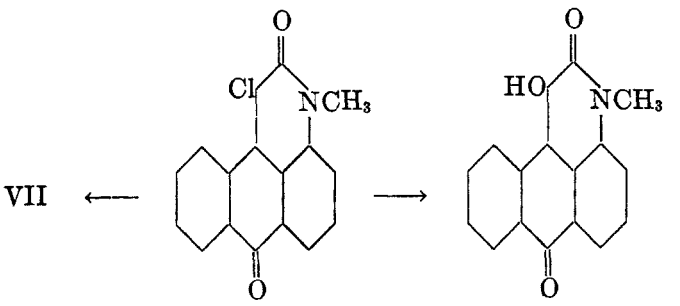
However, 1-nitro-3-methylanthrapyridone, VI, was secured by a novel reaction, the ring closure of N-bromoacetyl-1-methylaminoanthraquinone, using sodium nitrite.



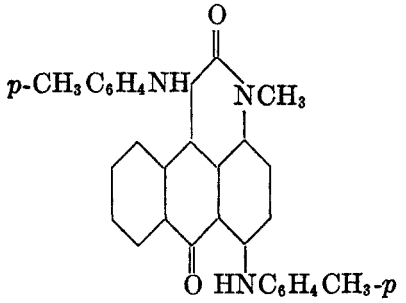
XVII VI VII

The nitro group is easily replaced by a toluidino group, on heating with *p*-toluidine, but the 1-*p*-toluidino-3-methylanthrapyridone, VII, is deep yellow, not red. Thus, it appears that nitro groups in both the 1- and 6-positions are easily displaced, but that only the 6-substituted anthrapyridones are highly colored.

While it seems obvious from the synthesis that the nitro group is in the 1-position, proof was obtained in three ways. The 1-chloro derivative, VIII, which is described in the literature (5), was prepared and (a) converted into the same 1-*p*-toluidino derivative, VII, and (b) into the known 1-hydroxy-anthrapyridone, IX, (6); the latter was also obtained by a hydrolysis of the 1-nitroanthrapyridone, VI. In addition, the same 1,6-ditoluidinoanthrapyridone, X, was synthesized from both 1-chloro-3-methyl-6-bromo- and 1-nitro-3-methyl-6-bromo-anthrapyridones.



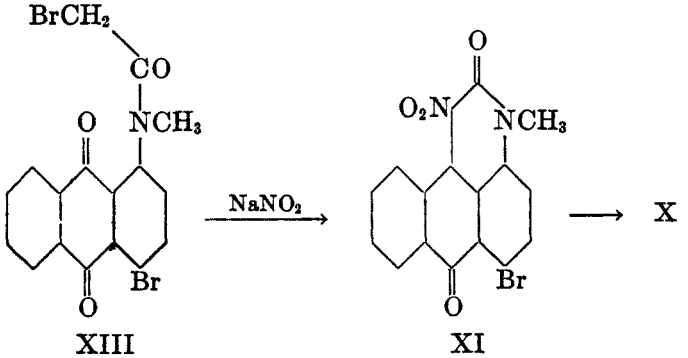
VIII IX



X

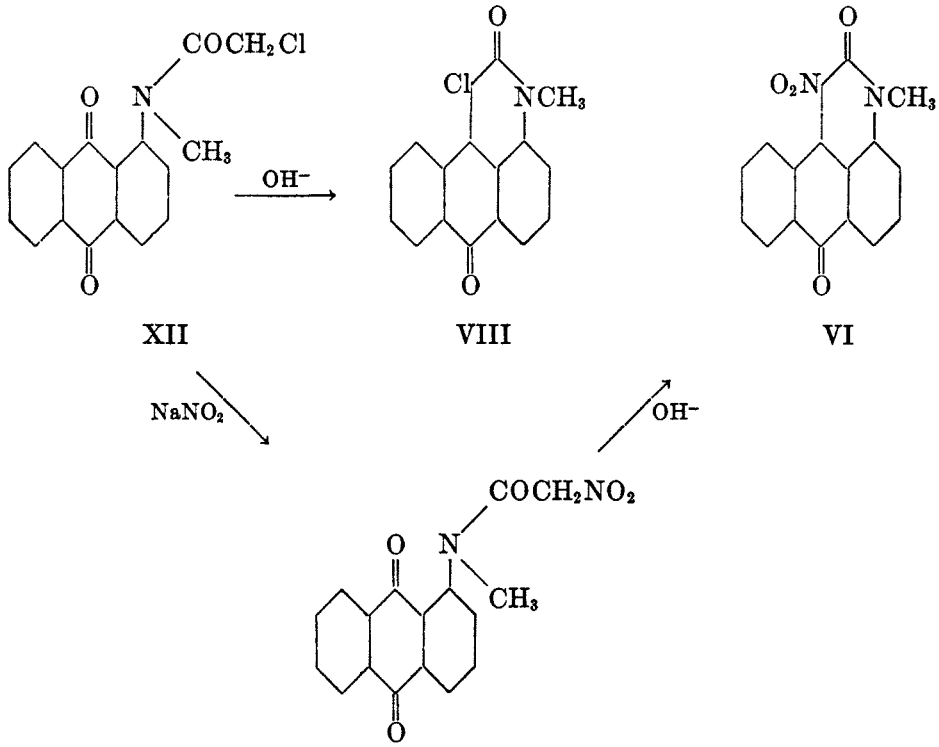
The 1-chloro-3-methylanthrapyridone, VIII, was prepared by the action of sulfuryl chloride upon 3-methylanthrapyridone in hot nitrobenzene solution (8). After treatment with *p*-toluidine, a very small amount of red 1,6-di-*p*-toluidinoanthrapyridone, X, was isolated; this indicated that the monochlorinated product was contaminated with a little 1,6-dichloro-3-methylanthrapyridone. It may be concluded that chlorination takes place preferentially in the 1-position (in contrast to nitration), but that the 6-position can also be substituted at a much slower rate.

The 1-nitro-3-methyl-6-bromoanthrapyridone, XI, was also prepared by a ring closure of N-bromoacetyl-1-methylamino-4-bromoanthraquinone by means of sodium nitrite, but 1-chloroacetaminoanthraquinone did not appear to react with sodium nitrite, being recovered unchanged.



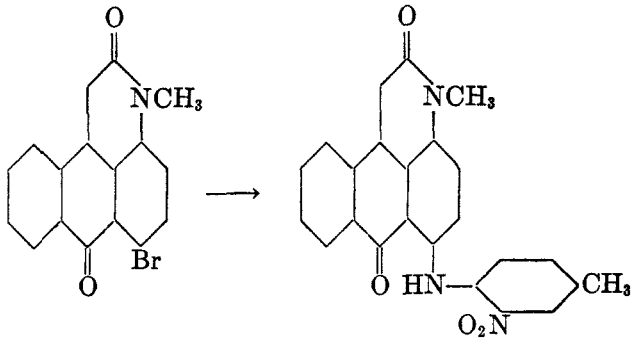
XIII XI

The new reaction described, formation of 1-nitroanthrapyridones by a ring closure from 1-haloacetylmethylaminoanthraquinones by means of alkali nitrite, could be explained in several ways. For example, the chlorine atom could be replaced by the nitro group, with subsequent ring closure. Alternatively, cyclization to the 1-chloroanthrapyridone could take place first, followed by a replacement of the halogen.



The available evidence, which favors the first mechanism, is as follows: (a) so far, it has not been found possible to replace the chlorine in 1-chloro-3-methylanthrapyridone by a nitro group, using alkali nitrite; (b) a by-product in the reaction appears to be N-hydroxyacetyl-1-methylaminoanthraquinone; this substance is not cyclized by sodium nitrite under the same conditions. This suggests that replacement reactions take place more readily in the open-chain compounds.

All these facts render it highly improbable that in the nitroanthrapyridone obtained by the action of *dilute* nitric acid upon Alizarin Rubinol R, the nitro group is attached to the heterocyclic ring; it appears more likely that it is on the toluidine ring. This conclusion was verified by treating 3-methyl-6-bromoanthrapyridone with 3-nitro-4-aminotoluene; the new nitroanthrapyridone, XIV, was found to be identical with the one prepared from the dye, Alizarin Rubinol R, and dilute nitric acid.



V XIV

When the dye base III is treated with concentrated nitric acid, a tetranitro derivative is obtained; apparently, the introduction of the basic toluidino group facilitates nitration. No attempt was made to locate the position of these nitro groups.

Some of the spectral absorption characteristics of these anthrapyridones are shown in Fig. 1.

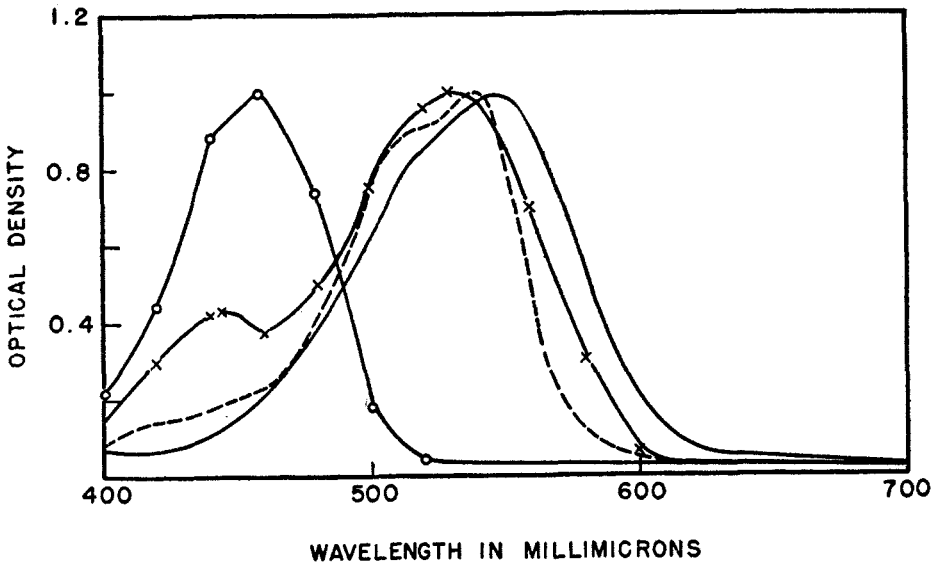


FIG. 1. 3-METHYLANTHRAPYRIDONES.

—— o —— o —— 1-*p*-Toluidino
—— x —— x —— 1,6-Di-*p*-toluidino
—— —— —— 6-(2′-Nitro-*p*-toluidino)
———————— 6-*p*-Toluidino

EXPERIMENTAL

A. *Starting materials.*[1] Many of the polynuclear intermediates required for this work are only mentioned in the patent literature, so their preparation is given in some detail.

[1] We take pleasure in acknowledging the assistance of Miss E. R. Webster in the preparation of some of these substances.

The use of the newer types of solvents, such as ethylene glycol monoethers and esters (7, 9), has been advantageous in those instances in which the nitrogen bears a substituent group. The laurylated compounds are new.

1-Laurylaminoanthraquinone, XV. A mixture of 12 g. of α-chloroanthraquinone, 30 g. of techn. laurylamine, and 60 cc. of pyridine was refluxed for 18 hours, and the cooled solution diluted with two volumes of methanol. The product was filtered and recrystallized from ether; the brilliant red substance, m.p. 86–87°, was obtained in a yield of 12 g. (63%). A run nine times this size gave the same per cent yield.

Anal. Calc'd for $C_{26}H_{33}NO_2$: C, 79.8; H, 7.4.
Found: C, 79.9; H, 7.6.

1-Laurylamino-4-bromoanthraquinone, XVI, was formed on brominating the laurylated derivative, employing the procedure described for 1-methylamino-4-bromoanthraquinone (16); 46 g., m.p. 67–68°, of the carmine bromoamine were obtained from 50 g. of 1-laurylaminoanthraquinone, 150 cc. of pyridine, and 35 cc. of bromine. It was recrystallized from methanol-ether (2:1).

Anal. Calc'd for $C_{26}H_{32}BrNO_2$: Br, 17.0. Found: Br, 16.9.

N-*Chloroacetyl-1-methylaminoanthraquinone*, XII, was prepared by refluxing for 20 minutes a mixture of 15 g. of 1-methylaminoanthraquinone, 150 cc. of benzene, and 15 cc. of chloroacetyl chloride; the initial red color became yellow. The hot mixture was filtered, and the product crystallized on cooling; the yield was 15 g. (75%), m.p. 170–171.5°.

The N-*bromoacetyl-1-methylamino-* (XVII, m.p. 162°) and N-*chloroacetyl-1-methylamino-4-bromo-anthraquinones* (XVIII, m.p. 239°) were obtained by a similar procedure, but xylene was used as a solvent in preparing the N-bromoacetyl-1-methylamino-4-bromoanthraquinone, XIII; the latter substance, after recrystallization from ethylene glycol monoethyl ether, had the melting point 233°.

Anal. Calc'd for $C_{17}H_{12}ClNO_3$ (XII): C, 65.2; H, 3.8; for $C_{17}H_{12}BrNO_3$ (XVII): Br, 22.3.
Found: (XII) C, 65.0; H, 4.1; (XVII) Br, 22.2.

1-Carboxyanthrapyridone was obtained by hydrolysis of the corresponding ester. To a solution of 50 g. of potassium hydroxide, 75 cc. of water, and 100 cc. of alcohol was added 13 g. of 1-carbethoxyanthrapyridone (14, 15), and the mixture refluxed, with stirring, for 5 hours; it was then poured into dilute hydrochloric acid, and the crude acid filtered. This product was extracted with dilute sodium carbonate solution, and the filtered solution chilled; the sodium salt of the acid crystallized in a yield of 10.8 g. (85%). This was converted to the free acid by means of hot, dilute hydrochloric acid. When heated in a capillary tube the acid appears to lose carbon dioxide without melting, and then melts about 400° with decomposition.

Anal. Calc'd for $C_{17}H_9NO_4$: C, 70.1; H, 3.1.
Found: C, 70.0; H, 3.0.

When attempts were made to hydrolyze 1-carbethoxy-3-methylanthrapyridone by this procedure, it was simultaneously decarboxylated to 3-methylanthrapyridone; the free acid could not be isolated.

It may be pointed out that many reactions exhibited by 3-methylanthrapyridone and 1-methylaminoanthraquinone cannot be duplicated with the unmethylated substances.

Anthrapyridone was prepared by decarboxylation of the above finely-ground carboxylic acid to which a trace of copper-bronze had been added (15) by heating for 2 hours at 285–295°. After four successive nitrobenzene extractions, a 65% yield of anthrapyridone, m.p. 406–407°, was obtained. The general procedure, in which 1-acetylaminoanthraquinone is heated with alkaline catalysts (17) gave very poor yields of a product very difficult to purify.

It may also be mentioned at this point that ring closure of N-propionyl-1-methylamino- and N-(ω-carbethoxyacyl)-1-methylaminoanthraquinones could not be accomplished under any conditions employed.

3-Methylanthrapyridone, I, was obtained by dissolving 4 g. of N-acetyl-1-methylaminoanthraquinone (4) in 25 cc. of ethylene glycol monoethyl ether at 110–120°, and adding 1 g. of potassium hydroxide in 1 cc. of water; the solid that separated was filtered after cooling. The yield of product, m.p. 268–269°, was 3.5 g. (93%); when recrystallized from the same

solvent or from nitric acid, the melting point was raised to 273°. This procedure is far better than those previously described, which require heating with dilute alkali for many hours (4) or involve methylation of anthrapyridone (3). The 6-bromo- derivative, V, was prepared in a similar manner; it melted at 282° after recrystallization [Dupont (8) gave 278°]. 4-Nitro-1-acetaminoanthraquinone (11) was hydrolyzed to the nitroamine, when submitted to this procedure.

B. *Ring closures. 1-Nitro-3-methylanthrapyridone*, VI. To a warm solution of 3 g. of N-bromoacetyl-1-methylaminoanthraquinone in 25 cc. of ethylene glycol monoethyl ether was added a concentrated aqueous solution of 1 g. of sodium nitrite; in a short time a solid separated. The new substance was filtered and recrystallized once from the reaction-solvent and once from nitrobenzene; it melted at 335–336° with decomposition.

Anal. Calc'd for $C_{17}H_{10}N_2O_4$: C, 66.7; H, 3.3; N, 9.2.
Found: C, 66.6; H, 3.3; N, 9.2.

No attempt was made to determine the conditions for an optimum yield; the 1-chloroacetyl derivative appeared to give a larger quantity (32%).

On longer standing the filtrate deposited a second substance, probably N-glycolyl-1-methylaminoanthraquinone, which, after recrystallization from the reaction-solvent, melted at 247°.

Anal. Calc'd for $C_{17}H_{13}NO_4$: C, 69.2; H, 4.4; N, 4.7.
Found: C, 69.7; H, 3.7; N, 5.0.

The *1-nitro-3-methyl-6-bromoanthrapyridone*, XI, was made by the same procedure but using β-hydroxyethyl acetate as a solvent. After recrystallization from nitrobenzene it melted at 332–334°.

Anal. Calc'd for $C_{17}H_9BrN_2O_4$: Br, 20.8. Found: Br, 20.9.

1-Chloroacetaminoanthraquinone (12) was recovered with unchanged melting point (222°) after a similar treatment, but 1-acetamino-4-nitroanthraquinone (11) was hydrolyzed to the known 1-amino-4-nitroanthraquinone (m.p. 298–300°) (13); when potassium acetate was substituted for the hydroxide, the acetyl derivative was recovered unchanged (m.p. 260–262°), but after 16 hours in boiling nitrobenzene the substance was charred.

C. *Nitrations.* (a) *Use of concentrated acid.* To 10 cc. of nitric acid (sp. gr. 1.59) was added 2.7 g. of 3-methylanthrapyridone (4, 10), and after 5 minutes the solution was poured into water. The washed and dried residue (3 g.) was recrystallized from nitrobenzene; 3-methyl-6-nitroanthrapyridone, II, melts at about 385° with decomposition.

Anal. Calc'd for $C_{17}H_{10}N_2O_4$: C, 66.7; H, 3.3; N, 9.2.
Found: C, 66.8; H, 3.3; N, 9.3.

3-Methyl- and 3-methyl-6-bromo-anthrapyridones were recrystallized unchanged from nitric acid (sp. gr. 1.49); the latter was thereby "purified" so that the melting point was raised from 275° (8) to 281°. Nitric acid (sp. gr. 1.59) degraded the second substance but no homogeneous substance could be isolated from the reaction product.

All attempts to nitrate anthrapyridone following Seka's directions (3), or by using other strengths of acid resulted in either the recovery of unchanged starting material, or the production of mixtures from which no single pure substance could be isolated.

When 1 g. of 3-methyl-6-*p*-toluidinoanthrapyridone, III, (10) was added to 7.5 cc. of nitric acid (sp. gr. 1.41), there was a rise in temperature and an evolution of oxides of nitrogen. After pouring the mixture into water, extracting the solid with methanol several times, and recrystallizing from chlorobenzene, deep red crystals of a tetranitro derivative were obtained. These did not melt, but turned black at 275–280°.

Anal. Calc'd for $C_{24}H_{14}N_6O_{10}$: C, 52.8; H, 2.6; N, 15.4.
Found: C, 53.0; H, 3.0; N, 14.9.

(b) *Use of dilute acid; 3-methyl-6-(2'-nitro-4'-methylanilino)anthrapyridone*, XIV. When 1 cc. of nitric acid (sp. gr. 1.41) was added to a warm solution of 1.1 g. of 3-methyl-6-*p*-toluidinoanthrapyridone in 50 cc. of acetic acid, the magenta color disappeared at once, and a red precipitate formed. This was collected and recrystallized, first from nitroben-

zene and then from trichlorobenzene. It melted rather poorly at 350–355°, and darkened at 320–350°.

Anal. Calc'd for $C_{24}H_{17}N_3O_4$: C, 70.1; H, 4.1; N, 10.2.
Found: C, 70.3; H, 4.4; N, 10.4.

The same substance was also formed when 20 g. of the dye, Alizarin Rubinol R, in 2 l. of hot water was treated with 100 cc. of nitric acid (sp. gr. 1.41).

Synthesis. A mixture of 1.4 g. of 3-methyl-6-bromoanthrapyridone (4), 1 g. of 3-nitro-4-aminotoluene, 0.5 g. of sodium acetate, a trace of copper acetate, and 15 cc. of trichlorobenzene was heated, with stirring, for 10 hours at 180°; it was finally heated to the boiling point and filtered. The product was recrystallized, and found to be identical with the specimens previously described, by analysis, melting point behavior, and absorption curve (Fig. 1).

When a purified specimen of the commercial dye, Brilliant Alizarin Light Red B, was dissolved in water and treated with nitric acid in a similar manner, it gave a red nitro derivative. The latter crystallized well from trichlorobenzene and pyridine. It did not melt up to 400°, but turned black at about 320°.

Anal. Calc'd for $C_{28}H_{18}ClN_3O_6$: N, 8.4; Cl, 7.0.
Found: N, 8.0; Cl, 7.2.

D. *Replacement reactions. 1-p-Toluidino-3-methylanthrapyridone*, VII. A mixture of 2 g. of 1-nitro-3-methylanthrapyridone, 1 g. of sodium acetate, and 15 g. of *p*-toluidine was heated, with stirring, at 175° for 4 hours. After pouring it into methanol and recrystallizing the solid from benzene-methanol, the deep yellow toluidino derivative melted at 239°.

Anal. Calc'd for $C_{24}H_{18}N_2O_2$: C, 78.7; H, 4.9; N, 7.7.
Found: C, 78.5; H, 5.2; N, 8.1.

The same substance was obtained from 1-chloro-3-methylanthrapyridone (8) by the same procedure, except that a trace of copper acetate was added. The identity of the two products was shown by analysis, melting points, and absorption curves (Fig. 1).

3-Methyl-6-p-toluidinoanthrapyridone, III, was formed by stirring a mixture of 1.8 g. of the nitro compound, 1 g. of sodium acetate, a trace of copper acetate, and 15 cc. of *p*-toluidine for 4 hours at 160–175°, isolating by appropriate manipulation, and recrystallizing from hot benzene. It melted at 270–271° and was identical with a specimen prepared as directed in the patent literature (10) from 3-methyl-6-bromoanthrapyridone.

1,6-Di-p-toluidino-3-methylanthrapyridone, X, was obtained by the same procedure, and recrystallized from benzene; m.p. 246°. The absorption curve is shown in Fig. 1.

Anal. Calc'd for $C_{31}H_{25}N_3O_2$: N, 8.9. Found: N, 9.0.

As starting materials there were used both 1-nitro- and 1-chloro-3-methyl-6-bromoanthrapyridones. The ditoluidino derivative was also isolated from the reaction product from *p*-toluidine and 1-chloro-3-methylanthrapyridone; the latter had been prepared by the chlorination of 3-methylanthrapyridone with sulfuryl chloride (10). Apparently there was a little dichlorination.

1-Hydroxy-3-methylanthrapyridone, IX, was obtained in two ways, the characteristic potassium salt separating during the reaction. For example, the salt separated when a mixture of 1 g. of 1-nitro- or 1-chloro-3-methylanthrapyridone, 1 g. of potassium hydroxide, and 30 cc. of alcohol were digested for 18 hours. The yellow hydroxy compound resulted upon digesting the salt with concentrated hydrochloric acid on the steam-bath for two hours. It melted at 301–302° after recrystallization from acetic acid; the literature gives 280° (6).

SUMMARY

Introduction of substituents into 3-methylanthrapyridone takes place most readily in the 1- and 6-positions. Chlorinating agents appear to attack the

1-position preferentially, whereas nitration has been shown to occur only at the 6-position.

1-Nitro-3-methylanthrapyridones can be secured by ring closure of suitably constituted N-haloacetyl-1-methylaminoanthraquinones. The mechanism of this reaction is discussed.

Replacement of groups in the 1- and 6-positions by arylamines takes place very easily without noticeable preference; this reaction cannot be used, therefore, to distinguish the location of substituents between these positions.

When treated with dilute nitric acid, Alizarin Rubinol R gives a mononitro-3-methyl-6-toluidinoanthrapyridone, having the nitro group in the 2′-position of the toluidino group. With concentrated nitric acid, a tetranitro derivative is formed.

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