Summary

The reaction of 1-acetylamino-7-methoxynaphthalene with succinic anhydride in the presence of aluminum chloride using nitrobenzene as a solvent proceeds smoothly to give β-(1-acetylamino-7-methoxy-3-naphthoyl)-propionic acid in 86% yield. The structure of the reaction product has been established.

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The So-Called "Anthraquinonediimines"; Symmetrical Trisubstituted Triazines

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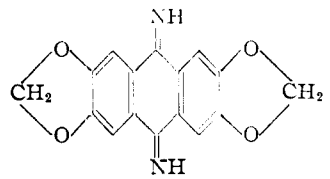
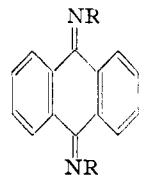
Some years ago Brown and Robinson[1] treated 3,4-methylenedioxybenzonitrile with chlorosulfonic acid in chloroform and obtained a substance that was sparingly soluble in the usual solvents, but dissolved in sulfuric acid to give a deep crimson solution. The color of the solution resembled those which are obtained with methoxyanthraquinones and sulfuric acid. On reduction with hydriodic acid followed by zinc dust distillation and subsequent oxidation a product was obtained which gave a positive color test in the oxanthranol reaction. This was interpreted as indicating the presence of anthracene. From these properties and the analysis of the compound, and despite the recorded fact that the substance was unchanged by boiling hydrochloric acid, Brown and Robinson assigned to it the structure I.



I



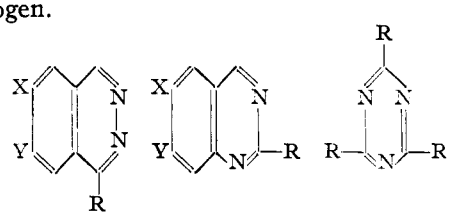
II

Later Keffler[2] attempted a molecular weight determination on the substance but found it so insoluble that he was unable to accomplish his purpose. However, he synthesized two closely related products from veratronitrile and 3-methoxy-4-ethoxybenzonitrile and found them sufficiently soluble in thymol to make possible molecular weight determinations by the cryoscopic method. On the basis of the results he concluded that the products were dimerides of the related nitriles and that the Brown and Robinson formulation was correct.

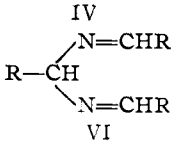
However, the properties recorded for these substances do not resemble those of 9,10-diiminoanthracene (II, R = H). The latter is prepared from the corresponding diamino compound with silver oxide, is soluble in ether, and is easily changed to anthraquinone with aqueous acids.[3] The latter property is also observed for the substituted diiminoanthracenes (II, R = C_6H_5, $CH_3C_6H_4$, etc.).[4] The great stability of the compounds reported by Keffler[2] toward concentrated hydrochloric acid is not compatible with the properties of the simple, unsubstituted 9,10-diiminoanthracene (II, R = H). It is difficult to believe that the substituents would alter this property of the diimine so markedly.

Since substituted anthraquinones that should be obtainable from these diiminoanthracenes were required in connection with another problem in these Laboratories, they were investigated further. A Zerewitinoff determination on the "piperonitrile dimer," prepared as described by Keffler,[2] showed no active hydrogen. This is not in agreement with the proposed structure, which should show two active hydrogens.

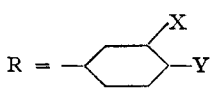
It is possible for the nitriles to polymerize in other ways. Thus they may dimerize by the diene synthesis to give phthalazines (III) or quinazolines (IV), or they may trimerize to triazines of structure V. Unlike the diiminoanthracene structure (I) these compounds would have no active hydrogen.

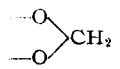


III IV V



VI



where X = Y = OCH_3, or X + Y = 

A literature survey revealed that the triazine (V, X + Y = $-OCH_2O-$) has been prepared by two different methods, and, surprisingly enough, the melting points recorded were the same as those given by Robinson[1] and Keffler[2] for the so-called dimer. In one of these methods[5] nitro-

(1) Brown and Robinson, *J. Chem. Soc.*, **111**, 957 (1917).
(2) Keffler, *J. Chem. Soc.*, **119**, 1476 (1921).
(3) German Patent 590,366 [*Frdl.*, **19**, 1908 (1934)].
(4) German Patent 529,484 [*Frdl.*, **19**, 1907 (1934)].
(5) Davis, *J. Chem. Soc.*, **87**, 1835 (1905),

gen tetrasulfide (N_4S_4) was digested with piperonal for forty-six hours and the triazine (m. p. 266°) was obtained, along with the sulfate of 3,4-methylenedioxybenzamidine. In the other method[6] "piperhydramide" (VI, X + Y = O—CH_2—O—) was prepared[7] and oxidized with iodine and sodium carbonate to form the triazine (m. p. 265°). In this work the triazine was prepared by the latter method and, after recrystallization from pyridine, melted at 270°, and showed no depression of the melting point when mixed with the compound obtained by Robinson's procedure.

This established the identity of the two compounds. There still remained the question of molecular weight which led Keffler to report the compounds as dimers. As the author pointed out, molecular weight determinations were made difficult because of the insolubility of the substances in most solvents. Since the methoxy derivative is the most soluble of the compounds under consideration, it was used in this work for molecular weight determinations. Use of the cryoscopic method proved unreliable so attention was turned to the ebullioscopic method.

The molecular weight of a closely related product obtained by the action of nitrogen sulfide on *p*-methoxybenzonitrile has been determined by the ebullioscopic method and the results are in agreement with the trimeric formula.[8] This method was applied to the compound in question using pyridine as a solvent. The values obtained for the molecular weight show that the compound is trimeric. There can be little doubt, therefore, that the so-called "anthraquinonediimines" of Keffler and Robinson are in reality trisubstituted triazines.

Since Keffler's molecular weight determinations had indicated that the compounds were dimeric, two possible dimeric substances were synthesized prior to investigating a trimeric form: the phthalazine (III, X + Y = —O—CH_2—O—) and the quinazoline (IV, X + Y = —O—CH_2—O—). The phthalazine was synthesized by condensing piperonoylhydrazine[9] with piperonal followed by ring closure with hydrogen chloride in amyl alcohol.[10] The quinazoline was prepared by treating the product from 6-aminopiperonal[11] and piperonoyl chloride with ammonia under pressure. An attempt to cyclize the Schiff base from piperonal and 6-aminopiperonitrile was abandoned when the quinazoline was obtained by the method described above.

The mechanism of the formation of a triazine is doubtful, but it can be accounted for by an extension of the ideas of Alder[12] and Kilpatrick.[13]

(6) Bougault and Robin, *Compt. rend.*, **169**, 978 (1919); Robin, *Ann. chim.*, [9] **16**, 120 (1921).
(7) Wallach, *Ber.*, **14**, 792 (1881).
(8) Francis and Davis, *J. Chem. Soc.*, **85**, 1537 (1904).
(9) McFadyen and Stevens, *ibid.*, 584 (1936).
(10) Aggarival, Darbari and Ray, *ibid.*, 1941 (1929).
(11) Marr and Bogert, THIS JOURNAL, **57**, 1329 (1935).
(12) Alder, *Die Chemie*, **55**, 55 (1942).
(13) Kilpatrick, THIS JOURNAL, **69**, 42 (1947).

Experimental

1,3,5-Tri-(3',4'-methylenedioxyphenyl)-*s*-triazine (V, X + Y = —O—CH_2—O—).—The so-called "2,3,6,7-dimethylenetetraoxyanthraquinonediimine" was prepared by the procedure described previously.[1,2] On recrystallization from pyridine it melted at 270°.

The triazine was also prepared by oxidizing "piperhydramide" (VI, X + Y = —O—CH_2—O—),[7] with iodine and potassium carbonate, as described by Robin.[6] The product obtained was recrystallized from pyridine, melted at 270°, and showed no depression of the melting point when mixed with the substance obtained by Robinson's procedure.

1,3,5-Tri-(3',4'-dimethoxyphenyl)-*s*-triazine was prepared by Keffler's procedure.[2] It melted, when recrystallized from pyridine, at 263°. A molecular weight determination by the cryoscopic method with *p*-bromophenol as a solvent gave the following results: 0.2 g. of the polymeric nitrile in 10 g. of *p*-bromophenol gave a depression of 0.68°, from which the molecular weight is 329 (calcd. for a dimer 326), the constant for *p*-bromophenol being 11.2. However, the substance gave a deep yellow solution in *p*-bromophenol indicating that some change had occurred. As a result other solvents were investigated. Cyclopentadecanone has a fairly high constant (21.3),[14] but the triazine crystallized from it above the setting point at a dilution of 1.4 parts per 100. With 2-aminopyridine the same difficulty was experienced. It is entirely possible that this crystallization above the setting point may be taking place also with the phenolic solvents, thymol and *p*-bromophenol. With camphor as a solvent it was found difficult to obtain consistent results.

When the ebullioscopic method was applied, pyridine was used as the solvent. The constant (K_{1000}) was determined using acetanilide, *p*-amino-N-ethylacetanilide, and *p*-nitrophenylacetonitrile as reference compounds. The average of the values thus obtained, 2.65, 2.68 and 2.63, respectively, was used as the constant. With this value 0.5115 g. of the methoxy derivative in 44.8380 g. of pyridine gave a boiling point elevation of 0.070° from which the molecular weight is 488; similarly, 1.0027 g. of the methoxy derivative in 46.7087 g. of pyridine gave a boiling point elevation of 0.115° from which the molecular weight is 494. Since the calculated value for a trimer is 489 the conclusion that the compounds are triazines is inevitable.

Piperonal-β-(3,4-methylenedioxybenzoyl)-hydrazone was made by condensing piperonal with piperonoylhydrazine,[9] as described for an analogous compound[10]; 5.4 g. of piperonal and 6 g. of the hydrazine were refluxed for two hours in 60 ml. of alcohol containing 1 ml. of 40% sodium hydroxide (later it was found that the alkali was unnecessary). The solid that separated on cooling was collected and washed with alcohol. The yield was 9.7 g.; m. p. at about 210–220°, with preliminary darkening at about 205°. A sample recrystallized from alcohol melted at 193–196°, but if the melting-point tube was inserted in a bath preheated to 150°, there appeared to be decomposition. The substance reacted similarly when recrystallized from propanol, acetic acid, or ethyleneglycolmonomethyl ether. For analysis, the material recrystallized from alcohol was dried in a vacuum oven at 110°.

Anal. Calcd. for $C_{16}H_{12}N_2O_5$: C, 61.5; H, 3.8; N, 8.9. Found: C, 61.3; H, 3.9; N, 8.8.

1-(3',4'-Methylenedioxyphenyl)-6,7-methylenedioxyphthalazine.—The hydrazone (4 g.) was added to 50 ml. of amyl alcohol which had been saturated at 10–15° with hydrogen chloride. The mixture was heated for one hour on the steam-bath and a further hour with a free flame. The resulting mixture was transferred to a beaker and the solvent allowed to evaporate spontaneously. When almost dry, the residue was digested with benzene and filtered. The remaining solid was shaken with 50 ml. of 10% sodium hydroxide, filtered, washed with water, and dried. One crystallization from alcohol gave 0.5 g.

(14) Giral, *Anales soc. espan. fis. quim.*, **33**, 438 (1935) [*C. A.* **29**, 6489 (1935)].

of a buff-colored product melting at 203–204°. It was recrystallized from a small volume of ethyl acetate.

Anal. Calcd. for $C_{16}H_{10}N_2O_4$: C, 65.3; H, 3.4; N, 9.5. Found: C, 64.6, 64.9; H, 3.4, 3.8; N, 9.5.

When the reaction was run in chloroform with phosphoryl chloride as the condensing agent, an imidchloride, which is probably an intermediate, was obtained. It melted at 166–167° after recrystallization from benzene.

Anal. Calcd. for $C_{16}H_{11}ClN_2O_4$: C, 58.2; H, 3.3; N, 8.5. Found: C, 58.0; H, 3.2; N, 8.6.

Veratroylhydrazine.—A mixture of 10 g. of methyl veratrate, 12 ml. of ethyl alcohol, and 10 ml. of 80% hydrazine hydrate was refluxed for two hours. The product was isolated by dilution with water and cooling; it was collected and recrystallized from alcohol. The yield was 6.7 g., m. p. 145°.

Anal. Calcd. for $C_9H_{12}N_2O_3$: N, 14.3. Found: N, 14.5.

Veratral β-(3,4-Dimethoxybenzoyl)-hydrazone.—A solution of 6.7 g. of veratroylhydrazine and 6 g. of veratral in 50 ml. of alcohol was treated with 1 ml. of 40% sodium hydroxide and refluxed for two hours. The clear, colored solution was allowed to cool (overnight) and the solid that formed collected on a filter. The solid was digested with 200 ml. of alcohol and again filtered. The yield was 6.5 g.; m. p. 198–205°. Recrystallization of the material from acetic acid or ethyleneglycolmonomethyl ether gave products that still showed indefinite melting points. The crude material was analyzed.

Anal. Calcd. for $C_{18}H_{20}N_2O_5$: C, 62.7; H, 5.8; N, 8.1. Found: C, 61.5; H, 5.8; N, 8.1.

1-(3′,4′-Dimethoxyphenyl)-6,7-dimethoxyphthalazine.—The hydrazone (5 g.) was placed in 50 ml. of amyl alcohol saturated with hydrogen chloride and heated under reflux for one hour on the steam-bath and for one hour at the boiling point. The cooled mixture was filtered and the solid shaken with 50 ml. of 10% sodium hydroxide. The solid was separated by filtration, washed with water, and recrystallized from alcohol. The yield of yellow crystals was 1.6 g.; m. p. 193–194°.

Anal. Calcd. for $C_{18}H_{18}N_2O_4$: C, 66.3; H, 5.5; N, 8.6. Found: C, 66.2; H, 5.9; N, 8.2.

6-Piperonoylaminopiperonal.—A mixture of 3.3 g. of 6-aminopiperonal,[11] 3.7 g. of piperonoyl chloride, 1.6 g. of pyridine, and 75 ml. of xylene was refluxed for one hour. The solution was filtered from a small amount of gummy material and the required product separated from the filtrate. The yield was 3.2 g.; m. p. 221°.

Anal. Calcd. for $C_{16}H_{12}NO_6$: C, 61.3; H, 3.5; N, 4.5. Found: C, 61.6; H, 4.0; N, 4.6.

This material was also prepared from the aminoaldehyde and the acid chloride in acetic acid containing sodium acetate. The yield was not as good.

2-(3′,4′-Methylenedioxyphenyl)-6,7-methylenedioxyquinazoline.—6-Piperonoylaminopiperonal (3 g.) was placed in a small pressure bottle, 125 ml. of ethanol added, and the mixture saturated with ammonia. The bottle was sealed and shaken for two and one-half hours at 80–85°. The mixture was cooled and filtered to recover the solid that separated. The yield was 2.5 g.; m. p. 248–249°. The solid was dissolved in xylene; the solution was decolorized and filtered. On cooling, yellow crystals of melting point 248–249° were obtained.

Anal. Calcd. for $C_{16}H_{10}N_2O_4$: C, 65.3; H, 3.4: N, 9.5. Found: C, 65.7; H, 3.8; N, 9.8.

6-Aminopiperonitrile.—6-Nitropiperonitrile[2] (20 g.) was added in portions to a solution of 100 g. of stannous chloride dihydrate in 100 ml. of hydrochloric acid. The temperature was maintained between 40–50° by cooling when necessary. When complete solution had resulted, the mixture was chilled in ice and treated slowly with sodium hydroxide solution until an excess had been added. During the addition, the temperature was maintained below 40°. The solid was collected on a filter, dried, and extracted with boiling methanol. On dilution with water, the methanol filtrate deposited, on cooling, 14 g. of pale yellow crystals; m. p. 142°.

Anal. Calcd. for $C_8H_6N_2O_2$: C, 59.3; H, 3.7; N, 17.3. Found: C, 59.2; H, 3.6; N, 17.0.

Schiff Base from 6-Aminopiperonitrile and Piperonal.—A solution of 8.7 g. of 6-aminopiperonitrile and 8.5 g. of piperonal in 170 ml. of alcohol was refluxed for one hour. The addition of a drop of sulfuric acid caused immediate formation of a precipitate. The mixture was allowed to reflux for one hour and then cooled. The solid was collected, washed with alcohol, and ether. The yield was 14 g., 88%. A small sample was recrystallized from alcohol; m. p. 184°.

Anal. Calcd. for $C_{16}H_{10}N_2O_4$: C, 65.3; H, 3.4; N, 9.5. Found: C, 65.9; H, 3.5; N, 9.4.

6-Aminoveratronitrile was prepared by a procedure very similar to that just described for 6-aminopiperonitrile. It was obtained in 82% yield and melted at 99–100°. McKee, McKee and Bost[15] record a melting point of 92–93.5° for the compound.

Summary

1. It has been shown that the so-called "anthraquinonediimines" obtained from certain nitriles are in reality triazine derivatives; the reaction is a trimerization rather than a dimerization, as originally reported.

2. The synthesis of certain quinazolines and phthalazines is described.

3. A procedure for the preparation of 6-aminopiperonitrile is given.

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(15) McKee, McKee and Bost, THIS JOURNAL, **68**, 1903 (1946).