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Studies of Quinazoline Pigments. II. Synthesis of Dimethyl Substituted Pyrido[2,1-*b*]pyrido[1′, 2′: 1, 2]pyrimido-[4,5-*g*]quinazoline-7,15-diones

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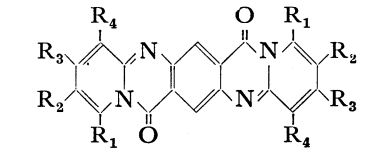
Synopsis. In the presence of alkali, 4,12-, 3,11-, 2,10-, and 1,9-dimethyl derivatives of 6, 14-dihydropyrido-[2,1-*b*]pyrido[1′,2′:1,2]pyrimido[4,5-*g*]quinazoline-7,15-dione reacted with nitrobenzene to give 2,5-bis(3-, 4-, 5-, and 6-methyl-2-pyridylamino) terephtharic acids. The intramolecular cyclization of 3-, 4-, and 5-methyl derivatives, gave 4,12-, 3,11-, and 2,10-dimethylpyrido[2, 1-*b*]pyrido[1′,2′: 1,2] pyrimido[4, 5-*g*]quinazoline-7,15-dione respectively, but the 6-methyl derivative did not give any cyclization product. The synthesis of the 1,9-dimethyl derivative was accomplished by the dehydrogenation of 1, 9-dimethyl-6, 14-dihydropyrido-[2,1-*b*]pyrido[1′,2′: 1,2]pyrimido[4,5-*g*]quinazoline-7, 15-dione with *p*-chloranil.

Recently, pyrido[2,1-*b*]pyrido[1′,2′: 1,2]pyrimido-[4,5-*g*]quinazoline-7,15-diones (**1**) have been reported to be valuable red pigments with excellent light-fastness and good tinctorial strength, but their published chemistry is still very limited. Although Wiedemann mentioned the synthesis of **1** by the dehydrogenation of 6, 14-dihydropyrido [2, 1-*b*] pyrido [1′, 2′: 1, 2] pyrimido-[4, 5-*g*] quinazoline-7, 15-diones (**2**), he reported no details.[1)]

In our previous paper, we described that the dehydrogenation of **2a** with a nitro compound in the presence of alkali is accompanied by ring opening to give 2,5-bis(2-pyridylamino)terephthalic acid (**3a**), which is then cyclized by treatment with acid to form **1a**.[2)] This paper will describe the dehydrogenation of **2b—e** under alkali conditions to give **1b—e**.



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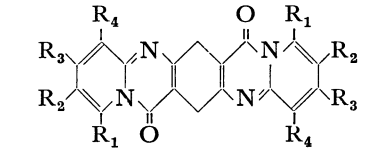

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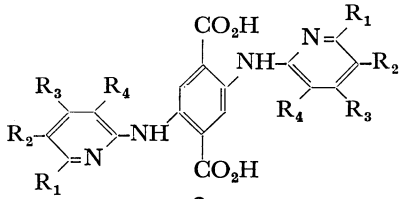

3

a : $R_1=R_2=R_3=R_4=H$
b : $R_1=R_2=R_3=H$, $R_4=CH_3$
c : $R_1=R_2=R_4=H$, $R_3=CH_3$
d : $R_1=R_3=R_4=H$, $R_2=CH_3$
e : $R_2=R_3=R_4=H$, $R_1=CH_3$

Results and Discussion

Diethyl 2,5-dioxocyclohexane-1,4-dicarboxylate reacts with 2-aminopyridine or substituted 2-aminopyridines under acid catalysis to give **2**.[1,3)] In glacial acetic acid, **2a** was obtained in an 80% yield, but the yields of **2b—d** were 50—65%. In the case of **2e**, under the same reaction conditions, only a 16% conversion was observed (Table 1). The low yield of **2e** is attributable to the steric hindrance of the methyl group.

The reactions of **2b—d** with nitrobenzene in the

Table 1. Physical properties of compounds **2**, **3**, and **1**

Compound	**2** Yield %	**2** NMR (δ)[a)] $H_{6,14}$	**2** NMR (δ)[a)] CH_3	**3** Found (Calcd) N%	**3** IR (cm^{-1}) νC=O	**3** NMR (δ)[b)] phenyl	**3** NMR (δ)[b)] CH_3	**1** Yield[c)] %	**1** Color	**1** Found (Calcd) N%	**1** IR (cm^{-1}) νC=O	**1** NMR (δ)[a)] $H_{6,14}$	**1** NMR (δ)[a)] CH_3
a	80	4.36 s 4H	—	15.97 (16.00)	1685	8.50 s 2H	—	97	red	17.79 (17.83)	1690	9.00 s 2H	—
b	50	4.39 s 4H	2.80 s 6H	14.81 (14.81)	1690	9.06 s 2H	2.30 s 6H	76	orange	16.52 (16.37)	1695	9.12 s 2H	2.87 s 6H
c	60	4.30 s 4H	2.78 s 6H	14.88 (14.81)	1680	8.43 s 2H	2.28 s 6H	97	red	16.46 (16.37)	1690	8.92 s 2H	2.80 s 6H
d	65	4.32 s 4H	2.67 s 6H	14.76 (14.81)	1680	8.41 s 2H	2.22 s 6H	97	red	16.18 (16.37)	1680	8.98 s 2H	2.68 s 6H
e	16	4.10 s 4H	3.22 s 6H	14.32 (14.81)	1670	8.04 s 2H	2.40 s 6H	69	orange	16.32 (16.37)	1690	8.72 s 2H	3.28 s 6H

a) Measured in CF_3COOH, with TMS as the internal standard. b) **3a—d**: in CD_3OD–NaOD; internal standard: TMS, **3e**: in D_2O–NaOD; internal standard: TSP. c) In overall yield from **2**.

presence of alkali gave **3b—d**, which cyclized easily to **1b—d** under acidic conditions. Since **3e** was not cyclized to **1e** under the same conditions, the synthesis of **1e** was achieved by heating **2e** with chloranil in glacial acetic acid. Some pertinent data on **1**, **2**, and **3** are compared in Table 1.

The hydrolytic ring opening of **1e** took place both in aqueous sulfuric acid and in alkali. On the other hand, **1a—d** were hydrolyzed in aqueous alkali, but not in acid. The ring opening of the same ring system has been studied. That is, it has been reported that the ring opening of 3-ethoxycarbonyl-6-methylpyrido[1,2-*a*]-pyrimidin-4-one is accelerated by the methyl group at the 6-position.[4]

Compounds **1b—e** are red to orange crystals, soluble in aqueous sulfuric acid but only sparingly soluble in organic solvents.

Experimental

The IR spectra were taken with a Shimadzu IR-27G spectrophotometer, while the NMR spectra were determined with a Varian HA-100 high-resolution NMR spectrometer.

*6,14-Dihydropyrido[2,1-*b*]pyrido[1',2': 1,2]pyrimido[4,5-*g*]quinazoline-7,15-diones (2).* The reactions of diethyl 2,5-dioxocyclohexane-1,4-dicarboxylate and 2-aminopyridines were carried out according to the methods reported by Wiedemann[1] and the products, **2a—e**, were characterized in the way described in the literature.[2] The yields of **2a—e** are listed in Table 1.

*Dimethylpyrido[2,1-*b*]pyrido[1',2': 1,2]pyrimido[4,5-*g*]quinazoline-7,15-diones (1b—e).* *a*): A mixture of 5.0 g of **2b**, 5.0 g of sodium *m*-nitrobenzenesulfonate, 10 g of a 50 wt% aqueous sodium hydroxide solution, and 100 ml of ethylene glycol was placed in a 500-ml round-bottomed flask equipped with a reflux condenser and a mechanical stirrer. The mixture was boiled and stirred under reflux for 2 h. The reaction mixture was allowed to cool to about 60 °C, diluted with 300 ml of cold water, and then neutralized with aqueous sulfuric acid. Pale yellow solids were collected on a filter, washed with water, and dried at 60 °C. IR, NMR, and analytical data are summarized in Table 1. These results proved that this compound was 2,5-bis(3-methyl-2-pyridylamino)terephthalic acid (**3b**).

Into 100 ml of 0.5 M-sulfuric acid, 5 g of **3b** was added after which the mixture was heated at 70—80 °C for 1 h. After cooling, the precipitate was collected by filtration, washed with water, and dried. The red product thus obtained was identified as **1b** on the basis of its IR, NMR, and analytical data. The total yield of **1b** was 3.8 g (76%).

Compounds **3c—e** were also obtained under the same reaction conditions. Compounds **3c—d** cyclized to give **1c—d**, except for **3e**. The yields, products, and analytical data for all the runs are listed in Table 1.

b): A mixture of **2e** (15 g) and chloranil (12 g) was refluxed in glacial acetic acid (300 ml) for 2 h. After the reaction mixture had been cooled, the resulting crystals were collected by filtration and dispersed in 300 g of a 2 wt% aqueous sodium hydroxide solution. The dispersion was filtered, and the resulting reddish orange crystals were thoroughly washed with water and dried to obtain 10.3 g of **1e**. Its IR, NMR, and analytical data are shown in Table 1.

Ring Opening of 1a—e (General Method). Compound **1a** (5.0 g) was heated in a 1 M aqueous sodium hydroxide solution (100 ml) for 3 h. Then the solution was neutralized with aqueous sulfuric acid. The precipitated **3a** (5.3 g) was filtered off as pale yellow crystals.

References

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