Synthesis of 4-Methoxycarbostyril

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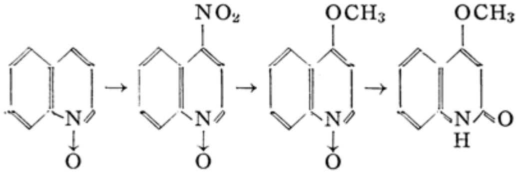
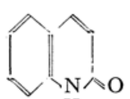
4-Methoxycarbostyril which had not yet been synthesized by reliable methods was synthesized by the following unambiguous method, as an intermediate product for synthesizing a certain natural product.

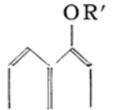
4-Nitroquinoline 1-oxide (II), given by nitration of quinoline 1-oxide (I) with potassium nitrate, was boiled with sodium methylate to convert to 4-methoxyquinoline 1-oxide (III). The synthetical methods and the structure proofs of (II) and (III) were previously worked out by Ochiai[1]. Henze[2] had reported that treatment of quinoline 1-oxide (I) with benzoyl chloride and potassium hydroxide gave carbostyril (V). Henze's procedure was confirmed by the author, and by the application of his method to 4-methoxyquinoline 1-oxide (III), 4-methoxycarbostyril (IV) was obtained as colorless needles, m.p. 257°.



(I) (II) (III) (IV)



(V)



(VI) $R=R'=H$
(VII) $R=CH_3$, $R'=H$
(VIII) $R=R'=CH_3$

It was soluble in 10% aqueous sodium hydroxide and in 20% hydrochloric acid when warmed. It gave negative ferric chloride test and no reaction occurred when boiled with acetic anhydride.

There are three reports concerning the synthesis of 4-methoxycarbostyril; Meyer and Heimann[3] obtained a compound, m.p. 271°, and Naito[4], another, m.p. 174–176°. The identity of both compounds is ambiguous because of the lack of structure proof. Arndt, et al.[5] reported recently that a monomethoxy compound, m.p. 257°, was obtained from 2,4-dihydroxyquinoline (VI) by treatment with diazomethane. They deduced that this compound must be 4-methoxycarbostyril (IV) but not 4-hydroxy-2-methoxyquinoline (VII) from the fact that mild hydrolysis of 2,4-dimethoxyquinoline (VIII) gave the same monomethoxy compound, m.p. 257°, and that in this case a methoxyl group at the 2-position is hydrolysed more easily than one at the 4-position[6]. On the other hand, it leaves no doubt that the structure of the compound, m.p. 257°, obtained by the author, is (IV), considered from the synthetical course of the author. Arndt and the author made mixed melting point determination individually. Both specimens showed m.p. 257° and both were unchanged by admixture. In view of this there is no doubt about their identity.

Experimental[7]

Quinoline 1-oxide (I)[1].—To 10 g. of quinoline in 244 ml. of glacial acetic acid was added 16 ml. of 30% hydrogen peroxide. The mixture was heated at 70° in a water bath for eight hours. The solvent was removed at reduced pressure and to the residue was added saturated aqueous sodium carbonate to make the solution alkaline. This alkaline solution was extracted with chloroform. A viscous syrup was obtained by removal of the solvent and solidified on standing. It was broken up under ether, filtered, and washed with ether, m.p. 45–50°. Yield 10 g. Pure quinoline 1-oxide dihydrate; m.p. 60–62°, b.p. 171–172°/4 mm.

4-Nitroquinoline 1-oxide (II)[1].—The crude product obtained above was dissolved in 24 ml. of conc. sulfuric acid. To this solution was added 7 g. of potassium nitrate. The mixture was heated at 70° in a water bath for three hours. On cooling, the reaction mixture was poured with stirring into 500 ml. of ice water. The yellow product was collected on a filter, washed successively with water, dilute aqueous sodium carbonate and finally with water. The solid was dried to give 8 g. of material, m.p. 152°. Recrystallization from acetone gave yellow needles, m.p. 154°.

4-Methoxyquinoline 1-oxide (III)[8].—To 0.65 g. of sodium metal dissolved in 250 ml. of absolute methanol was added 5 g. of 4-nitroquinoline 1-oxide. The solution was heated for 4.5 hr. in a water bath and the solvent was removed. Water was added and the product was extracted with chloro-

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[1] E. Ochiai, *J. Org. Chem.*, **18**, 534 (1953).

[2] M. Henze, *Ber.*, **69**, 1566 (1936).

[3] A. Meyer and P. Heimann, *Compt. rend.*, **203**, 335 (1936). See also Ref. 5).

[4] Naito, *J. Pharm. Soc. Japan*, **67**, 144 (1947).

[5] F. Arndt, L. Ergener and O. Kutlu, *Chem. Ber.*, **86**, 951 (1953).

[6] F. Arndt and L. Loewe, *Chem. Ber.*, **84**, 319 (1951).

[7] All melting points were un-corrected.

[8] E. Ochiai, et al., *J. Pharm. Soc. Japan*, **63**, 265 (1943).

form. The solvent was removed and the residue was poured in a dish. It soon solidified. The solid was triturated with ether to give colorless pillars, m.p. 54–55°, yield 3.5 g. (76%).

4-Methoxycarbostyril (IV).—To a solution of 4.6 g. of sodium hydroxide in 180 ml. of water was added 7 g. of 4-methoxyquinoline 1-oxide. Benzoyl chloride (7 ml.) was added dropwise with vigorous stirring. The thick white solid thus obtained was collected on a filter, washed with dilute aqueous sodium hydroxide and water. The yield of colorless solid, m.p. 251–253°, was 3 g. (43%). Three recrystallizations from methanol gave an analytical sample as colorless needles, m.p. 257°. No depression in melting point was observed on admixture with the specimen received from Prof. Arndt.

Found: C, 68.03; H, 5.06; N, 7.99. Calcd. for $C_{10}H_9NO_2$: C, 68.55; H, 5.18; N, 7.99.

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