Synthesis of New Fundamental Heterocycles. Part VII (1). Synthesis of 2-Azaxanthene

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2-Azaxanthone (**5**) has been conveniently prepared by condensation of the morpholine enamine of 1-benzyl-4-piperidone with salicylaldehyde followed by chromium trioxide oxidation and subsequent aromatization. Lithium aluminum hydride reduction of **5** afforded the new fundamental heterocycle 2-azaxanthene.

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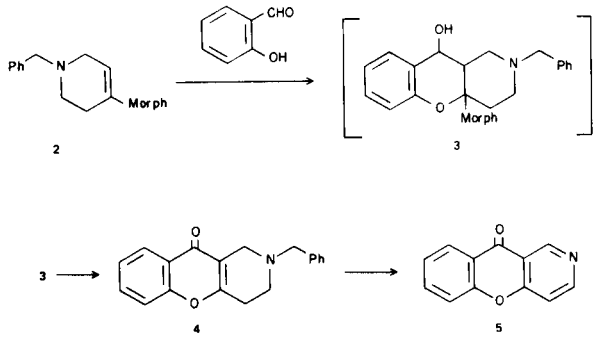
The recent reports by Villani and coworkers (2) and Nakamura, *et al.*, (3-5) concerning synthesis of some benzopyranopyridine derivatives which exhibit pharmacological properties, prompt us to relate our results obtained in this field. In this paper, we present more particularly the synthesis of a new fundamental heterocycle: 2-azaxanthene (**1**).

As part of a continuing effort in our laboratory to synthesize C_5O-C_5N condensed heterocycles and in order to get a new approach to alkaloids of *Elaeocarpus polydactylus* Schl., (6,7) we achieved the preparation of 2-azaxanthone (**5**) according to the following scheme (8).



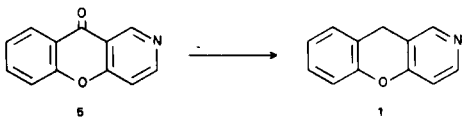
The first step of this synthesis is an extension to the morpholine enamine of 1-benzyl-4-piperidone (**2**) of the condensation reaction of enamines with variously substituted salicylaldehydes which has been described by Paquette (9,10).

The carbinol intermediate **3** was not isolated but was directly oxidized with chromium trioxide-pyridine to the 4-pyrone structure **4**, which was obtained in a 35% yield after recrystallization.

Debenzylation and aromatization of this compound could be readily accomplished by refluxing a xylene solution of **4** for 48 hours in the presence of 10% palladium-on-charcoal; 2-azaxanthone (**5**) was thus isolated in a 78% yield as a crystallized solid.

Although the yields of the two above steps have not been optimized, this sequence represents a convenient procedure for the preparation of 2-azaxanthone previously isolated in low yields by Kruger and Mann (11) and obtained by a four-step synthesis from 4-nitro-3-picoline 1-oxide by Villani, *et al.*, (2,12).

Conversion to the fundamental structure 2-azaxanthene (**1**) was carried out by lithium aluminum hydride reduction of **5**.



This new fundamental heterocycle, which provides the first example of a 4*H*-pyrano[3,2-*c*]pyridine structure (fused to a benzene ring), is the third unsubstituted member of the azaxanthene series to be reported (1a,13).

EXPERIMENTAL

Melting points were determined in capillary tubes on a Büchi apparatus and are uncorrected. Infrared spectra were obtained in potassium bromide pellets on a Perkin-Elmer Model 337 spectrophotometer. Pmr spectra were recorded in deuteriochloroform on a Varian A-60 spectrometer; chemical shifts are reported in parts per million (δ) downfield from an internal TMS reference and were assigned on integral information and coupling patterns (assignments are indicated using the numbering system adopted by the *Chemical Abstracts* for 10*H*-[1]benzopyrano[3,2-*c*]pyridine).

Morpholine Enamine of 1-Benzyl-4-piperidone or 4-(1-benzyl-1,2,3,6-tetrahydro-4-pyridyl)morpholine (**2**).

This enamine has been precedently reported by us (14).

2-Benzyl-1,2,3,4-tetrahydro-2-azaxanthone or 2-Benzyl-1,2,3,4-tetrahydro-10*H*-[1]benzopyrano[3,2-*c*]pyridin-10-one (**4**).

A solution of the morpholine enamine of 1-benzyl-4-piperidone (33.9 g., 0.131 mole) in dry hexane (40 ml.) was treated in one portion with an equimolar quantity of salicylaldehyde (16.0 g., 0.131 mole) in the same volume of dry hexane. The reaction was mildly exothermic and gave a viscous oil which became a glassy yellow product when the solution was allowed to stand at room temperature for a period of 24 hours. The adduct was decanted and the residual solvent was removed *in vacuo*. A pale yellow solid (49.9 g., 100%) was obtained and used without purification. (This alcohol could not be purified by crystallization and therefore was not prepared for elemental analysis).

This crude product in a solution of dichloromethane (200 ml.) was added in one portion with stirring to a dichloromethane solution of chromium trioxide-pyridine complex (224 g.), prepared in a 95% yield from anhydrous chromium trioxide (91.7 g., 0.919 mole) and pyridine (670 ml.) by a known procedure (15). The oxidation proceeded to completion within 15 to 20 minutes with the deposition of brownish-black reduced chromium-pyridine products. The supernatant liquid was decanted from the precipitate and the precipitate was rinsed thoroughly with dichloromethane. The combined dichloromethane extracts were washed with saturated sodium bicarbonate solution, dried and evaporated under reduced pressure. The crude solid was purified by rapid elution (benzene) through a small column of basic aluminum oxide. Recrystallization from alcohol-petroleum ether (4:1) gave **4** as a colorless crystalline product, 13.4 g. (35%), m.p. 111° (reported m.p. 111-112° (4)); ir ν (cm^{-1}): 1650 (C=O); pmr δ (ppm): 2.68 (broad singlet, 4H, 3-H and 4-H), 3.53 (singlet, 2H, benzylic CH_2), 3.70 (broad singlet, 2H, 1-H), 7.36 (multiplet, 8H, phenyl H and 6-H, 7-H and 8-H), 8.25 (multiplet, 1H, 9-H).

Anal. Calcd. for $C_{19}H_{17}NO_2$: C, 78.32; H, 5.88; N, 4.81. Found: C, 78.40; H, 5.89; N, 4.82.

2-Azaxanthone or 10*H*-[1]Benzopyrano[3,2-*c*]pyridin-10-one (**5**).

A solution of **4** (11.5 g., 3.95 x 10^{-2} moles) in dry xylene (150 ml.) was refluxed for 48 hours in the presence of 10% palladium-on-charcoal (1.15 g.). The cooled solution was filtered and the catalyst was well washed with several portions of chloroform. The filtrate was evaporated *in vacuo* leaving the crude azaxanthone. Recrystallization from alcohol gave pure **5**, 6.05 g., (78%), m.p. 184-185° (reported m.p. 183-185° (2), m.p. 184.5° (11)); ir ν (cm^{-1}): 1650 (C=O); pmr δ (ppm): 7.35-7.95 (complex multiplets, 4H, 4-H, 6-H, 7-H and 8-H), 8.38 (multiplet, 1H, 9-H), 8.92 (doublet, 1H, 3-H), 9.56 (singlet, 1H, 1-H).

Anal. Calcd. for $C_{12}H_7NO_2$: C, 73.09; H, 3.58; N, 7.10. Found: C, 72.74; H, 3.70; N, 6.95.

2-Azaxanthene or 10*H*-[1]Benzopyrano[3,2-*c*]pyridine (**1**).

A solution of **5** (2.00 g., 1.02 x 10^{-2} moles) in dry benzene (60 ml.) was added dropwise at room temperature to a well stirred suspension of lithium aluminum hydride (1.40 g.) in dry ether (90 ml.). The reaction mixture was stirred and heated to reflux for 3 hours, then allowed to stand at room temperature overnight. Water (1.4 ml.) was slowly added to the solution, followed by dilute sodium hydroxide solution (15%, 1.4 ml.) and then water (4.2 ml.). The precipitate was filtered and washed with ether. The filtrate was evaporated under reduced pressure leaving a yellow viscous oil which was purified by rapid elution (ether) through a column of alumina. Recrystallization of the solid obtained from petroleum ether afforded pure **1**, 393 mg. (21%), m.p. 70.5-71°; the ir spectrum showed no carbonyl absorption; pmr δ (ppm): 3.92 (singlet, 2H, 10-H), 6.86 (doublet, 1H, 4-H), 7.10 (multiplet, 4H, 6-H, 7-H, 8-H and 9-H), 8.35 (singlet + doublet, 2H, 1-H and 3-H).

Anal. Calcd. for $C_{12}H_9NO$: C, 78.67; H, 4.95; N, 7.64. Found: C, 78.78; H, 5.03; N, 7.59.

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(12) Though Villani has called this compound 3-azaxanthone, the name of 2-azaxanthone seems to be more appropriate. In any case the proper designation is that of the *Chemical Abstracts*: 10*H*-[1]benzopyrano[3,2-*c*]pyridin-10-one.

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