A New Route to 6-Azachromones. An Improved Synthesis of 2-Azaxanthone

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Condensation of the morpholine enamine of 1-benzyl-4-piperidone with β-ketoesters yielded 6-azatetrahydrochromones which were debenzylated and aromatized to 6-azachromones; 2-azaxanthone has been thus obtained with an improved yield as compared to previous syntheses.

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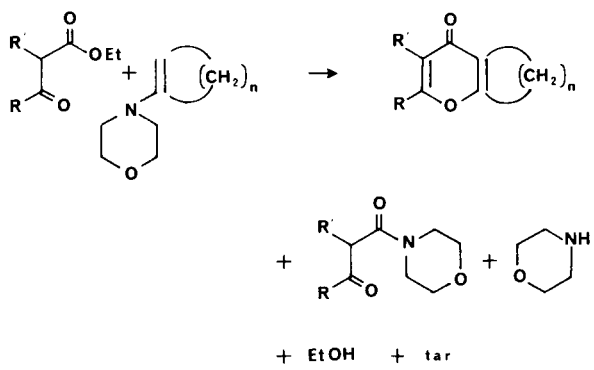
In the field of new fundamental heterocycles, we have previously reported the synthesis of 1- and 2-azaxanthenes [1-3]. As 2-azaxanthone was a key intermediate in the preparation of 2-azaxanthene, we have studied a new route to this compound for which the few syntheses which have been devised [4-5] give low yields or involve multistep procedures.

Our previous synthesis of 2-azaxanthone consisted of an extension to the heterocyclic enamine of Paquette's condensation of enamines with salicylaldehydes yielding 2-amino-4-chromanols [6]. Although this condensation usually proceeds in good yield, some loss was observed during subsequent oxidation to a chromone structure. A way to avoid this oxidation step was to envisage condensation of enamines either with derivatives of salicylic acid, which indeed have been used to prepare chromones [7-9], or with β-ketoesters according to a reaction reported by Monson [10]. This latter seemed to us more convenient for 2-azaxanthone synthesis if some improvement in yields could be obtained. This author reported the synthesis of γ-pyrones annelated to carbocyclic rings in variable yields ranging from 10 to 50% according to the following scheme.

Scheme 1



Monson performed these reactions by heating at reflux an equimolar mixture of the reagents, either without solvent (method A) or in a xylene solution (method B), allowing morpholine and ethanol to distil slowly from the reaction vessel over a period of 30-50 minutes (method A) or 20-94 hours (method B). In both cases the work up procedures consisted of treatment with sodium bisulfite solution prior to ether extraction. The bisulfite treatment was supposed to hydrolyze the morpholide and precipitate the bisulfite addition product of the decarboxylated ketone. Slightly better yields were generally obtained when the reaction was carried out in xylene. However, substantial amounts of tar were produced in method A which was performed at higher temperatures (185-256°).

Condensation of the Morpholine Enamine of 1-Benzyl-4-piperidone with β-Ketoesters.

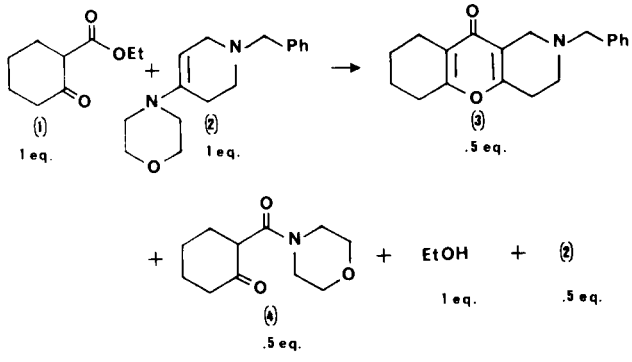
In order to obtain 2-benzyl-1,2,3,4,5,6,7,8-octahydro-2-azaxanthone **3**, we have first condensed an equimolar mixture of 2-carbethoxycyclohexanone **1** with the morpholine enamine of 1-benzyl-4-piperidone **2** in xylene solution at reflux, allowing volatile components to distil slowly. Heating in an oil bath at 170° during 4.5 days was necessary to observe complete disappearance of one of the reagents (*i.e.* the ketoester **1**). No morpholine was present in the distillate which contained only one equivalent of ethanol.

This result shows that the produced morpholine was probably entirely trapped by the ketoester giving rise to the ketomorpholide **4** and a supplementary quantity of ethanol; for this reason the yield in resulting γ-pyrone could not exceed more than 50%. Indeed we obtained a yield of 27% of recrystallized pyrone **3**. Furthermore we were able to recover the unreacted 1-benzyl-4-piperidone by basic hydrolysis of the adducts formed in the bisulfite treatment of the crude reaction mixture. This treatment did not hydrolyze and decarboxylate the morpholide as reported by Monson, since no cyclohexanone was characterized in our case among the hydrolysate. So the preceding scheme given by Monson [10] has to be rectified in the following manner which gives the balance between products and reagents in the case of the condensation of enamine **2** and ketoester **1**.

It is obvious from these results that two equivalents of ketoester must be used in order to improve the yield of

this synthesis. In effect, when the condensation was performed in this ratio, reaction was brought to completion in 3.5 days at 170° and gave a 92% yield in crude **3** sufficiently pure as shown by its proton nmr spectrum.

Scheme 2



This success prompted us to reinvestigate the condensation of ketoester **1** with morpholinocyclohexene **5**. Heating two equivalents of **1** with one equivalent of **5** in xylene at 170° during 3 days gave a similar yield in crude octahydroxanthone **6** from which a pure recrystallized product was isolated in a 70% yield.

Here also only ethanol was observed in the distillate collected during heating and the bisulfite treatment was ineffective in hydrolyzing the morpholide **4**. This product was hydrolyzed by refluxing it in 70% aqueous sulfuric acid over half an hour.

In order to test the potential of this condensation as a novel route to 6-azachromones [11], the morpholine enamine of 1-benzyl-4-piperidone **2** has been also reacted with acyclic β-ketoesters. With ethyl 2-methylacetoacetate, condensation required 3.5 days at 165° and afforded the tetrahydro-6-azachromone **7** in a 54% yield after recrystallization. In addition to ethanol the distillate produced during condensation contained traces of butanone which probably arose from thermal or base catalyzed decomposition of the ketoester.

Reaction of the morpholine enamine **2** with ethyl benzoylacetate was faster, since it was brought to completion by heating at 170° over 1.5 days, but only a 22% yield of recrystallized 6-benzyl-5,6,7,8-tetrahydro-6-azaflavone **8** was obtained. This low yield was probably due to difficulty encountered during extraction of the pyrone **8** by an acidic aqueous solution which did not seem to be complete.

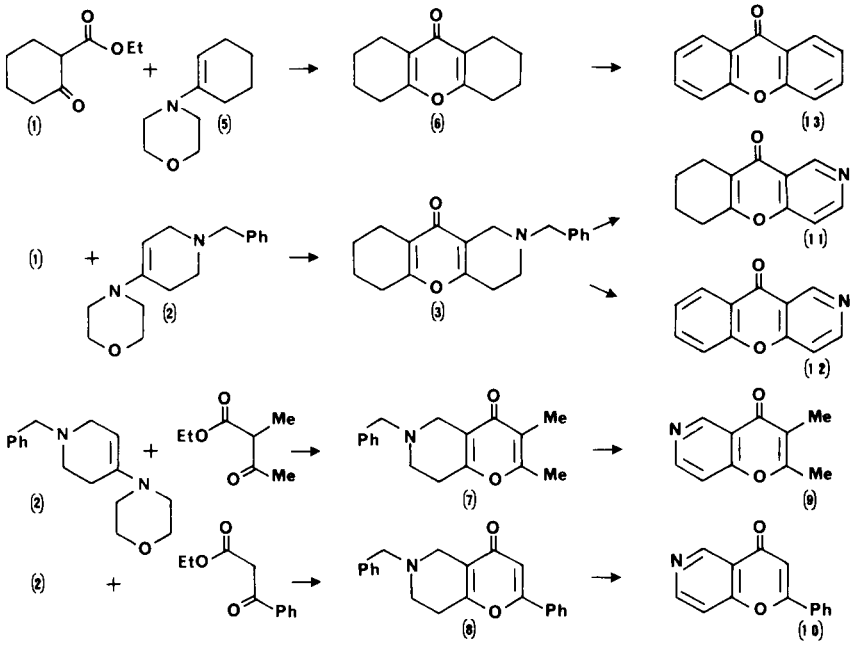
In the above two cases the morpholide produced by reaction of the eliminated morpholine with the excess of ketoester has been characterized and even isolated by distillation in one of these cases (see Experimental).

Aromatization to 6-Azachromones.

Debenzylation and aromatization to 6-azachromones of the above condensation products, depicted in the table, could be easily obtained in one step by refluxing the tetrahydro derivatives in xylene in the presence of 10% palladium on charcoal over a period of 2 or 3 days.

2,3-Dimethyl-6-azachromone **9** was thus obtained in a quantitative yield as a crude procuct (70% yield after recrystallization) while 6-azaflavone **10** was isolated in 82% yield as a crude solid (52% yield after recrystallization). If the latter has been previously described [12], the former is a new member of the series and has been characterized by ir, proton nmr, mass spectroscopy and elemental analysis.

Table



Concerning the octahydro derivative **3**, a partial and selective aromatization could be realized by refluxing this compound in xylene during 2 days with an amount of catalyst equal to one tenth of the mass of the substrate. The reaction led quantitatively to 5,6,7,8-tetrahydro-2-azaxanthone **11** (72% yield of recrystallized product) which appears to have not been previously described.

Aromatization of the carbocyclic ring required more severe conditions and has been achieved at the reflux temperature of decaline over a period of 2 days using an amount of catalyst equal to that of the reagent. 2-Azaxanthone **12** was thus obtained in 94% yield as a crude solid which appeared pure as shown by its nmr spectrum.

This route in two steps to 2-azaxanthone represents a convenient synthesis of this heterocyclic derivative, the overall yield being improved as compared to the previously reported syntheses [2,4,5].

Since xanthone **13** itself did not seem to have been prepared from its octahydro derivative, we realized also aromatization of this latter compound under the same conditions as described above. Xanthone **13** was thus obtained in a 68% yield as a pure recrystallized solid.

In conclusion, this work shows that the earlier reported condensation of β-ketoesters with morpholine enamines can be improved if two equivalents of ketoester were used, since at least in xylene solution at reflux, no morpholine was evolved, so that an equivalent of the ketoester was consumed by conversion to the corresponding morpholide. Furthermore this condensation can be extended to heterocyclic enamines as that derived from 1-benzyl-4-piperidone, providing a new entry to 6-azachromones if the condensation was followed by subsequent aromatization. Applied to 2-carbethoxycyclohexanone this procedure represents an improved synthesis of 2-azaxanthone.

EXPERIMENTAL

Melting points were determinated in capillary tubes on a Büchi SMP 20 apparatus and are uncorrected. Infrared spectra were obtained in potasium bromide pellets on a Perkin-Elmer Model 1420 spectrophotometer. Proton nmr spectra were recorded in deuteriochloroform on a Varian A-60A 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 these products). Mass spectra were taken on a R-10-10 Riber spectrometer under 70 ev. Microanalyses were performed by the Centre National de la Recherche Scientifique.

Morpholine Enamine of 1-Benzyl-4-piperidone or 4-(1-Phenylmethyl)-1,2,5,6-tetrahydro-4-pyridyl)morpholine **2**.

We have previously described the preparation of this heterocyclic enamine [13].

2-Benzyl-1,2,3,4,5,6,7,8-octahydro-2-azaxanthone or 2-(Phenylmethyl)-1,2,3,4,6,7,8,9-octahydro-10*H*-[1]benzopyrano[3,2-*c*]pyridine-10-one **3**.

A mixture of freshly prepared enamine **2** (25.8 g, 0.1 mole) and freshly distilled 2-carbethoxycyclohexanone **1** (34.0 g, 0.2 mole) in 50 ml of dry xylene was slowly heated in an oil bath. A temperature of 170° was necessary to allow ethanol and some xylene to distil from the reaction vessel. The distillate so obtained was progressively analysed by nmr, the reaction was thus brought to completion in 3.5 days. The solvent was then evaporated under reduced pressure and the residue was correctly extracted by aqueous sulfuric acid (*N*, 100 ml and 2 x 50 ml). The organic layer was used to identify the second product of the condensation reaction (see below).

The acid aqueous layer was neutralized with sodium hydroxide pellets and then extracted with chloroform. The organic layer was twice washed with water and dried over sodium sulfate. The chloroform was distilled off under reduced pressure and the residual pyrone was triturated with cold ether and collected. The yield of crude product was 92%, this compound was about 90% pure as shown by its proton nmr spectrum. Recrystallization from a mixture of acetone and ether (3:7) furnished 13.8 g (47%) of octahydroxanthone **3**, as pale yellow crystals, mp 121-121.5°; ir: ν (cm^{-1}) 1665 (C=O), 1610 (C=C); pmr: δ (ppm) 1.7 (multiplet, 2H, 7-H and 8-H), 2.45 (very broad singlet, 2H, 6-H and 9-H), 2.65 (broad singlet, 2H, 3-H and 4-H), 3.45 (singlet, 2H, benzylic CH_2), 3.7 (singlet, 1H, 1-H), 7.3 (multiplet, 5H, phenyl-H); ms: $M^{+\cdot}$ 295 (25.2%), 205 (17.6%), 204 (100%), 91 (51.9%), 65 (19%).

Anal. Calcd. for $C_{19}H_{21}NO_2$: C, 77.26; H, 7.17; N, 4.75. Found: C, 77.28; H, 7.03; N, 4.63.

Morpholine Amide of 2-Carboxycylohexanone **4**.

The first organic layer of the preceding condensation was dried over potassium carbonate, filtered and concentrated by evaporation of the solvent *in vacuo* leaving an oil which gradually solidified. After several recrystallizations from hexane, we were able to obtain crystals of a white product melting at 81-82° and identify this solid as the presumed morpholide **4** by analysis of its proton nmr spectrum: 1.6-2.6 (8H, 2 multiplets, poor resolution), 3.5 and 3.7 (9H, 2 broad singlets, poor resolution) and its ir spectrum: 1705 and 1635 cm^{-1}. These observations were in accordance with those reported previously by Monson [10].

2-Benzyl-2,3-dimethyl-5,6,7,8-tetrahydro-6-azachromone or 2,3-Dimethyl-6-(phenylmethyl)-5,6,7,8-tetrahydro-4*H*-pyrano[3,2-*c*]pyridin-4-one **7**.

A mixture of enamine **2** (25.8 g, 0.1 mole) and freshly distilled ethyl 2-methylacetoacetate (28.8 g, 0.2 mole) in 50 ml of dry xylene was heated at 165° during 3.5 days in the same manner as described for the preparation of **3**. Pmr analysis of the distillate showed the absence of morpholine but the presence of traces of butanone due to probable decomposition of the starting β-ketoester. The solvent was eliminated by evaporation *in vacuo*, the residue being extracted with 1*N* sulfuric acid (100 ml and 2 x 50 ml). The organic layer was subsequently used for characterization of the corresponding morpholide obtained as a by-product of the reaction (see below). The acid layer was worked up as above. Evaporation of the solvent furnished a crude solid which by recrystallization in a mixture of acetone and ether (2:3) led to 14.4 g (54%) of tetrahydroderivative **7**, pale yellow crystals, mp 121-121.5°; ir: ν (cm^{-1}) 1665 (C=O), 1605 (C=C); pmr: δ (ppm) 1.90 (singlet, 3H, 2-CH_3), 2.25 (singlet, 3H, 3-CH_3), 2.65 (singlet, 4H, 7-H and 8-H), 3.45 (singlet, 2H, benzylic CH_2), 3.70 (singlet, 2H, 5-H), 7.35 (singlet, 5H, phenyl-H); ms: $M^{+\cdot}$ 269 (23.9%), 179 (12.8%), 178 (100%), 91 (56.6%), 65 (20.2%).

Anal. Calcd. for $C_{17}H_{19}NO_2$: C, 75.81; H, 7.11; N, 5.20. Found: C, 75.89; H, 7.07; N, 5.25.

Morpholine Amide of 3-Carboxy-2-butanone.

The preceding acid organic layer was dried over potassium carbonate, concentrated and distilled under reduced pressure; 7 g was thus obtained as a yellow liquid (bp 132°/2 torr) which was identified as the expected morpholide [14] by analysis of its pmr spectrum: δ (ppm) 1.3 (doublet, 3H, 3-CH_3, J = 7 Hz), 2.15 (singlet, 3H, 1-CH_3), 3.6 (broad singlet, 8H, morpholine-CH_2), 3.85 (quadruplet, 1H, 3-H, J = 7 Hz) and ir spectrum: ν (cm^{-1}) 1720 (ketone C=O) and 1640 (amide C=O).

6-Benzyl-5,6,7,8-tetrahydro-6-azaflavone or 2-Phenyl-6-(phenylmethyl)-5,6,7,8-tetrahydro-4*H*-pyrano[3,2-*c*]pyridin-4-one **8**.

A mixture of enamine **2** (25.8 g, 0.1 mole) and freshly distilled ethyl benzoylacetate (38.4 g, 0.2 mole) in 50 ml of dry xylene was heated to 170° over a period of 1.5 days which was sufficient for complete disappearance of the two starting reagents. The solvent was eliminated by evaporation *in vacuo*, the residue was then diluted with 100 ml of chloroform and extracted with 1*N* sulfuric acid (100 ml and 4 x 50 ml). This chloroform layer was later treated for identification of the morpholide by-product (see below). The aqueous layer was neutralized with sodium hydroxide pellets and then thoroughly extracted with chloroform (5 x 100 ml). The organic layer was separated, washed with water, dried over magnesium sulfate and concentrated by evaporation under reduced pressure. Recrystallization in a mixture of hexane-acetone (3:2) of the crude solid so obtained furnished the tetrahydroflavone derivative **8** as pale yellow crystals in a 22% yield (6.8 g), mp 132-132.5°; ir: ν (cm^{-1}) 1660 (C=O), 1615 (C=C); pmr: δ (ppm) 2.7 (singlet, 4H, 7-H and 8-H), 3.45 (singlet, 2H, benzylic CH_2), 3.7 (singlet, 2H, 5-H), 6.65 (singlet, 1H, 3-H), 7.2-7.8 (multiplet, 10H, phenyl-H); ms: $M^{+\cdot}$ 317 (32.3%), 227 (18%), 226 (100%), 91 (71.9%), 77 (11.1%), 65 (19.5%).

Anal. Cald. for $C_{21}H_{19}NO_2$: C, 79.47; H, 6.04; N, 4.41. Found: C, 79.25; H, 5.90; N, 4.45.

Distillation of the organic layer obtained after acid extraction of the azaflavone derivative furnished some acetophenone and morpholide of benzoylacetic acid, these products being identified by nuclear magnetic resonance spectroscopy.

Octahydroxanthone or 1,2,3,4,5,6,7,8-Octahydroxanthen-9-one **6**.

A mixture of freshly prepared, as usual [15], morpholinocyclohexene **5** [16] (15.0 g, 0.09 mole) and 2-carbethoxycyclohexanone **1** (30.6 g, 0.18 mole) in 50 ml of dry xylene was heated at 170° during 3 days in the same manner as described above. The solvent was evaporated and the white solid residue, analyzed by nmr, showed that it essentially consisted of a 1:1 mixture of octahydroxanthone **6** and morpholide **4**. Attempted fractionnal crystallizations of the two components were unsuccessful, so that we obtained pure **6** by acid hydrolysis of the amide **4**. The preceeding cruded residue (38.3 g) was treated by 70% aqueous sulfuric acid (290 ml of concentrated sulfuric acid + 220 ml water under reflux over a period of 0.5 hour. The resulting dark solution was filtered and then extracted thoroughly with chloroform (5 x 100 ml). The organic layer was washed with water, dried over magnesium sulfate, filtered and evaporated *in vacuo*, giving an oil which rapidly crystallized. Recrystallization from hexane furnished pure octahydroxanthone **6** (12.8 g, 70% yield), mp 131°; ir: ν (cm^{-1}) 1665 (C=O), 1615 (C=C); pmr: δ (ppm) 1.75 (multiplet, 8H, 2-H, 3-H, 6-H and 7-H), 2.45 (multiplet, 8H, 1-H, 4-H, 5-H and 8-H) (17).

5,6,7,8-Tetrahydro-2-azaxanthone or 6,7,8,9-Tetrahydro-10*H*-[1]benzopyrano[3,2-*c*]pyridin-10-one **11**.

A solution of octahydro-2-azaxanthone **3** (5.9 g, 0.02 mole) in dry xylene (100 ml) was refluxed for 48 hours in the presence of 10% palladium on charcoal (0.6 g). The hot solution was filtered and the catalyst was well washed with hot chloroform. The filtrate was evaporated *in vacuo* leaving 4.1 g of crude tetrahydro-2-azaxanthone **11** (100% yield, as shown by nmr spectroscopy). Recrystallization from a mixture of hexane and alcohol (4.1) gave pure **11**, 2.88 g, (72%), mp 124.5°; ir: ν (cm^{-1}) 1655 (C=O), 1640 and 1605; pmr: δ (ppm) 1.85 (multiplet, 4H, 7-H and 8-H), 2.55 (multiplet, 4H, 6-H and 9-H), 7.25 (doublet, 1H, 4-H, J = 6 Hz), 8.70 (doublet, 1H, 3-H, J = 6 Hz), 9.30 (singlet, 1H, 1-H); ms: $M^{+\cdot}$ 201 (100%), 200 (87.9%), 186 (75.5%), 122 (24.3%), 77 (30.7%).

Anal. Calcd. for $C_{12}H_{11}NO_2$: C, 71.63; H, 5.51; N, 6.96. Found: C, 71.86; H, 5.34; N, 6.81.

2-Azaxanthone or 10*H*-[1]Benzopyrano[3,2-*c*]pyridin-10-one **12**.

A solution of the octahydro derivative **3** (5.9 g, 0.02 mole) in decalin (50 ml) was refluxed in the presence of 6 g of 10% Pd/C over a period of 48 hours. The resulting mixture was cooled at -10° overnight and then filtered; the solid residue was well dried and the filtrate was discarded. The solid was thoroughly washed with several portions of hot chloroform and the filtrate was evaporated under reduced pressure leaving 3.7 g of crude 2-azaxanthone (94% yield, as shown by analysis of its nmr spectrum). Recrystallization from alcohol gave **12**, as very pale greenish needles (2.20 g, 56%), mp 185°; ir: ν (cm^{-1}) 1655 (C=O), 1620 and 1600 (aromatic rings); pmr: δ (ppm) 7.2-8.0 (complex multiplets, 4H, 4-H, 6-H, 7-H and 8-H), 8.4 (multiplet, 1H, 9-H), 8.9 (doublet, 1H, 3-H), 9.55 (singlet, 1H, 1-H) [18]; ms: $M^{+\cdot}$ 197 (100%), 169 (32.1%), 63 (14.9%), 50 (16.4%).

2,3-Dimethyl-6-azachromone or 2,3-Dimethyl-4*H*-pyrano[3,2-*c*]pyridin-4-one **9**.

A solution of 5.4 g (0.02 mole) of tetrahydro derivative **7** in dry xylene (100 ml) was refluxed for 48 hours in the presence of 10% palladium on charcoal (0.55 g). The resulting mixture was worked up as described for the preparation of **11**. Crude **9** (3.5 g, 100% yield) was so obtained; recrystallization from ethyl acetate furnished 2.45 g (70% yield) of pure 2,3-dimethyl-6-azachromone **9**, mp 103-103.5; ir: ν (cm^{-1}) 1655 (C=O), 1605; pmr: δ (ppm) 2.0 (singlet, 3H, 2-CH_3), 2.4 (singlet, 3H, 3-CH_3), 7.4 (doublet, 1H, 8-H, J = 6 Hz), 8.7 (doublet, 1H, 7-H, J = 6 Hz), 9.3 (singlet, 1H, 5-H); ms: $M^{+\cdot}$ 175 (100%), 122 (48.8%), 53 (31.9%), 43 (29.3%).

Anal. Calcd. for $C_{10}H_9NO_2$: C, 68.57; H, 5.18; N, 7.99. Found: C, 68.77; H, 5.11; N, 7.99.

6-Azaflavone or 2-Phenyl-4*H*-pyrano[3,2-*c*]pyridin-4-one **10**.

A solution of 6-benzyl-5,6,7,8-tetrahydro-6-azaflavone **8** (3.17 g, 0.01 mole) in dry xylene (50 ml) was refluxed for 72 hours in the presence of 10% palladium on charcoal (1.5 g). After usual work up, 1.9 g (84%) of crude 6-azaflavone could be obtained. Recrystallization from ethanol gave pure **10** (1.16 g, 52%) as yellow crystals, mp 163-164°; ir: ν (cm^{-1}) 1665 (large C=O), 1605; pmr: δ (ppm) 6.85 (singlet, 1H, 3-H), 7.45-7.65 (complex multiplet, 4H, 8-H + 3'- and 4'-phenyl-H), 7.8-8.0 (multiplet, 2H, 2'-phenyl-H), 8.84 (doublet, 1H, 7-H, J = 6 Hz), 9.45 (singlet, 1H, 5-H); ms: $M^{+\cdot}$ 223 (100%), 222 (25.3%), 195 (54.1%), 102 (67.9%), 51 (24.5%).

Xanthone **13**.

A solution of 0.80 g of the octahydroxanthone **6** (3.92 10^{-3} moles) in decalin (25 ml) was refluxed in the presence of 0.8 g of 10% Pd/C for 48 hours. About 15 ml of solvent was eliminated by distillation, the residue was then cooled at -10° overnight and then filtered; the solid residue was well dried and the filtrate was discarded. The solid was then thoroughly washed with hot chloroform (15 x 10 ml) and the filtrate was evaporated *in vacuo*. Recrystallization from alcohol gave 0.52 g (68% yield) of pure known xanthone [19], mp 174-175°; ir: ν (cm^{-1}) 1660 (C=O), 1610 (aromatic rings).

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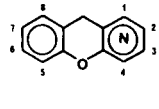
[3] For consistency and convenience throughout this series, we consider these compounds as derivatives of xanthene or xanthone and indicate the position of the nitrogen atom and other substituents on the ring by the numbering system shown in the following representation:



The correct *Chemical Abstracts* names for these two compounds are 10*H*-[1]benzopyrano[3,2-*b*]pyridine and 10*H*-[1]benzopyrano[3,2-*c*]pyri-

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[11] For convenience we consider these products as derivatives of chromone or flavone. For more precision see Experimental.

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[16] So obtained in a 76% yield; pmr spectrum: δ (ppm) 1.4-2.4 (2 multiplets, 8H, carbocyclic ring - CH_2), 2.8 (multiplet, 4H, N-CH_2), 3.75 (multiplet, 4H, O-CH_2), 4.7 (triplet, 1H, vinylic-H, J = 3 Hz).

[17] In good agreement with the literature: I. Belsky, *Tetrahedron*, **28**, 771 (1972); B. S. Kirkiacharian, *Compt. Rend.*, **293**, 149 (1981).

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