SYNTHESIS OF NEW FUNDAMENTAL HETEROCYCLES VI. SYNTHESIS OF 1-AZAXANTHENE [1]

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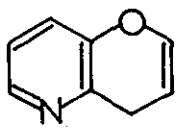
Condensation of the Mannich base of 3-pyridinol with 1-ethoxycyclohexene yielded 5,6,7,8,8a,10a-hexahydro-10a-ethoxy-1-azaxanthene (5) which was converted to 5,6,7,8-tetrahydro-1-azaxanthene (3). In contrast, the condensation product resulting from cyclohexanone could not be dehydrated to (3). The tetrahydro derivative (3) was aromatized to the novel and fundamental heterocycle, 1-azaxanthene (2).

Among the condensed heterocycles which contain a pyran ring fused to a pyridine nucleus, the only ones known as fundamental heterocycles† are 2H-pyrano [2,3-b] pyridine [2] and 2H-pyrano [3,2-c] pyridine [3]. Up to now, neither 2H-pyrano [3,2-b] pyridine nor its 4-H isomer (1) have been descri-

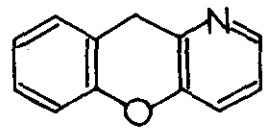
† (i.e. as unsubstituted and most fully unsaturated heterocycles).

bed.

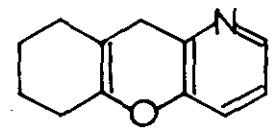
We report in the present note the synthesis of 1-azaxanthene (2) and that of its tetrahydro derivative (3) which are derived from the fundamental structure (1) by fusion of a benzene and a cyclohexene ring, respectively.



(1)



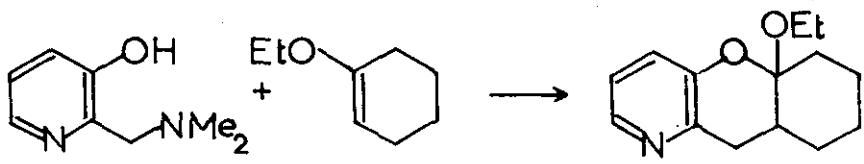
(2)



(3)

In order to synthesize 1-azaxanthene derivatives, of which only a few examples are known [4-7], the condensation we recently reported [7] of the Mannich base of 3-hydroxypyridine (4) with vinyl ethers to yield 2-alkoxy-5-aza-chromans was extended to include 1-ethoxy-cyclohexene.

The condensation (scheme 1) was performed by refluxing under nitrogen a solution of the Mannich base (4) in an excess (3 equiv.) of 1-ethoxy-cyclohexene to give (5) (distilled, 77 % yield).



(4) (5)

Scheme 1

The reaction may be interpreted, either as proceeding through a pyridine ortho methylene quinone resulting from the thermal deamination of the Mannich base [9], or by invoking a concerted mechanism as has been suggested in the case of a similar condensation with enamines [4].

In addition the condensation of (4) with cyclohexanone to afford the

trans. However, a mixture of these isomers could not be discerned. Probably the solid product, which exhibits a sharp melting point, is a pure isomer to which the more stable *trans* structure may be assigned since it allows a *trans* diequatorial ring junction with an axial position for the OH group which is favoured by the anomeric effect. Dreux *et al.* have also ascribed this *trans* configuration to the only stable isomer isolated for 1, 2, 3, 4, 4a, 9a-hexahydro-4a-hydroxyxanthene [12]. As far as the structure of the ketal (5) is concerned, it proved to be homogeneous both in gpc and tlc ; however, spectrographic data do not allow the assignment of a definite stereochemistry.

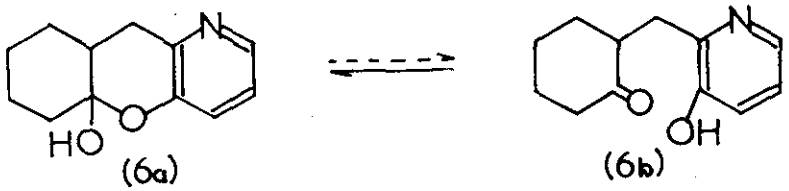
In order to obtain 5,6,7,8-tetrahydro-1-azaxanthene (3) the above products were subjected to pyrolysis. While the hemiketal (6) resisted to dehydration attempted in boiling xylene in the presence of p-toluenesulfonic acid, the ketal (5) underwent ethanol elimination when heated at 220°C under reduced pressure (100 torr) affording in quantitative yield as the first example of a 4H-pyrano [3,2-b] pyridine structure fused to an homocycle, the expected tetrahydroazaxanthene (3) : b p 92°C/0.1 torr ; m p 24°C ; ir (liquid ; cm^{-1}) 1710 (vinyl ether νC=C) ; pmr ($CDCl_3$, δ from TMS) 1.4-2.2 (m, 8H, 5-,6-,7- and 8- CH_2), 3.35 (s, 2H, benzylic 9- CH_2), 7.06 (m, 2H, 3-H and 4-H), 8.24 (d d, 1H, 2-H).

Conversion to the fundamental structure (2) was realized by refluxing (3) in xylene for 48 hours in the presence of 10 % palladium-carbon catalyst. Under these conditions a disproportionation took place affording a mixture of hexahydroazaxanthene (7) and azaxanthene (2).

corresponding hemiketal (6) was of interest since a similar reaction which probably implies the enolic tautomer of cyclohexanone has been observed with the Mannich base of phenol [10], furthermore, this reaction would provide a more convenient entry to dihydropyran derivatives fused to an heterocycle which have been reported to exhibit gram positive antimicrobial and hypotensive activity [5].

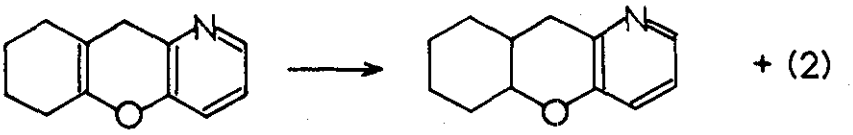
Actually, refluxing a solution of (4) in an excess of cyclohexanone (10 equiv.) for 5 hours afforded the hemiketal (6) (62 % yield, m.p. 158°C) In contrast, the hemiketal (6) has been prepared in a 39 % yield by the condensation of (4) with the pyrrolidine enamine of cyclohexanone in refluxing dioxane for two weeks followed by hydrolysis [5].

From a structural point of view, it is possible that the compound (6) can give rise to a ring-chain tautomerism leading to an aquilibrium with the open form (6b).



(6a) (6b)

The infra red spectrographic study showed that this equilibrium, which we have already observed for 2-hydroxy-5-aza chromans [11], indeed occurs in chloroform solution where the open form (6b) exhibits an absorption at 1690 cm^{-1} ; on the other hand in the solid state, the compound (6) only presents the cyclic hemiketal structure (6a) as may be inferred from the absence of the above absorption in a KBr pellet. Concerning the stereochemistry of the latter, two isomeric structures are possible depending on whether the ring fusion of the two non aromatic nucleus is *cis* or



(3) (7)

Chromatography on basic alumina allowed the separation of the hexahydro derivative (hexane - benzene, 3/1, 50 % yield) from 1-azaxanthene (benzene-ether, 3/1, 26 %yield) which was characterized by the following data : m p 74.5°C ; b p 92°C/0.2 torr ; ir (KBr : cm^{-1}) 755 (δC-H of ortho disubstituted benzene) ; pmr ($CDCl_3$, δ from TMS) 4.2. (s, 2H, CH_2), 6.9-7.4 (m, 6H, 3-H, 4-H and benzene protons) 8,6 (d d, 1H, 2-H) and elemental analysis.

Attempts to reduce the amount of the hexahydro derivative in order to improve the yield of the aromatization step are presently under invertigation.

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