SYNTHESIS OF NEW FUNDAMENTAL HETEROCYCLES VI.

SYNTHESIS OF I-AZAXANTHENE 1)

Henri Sliwa * and Dominique Blondeau

Laboratoire de Chimie Organique II et

Groupe I.N.S.E.R.M. U-62

Université des Sciences et Techniques de Lille

BP 36 - 59650 Villeneuve d'Ascq - France

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

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 descrit (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.

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 $(\underline{4})$ with vinyl ethers to yield 2-alko-xy-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 $(\underline{4})$ in an excess (3 equiv.) of 1-ethoxy-cy-clohexene to give $(\underline{5})$ (distilled, ?7% yield).

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 disquatorial 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 vC=C); pmr (CDCl₃, & from TMS) 1.4-2.2 (m, 8H, 5-,6-,7- and 8- CH₂), 3.35 (s, 2H, benzylic 9- CH₂), 7.06 (m, 2H, 3-H and 4-H), 8.24 (d d, 1H, 2-H).

Conversion to the fundamental structure $(\underline{2})$ was realized by refluxing $(\underline{3})$ 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 $(\underline{7})$ and azaxanthene $(\underline{2})$.

corresponding hemiketal $(\underline{6})$ 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 $(\frac{1}{4})$ in an excess of cyclohexanone (10 equiv.) for 5 hours afforded the hemiketal $(\frac{6}{6})$ (62 % yield, m.p. 158°C) In contrast, the hemiketal $(\frac{6}{6})$ has been prepared in a 39 % yield by the condensation of $(\frac{1}{4})$ with the pyrrolidine enamine of cyclohexanone in refluxing dioxane for two weeks followed by hydrolysis $(\frac{5}{6})$.

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).

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

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 (&C-H of ortho disubstituted benzene); pmr (CDCl₃, & from TMS) 4.2. (s, 2H, CH₂), 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.

REFERENCES

- 1 Part V: G. Lhommet, H. Sliwa, and P. Maitte, <u>Bull</u>. <u>Soc. chim</u>. <u>France</u>, 1972, 1442.
- 2 H. Sliwa, C.R. Acad. Sci., Ser. C, 1967, 264, 1893; <u>Bull. Soc. chim.</u> France, 1970, 631.
- 3 G. Lhommet, H. Sliwa and P. Maitte, <u>C.R. Acad. Sci.</u>, Ser. C, 1971, <u>272</u>, 2197; <u>Bull. Soc. chim. France</u>, 1972, 1435.
- 4 M. von Strandtmann, M.P. Cohen and J. Shavel Jr., <u>J. Heterocyclic Chem.</u>, 1970, 7, 1311.
- 5 M. von Strandtmann, M.P. Cohen and J. Shavel Jr., <u>U.S</u>. Pat., 3,518,

- 273 (Cl. 260-289) C 07 d, June 30, 1970.
- 6 F.J. Villani, T.A. Mann, E.A. Wefer, J. Hannon, L.L. Larca, M.J. Landon, W. Spivak, D. Vashi, S. Tozzi, G. Danko, M. del Prado, and R. Lutz, <u>J. Med. Chem.</u>, 1975, 18, 1.
- 7 P. Nantka-Namirski, and A. Rykowski, Pol.J. Pharmacol. Pharm., 1973, 25, 455.
- 8 H. Sliwa and D. Blondeau, J. Heterocyclic Chem., 1976, 13, 419.
- 9 J.H. Brewster and E.L. Eliel. Org. Reactions, Vol. 7, 128 (1953), John Wiley and Sons Inc., New York, third printing, 1963.
- 10 M. Moreau, R. Quagliaro, R. Longeray and J. Dreux, <u>Bull. Soc. chim.</u> France, 1968, 4251.
- 11 D. Blondeau and H. Sliwa, C.R. Acad. Sci., Ser. C, 1975, 281, 947.
- 12 M. Moreau, R. Longeray and J. Dreux, <u>Bull. Soc. chim. France</u>, 1969, 997.

Received, 15th June, 1976