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NOVEL FORMATION OF 9,18-DIFORMYL-5,6,14,17-TETRAHYDRO-8,17-EPOXY-6H,15H-[1,5] DIAZOCINO[2,1-g : 6,5-g']DIISOQUINOLINES FROM (3,4-DIHYDROISOQUINOLINYL-1) PROPAN-1,3-DIALS

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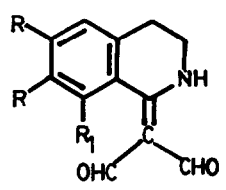
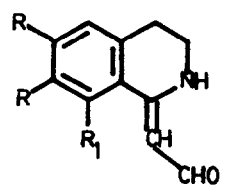
Abstract : The title compounds 7-10 are formed from the dialdehydes 1 on treatment with acetic anhydride.

We wish to report the formation of interesting title compounds from the dialdehydes 1, which became available to us along with the monoaldehydes 2 from 1-methyl-3,4-dihydro-isoquinolines by a Vilsmeier reaction[1]. Our objective was the construction of the 8H-isoquino[2,1-b][2,7]naphthyridin-8-one ring system 3 present in the Alangium alkaloids[2] by means of a Hantzsch-type pyridine synthesis from 2 or 1. Reaction of 2 (R=R_1=H) with methyl acetoacetate and ammonia resulted only in deformylation to 1-methyl-3,4-dihydroisoquinoline, while the dialdehyde 1 (R=R_1=H) gave the benzoquinolizine 4[3] (14%), m.p. 170-2°, $C_{16}H_{13}NO_3$, M^+ 267 and the dihydropyridine 5[3] (4%), m.p. 224-6°, $C_{26}H_{26}N_2O_6$, M^+ 462 [with fragments corresponding to the benzoquinolizine (m/z 238) and the dihydropyridine (m/z 224) moieties].



1



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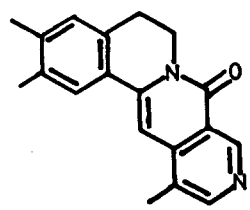

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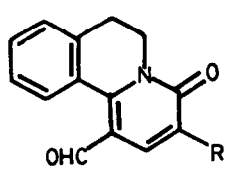
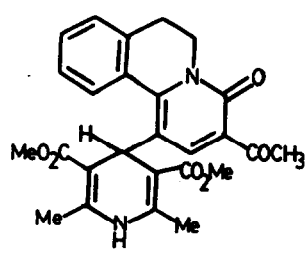


4 R= $COCH_3$

6 R= H



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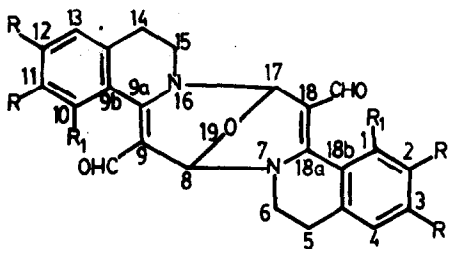
The formation of 4 and 5 from 1 (R=R_1=H) indicated that a Knoevenagel reaction of 1 with methyl acetoacetate preceded the Hantzsch reaction. Hence we attempted to protect the NH group in 1 by acetylation. Treatment with acetic anhydride again gave rise to two products, one being the mono-Perkin condensation product, the benzoquinolizine 6 (4%)[3], m.p. 151-2°, $C_{14}H_{11}NO_2$, M^+ 225. The other product (28%), m.p. 247-8° proved to have the more interesting 9,18-diformyl-5,6,14,17-tetrahydro-8,17-epoxy-6H,15H-[1,5]diazocino[2,1-a : 6,5-a']diisoquinoline structure 7. Although elemental analysis checked for the monohydrate of the molecular formula, $C_{24}H_{20}N_2O_3$, high resolution mass spectrum (HRMS) confirmed it (found mass 384.1475; calculated mass 384.1474); λ_{max} ($CHCl_3$) 253, 322 nm (log ϵ 4.37, 4.37) [spectrum similar to that of 1 (R=R_1=H)], IR ($CHCl_3$), 1595, 2820 cm^{-1} (enaminic aldehyde). The ^1H NMR spectrum (300 MHz) indicated a symmetrical structure, diagnostically useful signals being those at δ 6.13 (s, 2H, C-8, C-17H) and δ9.29 (s, 2H, CHO). The eight methylene protons gave rise to four groups of signals assigned as follows : δ 2.77 (C-5, C-14He), 2.96 (C-5, C-14Ha), 3.52 (C-6, C-15Ha) and 4.51 (C-6, C-15He), with the right multiplicities and supported by proton-proton decoupling. Symmetry was again evident from the ^{13}C NMR (50 MHz) spectrum : δ29.0 (C-5, C-14), 45.4 (C-6, C-15), 81.2 (C-8, C-17), 107.6 (C-9, C-18), 125.93 (C-4a, C-13a), 125.96, 127.7, 131.1, 131.4 (C-1, C-10 ; C-2, C-11 ; C-3, C-12 ; C-4, C-13), 139.3 (C-9b, C-18b), 152.7 (C-9a, C-18a) and 184.5 (2 x CHO), the signal at δ81.2 being characteristic of an allylic carbinolamine carbon atom.

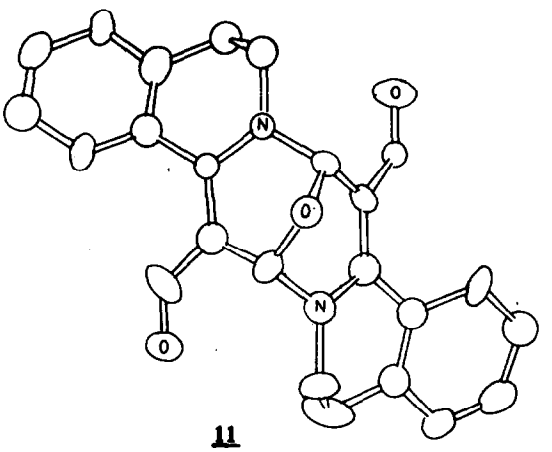


7 R= R_1= H

8 R= OCH_3, R_1= H

9 R,R= OCH_2O, R_1= H

10 R= R_1= OCH_3



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The structure was further supported by X-ray analysis of single crystals of 7. The ORTEP drawing is shown as 11. Some crystal data are :

monoclinic, space group Cc, a=26.892(4), b=9.760(2), c=17.708(2)Å, β=127.11(1)°, V=3706.5 Å^3, F.W. in the asymmetric unit = 786.89 corresponding to $(C_{24}H_{20}O_3N_2)_2.H_2O$, Z=4, D_c=1.410 g. cm^{-3}, μ=7.32 cm^{-1}, F(000)=1656, λ(CuKα)=1.5418 Å. Cell parameters were determined by a least-squares fit of setting angles of 25 reflections (θ in the range of 11 - 41°) measured on a CAD4 diffractometer. Three dimensional data were measured to a Bragg angle of 75° by ω-2θ scan method. There were 4176 (3170 $\geqslant 3\sigma$) unique reflections. The structure was solved by direct methods using the program SHELX-86 and refined by full matrix least-squares (including hydrogens in structure factor calculation) to an R index of 0.040 (R_W= 0.057). Bond angles around the N atoms indicated them to be almost completely planar. In keeping with the observed chemical shift of δ 9.29 ppm for the formyl protons, it was found that the nitrogen atoms were conjugating well with these groups through the double bonds, the relevant torsion angles for N-C=C-CHO and N-C=C-CH being around -18° and 162° respectively.

The formation of 7 is easily rationalized on the basis of two molecules of 1 (R=R_1=H) forming a bis-carbinolamine followed by dehydration to introduce the oxygen bridge. The reaction has not been optimised yet but found to be general as evidenced by the formation of 8, m.p. 258-60° (9%), 9, m.p. 318-20° (19%) and 10, m.p. 248-50° (12%). 8 and 10 analysed for a monohydrate while 9 was a hemihydrate. Structures were supported by all usual spectral data in addition to HRMS for 9. Micro KBr IR spectra of 8 and 10 showed the presence of water of crystallization.

Possessing multiple sites for hydrophobic, polar and covalent interactions, epoxydiazocines of the type 7, and more so, their 9, 9a, 18, 18a - tetrahydro derivatives offer interesting scope for host-guest studies. Exploratory experiments are in progress towards this end.

Apart from the simple epoxydiazocine, not many condensed analogues are discernible in the literature. Epoxydibenzodiazocines with CNS activity have been reported[4]. The formation of epoxybispyridodiazocine has been noted in the preparation of 2-aminopyridine-3-carboxaldehyde[5]. A biscarbazole derivative has been made as a model for a curare alkaloid artefact, ultracurine[6], while a highly complex derivative has been cited in the ring index[7].

Although in principle, molecules with a 3-aminopropanal unit can give rise to epoxydiazocines, these have not been reported for the dialdehydes readily obtained by a Vilsmeier reaction on quinaldine, 2-methylbenzimidazole, 2-methylbenzoxazole, etc. Our deliberate attempts to transform these dialdehydes to the bridged systems have been unsuccessful, indicating a unique propensity for the (3,4-dihydroisoquinolinyl-1)propan-1,3-dials 1.

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3. The compounds had correct C,H,N analyses and UV, IR and NMR spectral characteristics.

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