SULFONATION OF 2,6-DIMETHYL-3,5-DIMETHOXYCARBONYL-4-2-DIFLUOROMETHOXYPHENYL)-1,4-DIHYDROPYRIDINE (PHORIDONE)

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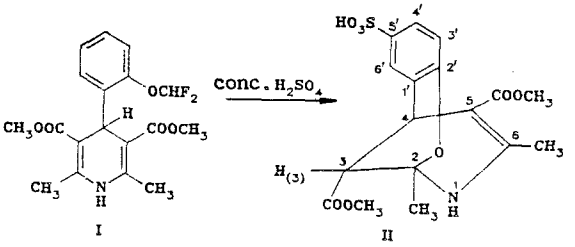
Sulfonation of 2,6-dimethyl-3,5-dimethoxycarbonyl-4-(2-difluoromethoxyphenyl)-1,4-dihydropyridine (I) with concentrated sulfuric acid gives a product (II), the ^1H NMR spectrum of which does not contain signals characteristic of the $OCHF_2$ group [1]. The nonequivalence of both the ester groups and both the C-methyl groups shows that the molecule has become asymmetric. In addition, the spectrum shows two doublets for the methine protons ($^3J_{HH}$ = 3.0 Hz). These findings indicate that intramolecular cyclization has taken place, involving the o-phenolic hydroxyl, to give the epoxy-compound (II) or its diastereoisomer differing in the orientation of the ester group.



I II

A choice between the possible diastereoisomers of (II) has now been made on the basis of $^3J_{3\text{-H},C(1')}$ and $^3J_{3\text{-H},C(5)}$ values. It is known [2] that the coupling constants when the interacting nuclei are antiperiplanar are much greater than for the other orientations. We have found these values to be ≈0 and 11.0 Hz, providing unambiguous support for the diastereoisomer (II). Under the reaction conditions, sulfonation of the phenyl ring also occurs giving, to judge from the ^1H and ^{13}C NMR spectra, the meta-derivative.

It is noteworthy that the NMR spectra obtained here for (II) are very similar to those of analogous epoxy-compounds obtained by goal-directed synthesis [3].

2,6-Dimethyl-3,5-dimethoxycarbonyl-4-(5-sulfophenyl)-2,2'-epoxy-1,2,3,4-tetrahydropyridine (II). A mixture of 3.67 g (0.01 mole) of the 1,4-dihydropyridine (I) and 40 ml of conc. sulfuric acid was stirred at room temperature for 1 h. It was then poured into 250 ml of water, neutralized with NaOH, and the crystals of sodium sulfate filtered off. On standing, crystals of (II) separated. Yield 0.4 g (10%), mp 237-240°C, R_f 0.80 (ethyl acetate–hexane–chloroform, 1:1:1). IR spectrum: 3460, 3310 (OH, NH), 1730, 1675 cm^{-1} (C=O). ^1H NMR spectrum (DMSO-D_6), δ: 1.78 (3H, s, 2-CH_3); 2.10 (3H, s, 6-CH_3); 3.05 (1H, d, J = 3.0 Hz, 3-H); 3.49 and 3.50 (3H and 3H, s, $COOCH_3$); 4.40 (1H, d, J = 3.0 Hz, 4-H); 6.67 (1H, d, J = 9 Hz, ArH); 7.29 (1H, d.d, J = 2 and 9 Hz, ArH); 7.83 ppm (1H, s, NH). ^{13}C NMR spectrum (DMSO-D_6), δ: 169.65 (3-COO): 167.01 (5-COO); 159.28 ($C_{(6)}$); 81.94 ($C_{(5)}$); 81.94 ($C_{(2)}$); 51.88 and 50.47 (CH_2O); 42.88 ($C_{(3)}$); 33.62 ($C_{(4)}$); 24.01 (6-CH_3); 19.21 (2-CH_3); 151.38 ($C_{(2')}$); 140.08 ($C_{(5')}$); 127.04 ($C_{(1')}$); 115.12 ($C_{(3')}$); 125.40 ($C_{(6')}$); 125.08 ($C_{(4')}$).

Selective coupling constants in the ^{13}C spectra wre measured as described in [4], the results being checked using the ^{13}C spectra obtained both without decoupling from protons, and with selective decoupling from ^1H.

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 0009-3122/89/2511-1316 $12.50

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ANNELATION OF THE BENZINDOLIZINE RING TO THE QUINOXALINE NUCLEUS

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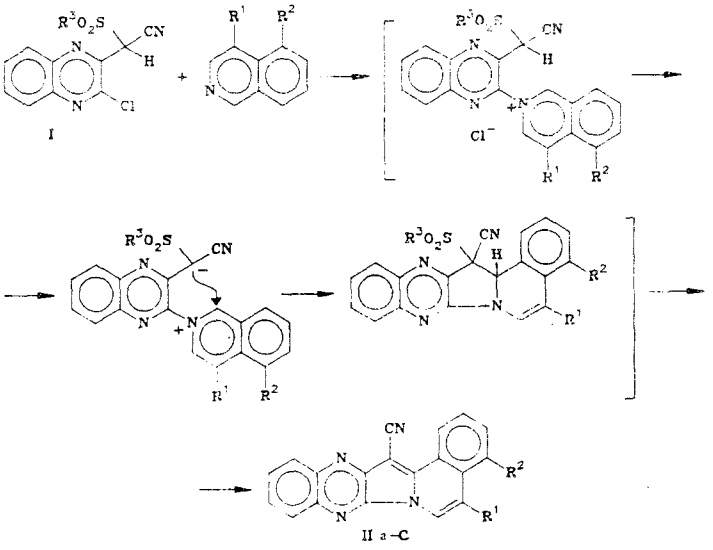
We have found that α-sulfonyl-3-chloro-2-quinoxalylacetonitriles (I) [1] react with isoquinolines (fusion at 160°C, or boiling for 2-4 h in DMF), to give benz[5,6]indolizino[2,3-b]-quinoxalines (II) [mp >300°C (from DMF)], in near-quantitative yields.



II a $R^1=R^2=H$, b $R^1=H$, $R^2=NO_2$, c $R^1=Br$, $R^2=NO_2$; $R^3=CH_3$, C_6H_5, 4-$CH_3C_6H_4$

Clearly, nucleophilic replacement of the chlorine atom occurs initially. It is characteristic that of the two possible routes for subsequent intramolecular nucleophilic attack (at $C_{(1)}$ or $C_{(3)}$ of the isoquinoline nucleus), in all instances only the first is followed, to give the above isomer. Finally, aromatization occurs by elimination of sulfinic acid. The structures of the products were established by their PMR spectra (solvent CD_3COOD), (IIa) and (IIb) showing two doublets (J = 9 Hz) at 7.9-8.6 ppm (5-H) and 9.20-9.36 ppm (6-H), and (IIc) a singlet at 9.44 ppm (6-H). The 1-H proton in the spectra of (IIa-c) resonates at low field (9.33-9.66 ppm, doublet, J = 9 Hz) owing to descreening by the adjacent nitrile group. The IR spectra of (IIa-c) show strong absorption for the conjugated nitrile group at 2210-2200 cm^{-1}.

Quinoline does not react with (I), obviously as a result of the considerable steric hindrance arising when the quaternary quinolinium salt is formed in the initial stage of the reaction.

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