NEW REARRANGEMENT IN THE QUINAZOLINE SERIES. RESOLUTION OF A RACEMATE UNDER THE INFLUENCE OF A CHIRAL SHIFT REAGENT

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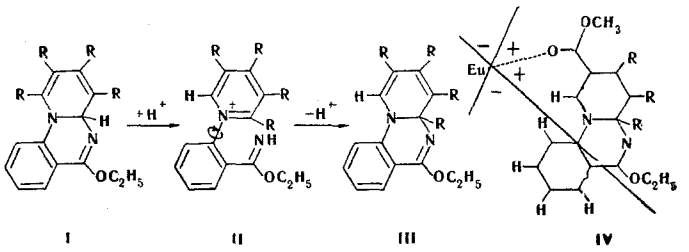
When 4-ethoxyquinazoline is refluxed with dimethyl acetylenedicarboxylate in acetonitrile it gives I, which is evidently formed in the usual way [1]. The chemical shifts* of the 4a-H (δ 5.75) and C(4a) (δ 67.8 ppm) atoms of I are determined by the orientation of the new ring. When I is refluxed with traces of hydrochloric acid it gives isomer III, the NMR spectra of which contain a 1-H peak at 8.04 ppm and the peak of an sp^3 C(4a) atom, not bonded to a proton, at 75.9 ppm. This type of rearrangement, which is apparently new in the dihydroquinazoline series, has also been observed in the thiazole series [2].



I II III IV

I-IV R=$COOCH_3$

Compound III also reacts readily with tris(dipivaloylmethanato)europium [Eu(DPM)$_3$]. The shifts of the signals of the aromatic protons induced by the Eu^{3+} ion, particularly 10-H, in contrast to the remaining protons, occur in the strong-field region. This indicates that the aromatic portion of the substrate in the adduct is found beyond the limits of the conical region, in which the geometrical factor of the dipole field of the Eu^{3+} ion has a positive sign [3]. Calculation by the method in [4] showed that this ion is coordinated primarily with the substituent in the 2 position (complex IV).

The chiral shift reagent tris[3-trifluoroacetyl-(+)-camphorato]europium [Eu(TFC)$_3$] (for example, see [5]) causes splitting of each of the peaks of the formation of two diastereomers. These splittings increase in magnitude as the $COOCH_3$ groups become more remote from the asymmetric center, i.e., in an inverse relationship to the change in their individual shifts; this is in agreement with the structure of adduct IV. Shortly after the start of the experiment, one series of four methyl signals vanishes, while the other increases correspondingly. We have also observed a change in the optical activity shortly after mixing III and Eu(TFC)$_3$ after the same interval. Being a strong Lewis acid, the shift reagent facilitates inversion of the optical center in structure III because of ring opening; as a chiral reagent, Eu(TFC)$_3$ shifts the equilibrium between the diastereomers to favor the more stable form.

*The ^1H and ^{13}C NMR spectra of solutions of the compounds (0.3 mole) in $CDCl_3$ were measured at 30° with Bruker spectrometers at 270 and 22.62 MHz, respectively, with tetramethylsilane as the internal standard. The chemical shifts are given on the δ scale, and the europium-induced shifts (in parentheses) correspond to the ratio [Eu]:[S] = 1:1.

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EXPERIMENTAL

Tetramethyl 6-Ethoxy-4a-H-pyrido[1,2-a]quinazoline-1,2,3,4-tetracarboxylate (I). A mixture of 4-ethoxyquinazoline [6] and 2.1 mole of dimethyl acetylenedicarboxylate in acetonitrile (dried with CaH_2) was refluxed for 15 h. Adduct I was chromatographed on Al_2O_3 with elution by toluene to give yellow prisms with mp 175-178° (from methanol) in 60% yield.

Tetramethyl 6-Ethoxy-4a-H-pyrido[1,2-a]quinazolino-2,3,4,4a-tetracarboxylate (IIIa). This compound was obtained in quantitative yield by refluxing I for 5 min in acetonitrile containing one drop of trifluoroacetic acid. The yellow prisms had mp 175-176° (from methanol). PMR spectrum: 1-H, 8.04 (8.50); 7-H, 7.79 dd (−0.45); 8-H, 7.32 t (−1.22); 9-H, 7.57, dt (−2.85); 10-H, 7.39 d (−5.30); $J_{7,8} = J_{8,9} = J_{9,10} = 7.8$; $J_{7,9} = 1.4$; $J_{8,10} < 1$ Hz; $OCH_aH_bCH_3$, 4.43 dq (0.34); $OCH_aH_bCH_3$, 4.27 dq (0.34); $OCH_aH_bCH_3$, 1.39 t (0.07); $J_{ab} = 11.9$; $J_{a,CH_3} = J_{b,CH_3}$ 7.3 Hz; 2-OCH_3, 3.73 (8.54); 3-OCH_3, 3.90 (1.94); 4-OCH_3, 3.73 (0.74); 4a-OCH_3, 3.55 (0.03). The results of elementary analysis of I and III for C, H, and N were in agreement with the calculated values.

LITERATURE CITED

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