An Anomalous Reaction of 10-Chloro-5*H*-benzoxazolo[3,2-*a*]quinolin-5-one with Sodium Diethyl Malonate to Form 9-Chloro-8-ethoxy-12-hydroxy-5*H*-dibenz[*c*,*f*]quinolizin-5-one

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Treatment of 10-chloro-5*H*-benzoxazole[3,2-*a*]quinolin-5-one (I) with an excess of sodium diethyl malonate at 190° for 3 hours in hexamethylphosphoramide gave, in 38% yield, 9-chloro-8-ethoxy-12-hydroxy-5*H*-dibenz[*c*,*f*]quinolizin-5-one (IV) which, on heating with acetic anhydride, afforded monoacetylated product, V. A possible reaction mechanism for the novel ring expansion reaction is suggested.

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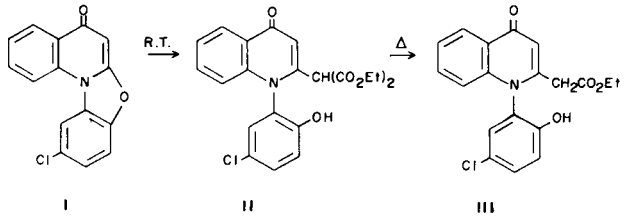
In a previous paper from these laboratories, it was reported that 10-chloro-5*H*-benzoxazolo[3,2,-*a*]quinolin-5-one (I), upon treatment with sodium diethyl malonate in hexamethylphosphoramide, affords [1-(5-chloro-2-hydroxyphenyl)-1,4-dihydro-4-oxo-2-quinolinyl]propanedioic acid diethyl ester (II). The latter underwent decarbethoxylation to give 1-(5-chloro-2-hydroxyphenyl)-1,4-dihydro-4-oxo-2-quinolinacetic acid ethyl ester (III) upon heating in hexamethylphosphoramide (1) (Scheme I).

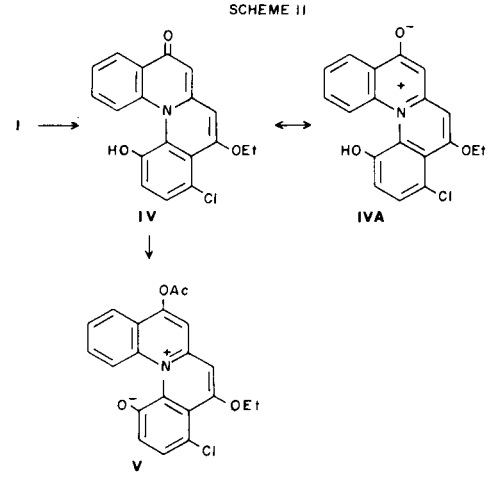
SCHEME I



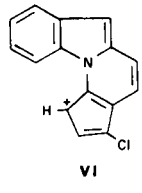
With the expectation of getting III directly from I in one pot, the reaction mixture of I and an excess of sodium diethyl malonate was heated in hexamethylphosphoramide at 190° for 3 hours. However, the product that was isolated in 38% yield from the reaction was not the expected III, but a pale yellow high melting compound (mp 294-296° dec).

The ^{1}H nmr spectrum of the product showed resonance signals at δ 1.43 (t, 3H, CH_3), 4.36 (q, 2H, CH_2), an exchangeable broad singlet at 11.50 (OH), and a complex aromatic multiplet, integrated for 8 protons, centered at 8.03. The ^{13}C nmr spectrum indicated the product to be a polycyclic aromatic compound (see Experimental Section). Based on these spectral data, elemental analysis, and physical properties of the product, the compound is proposed to have the structure of 9-chloro-8-ethoxy-12-hydroxy-5*H*-dibenz[*c*,*f*]quinolizin-5-one (IV) which probably exists mainly in a highly aromatic zwitter ionic resonance form IVA. A careful examination of the ^{1}H nmr spectrum revealed the position of the ethoxy group to be at the C_8 position: A small long range coupling (J = ~1 Hz) shown by one of the aromatic protones, presumably the proton at the C_6 eliminates other possible isomeric structures, the 7-ethoxy derivatives.

SCHEME II



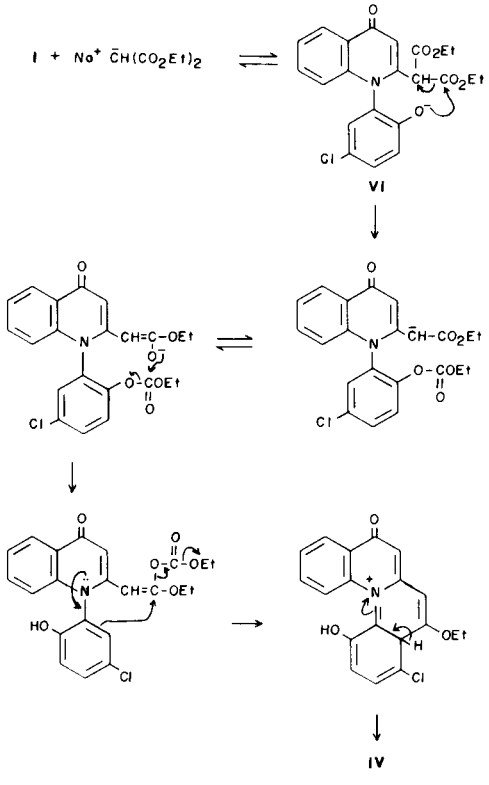
In agreement with the proposed structure, the mass spectrum of IV showed the molecular ion at m/e 339 with a relative intensity of 100. An abundant ion at m/e 238 formed by successive losses of all functional groups may be formulated as VI.



In the infrared spectrum, the only absorption band shown in the range of 1600-1800 cm^{-1} was at 1639 cm^{-1} which is ascribable to stretching vibrations of aromatic C=C bonds. When IV was allowed to react with acetic anhydride, there was obtained V, which showed an acetate methyl proton signal at δ 2.50 in the nmr spectrum. A possible alternative structure such as the 12-acetoxy derivatives, however, can not be ruled out completely, although the formation of such a compound is highly unlikely due to steric reasons.

The mechanistic pathway depicted in Scheme III is suggested for the formation of IV. The diethyl malonate attacks at the 7-position of I with resultant cleavage of the oxazole ring, giving VI. The sequential double migrations of the ethoxycarbonyl group (4) which ensue as shown in the Scheme give IX with generation of a facile leaving group at the vinylic position. Subsequent intramolecular cyclization affords IV.

SCHEME III



EXPERIMENTAL

Melting points were taken in capillary tubes (Thomas-Hoover Melting point apparatus) and are uncorrected. Ir spectra were obtained in potassium bromide pellets using a Perkin-Elmer 21 spectrophotometer. Uv absorption spectra were recorded with a Perkin-Elmer Model 450-uv-visible NIR spectrophotometer. ^{1}H and ^{13}C-nmr spectra were determined in DMSO-d_6 solution on a Varian FT-88 nmr spectrometer using tetramethylsilane as the internal reference. Combustion elemental analyses were performed by the Analytical Section of these Laboratories using Perkin Elmer model 240 elemental analyzer. Mass spectra were obtained with an Associated Electrical Industries MS-9 high resolution mass spectrometer.

9-chloro-8-ethoxy-12-hydroxy-5*H*-dibenz[*c,f*]quinolizin-5-one (IV).

Sodium hydride (1.0 g of 50% oil dispersion) was washed with hexane 3 times, then suspended in hexamethylphosphoramide (50 ml). Diethyl malonate (3.5 g) was added and the mixture was stirred at room temperature for 0.5 hour. Addition of 10-chloro-5*H*-benzoxazolo[3,2-*a*]quinolin-5-one (I, 5.4 g) followed. The resulting mixture was heated at 190° for 1 hour. At this point an additional amount of sodium hydride (0.5 g of oil dispersion) was added and heating was continued for 2 hours. After cooling to room temperature, it was diluted with water (350 ml) and the aqueous solution was neutralized with concentrated hydrochloric acid. The precipitate that separated was collected on a filter and recrystallized from dimethylformamide giving IV (2.6 g, 38%), mp 294-296° dec; ir: 1639 cm^{-1}; uv max (ethanol) mμ (ϵ): 226 (shoulder, 24900), 239 (31200), 272 (28400), 281 (24600), and 298 (20100); ^{13}C-nmr: δ 15.22, 59.68, 95.32, 96.78, 114.66, 177.20, 120.00, 122.17, 124.37, 124.54, 124.98, 126.73, 128.57, 131.81, 133.22, 136.21, 144.53, 154.84, 165.07; ms (E.I.): m/e (relative intensity) 339 (M^+, 100), 311 (M^+-CO, 28), 294 (M^+-OEt, 26.5), 267 (22), 266 (10), 238 (8), 203 (7), 202 (8).

Anal. Calcd. for $C_{19}H_{14}ClNO_3$: C, 67.17; H, 4.31; N, 4.12. Found: C, 67.16; H, 4.15; N, 4.12.

5-(Acetoxy)-9-chloro-8-ethoxy-10-hydroxydibenz[*c,f*]quinolizium Hydroxide Inner Salt (V).

A mixture of IV (1.7 g), acetic anhydride (50 ml) and pyridine (10 drops) was heated under reflux for 45 minutes, then chilled in ice. The precipitate that separated was collected on a filter and washed with ethanol, giving V (1.75 g, 92%), mp 166-168°; ir: 1770, 1690 cm^{-1}; uv max (ethanol) mμ (ϵ): 226 (shoulder, 27500), 242 (32900), 267 (28700), 275 (32400), 284 (shoulder, 25000), and 295 (20800); nmr: δ 1.42 (3H, t), 2.50 (3H, s), 4.36 (2H, q) and 8.03 (8H, aromatic multiplet); ms (E. I.): m/e 381 (M^+), 339, 311, 294 and 267.

Anal. Calcd. for $C_{21}H_{16}ClNO_4$: C, 66.06; H, 4.22; N, 3.67. Found: C, 66.08; H, 4.15; N, 3.71.

REFERENCES AND NOTES

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