Tetrahedron Vol. 41, No. 23, pp. 5615 to 5618, 1985
Printed in Great Britain.

0040-4020/85 $3.00 + .00
Pergamon Press Ltd.

INTRAMOLECULAR, TWO-SUBSTITUENT, CONSECUTIVE AND SEQUENTIAL (CONSEQ) MIGRATIONS: X-RAY STRUCTURE OF AN INDENO[1,2,3-DE]QUINOLINE PRODUCT

LOUIS DENNER, JOHANNES L.C. MARAIS, and BENJAMIN STASKUN*

Department of Chemistry, University of the Witwatersrand,
Johannesburg, South Africa.

(*Received in UK* 11 *July* 1985)

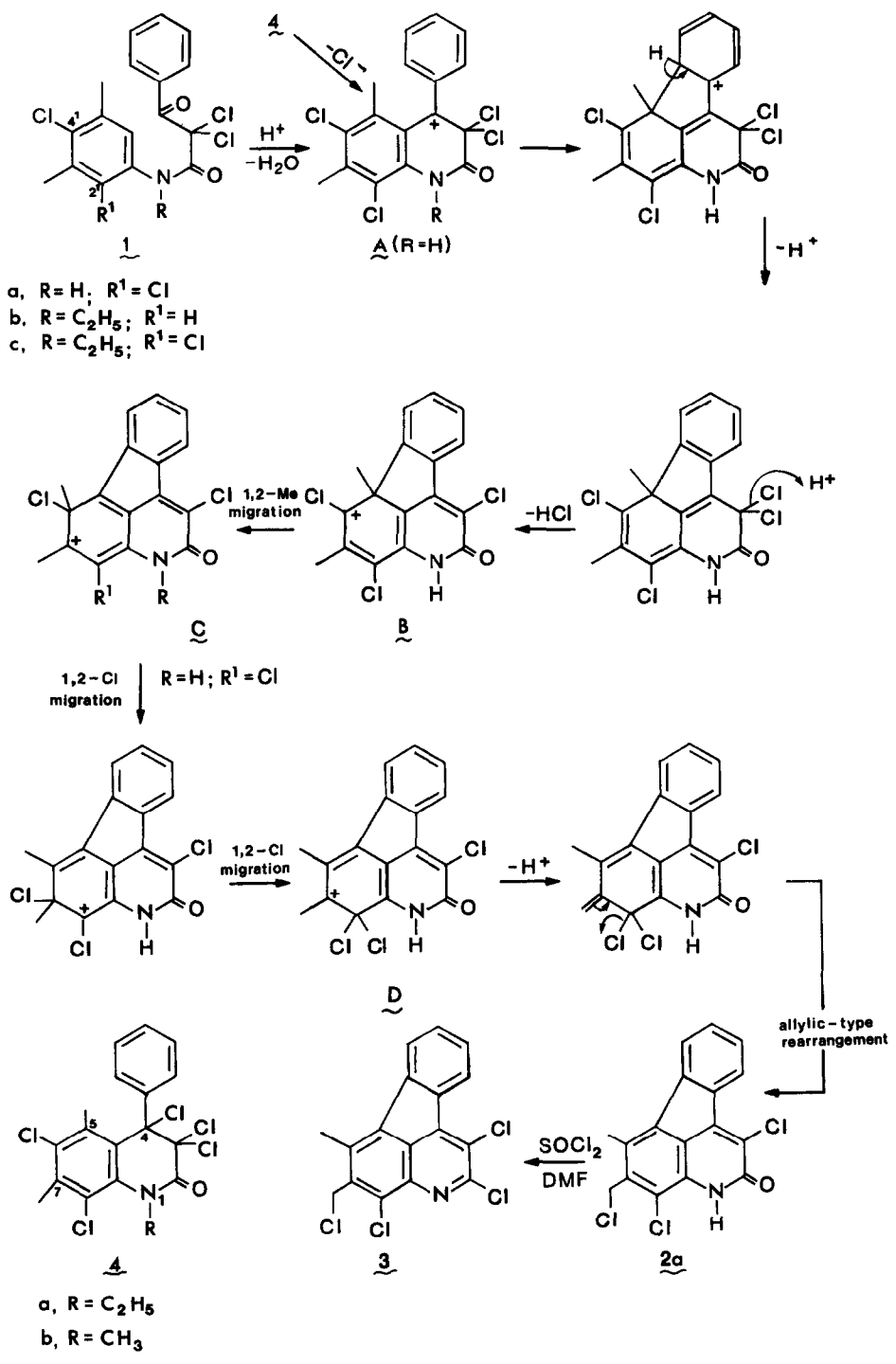
Abstract - Evidence, including the X-ray structure verification of a crucial reaction product, is presented in support of the postulation that intramolecular, two-substituent, consecutive and sequential migrations accompany the formation of certain indeno[1,2,3-de]quinolinones.

Whereas intramolecular substituent migrations accompanying chemical reactions are extensively documented, there is little concerning intramolecular, two-substituent 1,2-shifts that occur consecutively and in sequence, and here termed conseq migrations. We present supporting evidence for the latter concept which was earlier invoked[1-3] in an attempt to rationalise the acid-catalysed conversion of 3-keto amide (1a) to indeno[1,2,3-de]quinolin-2-one (2a). This transformation (Scheme 1) envisages the initial cyclisation of (1a) with production of an ion, (A; R = H), endowed with the propensity to undergo ring junction. There then forms an intermediate ion, (B), (the migration origin) from which issues a sequence of 1,2-substituent (conseq) migrations eventually leading to (D), (the migration terminus). Product (2a) then arises from (D) via an allylic-type rearrangement[4] as indicated.

Such a succession of migratory events (B → D) appears to have no literature analogy and is obviously based on the validity of the structure assigned to (2a). Because of uncertainty[1] attending this latter aspect an X-ray structure verification was deemed essential. In the absence of a suitable crystal of (2a), an acceptable one of the 2-chloro derivative (3) (formed from (2a) and thionyl chloride)[5] was grown (in $CHC\ell_3$ overlaid with hexane). The crystal structure of (3) (Fig. 1) which, incidentally, is the first of the indeno[1,2,3-de]quinoline system, completely vindicates the formulation of (3), and by extension, also that of the crucial product (2a).

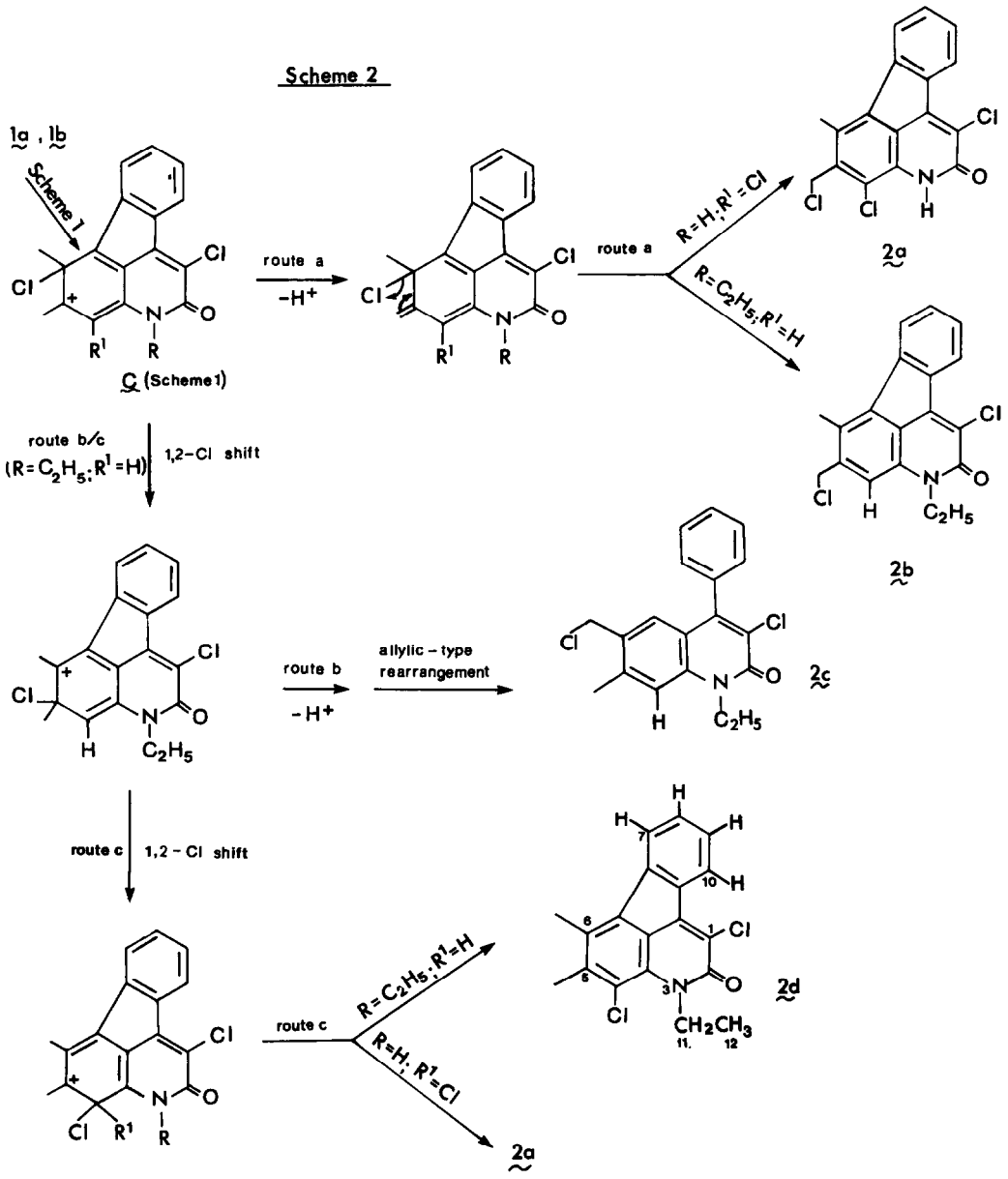
We next considered the feasibility of (2a) arising from (1a) via a shorter and more direct pathway (route a, Scheme 2) and which would obviate the need for the postulated consecutive and sequential two-substituent 1,2-shifts. To examine this prospect, the 3-keto amide (1b)[1] was cyclised in conc H_2SO_4 with due consideration of the reaction options available to an intervening ion (C) ($R=C_2H_5$; $R^1=H$) (Scheme 2): One possibility (route a) envisages a proton loss followed by an allylic rearrangement and production of (2b); another option (route b) invokes a preferential[6] 1,2-Cℓ migration followed by a proton loss and an allylic rearrangement to give (2c). In essence, progression of (C) along either route a and/or route b would be expected to provide the chloromethyl derivative(s) (2b) [and/or (2c)]. A third alternative (route c) makes use of two consecutive 1,2-Cℓ shifts, and should yield (ultimately), in contrast, a product (2d) void of a chloromethyl group. In the event, the ^{1}H-NMR spectrum ($CDC\ell_3$) of the crude, total product [TLC ($CHC\ell_3$-benzene) revealed 3 yellow constituents] exhibited no significant signal(s) attributable to

Scheme 1



the aforementioned methylene protons near δ 5. Furthermore, the major indenoquinolinone product which was isolated had analytical and spectral properties[1] including a nuclear Overhauser effect[7] consistent with a structure (2d). Accordingly, we discount the speculations depicted in route(s) a and/or b in Scheme 2, in favour of route c [for (2d)] and its continuation with an allylic rearrangement in the case of (1a) to yield (2a).

Scheme 1 also accommodates and receives support from observations[3,8] with the recently



accessible 3,4-dihydro-3,3,4-trichloroquionolin-2-one 4 in conc H_2SO_4: it is contended that 4 ionises directly affording precursor ion A (R = CH_3 or C_2H_5); A then traverses the conseq pathway outlined in the scheme to yield the corresponding 5-chloromethylindeno[1,2,3-de]quinolin-2-one 2. The structure of the substrate (e.g., 4a), originally[3] assigned on the basis of spectroscopic data, has now been unequivocally verified from an X-ray determination (Fig. 2). This result allows for the specification of each substituent's disposition in the species A (R = C_2H_5) immediately prior to the onset of the aforementioned cyclisation-rearrangement events.

EXPERIMENTAL

The ^{1}H-NMR (normal) spectrum of 2d and that of the crude reaction product from 1b were recorded at 80MHz on a Bruker WP-80 instrument using TMS as internal standard. The NOESY experiment ($CDC\ell_3$, 30°C; mixing time = 0.5 sec) was done at 500 MHz using a Bruker WM-500 spectrometer. 1,4-Dichloro-5,6-dimethyl-3-ethylindeno[1,2,3-de]quinolin-2-one 2d. A mixture of substrate 1b (115mg; purified by preparative TLC) and conc H_2SO_4 (0.3ml) was reacted at 95°C for 3 min and diluted with water (∿10ml). The acid-insoluble product was collected by filtration, washed with water, and air-dried (100mg; TLC (benzene-$CHC\ell_3$ 3:1) showed a mixture with 2d as a

major component; the δ 4.85-5.5 region in the ^{1}H-NMR($CDC\ell_3$) was free of significant absorptions). A pure sample of 2d was obtained by chromatography[1]: ^{1}H-NMR($CDC\ell_3$) δ 1.49 (3H,t,J=7Hz,CH_2CH_3), 2.52(3H,s,5-CH_3), 2.61(3H,s,6-CH_3), 4.76(2H,q,J = 7Hz, $\underline{CH_2}CH_3$). 7.3-7.6(2H,m,8-H,9-H), 7.85(1H,dd,J = 7,2 Hz,7-H),[3] 8.3(1H,dd,J = 7,2 Hz,10-H). The NOESY spectrum of 2d was obtained as a 2-D contour plot. Off-diagonal peak correlations were established with assurance between 7-H and 6-CH_3; 8-H and 9-H; 11-CH_2 and 12-CH_3. No significant interaction of the 11-CH_2 protons with either of the aromatic methyl[2] groups was revealed. The expected peak correlations between 6-CH_3 and 5-CH_3; 7-H and 8-H; 9-H and 10-H, could not be established with a high level of confidence.

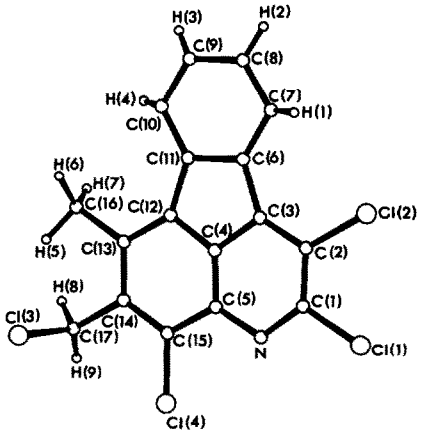


Figure 1 The structure of 3 showing the crystallographic numbering scheme

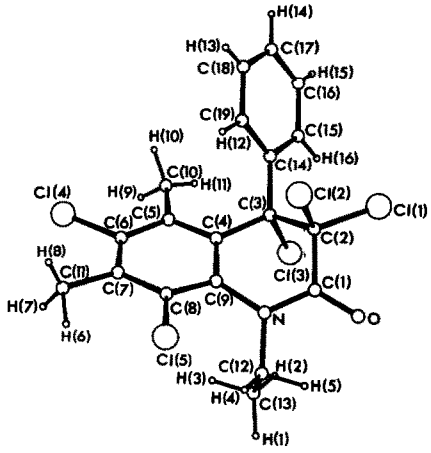


Figure 2 The structure of 4a showing the crystallographic numbering scheme

X-Ray crystallographic analysis

Crystal data for (3): $C_{17}H_9NC\ell_4$, M = 369.1, triclinic, space group $P\bar{1}$, a = 10.417(1), b = 9.455(1), c = 8.555(1)Å, α = 106.64(1), β = 90.68, γ = 111.51°, U = 744.5Å^3, Z = 2, D_c = 1.77g cm^{-3}, F(000) = 372, Cu-Kα radiation, λ = 1.5418Å, μ(Cu-Kα) = 59.9 cm^{-1}. Data were collected on a Philips PW1100 diffractometer to θ = 55°. A total of 2205 independent reflections were measured; of these 2165 had $|Fo|>\sigma(|Fo|)$ and were treated as observed and used in the subsequent analysis. The crystal used was 0.25 x 0.21 x 0.15 mm^3 in size. No absorption correction was applied. The structure was solved by direct methods and refined by full matrix least squares to R 0.0640 and R_w 0.0598 using the program SHELX[9]. Anisotropic temperature factors were used for all non-hydrogen atoms.

Crystal data for (4a): $C_{19}H_{16}NOC\ell_5$, M = 451.6, monoclinic, space group $P2_1/n$, a = 19.818(1), b = 10.714(1), c = 9.214(1)Å, β = 99.43(1)°, U = 1929.9Å^3, Z = 4, D_c = 1.55g cm^{-3}, F(000) = 920, Mo-Kα radiation, λ = 0.7107Å, μ(Mo-Kα) = 6.91 cm^{-1}. Data were collected on a Philips PW1100 diffractometer to θ = 25°. A total of 2639 independent reflections were collected; of these 2472 had $|Fo|>\sigma(|Fo|)$ and were treated as observed and used in the subsequent analysis. The crystal used was 0.56 x 0.11 x 0.12 mm^3 in size. No absorption correction was applied.[9] The structure was solved by direct methods using SHELX. Final full matrix least squares refinement utilised anisotropic temperature factors for all non-hydrogen atoms and converged to R 0.0655 and R_w 0.0650. To ensure meaningful refinement of the structure, the C(12)-C(13) bond length was constrained to a value of 1.54Å rendering the estimated standard deviation for this bond statistically meaningless.

The atomic co-ordinates for this work are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW. Any request should be accompanied by the full literature citation for this communication.

Acknowledgements - We thank the CSIR (Pretoria) for financial support and computing facilities, and Jon Albain for intensity data collection.

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