One-pot Preparation of Derivatives of the Unknown Fluoreno[2,3,4-*i,j*]isoquinoline Ring from Conjugated Ketenimines by a Consecutive Electrocyclic Ring-closure/Claisen Rearrangement/Intramolecular Diels–Alder Cycloaddition/Double Aromatization Process

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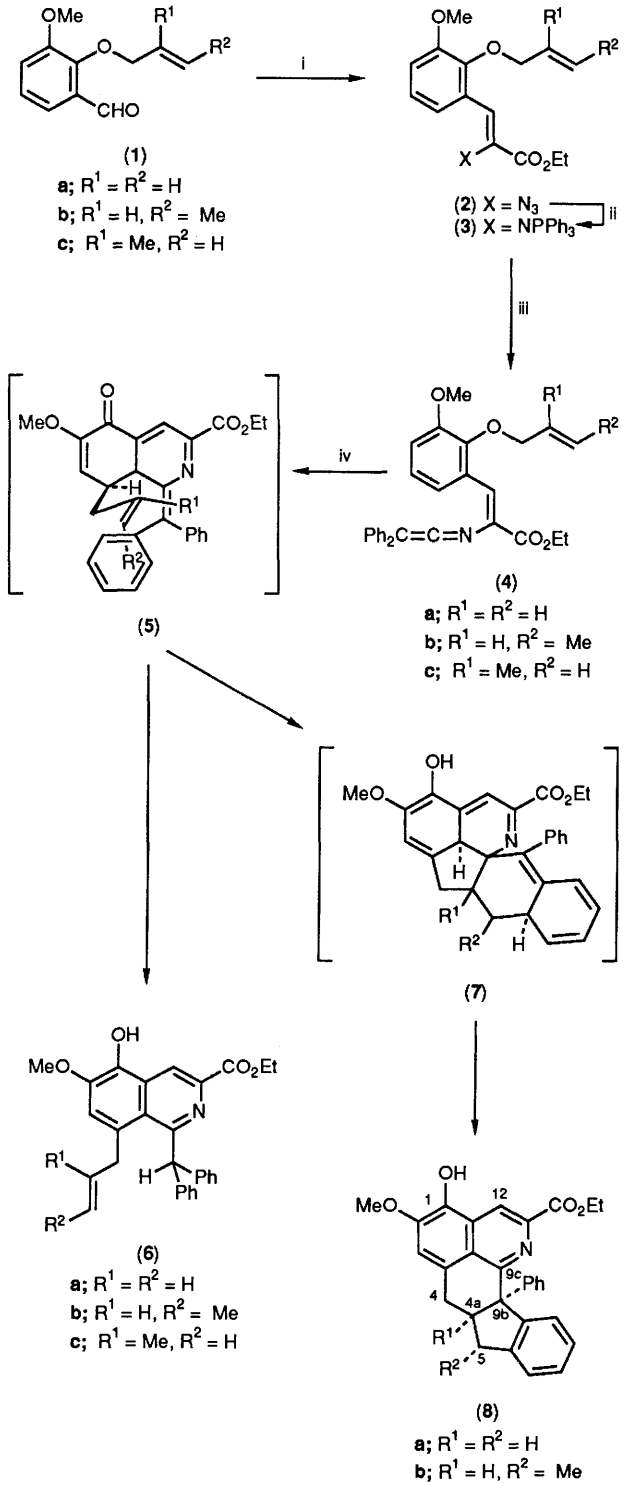
A short synthesis of fluoreno[2,3,4-*i,j*]isoquinoline derivatives (**8**) based on a new method of three consecutive annelations which involves thermal cyclization of conjugated ketenimines is described; the crystal structure of (**8**) has been determined.

Conjugated heterocumulenes exhibit a rich chemistry of unusual synthetic promise.[1] Especially, cycloaddition reactions of such unsaturated heterocumulenic systems as ketenes, isocyanates, isothiocyanates, and carbodiimides, provide an attractive entry to a variety of carbocycles and heterocycles. However, the chemistry of conjugated ketenimines has received limited attention; only the preparation and some intra- and inter-molecular cycloaddition reactions have been reported.[2] Continuing our interest in the preparation and synthetic applications of C=C-conjugated heterocumulenes,[3] we report herein an efficient synthesis of the unknown fluoreno[2,3,4-*i,j*]isoquinoline ring system, related to the aporphine skeleton, based on the strategy shown in Scheme 1. Our synthetic approach, which involves as the key step a consecutive electrocyclic ring-closure/Claisen rearrangement/intramolecular Diels–Alder reaction/double aromatization process, has surprisingly been found to be useful in the construction of two fused carbocycle rings.



Scheme 1. *Reagents and conditions*: i, $EtO_2CCH_2N_3$, NaOEt, EtOH, −15 °C; ii, Ph_3P, ether, room temp.; iii, $Ph_2C{=}C{=}O$, toluene, room temp.; iv, sealed tube, toluene, 150 °C, 16 h.

The key intermediates (**3**) were easily prepared in 50% overall yield from the commercially available 2-hydroxy-3-methoxybenzaldehyde by standard chemistry: *O*-allylation, condensation with ethyl azidoacetate, and Staudinger reaction with triphenylphosphine. Aza Wittig-type reaction of the

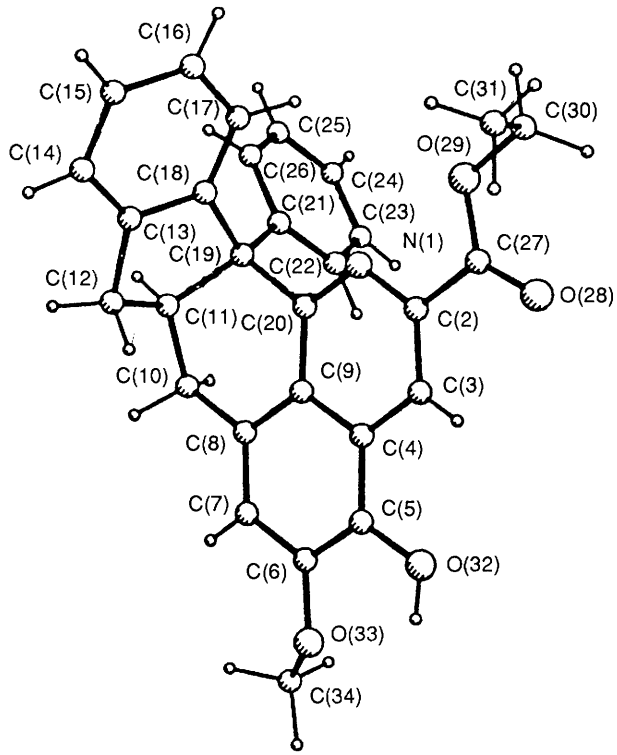


Figure 1. Structure of (**8a**), showing the numbering of the atoms.[7]

Table 1. Yields of isoquinolines (**6**) and fluoreno[2,3,4-*i*,*j*]isoquinolines (**8**).[a]

R^1	R^2	(**6**)/%	(**8**)/%
H	H	17	36
H	Me	27	35
Me	H	46	—

[a] All new compounds described here had spectral and microanalytical properties in agreement with the assigned structures.

iminophosphoranes (**3**) with diphenylketene in dry toluene at room temperature led to the corresponding ketenimines (**4**), which could be isolated as viscous oils by means of short column chromatography. When a toluene solution of (**4a**) was heated at 150 °C for 16 h two compounds were obtained and separated by chromatography (silica gel, ethyl acetate/hexane 4:6 as eluent). The minor product (17%; see Table 1) was found to be the 1-benzyl isoquinoline derivative (**6a**). The major product (36%) has a complex structure. The ^1H and ^{13}C NMR spectra indicated that the two phenyl groups are nonequivalent and one of them shows an *ortho*-disubstituted pattern. The original allyl moiety now appears as a three-sp^3-carbon chain with two methylene and one central methine group, all of them linked to quaternary carbons; the methylene protons of the ester moiety and the aforementioned methylene proton are anisochronous, which clearly indicates the presence of at least one asymmetric centre. In addition the ^{13}C NMR spectrum reveals the presence of one sp^3 quaternary

carbon atom.† An *X*-ray structure determination‡ confirmed the structure (**8a**) shown in Figure 1.

Reaction of the related ketenimine (**4b**) also resulted in smooth formation of the isoquinoline derivative (**6b**) and the pentacyclic compound (**8b**). The ^1H and ^{13}C NMR spectra of (**8b**) exhibited signals very similar to those of compound (**8a**). Likewise, other analytical and spectral data confirmed the structure shown. However, ketenimine (**4c**) by thermal treatment led to (**6c**) as the only reaction product in moderate yield.

Compounds (**6**) were recovered unchanged after prolonged heating (toluene, 160 °C, 3 days). This observation and the fact that heating of (**4**) in the presence of radical scavengers did not affect the product composition, strongly suggest a mechanism for the conversion (**4**) → (**6**) + (**8**) involving initial 6π-electrocyclization with the aryl group as a 2π-component and subsequent Claisen rearrangement to give (**5**). Aromatization of (**5**) to (**6**) occurs by two consecutive proton shifts. The formation of the pentacyclic compounds (**8**) from intermediate (**5**) can be explained if initial intramolecular Diels–Alder cycloaddition leading to the pentacyclic fused blocked ring system (**7**) takes place. This cycloadduct, under the reaction conditions, undergoes aromatization of both phenyl and isoquinoline rings with concomitant migration of a substituent at the ring juncture of the fused blocked ring, involving a ring-opening/ring-closure sequence to afford (**8**).

In conclusion, this work shows for the first time that easily available conjugated ketenimines undergo a one-pot consecutive four-step process to afford derivatives of the previously unreported fluoreno[2,3,4-*i,j*]isoquinoline ring system. Essentially, this process involves the formation of four C–C single bonds, and two asymmetric centres, one of them being a quaternary carbon atom, with a high degree of stereochemical control. It can be presumed that related ketenimines may also undergo this new type of consecutive process to give structurally complex nitrogen heterocycles related to the aporphine alkaloids.

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† *Spectroscopic data* for (**8a**): ^1H NMR (200 MHz, $CDCl_3$) δ 1.34 (t, 3H, *J* 7.1 Hz, *Me*–CH_2), 2.67 [dd, 1H, *J* 14.8 and 10.4 Hz, H-C(5)], 2.91 [dd, 1H, *J* 15.6 and 1.7 Hz, H-C(4)], 3.00 [dd, 1H, *J* 14.8 and 2.3 Hz, H-C(5)], 3.14 [dddd, 1H, *J* 10.4, 4.4, 2.3, and 1.7 Hz, H-C(4a)], 3.23 [dd, 1H, *J* 15.6 and 4.4 Hz, H-C(4)], 3.90 (s, 3H, MeO), 4.33 (dq, 1H, *J* 11.0 and 7.1 Hz, CH_2O), 4.40 (dq, 1H, *J* 11.0 and 7.1 Hz, CH_2O), 6.22 (s, 1H, OH), 6.85—6.90 (m, 2H, aromatic), 7.13—7.32 (m, 7H, aromatic), 7.80 (d, 1H, *J* 7.2 Hz, aromatic), and 8.63 [s, 1H, H-C(12)]; ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.25 (*Me*–CH_2), 28.52 [C(4)], 35.76 [C(5)], 50.91 [C(4a)], 58.54 (*Me*O), 61.03 (Me–CH_2), 62.28 [C(9b)], 114.24 [C(3)], 115.89 [C(12)], 122.25 (q), 123.61, 125.97, 126.12 (q), 126.34, 127.13, 127.94, 128.27, 129.20, 137.99 (q), 141.37 (q), 142.61 (q), 144.47 (q), 148.17 (q), 148.88 (q), 159.92 [C(9c)], and 166.21 (CO) (one quaternary carbon not observed). Values assigned by decoupling methods and 2D ^1H-^{13}C correlation techniques.

‡ *Crystal data* for (**8a**): $C_{29}H_{25}NO_4$, *M* = 451.1, triclinic, space group $P\bar{1}$, *a* = 7.857(2), *b* = 11.039(3), *c* = 14.512(6) Å, α = 73.80(3), β = 78.92(3), γ = 72.98(2)°, *U* = 1147.4(6) Å^3, *Z* = 2, D_x = 1.31 g cm^{-3}, Mo-K_α, λ = 0.71069 Å, μ = 0.9 cm^{-1}, *F*(000) = 476, *T* = 291 K. D_m not measured. Parallelepiped crystal with dimensions 0.3 × 0.3 × 0.25 mm. Lattice parameters refined using fifteen reflections in the range 4 ≤ 2θ ≤ 21°. Syntex $P2_1$ four circle diffractometer, graphite monochromatized Mo-K_α radiation. 4515 Independent reflections with sin θ/λ ≤ 0.62 Å^{-1}; $-9 \leq h \leq 9$, $-12 \leq k \leq 13$, $0 \leq l \leq 17$, 2550 with $I \geq 2.5\sigma(I)$. A standard reflection (1 0 0) was checked every 50 reflections, no significant deviation. Structure solved by direct methods using SHELXS86.[4] H atoms from difference Fourier synthesis, except those of C(34) in computed positions. Anisotropic least squares refinement[5] using *F*; H isotropic with common refined temperature factor (*B* = 5.57 Å^2). $w = 1/(\sigma^2 + 0.00112F^2)$, *R* = 0.056, R_w = 0.060, *S* = 1.39 for 2550 observed reflections. Final maximum shift to error = 0.06. Maximum and minimum heights in final difference Fourier synthesis = 0.34 and −0.29 e Å^{-3}. Atomic scattering factors from International Tables.[6] Atomic co-ordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors, Issue No. 1.

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