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The Preparation and Crystal Structure of Ethyl 5-*p*-Tolylsulfonyl-2,4,5,6-tetrahydropyrrolo[3,4-*c*]pyrrole-1-carboxylate

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The potential porphyrin precursor ethyl 5-*p*-tolylsulfonyl-2,4,5,6-tetrahydropyrrolo[3,4-*c*]pyrrole-1carboxylate has been synthesized and its crystal structure determined by X-ray methods, giving a refinement residual $R \ 0.038$ for 5130 observed reflections. Crystals are triclinic, space group $P \ 1$, with Z = 4 in a cell of dimensions $a \ 10.5030(6)$, $b \ 11.2843(8)$, $c \ 15.236(1)$ Å, $\alpha \ 109.419(6)$, $\beta \ 97.697(6)$, $\gamma \ 95.651(6)^{\circ}$. The two molecules in the crystallographic repeating unit are pseudo-mirror-related, and the heterocyclic system is almost planar in both molecules.

Introduction

For some years we have been interested in pyrroles with fused heterocyclic rings, particularly the tetrahydropyrrolo[3,4-c]pyrrole system, e.g. (1), as precursors to synthetic hydrophilic porphyrins with pyrroline rings fused to the β -positions. We reported syntheses and Xray crystal structures of two related molecules, namely 2methylpyrrolo[3,4-c]pyrrole-1,3(2H,5H)-dione (2)¹ and N^3, N^4 -dimethylpyrrole-3,4-dicarboxamide (3),² and our efforts (published jointly with Brown and coworkers)³ to produce the fused ring by cyclizations of various 3,4-disubstituted pyrroles. Recently, Smith's group succeeded in preparing porphyrins with one β -fused pyrroline ring, and dimers and trimers incorporating such units.^{4,5} We⁶ and others⁷⁻⁹ independently



developed the cycloaddition of ethyl isocyanoacetate to vinyl sulfones as a useful method of preparation of various pyrrole-2-carboxylic esters. By using 3-sulfonylpyrrolines as substrates, this modification of the Barton–Zard synthesis¹⁰ affords the desired pyrrolo[3,4-c]pyrrole-1-carboxylates. As part of these studies, we prepared the N-tolylsulfonyl derivative (4) from the corresponding pyrroline (5), and obtained good quality single crystals of the former. We now report the results of our X-ray structure determination of (4), which constitutes the first crystal structure of the tetrahydropyrrolo[3,4-c]pyrrole ring system.

Results and Discussion

The precursor pyrroline (5) was prepared by treatment of 2,3-bis(phenylsulfonyl)buta-1,3-diene¹¹ with *p*-toluenesulfonamide and sodium hydride in tetrahydrofuran. This method was suggested by the work of Padwa and Norman on similar cyclizations using primary amines.¹² We also tried sodium methoxide, triethylamine and 1,8-diazabicyclo[5.4.0]undec-7-ene as bases. Only the last of these produced useful yields of the pyrroline, but we were unable to purify the product without severe losses during column chromatography. Using a large excess of both sodium hydride and sulfonamide, we obtained over 80% crude yield of (5), pure enough to carry forward to the second cyclization. Addition of (5) and ethyl isocyanoacetate to sodium hydride in tetrahydrofuran in the usual molar ratio of $1:2:2^6$ gave (4) after column purification. The crystals that formed directly from evaporation of pure fractions in ethyl acetate/hexane were found to be suitable for X-ray structure determination.



Fig. 1. Molecular conformation and atom numbering scheme for molecule 1 in crystals of compound (4). Unless otherwise indicated, atoms are carbon.

Compound (4) was found to crystallize with two independent and conformationally different molecules (molecules 1 and 1') in the crystallographic asymmetric unit (Fig. 1 shows molecule 1). These molecules are pseudo-mirror-related, one being transformed into the other by rotation of the p-tolyl group about the N(7)-S(1) bond vector. The similarities between the molecules may be observed in the respective magnitudes of the torsion angles along the ethoxycarbonyl and p-tolyl groups for molecules 1 and 1' (although the signs are opposite) {N(1)-C(2)-C(16)-O(4) $[176 \cdot 5, -171 \cdot 9(2)^{\circ}];$ C(2)-C(16)-O(4)-C(17) [-176.0, 178.4(2)°]; C(16)-O(4)-C(17)-C(18) [-178.4, 173.6(2)°]; N(7)-S(1)-C(9)-C(10) [-86·3, 86·4(2)°]; C(6)-N(7)-S(1)-C(9) $[73 \cdot 9, -69 \cdot 5(2)^{\circ}]$. The ester carbonyl lies in the syn orientation with respect to the pyrrolic N–H. The folding of the reduced ring is greater for molecule 1 than for molecule 1', as measured by the torsion angles C(4)-C(3)-C(6)-N(7) [8 · 4, $-3 \cdot 0(2)^{\circ}$] and C(3)-C(3)-C(3)-C(3)-C(3)-C(3)C(4)-C(8)-N(7) $[-6\cdot9, 1\cdot4(2)^{\circ}]$, but the deviations of the bicyclic core from planarity are small for both molecules.

The ethyl ester (4) was subjected to saponification and decarboxylation by heating with a 50-fold excess of potassium hydroxide in ethylene glycol at 165°. The α free pyrrole (1) was isolated by column chromatography and crystallized to give a product indicated to be pure by elemental analysis and spectroscopy, with melting point 190–192°. This compound was previously reported by Jendralla and Fischer, who prepared it on a large scale by a totally different route from 1,4-dibromo-2,3-bis(bromomethyl)but-2-ene.¹³ Their product had identical spectral data to ours, but a different melting point $(176-178^{\circ})$.

Attempts to form porphyrins by cyclotetramerization of (1) by using either formaldehyde or benzaldehyde under various acidic conditions met with very limited success. Traces of porphyrin were detected by the presence of a Soret band in the visible spectra of the crude tarry products, but no pure porphyrins have so far been isolated.

Experimental

Ethyl isocyanoacetate¹⁴ and 2,3-bis(phenylsulfonyl)buta-1,3diene¹¹ were prepared as described. Tetrahydrofuran was freshly distilled from sodium and benzophenone. All solvents were analytical reagent grade. Silica gel for flash chromatography was Merck 9385, 230–400 mesh.

3-(Phenylsulfonyl)-N-(p-tolylsulfonyl)-3-pyrroline (5)

To a suspension of sodium hydride (0.69 g of 60% dispersion)in oil, c. 17 mmol, prewashed with hexane) in tetrahydrofuran (60 ml), under nitrogen, was added 2,3-bis(phenylsulfonyl)buta-1,3-diene (1 \cdot 2 g, 3 \cdot 6 mmol). Solid *p*-toluenesulfonamide (2 \cdot 66 g, $15 \cdot 5$ mmol) was added in c. $0 \cdot 5$ g portions over a few minutes, causing evolution of hydrogen. After 20 min, t.l.c. analysis showed the absence of starting butadiene. Ethanol (1 ml) was added to quench excess sodium hydride, then the solvents were removed under vacuum. Dichloromethane (100 ml) was added, and the solution was washed successively with 2 M HCl, water, 10% NaOH, and water (2×50 ml each). The dichloromethane solution was dried over anhydrous sodium sulfate, and the solvent was evaporated under vacuum to yield a pale yellow oil $(1 \cdot 16 \text{ g})$ which was used without further purification for the next step. N.m.r. (CDCl₃) δ 2·44, s, CH₃; 4·23, symmetrical m, $2 \times CH_2$; 6.61, quintet, J 1.8 Hz, =CH; 7.31, 7.85, AA'BB', tolyl ring H; 7.5-7.7, m, Ph ring H. Mass spectrum (e.s.i.) $386 \cdot 3 (M+Na)^+$.

Ethyl 5-(p-Tolylsulfonyl)-2,4,5,6-tetrahydropyrrolo[3,4c]pyrrole-1-carboxylate (4)

To a suspension of sodium hydride (0.27 g of 60% dispersion)in oil, c. 6.8 mmol, prewashed with hexane) in tetrahydrofuran (20 ml) was added dropwise over 10 min, under nitrogen, a mixture of the crude 3-pyrroline (5) $(1 \cdot 16 \text{ g}, c. 3 \cdot 2 \text{ mmol})$ and ethyl isocyanoacetate (0.7 ml, 6.4 mmol) in tetrahydrofuran (20 ml). After stirring for 2 h at room temperature, ethanol (0.5 ml) was added, and the solvents were removed under vacuum. Dichloromethane (100 ml) was added, and the solution was washed with saturated brine $(2 \times 50 \text{ ml})$, dried over anhydrous sodium sulfate, and the solvent was evaporated under vacuum to yield a brownish oil. N.m.r. spectroscopy showed the presence of the required ester and a large number of minor components. The crude product was subjected to column chromatography, eluting with 1:1 ethyl acetate/hexane. T.l.c. and n.m.r. analysis of the fractions showed a narrow band of very pure material, which formed colourless plates upon slow evaporation of the combined solutions (83 mg, 8%), m.p. 187.5-189° (Found: C, 57.4; H, 5.4; N, 8.2. C₁₆H₁₈N₂O₄S requires C, 57.5; H, 5.4; N, 8.4%). ¹H n.m.r. (CDCl₃) δ 1.33, t, CH₂CH₃, J 7·0 Hz; 2·41, s, ArCH₃; 4·27, q, CH₂CH₃, J7·0 Hz; 4·42, 4·56, br s, 2×CH₂; 6·61, d, pyrrole CH; 7·31, 7·77, AA'BB', tolyl ring H; 8·93, br, NH. ^{13}C n.m.r. (CDCl₃) δ 14.4, 21.36, 48.0, 48.9, 60.4, 113.6, 114.5, 124.4, 127.3, 129.4, 127.7, 134.4, 143.3, 160.4. Mass spectrum (e.s.i.) 357 (M+Na)⁺. I.r. ν_{max} (KBr) 3721s, 1682s, 1432m, 1346m, 1328s, 1166s, 1145m, 664m cm⁻¹.

 Table 1. Atomic coordinates and equivalent isotropic displacement parameters for (4)

 $U_{\rm eq}$ is defined as one-third of the trace of the orthogonalized $U_{\rm eq}$ is defined as one-third of the trace of the orthogonalized

		U_{ij} tensor		
Atom	X/a	Y/b	Z/c	$U_{\rm eq}~({\rm \AA}^2)$
S(1)	0.75120(5)	0.98674(5)	0.41271(3)	0.04768(14)
O(1)	0.8253(2)	0.98036(14)	0.49642(9)	0.0581(4)
O(2)	0.61463(14)	0.9892(2)	0.40489(11)	0.0636(4)
O(3)	$1 \cdot 11372(14)$	0.53782(13)	0.11267(9)	0.0565(4)
O(4)	$1 \cdot 13498(13)$	0.67127(13)	0.26260(9)	0.0520(3)
N(1)	0.8754(2)	0.6274(2)	0.07085(11)	0.0473(4)
N(7)	0.7701(2)	0.8629(2)	0.32600(10)	0.0471(4)
C(2)	0.9524(2)	0.6651(2)	0.15906(12)	0.0443(4)
C(3)	0.8869(2)	0.7463(2)	0.22017(12)	0.0428(4)
C(4)	0.7721(2)	0.7569(2)	0.16853(12)	0.0438(4)
C(5)	0.7667(2)	0.6832(2)	0.07573(13)	0.0469(4)
C(6)	0.9012(2)	0.8225(2)	0.32247(13)	0.0514(5)
C(8)	0.6930(2)	0.8404(2)	0.23010(13)	0.0502(5)
C(9)	0.8222(2)	$1 \cdot 1216(2)$	0.39341(13)	0.0486(4)
C(10)	0.9541(2)	$1 \cdot 1660(2)$	0.4255(2)	0.0571(5)
C(11)	1.0088(3)	$1 \cdot 2711(2)$	0.4096(2)	0.0712(6)
C(12)	0.9350(3)	$1 \cdot 3344(2)$	0.3618(2)	0.0749(7)
C(13)	0.8045(3)	$1 \cdot 2880(3)$	0.3308(2)	0.0764(7)
C(14)	0.7474(2)	$1 \cdot 1831(2)$	0.3456(2)	0.0621(6)
C(15)	0.9948(4)	$1 \cdot 4496(3)$	0.3448(3)	0.1172(12)
C(16)	1.0731(2)	0.6170(2)	0.17345(12)	0.0441(4)
C(17)	$1 \cdot 2620(2)$	0.6378(2)	0.2853(2)	0.0607(6)
C(18)	$1 \cdot 3076(3)$	0.7082(3)	0.3894(2)	0.0855(9)
S(1')	0.58509(5)	0.23396(5)	0.97837(3)	0.04983(14)
O(1')	0.4936(2)	0.1197(2)	0.93296(9)	0.0634(4)
O(2')	0.6156(2)	0.3168(2)	0.92849(10)	0.0631(4)
O(3')	$0 \cdot 4118(2)$	0.3370(2)	$1 \cdot 44335(10)$	0.0764(5)
O(4')	0.39190(14)	$0 \cdot 18063(13)$	$1 \cdot 30375(9)$	0.0534(3)
N(1')	0.5459(2)	0.5016(2)	$1 \cdot 36665(14)$	0.0600(5)
N(7')	0.5267(2)	0.3170(2)	$1 \cdot 06875(11)$	0.0498(4)
C(2')	0.4873(2)	0.3787(2)	$1 \cdot 31589(13)$	0.0493(4)
C(3')	0.5032(2)	0.3566(2)	$1 \cdot 22379(13)$	0.0454(4)
C(4')	0.5704(2)	0.4667(2)	$1 \cdot 21995(14)$	0.0489(4)
C(5')	0.5970(2)	0.5557(2)	$1 \cdot 3092(2)$	0.0581(5)
C(6')	$0 \cdot 4741(2)$	0.2518(2)	$1 \cdot 13034(13)$	0.0523(5)
C(8')	0.5929(2)	0.4507(2)	$1 \cdot 12252(14)$	0.0559(5)
C(9')	0.7303(2)	0.1918(2)	$1 \cdot 02270(13)$	0.0483(4)
C(10')	0.7255(2)	0.0830(2)	$1 \cdot 0462(2)$	$0 \cdot 0599(5)$
C(11')	0.8373(3)	0.0547(2)	$1 \cdot 0875(2)$	0.0721(7)
C(12')	0.9555(3)	$0 \cdot 1321(3)$	$1 \cdot 1062(2)$	$0 \cdot 0689(6)$
C(13')	0.9588(2)	$0 \cdot 2383(3)$	$1 \cdot 0802(2)$	$0 \cdot 0693(6)$
C(14')	0.8479(2)	0.2692(2)	$1 \cdot 0386(2)$	0.0605(5)
C(15')	$1 \cdot 0766(3)$	$0 \cdot 1010(4)$	$1 \cdot 1532(2)$	0.1068(11)
C(16')	0.4278(2)	0.3002(2)	$1 \cdot 36203(13)$	0.0508(5)
C(17')	0.3336(2)	0.0911(2)	$1 \cdot 3429(2)$	0.0589(5)
C(18')	0.3157(3)	-0.0380(2)	$1 \cdot 2685(2)$	0.0757(7)

2-(p-Tolylsulfonyl)-1,2,3,5-tetrahydropyrrolo[3,4-c]pyrrole (1)

A mixture of (4) (0.23 g, slightly impure material from)column separation as above) and potassium hydroxide (1.9)g, large excess) in ethylene glycol (5 ml) was stirred under nitrogen and heated at 165° by immersion of the flask in an oil bath. After 1.5 h, water (10 ml) was added, and the product was extracted with ether $(4 \times 50 \text{ ml})$. The combined ether layers were washed with water $(2 \times 50 \text{ ml})$, dried over anhydrous sodium sulfate, and evaporated to yield a brownish oil. Alternatively, the compound was exhaustively extracted from the aqueous ethylene glycol with hexane; this resulted in a purer product but a lower total yield. The crude product was purified by column chromatography, eluting with 1:1 ethyl acetate/hexane containing 3% triethylamine. The fractions containing pure (1) were combined and the solvents allowed to evaporate to yield the pure colourless product, m.p. $190\text{--}192^\circ$ (dec.) (lit.¹³ 176–178°) (Found: C, $59 \cdot 5$; H, $5 \cdot 4$; N, $10 \cdot 6$. Calc. for $C_{13}H_{14}N_2O_2S$: C, 59.5; H, 5.4; N, 10.7%). ¹H n.m.r. (CDCl₃) δ 2·39, s, ArCH₃; 4·42, s, 2×CH₂; 6·45, d, pyrrole CH; 7·29, 7·75, AA'BB', tolyl ring H; 8·23, br, NH. ¹³C n.m.r. (CDCl₃) δ 21·3, 48·0, 108·6, 122·6, 127·4, 129·6, 134·4, 143·2. I.r. $\nu_{\rm max}$ 3447s, 1332m, 1314m, 1163s, 1100m, 1052m, 663s, 584s, 547s cm⁻¹. Mass spectrum (e.s.i.) 285 (M+Na)⁺.

Crystallography

Crystal data for (4). C₁₆H₁₈N₂O₄S, mol. wt 334 · 39, triclinic, space group $P\bar{1}$, a 10 · 5030(6), b 11 · 2843(8), c 15 · 236(1) Å, α 109 · 419(6), β 97 · 697(6), γ 95 · 651(6)°, V 1667 · 8(2) Å³, F(000) 700, $D_c(Z = 4)$ 1 · 328 g cm⁻³, λ (Cu Kα) 1 · 54180 Å, μ (Cu Kα) 19 · 1 cm⁻¹, temperature 290 K.

Data collection, structure solution and refinement. X-Ray diffraction data were collected on a crystal of approximate dimensions 0.33 by 0.13 by 0.07 mm on an Enraf-Nonius four-circle diffractometer (nickel-filtered Cu K α radiation). A decrease of less than 2% in the intensities of three standards monitored throughout the data collection period indicated only minor crystal damage and a linear correction was applied. Of 6685 reflections collected up to $2\theta_{\rm max}$ 140° (collection range: h, from -12 to 12; k, from -13 to 13; l, from 0 to 18), 6308 were unique ($R_{\rm int} 0.0165$) while 5130 with $I > 2.0\sigma(I)$ were considered observed and were used in the expression of the conventional refinement residual. Data were corrected for Lorentz and polarization effects and extinction, [extinction coefficient 0.0011(2)], with an analytical absorption correction being applied $(T_{\text{max,min}} \ 0.88, \ 0.64)$.¹⁵ The structure was solved by direct methods¹⁶ and refined using full matrix least squares (on F^2).¹⁶ Anisotropic thermal parameters were used for all non-hydrogen atoms giving conventional residuals^{*} R_1 , wR_2 and S of 0.038, 0.099 and 1.03, respectively (largest difference peak and hole: 0.30, -0.28 e Å⁻³). A weighting scheme of the type $w = [\sigma^2 (F_0)^2 + (0.0532P)^2 + 0.4271P]^{-1}$ where $P = (F_{o} + F_{c}^{2})/3$, was used. All hydrogen atoms were included in the refinement at calculated positions as riding models. A check, prompted by the presence of two independent molecules in the crystallographic repeating unit, failed to reveal any higher symmetry.

Final atomic coordinates for (4) are listed in Table 1; bond distances and angles, anisotropic thermal parameters, observed and calculated structure factors, and hydrogen atom coordinates have been deposited as an Accessory Publication.[†] The atom numbering scheme for molecule 1 is shown in Fig. 1.

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