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Studies on the Acid-Catalyzed Dimerization of 2-Prenylindoles

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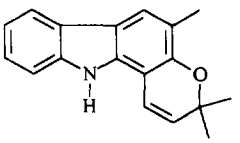
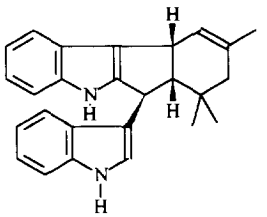
Abstract: Acid-catalyzed dimerization of 2-prenylindole derivatives **11**, **16**, and **27** have been examined. While 2-dehydroprenylindole **11** underwent polymerization, alcohols **16** and **27** gave indolo[3,2-b]carbazole derivatives **18** and **29** respectively. The structure of **29** has been determined by X-ray crystallography. Mechanisms for the formation of **18** and **29** from **16** and **27** have been proposed.



Girinimbine 1



Yuehchukene 2

Girinimbine **1** is a carbazole alkaloid which was identified among other compounds in an extensive survey of the bis-indole alkaloid yuehchukene **2** in Murraya sp.[1] In this survey, not only was the richest source of yuehchukene **2** identified, but its complementary existence with girinimbine **1** in Murraya sp. was also observed[2]. The biosynthesis of yuehchukene **2** has been postulated to occur via the dimerization of 3-dehydroprenylindole **6**[3], a proposal that has been substantiated by experiment[4]. In addition, Sheu et al.[5] observed that acid treatment of the tertiary alcohol **4** resulted in the formation of yuehchukene **2**. Synthetically, Sheu's work[5] provided a short and economic route to yuehchukene **2**; as well as shed light on the biosynthetic origin of 3-dehydroprenylindole **6**. One can envisage 3-prenylindole **3**, which can be formed *in vivo* by the prenylation of indole, as the key precursor in yuehchukene biosynthesis. Enzymatic allylic oxidation of **3** would give alcohol **4**, which, under acidic conditions, would dehydrate to generate 3-dehydroprenylindole **6** and its protonated form **5**. Subsequent Diels Alder reaction between **5** and **6** would result in yuehchukene **2** formation (Scheme 1).

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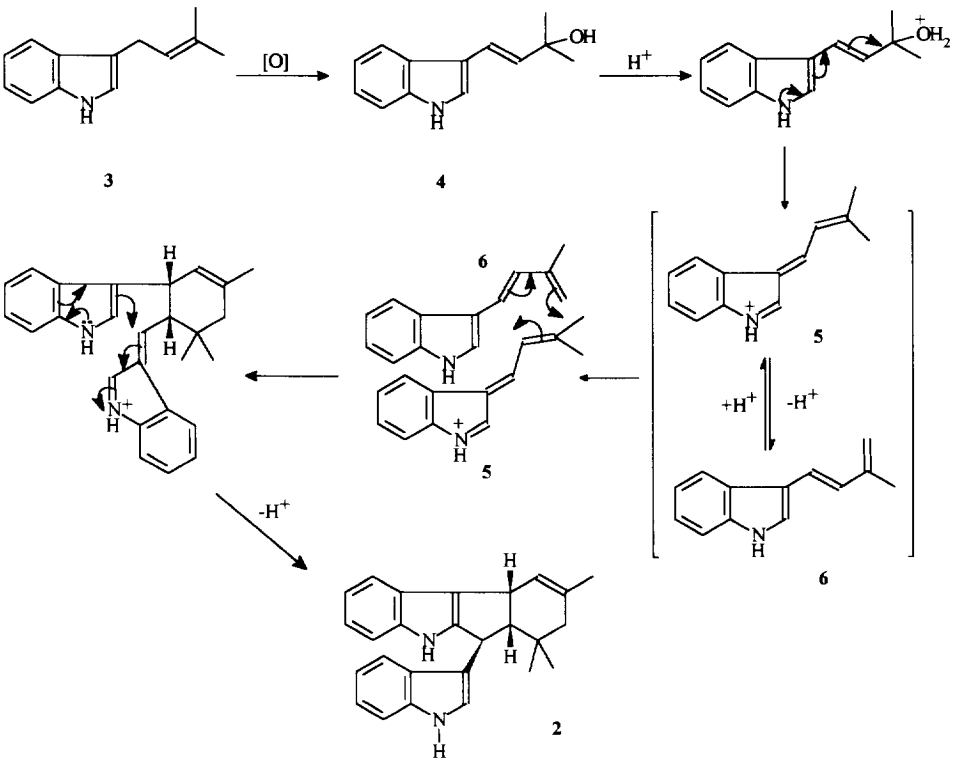
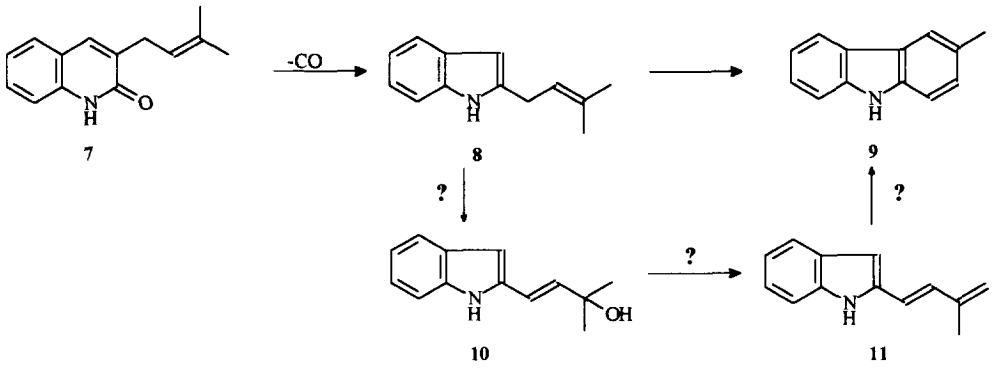
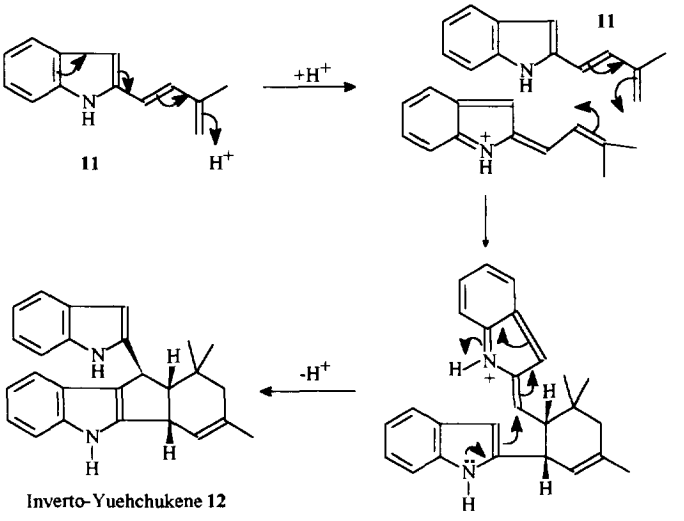


Scheme 1. Mechanism of formation of yuehchukene **2**

While a reasonable biosynthetic pathway for yuehchukene formation has been proposed, the origin of girinimbine **1**, or more generally, carbazole alkaloids, is not well-understood. The biogenesis of carbazole alkaloid **9** has been thought to start from quinolone **7**[3] undergoing decarbonylation to give 2-prenylindole **8**, followed by direct cyclization to form the carbazole nucleus (Scheme 2). However, it is also plausible that 2-prenylindole **8** first hydroxylates to give alcohol **10**. Subsequent dehydration of **10** affords 2-dehydroprenylindole **11** which then undergoes enzyme-catalyzed cyclization to generate the carbazole nucleus. It is tempting to speculate on the fate of 2-dehydroprenylindole **11** if part of the biological machinery for the conversion of **11** into carbazole were absent. One can imagine a pathway in which 2-dehydroprenylindole **11** could dimerize, in analogous fashion to the yuehchukene **2** biosynthesis, to give inverto-yuehchukene **12** instead (Scheme 3).

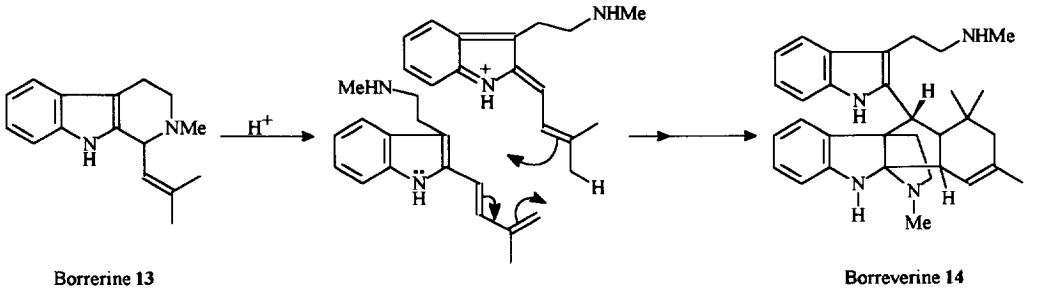


Scheme 2. Proposed biogenetic formation of carbazole alkaloid 9



Scheme 3. Proposed formation of inverto-yuehchukene 12

This proposal parallels the mechanism of cyclization in the chemical conversion of borrerine 13 into borreverine 14[6] through a 2-prenylated intermediate (Scheme 4). Herein we report our investigation of the chemistry of 2-prenylindoles which may have relevance to the biochemical profile for girinimbine 1 of Murraya sp.

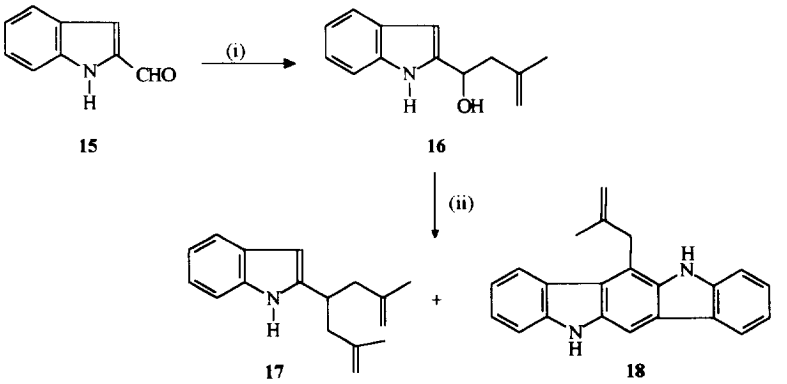


Borrerine **13** Borreverine **14**

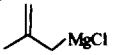
Scheme 4. Mechanism of formation of borreverine **14**

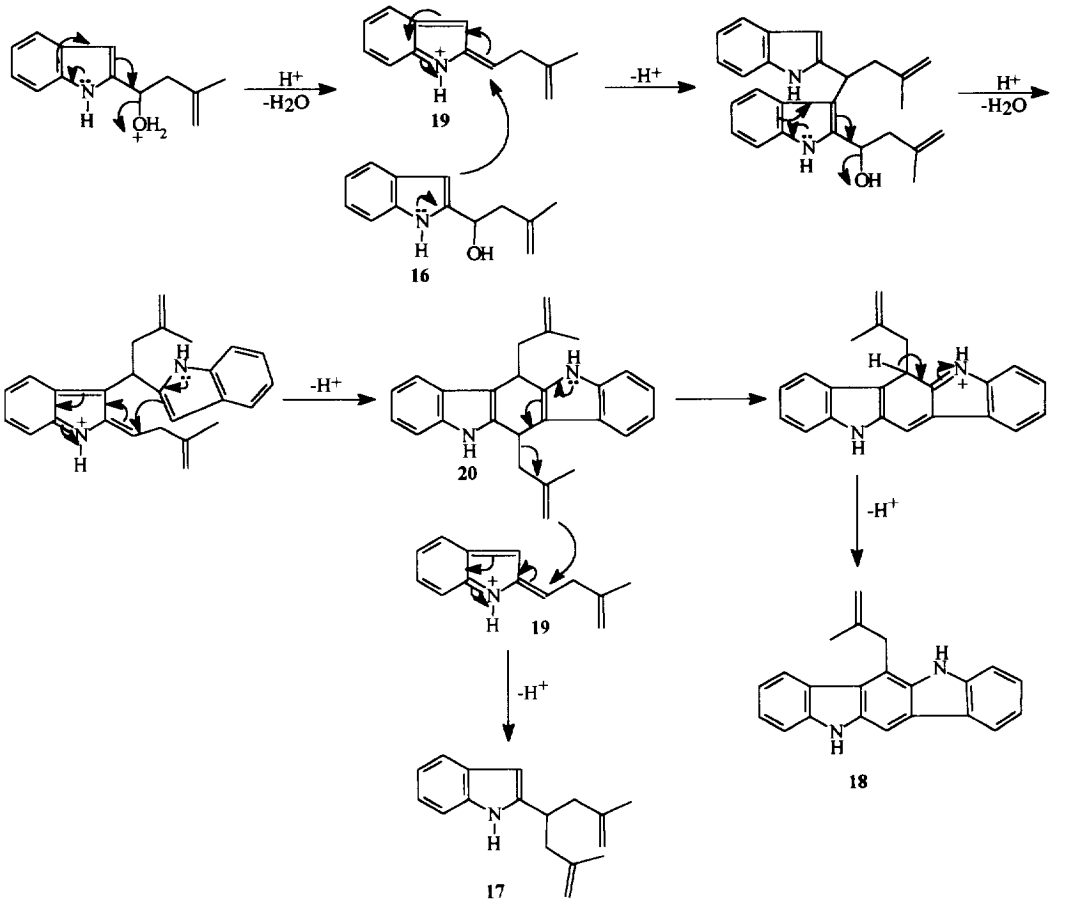
RESULTS AND DISCUSSION

Our initial target was to prepare diene **11**. Indole-2-carbaldehyde **15** with 2-methylpropenyl magnesium chloride gave alcohol **16**. However, attempts to dehydrate **16** with $MsCl/Et_3N$[7] led only to complete decomposition. In view of the difficulty in this dehydration step, we considered the possibility of inducing dehydration and cyclization in one-pot under acidic conditions. Thus, alcohol **16** in benzene was treated with silica gel impregnated with TsOH. A complex mixture of products was obtained from which two major products **17** and **18** were purified to homogeneity and identified by correlation of the spectroscopic data.[8] In particular, compound **17** exhibited a quintet at δ 3.15 and a doublet at δ 2.36 with the same coupling constant (J= 7.20 Hz) corresponding to 1'-H and 2'-H respectively, and 3-H of indole appeared at δ 6.24. Compound **18** showed a broad singlet at δ 4.24 for the phenyl vinyl methylene protons (Scheme 5). A possible mechanism to account for their formation is shown in Scheme 6.



15 **16** **17** **18**

Scheme 5. Synthesis of **16** and its reaction with acid
Reagents: (i)  (ii) TsOH / silica gel

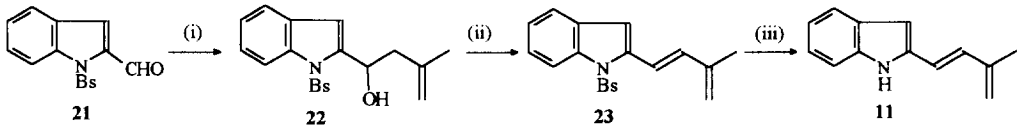


Scheme 6. Proposed mechanism of formation of **17** and **18**

Two aspects of the outcome of this experiment are noteworthy. Firstly, the anticipated *in situ* diene formation was not observed (see below). This may be due to the stability of the delocalised carbocation **19** and its rapid trapping by unreacted alcohol **16**. Secondly, a facile transfer of the methylpropenyl group from **20** to **19** occurred. The C-C bond scission in **20** apparently became thermodynamically favourable because of the gain in aromaticity after alkyl transfer.

The apparent failure to generate diene **11** in a one-pot acid-catalyzed reaction prompted us to reconsider its synthesis. We suspected that the electron-rich indole nucleus of **16** was responsible for the complex side reactions observed in the dehydration. Therefore, in an attempt to obviate any unwanted reactions, we decided to start with an N-protected indole. The benzenesulphonyl protecting group[9] was chosen because of its ease of removal[10] and its electron-withdrawing ability. To that end, benzenesulphonylindole-2-carbaldehyde **21**, obtained from indole in two steps,[11] was treated with 2-methylpropenylmagnesium chloride to give alcohol **22**, which, on

dehydration with $MsCl/Et_3N$, gave diene **23**. The benzenesulphonyl group was then removed with sodium amalgam[12] to afford the desired diene **11** (Scheme 7). This sets the stage for the investigation of the acid-catalyzed cyclization.



21 **22** **23** **11**

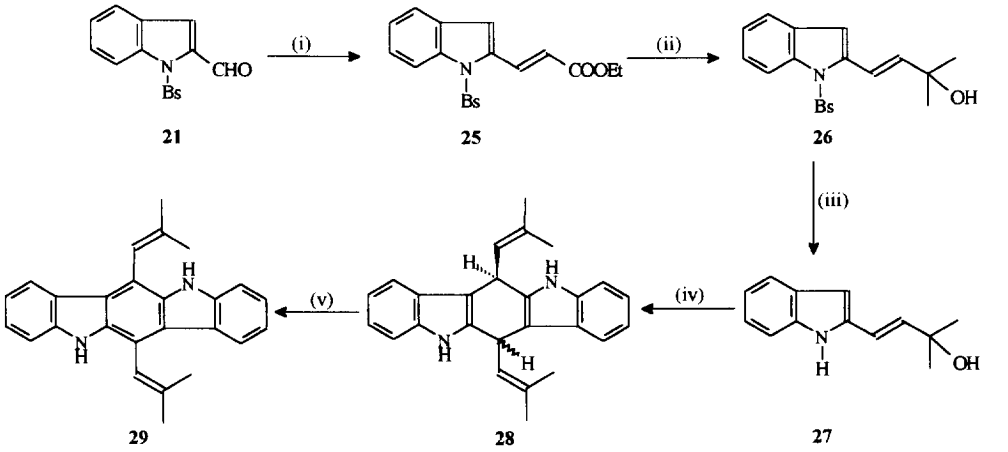
Bs = $PhSO_2$

Scheme 7. Synthesis of **11**
Reagents: (i)  (ii) MsCl / Et_3N, (iii) Na / Hg

To our disappointment, diene **11** polymerized under the reaction conditions to give an intractable mixture. This could be explained by reasoning that the actual site of protonation in diene **11** was at C-3 of the indole nucleus to produce a conjugated enamine, which could undergo cationic polymerization.

We further reasoned that if diene **11** were generated at a low concentration *in situ* and were then trapped immediately by the dienophile, the formation of polymerization products would be significantly reduced. We anticipated that alcohol **27** could be used as the precursor of diene **11** since the double bond is in conjugation with the indole ring.

Once again, we believed that the electron rich indole ring would interfere with the reaction and protection of the indole nitrogen was therefore necessary. By subjecting N-benzenesulphonylindole-2-carbaldehyde **21**[11] to the Horner-Wadsworth Emmons reaction,[12] followed by treatment with methyl Grignard reagent, alcohol **26** was obtained via ester **25**. Removal of the benzenesulphonyl group using the usual protocol produced alcohol **27** (Scheme 8).



21 **25** **26** **27** **28** **29**

Scheme 8. Synthesis of **27** and its reaction with acid.
Reagents : (i) $MgBr_2$ /Et_3N /$(EtO)_2P(O)CH_2COOEt$, (ii) MeMgI, (iii) Na / Hg, (iv) CF_3COOH, (v) air

When alcohol **27** was subjected to treatment with acid, two compounds with symmetrical structures, **28** and **29**, were initially isolated. The structure of **29** was established by X-ray crystallography (Figure 1). Compound **28**, as shown by ^{13}C nmr spectrometry, was a mixture of diastereoisomers which differed in the relative stereochemistry of the two alkyl side chains. On standing, **28** was converted into **29**, whose mass was two a.m.u. less, as a result of aromatization. To rationalize the formation of **28** and **29**, the mechanism as depicted in Scheme 9 has been proposed. In this instance, alkyl transfer was not observed.

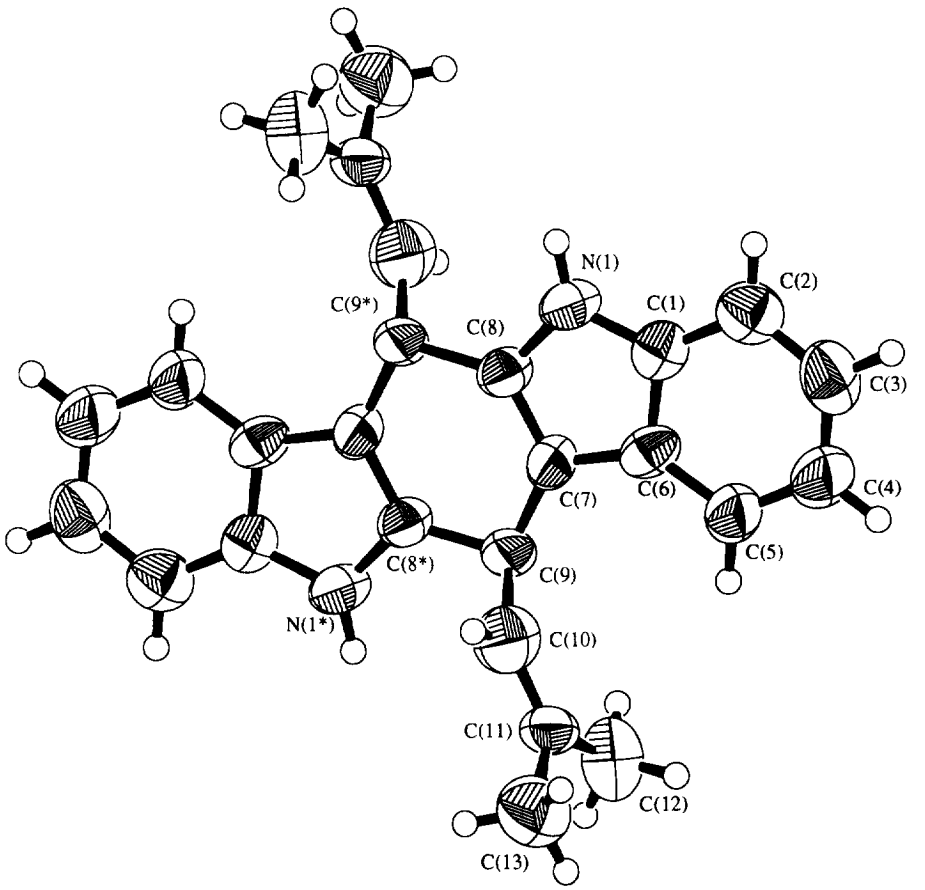
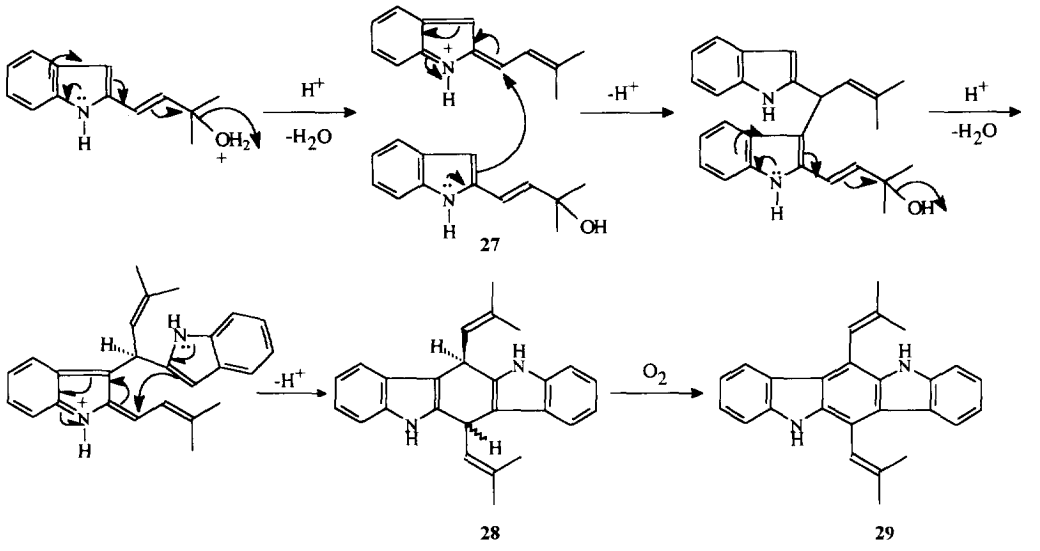


Figure 1. ORTEP drawing for compound 29



Scheme 9. Proposed mechanism for the formation of **28** and **29**

The results of these experiments reflected the differences in the chemistry of 2-prenylindoles and 3-prenylindoles. The presence or absence of a substituent at C-3 of indole appears to dictate the mode of dimerization. When C-3 of 2-prenylindole is unsubstituted, dimerization to generate the carbazole nucleus was the preferred mode of cyclization observed. This reactivity pattern of prenylated indoles may explain why the desired inverto-yuehchukene has not yet been observed. While it has the basic skeleton of borreverine **14**[6], one significant difference is that the inverto-yuehchukene indole nucleus has an unsubstituted C-3. Moreover, the intrinsic instability of diene **11** may imply that it is not an intermediate in the biosynthesis of carbazole alkaloids. Further work on the acid catalyzed cyclization of 3-substituted 2-prenylindole derivatives to synthesize inverto-yuehchukene is underway.

EXPERIMENTAL

M.p.s were measured on a "LiuKam" heating stage for crystal melting point study adapted to a Zeiss microscope and are uncorrected. IR spectra were recorded on a Bio-Rad FIS-7IR spectrophotometer. NMR spectra were recorded on JEOL FX-90Q and GSX-270 spectrometers for solutions of samples in deuterochloroform unless otherwise stated, with tetramethylsilane as internal standard. J-values are given in Hz. Mass spectra were recorded on Hitachi RMS-4 and high-resolution Finnigan MAT-95 mass spectrometers. UV spectra were recorded on a Shimadzu UV 240 spectrophotometer. TLC was performed using Merck pre-coated

silica gel F-254 plates (thickness 0.25 mm). Column chromatography was carried out with Kieselgel 60 (Merck) as the stationary phase. Analytical HPLC was performed on a Beckmann Model 331 HPLC System with Model 163 variable-wavelength UV-VIS detector. Working up refers to the drying of organic extracts over anhydrous magnesium sulphate and evaporated at aspirator pressure on a rotary evaporator. Petroleum ether (PE) refers to the fraction boiling in the range 40-60°C and was redistilled before use. All reactions requiring anhydrous conditions were conducted with oven-dried apparatus at 120°C and under a static atmosphere of dry nitrogen or argon. New compounds were established through accurate mass determination were shown to be homogeneous by spectroscopic and chromatographic methods. All compounds described were racemic.

2-(1'-Hydroxy-3'-methyl-3'-butenyl)indole ***16***

To a mixture of magnesium (5.10g, 0.21mol) in anhydrous THF (44ml) with a few crystals of iodine under an atmosphere of nitrogen was added 3-chloro-2-methylpropene (22.7ml, 0.23mol) in anhydrous THF (20ml) dropwise. When the vigorous reaction had subsided, indole-2-carbaldehyde **15** (3.10g, 0.02mol) in anhydrous THF (103ml) was added dropwise. The mixture was heated to 60-70°C for 2 hours. The mixture was cooled and aqueous ammonium chloride (2.1M, 100ml) was added. The organic layer was separated and the aqueous layer was extracted with ether (3 x 100ml). Working up and purifying the crude product by column chromatography (PE:Et_2O = 6:4) gave compound **16** as a light yellow solid (2.17g, 54%), m.p. 73-74°C; ν_{max} (KBr) 3454 (NH), 3234 (O-H), 3074, 2914, 1644 (C=C), 1455, 1424, 1217, 1166, 1047, 7411 cm^{-1}; λ_{max} (EtOH) 215, 270, 280, 288 nm; δ_H (90 MHz, $CDCl_3$) 1.73 (3H, s, 3'-H), 2.50 (2H, d, J 7.43 Hz, 2'-H), 4.60-5.04 (3H, m, 1'-H and 4'-H), 6.28 (1H, d, J 1.75 Hz, 3-H), 6.92-7.36 (3H, m, Ar-H), 7.40-7.68 (1H, m, 7-H), 8.45 (1H, br.s., NH) ppm; δ_C (22.5 MHz, $CDCl_3$) 22.43 (3'-CH_3), 46.32 (C-2'), 66.04 (C-1'), 98.65 (C-3), 110.95 (C-7), 114.41 (C-4'), 119.89 (C-2), 120.54 (C-5), 121.89 (C-6), 128.44 (C-3a), 135.87 (C-2), 140.69 (C-7a), 141.77 (C-3') ppm; m/z 201; Anal. Calcd. for $C_{13}H_{15}NO$: C, 77.6; H, 7.5; N, 6.9%. Found: C, 77.7; H, 7.5; N, 7.1%.

Acidic dimerization of the alcohol ***16***

To silica gel for chromatography (100g, Merck Kiesel gel 60, particle size 0.063-0.200 mm, 70-230 mesh) under vigorous stirring was added p-toluenesulphonic acid (3g) in acetone (200ml). The solvent was removed under reduced pressure and the silica gel was kept under reduced pressure (2 Torr) at 45-50°C.

A mixture of this silica gel (24g) and the alcohol **16** (0.997g, 4.6mmol) in benzene (170ml) was stirred at room temperature for 1 hour. The silica gel was filtered and washed with benzene (100ml). The filtrate and washing were combined and evaporated. Purification by repeated flash column chromatography[8] (PE:Et_2O = 9:1) gave **17**, (61mg, 5.1%) as a light yellow waxy solid, m.p. 30-33°C; (Found: M^+, 239.1678. $C_{17}H_{21}N$ requires M, 239.1674); ν_{max} (KBr) 3412 (NH), 3075, 2932, 1643 (C=C), 1458, 742 cm^{-1}; λ_{max} (EtOH) 218, 222, 278,

288 nm; δ_H (90 MHz, $CDCl_3$) 1.68 (6H, s, CH_3), 2.36 (4H, d, J 7.20 Hz, CH_2), 3.15 (1H, q, J 1.75 Hz, 3-H), 4.52-4.88 (4H, m, $=CH_2$), 6.24 (1H, d, J 1.75 Hz, 3-H), 6.80-7.36 (3H, m, Ar-H), 7.36-7.60 (1H, m, 7-H), 7.89 (1H, br.s., NH) ppm; δ_C (22.5 MHz, $CDCl_3$) 22.43 (CH_3), 35.38 (C-1'), 43.34 (C-2'), 99.14 (C-3), 110.41 (C-7), 112.57 (C-4'), 119.51 (C-4), 119.94 (C-5), 120.97 (C-6), 128.61 (C-3a), 135.76 (C-2), 142.76 (C-7a), 143.72 (C-3') ppm.

Further elution gave **18** (32 mg, 2.1%) as yellow crystals, m.p. 255°C, (Found: M^+, 310.1456. $C_{22}H_{18}N_2$ requires M, 310.1469); ν_{max} (KBr) 3399 (NH), 3054, 2904, 1643 (C=C), 1457, 749 cm^{-1}; λ_{max} (EtOH) 199, 222, 273, 282, 290 nm; δ_H (90 MHz, $CDCl_3$) 1.96 (3H, s, CH_3), 4.24 (2H, br s, CH_2), 4.77 (1H, br.s., $=CH_2$), 4.91 (1H, br.s., $=CH_2$), 7.00-7.50 (6H, m, Ar-H), 7.68-8.20 (5H, m, NH and Ar-H) ppm; δ_C (22.5 MHz, acetone-d_6) 23.35 (CH_3), 37.22 (CH_2), 99.52, 111.16, 111.43, 115.71, 118.80, 118.91, 120.91, 122.76, 123.41, 123.95, 124.22, 124.54, 125.79, 126.33, 136.14, 137.00, 142.48, 142.64, 143.51 ppm.

1-Benzenesulphonyl-2-(1'-hydroxy-3'-methylbut-3'-enyl)indole 22

To a suspension of magnesium turnings (60 mg, 2.50 mmol) in anhydrous THF (2 ml) was added a drop of 3-chloro-2-methylpropene and a small crystal of iodine. The mixture was warmed until the iodine colour disappeared and the exothermic Grignard reaction was started. A solution of aldehyde[11] **21** (560 mg, 1.96 mmol) and 3-chloro-2-methylpropene (0.25 ml, 4.2 mmol) in anhydrous THF (7 ml) was added at such a rate that a gentle reflux is maintained. After addition was completed, the solution was heated at 60°C for 30 min and then poured into saturated ammonium chloride solution (5 ml). Dilute hydrochloric acid was added until the aqueous layer was acidic to litmus. The organic layer was separated, washed with water (3 ml) and brine (3 ml), dried over anhydrous $MgSO_4$ and filtered. Removal of solvent yielded a brown viscous liquid which on purification by column chromatography (SiO_2, Et_2O:PE=1:1) gave alcohol **22** (0.35g, 53%) as a light yellow viscous liquid; ν_{max} ($CHCl_3$) 3423 (OH), 3076, 1370 (S=O, asym.), 1174 (S=O, sym.) cm^{-1}; δ_H(270 MHz, $CDCl_3$) 1.78 (3H, s, CH_3), 2.54-2.62 (1H, dd, J 14.16 Hz, 8.79 Hz, 2'-H), 2.78-2.85 (1H, dd, J 14.16 Hz, 4.39 Hz, 2'-H), 3.13 (1H, br.s, OH), 4.84 (1H, s, 4'-H), 4.89 (1H, s, 4'-H), 5.41-5.46 (1H, dd, J 8.79Hz, 4.39Hz, 1'-H), 6.74 (1H, s, 3-H), 7.17-8.24 (9H, m, Ar-H) ppm; δ_C (22.5 MHz, $CDCl_3$) 22.27 (CH_3), 45.29 (C-2'), 65.12 (C-1'), 113.79 (C-4'), 109.51, 114.82, 121.10, 123.89, 124.82, 126.25, 129.18, 133.78, 137.30, 138.55, 142.10, 143.83 ppm; m/z 341.15 (2, M^+), 286.10 (100, M^+-C_4H_7), 258.00 (15, M^+-C_5H_7O), 145.10 (70, M^+-C_4H_7-$C_6H_5SO_2$), 117.10 (87, M^+-C_5H_7O-$C_6H_5SO_2$).

1-Benzenesulphonyl-2-(3'-methyl-E-buta-1',3'-dienyl)indole 23

To a mixture of alcohol **22** (1.25 g, 3.67 mmol) in anhydrous THF (20 ml) and dry triethylamine (1.53 ml, 0.01 mmol) under N_2 atmosphere at -78°C was added mesyl chloride (0.43 ml, 5.50 mmol) slowly over a period of 5 min. The solution was allowed to warm to rt in 1.5 hr and was heated under gentle reflux (70-80°C)

for 20 min. The precipitate formed was filtered off and the filtrate was concentrated in vacuo, affording a brown viscous liquid. The crude product was purified by column chromatography (SiO_2, CH_2Cl_2 : PE=2 : 3) yielding diene **23** (550mg, 46%) as a pale yellow viscous oil; ν_{max} ($CHCl_3$) 1590 (C=C), 1385 (S=O, asym.), 1200 (S=O, sym.) cm^{-1}; δ_H (90 MHz, $CDCl_3$) 2.02 (3H, s, CH_3), 5.13 (2H, s, 4'-H), 6.72 (1H, s, 3-H), 6.76 (1H, d, J 15.97 Hz, 2'-H), 7.17-8.25 (10H, m, 1'-H and Ar-H) ppm; δ_C (22.5 MHz, $CDCl_3$) 18.50 (CH_3), 108.29, 115.12, 118.59 (C-4'), 118.83, 120.59, 124.00, 124.63, 126.49, 128.93, 130.12, 133.59, 135.32, 137.44, 138.47, 139.69, 142.02 ppm; m/z 323.15, (10, M^+), 182 (100, M^+-$C_6H_5SO_2$), 167 (64, M^+-$C_6H_5SO_2$-CH_3).

2-(3'-Methyl-E-but-1',3'-dienyl)indole ***11***

A mixture of **23** (100 mg, 0.31 mmol) in anhydrous THF (3 ml) and anhydrous methanol (6 ml), disodium hydrogenphosphate (2.3 g) and sodium amalgam (5%, 2.3 g) was stirred at rt until all of the amalgam had become liquid mercury. Water (3 ml) and diethyl ether (3 ml) were added and the supernatant was decanted. The residue was washed again with diethyl ether (5 ml x 3). The organic extracts were combined, washed with brine (6 ml), dried over anhydrous $MgSO_4$ and filtered. Removal of the solvent and purification of the residue by column chromatography (SiO_2, Et_2O : PE = 2:8) gave diene **11** (47.1 mg, 83%) as a brown solid, m.p. 132-133°C; ν_{max} (Nujol) 3352 (NH), 1623 (C=C), 1462, 1185, 749 cm^{-1}; δ_H (90 MHz, $CDCl_3$) 1.96 (3H, s, CH_3), 5.09 (2H, s, 4'-H), 6.51-7.59 (7H, m, Ar-H), 8.11 (1H, br.s, NH) ppm; δ_C (22.5 MHz, $CDCl_3$) 18.39 (CH_3), 103.50 (C-3), 110.54 (C-7), 117.31 (C-4'), 119.13, 120.10, 120.54, 122.68, 129.04, 130.31, 136.35, 136.90, 141.66 ppm; m/z 183 (M^+).

Ethyl (E)-1-benzenesulphonylindole-2-propenoate ***25***

A mixture of anhydrous magnesium bromide (1.12 g, 6.06 mmol), triethyl phosphonoacetate (1.08 g, 4.85 mmol) in anhydrous THF (18 ml) and triethylamine (0.74 ml, 6.06 mmol) was stirred for 10 min at rt. To this solution, aldehyde **21** (1.15 g, 4.04 mmol) in anhydrous THF (12 ml) was added and the resulting solution was stirred for 12 hrs at rt. The reaction was quenched by pouring into saturated NH_4Cl solution (15 ml). Working up and purifying the crude product by column chromatography (SiO_2, Et_2O : PE = 3:7) afforded the ester **25** (1.20 g, 84%) as light fine white crystals, m.p. 68°C; ν_{max} (Nujol) 3094, 3069 (aromatic CH), 1710 (C=O), 1618 (C=C), 1370 (S=O, asym.), 1156 (S=O, sym.) cm^{-1}; δ_H (90 MHz, $CDCl_3$) 1.37 (3H, t, J 7.00 Hz, CH_3), 4.30 (2H, q, J 7.00 Hz, CH_2), 6.37 (1H, d, J 16.19 Hz, 2'-H), 6.97 (1H, s, 3-H), 7.23-8.47 (10H, m, 1'-H and Ar-H) ppm; δ_C (22.5 MHz, $CDCl_3$) 14.30 (CH_3), 60.73 (CH_2), 112.20, 115.23, 115.39, 119.02, 121.19, 121.51, 123.63, 124.33, 124.87, 126.33, 129.15, 129.37, 133.87, 134.24, 166.10 (C=O) ppm; m/z (relative intensity) 355 (55, M^+), 214 (67, M^+-$C_6H_5SO_2$), 186 (100, M^+-$C_6H_5SO_2$-C_2H_4), 169 (28, M^+-$C_6H_5SO_2$-C_2H_5O).

1-Benzenesulphonyl-2-(3'-hydroxy-3'-methyl-E-but-1'-enyl)indole **26**

To a solution of methylmagnesium iodide, prepared from magnesium turnings (220 mg, 9.12 mmol) and methyl iodide (0.53 ml, 8.45 mmol) in anhydrous diethyl ether (30 ml), was added ester **25** (1.20 g, 3.38 mmol) in anhydrous benzene (15 ml) dropwise in 15 min. The reaction mixture was stirred at rt for 2 hrs and poured into saturated NH_4Cl solution (20 ml). Working up and purifying the crude product by column chromatography (SiO_2, Et_2O : PE = 1:1) gave alcohol **26** (887.6 mg, 77%) as a brown amorphous solid, m.p. 73°C; ν_{max} (Nujol) 3430 (OH), 1610 (C=C), 1367 (S=O, asym.) 1174 (S=O, sym.) cm^{-1}; δ_H (270 MHz, $CDCl_3$) 1.45 (6H, s, CH_3 x 2), 2.47 (1H, br.s, OH), 6.24 (1H, d, J 16.11Hz, 2'-H), 6.61 (1H, s, 3-H), 7.16-8.20 (10H, m, 1'-H and Ar-H) ppm; δ_C (22.5 MHz, $CDCl_3$) 29.63 (CH_3), 70.97 (C-3'), 108.56, 115.06, 117.47, 120.59, 123.92, 124.60, 126.58, 128.96, 129.96, 133.67, 137.36, 138.58, 139.17, 142.20 ppm; m/z 341 (M^+).

2-(3'-Hydroxy-3'-methyl-E-but-1'-enyl)indole **27**

The N-protected alcohol **26** (200 mg) was deprotected by the same procedure as in the preparation of **11**: The deprotected alcohol **27** thus obtained (115mg, 97%) was a brown amorphous solid, m.p. 110°C; (Found M^+, 201.1156. $C_{13}H_{15}NO$ requires M, 201.1154); ν_{max} (Nujol) 3405 (O-H), 3313 (N-H), 1621 (C=C), 1568, 1199, 1119, 794, 740 cm^{-1}; λ_{max} (EtOH) 206 (log ε, 4.1), 222 (4.2), 294 (3.8), 306 (3.8) nm; δ_H (90 MHz, $CDCl_3$) 1.35 (6H, s, CH_3 x 2), 2.60 (1H, br.s, OH), 6.11 (1H, d, J 16.40 Hz, 2'-H), 6.40 (1H, s, 3-H), 6.49 (1H, d, J 16.41 Hz, 1'-H), 6.96-7.56 (4H, m, Ar-H), 8.67 (1H, br.s, NH) ppm; δ_C (22.5 MHz, $CDCl_3$) 29.61 (CH_3), 71.18 (C-3'), 102.26 (C-3), 110.81, 117.69, 119.89, 120.43, 122.32, 128.80, 135.89, 136.30, 136.79 ppm.

Acid dimerization of alcohol 27

To a solution of alcohol **27** (200 mg, 1.00 mmol) in anhydrous benzene (20 ml) was added a catalytic amount of TFA. The resulting purplish red solution was stirred at rt and the progress of reaction was monitored by TLC analysis. When the starting alcohol had been fully consumed, the reaction mixture was worked up. Purifying the crude product by column chromatography (SiO_2, Et_2O : PE = 1:9) first gave compound **29** (45.2 mg, 25%) as fine greenish yellow crystals, m.p. 269°C, (Found M^+ 364.1936, $C_{26}H_{24}N_2$ requires M, 364.1939); ν_{max} (Nujol) 3397 (NH), 3057, 1618 (C=C) cm^{-1}; λ_{max} ($CHCl_3$) 283, 322, 338 nm; δ_H (270 MHz, $CDCl_3$) 1.68 (6H, s, 2 x CH_3), 2.21 (6H, s, 2 x CH_3), 6.84 (2H, s, H_a), 7.15 (2H, m, 2-H), 7.35-7.48 (4H, m, 3-H, 4-H), 7.91 (2H, br.s, NH), 8.17 (2H, d, J 7.81 Hz, 1-H) ppm; δ_C (67.5 MHz, $CDCl_3$) 20.09 (CH_3), 25.69 (CH_3), 110.03 (C-4), 113.29, 118.53 (C-2), 119.75 (C-Ha), 120.30, 122.64 (C-1), 124.41, 125.22 (C-3), 133.39, 139.08, 140.70 ppm.

Further elution gave compound **28** (57.3 mg, 31%) as white crystals, m.p. 167-169°C, (Found M^+ 366.2095. $C_{26}H_{26}N_2$ requires M, 366.2096); ν_{max} (Nujol) 3418 (NH), 3059, 1617 (C=C) cm^{-1}; λ_{max} ($CHCl_3$) 282, 292, 324, 336 nm; δ_H (270 MHz, $CDCl_3$) 1.77 (6H, s, 2 x CH_3), 2.15 (6H, s, 2 x CH_3), 4.97-5.15 (4H, m, =CH

and CH), 6.93-7.07 (4H, m, 2-H, 3-H), 7.31-7.38 (4H, m, 1-H, 4-H), 10.64 and 10.69 (2H, br.s, NH) ppm; δ_C (67.5 MHz, $CDCl_3$) 18.50 (CH_3), 25.82 (CH_3), 32.88, 109.69, 109.76, 110.73, 110.76, 118.76, 118.79, 119.31, 119.34, 121.41, 121.46, 126.79, 127.07, 127.11, 132.29, 132.34, 135.56, 135.62, 136.57, 136.60 ppm.

X-Ray Study of Compound **29**–*Crystal Data*

$C_{26}H_{24}N_2$, colourless rectangular block with dimensions 0.20 x 0.22 x 0.44 mm was mounted on a glass fibre using epoxy resin. M = 364.49, tetragonal, space group $P4_{2/n}$ (No. 86), a = 18.467(1), c = 5.995(2) Å, V = 2044.3(8) $Å^3$, $\underline{Z}$ = 4, $\underline{D}_c$ = 1.184 g cm^{-3}, μ (Mo-Kα) = 0.69 cm^{-1}, F(000) = 776, $\underline{T}$ = 298 K. Intensity data were collected on a Rigaku AFC7R diffractometer with graphite monochromated Mo-Kα radiation (λ = 0.71073 Å) using ω-2θ scanning technique. A total of 2113 reflections were measured and 858 with $I > 3\sigma(I)$ were considered to be observed and used in subsequent calculations. The space group was determined by the systematic absences and confirmed by successful solution and refinement of the structure.

Solution and refinement

The structure was solved by direct methods (SIR88)[13] from which all the non-hydrogen atoms were located. Hydrogen atoms were introduced in their idealised position (C-H, 0.95 Å). The structure was refined by full matrix least-squares analysis with all non-hydrogen atoms anisotropically and converged to R = 0.09, wR = 0.054. Atomic scattering factors were obtained from reference 14. All calculations were performed on a Silicon Graphics workstation using teXsan[15] program package. The ORTEP drawing of the molecule (Figure 1) shows thermal ellipsoids at the 50% probability level and the numbering scheme. Tables of bond lengths and angles and thermal parameters are available on request from the Cambridge Crystallographic Data Centre**.

** *Supplementary material*: Tables of hydrogen-atom parameters, thermal parameters, bond lengths and bond angles are available on request from the Cambridge Crystallographic Data Centre.

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REFERENCES AND NOTES

1. Kong, Y. C.; Ng, K. H.; But, P. P. H.; Li, Q.; Yu, S. X.; Chang, H. T.; Cheng, K. F.; Soejarto, D. D.; Kan, W. S.; Waterman; P. G. *J. Ethnopharmacology*, **1986**, 15, 95.
2. Kong, Y. C.; Cheng, K. F.; Ng, K.H.; But, P.P.H.; Li, Q.; Yu, S.X.; Chang, H.T.; Cambie, R.C.; Kinoshita, T.; Kan, W.S.; Waterman, P.G. *Biochem. System Ecol.*, **1986**, 14, 491.
3. Kinoshita; T.; Tatara; S.; Ho; F.C.; Sankawa, U. *Phytochemistry*, **1989**, 8, 147.
4. Cheng, K.F.; Kong, Y.C.; Chan, T.Y. *J. Chem. Soc., Chem. Comm.*, **1985**, 48.
5. Sheu, J. H.; Chen, Y.K.; Hong, Y.L.V. *Tetrahedron Lett.*, **1991**, 32, 1045.
6. Tillequin, F.; Koch, M.; Pousset, J.L.; Cave, A. *J. Chem. Soc, Chem.Comm.*,**1978**, 826.
7. Creary, X.; Geiger, C.S. *J. Am. Chem. Soc.*, **1982**, 104, 4158.
8. A third compound ($M^+ = 549$) was also isolated from the product mixture (26.3 mg). The molecular weight suggests that it is probably a trimeric indole compound. The proposed mechanism can explain why such a complex product mixture resulted from the acid-catalyzed dehydration. The indoleninium intermediate **19** can react intermolecularly with **16** or **20** as shown in Scheme 6, or with other nucleophiles in the reaction mixture such as **17**. Similarly, beside undergoing intramolecular cyclization, the indoleninium precursor to **20** can also react with **17**, or with **19**. Furthermore, each condensation can potentially produce a new indoleninium intermediate upon dehydration, which can still undergo further electrophilic additions. All of these reactions may account for the numerous products that were obtained.
9. Illi, V.O. *Synthesis*, **1979**, 136.
10. Trost, B.M.; Arndt, H.C.; Strege, P.E.; Verboeven, T.R. *Tetrahedron Lett.*, **1976**, 3477.
11. Saulnier, M.G.; Gribble, G.W. *J. Org. Chem.*, **1982**, 47, 757.
12. Aristoff, P.A.; Johnson, P.D.; Harrison, A.W. *J. Am. Chem. Soc.*, **1985**, 107, 7967.
13. Burla, M.C.; Camalli, M.; Cascarano, G.; Giacovazzo, C.; Polidori, G.; Spagna, R.; Viterbo, D. *J. Appl. Crystallogr.*, **1989**, 19, 3899.
14. Cromer, D.T.; Waber, J.T. International Tables for X-Ray Crystallography, Kynoch Press, Birmingham, **1974**, 4, (a) Table 2.2B, (b) Table 2.3.1
15. teXsan: Crystal Structure Analysis Package, Molecular Structure Corporation, the Woodlands, TX, **1985** and **1992**.

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