Synthesis of Protopine. A Novel Conversion of The Protoberberine Alkaloid Stylopine to a Tetrahydrodibenz[*c*,*g*]azecine Derivative[+]

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Treatment of the methiodide of the protoberberine alkaloid, stylopine, (**3**) with sodium hydride in dimethyl sulfoxide afforded in 70% yield the tetrahydrodibenz[*c*,*g*]azecine derivative **4**, a key intermediate in the synthesis of protopine.

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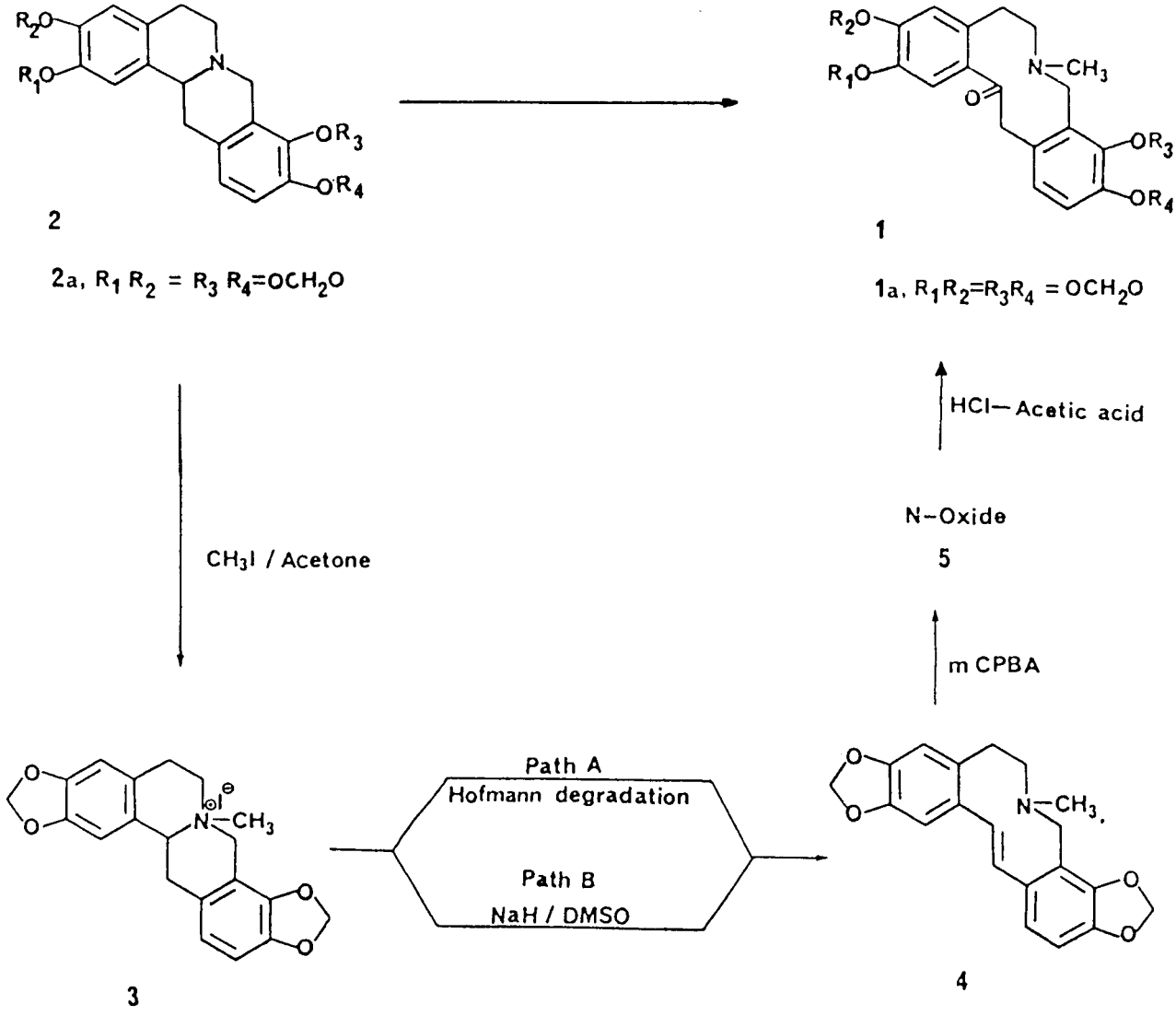
The benzazecine alkaloid, protopine (**1a**) has been of interest for us [1] as a potential antimalarial lead compound [2]. Since gram quantities of the compound were needed for our research programmes, and reported [3] yields of the compound from natural sources are in the range merely of 0.5-0.7%, we considered meeting our requirement through synthesis of the molecule.

About six different methods are reported for the synthesis of the protopine class of alkaloids [4]. Most of these methods use as starting material a protoberberine alkaloid

Scheme



such as **2**, which is essentially converted to the corresponding protopine alkaloid **1** by selective cleavage of the C_{13a}-N bond in **2**, followed by introduction of oxygen at the generated C_{14}-position in **1**.

This approach was adopted already in 1926 for the synthesis of protopine (**1a**) itself by the classical method of Haworth and Perkin [5]. Hofmann degradation (Scheme, Path A) of the metho salt **3** of the protoberberine alkaloid, stylopine (**2a**), provided the 10-membered anhydro base **4** which was converted to its *N*-oxide **5** and subjected to an acid-catalysed transannular rearrangement to give protopine (**1a**). No other report is to be found, to our knowledge, for the synthesis of protopine. We chose to repeat and, if necessary, modify the procedures of Haworth and Perkin to fulfil our requirements of protopine. This paper describes the introduction of the modifications of the reported route.

The first modification applies to the conversion of stylopine (**2a**) to the metho salt **3**. This was readily achieved in 77% yield by treating **2a** with methyl iodide in acetone at room temperature, thus avoiding the inconvenient sealed tube conditions of the reported procedure.

The second and more significant modification relates to the conversion of **3** to **4**. In the previously reported synthesis this conversion was effected by Hofmann degradation of **3**. This step, repeated in our hands, provided compound **4** in a poor yield of 36%. In the modification we introduced, the methiodide **3** was treated with sodium hydride in dimethyl sulfoxide at room temperature, (Scheme, Path B), under which conditions no dimsylsodium is formed. Compound **4** was formed in a yield as high as 70%. The ir spectrum (Figure 1) of **4** showed a band at 950-940 cm^{-1} (due to the C-H out-of-plane deformations), characteristic of a *trans*-disubstituted olefin conjugated with aromatic nucleii. The absence of bands below 700 cm^{-1} (characteristic of the corresponding *cis*-olefin) and of bands at 990 and 910 cm^{-1} (characteristic of a vinyl group) provided the additional support for the structure **4**. In the ^1H nmr spectrum (Figure 2) of **4**, a pair of doublets at δ 6.42 and 7.21 (J = 18 Hz each) was assigned to the C_{13} and C_{14} olefinic protons respectively. The mass spectrum of **4** (Figure 3) provides the molecular ion (m/z: 337) and the fragment ions (m/z: 323 (M^+-14), 294 (M^+-43), 293 (M^+-44), 188 and 148 (formed by transannular ring closure followed by retro-Diels-Alder cleavage of ring C), comparable to those obtained for the protopine class of alkaloids [6].

These data, in clearly establishing the structure assigned to **4**, also distinguished it from two other potential pro-

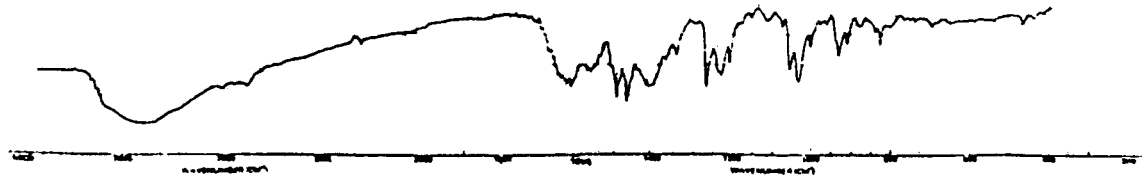


Figure 1. The ir spectrum of **4**.

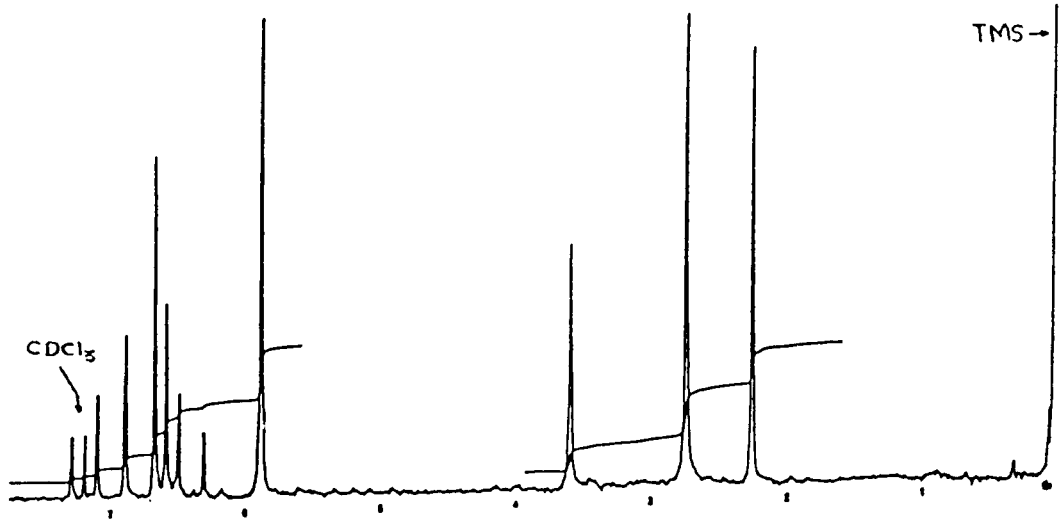


Figure 2. The ^1H nmr spectrum (90 MHz) of **4**.

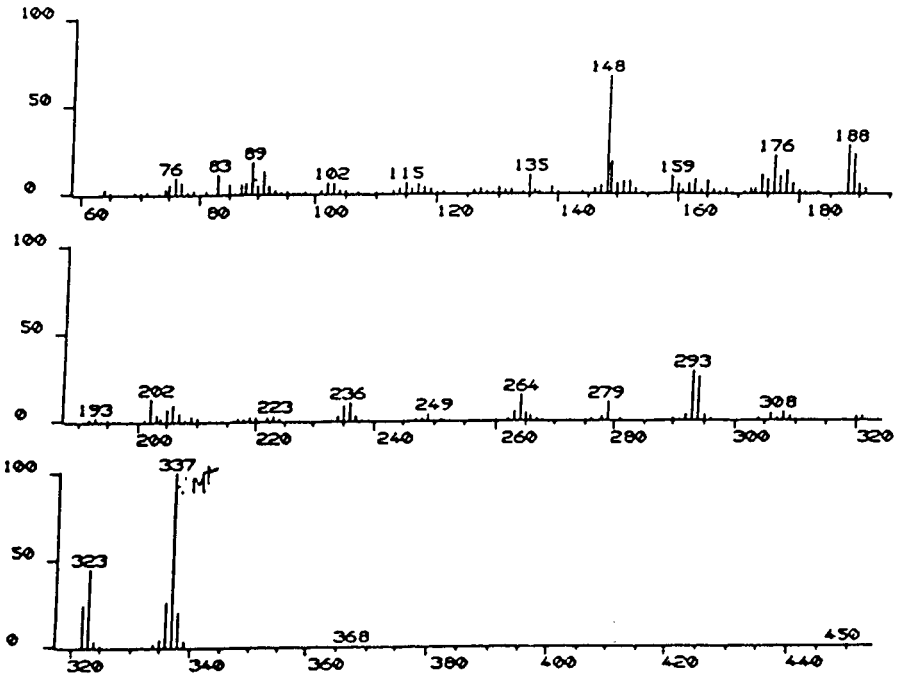
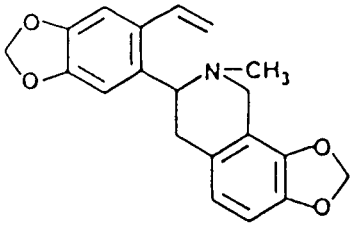


Figure 3. The mass spectrum of **4**.

ducts, the isomeric mono-substituted olefin **6** and the spiro compound **7**.



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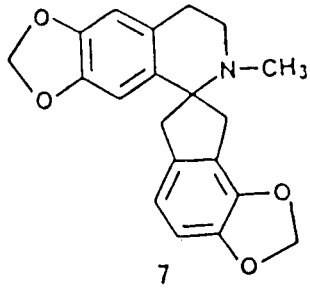

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This is the first report of the use of sodium hydride to effect the conversion of a protoberberine metho salt such as **3** to a tetrahydrodibenz[*c,g*]azecine like **4**. The base-induced Stevens rearrangement of nonphenolic protoberberine metho salts is well-known [7] wherein the bases used are phenyllithium, lithium aluminium hydride, *n*-butyllithium, sodium amalgum and dimsylsodium. The products have invariably been spiro compounds like **7**, with two exceptions of a B-homoprotoberberine [8] and a 13-methylprotoberberine [9], which gave a ring expanded Hofmann degradation product using dimsylsodium.

The preferred formation of **4** over the olefin **6** or the spiro compound **7** with the use of sodium hydride is apparently through the initial abstraction of the C_{13}–H (β- proton) rather than that of C_5 or C_{13a} which would be required for the formation of compounds **6** and **7** respectively.

The olefin **4** was readily converted to protopine (**1a**) in 49% yield through the *N*-oxide **5**, following the reported procedures [5], which further confirmed the structure of **4**.

EXPERIMENTAL

All melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. The IR spectra were recorded on a Perkin-Elmer 157 spectrophotometer. The ^{1}H nmr spectra were taken on a Varian T-60 and JEOL JNM/FX90Q spectrometer using TMS as an internal standard. The mass spectra were obtained on a Shimadzu GCMS-QP 1000 and Kratos RSA-80 spectrometer.

Stylopine Methiodide (**3**).

Stylopine (**2a**) [10] (2.7 g, 8.4 mmoles) was suspended in dry acetone (20 ml) and methyl iodide (5 ml) was added with stirring. The stirring was continued for 1 hour (monitored by tlc). The separated solid was filtered, washed with acetone and dried to give 3.0 g (77%) of the product **3**, mp 250° dec.

Anal. Calcd. for $C_{20}H_{20}INO_4$: C, 51.61; H, 4.33; N, 3.01; I, 27.29. Found: C, 51.82; H, 4.42; N, 3.02; I, 26.97.

Bis(2,3,9,10-dioxolo)-7-methyl-5,6,7,8-tetrahydrodibenz[*c,g*]-azecine (**4**).

The methiodide **3** (0.465 g, 1 mmole) was dissolved in warm dimethyl sulfoxide (3 ml) and added to a suspension of sodium hydride in dimethyl sulfoxide (2 ml) and stirred for 1 hour at room temperature. The reaction mixture was poured over ice and extracted with chloroform (2 x 20 ml). The combined chloroform extract was washed with water, dried (sodium sulfate) and evaporated under reduced pressure. The gummy mass was crystallised from acetone to yield 0.232 g (70%) of **4**, mp 127-128° (Lit [5] mp

118-120°); ir (potassium bromide): 1640 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.23 (s, 3, CH_3), 2.78 (s, 4, $ArCH_2CH_2N$), 3.60 (s, 2, $ArCH_2N$), 5.85 (s, 4, 2 x OCH_2O), 6.42 (d, J = 18 Hz, 1, olefinic H), 6.61 (s, 1, ArH), 6.65 (s, 2, ArH), 6.86 (s, 1, ArH), 7.21 (d, J = 18 Hz, 1, olefinic H); ms: m/z 337 (M^+), 323 (M^+-CH_2), 294 (M^+-43), 293 (M^+-44), 188, 148.

Anal. Calcd. for $C_{20}H_{19}NO_4$: C, 71.20; H, 5.68. Found: C, 71.45; H, 5.78.

Bis(2,3,9,10-dioxolo)-7-methyl-5,6,7,8-tetrahydrodibenz[*c*,*g*]azecine *N*-Oxide (**5**).

To an ice cold solution of *m*-chloroperbenzoic acid (0.2 g) in dry diethyl ether (5 ml) was added a pre-cooled solution of the olefin **4** (0.34 g) in chloroform (1 ml). A precipitate appeared as soon as the latter was added. The reaction mixture was kept at 0° overnight, and the precipitate filtered and washed with diethyl ether to furnish 0.35 g (98%) of the *N*-Oxide **5** as a white solid, mp 128-129° (Lit [5] mp 140° dec); ^1H nmr (deuteriochloroform): δ 3.34 (s, 3, CH_3), 3.60-3.96 (m, 4, $ArCH_2CH_2N$), 4.60 (d, J = 18 Hz, 1, C_8-H), 4.84 (d, J = 18 Hz, 1, C_8-H), 5.92, 5.96 and 6.04 (s each, total 4H, 2 x OCH_2O), 6.38 (d, J = 18 Hz, 1, olefinic H), 6.66 (s, 1, ArH), 6.76 (s, 1, ArH), 6.90 (s, 2, ArH), 6.92 (d, J = 18 Hz, 1, olefinic H).

Protopine (**1a**).

The *N*-oxide **5** (0.3 g, 0.85 mmole) was heated in a mixture of hydrochloric acid-acetic acid (2 ml:3 ml) at 50° for 1 hour. Work up according to the literature procedure [5] and crystallisation from methanol gave 0.15 g (50%) of protopine (**1a**), mp 206-207° (Lit [5] mp 205-207°); ir (potassium bromide): 1670 cm^{-1}. The ^1H nmr and mass spectra were identical to those previously reported [11,6].

Anal. Calcd. for $C_{20}H_{19}NO_5$: C, 67.98; H, 5.42; N, 3.96. Found: C, 67.85; H, 5.47; N, 3.69.

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REFERENCES AND NOTES

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