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A NOVEL TRANSFORMATION OF 6,7-DIMETHOXY- AND 6,7-METHYLENEDIOXY-1-(2-BROMO-4,5-METHYLENEDIOXY-α-METHYL)BENZYL-1,2,3,4-TETRAHYDROISOQUINOLINES TO BENZOXAZEPINOISOQUINOLINES*† +

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The synthesis of tetrahydroprotoberberines[1] by the reaction of 1-benzyl-1,2,3,4-tetrahydroisoquinolines with formaldehyde by a Pictet-Spengler type reaction[2] is well documented and provides few surprises. However, we wish to report on the unusual behaviour of 1-(2-bromo-4,5-methylenedioxy-α-methyl) benzyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (I) towards formaldehyde. The reaction conducted with excess aqueous 30% formaldehyde in hydrochloric acid at 100° for 3 hr did not yield the bromoprotoberberine (II) which could be subsequently debrominated to give (±) Base II[3] (III), but an anomalous product in 75% yield. This communication presents data which establish its structure as the benzoxazepinoisoquinoline (IV). IV, m.p. 210° (from ethyl-acetate), $C_{21}H_{23}NO_5$ (M^+ at m/e 369) had no OH, NH or C=O bands in the IR spectrum (Nujol). Its NMR spectrum in $CDCl_3$ showed signals at δ 1.65 (3H; d, J = 6.5 Hz, MeCH), 2.75 (4H, m), 3.82 (3H; s, OMe), 3.88 (3H; s, OMe), 3.88 (1H at C-8; d, J = 15 Hz), 4.71 (1H at C-8; d, J = 15 Hz), 5.2 (1H at C-13; q, J = 6.5 Hz), 5.6 (1H at C-15; s) and 5.95 ppm (2H, s, CH_2O_2). Four aromatic protons were present at δ 6.55 (1H, s), 6.75 (2H, s) and 6.82 ppm (1H, s). Significant for the structure elucidation of IV was its UV spectrum : λ_{max} (EtOH) 247, 290, 312, 368 nm (log ε 4.23, 3.86, 3.57, 3.54); $\lambda_{max}^{EtOH-HCl}$ 247,

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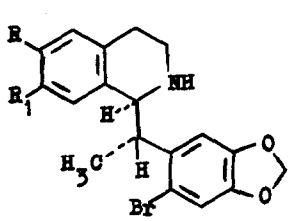
† Dedicated to Prof. T.R. Govindachari on the occasion of his 60th Birthday

+ Studies in Protoberberine Alkaloids. Part V. For Part IV see Indian J. Chem., 9, 1313 (1971).

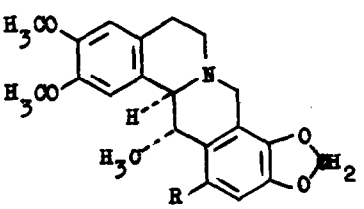
311, 365 nm (log ε 4.34, 4.05, 4.03); $\lambda_{max}^{EtOH-NaOH}$ 230 (sh), 285 nm (log ε 4.03, 3.86); $\lambda_{max}^{CHCl_3}$ 288 nm (log ε 3.88); $\lambda_{max}^{CHCl_3-HCl}$ 292 (sh), 312, 366 nm (log ε 3.91, 3.95, 3.99). The UV spectrum of IV in EtOH-HCl was closely similar to that of 2-(3,4-methylenedioxybenzyl)-6,7-dimethoxy-3,4-dihydroisoquinolinium iodide (VIII); λ_{max}^{EtOH} 248, 312, 367 nm (log ε 4.34, 4.07, 4.07); in EtOH-NaOH, the UV spectrum of VIII had a single maximum at 284 nm (log ε 3.92) again resembling that of IV in EtOH-NaOH or in $CHCl_3$.

Treatment of IV with sodium borohydride in methanol gave a dihydro derivative (V), m.p. 151° (from hexane), $C_{21}H_{25}NO_5$ (M^+ at m/e 371); IR (Nujol) γ_{OH} 3175 cm^{-1}; NMR ($CDCl_3$) δ 1.52 (3H; MeCH; d, J = 6.5 Hz), 2.8 (4H, broad s), 3.3 (1H; d, J = 12.5 Hz), 3.8 (6H, s, 2 OMe), 4.1 (1H, d, J = 12.5 Hz), 5.0 (1H, q, J = 6.5 Hz), 5.95 (2H, s, CH_2O_2), 6.45 (1H, s), 6.55 (1H, s), 6.75 (1H, s) and 6.95 ppm (1H, s). V formed a mono O-acetate (VI), m.p. 144° (from ether), $C_{23}H_{27}NO_6$ (M^+ at m/e 413); λ_{max}^{EtOH} 230 (sh), 286 nm (log ε 4.26, 3.88), NMR ($CDCl_3$) δ $\overset{CH_3}{\underset{CH-OAc}{}}$ 6.22 ppm (q, J = 6.5 Hz). Catalytic hydrogenation of V in HCl solution using palladised charcoal led to the formation of VII, $C_{21}H_{25}NO_4$, (M^+ at m/e 355), m.p. 113-115° (from ether), identical with a sample synthesised from 2-(2-ethyl-4,5-methylenedioxy-benzyl)-6,7-dimethoxy-3,4-dihydroisoquinolinium iodide (IX) by reduction with sodium borohydride in methanol; λ_{max}^{EtOH} 230 (sh), 286 nm (log ε 4.11, 3.90); NMR ($CDCl_3$) δ 1.17 (3H, t, J = 7 Hz, Me-CH_2), 2.7 (2H, q, J = 7 Hz; CH_2-Me), 2.75 (4H, s), 3.57 (4H, broadened s), 3.80 (3H, s, OMe), 3.83 (3H, s, OMe), 5.9 (2H, s, CH_2O_2), 6.5 (1H, s), 6.6 (1H, s), 6.7 (1H, s) and 6.95 ppm (1H, s).



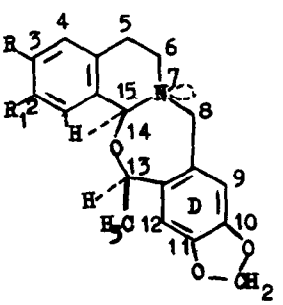
I : R = R_1 = OMe

XI : R,R_1 = $-OCH_2O-$



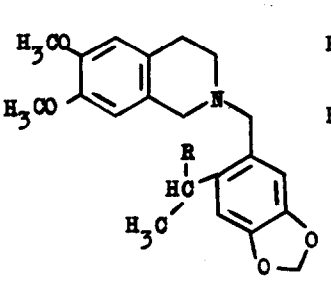
II : R = Br

III : R = H

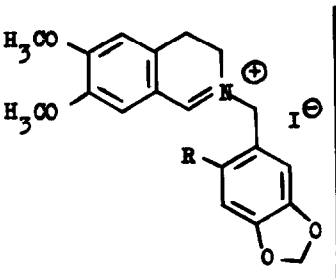


IV : R = R_1 = OMe

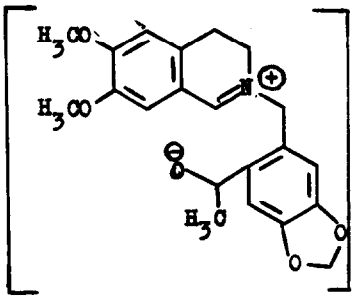
XII : R,R_1 = $-OCH_2O-$



V : R = OH
VI : R = OAc
VII : R = H

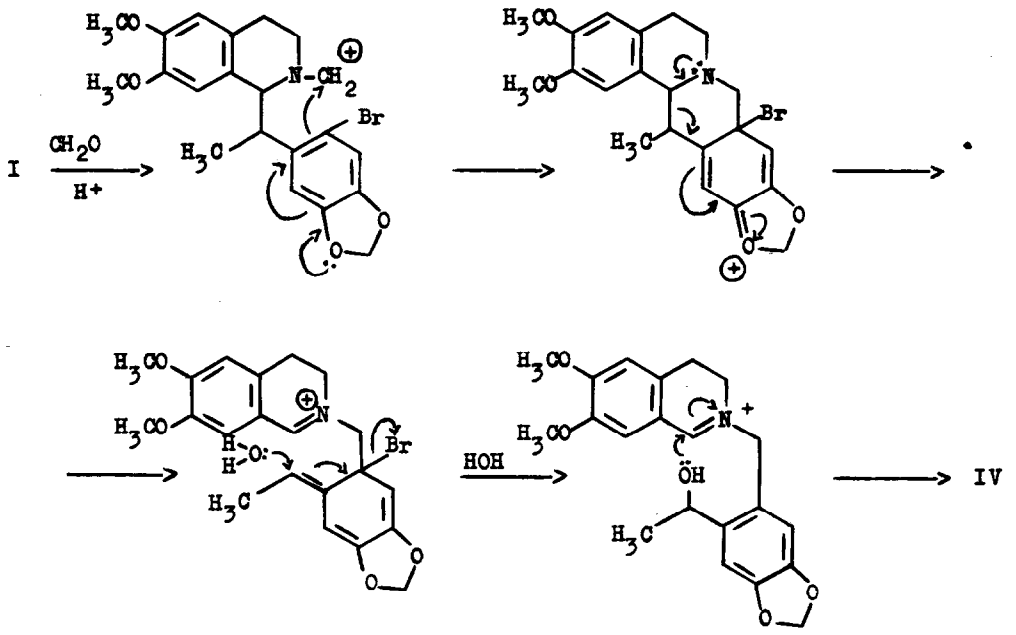


VIII : R = H
IX : R = C_2H_5



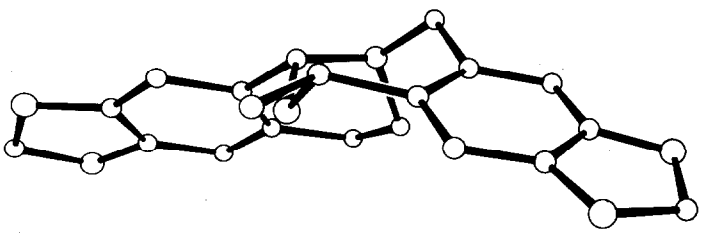
X

A possible mechanism for the formation of IV from I is indicated below:



The UV spectrum of IV in alcohol indicated that it exists in equilibrium with species X (or its protonated form), the latter in preponderance. The equilibrium is shifted completely towards IV by the addition of alkali to the alcohol solution or in solutions in an aprotic solvent like chloroform.

X-ray studies were undertaken on XII, the bismethylenedioxy analogue of IV, prepared from XI. Crystals grown from EtOAc-hexane are colourless prisms: monoclinic, a = 16.0072 (5), b = 8.0507 (3), c = 14.0043 (6) Å, β = 112.536 (3)°; D_c = 1.41 g cm^{-3} for cell contents of 4 ($C_{20}H_{19}NO_5$), D_m = 1.41 (2) g cm^{-3}. The space group is uniquely identifiable as $P2_1/n$, Z = 4. The structure was solved by direct methods from 3163 intensities measured on a diffractometer (of which 285 were judged unobservable), and has been refined to R 0.052. The diagram confirms the proposed skeleton and shows that the hydrogen atoms at C-13 and C-15 and the lone pair at N are all cis.



Further studies on various aspects of this unusual reaction, such as scope and stereospecificity are in progress.

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