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A New Synthetic Route to (±)-Lysergic Acid

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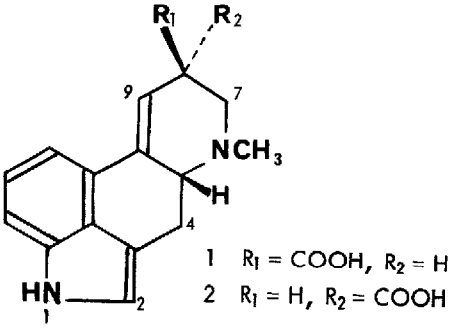
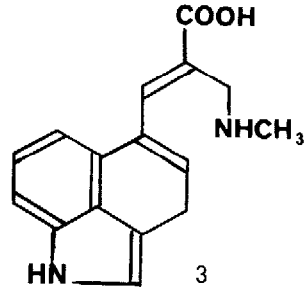
Our approach to the synthesis of lysergic acid (1) is related to the intriguing epimerisation of (1) and isolysergic acid (2) which is accompanied by racemisation.[1] In order to reconcile these processes Woodward proposed[2] a mechanism involving ring opening to (3)[3] which is devoid of chirality and has the capability of cyclisation to (±)-(1) and (±)-(2). Paspalic acid (4) would be another cyclisation product but this is thermodynamically less stable[4] than (1) or (2). If this hypothesis is correct then construction of (3), followed by spontaneous cyclisation, would afford a synthesis of (1) and (2). In order to circumvent difficulties due to indole-naphthalene tautomerism in (3) it was decided to aim for the modified target (5) which has the masked indolic system employed in both previous synthesis[5,6] of (±)-lysergic acid (1).



1 R_1 = COOH, R_2 = H

2 R_1 = H, R_2 = COOH



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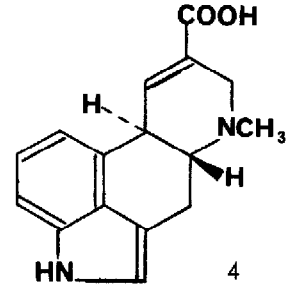

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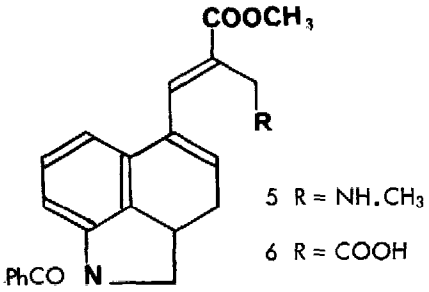
The known aldehyde (8)[5] was reacted with (9)[7] (benzene/Bu^tOH, reflux, 4 days) to give the diester,[8] m.p. 162-164° which was converted (90% TFA, 25°, 2 hr) into the corresponding acid (6), m.p. 176-178° in 70% yield from (8). This substance (6) exhibited, inter alia : ir($CHCl_3$) 1710, 1646 cm^{-1}; uv(C_2H_5OH) 254 nm (4.43); NMR($CDCl_3$) δ 2.40(2H,m), 3.45(2H,s), 3.74(3H,s), 4.40(1H,m) 3.70(2H,m), 6.04(1H,br.d), 6.70-7.70(9H,m), 9.80(1H,s). The stereochemistry of the acyclic double bond may be assigned by NMR comparison of model systems with particular reference to the

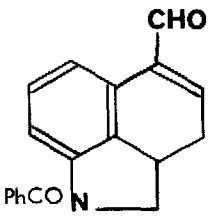
acyclic vinyl H resonance.[7,9] Curtius degradation of (6) to the primary amine (7) was achieved in 80% yield by (i) Ph_2POCl/N-methylmorpholine/CH_2Cl_2/-20°/20 min., (ii) tetramethylguanidinium azide[10]/CH_3CN/0°/1.5 hr., (iii) benzene/reflux/1 hr., (iv) p-toluenesulphonic acid monohydrate/ether-benzene/25°/16 hr. This produced the p-toluenesulphonate of (7), m.p. 166-170°; ir(KBr) 2700-3300, 1730, 1640 cm^{-1}; uv(C_2H_5OH) 234(4.23), 255 nm (4.27); NMR(TFA) δ2.90(2H,m), 2.42 (3H,s), 4.05(5H,m), 4.03(3H,s), 6.05(1H,br.d), 6.26(1H,br.s), 6.90-8.20(15H,m).



5 R = $NH.CH_3$

6 R = COOH

7 R = NH_2



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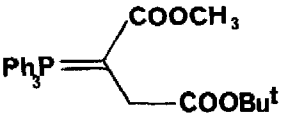

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Although (7) did not cyclise spontaneously it was anticipated that N-alkylation would greatly facilitate this process. Indeed it was found that methylation (HCHO-HCOOH/100°/3 hr.) did not proceed to the tertiary amine but instead the secondary amine (5) cyclised to give a 62% yield of (10), (11) and (14) (9:3:2 respectively). Fractional crystallisation gave (11), m.p. 149-153°; ir($CHCl_3$) 1733, 1633 cm^{-1}; uv(C_2H_5OH) 242(4.30), 305nm(3.67); NMR($CDCl_3$)δ 2.38(3H,s), 3.73(3H,s), 6.19(1H,br.s,$W_{\frac{1}{2}}$6Hz), 6.90-7.60(8H,m). The mixture of (10) and (14) was separated by TLC (silica/7% CH_3OH-$CHCl_3$) to give (10), m.p. 165-168°; ir($CHCl_3$) 1728, 1632 cm^{-1}; uv(C_2H_5OH) 253(4.59), 307 nm (3.89); NMR($CDCl_3$)δ 2.48(3H,s), 3.73(3H,s), 6.52(1H,br.s,$W_{\frac{1}{2}}$ 6Hz), 6.80-7.70(8H,m)and (14), m.p. 152-7°; ir($CHCl_3$) 1708, 1635 cm^{-1}; uv(C_2H_5OH) 220, 292 nm; NMR($CDCl_3$)δ 2.44(3H,s), 3.73(3H,s), 6.90-7.70 (9H,m) which was contaminated with (11) due to rearrangement on silica. Hydrogenation of the mixture (10)/(11) gave a dihydro product confirming the presence of only one olefinic double bond and hence the tetracyclic nature of these compounds. The stereochemical assignment at C-8 in (10) and (11) follows from the greater thermodynamic stability of the equatorial β-$COOCH_3$ in the lysergic series.[11] In (10) and (11) the cis configuration at C-3 and C-5 may be attributed the maximal resonance delocalisation of the styrene chromophore in contrast to the situation prevalent with the corresponding trans configuration.[12]