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1,6-DIHYDRO-3(2*H*)-PYRIDINONES AS SYNTHETIC INTERMEDIATES. FORMAL SYNTHESIS OF (±)-TABERSONINE AND (±)-CATHARANTHINE

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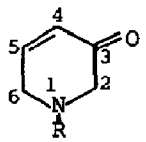
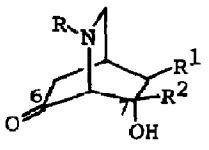
Summary: Formal synthesis of (±)-tabersonine (3) and (±)-catharanthine (4) has been achieved starting from ethyl 1,6-dihydro-3(2*H*)-pyridinone-1-carboxylate (1a) as a common synthon.

Tabersonine, one of the *Aspidosperma* alkaloids, is known to be the *in vivo* progenitor[1] of the *Iboga* alkaloids, e.g. catharanthine, which has been shown to play a potential role for synthesis of an antitumor alkaloid vinblastine.[2] Total syntheses of (±)-tabersonine[3,4,5] and (±)-catharanthine[6,7] have so far been accomplished by several groups independently.

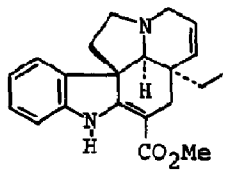
Recently, we described the first preparation of N-substituted 1,6-dihydro-3(2*H*)-pyridinones[8] (1) and their novel conversion to 2-azabicyclo[2.2.2]octan-6-one system (2).[9] At present we are investigating synthetic applications of the dihydropyridinones to some natural products and now wish to report formal synthesis of (±)-tabersonine (3) and (±)-catharanthine (4) using 1a as a common starting material.



1a R=CO_2Et
b R=SO_2Me



2 R^1=CO_2R',CONHPh,H
R^2=Et,Me



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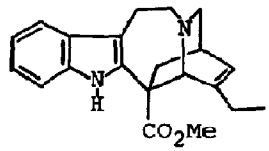

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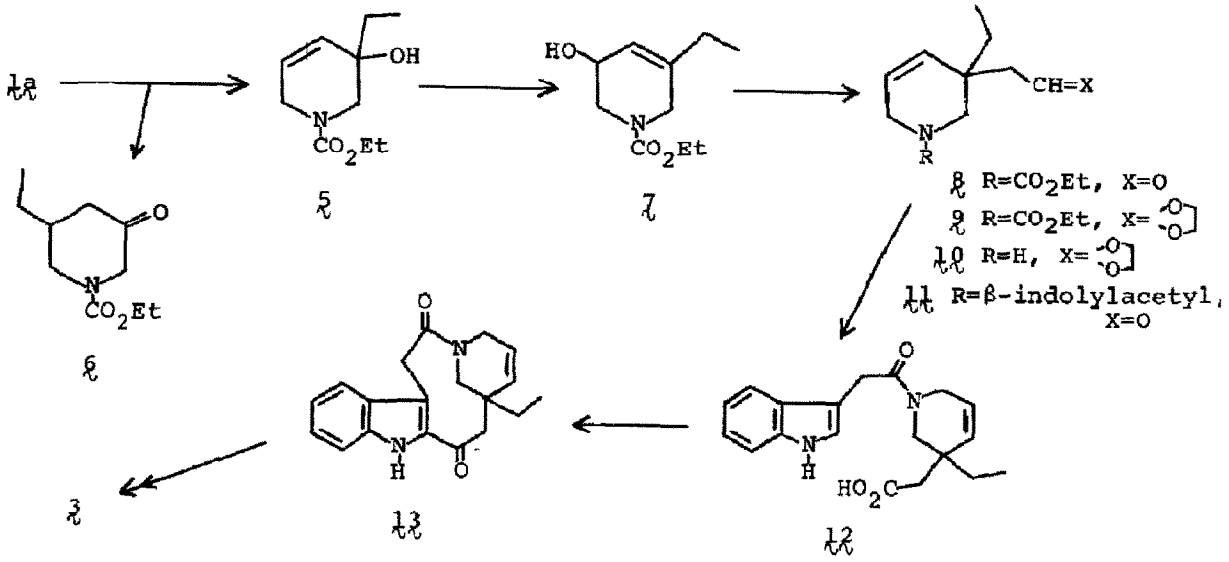
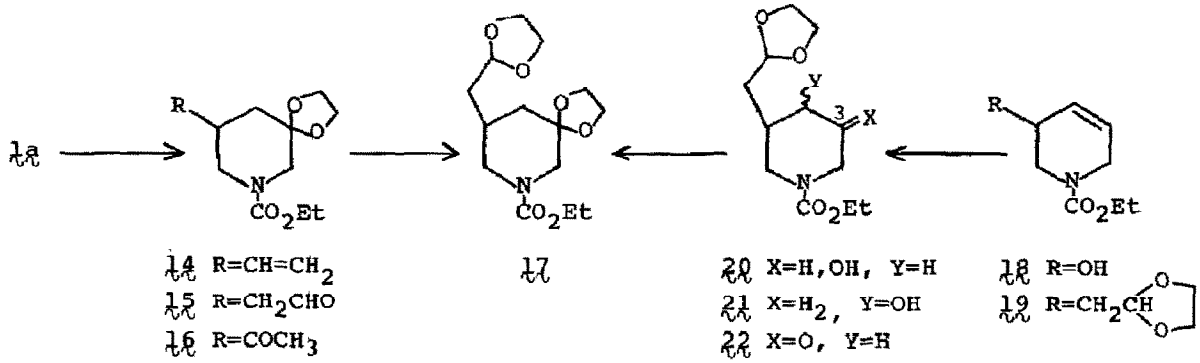
Ethyl 1,6-dihydro-3(2*H*)-pyridinone-1-carboxylate (1a) was treated with ethylmagnesium bromide in ether at 0° to give the 1,2-adduct (5)[10a] and 1,4-adduct (6) in 41% and 11% yields, respectively. On reaction of the former (5) with 1% hydrochloric acid in acetone smoothly proceeded an allylic rearrangement to give the secondary alcohol (7)[10b] in 83% yield. The Claisen rearrangement of 7 with ethyl vinyl ether in the presence of mercuric acetate[11] at 205° for 43 hr yielded the aldehyde (8), which without any purification was acetalized in an usual manner to give the ethylene acetal (9;[10c] 59% from 7). Hydrolysis of 9 with potassium hydroxide in boiling aqueous ethanol for 72 hr afforded the amine (10[10d]; 37%) along with 53% of the unchanged starting material. Condensa-

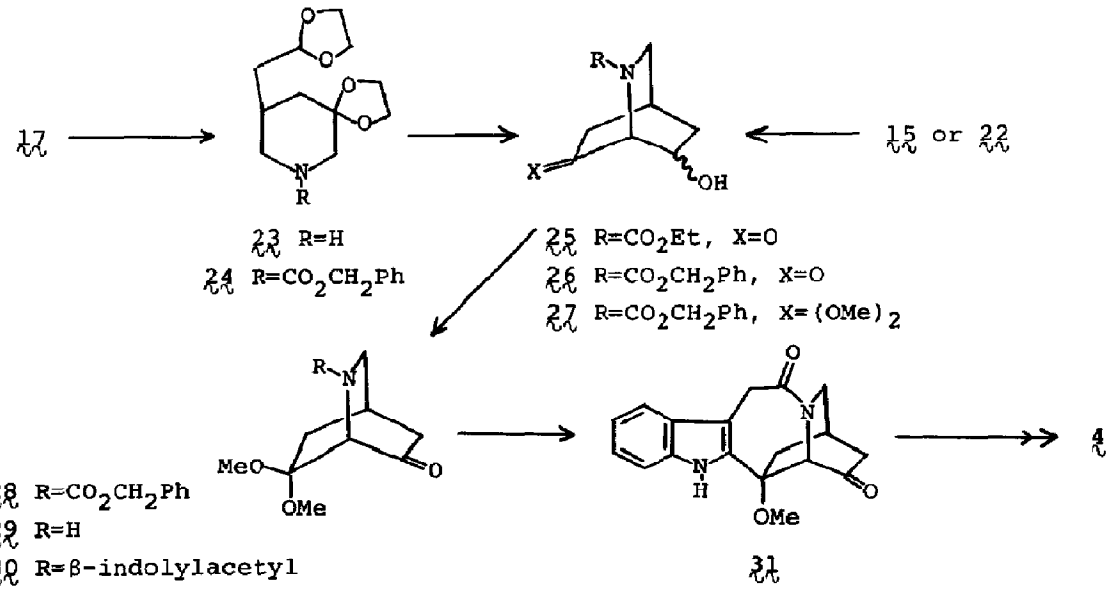
tion of 10 with β-indolylacetyl chloride,[12] followed by acid hydrolysis [10%HCl, THF-H_2O, reflux for 8 hr] yielded the aldehyde (11)[10e] in overall 81% yield. Oxidation of 11 with silver(I) oxide, prepared *in situ* from silver nitrate and potassium hydroxide,[13] gave the carboxylic acid (12) in 68% yield. The intramolecular cyclization of 12 according to the method of Ziegler[3] furnished (±)-5,16-dioxo-14,15-dehydroquebrachamine (13)[10f] in 47% yield, which was identical with the authentic sample in pmr spectra. Since the conversion of 13 into (±)-tabersonine has already been described,[3] our present synthesis means a formal synthesis of this alkaloid.



On the other hand, the Grignard reaction of 1a with vinylmagnesium bromide in the presence of cuprous chloride, followed by ketalization gave the ketal (14)[10g] though in a low yield (18%). Hydroboration-oxidation[14] of 14 and the subsequent PCC oxidation[15] yielded the desired aldehyde (15)[10h] in 59% yield with a small amount of the ketone (16). Acetalization of the former (15) gave the diketal (17;[10i] 86%), which was also obtained more efficiently by the



following alternative method. The allylic alcohol (18),[8] the synthetic precursor of 1a, was converted to the acetal (19) in 69% yield by the Claisen rearrangement and subsequent acetalization in the manner similar to that for 9. Hydroboration-oxidation of 19 afforded the 3-hydroxyl derivative (20; 52%) and its regioisomer (21; 13%) as both diastereoisomeric mixtures. PCC oxidation of the former was followed by ketalization to give the ketal (17) in 86% yield. Hydrolysis of 17 with potassium hydroxide in aqueous ethanol under reflux for 36 hr gave the amine (22;[10j] 79%), which was treated with carbobenzoxy chloride to afford 24 in 92% yield. On acid hydrolysis of 15 or 22 an intramolecular aldol reaction took place efficiently to yield the same azabicyclo[2.2.2]octanone (25)[10k] in 70% or 98% yield, respectively, and a similar treatment of 24 gave 26[10l] in 87% yield. Reaction of 26 with methyl orthoformate afforded the ketal (27; 74%), which was oxidized with PCC to give 28[10m] in 77% yield. On its hydrogenolysis over 5% palladium on carbon in methanol formed the labile amino ketone (29)[10n], which was immediately converted to the amide (30; 65% from 28). Cyclization of 30 with *p*-toluenesulfonic acid yielded the pentacyclic ketone (31)[10o] in 69% yield, which was proved to be identical with the known intermediate (31)[6] to (±)-catharanthine (4) by spectral comparison. Thus, we have also accomplished a formal synthesis of (±)-catharanthine.



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10. *a*) ir 3575, 1680, 1650, pmr 0.97(3H,t,J=8), 1.55(2H,q,J=8), 5.70(2H,s); *b*) ir 3575, 1680, 1660, pmr 1.06(3H,t,J=7), 2.04(2H,q,J=7), 5.62(1H,m); *c*) ir 1680, pmr 0.87(3H,t,J=7), 1.70(2H,d,J=5), 4.80(1H,t,J=5), 5.60(2H,m); *d*) ir 3400, 1635, pmr 0.86(3H,t,J=8), 1.41(2H,q,J=8), 1.69(2H,d,J=5), 2.50(1H,s, NH), 4.90(1H,t,J=5), 5.55(1H,d-m,J=10), 5.70(1H,d-t,J=10,3), *m/e* 197(M^+); *e*) ir 3460, 2725, 1715, 1650, 1625, pmr 0.83(3H,t,J=7), 5.63(2H,s), 9.50(1H, m), *m/e* 310(M^+); *f*) mp 225-226°(lit[3] mp 225-226°), ir 3450, 1650, 1630, pmr 0.97(3H,t,J=8), 1.42(2H,q,J=8), 2.76 and 3.04(2H,AB-q,J=12), 3.22 and 4.16 (2H,AB-q,J=14), 3.45 and 4.88(2H,AB-q,J=18), 4.27(2H,s), 5.76(2H,s), 7.1-7.7 (4H,m), 9.06(1H,s), *m/e* 308(M^+), uv(MeOH) 243(14000), 319.5(16100); *g*) ir 1680, pmr 3.98(4H,s), 5.02(1H,d,J=10), 5.05(1H,d,J=18), 5.71(1H,d-d-d,J=18, 10,7); *h*) ir 2720, 1720, 1685, pmr 3.98(4H,s), 9.76(1H,s); *i*) ir(film) 1690, pmr 3.8-4.0(8H,m), 4.88(1H,t,J=4.5), *m/e* 301(M^+); *j*) ir 3300, pmr 3.7-4.0 (8H,m), 4.83(1H,t,J=4.5); *k*) Its benzoate: mp 100-101°, ir 1738, 1715, 1690, 1600, 1582, pmr 4.58(1H, broad), 5.42(1H,d-d-d,J=9,4.5,3), *m/e* 317(M^+); *l*) Its benzoate: mp 95-96.5°, ir 1735, 1710, 1685, pmr 4.2-4.5(2H,m), 5.10(2H, s); *m*) ir 1740, 1690, pmr(at 70°) 3.19(6H,s), 4.54(1H,s) 5.14 and 5.17(2H, AB-q,J=14), 7.32(5H,s); *n*) ir 3360, 1720; *o*) mp 281-282°(lit[6] mp 283-284°), ir(Nujol) 3130, 1742, 1640, pmr 3.05(3H,s), 4.02 and 3.74(2H,AB-q,J=16), 4.79 (1H,s), 7.0-7.6(4H,m), 8.28(1H,s), *m/e* 310(M^+), uv(MeOH) 221.5(34000), 283.5 (7500), 292.5(6500).
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