SYNTHESIS OF CEPHALOTAXINE ANALOGS[1]

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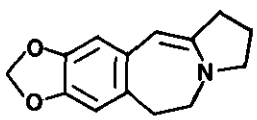
Abstract - The efficient preparation of a pentacyclic analog **4** of the cephalotaxine skeleton is described.

The Cephalotaxus alkaloids[2] have been targets of intense synthetic interest since the demonstration that the ester alkaloids displayed significant antileukemic activity;[3] harringtonine and homoharringtonine have subsequently reached clinical trials and effected high levels of remission in nonlymphocytic leukemias.

The parent base, cephalotaxine (1), has been synthesized by two groups.[4] Weinreb and Auerbach[5] completed a total synthesis by constructing the functionalized cyclopentane ring last, using an intramolecular Michael reaction to join this ring to amine **2**, while Semmelhack and co-workers[6] linked the aromatic ring to the nitrogen of a preformed azaspirononane to form **3**, then completed the seven-membered ring by a photochemical ring closure. Of numerous other published approaches, only two (those of Dolby[7] and Kupchan[8]) have reached a pentacyclic stage.



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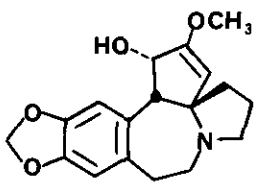
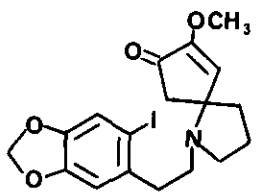


1 CEPHALOTAXINE



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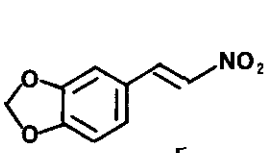
We report here the application of a strategy, different from any published route, which has led to the pentacyclic cephalotaxine analog **4** and which has the potential of leading to the cephalotaxine skeleton itself. While this scheme will require extra steps to correct the sizes of rings B and C, it has the advantage of constructing the crucial azaspirane system quickly and efficiently from a nitrocycloalkane.[9]

The known[10] Diels-Alder adduct **6** was prepared by addition of butadiene (or, more conveniently, the butadiene equivalent 3-sulfolene) to 3,4-methylenedioxy-β-nitrostyrene (**5**). Michael addition of methyl acrylate to **6** gave the nitroester **7** in high yield. The Michael adduct is a single crystalline stereoisomer; we tentatively assign the "natural" configuration shown on the argument that addition should occur from the less hindered face of the aci-nitro anion. The stereochemistry is not critical at this stage, since the B/C ring junction can be equilibrated to the more stable "natural" configuration in cephalotaxinone.[4]

In order to preserve the cyclohexene double bond for eventual ring contraction, the nitro group was reduced with zinc in ethanolic HCl to afford the crystalline lactam **8**, which was further reduced by "Red-Al" to the pyrrolidine **9**. This key intermediate is thus available in 63% overall yield from **6**, or in 39% overall yield in five easy steps from piperonal.

Our initial attempts to effect direct completion of the seven-membered ring B by Lewis acid-promoted cyclization of **8** (R = CH_2COOH or -COCOCl) or **9** (R = COCOCl, COCOOH, or CH_2CO_2Et), or by photolysis of **9** (R = $COCH_2Cl$), all proved unsuccessful. By contrast, ring closure to the six-membered ring B of **4** proceeded smoothly. Pictet-Spengler cyclization of **9** with formaldehyde gave crystalline **4** in 72% yield. Alternatively, **7** could be formylated, cyclized to iminium salt **10** by the Bischler-Napieralski procedure, and reduced to **4** with sodium borohydride.



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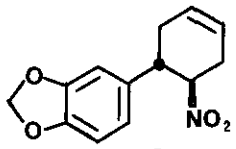

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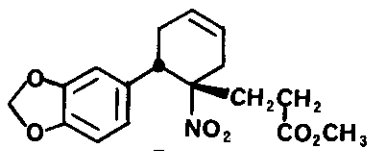

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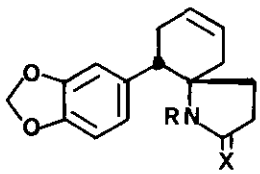
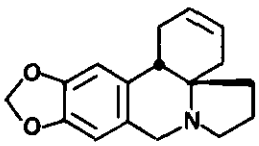


8. X=O, R=H
9. $X=H_2$, R=H



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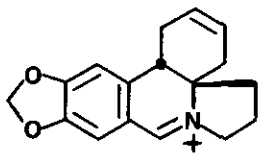

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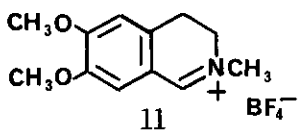
Amine **4** represents an interesting isomer of the cephalotaxine skeleton in which ring B is one member smaller and ring C one member larger. The double bond in ring C allows the obvious possibility of oxidation followed by aldol or Dieckmann cyclizations to effect ring contraction. The more challenging problem is the expansion of the heterocyclic ring B. A model for one solution to this problem has been successfully tested: iminium salt **11** was treated with diazomethane by the procedure of Leonard,[11] and the resulting aziridinium salt **12** was cleaved at the benzylic position by catalytic hydrogenation to afford the benzazepine derivative **13**. Application of this procedure to iminium salt **10** and elaboration of these intermediates to structures closer to cephalotaxine are in progress.



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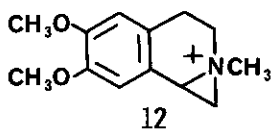

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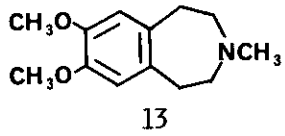

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EXPERIMENTAL

trans-4-(3,4-Methylenedioxyphenyl)-5-nitrocyclohexene (**6**).- This adduct was prepared in 63% yield by the addition of butadiene to 3,4-methylenedioxy-β-nitrostyrene (**5**),[12] as described by Maxon and Wildman.[10] Alternatively, a mixture of **5** (5.0 g), butadiene sulfone (10.0 g), hydroquinone (100 mg) and toluene (50 ml) was heated in a steel bomb at 130°C for 96 h. After cooling, the bomb was rinsed with $CHCl_3$ (100 ml) and hexane (450 ml); the mixture was stirred with 6 g of silica gel and filtered. The filtrate was concentrated to a volume of 15 ml and kept at 7°C for 2 days, giving a crop of adduct, 1.4 g, mp 95-98°C. A second crop of 2.5 g was obtained by concentrating the filtrate and adding 10 ml of absolute ethanol, bringing the total yield to 3.9 g (61%). Recrystallization from methanol raised the mp to 96-98°C (lit[10] mp 97-99°C).

4-(2-Carbomethoxyethyl)-5-(3,4-methylenedioxyphenyl)-4-nitrocyclohexene (**7**).- A solution of **6** (24.0 g) in 100 ml of THF was stirred with methyl acrylate (40 ml) in 200 ml of t-butyl alcohol and 40 drops of a 35% solution of Triton B in methanol at room temperature for 38 h. The first crop of product was collected and washed with methanol, giving 14.5 g, mp 94-96°C. The filtrate was diluted with 200 ml of ether and washed with 2% HCl, saturated $NaHCO_3$, water, and brine, then dried and concentrated. Two crops were collected, bringing the total to 28.9 g (89.3%). Recrystallization from methanol gave colorless crystals, mp 94-96°C; ir (KBr): 3040, 1740, 1655, 1610, 1535, 1375, 1250, 1240 cm^{-1}; nmr ($CDCl_3$): δ 6.73 (1H, s), 6.63 (2H, s), 5.85 (2H, s), 5.80 (2H, m), 3.62 (3H, s), 3.38 (2H, m), 2.40 (8H, m).

6-(3,4-Methylenedioxyphenyl)-2-oxo-1-zazspiro[4.5]dec-8-ene (**8**).- Zinc dust (9.0 g, activated[13] by treatment with HCl) was added in small portions to a magnetically stirred solution of **7** (5.2 g) in 100 ml of absolute ethanol containing 20 ml of conc HCl. The temperature rose to 59°C. After stirring for 1 h the mixture was filtered and the filtrate treated with 20% NaOH until alkaline. The mixture was stirred for 2 h, cooled in ice, and acidified with conc HCl, then extracted with four 50 ml portions of CH_2Cl_2. The extracts were washed with water and brine, dried, and concentrated at reduced pressure. Methanol (10 ml) was added to the residue, which crystallized on standing. The product (3.4 g, 80%) had mp 174-175°C, raised to 175.5-177.5°C by recrystallization from methanol; ir (KBr): 3200, 3020, 2960, 2890, 1680, 1600, 1240, 1230 cm^{-1}; nmr ($CDCl_3$): δ 7.13 (1H, s), 6.85 (1H, s), 6.78 (2H, s), 5.93 (2H, s), 5.80 (2H, m), 3.4 (1H, m), 2.58 (4H, m), 1.88 (4H, m). Anal. Calc for $C_{16}H_{17}NO_3$: C, 70.83; H, 6.32; N, 5.16. Found: C, 70.72; H, 6.12; N, 5.45.

6-(3,4-Methylenedioxyphenyl)-1-azaspiro[4.5]dec-8-ene (**9**).- To a suspension of 2.0 g of $LiAlH_4$ in 25 ml of dry THF was added dropwise, at reflux, a solution of 3.0 g of **8** in 135 ml of THF. After eight days stirring at reflux the mixture was cooled and treated dropwise with 14 ml of saturated aqueous Na_2SO_4. The mixture was filtered, and the filtrate, after dilution with 100 ml of CH_2Cl_2, was washed with 10% NaOH, water, and brine, then dried and concentrated at reduced pressure, leaving a yellow oil (2.0 g, 70%); ir (thin film): 3350, 3020, 2950, 2880, 1610, 1550, 1240, 805 cm^{-1}; nmr ($CDCl_3$): δ 6.98 (1H, s), 6.68 (2H, s), 5.82 (2H, s), 5.73 (2H, m), 3.7 (1H, m), 2.9-1.6 (11H, m).

Alternatively, reduction was effected in 89% yield by overnight reflux with a 70% solution of sodium bis(2-methoxyethoxy)-aluminum hydride ("Red-Al") in benzene.

Amine **9** formed a crystalline hydrobromide, mp 224-225°C, for which a satisfactory elemental analysis could not be obtained.

N-Oxalyl Derivative (**9**, R = $COCO_2H$) was prepared by refluxing a mixture of 1.13 g of **9**, 1.53 g of oxalyl chloride, and 1 g of anhydrous K_2CO_3 in 12 ml of tetrahydrofuran for 5 h. After filtering, the filtrate was concentrated at reduced pressure and the residue was hydrolyzed with 1:1 tetrahydrofuran-50% HCl. The colorless solid had mp 191.5-192°C.

N-Carbethoxymethyl Derivative (**9**, R = $CH_2CO_2C_2H_5$) was prepared by stirring overnight at reflux a mixture of 0.43 g of **9**, 0.33 g of ethyl bromoacetate, 0.3 g of anhydrous K_2CO_3, and 15 ml of acetone. After filtering the solids, concentration of the filtrate at reduced pressure left a yellow oil (0.48 g) which crystallized on standing. Chromatography on silica gel, eluting with benzene-ethyl acetate, gave colorless needles, mp 77.5-79°C; ir (KBr): 3010, 1735, 1235, 1190, 1180, 1040, 935, 810 cm^{-1}.

8,9-Methylenedioxy-1,4,4a,10b-tetrahydrocyclopenta[e]phenanthridinium Iodide (**10**).- Acetic anhydride (2.0 ml) was heated with 88% formic acid (1.0 ml) for 2 h at 50-60°C. After cooling to 25°C, amine **9** (1.5 g) in 10 ml of ether was slowly added, keeping the temperature at 30-34°C. After stirring 8 h at room temperature, the solution was washed with water, saturated $NaHCO_3$, and brine, then dried and concentrated at reduced pressure to leave a yellow oil (800 mg, 48%), ir (thin film) 1650, 800 cm^{-1}.

A solution of this crude formamide (450 mg) in 2.5 ml of toluene was heated at reflux with 1.5 ml of $POCl_3$ for 130 min, then kept at room temperature 4 h. Ligroin (6 ml) was added, and after standing for 45 min the solvent was decanted and the gummy residue taken up in ethanol (6 ml). The solution was diluted with 20 ml of water and washed with 30 ml of benzene. The aqueous solution was treated with 350 mg of NaI and kept 12 h in the refrigerator. Orange meedles (140 mg), mp 199-201°C, were collected and washed with a little water and absolute ethanol. A second crop (48 mg) was collected after adding 1 g of NaI to the filtrate. The total yield was 188 mg (30%); recrystallization from chloroform-benzene gave mp 202-203.5°C. ir (KBr): 3000, 2960, 2900, 1650, 1605, 1590, 1275 cm^{-1}; nmr ($CDCl_3$): δ9.53 (s, 1H), 7.5 (s, 1H), 6.93 (s, 1H), 6.17 (s, 2H), 5.73 (2H, m), 4.58 (2H, m), 3.63 (1H, m), 2.77 (2H, m), 2.23 (6H, m).

8,9-Methylenedioxy-1,4,4a,5,6,10b-hexahydrocyclopenta[e]phenanthridine (**4**).- (a) A solution of $NaBH_4$ (109 mg) in 1 ml of water was added dropwise to an ice-cold solution of iodide **10** (65.7 mg) in 1 ml of methanol. After keeping 4 h at 0°C the amine (33.8 mg, 75%), mp 86-89°C, was collected and washed with cold water.

(b) A mixture of **9** (4,8 g), 37% formalin solution (50 ml), and 2N HCl (100 ml) was heated under reflux for 2 h. After cooling, the solution was made alkaline with 40 ml of 20% NaOH and extracted three times with ether. The extracts were washed with water and brine, dried over $MgSO_4$, and concentrated at reduced pressure, leaving a pale yellow solid (3.6 g, 72%), mp 88-90°C. Recrystallization from 85% aqueous methanol raised the mp to 89-90.5°C. Anal. Calc for $C_{17}H_{19}NO_2$: C, 75.84; H, 7.06; N, 5.20. Found: C, 75.75; H, 7.13; N, 5.18; ir (KBr): 3020, 2970, 2900, 2850, 1650, 1620, 1270 cm^{-1}; nmr ($CDCl_3$): δ6.72 (1H, s), 6.68 (1H, s), 5.90 (2H, s), 5.63 (1H, m), 5.55 (1H, m), 3.83 (2H, AB quartet), 3.1 (1H, m), 2.67 (4H, m), 1.91 (4H, m), 1.63 (2H, m); mass spectrum: m/z 268 (3, M^+), 216 (14), 215 (72), 214 (100), 186 (12), 156 (13), 128 (10), 78 (21), 39 (11).

7,8-Dimethoxy-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine (**13**).- To a solution of 1.00 g of 6,7-dimethoxy-3,4-dihydroisoquinoline methiodide[14] in 22 ml of water, cooled in ice, was added portionwise 6.1 g of fluoroboric acid. After keeping for 8 h at 7°C the crystals of the fluoroborate **11** were collected and washed with water, then ethanol. The yield of fluffy yellow crystals, mp 185-187°C, was 580 mg (66%).

The salt was dissolved in 50 ml of CH_2Cl_2, cooled to 0°C, and treated with stirring with cold ethereal diazomethane until a colorless solid precipitated and the yellow color persisted for a few minutes. The solid was collected and washed with CH_2Cl_2 and ether; the yield of aziridinium salt **12** was 525 mg (86%), mp 119-123°C.

A solution of 0.71 g of **12** in 130 ml of ethanol and 30 ml of water was hydrogenated over W-2 Raney nickel for 12 h at 60 psi in a Parr shaker. The mixture was filtered through Celite and concentrated at reduced pressure. The residue was rendered alkaline with NaOH and extracted with ether. Concentration of the ether extracts left 0.44 g (85%) of amine **13** as an oil; ir (thin film) 3000, 2960, 2940, 2840, 2800, 1610, 1520 cm^{-1}; nmr ($CDCl_3$): δ6.65 (2H, s), 3.77 (6H, s), 2.72 (8H, m), 2.38 (3H, s); mass spectrum: m/z 221 (53), 206 (15), 192 (10), 178 (17), 165 (100), 164 (10), 107 (18), 91 (25), 77 (15), 65 (10), 57 (32), 44 (29), 42 (67); ^{13}C-nmr ($CDCl_3$): 147, 134, 113.5, 58, 56, 48, 36.5. The hydrochloride, after recrystallization from ethanol, had mp 254-256°C (lit.[15] mp 262-263°C).

REFERENCES

1. Dedicated with gratitude, admiration, and respect to Prof. Gilbert Stork.
2. Reviews: (a) L. Huang and Z. Xue, in The Alkaloids, Vol. 23 (A. Brossi, ed.), Academic Press, Inc., Orlando, 1984, p. 157; (b) T. Hudlicky, L.D. Kwart, and J.W. Reed, in Alkaloids: Chemical and Biological Perspectives, Vol. 5 (S.W. Pelletier, ed.), John Wiley and Sons, New York, 1986.
3. C.R. Smith, Jr., K.L. Mikolajczak, and R.G. Powell, in Anticancer Agents Based on Natural Product Models (J.M. Cassady and J.D. Douros, eds.), Academic Press, New York, 1980, p. 392.
4. S.M. Weinreb and M.F. Semmelhack, Acc. Chem. Res., 1975, **8**, 158.
5. S.M. Weinreb and J. Auerbach, J. Am. Chem. Soc., 1975, **97**, 2503.
6. M.F. Semmelhack, B.P. Chong, R.D. Stauffer, T.D. Rogerson, A. Cong, and L.D. Jones, J. Am. Chem. Soc., 1975, **97**, 2507.
7. L.J. Dolby, S.J. Nelson, and D. Senkovich, J. Org. Chem., 1972, **37**, 3691.
8. S.M. Kupchan, O.P. Dhingra, and C.-K. Kim, J. Org. Chem., 1978, **43**, 4464.
9. R.K. Hill, J. Org. Chem., 1957, **22**, 830.
10. L.H. Mason and W.H. Wildman, J. Am. Chem. Soc., 1954, **76**, 6194.
11. N.J. Leonard and K. Jann, J. Am. Chem. Soc., 1962, **84**, 4806; cf. H.O. Bernhard and V. Snieckus, Tetrahedron, 1971, **27**, 2091.
12. E. Knoevenagel and L. Walter, Chem. Ber., 1904, **37**, 4502.
13. R.L. Shriner and F.W. Neumann, Org. Synth., Coll. Vol., 1955, **3**, 73.
14. W.M. Whaley and M. Meadow, J. Chem. Soc., 1951, 1069.
15. B. Pecherer, R. Sunbury, and A. Brossi, J. Heterocyl. Chem., 1972, **9**, 609.

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