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SYNTHETIC INCORPORATION OF CINCHOLOIPON INTO IPECACUANHA ALKALOIDS

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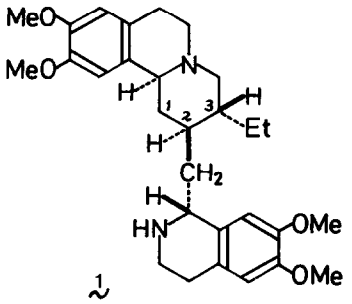
Continuing interest in syntheses of the ipecacuanha and analogous alkaloids prompts us to record the title incorporation accomplished in our laboratory. Although the extensive effort by many groups toward a total synthesis of the principal alkaloid emetine (1) had culminated in at least a dozen successful achievements,[1] the present synthesis was undertaken as the vehicle for synthetic efforts toward general preparations of these alkaloids from the major cinchona alkaloids (4) through the ethyl ester (2) of cincholoipon where the later reaction steps could take advantage of high stereoselectivity due to the two asymmetric centers[2] at C-3 and C-4 and of omitting optical resolution.

Of the various strategies conceivable for transformation of cis-ester 2 into an appropriate, known key intermediate leading to 1 and related alkaloids, the one we selected required four main operations: (i) introduction of the 3,4-dimethoxyphenethyl skeleton into 2 at N-1; (ii) construction of the lactam carbonyl function at C-6; (iii) epimerization at C-4 to form the 3,4-trans configuration which should correspond to the relative and absolute configuration of 1 at the 2- and 3-positions; (iv) ring closure to complete the benzoquinolizidine part (24). To embody the second operation by the mercuric acetate—(ethylenedinitrilo)tetraacetic acid (EDTA) oxidation method,[3,4] the incoming carbon skeleton in the first operation should carry a hydroxyl group or its equivalent at the benzylic position. Thus, treatment of (+)-2, prepared in 31% overall yield from cinchonine (5) by the known method,[2a,5] with 3,4-dimethoxyphenacyl bromide and K_2CO_3 in benzene furnished (+)-6 [89% yield; $[\alpha]_D^{24}$ +2.3° (c 2.5, EtOH)],[6] which was reduced ($NaBH_4$, EtOH, 0–5°, 4 hr) to yield a diastereoisomeric mixture of 7 in 90% yield.

Oxidation of the mixture (7) with $Hg(OAc)_2$—EDTA (1% aqueous AcOH, reflux, 1.5 hr)[3,4] and hydrogenolysis of the resulting lactamalcohols (Pd-C/H_2, EtOH—70% $HClO_4$, 20°, 4.2 atm, 24 hr) gave (−)-8 [44%; $[\alpha]_D^{18}$ −8.4° (c 1, EtOH)], (−)-11 [4%; $[\alpha]_D^{25}$ −3.5° (c 1, EtOH)], and (+)-13 [30%; $[\alpha]_D^{25}$



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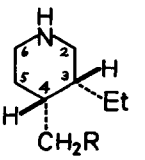
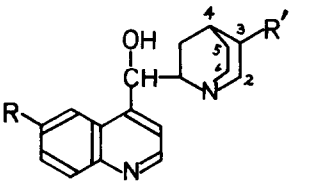
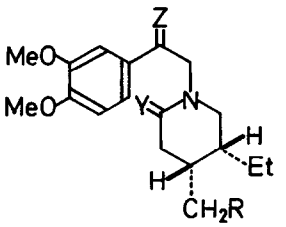


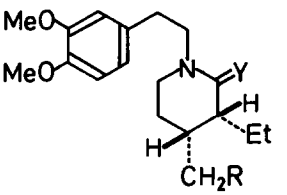
2, R = CO_2Et
3, R = CH_2OH



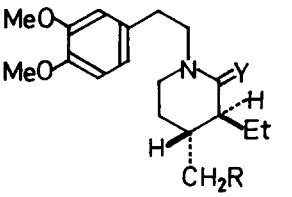
4, R = H or OMe; R′ = vinyl or Et
5, R = H; R′ = vinyl



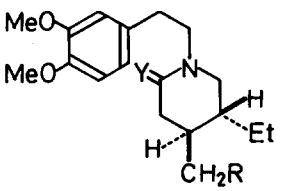
6, R = CO_2Et; Y = H_2; Z = O
7, R = CO_2Et; Y = H_2; Z = H, OH
8, R = CO_2Et; Y = O; Z = H_2
9, R = CO_2H; Y = O; Z = H_2
(±)-10, R = CO_2Me; Y = O; Z = O



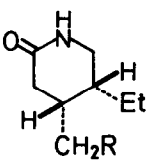
11, R = CO_2Et; Y = O
12, R = CH_2OH; Y = H_2



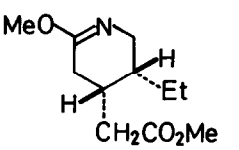
13, R = CO_2Et; Y = O
14, R = CH_2OH; Y = H_2



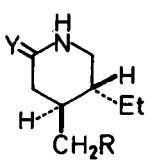
15, R = CO_2H; Y = O
16, R = CO_2Et; Y = O
17, R = CH_2OH; Y = H_2



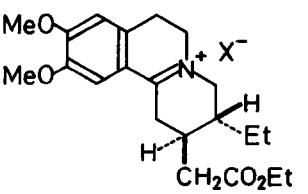
(±)-18, R = CO_2H
(±)-19, R = CO_2Me



(±)-20



(±)-21, R = CO_2Et; Y = O
(±)-22, R = CH_2OH; Y = H_2



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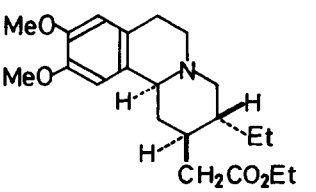

24

+26.1° (c 1, EtOH)]. The structure of (−)-8 was confirmed by hydrolysis (1 N NaOH—EtOH, 20°) leading to (−)-9 [96%; $[\alpha]_D^{20}$ −1.4° (c 1, EtOH)] and spectral comparison of the acid with (±)-9 synthesized by the following reaction sequence. Esterification of (±)-18 (mp 203–204°)[7] with diazomethane and treatment of the resulting (±)-19 with dimethyl sulfate (benzene, reflux, 3 hr) produced (±)-20 [60% overall yield; bp 97° (2 mm)], which reacted with 3,4-dimethoxyphenacyl bromide (60°, 5 hr) to provide (±)-10 (84%; mp 122–123°).[8] Conversion of (±)-10 into (±)-9[9] (90% overall yield; mp 150–152°) was effected by the $NaBH_4$ reduction followed by hydrogenolysis (Pd-C/H_2) and alkaline hydrolysis. On the other hand, the $LiAlH_4$ reduction of (−)-11 in ether afforded (+)-12,[10] identical with a sample [$[\alpha]_D^{30}$ +9.1° (c 2.4, EtOH)] obtained by the reaction of (+)-3[2a] with 3,4-dimethoxyphenethyl bromide (K_2CO_3, benzene, reflux). Likewise, the reduction of (+)-13 gave (−)-14 [$[\alpha]_D^{30}$ −41.6° (c 2, EtOH)] and its 3,4-trans structure was established by spectral comparison with (±)-14[10] derived from (±)-21 (mp 93–94°)[7] through (±)-22. The occurrence of (+)-13 is probably due to epimerization of (−)-11 at C-3, hence in the $Hg(OAc)_2$—EDTA oxidation of 7 the ratio of the 6- to the 2-oxidation may be compared with that[11] observed for simpler 3-alkylpiperidine derivatives.

Isomerization of (−)-cis-acid 9 to (+)-trans-acid 15 [mp 129–130°; $[\alpha]_D^{26}$ +63° (c 1, EtOH); solution ir and nmr spectra identical with those of authentic (±)-15[12]] was carried out in boiling 10% hydrochloric acid or, more efficiently, without the solvent at 180° for 80 min, resulting in an equilibrated mixture (9 : 15 = 33 : 67). Yield of (+)-15 could be raised to 83% when the cis-acid recovered from the mixture was repeatedly subjected to the same reaction. The isomerization appears most probably to proceed through hydrolytic ring opening and recyclization[13] or through intramolecular participation of the exocyclic carboxyl group whereby the side chain at C-4 exchanges places with the endocyclic C-5—C-6 chain. Esterification of (+)-15 (EtOH—HCl, 25°) furnished (+)-16 [92%; $[\alpha]_D^{28}$ +54.3° (c 1, EtOH)], which gave (+)-17 [96%; $[\alpha]_D^{30}$ +40.4° (c 2.1, EtOH)], the enantiomer of (−)-14, on reduction with $LiAlH_4$.

Compound (+)-16 was cyclized ($POCl_3$, toluene, reflux, 1.5 hr) to 23 (X=I) (95%; mp 153–154°). Conversion of the iodide salt into 23 (X = ClO_4) (mp 133–134°) and subsequent catalytic hydrogenation (PtO_2, EtOH, 20°) produced 24·$HClO_4$ (mp 149–150°), from which base (−)-24 [98% overall yield; mp 90–91°; $[\alpha]_D^{30}$ −39.3° (c 1, EtOH)] was obtained.[14] The physical properties of this sample, in good agreement with those reported,[15] and spectral comparison with authentic (±)-24[12] unequivocally established its structure. Since tricycle (−)-24 has been shown to lead to O-methylpsychotrine,[15] emetine (1),[15b] psychotrine,[16] protoemetine,[17] and tubulosine alkaloids,[18] the preparation of this substance formally concluded syntheses of these alkaloids. (−)-cis-Acid 9 should give an enantiomer of

cis-emetine by following the same route as reported for the (±)-series.[9a]

The synthetic scheme described may serve as a valid model for the preparation of other analogous alkaloids[1] which still remain to be synthesized.

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