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A NEW ROUTE TO THE EMETINE ALKALOIDS INTENDING FOR A CHIRAL SYNTHESIS. A SYNTHESIS OF *(dl)*-PROTOEMETINOL AND A FORMAL SYNTHESIS OF *(dl)*-EMETINE FROM *(dl)*-NORCAMPHOR

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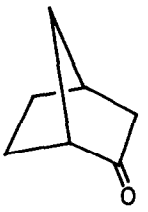
Optically active norcamphor(1) is one of the most accessible compounds through the asymmetric induction of norbornylene[1] and therefore, the utilization of 1 as a chiral synthon would take of great advantage in the synthesis of natural products. On this premise a preliminary experiment was carried out to synthesize racemic protoemetinol(13)[2,3] and its oxidation product(15)[3~7], a synthetic precursor of emetine, using racemic norcamphor(1) as a building block of the non-phenethylamine moiety of the alkaloids.

Racemic norcamphor[8](1) was oxidized with *m*-chloroperbenzoic acid(1.3 equiv) to give the lactone(2)[9](88%); bp 132-135°(16 Torr) which was treated with ethyl bromide in THF(LDA:HMPT) to give the ethyl lactone[11](3)(55%); bp 100-105°(14 Torr, Kugelrohr) as a sole stereoisomer accompanied with the dialkylated product(11%); bp 108-110°(14 Torr, Kugelrohr) and the starting material(20%). Heating of 3 with homoveratrylamine at 180°C provided the amide(4)(76%), mp 131.5-132.5°, which was oxidized to the keto amide(5)(91%), mp 109-110°, with Jones reagent. Enamine formation of 5 with pyrrolidine, followed by treatment with trimethylene dithiotosylate[12] furnished the α-diketone monothioketal(6)(58%), mp 155-156°. Cleavage of the α-diketone monothioketal bond[13] of 6 with potassium hydroxide afforded the carboxylic acid(7)(100%), which on exposure to methyl iodide in boiling aqueous acetonitrile[14] induced the concurrent dethioacetalization and the Pictet-Spengler type cyclization[15] to yield an epimeric mixture of two lactam acids, the α(11*b*-H) epimer(8)(30%), mp 187-188°(lit.[4,5] 190-191°), and the β(11*b*-H) epimer[16](9)(64%),

mp 224-225.5°(lit. 226-227°[4], 223-225°[5]). They were transformed into the corresponding methyl esters, (11), mp 56-57°(lit.[5] 53-54°), and (12), mp 139-141°(lit.[5] 140-142°), by treating with methanolic hydrogen chloride, respectively. Stereochemical outcome of the cyclization may be resulted from intervention of a bicyclic lactone(10) in which favorable cyclization from the α-face allows the predominant formation of the latter(9). Reduction of the former lactam acid(8) with $LiAlH_4$ in boiling THF yielded the *dl*-protoemetinol[17](13), gum, mp 178-181° (perchlorate)(lit.[5] 178-181°(perchlorate)), while the latter 9, to our surprise, formed *dl*-protoemetinol(13)(12.5%), besides the expected alcohol[18](14)(83%), gum, mp 95-98°(perchlorate). The epimer(14) could be converted into *dl*-protoemetinol (13) in 60.5% overall yield *via* a four step sequence; i) acetylation(Ac_2O:pyridine) ii) dehydrogenation($Hg(OAc)_2$)[6] iii) reduction($NaBH_4$)[6] iv) deacetylation(K_2CO_3-MeOH)

Treatment of the lactam ester(11), with phosphorus oxychloride[21] in boiling benzene, followed by reduction with $NaBH_4$ gave the emetine precursor(15)[17](55%), mp 77-79°(lit.[6] 79.5-82°), mp 193-194°(perchlorate)(lit.[6] 192-193°) and similarly the isomeric lactam(12) was converted into the epimer(16)(53%), gum, mp 125-126° (perchlorate). Upon dehydrogenation with mercuric acetate and subsequent reduction with sodium borohydride, the latter(16) was converted into the emetine precursor (15) in 63% overall yield. Since 15 has been converted to emetine[3~7], this constitutes a formal synthesis. When 12 was treated with $NaBH_4$ after boiling with an excess of neat phosphorus oxychloride, the emetine precursor(15) was also formed directly in 31% yield accompanied with the isomeric compound(16)(16%). As observed in the reduction with $LiAlH_4$, a concomitant epimerization of the C-11*b* carbon of 12 undoubtedly occurred and it was presumably resulted from transient formation of a B/C seco-intermediate such as 17(X=O-aluminum complex or Cl).

As none of drastic conditions which would induce racemization were involved in the present synthesis, optically active products could be expected from the chiral starting material. Further synthetic studies to utilize chiral norcamphor (1) as a synthon of the so-called C-9 or C-10 unit in the isoquinoline and the indole alkaloids are under active investigation.



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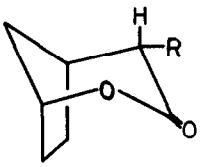
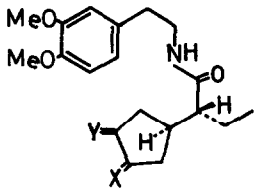


2, R=H

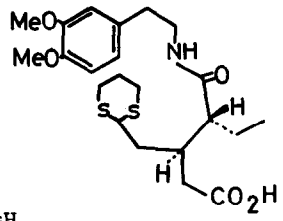
3, R=Et



4, X=α-H, β-OH, Y=H_2

5, X=O, Y=H_2

6, X=O, Y=-$S(CH_2)_3S$-



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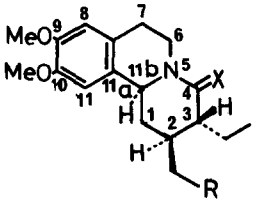
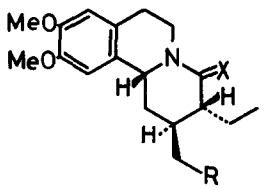


8, R=CO_2H, X=O

11, R=CO_2Me, X=O

13, R=CH_2OH, X=H_2

15, R=CO_2Me, X=H_2

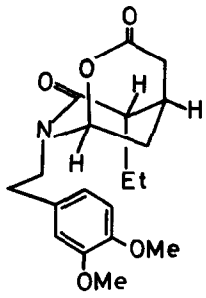


9, R=CO_2H, X=O

12, R=CO_2Me, X=O

14, R=CH_2OH, X=H_2

16, R=CO_2Me, X=H_2



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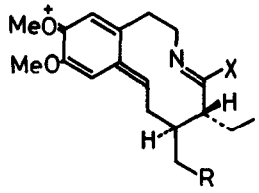

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2. Cf. T. Kametani, The Chemistry of Isoquinoline Alkaloids, Vol.2, The Sendai Institute of Heterocyclic Chemistry, 1974, p. 263.
3. Cf. M. Shamma, The Isoquinoline Alkaloids, Academic Press, 1972, pp. 426-457 and A. Brossi, S. Teitel, and G.V. Parry, The Alkaloids(R.H.F. Manske, ed.,), Vol. XIII, pp. 189-212, Academic Press, 1971.
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11. At this point an actual stereochemistry of the ethyl group could not be determined. Satisfactory mass spectroscopic data and analytical data were obtained for all new compounds.
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16. This compound has been tentatively assinged as the C-2 epimer of 8 by Burgstahler and Bithos.[5]
17. Tlc behavior and spectra(IR, NMR, MS) were indistinguishable from those of the synthetic specimen.[7]
18. Since this compound was not identical with either the C-2 epimer[19] or the C-3 epimer[20] of 13, we could rule out the lactam(9) to be the C-2 or the C-3 epimer of 8.
19. S. Takano, Y. Takahashi, S. Hatakeyama, K. Shishido, and K. Ogasawara, to be published.
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22. This conversion further confirmed the structure of 16 since the emetine precursor(15), as shown by Openshaw and Whittaker,[6] was not formed from the alternative precursors, the C-2 or C-3 epimers of 15.