25-Hydroxycholesterol 3-acetate (IVa) was obtained (85%) by oxymercuration-demercuration of III, as previously described.[8] The presence of 25-hydroxy function was found to be no significant obstacle to the application of Barton's procedure.[6] Thus, 25-hydroxycholesterol (IVb) was dehydrogenated with 3.3 mole equivalents of dichlorodicyanobenzoquinone in dioxane (15 hr at 90° and 4 hr at reflux) giving 25-hydroxycholesta-1,4,6-trien-3-one (V) (50%), mp 178—179° (EtOH), UV, λ_{max} 223, 256 and 298 nm, NMR ($CDCl_3$), δ (ppm), 1.19 (3H, s, 19-CH_3), 6.0—6.1 (3H, m, C-4,6,7-Hs), 6.22 (1H, dd, J=11 and 1.5 Hz, C-2-H) and 7.07 (1H, d, J=11 Hz, C-1-H).

By reaction of V with 35% H_2O_2 in 1N NaOH (15 hr, 20°), 1α,2α-epoxide (VI) was obtained in 70% yield: VI, mp 150—152° (acetone-hexane), UV, λ_{max} 292 nm, NMR ($CDCl_3$), δ (ppm), 1.18 (3H, s, 19-CH_3), 3.42 (1H, dd, J=4 and 1.5 Hz, C-2-H), 3.58 (1H, d, J=4 Hz, C-1-H), 5.63 (1H, d, J=1.5 Hz, C-4-H) and 6.07 (2H, s, C-6, 7-Hs). Treatment of VI with large excesses each of Li metal and NH_4Cl in ammonia-tetrahydrofuran (*ca.* 1: 1) at reflux, produced 1α,25-dihydroxycholesterol (VII) (40%), identified by direct comparison with an authentic sample.[2]

As VII had already been converted to 1α,25-dihydroxycholecalciferol,[9] the present work may pave one of the most practical route to the biological active metabolite of vitamin D_3.

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8) M. Morisaki, J. Rubio-Lightbourn and N. Ikekawa, *Chem. Pharm. Bull.* (Tokyo), **21**, 457 (1973).
9) E.J. Semmler, M.F. Holick, H.K. Schnoes and H.F. DeLuca, *Tetrahedron Letters*, **1972**, 4147.

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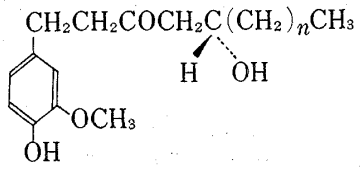
Synthesis of Natural Gingerol

Gingerol (I, n=4), $[\alpha]_D^{24}$ +25.1° (c=1.0, $CHCl_3$),[1] is a major pungent principle in the gingerol homologues[2] (I) isolated from ginger, the root of *Zingiber officinale* ROSCOE. In the preceding paper[3] we reported the first synthesis of *dl*-gingerol *via dl*-benzylgingerol (*dl*-II) obtained by the condensation of benzylzingerone (III) with caproic aldehyde. The present

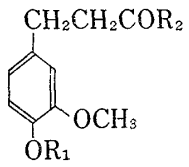
1) M. Miyamoto, M. Shinohara and J. Murata, the 88th Annual Meeting of Pharmaceutical Society of Japan, Abstract Papers, 1968, p. 231; They reported the isolation of crystalline gingerol (I, n=4) mp 29—31°, though gingerol is described in the earlier literature as an oil.
2) *a*) D.W. Connell and M.D. Surtherland, *Aust. J. Chem.*, **22**, 1033 (1969); The absolute configuration of gingerol (I, n=4) has been shown by them; *b*) Y. Shoda, K. Hashimoto, T. Inoue, M. Fujioka and J. Murata, The 92th Annual Meeting of Pharmaceutical Society of Japan, Abstract Papers, 1972, IV, p. 82; *c*) T. Murata, M. Shinohara and M. Miyamoto, *Chem. Pharm. Bull.* (Tokyo), **20**, 2291 (1972).
3) N. Hirao, T. Toyama, A. Takahata and B. Yasui, *Chem. Pharm. Bull.* (Tokyo), **20**, 2287 (1972).

paper describes the total synthesis of optically active natural gingerol using *dl*-II yielded by the modification of the preceding method.

Reaction of the self-condensation product (IV) of III with caproic aldehyde in the presence of N-methylanilinomagnesium bromide[4] gave *dl*-II. This method was favorable for preparing highly purified *dl*-II though the yield (7%) was lower. For the resolution of racemic alcohol, *dl*-II was converted to its diastereoisomeric esters, *dl*-benzylgingerol *l*-menthoxyacetate (*dl-l*-V), by the reaction of highly purified *dl*-II with *l*-menthoxyacetyl chloride.[5] Fractional crystallization of *dl-l*-V from *n*-pentane followed by methanol gave a colorless needles, mp 63—64°, $C_{36}H_{52}O_6$, $[\alpha]_D^{10}$ −39.0° (*c*=1.0, $CHCl_3$), infrared (IR) spectrum ν_{max}^{Nujol} cm^{-1}: 1745, 1703 (C=O), 1590 (aromatic), nuclear magnetic resonance (NMR) spectrum ($CDCl_3$) δ: 0.7—0.98 (12H, multiplet, 4×CH_3), 2.55—2.90 (6H, multiplet, $ArCH_2CH_2COCH_2$-), 3.88 (3H, singlet, -OCH_3), 4.06 (2H, singlet, -$COCH_2O$-), 5.10 (2H, singlet, $ArOCH_2Ar$), 5.30 (1H, broad, >CHOCO-). These data were identical with those of *d*-benzylgingerol *l*-menthoxyacetate (*d-l*-V), mp 62—63°, $[\alpha]_D^{12}$ −36.5° (*c*=1.0, $CHCl_3$), derived from natural gingerol. The attempted separation of the isomeric ester (*l-l*-V) from the oily residue was unsuccessful.



I : n=1, 2, 3, 4, 6, 8 and 10

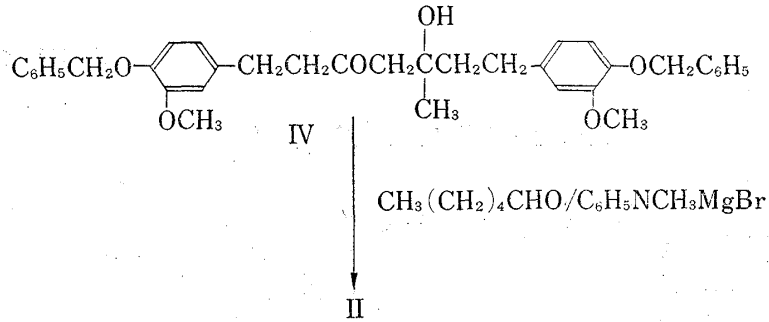


II : R_1=-$CH_2C_6H_5$, R_2=-$CH_2CH(CH_2)_4CH_3$ (OH)

III : R_1=-$CH_2C_6H_5$, R_2=-CH_3

V : R_1=-$CH_2C_6H_5$, R_2=-$CH_2CH(CH_2)_4CH_3$ ($OCOCH_2OC_{10}H_{19}$)

VI : R_1=-$C_6H_3(NO_2)_2$, R_2=-$CH_2CH(CH_2)_4CH_3$ (OH)



IV

$CH_3(CH_2)_4CHO/C_6H_5NCH_3MgBr$

II

The hydrolysis of *d-l*-V to active alcohol (*d*-II) with alkali or acid failed in the various conditions. This was caused by the highly labile properties of gingerol involving β-ketol which is readily subjected to the retrograde aldol reaction and dehydration. The successful result, even though the yield (2%) was very poor, was obtained by ammonolysis. Thus, the

4) A.T. Nielson, C. Gibbons and C. Zimmerman, *J. Am. Chem. Soc.*, **73**, 4696 (1951).
5) J. Read and W.J. Grubb, *J. Soc. Chem. Ind.*, **51**, 329T (1932).

reaction of *d-l*-V with ammonia-saturated methanol at 40° in a sealed tube for 2.2 hr. followed by careful chromatography on silica gel eluted with a mixture of *n*-hexane and acetone gave a colorless needles, mp 67°, $C_{24}H_{32}O_4$, $[\alpha]_D^{15}$ +20.0° (c=0.25, $CHCl_3$). This was confirmed to be identical with *d*-benzylgingerol (*d*-II), mp 67°, $[\alpha]_D^{16}$ +21.6° (c=1.0, $CHCl_3$), derived from natural gingerol by comparison of IR spectra (Nujol) and mixed melting point determination.

Reductive debenzylation of *d*-II gave a phenolic oil,[1] $[\alpha]_D^{27}$ +23.9° (c=1.0, $CHCl_3$), whose IR and NMR spectra were superimposable on those of natural gingerol. For the sake of further confirmation of the synthetic oil, the oil was treated with 2,4-dinitrofluorobenzene to give a slightly yellow needles, mp 84°, $C_{23}H_{28}O_8N_2$, $[\alpha]_D^{14}$ +13.8° (c=0.25, $CHCl_3$). This was identical with DNP-gingerol (VI), mp 84°, $[\alpha]_D^{16}$ +14.0 (c=1.0, $CHCl_3$), derived from natural gingerol in all respects.

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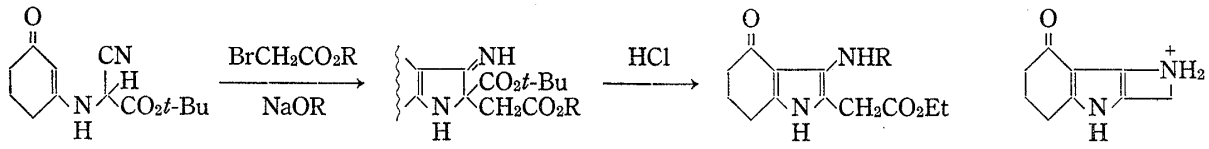
Intramolecular Reactions of Enaminonitriles. I. A Novel Synthesis of New β-Aminopyrroles and Related Heterocycles[1]

Chemistry of β-aminopyrroles has little been studied apparently owing to the scanty of versatile synthetic procedure for the compounds. Thus only a few β-aminopyrroles have been prepared by nitration or nitrosation of appropriate α-substituted pyrroles followed by reduction, a classical method.[2] We now wish to describe simple routes for several new β-aminopyrroles and related compounds including substituted 3-amino-4-oxo-4,5,6,7-tetrahydroindoles (**5**, **15**, **18**), pyrido[3,2-*b*]indole (**9**) and pyrrolo[3,2-*b*] pyridine derivatives (**25**, **26**),[3] which have a distinctive feature comprising an intramolecular addition of an enamine to a nitrile group.[4]



1 — 2: R=Me, 3: R=Et — 5: R=H, 6: R=Ac — 4

Chart 1

1) Satisfactory analyses were obtained for all new compounds. Melting points were measured on Kofler block and uncorrected.
2) K. Schofield, "Hetero-Aromatic Nitrogen Compounds-Pyrroles and Pyridines, "Butterworths & Co., London, 1967, p. 27; F. Troxler, "Chemistry of Heterocyclic Compounds," (A. Weissberger and E.C. Taylor ed.), Vol. 25, Part II, W. Houlian ed., John Wiley & Sons, Inc., New York, 1972, p. 210.
3) R.E. Willete, "Advances in Heterocyclic Chemistry," Vol. 9, A.R. Katritzky and A.J. Boulton ed., Academic Press, New York, 1968, p. 27.
4) A.I. Meyers and J.C. Sircar, "The Chemistry of the Cyano Group," Z. Rappoport ed., Interscience Publishers, London, 1970, p. 341.