As shown in Fig. 2, the activity of cyclocytidine dissolved in RPMI 1640 medium increased with time and the incorporation of thymidine into DNA for 30 min therefore decreased, while the activity of aracytidine was not affected under the same conditions. Metabolites of cyclocytidine after incubation for 4 hr without leukemia cells were further examined by thin-layer chromatography and aracytidine was detected as the sole metabolite of the compound. Therefore, the decrease in thymidine incorporation was considered to be due to the "transformed" aracytidine. Transforming ratio of cyclocytidine to aracytidine after standing for 4 hr was about 50% when calculated by the dose-response line for aracytidine.

It is concluded that cyclocytidine shows a marked antitumor activity *in vitro* as well as *in vivo* through the specific depression of DNA biosynthesis similar to aracytidine. This inhibition seems to be due to aracytidine "transformed" from cyclocytidine. In other words, cyclocytidine is considered to be a "transport form" of aracytidine with low toxicity.

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Synthesis of *dl*-Gingerol

Sufficient evidence[1,2a)] has been reported on the structures of gingerol homologues[2)] (I), pungent principles isolated from the root of *Zingiber officinale* Roscoe. No synthetic work has appeared in the literature in spite of their widespread uses in medicine and food industries. We describe here the first synthesis of racemate of gingerol (I, $n=4$), a major component[3)] in the homologues.

Attempted one-step synthesis of it, the aldol condensation of zingerone (II) with caproic aldehyde in the presence of alkali such as KOH or K_2CO_3 under various conditions, however, was almost unsuccessful giving a number of undesirable products, recovered II, selfcondensation product of II, shogaol[4)] (III) and others, along with a slight amount of *dl*-gingerol. No satisfactory method for the separation of gingerol from the mixture with chromatography could be developed due to the unavoidable decompositions of it to II on alumina and to III

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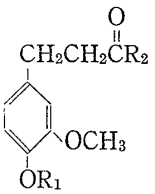
even on silica gel in consequence of the longer residence times. This unfavorable result must be caused by the highly labile properties of I, having a β-ketol, to be easily subjected to retrograde aldol reaction and dehydration.

On the other hand, the successful result was obtained by use of methylanilinomagnesium bromide as a condensing agent in aprotic solvent, with which ketol formation is favored.[5] The condensation of benzylzingerone (IV) with caproic aldehyde in a mixture of ether and benzene in the presence of N-methylanilinomagnesium bromide at $-10°$ afforded mainly two products as an oil. The careful chromatography with a short column of silica gel followed by the repeated recrystallizations gave two crystals, mp 67° and 97°, respectively. The former (20% yield) had following data: $C_{24}H_{32}O_4$, IR cm^{-1}: ν_{OH}3550, ν_{CO} 1700, ν_{arom} 1600, 1590 ($CHCl_3$), NMR ($CDCl_3$) δ: 0.95 (3H, diffused triplet, -CH_2-CH_3), 2.40—2.90 (6H, multiplet, $ArCH_2CH_2COCH_2$-), 3.87 (3H, singlet, -OCH_3), 5.10 (2H, singlet, $ArOCH_2Ar$), to be proved as *dl*-benzylgingerol (V), but not branched structure (VI), another possible condensation product, by the absence of a nuclear magnetic resonance (NMR) signal due to methyl ketone. The latter was also determined to VII, self-condensation product of IV, by the following data: $C_{36}H_{40}O_6$, IR cm^{-1}: ν_{OH} 3480, ν_{CO} 1698, ν_{arom} 1600, 1590 ($CHCl_3$), NMR ($CDCl_3$) δ: 1.25 (3H, singlet, $CH_3\underset{OH}{C}\!<$), 3.85 (6H, singlet, two -OCH_3), 5.09 (4H, singlet, two -OCH_2Ar).

Reductive debenzylation of V over Pd-C in methanol gave the corresponding phenolic oil, whose IR ($CHCl_3$) and NMR spectra were identical with them of natural gingerol isolated from fresh ginger by the method of Miyamoto.[3b)]



I: $R_1=H,\ R_2=-CH_2\underset{OH}{CH}(CH_2)_nCH_3$

$n=1, 2, 3, 4, 6, 8, 10$

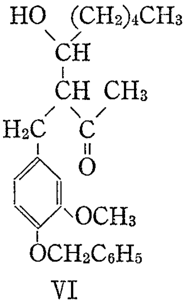
II: $R_1=H,\ R_2=CH_3$

III: $R_1=H,\ R_2=CH{=}CH(CH_2)_4CH_3$

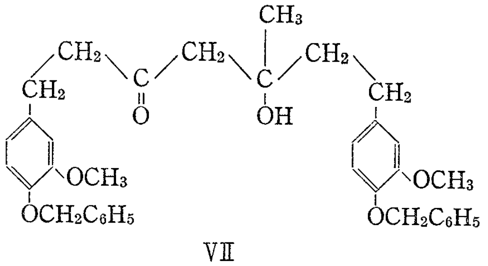
IV: $R_1=CH_2C_6H_5,\ R_2=CH_3$

V: $R_1=CH_2C_6H_5,\ R_2=CH_2\underset{OH}{CH}(CH_2)_4CH_3$

VIII: $R_1=C_6H_3(NO_2)_2,\ R_2=CH_2\underset{OH}{CH}(CH_2)_4CH_3$



VI



VII

The taste of *dl*-gingerol in comparison with that of ginger seems quite similar though it possesses no characteristic fragrance of ginger.

The structure of synthesized gingerol was further confirmed as follows. Treatment of both gingerols (*dl*- and natural) with 2,4-dinitrofluorobenzene at room temperature gave *dl*-DNP-gingerol (VIII), $C_{23}H_{28}O_8N_2$, mp 102° and DNP-gingerol, mp 84°, $[\alpha]_D^{16}$ $+14.0$ (c= 1.0 $CHCl_3$), respectively. IR ($CHCl_3$) and NMR spectra of both derivatives were identical.

The above synthesis may be applicable to a method for the preparation of gingerol homologues and yashabushiketol series[6] extracted from the young shoots of *Alnus firma.*

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The Structure and Internal Acyl Migration of Gagaminin

Recently, Nomura, *et al.* isolated the diester of sarcostin with a cinnamic acid and a nicotinic acid from *Metaplexis japonica* MAKINO,[1] *Marsdenia condurango* REICH.,[2] and *Marsdenia tomentosa* DECNE.[3] The determination of the location of diester linkages in polyoxy pregnane is usually rather difficult, so the exact structure has not been decided till present. We newly isolated the same diester from *Cynanchum caudatum* MAX. and determination of the structure of this diester, which was named gagaminin,[4] is described here.

Gagaminin (I) has the following physical constants, $C_{36}H_{43}O_8N$, mp 166—170°, $[\alpha]_D^{20}$ $+143.8°$ ($c=0.7$, $CHCl_3$). Its nuclear magnetic resonance (NMR) spectrum[5] shows the signal for C-12α H at δ 4.82 (double-doublet, $J=5$ and 9 Hz), for C-20 H at δ 4.88 (quartet, $J=$ 6 Hz), and for C-21-methyl at δ 1.31 (doublet, $J=6$ Hz), suggesting the location of each acid at either the C-20 or C-12β of sarcostin (II).[6]

Acetylation of gagaminin with Ac_2O–pyridine gave an amorphous, $C_{38}H_{45}O_9N$, monoacetate (V), IR $\nu_{max}^{CHCl_3}$ 1720, 1710, 1640, 1595, 1580 cm^{-1}, mass spectrum, *m/e* 659 (M^+), 599 (M^+-60), 511 (M^+-cinnamic acid). Oxidation of gagaminin with lead tetraacetate in acetic acid for 4 hr gave an amorphous, $C_{36}H_{39}O_8N$, 8,14-*seco*-gagaminin (VIII), IR $\nu_{max}^{CHCl_3}$ 1740 (5-membered ring ketone), 1720, 1715 cm^{-1}; mass spectrum, *m/e* 615 (M^+), 467 (M^+-cinnamic acid), NMR δ 0.73 (C-18-methyl), 1.40 (C-19-methyl), 1.40 as a doublet (C-21-methyl), 3.5 as a multiplet (C-3α H).

Gagaminin on mild alkaline hydrolysis (K_2CO_3 in MeOH) formed monoester-I (III), monoester-II (IV), and II. Reduction of gagaminin with $LiAlH_4$ (one equivalent) in tetrahydrofuran gave only the monoester-II (IV), mp 145—150°, $[\alpha]_D^{20}$ $+6.83°$ ($c=1$, $CHCl_3$), $C_{30}H_{40}O_7$, whose physical constants were in good agreement with those of penupogenin.[7] The identity was established by direct comparison with the authentic sample. The monoester-I (III), mp 154—158°, $C_{30}H_{40}O_7$, exhibits the signals for C-20 H at δ 5.31 (quartet, $J=6$ Hz) and for C-21-methyl at δ 1.31 (doublet, $J=6$ Hz), and for cinnamoyl at δ 6.42 (doublet, $J=16$ Hz), 7.66 (doublet, $J=16$ Hz), and 7.2—7.6 (multiplet) in its NMR spectrum,

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