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STUDIES ON THE CONSTITUENTS OF UMBELLIFERAE PLANTS—IX

STRUCTURE OF CNIDILIDE AND NEOCNIDILIDE

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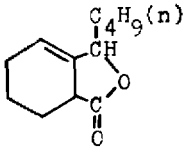
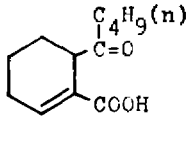
Abstract—The structures of cnidilide (VIIa) and neocnidilide (XVIIIa), new phthalides from *Cnidium officinale*, have been proposed and the structures of related substances elucidated.

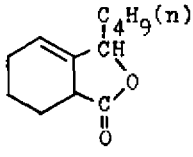
THE root of *Cnidium officinale* Makino (Japanese name "Senkyu") long used as an important crude drug, has been investigated by many workers. Sakai[1] studied it pharmacologically and chemically, and reported the isolation of an active component, cnidium lactone (I), $C_{12}H_{18}O_2$. Murayama *et al.*[2,3] isolated I and sedanonic acid (II) from Senkyu, and after a comparison of I and sedanolide (III) isolated from *Apium graveolens* L. by Ciamician,[4] concluded that the difference between these compounds is the position of double bond. Noguchi[5] after a similar chemical comparison of I and III, concluded that the two compounds are stereoisomers (Chart 1).



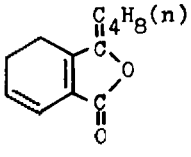
I
Cnidium lactone
(T. Noguchi)



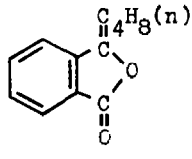
II
Sedanonic acid
(G. Ciamician et *al.*)



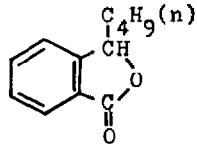
III
Sedanolide
(G. Ciamician et *al.*)



IV
Ligustilide



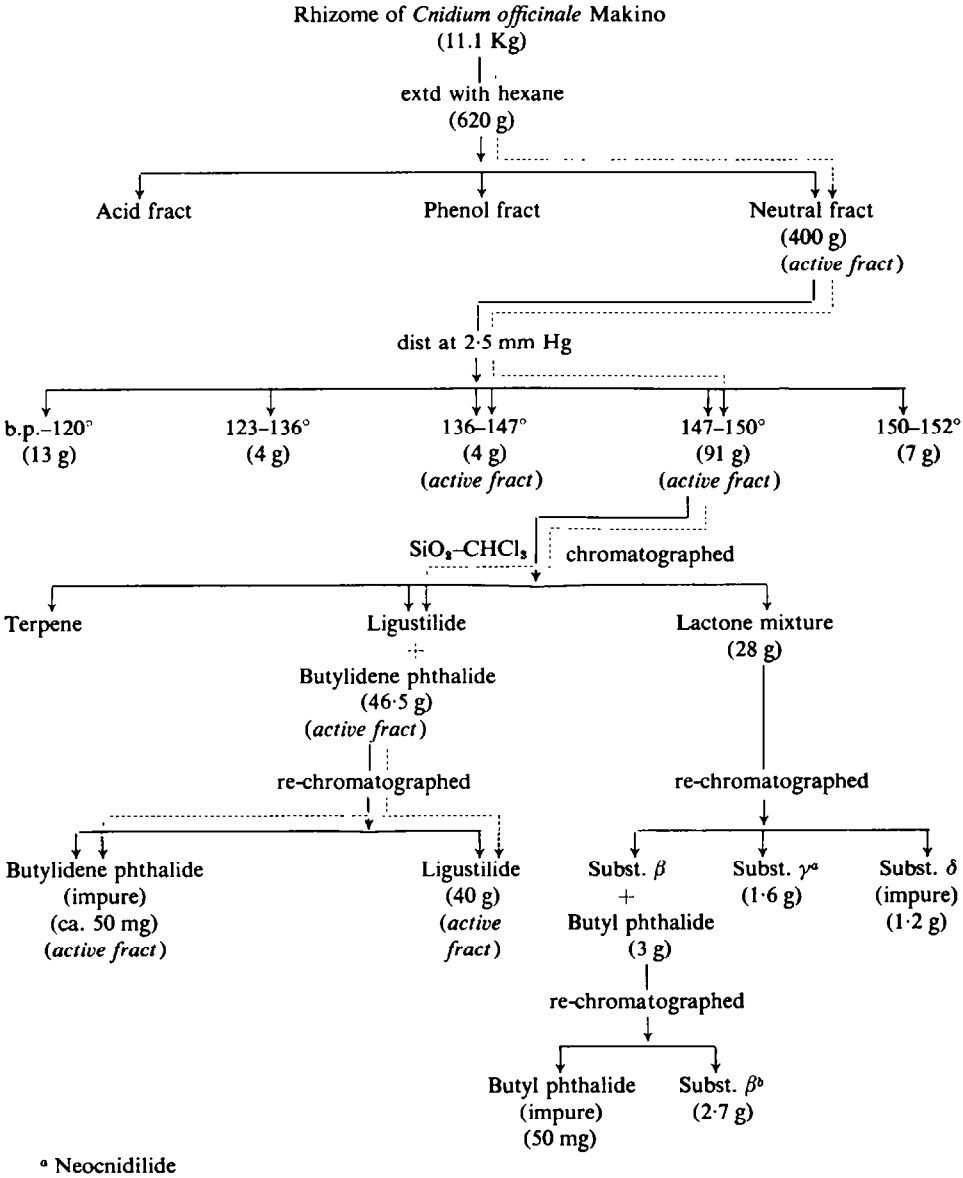
V
Butylidene phthalide



VI
Butyl phthalide

Chart 1

[1] W. Sakai, Tokyo, *J. Med. Sci.* **30**, 935 (1916).
[2] Y. Murayama, *J. Pharm. Soc. Japan* **41**, 951 (1921).
[3] Y. Murayama and T. Itagaki, *J. Pharm. Soc., Japan* **43**, 143 (1923).
[4] G. Ciamician and P. Silber, *Ber. Dtsch. Chem. Ges.* **30**, 492, 501, 1419, 1424 and 1427 (1897).
[5] T. Noguchi, *J. Pharm. Soc., Japan* **54**, 913 (1934).



[a] Neocnidilide
[b] Cnidilide
· · · · passway of the anticholinergic activity.

Chart 2

The root of Senkyu contains ligustilide[6–8] and three other 3-butyl phthalide compounds. Ligustilide (IV) shows anticholinergic activity, but the other 3-butyl phthalides possess only weak or no activity (Chart 2). These compounds are tentatively named β, γ and δ. Since, a careful physical and chemical comparison of the

[6] H. Mitsuhashi, U. Nagai, T. Muramatsu and H. Tashiro, *Chem. Pharm. Bull., Japan* **8**, 243 (1960).
[7] H. Mitsuhashi, U. Nagai and T. Muramatsu, *Chem. Pharm. Bull., Japan* **9**, 115 (1961).
[8] H. Mitsuhashi and U. Nagai, *Tetrahedron* **19**, 1277 (1963).

properties of I with β and γ, has shown that β and γ are different, they were named cnidilide (β, VIIa) and neocnidilide (γ, XVIIIa) (Table 1). Chromatographic separation with silicic acid is very efficient and yielded pure VIIa. The IR spectrum of VIIa indicates the presence of an isolated double bond, but its UV spectrum shows weak absorption maxima at 227, 274 and 280 mμ, which corresponds with those of butyl phthalide (VI). This result indicates contamination with VI. The NMR and UV spectra indicate about 10% contamination of VI in VIIa. Purification of the VIIa fraction was in vain apparently due to a tendency of VIIa to change into VI. This phenomenon was observed during the synthesis of Δ^5-tetrahydrobutyl phthalide, which readily changes to VI. Measurement of physical data and examination of chemical reactions of VIIa were made with a material containing about 10% of VI, but the chemical reactions were carefully selected so as not to include the contaminating VI. Compound VIIa has a molecular formula of $C_{12}H_{18}O_2$ and its IR indicates the presence of a γ-lactone and an isolated double bond. Catalytic hydrogenation of VIIa with palladized charcoal affords a dihydro compound (VIII) m.p. 49–49·8°, $[\alpha]_D^{25}$ −15·1°, which is identical with β-dihydrosedanolide obtained by Noguchi,[5] by PtO hydrogenation of cnidium lactone (I), and also with hexahydrobutyl phthalide prepared by Barton[9] from butyl phthalide.

Alkaline hydrolysis of VIII followed by careful acidification at a low temperature yields an hydroxy acid (IX), m.p. 87–89°, $[\alpha]_D^{25}$ −27·29°, which is also identical with β-dihydrosedanolic acid.[5]

Alkaline treatment of VIIa and acidification with heating yields a new lactone which has a strong absorption at 216 mμ (log ε 3·87) in the UV region and its IR spectrum shows absorptions at 1770 and 1690 cm^{-1}; $[\alpha]_D^{29}$ −80·0°. These properties suggest that the double bond moves from the $\beta\gamma$ to the $\alpha\beta$ position of carbonyl group during hydrolysis and lactone ring closure. This compound was named isocnidilide (XI). Alkaline hydrolysis of XI and acidification at −15° yields an hydroxy acid, m.p. 29–32°. Oxidation of this acid with chromium trioxide in pyridine affords a keto acid, the phthalazone of which melts at 134–135°, alone and in admixture with sedanonic acid phthalazone (XII). From these results, four structures (VIIa to VIId) are the most probable for cnidilide (Chart 3).

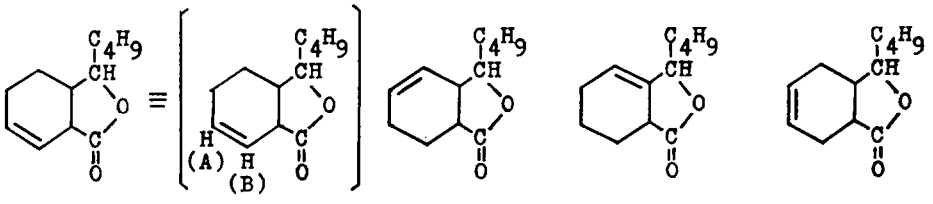


Chart 3

Ozonolysis of VIIa was attempted to confirm the position of the double bond.

[9] D. H. R. Barton and J. X. deVries, *J. Chem. Soc.* **19**, 1916 (1963).

Hydrogen peroxide oxidation of the ozonide under slightly alkaline condition affords very small amount of butyl phthalide (VI), an acid fraction and a neutral compound of molecular formula $C_{11}H_{18}O_3$ as the main product. From the acid fraction, equal amounts of succinic and glutaric acids were confirmed by paper chromatography and by preparation of the anilides, but adipic acid was not confirmed. These results suggest structures VIIa and VIIb. A possible degradation mechanism of the ozonide is shown in Chart 4. Similar oxidative degradation was observed in irone[10] and ionone.[11] The position of the double bond in cnidilide (VIIa) was examined by osmylation which yields a glycol (XIV), as the main product, and XV. Both XIV and XV give a diacetate on acetylation with acetic anhydride in pyridine at 25°. Periodic acid oxidation of XIV produces formaldehyde together with a neutral compound (XIII) which exhibits an IR spectrum very similar to that of the oxidation product of the ozonide of VIIa. The IR spectrum of XIII shows absorption peaks at 3500 and 1770 cm^{-1}, but after chromium trioxide–pyridine oxidation, the absorption changes to 1770 and 1745 cm^{-1}, characteristic of a five membered ring ketone. Only the structure XIII, probably formed by aldol condensation, would account for these properties.

The difference between isocnidilide (XI) and cnidilide (VIIa) is reasonably explained by the migration of the double bond from the $\beta\gamma$ to the $\alpha\beta$ of the lactone ring during lactone ring cleavage and closure. Similar experiments for Δ^5-tetrahydrobutyl phthalide resulted in the recovery of the starting material and a small amount of VI. It is apparent at this stage that the position of the double bond is restricted as VIIa. The IR and NMR spectra of VIIa and allied compounds are shown in Fig. 1.

The NMR spectrum of VIIa exhibits a very simple peak at 4·5τ. Chemical shift of proton of A and B in VIIa must be small compared with the coupling constant (J_{AB}). The case of lactone ring cleavage and closure indicates that the possible fusion of cyclohexane and lactone ring is reasonably restricted to *cis*.* In such a case, proton B is free from the long-range shielding effect of the carbonyl group, and the chemical shift of B is rather small.

Alkaline treatment, proved that VIIIa easily changes to XI, and the optical rotation of VIIa (−122·52°), XI (−80·0°), and cnidium lactone (I) (−71·88°) shows XI and I to have similar values. Noguchi isolated I by distillation and alkaline treatment, but our experiments show that VIIa is very difficult to obtain in a pure form and even repeated chromatography on silicic acid or other adsorbents always shows the presence of VI. It is assumed that I is a mixture of VIIa, XI, XVIIIa, and VI, and the complicated results of hydrogenation and oxidation of I reported by Noguchi are explained by this assumption.

Neocnidilide (XVIIIa) has a molecular formula of $C_{12}H_{18}O_2$, an isomer of VIIa, the UV absorption at 216 mμ, and IR absorption at 1770 and 1690 cm^{-1}. These absorptions require the presence of a $\Delta^{\alpha,\beta}$ carbonyl group (Table 1).

Compound XVIIIa forms a phthalazone (XII), after hydrolysation and oxidation identical with sedanonic acid phthalazone. Thus, the possible structure of neocnidilide

* Stereochemical relations of these compounds would be a subject of following paper.

[10] L. Ruzika *et al.*, *Helv. Chim. Acta* **31**, 160, 257 (1948).
[11] F. Tiemann, *Ber. Dtsch. Chem. Ges.* **31**, 870 (1898).

is limited to XVIIIa or XVIIIb (Chart 5). The latter (XVIIIb) corresponds to tetrahydroligustilide obtained by partial hydrogenation of IV.[6,8] Tetrahydroligustilide (XVIIb) has absorptions at 1740 and 1675 cm^{-1} in the IR region and yields a keto acid on alkaline hydrolysis. In view of these facts, the structure (XVIIIb) for neocnidilide is inconsistent. Both XVIIIa and XI are similar except for optical rotation and the finger print region of IR absorption. The difficulty of lactone formation by two hydroxy acids obtained from iso- and neo-cnidilide is apparent. Hydroxy acid (X) from XI is a crystalline compound, m.p. 29–32°, and only after heating, changes to XI. On the other hand, hydroxy acid (XIX) from neocnidilide can be crystallized only at a low temperature and readily undergoes lactonization even at room temperature. This behaviour strongly suggests that iso- and neo-cnidilide are stereoisomers and that neocnidilide should be represented by formula XVIIIa.

Barton examined celery oil,[9] and reported the isolation of VI instead of III using Ciamicians' method. For this result, Barton assumed that an unstable III might change to VI. He proposed the structure of $\alpha\beta$-unsaturated lactone (XVIIIa) for sedanolide (III). A comparison has been made of neocnidilide (VXIIIa) and data of

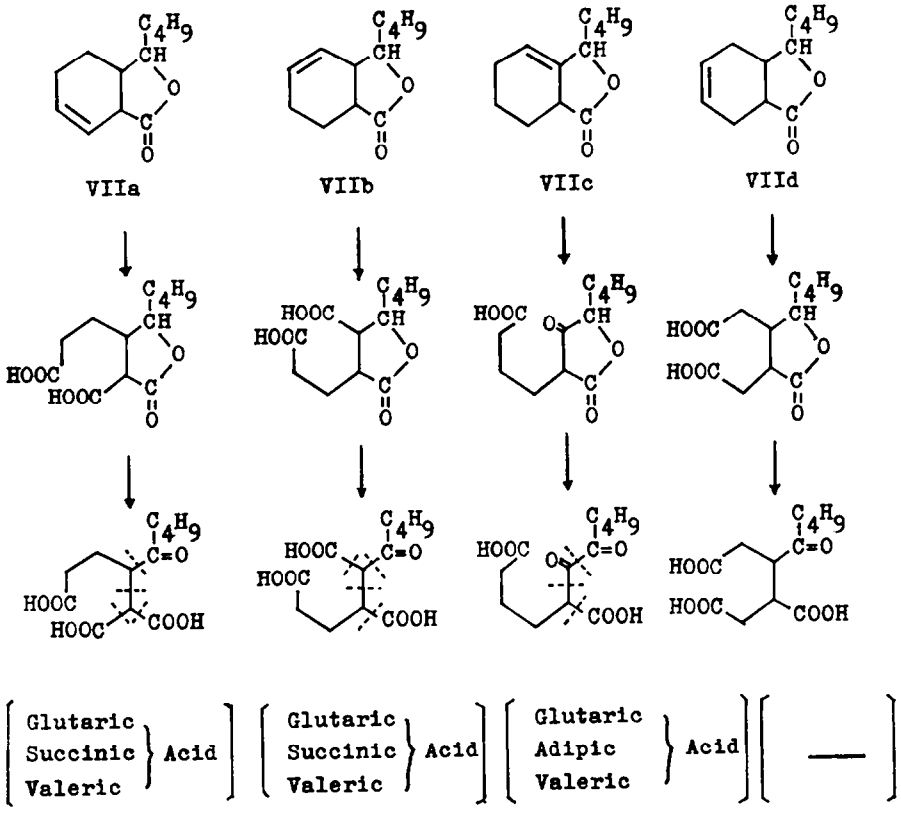
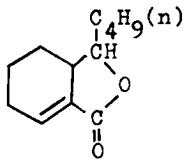
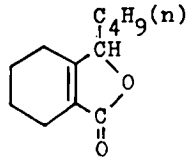


Chart 4



XVIIIa



XVIIIb

Chart 5

sedanolide reported by Ciamician and Noguchi (Table 2). Neocnidilide was also isolated from celery oil. These results are very similar to the relation between cnidium lactone and cnidilide, and it was concluded that sedanolide is at least a mixture of neocnidilide and butyl phthalide, and the name neocnidilide is proposed for the compound corresponding to XVIIIa. These results are summarized in Chart 6.

EXPERIMENTAL

Silicic acid of Mallinkrodt 100 mesh for chromatogaphy was used in all cases. All m.ps reported were taken on a micro-hot-stage and are not corrected.

TABLE 1. COMPARISON OF CNIDILIDE (VIIa) AND NEOCNIDILIDE (XVIIIa)

	Cnidilide (VIIa)	Neocnidilide (XVIIIa)
Anal.		
Calc. for $C_{12}H_{18}O_2$	C, 74·19; H, 9·34	C, 74·19; H, 9·34
Found	C, 74·47; H, 9·15	C, 73·86; H, 9·12
b.p.	145–146°/2·5	147–148°/4 (m.p. 24–27°)
N_D	1·4929 (15°)	1·5010 (21°)
$[\alpha]_D$ (in $CHCl_3$)	−122·52° (c = 3·5, 25°)	−62·55° (c = 1·1, 11°)
UV λ_{max} (log. E)	227, 274, 282 mμ (3·00, 2·30, 2·27)	216 mμ (3·85)
IR $\nu_{C=O}$	1775 cm^{-1}	1770 cm^{-1}
$\nu_{C=O}$	1665 cm^{-1} (v.w.)	1690 cm^{-1} (s)

TABLE 2. COMPARISON OF SEDANOLIDE (III) AND NEOCNIDILIDE (XVIIIa)

	Sedanolide (III)		Neocnidilide (XVIIIa)
	G. Ciamician, *et al.*	T. Noguchi	H. Mitsuhashi, T. Muramatsu
b.p.	185°/7	147–149°/3	147–148°/4
N_D	1·49123	1·50952	1·5010
$[\alpha]_D$	−23·66°	−50·20°	−62·55°
Product of hydrolysis* (m.p.)	88–89°	Oil	81–82°

* Hydroxy acid

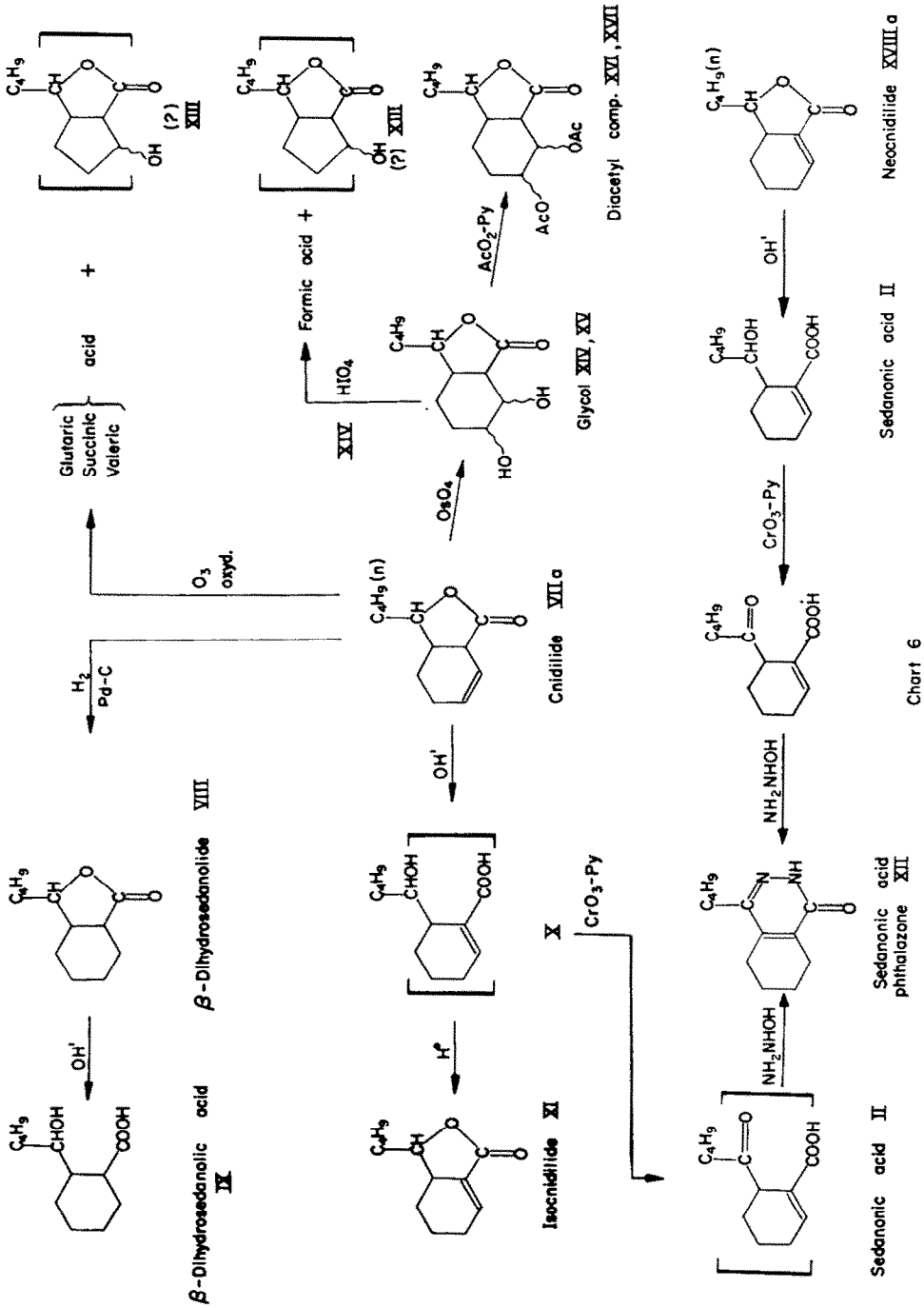


Chart 6
Summary of the reactions of the cnidilide (VIIIa)

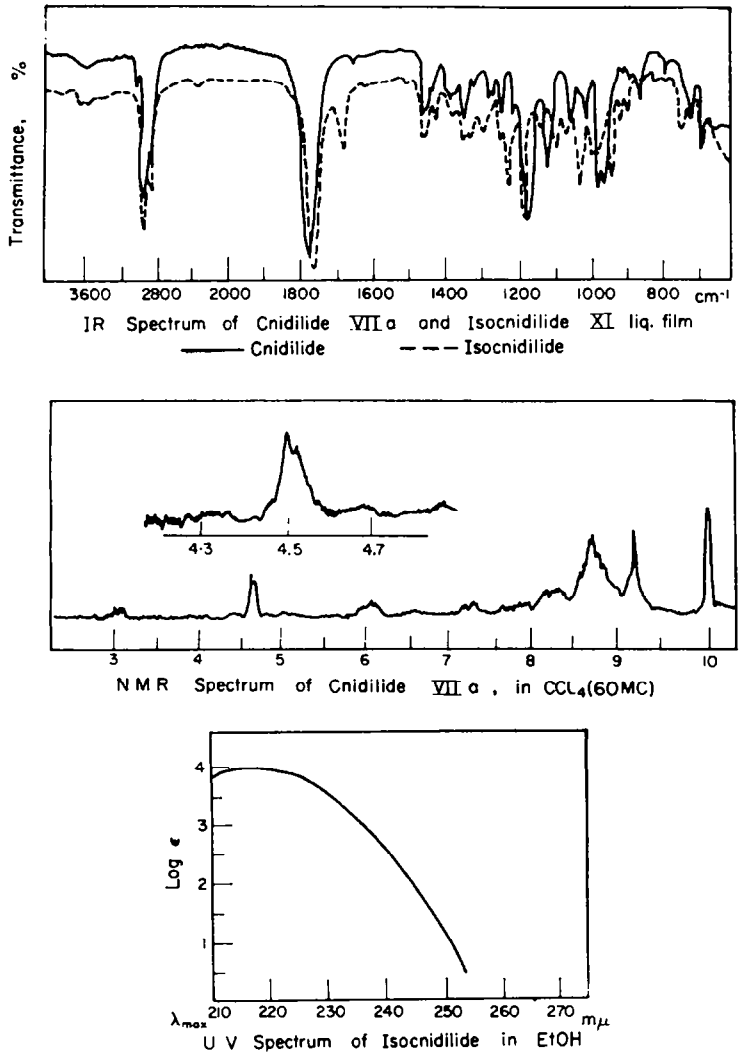


FIG. 1 (Part I)

Isolation of cnidilide (VIIa)

Dried and pulverized crude drug of *Cnidium officinale* (11·1 kg) was percolated with about 30 l. hexane at room temp. and 620 g of the extract so obtained dissolved in ether (2 l.). The solution was treated with 10% $NaHCO_3$ aq, 10% Na_2CO_3 aq and 10% NaOH washed with water, and dried over Na_2SO_4. On evaporation of ether, 400 g of neutral oil was obtained which was distilled (red. press.) and the fractions, b.p. 135–155° (2·5 mm) were collected, yield, 91 g. This was chromatographed over a column of 1·25 kg silicic acid and eluted with chloroform. At first, some terpene-like substances were eluted. After an interval, crude ligustilide (IV, 46·5 g) and lactone mixture (28 g) were obtained partially overlapping in this order. From the lactone mixture, VIIa (3·0 g), XVIIIa (1·6 g) and substance δ (1·2 g) were separated by rechromatography.

Reduction of cnidilide (VIIa)

Compound VIIa (1 g) in ethanol (20 ml) was shaken in H_2 at 22° and 752·9 mm with 5% Pd-C (250 mg), for about 5 min and 112 ml H_2 was absorbed (calc. 113 ml). The catalyst was filtered off

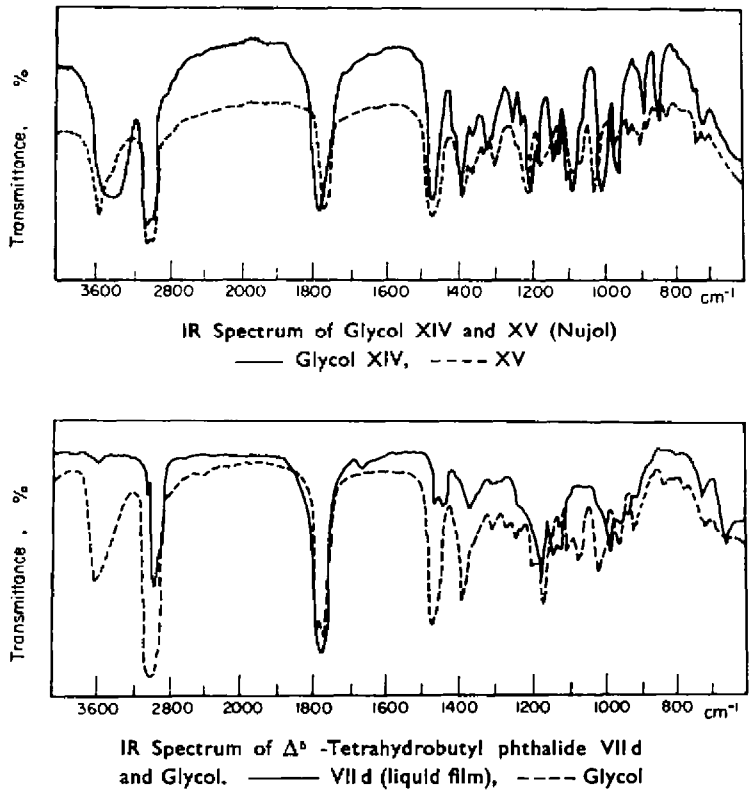


FIG. 1 (Part II)

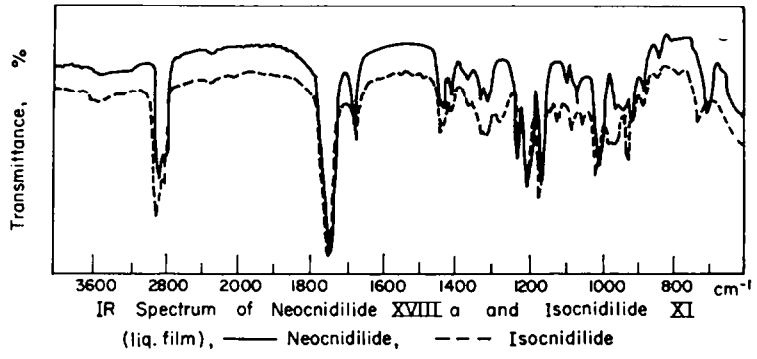
and the solvent removed. Recrystallization from ethanol gave β-dihydrosedanolide (VIII), white crystals, m.p. 49–49·8°, yield 1 g. ν_{max}^{nujol} 1760 cm^{-1}. $[\alpha]_D^{25}$ −15·1° (*c* 6·2, $CHCl_3$). (Found: C, 73·36; H, 10·16. $C_{12}H_{20}O_2$ requires: C, 73·41; H, 10·28%).

Hydrolysis of β-dihydrosedanolide (VIII)

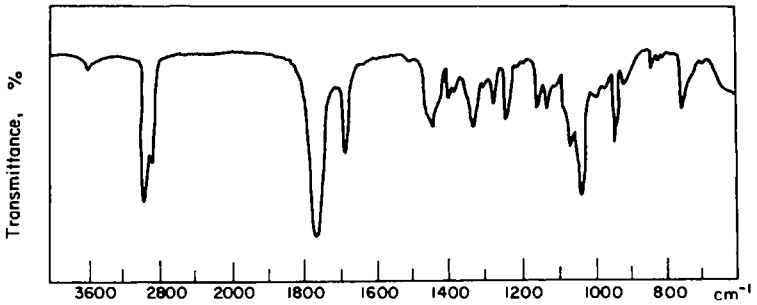
Compound VIII (150 mg) was refluxed 6 hr with 5% ethanolic KOH (6 ml). The resulting alkaline solution was acidified with 10% HCl at −15°. During acidification, crystals separated out. The crystals were dissolved in ether, and pet. ether at −15°, yielding 100 mg crude crystals which recrystallized from the same solvent, yielding 20 mg IX, m.p. 87–89°. $[\alpha]_D^{25}$ −27·59° (*c* 0·29, $CHCl_3$).

Hydrolysis of enidilide (VIIa)

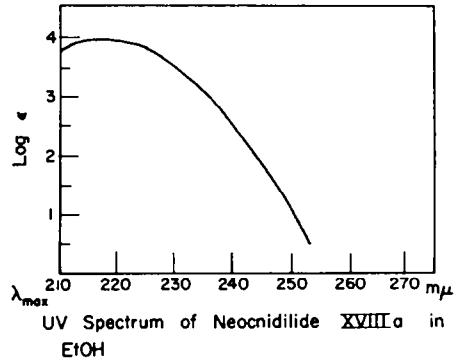
Compound VIIa (330 mg) was refluxed for 5 hr with 5% methanolic KOH (25 ml). The methanol was replaced by water by adding water dropwise at the same rate as methanol was distilled off under red. press. The aqueous alkaline solution was extracted with ether. The neutral fraction obtained from the ether solution was identified as butyl phthalide (VI), yield 87·1 mg. The resulting alkaline solution was acidified with 10% HCl at 0°, and extracted with ether. This fraction (211·4 mg) was hydrolysed under the same conditions and separated into a neutral fraction (87·5 mg) and an acid fraction (120·9 mg). The neutral fraction was isocnidilide (XI), b.p$_3$ 145°. λ_{max} 216 mμ (log ε 3·87). ν_{max}^{liquid} 1770, 1690 cm^{-1}. $[\alpha]_D^{29}$ −80·0° (*c* 1·52, $CHCl_3$). The acid fraction (X) m.p. 29–32°. λ_{max} 215 mμ (log ε 3·86). ν_{max}^{nujol} 3600–3200, 1695, 1640 cm^{-1}. X (20 mg) was refluxed with xylene (5 ml) for 5 hr in gaseous N_2. The solvent was removed and from the resulting neutral oil, 10 mg of isocnidilide was obtained.



IR Spectrum of Neocnidilide XVIII a and Isocnidilide XI
(liq. film), —— Neocnidilide, – – – Isocnidilide



IR Spectrum of Tetrahydroligustilide XVIII b (liq. film)



UV Spectrum of Neocnidilide XVIII a in EtOH

FIG. 2

Sedanonic acid phthalazone (XII)

Compound X (96·4 mg) was oxidized by CrO_3–pyridine complex in pyridine at room temp. The resulting oily substance (69·8 mg) and an equal amount of ethanol and hydrazine hydrate were sealed in a test tube and heated in a boiling water bath for 3 hr. When cool, sedanonic acid phthalazone (XII; 49·0 mg) crystallized out and was recrystallized from ethanol, m.p. 135–136°.

Ozonolysis of cnidilide (VIIa)

(i) Ozonized oxygen (3·5%) was passed through a solution of cnidilide (VIIa) in CCl_4 for 1 hr at −10°. The solvent was evaporated at room temp, 1N NaOH (30 ml) and 5% H_2O_2 (30 ml) were added, the solution was kept 1 hour at room temp and 5% H_2O_2 (10 ml) added, and then the solution was carefully heated for 3 hr at 60–80°. The solution was acidified and steam distilled. The volatile fraction was collected (200 mg) and the residue extracted with ether (1·1 g).

(ii) The volatile fraction (200 mg) was dissolved in ether (20 ml) and extracted with 10% $NaHCO_3$. In the ether-soluble part, VI was detected. The $NaHCO_3$ solution was acidified and extracted with ether. The acid fraction obtained from the ether solution was identified as valeric acid by paper chromatography and comparison of its anilide with an authentic sample.

(iii) The non-volatile portion (1·1 g) was chromatographed on silicic acid (300 g) and eluted with chloroform–buthanol (95:5). At first, an oily substance (800 mg) eluted out. After an interval, glutaric acid (50 mg) and succinic acid (50 mg) eluted in this order. The oily fraction was distilled and fraction of b.p_2 180–200° was collected. ν_{max}^{liquid} 3500, 1770 cm^{-1}. (Found: C, 67·00; H, 8·98. $C_{11}H_{18}O_3$ requires: C, 66·64; H, 9·15%). The structure was assumed as XIII, but further investigation was abandoned due to shortage of material.

Oxidation of cnidilide (VIIa) *with osmium tetroxide*

Cnidilide (VIIa, 3·0 g) in dry ether (30 ml) was treated with 15 ml dry ether solution of OsO_4 (3 g). The mixture, which began to deposit solid within a few min, was left at 25° for 24 hr. Ether was then removed and the residue washed 3 times with ether, then boiled under reflux with a solution of 40% $NaHSO_4$ (8 ml) and 20% Na_2SO_3 (20 ml) in methanol (30 ml). After 2 hr, the solution was cooled and filtered, and the residue extracted again with the same mixture of $NaHSO_4$ and Na_2SO_3 in methanol. The combined alcoholic solutions were evaporated to dryness under a red. press., the gummy residue extracted with ether (150 ml), and the ether solution washed with water, dried (Na_2SO_4), and evaporated to dryness. The residual oil (2·85 g) was chromatographed on silicic acid, and glycols (XV, 83 mg, and XIV, 2·74 g) were eluted with chloroform–methanol (99:1). XIV melted at 64–65°. ν_{max}^{nujol} 3350, 1765 cm^{-1}. $[\alpha]_D^{26}$ −23·1° (*c* 0·91, $CHCl_3$). (Found: C, 63·04; H, 8·93. $C_{12}H_{20}O_4$ requires: C, 63·14; H, 8·83%). XV crystallized from diisopropyl ether, as colorless plates, m.p. 186–187°. ν_{max}^{nujol} 3490, 1755 cm^{-1}. $[\alpha]_D^{26}$ +6·76° (*c* 0·73. $CHCl_3$). (Found: C, 63·20; H, 8·82. $C_{12}H_{20}O_4$ requires: C, 63·14; H, 8·83%). The IR spectra of XIV and XV were quite different in detail. XIV consumed 0·92 mole periodic acid at 22° for 19 hr, and XV, 1·12 moles.

Acetylation of glycol

The glycol (XIV, 128 mg) in pyridine and acetic anhydride (2 ml) was left at 25° for 12 hr. The solution was poured into water and extracted with ether. The extract was washed successively with 0·5N HCl, 5% $NaHCO_3$, and water, dried (Na_2SO_4) and evaporated to dryness. The crystalline residue, on recrystallization from methanol, deposited needles (165 mg), m.p. 112–113°. $\nu_{max}^{chloroform}$ 3500 (broad), 1765 cm^{-1}. (Found: C, 61·50; H, 7·75. $C_{16}H_{24}O_6$ requires: C, 61·52; H, 7·75%). The glycol (XV, 58 mg) was treated as XIV, and recrystallization from methanol–water gave plates (55 mg) of the crystalline residue. $\nu_{max}^{chloroform}$ 3500, 1765 cm^{-1}. (Found: C, 61·62; H, 7·84. $C_{16}H_{24}O_6$ requires: C, 61·52; H, 7·75%).

Cleavage of glycol with periodic acid

The glycol (XIV, 285 mg) in dioxan (10 ml), was treated with aqueous periodic acid (0·5 mole, 10 ml). The mixture was left for 24 hr at 25°, water (10 ml) was added, and dioxan evaporated below 60°. The water layer was extracted with ether and from this solution a neutral fraction (268 mg) and an acid fraction (11 mg) were separated using 10% Na_2CO_3. The neutral fraction had an IR spectrum similar to that of XIII. The acid fraction was subjected to gas chromatography analysis (Shimadzu GC-2A, STA Column, H_2 gas, 75 ml/min, column temp 113°), and paper chromatography (Toyo Roshi No. 50 paper, n-BuOH saturated with 1·5N NH_4OH as solvent, 10°). Formic acid was identified by both analyses.

Synthesis of Δ^5*-tetrahydrobutyl phthalide* (VIId)

The ether solution of butylmagnesium bromide was prepared in the usual way from 1·2 g Mg and 10 g butyl bromide and converted into the Cd-derivative by treating with 4·52 g anhydrous $CdCl_2$. The solvent was replaced by benzene and the benzene solution of this reagent, 3·75 g *cis*-Δ^4-tetrahydrophthalic anhydride was added and the mixture refluxed 2 hr. To the reaction mixture, 10% H_2SO_4 was added and the whole extracted with ether. On evaporation of ether, 4·36 g of oil, contaminated with *cis*-Δ^4-tetrahydrophthalic acid, which was removed with dry benzene, was obtained. The residue yielded, keto acid (2·6 g), the 2,4-dinitrophenylhydrazone prepared by the usual way melted at 203–205°. (Found: C, 55·43; H, 5·70. $C_{18}H_{22}O_8N_4$ requires: C, 55·38; H, 5·68%).

To a solution of the keto acid (2·3 g) in 5 ml of 10% NaOH aq, 0·5 g $NaBH_4$ in water (5 ml) was added. The mixture was kept at 37° for 24 hr. The reaction mixture was acidified with 10% HCl and extracted with ether. The ether solution was dried (Na_2SO_4), evaporated *in vacuo*, and 2·12 g of an oily residue dissolved in toluene. This solution was refluxed for 5 hr and after cooling, treated with 10% Na_2CO_3, to remove the acidic fraction. Neutral oil (0·5 g) was obtained from the toluene. ν_{max}^{liquid} 1770, 1655 cm^{-1} (v.w.).

Oxidation of Δ^5*-tetrahydrobutyl phthalide* (VIId) *with osmium tetroxide*

Compound VIId (0·4 g) was treated with OsO_4 (0·7 g) as described for cnidilide (VIIa) and 0·32 g crystals were obtained from diisopropyl ether, m.p. 114–115°. ν_{max}^{nujol} 3550, 1775, 1760 cm^{-1}. (Found: C, 63·01; H, 8·77. $C_{12}H_{20}O_4$ requires: C, 63·13; H, 8·83%).

Hydrolysis of Δ^5*-tetrahydrobutyl phthalide* (VIId)

Δ^5-Tetrahydrobutyl phthalide (VIId, 10·94 mg) was sealed in a glass tube with 5% KOH–ethanol (1 ml) and heated for 8 hr on a steam bath. When cool, ethanol was evaporated and the residue extracted with ether. The ether solution was evaporated and yielded an oily residue (5·14 mg), λ_{max} 227, 278, 281 mμ, which indicates the formation of butyl phthalide (VI) during these treatments. This oily residue also has absorptions at 1770 and 1655 cm^{-1} in its IR spectrum.

Hydrolysis of neocnidilide (XVIIIa)

Neocnidilide (XVIIIa, 150 mg) was refluxed for 6 hr with 5% KOH–ethanol (20 ml). Water (20 ml) was added and the solution was concentrated *in vacuo*. The resulting aqueous alkaline solution was acidified at −15° and crystals precipitated out. The crystals were dissolved in 10% $NaHCO_3$, washed with ether to remove neutral compound, acidified again with 10% HCl, and white crystals separated, m.p. 81–82°. ν_{max}^{nujol} 3200, 1665 cm^{-1}. This acidic substance is very easily changed to neocnidilide.

Phthalazone of neocnidilide (XVIIIa)

Neocnidilide (XVIIIa, 60 mg) was hydrolysed with 10% KOH–ethanol (10 ml), water (10 ml) was added and the solution concentrated *in vacuo* until the distillate was 10 ml. The resulting aqueous alkaline solution was acidified with 10% HCl. The acid fraction that precipitated out was dissolved in pyridine (5 ml) and oxidized with CrO_3–pyridine complex for 14 hr at room temp. The keto acid obtained was sealed in a test tube with hydrazine hydrate and ethanol, and phthalazone crystallized out; m.p. and mixed m.p. 134·5–135° with sedanonic acid phthalazone

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