356. *The Constitution of Sedanolide.*

By D. H. R. Barton and Juan X. de Vries.

Celery oil has been found to furnish 3-n-butylphthalide and sedanonic acid. Sedanolide could not be reisolated. However, reduction of sedanonic acid with sodium borohydride afforded racemic sedanolide, thus confirming a revised formulation for this compound.

The investigation of the constitution of sedanolide by Ciamician and Silber[1] is one of the early classics of natural-products chemistry. Sedanolide occurs in celery-oil residues along with a further lactone which gives sedanonic acid on alkaline hydrolysis. For the latter acid Ciamician and Silber[1] proposed the constitution (I), which we do not dispute. For sedanolide the formula (II) was suggested. We were interested in these compounds from two points of view. First, their biogenesis might involve the head-to-tail linkage of six " acetate " or " malonate " units and, secondly, the formula (II) proposed for sedanolide did not explain the ready addition of potassium cyanide to give a nitrile furnishing a carboxylic acid on hydrolysis. Review of the earlier work[1] suggested that sedanolide should have structure (III), leading to a cyanide adduct (IV; R = CN) which would be hydrolysed to the acid (IV; R = CO_2H). There appears to be nothing in more recent work,[2,3] especially the authoritative studies of Mitsuhashi *et al.*,[4,5] to contradict our views.

Processing celery-oil residues according to the directions of Ciamician and Silber[1] gave a " sedanolide " fraction which was shown to be 3-n-butylphthalide (V). From the acid fraction there was no difficulty in isolating sedanonic acid (I) with properties in agreement with the literature. This compound is, of course, racemic because of the alkaline conditions used in the extraction. Hydrogenation of 3-n-butylphthalide in acetic acid over platinum gave the crystalline hexahydro-derivative (VI) which afforded a crystalline hydroxy-acid on opening of the lactone ring. Reduction of 3-n-butylphthalide with lithium aluminium hydride gave the crystalline diol (VII). Celery oleoresin and celery-seed oil also yielded 3-n-butylphthalide but no sedanolide. 3-n-Butylphthalide has, of course, been isolated before from plant sources.[3] Reconsideration of the data (especially the ultraviolet spectra) reported by Noguchi[2] for his " sedanolide " suggests that he also was working with 3-n-butylphthalide.

---

[1] Ciamician and Silber, *Ber.*, 1897, **30**, 492, 501, 1419, 1424, 1427.

[2] Noguchi *et al.*, *J. Pharm. Soc. Japan*, 1934, **54**, 913; 1937, **57**, 769, 783.

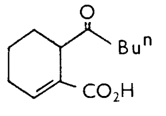
[3] Naves, *Helv. Chim. Acta*, 1943, **26**, 1281.

[4] Mitsuhashi *et al.*, *J. Pharm. Soc. Japan*, 1958, **78**, 539; *Chem. and Pharm. Bull.* (*Japan*), 1960, **8**, 243; 1961, **9**, 115.

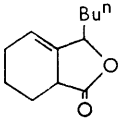
[5] Mitsuhashi, Nagai, Muramatsu, and Tani, 5th Symposium on the Organic Chemistry of Natural Products, Sendai, Japan, 1961; personal communication from Professor H. Mitsuhashi.

The constitution of sedanonic acid was confirmed by its ultraviolet spectrum. Catalytic hydrogenation in acetic acid over platinum gave the racemate (infrared comparison) corresponding to the optically active lactone (VI). Fission of the lactone ring under mild alkaline conditions afforded the racemic hydroxy-acid corresponding to the enantiomer obtained earlier from 3-n-butylhexahydrophthalide.

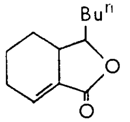
In view of the difficulty in isolating again sedanolide it was decided to synthesize a racemic sedanolide for comparison with the properties recorded by Ciamician and Silber.[1]



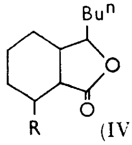
(I)



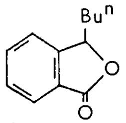
(II)



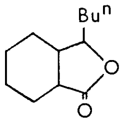
(III)



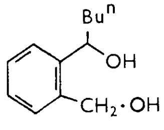
(IV)



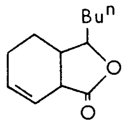
(V)



(VI)



(VII)



(VIII)

Reduction of sedanonic acid with sodium borohydride gave the corresponding hydroxy-acid which lactonised to racemic lactone (III). So far as comparison could be made this lactone corresponded to sedanolide.

The formula (III) also represents " iso-cnidium lactone " and " substance-γ," both of which have been studied by Mitsuhasi, Nagai, Muramatsu, and Tani.[5] Cnidium lactone [2] itself has structure (VIII).[5]

There are several possible explanations for our failure to isolate " sedanolide " again. One may be that cnidium lactone (VIII) is the true lactone and that it is dehydrogenated by autoxidation during processing on a relatively small scale. Another is that the strain of celery may have changed, at least in its chemical constituents, since the end of the last century.

Since Professor Mitsuhashi [5] is examining these matters in detail and has views on the stereochemistry of the compounds involved, we refrain from further investigation or discussion.

EXPERIMENTAL

M. p.s were taken on the Kofler block. $[\alpha]_D$ are for $CHCl_3$ solutions. Ultraviolet spectra were for EtOH solutions. Gas chromatograms were carried out on the Pye Argon instrument with a Peg A column at 180° and a gas flow of 20 ml./min. Infrared spectra were for $CHCl_3$ solutions unless specified to the contrary. We thank Mr. R. G. Foster for the determination and interpretation of the nuclear magnetic resonance spectra. Light petroleum refers throughout to the fraction of b. p. 60—80°.

Isolation of 3-*n-Butylphthalide.*—The " sedanolide " fraction from oil of celery (143 g.) was distilled *in vacuo* at 128—164°/0·8 mm. The distillate (78·5 g., 51%), $n_D^{24°}$ 1·5257, $[\alpha]_D$ −34° (*c* 2·19), $\lambda_{max.}$ 213, 226, 275, and 281 mμ ($\epsilon^{1\%}_{1\,cm.}$ 312, 326, 118, and 118, respectively), $\nu_{max.}$ 1750 ($\alpha\beta$-unsaturated γ-lactone) cm.$^{-1}$, was shaken for 3 hr. with 2·5% aqueous potassium hydroxide; (360 ml.) and then extracted with ether. The ethereal layer was treated again in the same way. The extract (52 g.) was then refluxed with 25% w/w aqueous potassium hydroxide (104 g.) and, after cooling, extracted with ether. The alkaline solution was acidified with 6N-sulphuric acid with cooling and again extracted with ether, to give a yellow-brown oil (42 g.). This oil was shaken with 10% w/w aqueous sodium carbonate (84 g.) for 17 hr. and extracted with ether. The sodium carbonate solution was processed for sedanonic acid (see below). The ethereal extract (21·5 g.) was distilled through a Vigreux column and the fraction (13·04 g.) with b. p. 120—130°/0·6 mm. was collected. This had physical constants essentially identical with those of pure 3-n-butylphthalide (V). For further purification the fraction, in benzene, was filtered through alumina (30 g.; grade III), and the residue (11·15 g.) redistilled to furnish pure[3,6] 3-n-butylphthalide (V), b. p. 106—108°/0·1 mm., $n_D^{22°}$ 1·5228, $[\alpha]_D$ −57° (*c* 1·96), $\lambda_{max.}$ 227, 274, and 281 mμ (ε 9800, 1740 and 1740, respectively), $\nu_{max.}$ 1755 (γ-lactone), 1600, 1580, and 1460 (aromatic) cm.$^{-1}$, τ (in CCl_4) 4·6 (C·CH·O·C:O) and aryl H (Found: C, 75·7; H, 7·65. Calc. for $C_{12}H_{14}O_2$: C, 75·75; H, 7·4%).

The 3-n-butylphthalide was further characterised by the following reactions. Hydrogenation of the phthalide (1·0 g.) in acetic acid (20 ml.) over platinum oxide (250 mg.) (3 mol. uptake) gave, after chromatography over alumina (grade III) in benzene and crystallisation from light petroleum, 3-n-butylhexahydrophthalide (VI), m. p. 48—49°, $[\alpha]_D$ −18° (*c* 1·10), $\nu_{max.}$ (in Nujol) 1760 (γ-lactone) cm.$^{-1}$ (Found: C, 73·55; H, 10·5. Calc. for $C_{12}H_{20}O_2$: C, 72·45; H, 10·25%). The infrared spectrum in chloroform was identical with that of racemic materal obtained (see below) from the hydrogenation of sedanonic acid. For crystalline dihydrocnidium lactone Noguchi[2] recorded m. p. 51°, $[\alpha]_D$ −16°.

The hexahydrophthalide (VI) (50 mg.) in 25% w/w aqueous potassium hydroxide (0·15 ml.) was heated on the steam-bath for 30 min. Dilution with water, saturation with solid carbon dioxide, acidification with 6N-sulphuric acid, and extraction in ether gave, after crystallisation from methylene dichloride–light petroleum, the hydroxy-acid as plates, m. p. 94—96°, $[\alpha]_D$ −15° (*c* 1·05), no ultraviolet absorption, $\nu_{max.}$ (in Nujol) 3330 (OH) and 1690 (CO_2H) cm.$^{-1}$. The infrared spectrum in chloroform was identical with that of the hydroxy-acid from sedanonic acid described below (Found: C, 67·05; H, 10·4. Calc. for $C_{12}H_{22}O_3$: C, 67·25; H, 10·35%). For β-dihydrosedanolic acid Noguchi[2] recorded m. p. 91°, $[\alpha]_D$ −26°.

Reduction of 3-n-butylphthalide (1·36 g.) in dry tetrahydrofuran (20 ml.) with lithium aluminium hydride (1·4 g.) in the same solvent (30 ml.) under reflux for 3 hr. and crystallisation of the product from methylene dichloride–light petroleum gave *2-1′-hydroxypentylbenzyl alcohol* (VII) as prisms, m. p. 73—74°, $[\alpha]_D$ −27° (*c* 1·07), $\lambda_{max.}$ 214, 256, 262, 268, and 273 mμ (ε 8,600, 140, 180, 150, and 90, respectively), $\nu_{max.}$ (in Nujol) 3640 and 3450 (OH) cm.$^{-1}$ (Found: C, 74·05; H, 9·2. $C_{12}H_{18}O_2$ requires C, 74·2; H, 9·35%).

3-n-Butylphthalide (91 mg.) in N-methanolic potassium hydroxide (10 ml.) was kept at room temperature for 12 hr.; $[\alpha]_D$ changed from −55° to +20° (constant). Acidification with gaseous hydrogen chloride gave, after filtration, an oil whose $[\alpha]_D$ −55° indicated relactonisation.

Isolation of Sedanonic Acid (I).—The sodium carbonate solution from the extraction of 3-n-butylphthalide (see above) was acidified with 6N-sulphuric acid and extracted thoroughly with ether, to furnish crude sedanonic acid (I) (16·55 g.). This was filtered through silica gel in benzene and crystallised from the same solvent. It had m. p. 110—111°, $[\alpha]_D$ 0°, $\lambda_{max.}$ 214 mμ (ε 8900), $\nu_{max.}$ 1710 (acyclic ketone), 1695 (αβ-unsaturated CO_2H), and 1650 (conjugated C=C) cm.$^{-1}$, τ (in CCl_4) 2·71 (olefinic H) (Found: C, 68·85; H, 8·7. Calc. for $C_{12}H_{18}O_3$: C, 68·55; H, 8·65%).

Sedanonic acid was hydrogenated (2 mol. uptake) over platinum as for 3-n-butylphthalide to give the lactone (VI). Recrystallised from light petroleum this formed plates, m. p. 39—40°, $[\alpha]_D$ 0°, no ultraviolet absorption, infrared spectrum (in $CHCl_3$) identical with that of 3-n-butylhexahydrophthalide (Found: C, 72·85; H, 10·1. Calc. for $C_{12}H_{20}O_2$: C, 73·45; H, 10·25%).

Alkaline hydrolysis as for 3-n-butylhexahydrophthalide (see above) gave the hydroxy-acid. Recrystallised from methylene dichloride–light petroleum this formed large plates, m. p. 104—105°, $[\alpha]_D$ 0°, no ultraviolet absorption, infrared spectrum (in $CHCl_3$) identical with that of the hydroxy-acid from 3-n-butylhexahydrophthalide (see above).

Sedanonic acid (300 mg.) in ethanol (10 ml.) was saturated with sodium metal (small portions) under reflux. Dilution with water, acidification with 6N-sulphuric acid, and extraction in ether gave the hydroxy-acid. Recrystallised from methylene dichloride–light petroleum this formed long needles, m. p. 124—125°, $[\alpha]_D$ 0°, no ultraviolet absorption, infrared spectrum (in $CHCl_3$) different from that of the isomer obtained by the catalytic hydrogenation sequence detailed above. The m. p. recorded[1] for this compound is 119—120°.

Reduction of Sedanonic Acid (I) *with Sodium Borohydride.*—Sedanonic acid (1·15 g.) in methanol (50 ml.) was neutralised with aqueous potassium hydroxide, and the methanol removed *in vacuo*. The residue was treated dropwise with sodium borohydride (1·2 g.) in water (10 ml.), and the resultant solution left overnight at room temperature. After acidification to pH 3—4 with methanolic hydrochloric acid and evaporation *in vacuo* (and repetition of this

---

[6] Schroeder, Wilcox, Trueblood, and Dekka, *Analyt. Chem.*, 1951, **23**, 1740.

process twice), the residue was taken up in ether and washed with aqueous sodium hydrogen carbonate and then with water. After drying (Na_2SO_4), removal of the ether gave a yellowish oil (1·04 g.). This was filtered in benzene through alumina (10 g.; grade 3) and then fractionally distilled. This procedure gave racemic *sedanolide* (III), b. p. 116—118°/0·2 mm., n_D^{25} 1·4938, $\lambda_{max.}$ 220 mμ (ε 9100), d_4^{27} 1·0335, $\nu_{max.}$ 1755 (αβ-unsaturated γ-lactone) and 1680 (C=C) cm.$^{-1}$ (Found: C, 74·35; H, 9·4. $C_{12}H_{18}O_2$ requires C, 74·2; H, 9·35%). The literature data [1] for natural " sedanolide " are b. p. 185°/17 mm., $n_D^{24\cdot5}$ 1·49234, $d_4^{24\cdot5}$ 1·0383.

Racemic sedanolide (162 mg.) was hydrolysed with potassium hydroxide as for 3-n-butylhexahydrophthalide (see above), to give the corresponding hydroxy-acid (132 mg.). Recrystallised from methylene dichloride–light petroleum this had m. p. 119—122°, $\lambda_{max.}$ 219 mμ (ε 9600), $\nu_{max.}$ (in Nujol) 3260 (HO), 1670 (αβ-unsaturated CO_2H) and 1630 (C=C) cm.$^{-1}$.

Further Investigations of Celery Oils.—(*a*) " Oleoresin Celery Fivefold " (Fritzsche Bros., New York) was taken up in ether, dried (Na_2SO_4), filtered, and distilled. The main fraction had b. p. 100—150°/0·1 mm., $[\alpha]_D$ $-61°$, $\lambda_{max.}$ 209 and 280 mμ ($E^{1\%}_{1\,cm.}$ 304 and 117, respectively). The " sedanolide " fraction of this oil was isolated by the procedure of Ciamician and Silber [1] and identified by $[\alpha]_D$, n_D, b. p., ultraviolet and infrared spectra, and by hydrogenation to 3-n-butylhexahydrophthalide as 3-n-butylphthalide.

(*b*) " Oil Celery Seed Extra " (Fritzsche Bros., New York) had $[\alpha]_D$ $+70°$, n_D^{24} 1·4840, $\lambda_{max.}$ 209, 224 (shoulder), and 276 ($E^{1\%}_{1\,cm.}$ 160, 92, and 45, respectively), $\nu_{max.}$ 1760 cm.$^{-1}$. Fractional distillation gave fractions (at 0·2 mm.) as follows: b. p. (i) 40—60°, (ii) 62—74°, (iii) 74—82°, (iv) 82—106°, (v) 106—120, and (vi) 120—130°. Fraction (i) showed no carboxyl absorption and on gas chromatography showed at least five peaks. The other fractions were processed acording to the directions of Ciamician and Silber [1] to obtain the " sedanolide " fractions. In each case the main component was shown by gas chromatography to be 3-n-butylphthalide.

We thank Professor H. Mitsuhashi (Institute of Pharmaceutical Sciences, Hokhaido University) for communicating his important results and for discussion. The celery-oil specimens used were all presented by Messrs. Fritzsche Bros. (New York). One of us (J. X. de V.) thanks the British Council for a Fellowship.

IMPERIAL COLLEGE, LONDON, S.W.7.

[*Received, November 2nd,* 1962.]