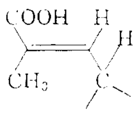
COMMUNICATIONS TO THE EDITOR

TERPENES. XIV. THE STRUCTURE OF VALERENIC ACID[1]

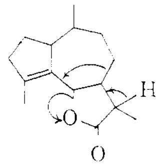
Sir:

The spasmolytic effects of extracts of *Valeriana officinalis* L. have been attributed to a carboxylic acid, $C_{15}H_{22}O_2$, m.p. 140–142°, $[\alpha]^{20}\text{D}$ $-120°$ (EtOH) of unknown structure which was named valerenic acid.[2] We have been able to show that valerenic acid is a sesquiterpene containing a novel carbon skeleton. The spectral properties (λ_{max}^{EtOH} 217 mμ, ϵ 13000; $\nu_{max}^{CHCl_3}$ 1685, 1625 cm.$^{-1}$) are those of an α,β-unsaturated acid and the presence of a second double bond was established by catalytic reduction to a saturated tetrahydrocarboxylic acid and epoxidation of methyl valerenate (II), b.p. 98–100° (0.05 mm.), $n^{23}\text{D}$ 1.5121, $[\alpha]^{20}\text{D}$ $-124°$ (EtOH), λ_{max}^{EtOH} 219 mμ, ϵ 13800, $\nu_{max}^{CHCl_3}$ 1710, 1640 cm.$^{-1}$, to the epoxide IV, b.p. 114–116° (0.05 mm.), $n^{24}\text{D}$ 1.5002, $\alpha^{24}\text{D}$ $-120°$ (EtOH), ν_{max}^{liq} 1710, 1642 cm.$^{-1}$. Ozonization of I yielded pyruvic acid (2,4-DNP, m.p. 218–220°, pure and mixed with authentic sample) while ozonization of IV gave the aldehyde V, b.p. 75° (0.05 mm.), $n^{23}\text{D}$ 1.4850, $[\alpha]^{20}\text{D}$ $-158°$ (EtOH), ν_{max}^{liq} 1725, 2720 cm.$^{-1}$, semicarbazone, m.p. 207–209°. The structure of the complete side chain in valerenic acid was ascertained in this way. Treatment of I with anhydrous hydrochloric acid in methanol led to methyl valerenate hydrochloride, b.p. 115–116° (0.03 mm.), $n^{25}\text{D}$ 1.5052, $[\alpha]^{20}\text{D}$ $-29°$ (EtOH), λ_{max}^{EtOH} 224 mμ, ϵ 15500, ν_{max}^{liq} 1710–1715, 1650 cm.$^{-1}$, which on ozonization was converted to a chloroaldehyde, $C_{12}H_{19}OCl$, b.p. 64–65° (0.005 mm.), $n^{23}\text{D}$ 1.4950, $[\alpha]^{20}\text{D}$ $-21°$ (EtOH), ν_{max}^{liq} 2710, 1725 cm.$^{-1}$. This, when treated with hydroxylamine acetate, furnished the unsaturated oxime, m.p. 147–148°, ν_{max}^{Nujol} 1660 cm.$^{-1}$. Reduction of the latter with lithium aluminum hydride then catalytic reduction and quaternization with methyl iodide gave the quaternary iodide (VI), m.p. 257–260°. Hofmann degradation afforded an olefin (VII), ν_{max}^{liq} 3080, 1642, 885 cm.$^{-1}$, which subsequently was transformed to the *ketone* (VIII), ν_{max}^{liq} 1710 cm.$^{-1}$, semicarbazone, m.p. 101–105°, by osmylation and glycol cleavage with lead tetraacetate.

The presence of the part structure A suggested expression I for valerenic acid which could be the result of a new biogenetic rearrangement of a guianolide (B).

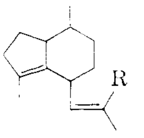


A

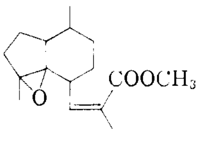


B

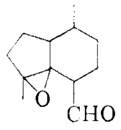
In agreement with this view, we found that the allylic alcohol (III), b.p. 112–114° (0.15 mm.), $n^{25}\text{D}$ 1.5182, $[\alpha]^{19}\text{D}$ $-70°$ ($CHCl_3$), prepared by reduction of II with lithium aluminum hydride, on dehydrogenation with selenium at 300° during 3.5 hr. gave the indane IX, b.p. 101–102° (1.1 mm.), $n^{25}\text{D}$ 1.5118, $[\alpha]^{20}\text{D}$ 0°, $\lambda_{max}^{isooctane}$ 218 (ϵ 10100), 223 (ϵ 9400), 256 (ϵ 280), 265 (ϵ 315), 272 (ϵ 235), 276 mμ (ϵ 138), ν_{max}^{liq} 1875, 1725 cm.$^{-1}$, characteristic of 1,2,3,4-tetrasubstituted benzenes.[3] The yield of gas chromatographically pure IX was 40%. Friedel–Crafts condensation of *p*-isobutyltoluene[4] with crotonyl chloride afforded 1,4-dimethyl-7-isobutyl-indan-3-one,[5] b.p. 101–102° (0.65 mm.), $\lambda_{max}^{isooctane}$ 246 (ϵ 10600), 255 (ϵ 10800), 294 (ϵ 29400), 305 mμ (ϵ 31200), ν_{max}^{liq} 1710, 1585 cm.$^{-1}$, semicarbazone, m.p. 168–169°; 2,4-DNP, m.p. 143–144°, which was reduced according to Clemmensen to 1,4-dimethyl-7-isobutylindan (IX). The ultraviolet, infrared and mass spectra[6] of synthetic IX were identical with those of the hydrocarbon from valerenic acid.



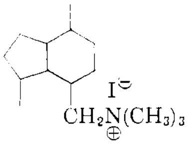
I, R = COOH
II, R = $COOCH_3$
III, R = CH_2OH



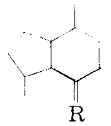
IV



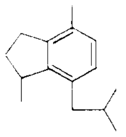
V



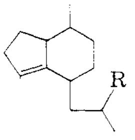
VI



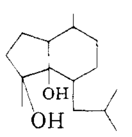
VII, R = CH_2
VIII, R = O



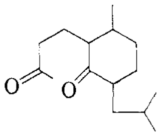
IX



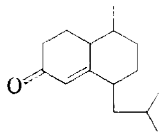
X, R = COOH
XI, R = CH_2OH
XII, R = $CH_2OSO_2C_7H_7$
XIII, R = CH_3



XIV/XV



XVI



XVII

We next determined the position of the nuclear double bond. Partial catalytic reduction of I gave dihydrovalerenic acid (X) which was reduced to XI with lithium aluminum hydride, converted to the tosylate XII, which in turn was hydrogenolyzed with lithium aluminum hydride to the gas chroma-

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(1) Part XIII, A. G. Armour, G. Büchi, A. Eschenmoser and A Storni, *Helv. Chim. Acta*, **42**, 2233 (1959).

(2) A. Stoll and E. Seebeck, *Ann.*, **603**, 158 (1957).

(3) C. W. Young, R. B. DuVall and N. Wright, *Anal. Chem.*, **23**, 709 (1951).

(4) H. Pines, D. R. Strehlau and V. N. Ipatieff, This Journal, **72**, 1563 (1950).

(5) For analogies see C. A. Thomas, "Anhydrous Aluminum Chloride in Organic Chemistry," Reinhold Publishing Corp., New York, N. Y., 1941, p. 212.

(6) The mass spectra were kindly measured by Prof. K. Biemann and Dr. J. Seibl, M.I.T.

tographically homogeneous olefin XIII, b.p. 56–60° (0.1 mm.), n^{24}_{D} 1.4834, $[\alpha]^{20}_{D}$ −75° (EtOH). Oxidation of XIII with osmium tetroxide afforded two diastereomeric diols. Diol XIV (80%), b.p. 120–125° (0.15 mm.), $[\alpha]^{26}_{D}$ +7° ($CHCl_3$), and diol XV (20%), b.p. 110–115° (0.15 mm.), $[\alpha]^{26}_{D}$ −31° ($CHCl_3$) with lead tetraacetate, were both cleaved to the same diketone (XVI), b.p. 140–145° (0.85 mm.), $[\alpha]^{19}_{D}$ −80° ($CHCl_3$), $\nu^{CCl_4}_{max}$ 1707, 1715, 1360 cm.$^{-1}$ (cyclohexanone, methyl ketone). The formation of a cyclohexenone (XVII), b.p. 80–83° (0.15 mm.), $[\alpha]^{24}_{D}$ −50° ($CHCl_3$), λ^{EtOH}_{max} 241, 289 mμ, ϵ 14100, 1440, $\nu^{CCl_4}_{max}$ 1670, 1618 cm.$^{-1}$; 2,4-DNP, m.p. 151–152°, by acid catalyzed cyclization of XVI is only possible if the nuclear double bond of valerenic acid is located as shown in I. In agreement with our proposal, the 56.4 mc./sec. n.m.r. spectrum of II in $CDCl_3$ exhibited these peaks: doublet (3H) centered at τ 9.22 (J 8 c./s.); singlet (3H) at τ 8.34; doublet (3H) at τ 8.09 (J ~1 c./s.); singlet (3H) at τ 6.28; doublet centered at τ 2.95 (J 9 c./s.) with additional fine splitting.[7] The spectrum of methyl valerenolate prepared by hydrolysis and esterification of naturally occurring acetylvalerenolic acid[2] had a strikingly similar spectrum: doublet (3H) centered at τ 9.29 (J 7 c./s.); singlet (3H) at τ 8.36; doublet (3H) at τ 8.09 (J ~1 c./s.); singlet (1H) at τ 7.22; singlet (3H) τ 6.26; quadruplet centered at τ 5.85; doublet (1H) centered at τ 2.97 (J 9 c./s.) with further splitting. This situation *tentatively* suggests that valerenolic acid may be a hydroxyvalerenic acid. We are indebted to the National Institutes of Health for a predoctoral fellowship to T.L.P. and to Dr. W. D. Phillips, E. I. du Pont de Nemours and Company, Inc., for the n.m.r. spectra.

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(7) *Cf.* the spectra of methyl angelate and methyl tiglate, L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy," Pergamon Press, Ltd., London, 1959, p. 119; R. R. Fraser, *Can. J. Chem.*, **38**, 549 (1960).

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EFFECTS OF NUCLEAR RECOIL IN THE CHROMIUM (III)-THIOCYANATE SYSTEM OF COMPLEXES

Sir:

A dilute solution of the $Cr(NCS)_6^{-3}$ ion has been irradiated with neutrons in order to study the chemical effects of the recoil following the $Cr^{50}(n,\gamma)Cr^{51}$ reaction. This system was chosen because all of the complexes in the series, $Cr(NCS)_n(H_2O)_{6-n}^{-n+3}$, where $n = 1, 2, \ldots, 6$, have been isolated, and at room temperature in neutral or acidic solution the rates of interconversion of the different species are slow.[1] Ion exchange recently has been applied[2,3] for the separation of the cations in the series, including the geometrical isomers of $Cr(NCS)_2(H_2O)_4^+$. The Cr^{51} nucleus formed in the above reaction may have an energy up to a maximum of 880 ev., depending on the number and energies of the γ rays emitted. Each vacant coördination site left by rupture of a Cr–NCS bond is expected to be filled by H_2O, provided the solution is sufficiently dilute and there is a low concentration of free NCS^-. Thus, measurement of the amount of 27-day Cr^{51} in each species after irradiation will give information about the probability of bond rupture.

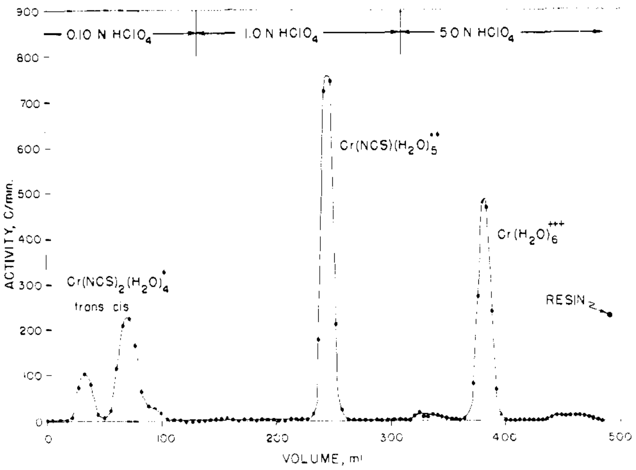

Fig. 1.

An aqueous solution, 1.69×10^{-3} mole fraction in $(NH_4)_3Cr(NCS)_6$, and containing no free NCS^-, was irradiated for 1 min. at a neutron flux of *ca.* 10^{13} neutrons cm.$^{-2}$ sec.$^{-1}$. The solution was passed through a Dowex-50 cation-exchange resin column, and then through a chromatographic alumina column. $Cr(NCS)_3(H_2O)_3$ was extracted into ether. The elution curve of Cr^{51} activity from the cation-exchange column is shown in Fig. 1, and the elution curve of total Cr from the alumina column in Fig. 2. The results are summarized in Table I, which gives the distribution of Cr^{51} radioactivity and total Cr found in each species.

TABLE I

DISTRIBUTION OF Cr^{51} RADIOACTIVITY AND TOTAL Cr IN DIFFERENT SPECIES

Species	Radioactivity, %	Total Cr, %
$Cr(NCS)_6^{-3}$	<0.1	31
$Cr(NCS)_5^{-2}$	0.1	57
$Cr(NCS)_4^-$	3.9	4.0
$Cr(NCS)_3$	1.9	0.3
cis-$Cr(NCS)_2^+$	15.5	1.9
trans-$Cr(NCS)_2^+$	4.8	0.6
$Cr(NCS)^{+2}$	33.6	3.7
Cr^{+3}	29.1	1.5
Others[a]	7.2	..
Resin[b]	4.0	..

[a] Total activity outside of main peaks. [b] Activity remaining on cation-exchange resin.

There is no retention of radioactivity in the parent species, and very little retention in any species with more than two NCS^- groups. In view of the large recoil energy available compared to chemical bond energies, it is surprising that any NCS^- groups could remain bound to the Cr. However, there may be mechanisms which would

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(1) N. Bjerrum, *Z. anorg. Chem.*, **118**, 131 (1921); **119**, 39, 54, 179 (1921).

(2) E. L. King and E. B. Dismukes, THIS JOURNAL, **74**, 1674 (1952).

(3) J. T. Hougen, K. Schug and E. L. King, *ibid.*, **79**, 519 (1957).