

otherwise noted in the table. The toxic dose for white mice was determined by Dr. O. M. Gruhzt by oral administration of the drug suspended in acacia and is the amount at which 60% of the animals survived, expressed as g./kg. These values are to be regarded as approximate since some of the compounds were so non-toxic the LD-50 was not determined; however, they served as a guide in choosing doses for the cat test.

Eight of the benzoxazoles exhibited definite anticonvulsant activity at the dose levels tested. The relative activity of the compounds in this series was not determined in these preliminary tests. Benzyl benzoxazole was chosen for further study because it was apparently the most active, least soporific and most readily available com-

pound of this series. The results of the tests with 2-methylbenzothiazole were invalidated since the animals died within twenty-four hours. Benzimidazole was active at a relatively high dose level; however, benzoilation of it destroyed its anticonvulsant properties. Neither 2-aminobenzimidazole nor benzoxazolone was active.

Summary

1. A series of 2-alkylbenzoxazoles have been prepared and tested for anticonvulsant activity.
2. Eight of the thirteen derivatives tested possessed anticonvulsant activity when administered in large doses.

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[CONTRIBUTION FROM THE STERLING CHEMICAL LABORATORY OF YALE UNIVERSITY]

American Musk. IV. On the Biological Origin of Animal Musk. Two More Large Ring Ketones from the Muskrat

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In the first paper¹ of this series it was shown that the musk of the muskrat, unlike that of the musk-deer and civet cat, consists mainly of a pair of odd-numbered macro-cyclic ketones, normuscone and dihydrocivetone. This suggested that these ketones² constitute a regular series analogous to that of the naturally occurring fatty acids. At that time, because of insufficient material, it was not possible to show the presence of the expected lower and higher macro-cyclic com-

pounds. Now, however, examination of the low and high boiling fractions of the ketone mixture³ resulting from the oxidation of the crude carbinols obtained from many thousands of glands, has indeed revealed the presence of two more macro-cyclic ketones: cyclotridecanone and cyclononadecanone. Furthermore, the relative amounts of these ketones parallel closely the amounts of the corresponding fatty acids with one more carbon atom, found in total rodent fat⁴ (Table I). Thus it is clear that these large ring ketones constitute a regular series like the fatty acids.

The structures of these two ketones, which are the first cyclic compounds yet found in nature with 13 or 19 atoms in the ring, were conclusively proven as shown in Table II.

The establishment of this series of macro-cyclic ketones from one animal is the first positive evidence⁵ that there is an intimate biological association of these ketones with the corresponding fatty acids. Ruzicka⁶ made this suggestion in 1926, pointing out a similarity between the structures of muscone and civetone with palmitic and oleic acids, respectively. The chemistry of this relationship, while still uncertain, most probably involves the change: C_{2n} fatty acid \rightarrow C_{2n-1} ring ketone, a change which could be valid for all ketones except muscone with its β methyl

(3) Many thanks are due to Givaudan-Delawanna, Inc., of New York, now in commercial production of this musk—"Musk Zibata"—(U. S. Patent 2,384,041), who so generously made this material available.

(4) Longenecker and Hilditch, *Biochem. J.*, **32**, 784 (1938).

(5) Evidence of a negative character comes from the fact that the anatomically similar beaver scent glands contain no large ring compounds, and little or no fatty acid; Stevens, *THIS JOURNAL*, **65**, 2471 (1943).

(6) Ruzicka, *Helv. Chim. Acta*, **9**, 230 (1926).

TABLE I

% Fatty acids ^a Total rodent fat ^{4,c}	% Macro-cyclic ketones ^b
C ₁₀ 0.3	C ₉ ..
C ₁₂ 0.7	C ₁₁ ..
C ₁₄ 8.1	C ₁₃ 1.0 ^d
C ₁₆ 29.9	C ₁₅ 40.0
C ₁₈ 59.3	C ₁₇ 58.0
C ₂₀ 1.5	C ₁₉ 0.7
C ₂₂ 0.2	C ₂₁ ?
Above C ₂₂ ..	C ₂₃ ..

^a Since the unsaturated acids could yield the saturated ketones upon subsequent hydrogenation, these values include both saturated and unsaturated acids. ^b Approximate only. ^c Professor J. L. E. Erickson of Louisiana State University has kindly informed me that a preliminary analysis of the fat of the muskrat scent glands indicates the presence of C₁₄, C₁₆, C₁₈ and C₂₀ acids, and also a high percentage of acids above C₂₂, a finding in harmony with the results of Simmons and Hills, *Analyst*, **58**, 154 (1935). ^d This value may seem low, considering the percentage of myristic acid, but it must be remembered that the C₁₃ ring is still in that size range where rings are hard to form, as evidenced by the relatively low yields obtained by Ziegler and Aurnhammer (*Ann.*, **513**, 43 (1934)) of the C₁₃ ketone compared to that of the C₁₅ and larger ketones.

(1) Stevens and Erickson, *THIS JOURNAL*, **64**, 144 (1942).

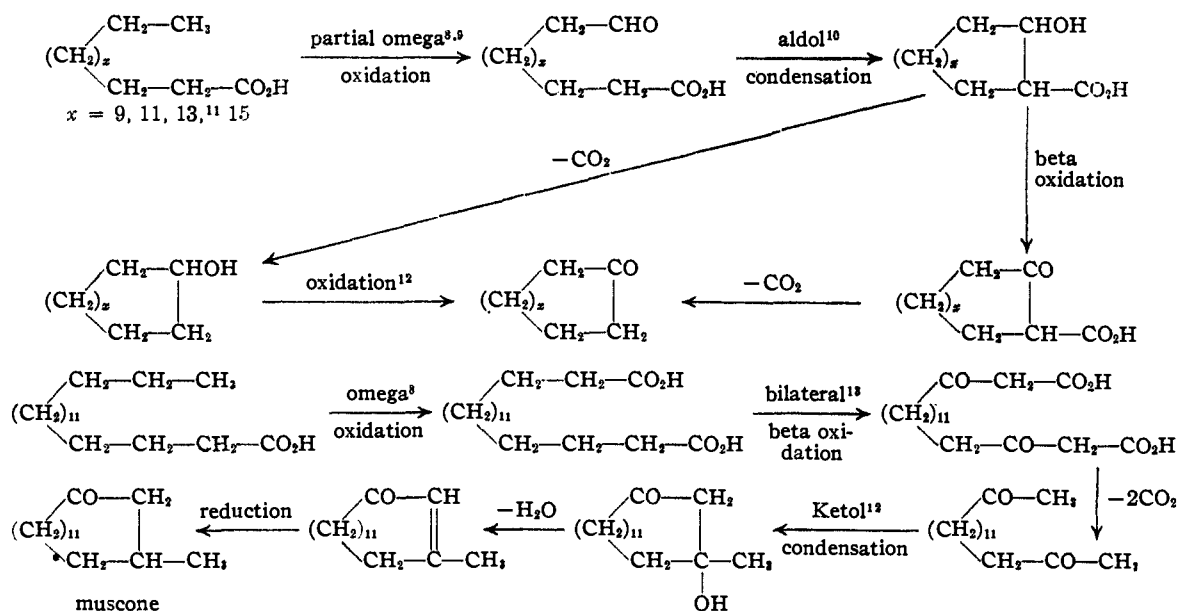
(2) And of course the corresponding carbinols.

TABLE II

Cyclotridecanone	M. p., °C.	°C.	B. p.	Mm.	M. p. of semicarbazone, °C.	M. p. of dibasic acid, °C.	Mixed m. p., °C.	M. p. of dimethyl ester, °C.
This paper	31-31.5	146		11	206-207	112.5-113 ^a	111-113 ^{b,c}	
Literature ^d	30-32	149		10	210-211	
Cyclononadecanone								
This paper	69-71	153		0.2	183.5-184.0	119-120	58.5-59.5	
Literature ^e	72	160		0.3	184	119-120.5	60.2 ^f	

^a Sintered at 112°. ^b Sintered at 110.5°. ^c Authentic brassylic acid,^g sinter 110.5°, m. p. 111-113°. ^d Ruzicka, Stoll, Huyser and Boekenogen, *Helv. Chim. Acta*, 13, 1152 (1930). ^e Ruzicka, Stoll and Schinz, *ibid.*, 11, 1174 (1928). ^f Chuit, *ibid.*, 9, 276 (1926).

group. A study of the reactions of the fatty acids reveals that it is possible to write for the above transformation a reasonable mechanism (first series of equations below); and muscone, the exception, can be derived by a variant of the general scheme, that of relating it to the C₁₈ acids instead of to palmitic acid as Ruzicka did (second series of equations).



(7) Thanks are due to the Emery Industries, Inc., Cincinnati, Ohio, for this sample of brassylic acid.

(8) Verkade and Van der Lee, *Rec. trav. chim.*, 54, 893 (1935); Flaschentrager and Bernhard, *ibid.*, 55, 278 (1936); Kuhn, Köhler and Köhler, *Z. physiol. Chem.*, 247, 197 (1937).

(9) The first step in ω -oxidation is undoubtedly the formation of a primary alcohol, which is then oxidized through the aldehyde to the acid. The occurrence of ω -hydroxy-pentadecanoic acid, juniperic and ambrettolic acids in certain plants, and aleuritic acid in shellac, is consistent with this hypothesis. Furthermore, if this partial oxidation is applied to linoleic acid, the formation of chaulmoogric acid may be envisaged as proceeding through a ring closure analogous to that of isopulegol from citronellal, followed by dehydration and selective hydrogenation.

(10) Analogous to the ring closure of dinitriles, Ziegler, Eberle and Ohlinger, *Ann.*, 504, 94 (1933).

(11) For civetone, use oleic acid.

(12) While the carbinols (from the muskrat) could arise from the ketones by reduction, yet because they (or their esters) constitute 98% of the large ring compounds it is quite possible that they are formed first. This could occur by decarboxylation of the β -hydroxy-acid intermediate as indicated above. The occurrence of civetol with civetone can be explained in the same manner. On the other

While large ring compounds related to capric and lauric acids would not be expected to be found in the scent glands, because such rings (C₉ and C₁₁) are formed with great difficulty, compounds with rings (C₂₁ and C₂₃) corresponding to the C₂₂ and C₂₄ acids might appear, and in substantial quantities, judging from the unusually high percentage of these acids present in the glands

(ref. c, Table I). However, except for a trace of a possible unsaturated C₂₁ ketone, none were found. Perhaps ω -oxidation (probably enzymatic) fails in the case of the extremely long chain acids, or the oxidized acids thus produced follow some other biological transformation.

Experimental Part

From every thousand pounds of glands, there was obtained from the distillation of the musk ketones, 77 g. of low-boiling forerun, and 155 g. of a high-boiling tail fraction.

The Low Boiling Material.—This had a cedar odor with a note of musk, $\alpha^26_D -0.23^\circ$. On rapid distillation through a modified Claisen flask, each unit of 77 g. yielded hand, the mechanism given above for the formation of muscone does not provide for prior carbinol formation and, in this connection, it may be significant that Ruzicka found no muscol accompanying muscone.

(13) Verkade and Van der Lee, *op. cit.*; Artom, *Z. physiol. Chem.*, 245, 276 (1937).

the following fractions at 0.3 mm.: A, 50–94.5° (7.2 g.); B, 94.5–98.5° (49.7 g.); C, 98.5–109° (7.5 g.); D, 109–117° (10 g. essentially cyclopentadecanone); E, residue (1 g.). Fraction B slowly distilled through an efficient 60-cm. column with a glass spiral gave at 0.2 mm.: F, 85.8–87° (5.8 g.); G, 87–89.1° (24.8 g.); H, 89.1–91° (12.3 g.); I, residue (5.9 g.). The semicarbazone (rhomboidal plates from methanol, *anal.* calcd. for $C_{14}H_{27}ON_2$: N, 16.6; found, N, 16.8) from fraction G (cyclotridecanone) on steam distillation from aqueous oxalic acid yielded the pure ketone, which was inert to aqueous potassium permanganate, gave no color with tetranitromethane, and absorbed bromine in acetic acid and carbon tetrachloride only after about thirty seconds and then with hydrogen bromide evolution. The odor was that of cedar with a faint musk. *Anal.* Calcd. for $C_{13}H_{24}O$: C, 79.5; H, 12.3. Found: C, 79.5; H, 12.0. Oxidation with chromic acid in acetic acid yielded an acid (recrystallized from ethyl acetate) which, by a mixed melting point determination, proved to be brassylic acid.

All the material boiling below 87° (0.2 mm.) was combined and refractionated through the same column at 10 mm., yielding: J, 82–101° (1.1 g.); K, 101–120° (2.6 g.); L, 120–125° (8 mm., 1.6 g.). Only fraction J yielded any semi-carbazone (and then in a very small amount), m. p. 119.5–121°, from methanol. This melting point suggested an open chain methyl ketone; and the nitrogen percentage of 21.9 was not far from that required for the semicarbazone of nonanone-2. Comparison with authentic samples,¹⁴ however, showed that it was not the semicarbazone of nonanone-2, nor of undecanone-2, but was possibly that of decanone-2,¹⁵ mixed m. p. 120–122.5° (semicarbazone of decanone-2, m. p. 122–123.3°). Conclusive proof of its structure must await a larger supply of material.

The High Boiling Material.—This viscous liquid, with no appreciable musk odor, $\alpha_D^{20} +0.36^\circ$, being mainly unoxidized carbinols, was first shaken with chromic acid in a benzene and dilute sulfuric acid suspension for twenty-four hours at about 25°. The neutral material was separated, dried, and fractionally distilled through a 100-plate Stedman column at 0.2 mm. Of each unit of 155 g., 140 g. was processed as above, yielding the following cuts: M, 90–131° (13.5 g.); N, 131–138° (37.8 g. essentially dihydrocivetone, which solidified on cooling); O, 138–146° (3.2 g.); P, 146–151° (5.8 g.); Q, 151–155° (28 g. solidified on cooling); R, 155–158° (4.8 g., partly solid); S, 158–165° (9.9 g.); T, 165–174° (2.7 g.); U, residue and hold-up (about 25 cc.).

Fraction Q (cyclononadecanone) was purified through the semicarbazone (rhomboidal plates, four times recrystallized from methanol; *anal.* calcd. for $C_{20}H_{40}ON_2$: N, 12.4; found, N, 12.4). The colorless and practically odorless ketone, regenerated by steam distillation from aqueous oxalic acid, was distilled *in vacuo*. *Anal.* Calcd. for $C_{19}H_{38}O$: C, 81.4; H, 12.9. Found: C, 81.6; H, 12.6. 3.2 g. of the ketone, treated with 2 g. of chromic acid in 100 ml. of acetic acid and 2.9 ml. of water at about 90° for twelve hours, yielded 1,19-nonadecane-dioic acid, which was recrystallized from ethyl acetate eight times. *Anal.* Calcd. for $C_{19}H_{38}O_4$: C, 69.5; H, 11.0. Found:

C, 69.4; H, 10.9. As no authentic specimen was available for comparison, the dimethyl ester was prepared using diazomethane, and was twice recrystallized from methanol. *Anal.* Calcd. for $C_{21}H_{40}O_4$: C, 70.7; H, 11.3. Found: C, 70.7; H, 11.0.

Fraction T yielded with semicarbazide only 0.54 g. of a crude semicarbazone, which, after nine recrystallizations from methanol, melted at 168–169.3° (cycloheicosanone semicarbazone melts at 177–178°).¹⁶ Steam distillation from aqueous oxalic acid gave a colorless ketone, the first part of which melted at 25°, the middle part at 18°, so that the semicarbazone represented a mixture. Accordingly fraction S was treated with semicarbazide and, as with fraction T, there was much non-ketonic material. The crude semicarbazones from both fractions were combined, reconverted to the ketones, using ethanolic aqueous hydrochloric acid, the alcohol removed by steam distillation, the ketones extracted with ether, and fractionally distilled through a 60-cm. micro-column with a glass spiral, yielding thus almost entirely cyclononadecanone, b. p. mainly 148–153.5° (0.2 mm.). The only higher boiling material was that left as hold-up. This was distilled over, appearing to boil at 165–175° (0.2 mm.). The semicarbazone after four recrystallizations from methanol, formed thin plates melting at 167–167.5°. The ketone was regenerated as before, and distilled *in vacuo*. The colorless oil obtained melted at 15–20°, gave a yellow color with tetranitromethane, and absorbed bromine in acetic acid immediately. *Anal.* Calcd. for $C_{21}H_{40}O$: C, 82.3; H, 12.5. Found: C, 83.0; H, 12.9. It is possible that this ketone is an unsaturated cycloheicosanone. The residue (fraction U) was distilled at 0.2–0.3 mm., yielding a small amount of a yellow oil boiling from 175–250°, from which no appreciable amount of a semicarbazone was obtained.

The residual material from the original distillation of the crude carbinols, which represented two-thirds of the total unseparable of the glands, was re-examined to see if any C_{23} or C_{25} ring compounds were present. Of this material (130 g.) from 2650 glands,¹ 109 g. was oxidized with chromic acid, and the neutral fraction (98.3 g.) was distilled in a simple Claisen flask. There was extensive decomposition, and it was not possible to maintain a pressure much below 1–2 mm. The distillate, 16.5 g., b. p. 140 (0.5 mm.)–250° (2 mm.) was quite mobile, and yielded on redistillation through a modified Claisen flask the following cuts: V, 77–147° (28 mm. 3 ml.); W, 65–118° (0.2 mm. 4–5 ml.); X, 118–165° (0.2 mm. 5.5 ml.); Y, 165–179° (0.2 mm. 1–2 ml.); Z, residue. Neither fraction Y nor the residue yielded any semicarbazone. Fraction Y had the composition $C_{16}H_{30}O$, and the residue had C, 85.4; H, 11.5.¹⁷ Obviously both were decomposition products, and no C_{23} nor C_{25} ketones were present.

Summary

1. Cyclotridecanone and cyclononadecanone have been isolated (after oxidation of the carbinol mixture) in small amounts from the scent glands of the muskrat.

2. A series of naturally occurring odd-numbered large ring compounds has been established, and a mechanism for their formation from the corresponding even-numbered fatty acids has been suggested.

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(16) Table II, ref. e.

(17) For these analyses thanks are due to R. A. Brooks and W. P. Pickhardt II, graduate students, Yale University.

(14) Thanks are due to P. R. Cunningham, P. L. Paulus and P. P. Van Ardel (Juniors, Yale University) for the preparation of the necessary ketones.

(15) Unless this ketone (if really decanone-2) is a product of processing the glands (which at present seems unlikely), it appears to be the second case known of the occurrence of a straight chain even-numbered methyl ketone in nature. Compare St. Pfau for the presence of decanone-2 in oil of rue (*Helv. Chim. Acta*, 15, 1267 (1932)). Thanks are due to Mr. A. Fiore of Givaudan-Delawanna, Inc., for this reference.