Chemical Artifacts from the Family *Labiatae*

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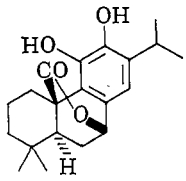
Carnosic acid, a derivative of ferruginol, is shown to be a major terpenic constituent of *Rosmarinus officinalis* L. A structure determination of rosmaricine, an alleged alkaloid of the plant, is presented. The ready oxidative conversion of carnosic acid into rosmaricine, carnosol, and other compounds of similar structure type is discussed.

While a few betaines have been isolated from the family *Labiatae*,[3] no alkaloids have been found in this plant source. Hence, the recent reports of the discovery of the alkaloid rosmaricine in *Rosmarinus officinalis* L.[4] seemed anomalous. The proposal of an apparently ferruginol-based part structure for this substance and the close botanical and chemical relationship of *R. officinalis* L. with several *Salvia* species, *e.g.*, the isolation of carnosol (**1**), a diterpenic compound of similar structure type,[5] from each of them, aroused our interest. As a consequence a determination of the structure of rosmaricine was undertaken.



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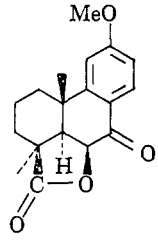
The Russian workers had shown rosmaricine to be a $C_{20}H_{27}NO_4$ γ-lactone which could be converted readily into an N,O,O-triacetyl derivative.[4] Diazomethane treatment of rosmaricine now yielded a dimethyl ether whose acetylation produced an N-acetyl derivative. The proton magnetic resonance (p.m.r.) spectra of the derivatives confirmed the presence of a ferruginoid isopropyl group and revealed two quaternary methyl functions and an aromatic hydrogen reminiscent of the carnosol system.[5] The spectra of the N-acetyl derivatives showed three downfield one-proton multiplets whose splittings patterns indicated the presence of a $-CO_2CHRCHR'NHAc$ function. On the assumption of the existence of a close structural relationship between carnosol (**1**) and rosmaricine, conversion of the latter into a derivative of the former was undertaken.

Deamination of rosmaricine dimethyl ether with nitrous acid yielded a hydroxy lactone whose manganese dioxide oxidation afforded a keto lactone. The latter also was obtained by hypochlorite oxidation of rosmaricine dimethyl ether, followed by acid hydrolysis. The infrared and ultraviolet spectra of the oxidation product were characteristic of those of a 7-keto 6-lactone, *e.g.*, the podocarpic acid derivative **2**.[6] Their p.m.r. spectra revealed diagnostic differences. The spectrum of a deuteriochloroform solution of lactone **2** showed a methoxy hydrogen singlet at 3.90, a C-11 H quartet at 6.78 (J = 2.5 and 1.0 c.p.s.), a C-13 H quartet at 6.85 (J = 2.5 and 9.0 c.p.s.), a C-14 H quartet at 7.83 (J = 9.0 and 1.0 c.p.s.), 4- and 10-methyl hydrogen singlets at 1.35 and 1.11, respectively, a C-5 H doublet at 2.35 (J = 5.8 c.p.s.), and a C-6 H doublet at 4.92 p.p.m. (J = 5.8 c.p.s.). The crucial 5- and 6-methine and nuclear methyl hydrogen signals of the spectrum of the keto lactone derived from rosmaricine possessed different chemical shifts: C-5 H broad singlet at 2.18, C-6 H broad singlet at 6.01, and methyl hydrogen singlets at 1.02 and 1.07 p.p.m. Furthermore, the less than 1-c.p.s. coupling between C-5 H and C-6 H indicated a nearly 90° dihedral angle relationship between these hydrogens, a stereochemical arrangement best described by the carnosol-related lactone **3a**. Zinc reduction of the lactone led to the keto acid **4**, previously prepared from carnosol (**1**).[7]



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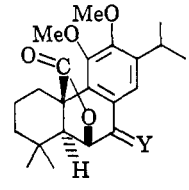
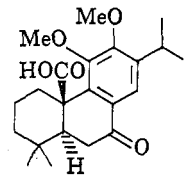


3a, Y = O
b, Y = NOH



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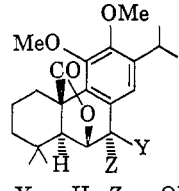
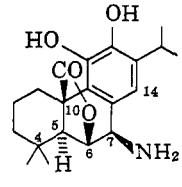
The hydroxy lactone product of the deamination of rosmaricine dimethyl ether (*vide supra*) proved to be a 7α-hydroxy compound (**5a**) in view of its nonidentity with the product **5b** of sodium borohydride reduction of the keto lactone **3a**, a process expected to lead to a 7β-hydroxy system. Oximination of the lactone **3a** yielded **3b** whose hydrogenation led to rosmaricine dimethyl ether (**5c**). Hence, rosmaricine possesses structure **6**.



5a, Y = H; Z = OH
b, Y = OH; Z = H
c, Y = NH_2; Z = H
d, Y = H; Z = OMe



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Rosmaricine's primary amino group, a rare functionality among alkaloids, seemed to mark the base as an artifact possibly resulting from the treatment of the

(1) NATO Postdoctoral Fellow, 1963–1964. A. F. wishes to thank the Deutscher Akademischer Austauschdienst for support of this work.

(2) National Science Foundation Cooperative Fellow, 1962–1965.

(3) *Cf.* W. W. Paudler and S. Wagner, *Chem. Ind.* (London), 1693 (1963).

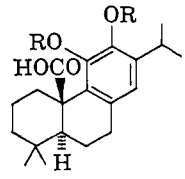
(4) L. D. Yakhontova and M. I. Anisimova, *Zh. Obshch. Khim.*, **32**, 1337 (1962); L. D. Yakhontova and A. D. Kuzovkow, *ibid.*, **33**, 308 (1963).

(5) C. H. Brieskorn, A. Fuchs, J. B. Bredenberg, J. D. McChesney, and E. Wenkert, *J. Org. Chem.*, **29**, 2293 (1964).

(6) E. Wenkert, P. Beak, R. W. J. Carney, J. W. Chamberlin, D. B. R. Johnston, C. D. Roth, and A. Tahara, *Can. J. Chem.*, **41**, 1924 (1963).

(7) C. H. Brieskorn and A. Fuchs, *Chem. Ber.*, **95**, 3034 (1962).

plant material with ammonia. When as a test of this hypothesis rosemary leaves were extracted without the use of ammonia, no rosmaricine or other basic substances could be detected among the plant constituents. Contrastingly, exposure of the same plant extracts to ammonia and air led to the production of rosmaricine. Exposure of the extracts to sodium carbonate solution yielded no rosmaricine. This confirmation of the artificial origin of the base necessitated a search for its nonnitrogenous precursor. On the assumption of the need for protection of the catechol system of the precursor, a hexane extract of rosemary leaves was acetylated and thereafter fractionated by column chromatography. The only substance isolated in appreciable quantity proved to be compound **7a**, first prepared by hydrogenolysis of carnosol diacetate[8] during the study of the structure elucidation of carnosol[5] and recently reported in an investigation of the constituents of *Salvia officinalis* L.[9] Exposure of an ethylene chloride solution of **7a** to aqueous ammonia for several days led to rosmaricine, characterized as its triacetyl derivative. Hence, the rosmaricine precursor and the actual natural product appears to be **7b**, herewith named carnosic acid. The latter was prepared for the first time by a boron tribromide induced demethylation[10] of the degradation product **7c** of carnosol.[5]



7a, R = Ac
b, R = H
c, R = Me

Having observed rosmaricine to be an oxidation product of carnosic acid (**7b**), it seemed reasonable to assume that carnosol might also be an artificially produced derivative thereof. Serious doubt regarding its natural product status derived from the observations of the presence of its diacetate in only a small extent among the products of acetylated extracts of rosemary leaves and its constant regeneration from solutions of extracts of sage.[11] The conversion of carnosic acid into carnosol by exposure of a methanolic solution of the acid to air for several weeks now confirmed this conjecture.

An investigation of rosemary oleoresin[12] designed to isolate further terpenic constituents, characterized as dimethyl ethers, led to the hydroxy lactone **5a** and its ether **5d** among other products. The C-7 stereochemistry of these substances was assigned on the basis of interpretation of the effect of their 7-oxygenated substituents on the chemical shifts of C-5 H and C-14 H.

Methylene chloride extraction of the leaves of *Salvia officinalis* L., followed by ammoniacal work-up, yielded rosmaricine not unexpectedly. This artificial production of the base from two species of the family *Labiatae* is reminiscent of the recently reported side-chain amination of quinones.[13] It would appear that carnosic acid (**7b**) functions as the main substrate for general oxidation leading to ferruginoid artifacts.[14]

(8) J. D. McChesney, unpublished observation.

(9) H. Linde, *Helv. Chim. Acta*, **47**, 1234 (1964).

(10) *Cf.* J. F. W. McOmie and M. L. Watts, *Chem. Ind.* (London), 1658 (1963).

(11) A. Fuchs, unpublished observation; *cf.* also A. I. White and G. L. Jenkins, *J. Am. Pharm. Assoc., Sci. Ed.*, **31**, 33 (1942).

(12) The authors thank Professor Brieskorn for a kind gift of the resin.

Experimental[15]

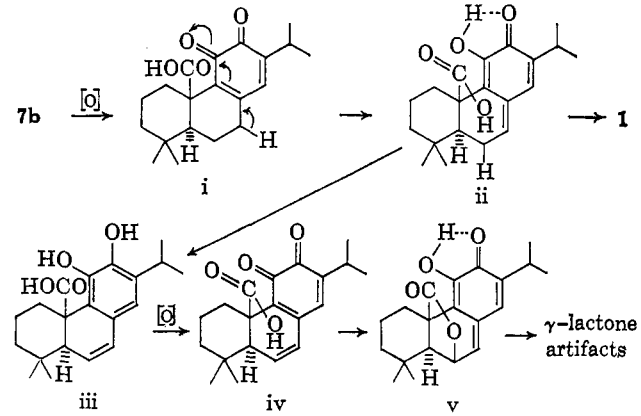
Extraction of *Rosmarinus officinalis* L. Leaves. A.—Isolation according to the reported procedure[4] (except the use of methylene chloride instead of ethylene chloride) yielded *ca.* 0.2% of crude rosmaricine (m.p. 200–205° dec.).

B.—Ground rosemary leaves (untreated with ammonia), 380 g., were extracted exhaustively with methylene chloride. This extract was washed repeatedly with 5% sulfuric acid and the layers separated. Basification of the acid extract with ammonia yielded no basic material upon extraction with chloroform. After acid washing, the methylene chloride extract was shaken repeatedly with 15% aqueous ammonia for 1 hr. Acidification of both organic and aqueous layers with 5% sulfuric acid, followed by extraction of the organic layer four times with fresh 5% sulfuric acid, yielded a dark aqueous extract. Basification with ammonia and extraction with chloroform gave *ca.* 100 mg. of basic material (identified by conversion to rosmaricine dimethyl ether). When 10% potassium carbonate solution was substituted for ammonia solutions in the above procedure, no basic material could be isolated.

Derivatives of Rosmaricine. A.—Acetylation of 70 mg. of crude rosmaricine with acetic anhydride in pyridine yielded rosmaricine triacetate. Fractional crystallization with hexane–ether indicated the presence of a mixture of triacetates whose chromatography on silica gel (impalpable powder) and elution with 1:1 hexane–ether gave 60 mg. of rosmaricine triacetate: m.p. 215–219° (lit.[4] m.p. 217–219°); infrared (Nujol), NH 2.98 (m), C=O 5.63 (s), 5.95 (s) μ; p.m.r., 3-proton singlets at 0.90 and 1.01 (C-4 methyls), 3-proton doublets at 1.12 and 1.14 (J = 7.0 c.p.s., isopropyl methyls), 3-proton singlets at 2.01, 2.27, and 2.30 (acetate methyls), 1-proton singlet at 2.07 (C-5 H), 1-proton doublet at 4.73 (J = 3.0 c.p.s., C-6 H), 1-proton quartet at 5.48 (J = 3.0 and 9.0 c.p.s., C-7 H), 1-

(13) D. W. Cameron, P. M. Scott, and Lord Todd, *J. Chem. Soc.*, 42 (1964).

(14) The oxidation of carnosic acid to ferruginoid artifacts most surely centers around the chemistry of the *o*-benzoquinone i formation in polar solvents. Thus, tautomerism of the quinone to the semiquinone ii may lead to the formation of the artifacts. Semiquinone ii may collapse upon itself by addition of the C-10 carboxyl group at C-7 yielding carnosol **1** or it may lose a proton at C-6 to yield Δ^6-carnosic acid iii. Oxidation of iii to a quinone iv followed by collapse of the C-10 carboxyl at C-6 yielding semiquinone v which may undergo nucleophile addition at C-7 leads to the γ-lactonic artifacts.



(15) All melting points are uncorrected. Infrared spectra were obtained on Perkin-Elmer spectrophotometers, Model 21 or 137B, with sodium chloride optics. The p.m.r. spectra were taken in dilute deuteriochloroform solution (with tetramethylsilane as internal standard) on a Varian Associates Model A-60 spectrometer. Optical rotations are of methanol solutions recorded on a Rudolph and Sons polarimeter, Model 70. Thin layer chromatography (t.l.c.) was run on 5 × 20 cm. or 20 × 20 cm. glass plates coated with silica gel G and developed with either wet chloroform or ethyl acetate. The spots were detected by means of iodine vapor.

proton broad doublet at 6.43 (J = 9.0 c.p.s., NH), and a 1-proton singlet at 7.23 p.p.m. (aromatic hydrogen).[16]

B.—Treatment of a methanolic solution of 490 mg. of crude rosmaricine with excess ethereal diazomethane for 2 days at room temperature yielded upon crystallization from 95% ethanol 260 mg. of rosmaricine dimethyl ether (**5c**): m.p. 215–218° upon sublimation; $[\alpha]^{22}D$ 34° (c 0.33); infrared (Nujol), NH 3.00 (m) and C=O 5.65 (s) μ; p.m.r., 3-proton singlets at 0.95 and 0.98 (C-4 methyls), 3-proton doublets at 1.20 and 1.20 (J = 7.0 c.p.s., isopropyl methyls), 3-proton singlets at 3.80 and 3.83 (methoxy methyls), 1-proton singlet at 1.94 (C-5 H), 1-proton doublet at 3.90 (J = 3.0 c.p.s., C-7 H), 1-proton doublet at 4.61 (J = 3.0 c.p.s., C-6 H), and a 1-proton singlet at 7.13 p.p.m. (aromatic hydrogen).

Anal. Calcd. for $C_{22}H_{31}NO_4$: C, 70.75; H, 8.37; N, 3.75. Found: C, 70.45; H, 7.99; N, 4.03.

C.—Acetylation of 30 mg. of rosmaricine dimethyl ether with acetic anhydride–pyridine yielded 32 mg. of crude N-acetylrosmaricine dimethyl ether. Crystallization from hexane gave colorless crystals: m.p. 200–203°; m.p. 205–207° after sublimation; infrared (Nujol), C=O 5.64 (s) and 6.10 (s) μ; p.m.r., 3-proton singlets at 0.92 and 1.00 (C-4 methyls), 3-proton doublets at 1.17 and 1.17 (isopropyl methyls), 3-proton singlet at 2.03 (N-acetyl methyl), 3-proton singlets at 3.77 and 3.81 (methoxy methyls), 1-proton singlet at 1.98 (C-5 H), 1-proton doublet at 4.70 (J = 3.0 c.p.s., C-6 H), 1-proton quartet at 5.60 (J = 3.0, 9.0 c.p.s., C-7 H), 1-proton doublet at 6.17 (J = 9.0 c.p.s., NH), and a 1-proton singlet at 6.93 p.p.m. (aromatic hydrogen).

Anal. Calcd. for $C_{24}H_{33}NO_5$: C, 69.37; H, 8.00; N, 3.37. Found: C, 69.27; H, 7.87; N, 3.34.

Degradation of Rosmaricine. A.—Treatment of a solution of 60 mg. of rosmaricine dimethyl ether and 30 ml. of 5% sulfuric acid, cooled in an ice bath, with 500 mg. of sodium nitrite gave 32 mg. of a precipitate which was removed by filtration. Basification of the filtrate caused precipitation of 12 mg. of basic material. Fractional sublimation in a gradient sublimator of the neutral precipitate yielded three zones, one as crystals and two as glasses. The crystalline zone was characterized as the deamination product **5a**: m.p. 205–208°; $[\alpha]^{23}D$ −6.5 (c 1.15); infrared (Nujol), OH 2.95 (s) and C=O 5.7 (s) μ; p.m.r., 3-proton singlets at 0.93 and 1.01 (C-4 methyls), 3-proton doublets at 1.19 and 1.19 (J = 7.0 c.p.s., isopropyl methyls), 3-proton singlets at 3.79 and 3.83 (methoxy methyls), 1-proton singlet at 2.18 (C-5 H), 1-proton doublet at 4.55 (J = 3.0 c.p.s., C-7 H), 1-proton doublet at 4.75 (J = 3.0 c.p.s., C-6 H), and a 1-proton singlet at 7.05 p.p.m. (aromatic hydrogen).

Anal. Calcd. for $C_{22}H_{30}O_5$: C, 70.56; H, 8.07. Found: C, 70.70; H, 7.95.

B.—Overnight stirring of 11 mg. of deamination product **5a** with 110 mg. of manganese dioxide in 10 ml. of anhydrous ether yielded 10 mg. of keto lactone **3a**: m.p. 120–121°; $[\alpha]^{23}D$ +65° (c 1.01); infrared (Nujol), C=O 5.60 (s) and 5.88 (s), C=C 6.30 (s) μ; p.m.r., 3-proton singlets at 1.01 and 1.07 (C-4 methyls), 3-proton doublets at 1.20 and 1.20 (J = 7.0 c.p.s., isopropyl methyls), 3-proton singlets at 3.81 and 3.89 (methoxy methyls), 1-proton singlet at 2.18 (C-5 H), 1-proton singlet at 6.02 (C-6 H), and a 1-proton singlet at 7.82 p.p.m. (aromatic hydrogen).

Anal. Calcd. for $C_{22}H_{28}O_5$: C, 70.94; H, 7.58. Found: C, 70.67; H, 7.51.

C.—Rosmaricine dimethyl ether, 140 mg., was dissolved in 40 ml. of methanol, a solution of 5 g. of potassium hydroxide in 5 ml. of water was added and the mixture was cooled in an ice bath. Chlorine was bubbled through the mixture until the pH approached neutrality (by litmus test). The reaction mixture was allowed to warm to room temperature over a period of 1 hr. The solution was acidified with 150 ml. of 2 N hydrochloric acid and extracted with ether. The extract was washed twice with water, dried over sodium sulfate and evaporated. Crystallization of the residue from methanol yielded 108 mg. of **3a**, whose physical properties were identical with those of the manganese dioxide oxidation product.

D.—A mixture of 88 mg. of keto lactone, 15 mg. of zinc dust, and 15 ml. of acetic acid was refluxed for 18 hr. The excess zinc was filtered, and the filtrate was partitioned between ether and water. The ether layer was washed five times with water, dried, and evaporated. The residue was crystallized from hexane yielding colorless crystals of keto acid **4**, m.p. and m.m.p. 215–218°, spectra identical with those of an authentic sample derived from carnosol.

Anal. Calcd. for $C_{22}H_{30}O_5$: C, 70.56; H, 8.07. Found: C, 70.65; H, 8.05.

E.—Reduction of 65 mg. of keto lactone **3a** in 20 ml. of anhydrous methanol with 100 mg. of sodium borohydride for 1 hr., followed by the usual work-up, yielded a solid whose crystallization from hexane, followed by sublimation, gave colorless needles of alcohol **5b**: m.p. 189–191°; $[\alpha]^{23}D$ +33° (c 0.74); infrared (Nujol), OH 2.87 (m) and 2.96 (m), C=O 5.70 (s) μ; p.m.r., 3-proton singlets at 0.95 and 1.00 (C-4 methyls), 3-proton doublets at 1.19 and 1.19 (isopropyl methyls), 3-proton singlets at 3.80 and 3.83 (methoxy methyls), 1-proton singlet at 1.93 (C-5 H), 2-proton broad singlet at 4.75 (width at half-height = 3.0 c.p.s., C-6 H and C-7 H), and a 1-proton singlet at 7.23 p.p.m. (aromatic hydrogen).

Anal. Calcd. for $C_{22}H_{30}O_5$: C, 70.56; H, 8.07. Found: C, 70.87; H, 7.71.

Partial Synthesis of Rosmaricine Dimethyl Ether.—Hydroxylamine hydrochloride, 150 mg., and 1 ml. of pyridine was added to a solution of 95 mg. of keto lactone **3a** in 2 ml. of absolute ethanol. The solution was refluxed for 2 hr. and thereupon the solvent was removed *in vacuo*. The residue was suspended in ice-cold water and filtered. Crystallization of the solid, 92 mg., from methanol yielded colorless needles of oxime **3b**: m.p. 256–258°; infrared (Nujol), OH 3.02 (m) and C=O 5.73 (s) μ; p.m.r., 3-proton singlets at 1.00 and 1.03 (C-4 methyls), 3-proton doublets at 1.20 and 1.20 (isopropyl methyls), 3-proton singlets at 3.80 and 3.85 (methoxy methyls), 1-proton singlet at 2.11 (C-5 H), 1-proton singlet at 6.05 (C-6 H), and a 1-proton singlet at 7.63 p.p.m. (aromatic hydrogen).

The oxime, 60 mg., was treated with acetic anhydride and pyridine and the resultant oxime acetate was hydrogenated over 5% palladium–charcoal in acetic acid solution at atmospheric pressure and room temperature for 24 hr. Extraction of the product with acid, followed by the usual work-up and crystallization from 95% ethanol, yielded 7 mg. of crystalline rosmaricine dimethyl ether (**5c**), identical in all respects with authentic material.

Carnosic Acid Diacetate (7a).—Extraction of 900 g. of ground *Rosmaricine officinalis* L. leaves with hexane in a Soxhlet extractor for 48 hr. gave 75 g. of green oil. Two treatments of the oil with hot methanol and filtration of the methanol-insoluble waxes yielded 45 g. of green solid. This solid was acetylated with acetic anhydride–pyridine, and 7.0 g. of acetylated extract was chromatographed on 350 g. of silica gel (50–200 mesh). Elution starting with hexane and progressing through 1:1 chloroform–ethyl acetate gave 2.27 g. of crude product. Rechromatography of the latter on silica (impalpable powder) using 1:1 benzene chloroform yielded a sharp green zone as the only major fraction. Crystallization from hexane gave 1.0 g. of colorless needles of **7a**, m.p. and m.m.p. 212–217° dec. (lit.[9] m.p. 196–215° dec.), identical with the carnosol degradation product below. The material isolated corresponded to *ca.* 0.7%, based on dry weight of plant material.

Carnosic Acid (7b).—To a solution of 480 mg. of **7c**[5] in 5 ml. of anhydrous methylene chloride cooled in a Dry Ice–acetone bath, there was added slowly a solution of 2 ml. of boron tribromide in 3 ml. of dry methylene chloride. The intensely purple solution was removed from the cooling bath and allowed to stand for 20 min. Solvent and excess reagent were removed under high vacuum, water was added, and the mixture was filtered. Crystallization of the crude material, 425 mg., from hexane gave colorless crystals of **7b**: m.p. 185–190° dec.; $[\alpha]^{23}D$ +191 (c 1.07); infrared (Nujol), OH 2.88 (m, sharp) and 2.99 (m, broad), C=O 6.06 (s) μ; p.m.r., 3-proton singlets at 0.89 and 1.00 (C-4 methyls), 3-proton doublets at 1.19 and 1.19 (isopropyl methyls), and a 1-proton singlet at 6.53 p.p.m. (aromatic hydrogen).

(16) Further elution with ether yielded 10 mg. of an isomer (probably isomeric at C-7): m.p. 286–287°; infrared (Nujol), identical (except for "fingerprint region") with spectrum of the above triacetate; p.m.r., 3-proton singlets at 0.90 and 0.95 (C-4 methyls), 3-proton doublets at 1.18 and 1.18 (J = 7.0 c.p.s., isopropyl methyls), 3-proton singlets at 2.03, 2.27, and 2.30 (acetate methyls), 1-proton singlet at 1.97 (C-5 H), 1-proton doublet at 4.72 (J = 3.5 p.p.m., C-6 H), 1-proton quartet at 5.20 (J = 3.5, 7.2 c.p.s., C-7 H), 1-proton broad doublet at 6.00 (J = 7.2 c.p.s., NH), and a 1-proton singlet at 7.17 p.p.m. (aromatic hydrogen).

Anal. Calcd. for $C_{20}H_{28}O_4$: C, 72.26; H, 8.49. Found: C, 72.33; H, 8.68.

Acetylation of **7b** with acetic anhydride–pyridine yielded diacetate **7a**: m.p. and m.m.p. 212–217°; infrared (Nujol), C=O 5.63 (s) and 5.9 (s) μ; p.m.r., 3-proton singlets at 0.85 and 0.95 (C-4 methyls), 3-proton doublets at 1.12 and 1.19 (isopropyl methyls), 3-proton singlets at 2.21 (acetate methyls), and a 1-proton singlet at 6.92 p.p.m. (aromatic hydrogen).

In Vitro **Formation of Rosmaricine.**—A solution of 350 mg. of carnosic acid diacetate in 100 ml. of ethylene chloride saturated with 30% aqueous ammonia was allowed to stand at room temperature in the dark with occasional shaking for 5 days. The organic layer was extracted three times with 5% sulfuric acid. The combined aqueous extracts were made basic with 5% aqueous ammonia and extracted with methylene chloride. The extract was washed three times with water, dried, and evaporated. The residue was acetylated immediately with acetic anhydride–pyridine. Usual work-up gave 150 mg. of a brown solid whose chromatography on 14 g. of silica (impalpable powder) and elution with hexane–ether mixtures yielded two triacetates, 68 mg. of rosmaricine triacetate, m.p. 215–219° (lit.[4] m.p. 217–219°), and its isomer, m.p. 286–287°. These compounds were identical with the triacetates derived from direct acetylation of crude rosmaricine.

In Vitro **Formation of Carnosol.**—A solution of 150 mg. of carnosic acid in 5 ml. of methanol was allowed to stand in the dark at room temperature for 3 weeks, whereupon crystals had separated. They were identified as carnosol by melting point, mixture melting point, and infrared (Nujol) spectral comparison.

Rosemary Oleoresin Lactones.—A methanol solution of 5 g. of oleoresin was exposed to an excess of ethereal diazomethane. Chromatography of 3 g. of the resulting methylated resin on 130 g. of silica (impalpable powder) and elution with 25-ml. fractions of hexane–ether mixtures of increasing polarity yielded first a lactone whose crystallization from methanol and subsequent sublimation afforded colorless crystals of **5d**: m.p. 171°; $[\alpha]^{23}D$ −5.0° (*c* 1.24); infrared (Nujol), C=O 5.64 (s) μ; p.m.r., 3-proton singlets at 0.95 and 1.00 (C-4 methyl), 3-proton doublets at 1.19 and 1.19 (isopropyl methyls), 3-proton singlets at 3.67, 3.78, and 3.80 (methoxy methyls), 1-proton singlet at 2.20 (C-5 H), 1-proton doublet at 4.28 (J = 3.0 c.p.s., C-7 H), 1-proton doublet at 4.72 (J = 3.0 c.p.s., C-6 H), and a 1-proton singlet at 6.97 p.p.m. (aromatic hydrogen).

Anal. Calcd. for $C_{23}H_{32}O_5$: C, 71.11; H, 8.30. Found: C, 71.74; H, 8.08.

Later fractions yielded colorless crystals of **5a**, m.p. and m.m.p. 205–208°, spectra identical with **5a** prepared by deamination of rosmaricine.

Tetrasodio Bis-β-diketones. Dicondensations with Electrophilic Compounds[1]

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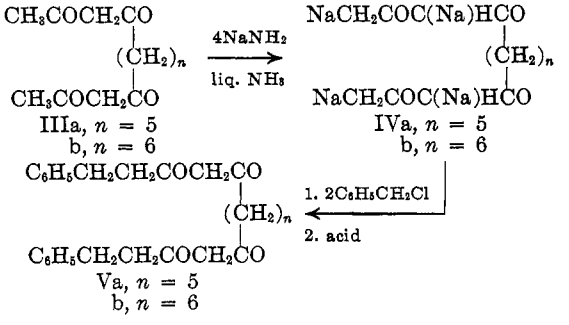
Certain bis-β-diketones of the type $(CH_3COCH_2CO)_2(CH_2)_n$ were converted by means of 4 mol. equiv. of sodamide in liquid ammonia to the corresponding tetrasodio salts, which were dialkylated with benzyl chloride to form the corresponding diterminal derivatives. One of the tetrasodio salts was also condensed at both terminal positions with methyl benzoate and benzophenone to give the corresponding diaroylation- and dialdol-type products, respectively. The diaroylation product was cyclized with ammonia to afford the dipyridone. Certain bis-β-diketones of the type $(C_6H_5COCH_2CO)_2(CH_2)_n$ were converted to their tetrasodio salts which were condensed with benzophenone or anisaldehyde to form, after treatment with methanolic acid, the dihydropyrones.

β-Diketones such as acetylacetone and benzoylacetone have previously been converted by 2 mol. equiv. of alkali amide in liquid ammonia to their dialkali salts I,[2,3] which were condensed with alkyl halides, aromatic esters, and aromatic ketones or aldehydes to form terminal derivatives. For example, I (R = CH_3, M = Na) was alkylated with benzyl chloride to give II.

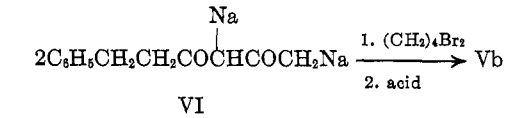
$RCOC(M)HCOCH_2M$ (I) $\qquad$ $RCOCH_2COCH_2CH_2C_6H_5$ (II)

Certain bis-β-diketones have now been converted by 4 mol. equiv. of sodamide in liquid ammonia to their tetrasodio salts, which were condensed with electrophilic compounds. Thus, bis-β-diketones IIIa, b



were converted to IVa, b, which were dialkylated with benzyl chloride to afford diterminal derivatives Va, b in yields of 67 and 62%, respectively.

Structures Va, b were supported by analysis and confirmed by independent synthesis (of Vb) involving twofold alkylation of disodio β-diketone VI with 1,4-dibromobutane as described recently.[4]



Tetrasodio salt IVa was treated with 1,3-dibromopropane to afford apparently poly(1,3-octanedione) (VII), the molecular weight of which indicated that n had an average value of 12–13.

$$+COCH_2CO(CH_2)_5+_n$$ (VII)

Tetrasodio salt IVa was diaroylated with methyl benzoate to give bis-β-triketone VIII in 30% yield; this reaction was effected in the presence of sodamide.[5]

(1) Supported by the Army Research Office (Durham).

(2) (a) C. R. Hauser and T. M. Harris, *J. Am. Chem. Soc.*, **80**, 6360 (1958); (b) R. J. Light and C. R. Hauser, *J. Org. Chem.*, **25**, 538 (1960); (c) *ibid.*, **26**, 1716 (1961); (d) K. G. Hampton, T. M. Harris, and C. R. Hauser, *ibid.*, **30**, 61 (1965).

(3) Such multiple dialkali salts have been employed without isolation; their carbanion resonance forms have generally been represented even though other resonance forms may make more important contributions to the structure of the anions.

(4) K. G. Hampton, R. J. Light, and C. R. Hauser, *J. Org. Chem.*, **30**, 1413 (1965).

(5) See S. D. Work and C. R. Hauser, *ibid.*, **28**, 725 (1963).