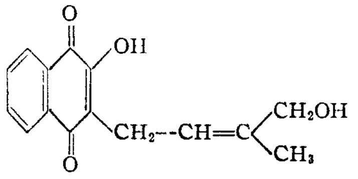
[CONTRIBUTION FROM THE MARIAN EDWARDS PARK LABORATORY OF BRYN MAWR COLLEGE]

A Synthesis of Lomatiol

BY MARSHALL GATES

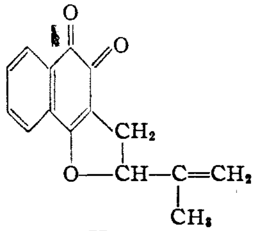
Lomatiol, the yellow coloring matter surrounding the seeds of several Australian species of *Lomatia*, was first investigated by Rennie[1] who, after demonstrating its close relationship to lapachol, left further investigation of the pigment to Samuel Cox Hooker. Hooker,[2] in a series of papers closely integrated with those describing his elegant work in the lapachol field, was able to show that the structure 2-hydroxy-3-(3′-hydroxymethyl-2′-butenyl)-1,4-naphthoquinone (I) is in complete harmony with the experimental facts. In the course of this work Hooker accomplished the conversion of lomatiol into lapachol.

We have now achieved the reverse transformation of lapachol into lomatiol, and, since lapachol has been prepared synthetically by several methods,[3,2b] this constitutes a synthesis of lomatiol. Our conversion made use of selenium dioxide oxidation of leucolapachol triacetate in the presence of acetic anhydride, essentially as described by Guillemonat,[4] to give a mixture containing both leucolomatiol tetraacetate and unchanged leucolapachol triacetate.[5] This crude product on saponification and air oxidation yielded a mixture from which lomatiol and lapachol were easily separated by chromatographic adsorption on magnesium sulfate. The lomatiol was fully identified by comparison with an authentic sample,[6] by conversion to its highly characteristic barium salts,[2b] and by conversion to dehydroiso-β-lapachone (II)[2b] which was compared with a sample prepared from authentic lomatiol.



I

Lomatiol



II

Dehydroiso-β-lapachone

Experimental Part[7]

Lomatiol.—Leucolapachol triacetate[8] (119 mg., m. p. 141–142.5°) dissolved in a mixture of 5 cc. of C. P. acetic anhydride and 3 cc. of glacial acetic acid (refluxed and distilled over chromium trioxide) was treated with 15 mg. of freshly sublimed selenium dioxide. There was no apparent action at room temperature, but on warming gradually to reflux during fifteen minutes the mixture darkened, the selenium dioxide began to go into solution and selenium, at first red, later black, began to separate. The mixture was held at reflux for twenty-five minutes, cooled and diluted with water. The precipitated oil was taken into peroxide-free ether, washed twice with water, twice with 2% sodium hydroxide, again with water, dried and concentrated. The residual clear pale-yellow very viscous oil (134 mg.) was dissolved in 5 cc. of methanol and treated with 5 cc. of water containing 2 g. of potassium hydroxide. The solution, which immediately became deep brown but quickly changed to deep red, was heated to reflux for ten minutes during which it was necessary to dilute with a small amount of water to redissolve some dark red oily sodium salt which had separated. After cooling the mixture was carefully acidified with 5% hydrochloric acid and the precipitated brown gummy solid was taken into peroxide-free ether, filtered from a small amount of insoluble material, washed twice with water, once with saturated brine, filtered through anhydrous sodium sulfate and concentrated. The residual brown very viscous oil (64 mg.) was taken into hot benzene (not entirely soluble), cooled and chromatographed on ignited magnesium sulfate. Development with benzene caused a broad yellow-tan band (1) followed by a thin, faint yellow band (2) to pass rapidly into the filtrate, and left three distinct bands on the column—toward the bottom a thin reddish band (3) overlain by a broad yellow band (4) and at the top a reddish-brown band (5)—which were sectioned out and eluted, (3) and (4) with ether, (5) with alcohol. Fractions 2 and 5 were discarded, fractions 1, 3 and 4 were concentrated and pumped out.

Fraction 1 (orange solid, 17 mg.) proved to be crude lapachol, and after three crystallizations from benzene-hexane, the final one with the aid of norite, yielded 5 mg. of beautiful bright yellow leaves, m. p. 139.2–139.8°, which did not depress the melting point of an authentic sample of lapachol of m. p. 139–140.3°.

Fraction 3 (yellow solid, 8 mg.) was sparingly soluble in benzene and gave no immediate red color with dilute aqueous potassium hydroxide, although on standing or fairly rapidly on heating a crimson color was produced with alkali. After boiling up twice with benzene the bright yellow material remaining insoluble melted with decomposition and the production of a blue-green color at 186–188°. It was not investigated further, although its properties indicate that it may be of the α-lapachone type.

Fraction 4 (orange solid, 21 mg.) was crystallized four times, once with the aid of norite, from benzene, in which it was rather sparingly soluble, to yield 11.5 mg. of beautiful bright yellow needles m. p. 127.3–128.5°, which did not

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[1] Rennie, *J. Chem. Soc.*, **67**, 784 (1895).

[2] Hooker, (a) *ibid.*, **69**, 1381 (1896); (b) THIS JOURNAL, **58**, 1181 (1936); (c) **58**, 1198 (1936); (d) **58**, 1207 (1936).

[3] Fieser, (a) THIS JOURNAL, **49**, 857 (1927); (b) Gates and Moesta, *ibid.*, **70**, 614 (1948).

[4] Guillemonat, *Ann. chim.*, [11] **11**, 147 (1939).

[5] It is of interest to note that even with the relatively complicated olefin represented by leucolapachol triacetate, the conditions recommended by Guillemonat (approximately 0.35 mole of selenium dioxide to 1 mole of ethylene) lead to much the same result obtained by him with simple ethylenes, *i. e.*, yields in the neighborhood of 30% for both product and unchanged ethylene.

[6] We are indebted to Professor Louis F. Fieser of Harvard University for a sample of lomatiol from the collection of the late Dr. Samuel Cox Hooker.

[7] All melting points are corrected.

[8] Monti, *Gazz. chim. ital.*, **45**, II, 53 (1915).

depress the melting point of an authentic sample[6] of lomatiol of m. p. 127.7–129°. It dissolved in dilute potassium hydroxide with a deep crimson color, and a drop of a solution of its barium salt, prepared as described by Hooker,[2b] allowed to evaporate on a microscope slide, exhibited the two characteristic forms and the highly characteristic behavior on rubbing described by him.

Dehydroiso-β-lapachone was prepared from a sample (7.1 mg.) of the synthetic lomatiol described above by the method of Hooker.[2b] After two crystallizations from dilute alcohol 3 mg. of orange-red needles were obtained which exhibited the following very characteristic melting point behavior. An initial melting point of 110–112° was observed (*cf.* refs. 1 and 2b) but if the capillary was held for some time at about 113° the material resolidified and then remelted at 115.2–116.2°. Likewise, if a freshly melted sample of the needles (m. p. 110–112°) was caused to solidify by brief removal from the bath it remelted at 115.2–116.2°. A precisely similar behavior was exhibited both by a sample of dehydroiso-β-lapachone prepared from an authentic sample[6] of lomatiol and by a mixture of the two. The lower of the two melting points corresponds to the metastable needles observed by Rennie,[1] whereas the higher corresponds to the stable prisms reported by Hooker. We have observed both forms, but have not had a sample composed exclusively of the prismatic form.

Summary

A conversion of lapachol to lomatiol has been accomplished.

BRYN MAWR, PENNSYLVANIA

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[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF NEW YORK UNIVERSITY]

Symmetrical Morpholinium Alkyl Sulfates

BY J. B. NIEDERL, H. W. SALZBERG AND J. J. SHATYNSKI[1]

Studies in the morpholinium type of "Invert Soaps"[2] have now been extended to those derived from symmetrical dialkyl sulfates and morpholines containing a long chain alkyl substituent on nitrogen.

Experimental

Dialkyl Sulfates.—Dimethyl and diethyl sulfates were commercial products; the others were prepared using the method of Barkenbus and Owen.[3]

N-Alkyl morpholines were prepared by refluxing equimolar quantities of morpholine and the appropriate alkyl bromide in absolute ethyl alcohol with anhydrous potassium carbonate for six hours. The solvent was distilled off, the residue washed with distilled water and the product distilled under reduced pressure.

Morpholinium sulfates were obtained by mixing equimolecular quantities of the alkyl morpholine and the dialkyl sulfate. With methyl sulfate the reaction was quantitative in the cold; with ethyl sulfate slight heating on a steam-bath was necessary; with *n*-butyl and *n*-hexyl sulfates prolonged heating in sealed ampules on a steam-bath was needed; and with hexadecyl sulfate prolonged refluxing of the reactants in toluene was required. The methyl sulfates were recrystallized from water in form of crystalline hydrates while the others were recrystallized from ethyl acetate.

Physiological.—In the phenol coefficient determinations using the U. S. Bureau of Standards technique toward *S. aureus*, the N-hexadecyl morpholinium series exhibited the maximum activity, reaching phenol coefficients of 500 to 600 depending on the *p*H of the solutions tested, with hardly any difference in the methyl, ethyl and *n*-butyl or *n*-hexyl sulfate series. Toward *E. typhosa*, the N-tetradecyl compounds showed the higher activity, the phenol coefficients being about 200. Equal activities toward both Gram-positive as well as Gram-negative microörganisms was reached with the hexyl sulfate compounds.

TABLE I

N-ALKYL MORPHOLINES AND MORPHOLINIUM SULFATES

R	R'	Formula	M. p., °C., (uncor.)	Analyses, % N Calcd.	Analyses, % N Found
		$O(CH_2CH_2)_2NR$			
Dodecyl	...	$C_{16}H_{33}NO$	15	5.72	5.70
Tetradecyl	...	$C_{18}H_{27}NO$	17	5.12	5.15
Hexadecyl	...	$C_{20}H_{31}NO$	40	4.65	4.68
Octadecyl	...	$C_{22}H_{35}NO$	25	4.25	4.31
		$[O(CH_2CH_2)_2NRR']SO_4R'$			
Dodecyl	Methyl[a]	$C_{18}H_{31}NSO_6$	47	3.59	3.52
Dodecyl	Ethyl	$C_{20}H_{33}NSO_5$	43	3.53	3.45
Dodecyl	*n*-Butyl	$C_{24}H_{47}NSO_5$	41	3.03	2.68
Dodecyl	*n*-Hexyl	$C_{28}H_{49}NSO_5$	160	2.74	2.93
Dodecyl	Hexadecyl	$C_{48}H_{99}NSO_5$	93	2.37	2.31
Tetradecyl	Methyl[a]	$C_{20}H_{35}NSO_5$	57	3.35	3.33
Tetradecyl	Ethyl	$C_{22}H_{37}NSO_5$	50	3.27	3.16
Tetradecyl	*n*-Butyl	$C_{26}H_{51}NSO_5$	90	2.86	2.52
Tetradecyl	*n*-Hexyl	$C_{30}H_{53}NSO_5$	167	2.59	2.71
Tetradecyl	Hexadecyl	$C_{50}H_{103}NSO_5$	127	2.26	1.88
Hexadecyl	Methyl[a]	$C_{22}H_{39}NSO_5$	68	3.19	3.21
Hexadecyl	Ethyl	$C_{24}H_{41}NSO_5$	64	3.08	3.03
Hexadecyl	*n*-Butyl	$C_{28}H_{55}NSO_5$	142	2.70	2.77
Hexadecyl	*n*-Hexyl	$C_{32}H_{57}NSO_5$	173	2.47	2.83
Hexadecyl	Hexadecyl	$C_{52}H_{107}NSO_5$	104	2.17	2.14
Octadecyl	Methyl[a]	$C_{24}H_{43}NSO_5$	81	2.96	2.88
Octadecyl	Ethyl	$C_{26}H_{45}NSO_5$	75	2.89	2.81

[a] Hydrate.

Acknowledgments.—The authors wish to express their appreciation for the phenol coefficient work involved in this investigation to Dr. C. T. Van Meter of Reed and Carnrick, Jersey City, N. J., and to Drs. F. E. Stirn and A. J. Weil of the Lederle Laboratories, Pearl River, N. Y.

Summary

A series of new symmetrical morpholium alkyl sulfates has been prepared and their phenol coefficients determined.

NEW YORK, N. Y.

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[1] Abstracted from the theses of Hugh W. Salzberg and John J. Shatynski presented to the Graduate School of New York University in partial fulfillment of the requirements for the degree of Master of Science, 1946. Presented before the Division of Organic Chemistry at the Atlantic City meeting of the American Chemical Society, April 16, 1947.

[2] J. B. Niederl and co-workers, THIS JOURNAL, **63**, 1476 (1941); **66**, 840 (1944); **67**, 1227 (1945).

[3] Barkenbus and Owen, *ibid.*, **56**, 1204 (1934).