The Dehydration of 4,4-Dimethyl-3-ethyl-2-Pentanol.—The dehydration of 4,4-dimethyl-3-ethyl-2-pentanol was effected by means of β-naphthalenesulfonic acid[14] in the following manner: A mixture of 86.5 g. (0.6 mole) of 4,4-dimethyl-3-ethyl-2-pentanol and 0.1 g. of β-naphthalenesulfonic acid (Eastman Kodak Company) was heated under the 25-plate column until a rapid reflux set in. After the removal of the foreshots (1.2 g.), an olefin-water mixture amounting to 77.2 g. distilled over at 128–129°, leaving a residue of 8.3 g. The olefinic material was dried over anhydrous sodium sulfate and redistilled. The dried product yielded 71.9 g. of unsaturated material, b. p. 129–132° (765 mm.), n^{25}D 1.4274.

Ozonolysis of the Dehydration Product.—The ozonolysis of the unsaturated material obtained above was carried out using a 60 cycle, 1-phase U. S. Ozone Company ozonizer. The ozonolysis of 71.9 g. of hydrocarbon was carried out using the procedure of Church, Whitmore and McGrew.[15] The oil layer was separated and allowed to stand over anhydrous sodium sulfate. The water layer gave a negative Tollens test for formaldehyde. The dried oily material, n^{25}D 1.4132, with a pronounced ketonic odor, was fractionated through a 25 × 0.8 cm. Whitmore–Lux column packed with $^3/_{64}$ inch glass helices and equivalent to 15 theoretical plates.

Identification of the Products of the Ozonolysis.—A small amount of material (0.8 g.) was obtained from the acetone–Dry Ice trap following the decomposition of the ozonide. It was identified as acetaldehyde by means of its 2,4-dinitrophenylhydrazone, m. p. and mixed m. p. 147°, and its semicarbazone, m. p. and mixed m. p. 162°. Fractionation of the ketonic oil above yielded the following substances: 3.7 g. of acetone, 2,4-dinitrophenylhydrazone, m. p. and mixed m. p. 126, semicarbazone, m. p and mixed m. p. 162°; 10.8 g. of ethyl isopropyl ketone, 2,4-dinitrophenylhydrazone, m. p. and mixed 145°, semicarbazone, m. p. and mixed m. p. 135–136°; and 40.0 g. of undehydrated 4,4-dimethyl-3-ethyl-2-pentanol, identified by its 3,5-dinitrobenzoate, m. p. and mixed m. p. 115–116°.

Summary

The dehydration of 4,4-dimethyl-3-ethyl-2-pentanol with β-naphthalenesulfonic acid yields 4,4-dimethyl-3-ethyl-2-pentene, the normal product, and 2,4-dimethyl-3-ethyl-2-pentene, the product of an intramolecular rearrangement, in the ratio of 3:4. The formation of the latter product is considered evidence that the 1,3-rearrangement of methyl groups may take place in the dehydration of highly-branched alcohols.

A synthesis of 4,4-dimethyl-3-ethyl-2-pentanol is presented, as well as the conditions for the optimum yield (56%) of methyl neopentyl ketone by the oxidation of diisobutylene.

4,4-Dimethyl-3-ethyl-2-pentanol, 4,4-dimethyl-3-ethylidene-2-pentanone, and ethyl-*t*-butylacetic acid have not been previously reported and their synthesis, properties, and the melting points of some of their derivatives are given.

NEWARK, DELAWARE RECEIVED OCTOBER 31, 1949

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[14] See Whitmore and Laughlin, THIS JOURNAL, **55**, 3732 (1933).

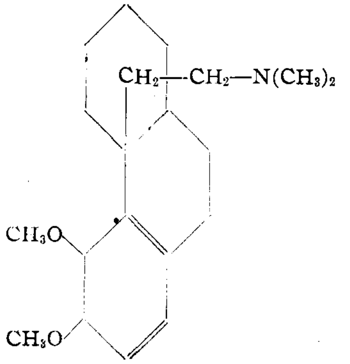
[15] Church, Whitmore and McGrew, *ibid.*, **56**, 176 (1934).

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF SMITH COLLEGE]

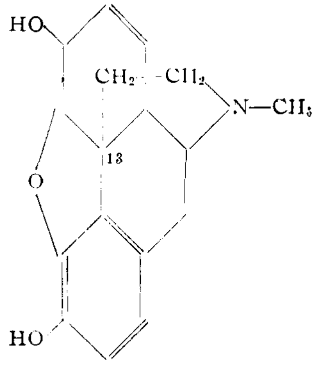
Syntheses in the Direction of Morphine. II.[1] Some Intermediates and Model Compounds

BY MILTON D. SOFFER, ROBERTA A. STEWART,[2a] J. CHARLES CAVAGNOL,[2b] HILDA E. GELLERSON AND ELIZABETH ANN BOWLER

Attention has been directed for some time[3] toward certain degradation products of morphine (*e. g.*, I[4]) whose synthesis by unambiguous methods would provide direct evidence concerning the main element of structure, in the Gulland and Robinson[5] formula (II), for which rigid experimental support has not yet been reported in the literature, *i.e.*, the attachment of the ethanamine chain to C_{13}. Many accomplishments in this direction, and toward morphine itself and re-



I



II

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[1] Soffer, Cavagnol and Gellerson, THIS JOURNAL, **71**, 3857 (1949).

[2] Present addresses: (a) Department of Chemistry, Wellesley College; (b) Department of Chemistry, University of Kentucky.

[3] Fieser and Holmes, THIS JOURNAL, **60**, 2548 (1938); **58**, 2319 (1936).

[4] Cahn, *J. Chem. Soc.*, 2565 (1926).

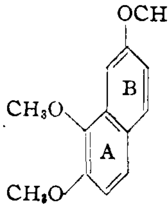
[5] *Mem. Proc. Manchester Lit. Phil. Soc.*, **69**, 79 (1925).

lated substances, have been reported recently.[6]

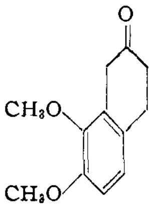
This paper describes the synthesis of 7,8-dimethoxy-2-tetralone[1] (IV) and certain 1,1-disubstitution products of 2-tetralone which may serve as model compounds (V, VI, VII) for the elaboration of the dimethoxytetralone in the direction of I.

2,7-Dihydroxynaphthalene was converted by established methods, with certain modifications, to 1,2,7-trimethoxynaphthalene[7] (III). Reduction[8] with sodium and alcohol and hydrolysis of the enol ether gave the crystalline ketone, whose structure was confirmed by oxidation to hemipinic acid.

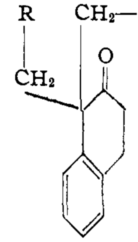
By analogy with other selective reductions with sodium and alcohol it was expected that the presence of a methoxyl group in the α position in ring A would enhance the reduction of ring B. This effect is well established in the case of the naphthols and naphthylamines where the presence of an hydroxyl or amino group in the β position directs reduction under similar conditions mainly to the substituted ring, and the presence of the same groups in the α position directs reduction almost entirely to the unsubstituted ring.[9] The products and yields obtained by Cornforth, Cornforth and Robinson,[8] and Grob and Jundt,[10] show that the effects of methoxyl groups in these positions are qualitatively the same as the effects of amino and hydroxyl groups.[11]



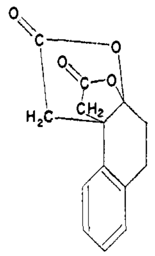
III



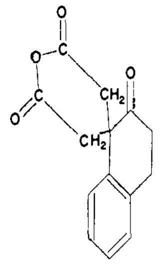
IV



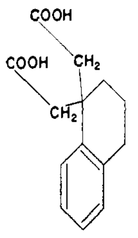
V, R = $COOCH_3$
VI, R = CN
VII, R = CH_2COOCH_3
VIII, R = H
IX, R = COOH
X, R = CH_2COOH



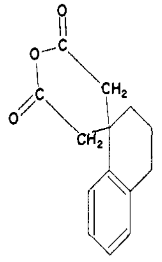
XI



XII



XIII



XIV

Compounds V, VI and VII were conveniently prepared by alkylation of 2-tetralone with methyl bromoacetate, chloroacetonitrile, or methyl β-bromopropionate, in the presence of sodium hydride and an inert diluent. These reactions proceeded in good yields, and there was no indication of any monosubstitution products. Although 5-methoxy- and 5,8-dimethoxy-2-tetralone undergo partial or exclusive dimethylation on proper treatment,[8,10,12] only monoalkylations have been reported previously from 2-tetralone directly.[8,13,14]

Alkylation with methyl iodide under essentially the same conditions also gave the disubstitution product (VIII) in good yield. The only simple derivative, suitable for identification purposes, which has been reported for 1-methyl-2-tetralone, is the semicarbazone, m. p. 200–202° (dec.).[8] The semicarbazone of the dimethyl product has almost identical properties (m. p. 200–204°, with dec.). Since the calculated analytical values for the mono- and dimethyl derivatives are close, we were reluctant to base the identification on combustion analyses alone,[15] although the complete data on the semicarbazone and dinitrophenylhydrazone were not ambiguous. However, a more reliable distinction between the two possibilities was obtained by titration of the p-carboxyphenylhydrazones.[16]

The evidence that monoalkylation of β-tetralone proceeds at C_1 rests upon methylation studies in which the point was firmly established[8] by in-

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[6] *E. g.*, Holmes, *et al.*, *Can. J. Research*, **22B**, 56, 109 (1944); THIS JOURNAL, **69**, 1996, 1998, 2000 (1947). MacDonald and Chechak, *ibid.*, **70**, 1972 (1948). Ghosh and Robinson, *J. Chem. Soc.*, 506 (1944). Koelsch, THIS JOURNAL, **67**, 569 (1945). Newman and Magerlein, *ibid.*, **69**, 942 (1947). Horning, *et al.*, *ibid.*, **69**, 2929 (1947); **70**, 2072, 2941, 2945 (1948); **71**, 1359 (1949). Baltrop, *J. Chem. Soc.*, 399 (1947). Gates, *et al.*, THIS JOURNAL, **70**, 2261 (1948); **72**, 228, 1141 (1950). Grewe, *Ber.*, **72**, 426, 785, 1314 (1939); **76**, 1072, 1076 (1943); *Naturwiss.*, **11**, 333 (1946); *Chemische Berichte*, **81**, 279 (1948); *Ann.*, **564**, 161 (1949). Schnider and Grussner, *Helv. Chim. Acta*, **32**, 821 (1949).

[7] The triether is a nicely crystalline substance, m. p. 38.5–39.5°, b. p. 133° at 1 mm. It has been described previously as an oil, with no statement of yield or physical properties (Chakravarti and Pasupati, *J. Chem. Soc.*, 1859 (1937)). Although the compounds in this series (through the triether) are known substances, they are described briefly in the experimental part because different reactions have been used or old ones have been improved and combined, and the early literature is in many cases incomplete and confused.

[8] Cornforth, Cornforth and Robinson, *J. Chem. Soc.*, 689 (1942).

[9] Gilman, ed., "Organic Chemistry," 2d ed., Vol. I, Fieser, p. 147 (1943); Green and Rowe, *J. Chem. Soc.*, **113**, 957 (1918); Waser and Mollering, *Org. Syntheses*, Coll. Vol. I, 2d ed., 499 (1941).

[10] Grob and Jundt, *Helv. Chim. Acta*, **31**, 1691 (1948).

[11] The effect of a substituted α-methyl group in the cases cited[8] is also consistent with these observations.

[12] Cornforth and Robinson, *J. Chem. Soc.*, 676 (1946).

[13] Andersag and Salzer, U. S. Patent 2,271,674 (1942).

[14] Baltrop, *J. Chem. Soc.*, 958 (1946).

[15] We also hesitated in this case to rely on a mixed melting point, in view of the decomposition at that temperature and the observation[10] that the semicarbazones of another pair of 1-methyl- and 1,1-dimethyl-2-tetralones gave no depression.

[16] Veibel, Blaaberg and Stevns, *Dansk. Tids. Farm.*, **14**, 184 (1940).

dependent syntheses. In the case of dialkylation it generally has been assumed[8,10,12] that the second group also enters in the 1-position.

That each of the present dialkylation products contains at least one substituent in the 1-position was supported by the fact that these products did not give the color reaction characteristic[8,10,12,17] of 2-tetralones bearing an unsubstituted 1-methylene group. Therefore proof that both substituents are on the same carbon atom (*vide infra*) demonstrates the 1,1-orientation.

Saponification of the diacetic ester (V) gave the unstable keto diacid (IX) which, although capable of transient existence in solution, could be isolated only as a stable anhydro derivative (XI). Acid hydrolysis of the dinitrile (VI) gave the same product. The substance is resistant to alcoholysis and hydrolysis in neutral or acid media and is also unaffected by sodium bicarbonate solution, but it is hydrolyzed by aqueous sodium hydroxide, consuming two equivalents of alkali.

The alternative keto anhydride structure (XII)[18] is ruled out first by the absence of ketone infrared absorption[19,20] which appeared as an intense band for all the other 2-tetralone compounds (2-tetralone, 5.83 μ; VIII, 5.84 μ; V, 5.82 μ[21]; VI, 5.84 μ[21]; VII, 5.83 μ[21]; X, 5.83 μ[21]), and further by the absence of the characteristic[20] anhydride maxima which were exhibited clearly by compound XIV (*vide infra*). In contrast, compound XI showed a strong band (5.52 μ) which is in the lactone region and may be assigned to the ketone hydrate dilactone structure.

The dilactone was inert to Clemmensen treatment and failed to react with ethyl mercaptan,[22] but did enter into the Wolff–Kishner reaction, giving in small yield the desoxydiacid, XIII (ir., 5.83 μ). The latter with acetyl chloride gave a carboxylic anhydride (ir., 5.54 μ, 5.68 μ) to which only formula XIV can apply, since the alternative structures consistent with substitution of at least one group at C_1 require an anhydride ring containing at least eight members.[23] This establishes the 1,1 orientation in compounds V, VI, and their derivatives, and by analogy in the other dialkylation products.

We hope to elaborate the readily available compounds V and VI, in the direction of I by substitution of a propionic ester chain for the ketone oxygen and cyclization to a 13-substituted hydrophenanthrene derivative. The utilization of VII involves a somewhat different route which we hope will lead to the analogous hydrophenanthrene with a propionic ester group in the aminoethyl (I) position.

We wish to express our appreciation to the Research Corporation for their support of this work through a Frederick Gardner Cottrell Special Grant-in-Aid.

Experimental[24]

1-Amino-2,7-dihydroxynaphthalene Hydrochloride.—A well-stirred solution of 240.2 g. (1.50 moles) of 2,7-dihydroxynaphthalene[25] in 250 ml. of 0.6 *M* sodium hydroxide (1.50 moles) was treated[26] with 110 g. (1.50 moles) of sodium nitrite and 360 ml. (4.0 moles) of 42% sulfuric acid. The brick-red suspension of **1-nitroso-2,7-dihydroxynaphthalene** was filtered and the product washed well with 0.1 *N* hydrochloric acid and with water. The wet product was usually used directly in the next step; the yield of dried material, m. p. 218° (dec.),[27] was 95-98%.

The purple-red nitroso compound is slightly soluble in ethanol, and the orange solution gives a brown color with aqueous ferric chloride or copper sulfate, a light green color with ferrous sulfate, orange-brown with nickel chloride, and bright red with cobalt chloride. The compound also gives a green color with concentrated hydrochloric acid and a cherry-red color with a 5% solution of sodium carbonate.

The moist nitroso compound was treated[28] with alkaline hydrosulfite, and the precipitated free base was taken up in hot hydrochloric acid and boiled with Norite. The chilled solution was saturated with gaseous hydrogen chloride and kept cold overnight in a nitrogen atmosphere. The crystalline hydrochloride[29] was dried thoroughly over calcium chloride; yield 230 g. (72.5% from 2,7-dihydroxynaphthalene). This yield is sufficiently reproducible so that it may be relied upon for calculation of the amount of reagents when the moist product is used directly in the next step.

In preliminary experiments less satisfactory results were obtained when the nitroso compound was reduced with stannous chloride in aqueous[27] or alcoholic[30] media and the amine stannichloride decomposed with hydrogen sul-

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[17] Colonge and Chambion, *Bull. soc. chim., France*, 1002 (1947).

[18] The keto diacid (IX) is related to two classes of labile dicarboxylic acids each of which is susceptible to elimination of water in a different way. β-Acylglutaric acids readily revert to their dilactones [Fittig, *et al., Ann.*, **314**, 1–96 (1901); Emery, *ibid.*, **295**, 94 (1897); *cf.* Volhard, *ibid.*, **267**, 51 (1892); Volander and Gartner, *ibid.*, **304**, 12 (1899); Quadrat-I-Khuda, *J. Chem. Soc.*, 713 (1929)] and β,β-dialkyl glutaric acids are unusually unstable with respect to their carboxylic anhydrides [Ingold, *ibid.*, **119**, 305 (1921); Bains and Thorpe, *ibid.*, **123**, 1210 (1923)]. *Cf.* the hypothetical acids corresponding to 3-methyl- and 3-phenyl-isoketocamphoric dilactone [Bredt-Savelsberg and Buchkremer, *Ber.*, **64**, 605 (1931); **66**, 1921 (1933)], and to cantharidine [Rudolph, *Arch. Pharm.*, **254**, 423 (1916); Woodward and Loftfield, This Journal, **63**, 3167 (1941)], and the dialkylmaleic anhydrides [Verkade, *Rec. trav. chim.*, **40**, 192 (1921)].

[19] We are indebted to Mr. Philip Sadtler of Samuel P. Sadtler and Son, Philadelphia, for the infrared determinations.

[20] Barnes, Gore, Liddel and Williams, "Infrared Spectroscopy," Reinhold Publishing Corp., New York, 1944; Randall, Fowler, Fuson and Dangl, "Infrared Determination of Organic Structures," D. Van Nostrand, New York, 1949. The solids were examined as Nujol mulls, the liquids in the free state.

[21] The polyfunctional compounds showed also the separate maxima for the other chromophores, *i. e.*, V, 5.76 μ (ester); VI, 4.45 μ (nitrile); VII, 5.77 μ (ester); X, 5.79 μ (carboxylic acid).

[22] Wolfrom and Karabinos, This Journal, **66**, 909 (1944).

[23] *Cf.* Blanc, *Compt. rend.*, **144**, 1356 (1907).

[24] The initial syntheses of some of the naphthalenic substances were carried out by Anne Willard (M.A. Thesis, 1946). In this connection we are also indebted to Elizabeth Hertz and Monica Riley.

[25] Prepared from sodium 2-naphthol-7-sulfonate by an adaptation of the method of Hartman (*Org. Syntheses*, Coll. Vol. I, 2 ed., 175 (1941)), and also by purification of a crude product generously supplied by E. I. du Pont de Nemours and Co. Material melting at 186° was found to be sufficiently pure.

[26] Marvel and Porter, *ibid.*, p. 411.

[27] Clausius reported material of m. p. "about 235°," but the yield was not stated (*Ber.*, **23**, 521 (1890)).

[28] Conant and Carson, *Org. Syntheses*, Coll. Vol. II, 33 (1943).

[29] The compound has been prepared previously in unspecified yield by stannous chloride reduction[27] (*vide infra*, *cf. Ber.*, **30**, 1123 (1897)), and also[7] by reduction (reagents and experimental data not stated) of the benzene azo compound (*cf. Ann.*, **399**, 42 (1913)).

[30] *Cf.* Goldstein and Genton, *Helv. Chim. Acta*, **20**, 1413 (1937).

fide or zinc turnings.[30] Hydrogenation with Raney nickel also gave inferior results. Reduction with zinc and acetic acid gave a 64% yield of crude amine hydrochloride, but the product had to be recrystallized with considerable loss before it could be used satisfactorily in the next step.

1,2,7-Trimethoxynaphthalene (III).[7]—A solution of 211.7 g. (1.00 mole) of the amine hydrochloride in 7.5 l. of water and 12 ml. of concentrated hydrochloric acid was clarified by the addition of 2.5 g. of sodium bisulfite (Norite) and treated[31] with 1000 ml. of a 2.2 *M* solution of ferric chloride containing 2.75 moles of hydrochloric acid. The blood-red suspension was filtered, and the precipitate was washed with water until the washings were free from iron salts.

The wet amorphous filter cake (**7-hydroxy-1,2-naphthoquinone**[7,27]; 91% dry yield; m. p. 194–197°) was suspended in 3330 ml. of water, and sulfur dioxide was bubbled through the mixture for three hours at 40°. At this point the *p*H was adjusted to about 5.5 by the addition of 50% sodium hydroxide solution, and 2.5 g. of sodium hydrosulfite was added after removal of a small amount of insoluble material. The solution was thoroughly extracted with ether, and the extract was washed with small portions of sodium bicarbonate solution containing a few crystals of sodium hydrosulfite. Removal of solvent, under nitrogen at reduced pressure, left 140 g. (79.5%) of light colored **1,2,7-trihydroxynaphthalene**,[32] m. p. 193–195°, which was sufficiently pure[33] for direct use in the next step.

A mixture of 176.2 g. (1.00 mole) of 1,2,7-trihydroxynaphthalene, 935 ml. (15.0 moles) of methyl iodide, 1000 ml. of dry acetone, and 830 g. of anhydrous potassium carbonate was refluxed for thirty-six hours in an atmosphere of nitrogen. The solution was decanted and the inorganic salts washed well with acetone. The volatile components were removed and an ether solution of the residue was washed well with alkali containing a little sodium hydrosulfite, and with water, and dried. Distillation of the residual oil gave 150 g. (85%) of colorless product, b. p. 133° at 1 mm., which crystallized in the receiver. The substance was readily recrystallized from petroleum ether, m. p. 38.5–39.5°.

Anal. Calcd. for $C_{13}H_{14}O_3$: C, 71.5; H, 6.5. Found: C, 71.4, 71.1; H, 7.0, 6.6.

The **picrate**[7] (from methanol) melted sharply at 113°.

Anal. Calcd. for $C_{19}H_{17}O_{10}N_3$: N, 9.4. Found: N, 9.55, 9.7.

7,8-Dimethoxy-2-tetralone (IV).—Over a period of one hour, 20.0 g. (0.87 mole) of sodium was added in portions to a solution of 21.8 g. (0.10 mole) of the foregoing triether in 200 ml. of absolute ethanol, while dry nitrogen was bubbled through the mixture. After hydrolysis[8] most of the ethanol was removed at reduced pressure in a nitrogen atmosphere. The aqueous solution was extracted with ether, and the washed ether extracts were evaporated to 50 ml. The concentrate was washed thoroughly with 15% sodium bisulfite solution, and the combined washings were saturated with sodium carbonate and extracted with ether. The washed and dried extract yielded 6.4 g. (31%) of crystalline material which melted sharply at 76° after recrystallization from hexane.

A considerable amount of unchanged 1,2,7-trimethoxynaphthalene was recovered, *via* the picrate, from the fraction remaining after the bisulfite extraction.

The product gave an intense purple-blue color in the "tetralone blue" test.[8]

Anal. Calcd. for $C_{10}H_8O(OCH_3)_2$: OCH_3, 30.1. Found: OCH_3, 29.5, 29.3.

The **semicarbazone**, recrystallized from methanol, melted at 191–191.5°.

Anal. Calcd. for $C_{13}H_{17}N_3O_3$: N, 16.0. Found: N, 16.5, 16.3.

The red **dinitrophenylhydrazone** melted sharply with decomposition at 167°.

Anal. Calcd. for $C_{18}H_{18}O_8N_4$: C, 56.0; H, 4.7; N, 14.5. Found: C, 55.7; H, 4.6; N, 15.0, 14.8.

Oxidation of 7,8-Dimethoxy-2-tetralone.—A mixture containing 10.00 g. of potassium permanganate, 0.3 g. of sodium carbonate, 300 ml. of water, and 1.00 g. of the ketone, was refluxed for one hour and allowed to stand at room temperature for three hours. After all permanganate was destroyed with sulfur dioxide, excess alkali was added and the manganese dioxide removed and washed with hot water. The aqueous solution, after washing with ether and addition of a few drops of hydrogen peroxide, was treated with Norite and evaporated. The residue was transferred with the aid of powdered sodium chloride to a Soxhlet extractor and leached with ether for thirty hours. The extract yielded 450 mg. of a gummy mixture which was separated into an unidentified crystalline material and a brown tar. Slow sublimation of the latter (130–160° at 1 mm.) and recrystallization from dry acetone gave 15 mg. of well formed needles which had the same melting point (166–167°) as **hemipinic anhydride**.[34]

Anal. Calcd. for $C_{10}H_8O_5$: C, 57.7; H, 3.9. Found: C, 57.25; H, 3.8.

The anhydride dissolved readily in alkali and on acidification gave the free acid, which crystallized on cooling: m. p. 177–179° (rapid heating), with effervescence. **Hemipinic acid** melts at "about 180°" under the same conditions.[35]

Anal. Calcd. for $C_{10}H_{10}O_6$: C, 53.1; H, 4.5. Found: C, 52.6; H, 4.45.

A sample of the acid was reconverted to almost pure anhydride (m. p. 165–167°) by heating at its melting point for ten minutes. A colorless solution of the anhydride in acetic acid showed a notable, pure blue fluorescence[34] in ultraviolet light, visible even in high dilution, and a weak violet-blue fluorescence in sunlight. The fluorescence was destroyed rapidly by addition of a small amount of aniline.

2-Tetralone was obtained essentially according to Cornforth, Cornforth and Robinson.[8] Although it was reported[8] that the substitution of propyl alcohol for absolute ethanol in the reduction step results in inferior yields, and that the reaction does not proceed in methanol, it was found that 95% ethanol could be used without sacrifice of yield and that 2-methoxynaphthalene could be satisfactorily replaced by the less expensive ethyl analog; yield 52%, b. p. 92° at 2 mm.

1,1-Di-(carbomethoxymethyl)-2-tetralone (V).—In a flame-dried, three-necked flask fitted with a mercury seal stirrer, a condenser, and a thermometer for measuring internal liquid temperature, was placed 150 ml. of anhydrous C. P. benzene, 45.13 g. (0.309 mole) of freshly distilled 2-tetralone, and 141.8 g. (0.927 mole) of methyl bromoacetate. An erlenmeyer flask, attached to one neck of the reaction vessel by means of a short piece of wide rubber tubing, contained 17.8 g. (0.74 mole) of sodium hydride. A three-way stopcock attached to the top of the condenser served as a nitrogen inlet and later as a hydrogen outlet. One arm of the stopcock was attached through a drying tube to either a mechanical gas meter or an apparatus for measuring volume by benzene displacement. The flask was immersed in an ice-bath and air was thoroughly swept from the system with dry nitrogen. The addition of a small amount of sodium hydride caused an immediate exothermic reaction. The sodium hydride was added over a period of one and one-half hours at such a rate that the temperature was not caused to exceed 20°. During this time the reaction mixture became cloudy and took on an

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(31) Fieser, *Org. Syntheses*, Coll. Vol. II, 430 (1943).

(32) Chakravarti and Pasupati[17] reported m. p. 197° (yield not stated).

(33) In another case, when an acid solution of the amine hydrochloride (prepared by reduction with stannous chloride and treatment[30] with metallic zinc) was treated with ferric chloride without preliminary separation or purification, the yield of quinone was 90%, but the product gave impure 1,2,7-trihydroxynaphthalene on subsequent reduction.

(34) Dobbie and Lauder, *J. Chem. Soc.*, **67**, 19 (1895).

(35) Perkin, *ibid.*, **109**, 922 (1916).

orange color which changed to purple and finally to gray. The flask was kept in the ice-bath four hours longer, at which point no more hydrogen was evolved. The mixture was refluxed for two and one-third hours causing a small additional evolution of the gas, making the total amount correspond to complete reaction.

Fifty milliliters of glacial acetic acid was added, followed by several drops of concentrated hydrochloric acid and 100 ml. of water. The mixture was extracted with large volumes of ether and the combined extracts were washed thoroughly with sodium bicarbonate solution, and with water, and dried. Removal of the solvent and excess methyl bromoacetate at reduced pressure gave the crude crystalline product in 98% (87.4 g.) yield. Recrystallization from ether–petroleum ether gave colorless well defined needles, m. p. 85.5–86°. Additional material recovered by distillation of the residues from the mother liquors made the total yield of pure keto diester 84.1 g. (94%). An analytical sample melted at 87.5–88°; b. p. 159° at 0.65 mm.

The crude and pure products both gave negative "tetralone-blue"[8] and ferric chloride tests, indicating that the final reaction mixture contained no unchanged 2-tetralone, or enolic products which might arise from Claisen condensation.

Anal. Calcd. for $C_{12}H_{12}O(COOCH_3)_2$: sapon. equiv., 145. Found: sapon. equiv., 140, 140.

In another experiment, potassium *t*-butoxide (from 7.8 g. (0.2 mole) of potassium and 180 ml. of anhydrous *t*-butyl alcohol) was used, instead of sodium hydride, with 7.3 g. (0.05 mole) of 2-tetralone and 38.25 g. (0.25 mole) of the bromoester. The crude viscous residual oil from the neutral fraction vitrified at −80° and could not be crystallized by the usual methods. Saponification, however, gave the diacid as crude crystalline dilactone (XI) (*vide infra*) in 92.5% (11.3 g.) yield.

The **diester semicarbazone** was prepared in 92% yield by the pyridine method, with absolute methanol. Recrystallization from aqueous methanol, and from benzene, gave the pure product, m. p. 157–157.5°.

Anal. Calcd. for $C_{17}H_{21}O_5N_3$: C, 58.8; H, 6.05; N, 12.1. Found: C, 59.4, 59.0; H, 6.35, 5.95; N, 12.4, 12.5.

1,1-Di-(cyanomethyl)-2-tetralone (VI).—The apparatus and technique were similar to that described for the keto diester (I). Twenty-four grams (1.0 mole) of sodium hydride was added in small portions, over a period of five hours, to a solution of 48 g. (0.32 mole) of 2-tetralone and 74.3 g. (0.98 mole) of chloracetonitrile in 150 ml. of anhydrous ether, cooled in an ice-bath. After one more hour at 0°, and the addition of 250 ml. of anhydrous ether, the solution was allowed to come to room temperature. The stirring was continued overnight although the hydrogen evolution ceased after a total reaction time of seven hours, when the theoretical amount of gas had been evolved.

Sixty milliliters of glacial acetic acid was added with vigorous stirring, followed cautiously with 70 ml. of water and 70 ml. of concentrated hydrochloric acid. The crystalline precipitate was filtered and washed with water and ether, until the washings were colorless. The vacuum-dried product was relatively pure, m. p. 135–136°; yield, 65.5 g. (91%). The melting point was not changed by recrystallization from methanol, ethanol, or benzene. In preliminary experiments at higher temperatures in xylene and benzene under different conditions, less satisfactory yields (0–87%) were obtained.

Anal. Calcd. for $C_{14}H_{12}ON_2$: C, 75.0; H, 5.4; N, 12.5. Found: C, 75.5, 75.5; H, 5.1, 5.2; N, 13.2, 12.95.

The **dinitrile semicarbazone** was prepared in pyridine–absolute ethanol, and recrystallized from aqueous and absolute ethanol; m. p. 214° (dec.).

Anal. Calcd. for $C_{15}H_{15}ON_5$: N, 24.9. Found: N, 25.0, 24.8.

1,1-Di-(β-carbomethoxyethyl)-2-tetralone (VII).—This preparation was carried out as described for the previous diester, using 10.00 g. (0.0685 mole) of 2-tetralone, 57.20 g. (0.3425 mole) of methyl β-bromopropionate, 50 ml. of anhydrous benzene, and 6.58 g. (0.274 mole) of sodium hydride. As in the previous cases, the addition of the hydride produced an immediate exothermic reaction, but the temperature was maintained for the most part at 10–20°. Benzene was added as needed to facilitate stirring. After treatment with acid and ether, and washing with aqueous sodium bicarbonate as usual, the solvent and excess methyl β-bromopropionate were removed from the neutral extract at reduced pressure. The residual viscous oil (18.84 g.) gave a negative test with ferric chloride, but gave an intense blue color with alcoholic sodium hydroxide, indicating the presence of unreacted 2-tetralone.

Ice and 2% aqueous sodium hydroxide were added to an ethereal solution of the product in a separatory funnel, and a stream of compressed air was bubbled through the mixture to complete the oxidation[36] of the 2-tetralone, and to provide the necessary agitation. The aqueous layer was drawn off and replaced with fresh alkaline solution, and the process was repeated until that treatment failed to produce the characteristic blue color. The washed and dried ether extract gave 15.80 g. (72.5%) of crude keto diester as a viscous, yellow residual oil.

For further purification the diester was converted to the acid by refluxing with aqueous potassium hydroxide in the usual way. The crude product was obtained by precipitation from the washed solution and, further, by extraction of the aqueous acid filtrates. The total yield of crystalline material melting over 173° was 13.71 g. (96%). Recrystallization from water, and from methanol–benzene, gave pure **1,1-di-(β-carboxyethyl)-2-tetralone** (**X**), m. p. 182–183°. The substance is soluble in methanol, 95% ethanol, and in hot water; insoluble in benzene.

Anal. Calcd. for $C_{14}H_{16}O(COOH)_2$: neut. equiv., 145. Found: neut. equiv., 145, 146.

Four grams (0.0138 mole) of the pure keto diacid was reconverted to the ester by refluxing for six hours with 100 ml. of absolute methanol and 3 ml. of concentrated sulfuric acid. Methanol was removed at reduced pressure and the neutral product isolated in the usual way. The entire residual oil was obtained as a viscous water-white distillate, b. p. 187° at 0.28 mm.; 4.30 g. (98%).

Anal. Calcd. for $C_{14}H_{16}O(COOCH_3)_2$: C, 67.9; H, 7.0; saponif. equiv., 159. Found: C, 68.55, 68.3; H, 6.8, 6.65; saponif. equiv., 156.

The **diester semicarbazone** was prepared in the presence of pyridine and methanol in the usual way. Recrystallization from methanol gave material of constant melting point, 120–122°. After further recrystallization from benzene, the melting point was 111–113° and remained unchanged upon repeated recrystallization from that solvent. Drying for sixteen hours at 0.05 mm. and 80° caused reversion to the constant value, 121.5–122°. The substance may be polymorphic, or form a labile solvate with benzene.

Anal. Calcd. for $C_{19}H_{25}O_5N_3$: C, 60.8; H, 6.7. Found: C, 60.8, 60.85; H, 6.55, 6.4.

1,1-Dimethyl-2-tetralone (VIII).—The reaction was carried out as described in this paper, using 8.21 g. (0.056 mole) of 2-tetralone, 8.7 ml. (0.14 mole) of methyl iodide, 40 ml. of anhydrous benzene and 4.3 g. (0.17 mole) of sodium hydride. The reaction was immediate and exothermic, and the addition of the sodium hydride was spread out over forty-five minutes while the temperature was kept below 25°. Stirring was continued for one and one-half hours at room temperature and for one hour at reflux temperature. The hydrogen evolution was approximately stoichiometric for dialkylation.

The mixture was treated with acid and worked up for the neutral fraction in the usual manner. The product distilled as a colorless oil, b. p. 73–77° at 0.1 mm. (7.8 g.,

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(36) This application of the tetralone-blue reaction results from the observation that although "tetralone-blue" distributes itself in favor of benzene[8] in the presence of aqueous alkali, the selectivity is reversed when the organic solvent is ether.

80%), and gave a negative tetralone-blue test. For further purification[8] the liquid was stirred overnight with 50 ml. of saturated aqueous sodium bisulfite, and washed and dried as usual. The distillate weighed 7.0 g. (72%); b. p. 92–96° at 0.5 mm., $d^{22.5}_4$ 1.045, n^{20}_D 1.538.

The **semicarbazone**, recrystallized from 95% ethyl alcohol, melted with decomposition at 200–204°.

Anal. Calcd. for $C_{13}H_{17}ON_3$: C, 67.5; H, 7.4; N, 18.2. Found: C, 67.7, 67.5; H, 7.55, 7.1; N, 18.2, 18.3.

The **2,4-dinitrophenylhydrazone**, prepared in the usual way, was recrystallized from ethanol and from benzene–petroleum ether; m. p. 140–141°.

Anal. Calcd. for $C_{18}H_{18}O_4N_4$: C, 61.0; H, 5.1; N, 15.8. Found: C, 60.7, 60.8; H, 5.05, 4.7; N, 16.3, 16.1.

A solution prepared by heating 1.5 g. of *p*-hydrazinobenzoic acid with 40 ml. of water and 1.0 ml. of concentrated hydrochloric acid, was refluxed for thirty minutes with 35 ml. of ethanol and 1.0 g. of the ketone. The ***p*-carboxyphenylhydrazone** melted (rapid heating) at 218–220° (dec.), after treatment with Norite and three recrystallizations from aqueous ethanol.

Anal. Calcd. for $C_{18}H_{19}N_2COOH$: neut. equiv., 308. Found: neut. equiv., 309, 310.

1,1-Di-(carboxymethyl)-2-tetralone Hydrate Dilactone (XI).—Ninety-nine grams of the keto diester (I) was saponified by refluxing for two and one-half hours with 15% aqueous potassium hydroxide. The alkaline solution was washed with benzene and ether, and acidified with concentrated hydrochloric acid. The turbid solution was extracted with ether and the extracts were washed with water and dried over anhydrous magnesium sulfate. Removal of solvent at reduced pressure gave 83 g. (100%) of crude crystalline material, which melted at 140–140.5° after recrystallization from 95% ethanol.

Anal. Calcd. for $C_{14}H_{12}O_4$: C, 68.8; H, 4.95; neut. equiv., 122; mol. wt., 244. Found: C, 68.6, 68.7; H, 4.7, 4.7; neut. equiv., 120, 120; mol. wt. (Rast), 256.

The same product was obtained from the keto dinitrile (1.06 g.), by refluxing for twelve hours with concentrated hydrochloric acid, adding fresh portions of acid periodically. The crystalline alkali-soluble material (0.54 g., 47%) was isolated by the usual extraction procedure and recrystallized from ethanol; m. p. 140–141°; m. m. p. 140–141°.

The crystals are insoluble in aqueous sodium bicarbonate. They dissolve immediately in hot dilute sodium hydroxide, and are only slowly soluble in the cold. The determinations of the neutral equivalent were carried out by boiling for fifteen minutes with excess 0.1 *N* alkali and titrating back with acid.

When an alkaline solution of the dilactone, *e. g.*, from the above titration mixtures (and also from the titration mixtures from the saponification of the keto-diester (V)) was mixed with excess dilute acid and quickly extracted with ether, nearly all of the original dilactone was subsequently recovered by immediate sodium bicarbonate extraction followed by acidification and re-extraction with ether; only a very small amount of organic residue, together with phenolphthalein indicator, was obtained from the ether extract from which bicarbonate-soluble material had been removed. When, on the other hand, the dilactone itself was dissolved in ether and washed well with bicarbonate, an almost quantitative recovery of the starting material was made from the washed ether solution. It is apparent that the diacid (IX) is actually formed under these conditions and is capable of at least transient[37] existence in aqueous and ethereal media.

The dilactone was recovered unchanged after refluxing for fourteen hours with absolute methanol in the presence of concentrated sulfuric acid, and was likewise unaffected by long boiling with ethanol, water, or concentrated hydrochloric acid. The substance was recovered unchanged in good yield after refluxing twelve days with hydrochloric acid and amalgamated zinc (or forty-four hours with the toluene modification). It also failed to react with ethyl mercaptan, even under drastic conditions.

1,1-Di-(carboxymethyl)-1,2,3,4-tetrahydronaphthalene (XIII).—A solution of 33.0 g. (0.14 mole) of the anhydro compound, and 84 g. (1.26 moles) of potassium hydroxide in 700 ml. of diethylene glycol was treated[38] with 70 ml. (1.4 moles) of hydrazine hydrate at *ca.* 200°. Water was added and the clear solution was saturated with carbon dioxide, causing the precipitation of a large amount of an unidentified nitrogenous product. The filtered bicarbonate solution, washed with chloroform and worked up for the acid fraction, gave 1.52 g. (4.5%) of the crystalline dicarboxylic acid. Treatment with Norite and recrystallization from benzene–petroleum ether (b. p. 90–100°), and from water, gave beautiful long needles, m. p. 162–162.5°.

Anal. Calcd. for $C_{14}H_{16}O_4$: C, 67.7; H, 6.45; neut. equiv., 124. Found: C, 67.95; H, 6.4; neut. equiv., 123, 123.

1,1-Di-(carboxymethyl)-1,2,3,4-tetrahydronaphthalene anhydride (XIV) was prepared by refluxing 200 mg. of the diacid with 5 ml. of acetyl chloride for three hours. Volatile material was removed at reduced pressure, and the residue (which sublimes readily) was recrystallized from hexane or petroleum ether (b. p. 90–100°). The delicate, pure white needles weighed 185 mg. (76%); m. p. 121–122°.

Anal. Calcd. for $C_{14}H_{14}O_3$: C, 73.0; H, 6.1; neut. equiv., 115. Found: C, 73.0, 73.0; H, 6.2, 6.0; neut. equiv., 116, 117.

Summary

The preparation of 7,8-dimethoxy-2-tetralone from 2,7-dihydroxynaphthalene is described.

1,1-Disubstituted derivatives were conveniently prepared from 2-tetralone by reaction with various halides in the presence of sodium hydride.

The products are of interest as possible intermediates for the synthesis of substances containing elements of the morphine structure.

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[37] In separate experiments it was shown, by the same extraction procedure, that the diacid in ether solution slowly reverts to the anhydro derivative; during a period of two weeks the ratio of neutral to acidic material changed progressively from 0.13 to 2.33. Rough kinetic data are in accord with a unimolecular reaction. In aqueous media, 90% conversion was effected by boiling for thirty minutes with dilute hydrochloric acid.

[38] Soffer, Soffer and Sherk, THIS JOURNAL, **67**, 1435 (1945); Huang-Minlon, *ibid.*, **68**, 2487 (1946).