[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

Preparation and Reactions of 2-Acyl-3-hydroxy-1,4-naphthoquinones[1]

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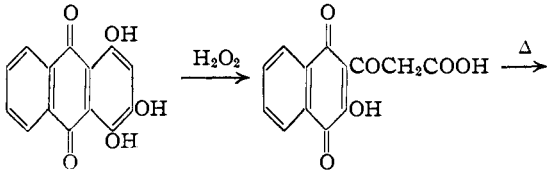
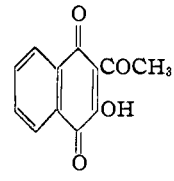
The growing importance of quinones as compounds of pharmaceutical and biological interest stimulated the present investigation of the preparation and reactions of 2-acyl-3-hydroxy-1,4-naphthoquinones. These substances, as well as compounds from which they are prepared, offer starting points from which a large variety of other quinones can be prepared, and the polyfunctional character of these substances has led in some cases to unexpected and interesting chemical reactions.

After the present study had been completed, several methods of synthesis of this type of compound were reported.[3] Previous to this work, only the simplest member, 2-acetyl-3-hydroxy-1,4-naphthoquinone (I), was known and had been prepared by the oxidation of purpurin.[4]

Repetition of the oxidation of purpurin resulted in a small yield of quinone I, as well as one of the precursors of this substance, the acid, II, which was converted to I through the action of heat.



II



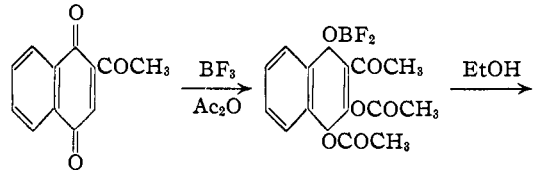
I

Treatment of 1,2,4-triacetoxynaphthalene with aluminum chloride resulted in a small yield of 2-acetyl-3-acetoxy-1,4-naphthohydroquinone (III), whose structure was demonstrated by synthesis from I. The hydroxyl group in I was acetylated by treatment of the silver salt with acetyl chloride to give 2-acetyl-3-acetoxy-1,4-naphthoquinone, reduction of which produced III. Compound III was also produced by reduction of I to 2-acetyl-3-hydroxy-1,4-naphthohydroquinone, which in turn was partially acetylated to give III. Further acetylation of III as well as the reductive acetylation of I produced 2-acetyl-1,3,4-triacetoxynaphthalene.

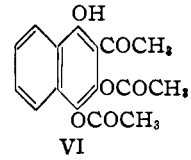
A Fries rearrangement of 1,4-diacetoxynaphthalene resulted in a poor yield of 2-acetyl-4-acetoxy-1-naphthol, which was also synthesized by the reduction of 2-acetyl-1,4-naphthoquinone[5] (IV) and partial acetylation of the product. Complete acetylation of 2-acetyl-4-acetoxy-1-naphthol produced 2-acetyl-1,4-diacetoxynaphthalene, which was also obtained by the reductive acetylation of 2-acetyl-1,4-naphthoquinone.

The most generally applicable approach to the synthesis of 2-acyl-3-hydroxy-1,4-naphthoquinones is illustrated by the following series of reactions. The compound 2-acetyl-4-acetylamino-1-naphthol[6] was oxidized with concentrated nitric acid in glacial acetic acid solution to produce good yields of 2-acetyl-1,4-naphthoquinone (IV).[7] An attempt was made to introduce a hydroxyl group into quinone IV by oxidation with hydrogen peroxide, but the oxide was obtained in only poor yields.

A new and general procedure for the introduction of a hydroxyl group into the 3-position of 2-acyl-1,4-naphthoquinones has been developed. When IV was subjected to a modified Thiele[8] reaction (boron trifluoride etherate as catalyst), the boron fluoride containing compound V separated from the reaction mixture, and was converted



IV V



VI

with boiling ethanol into VI. The structure of this diacetate was demonstrated in the following manner. Acetylation of 2-acetyl-3-acetoxy-1,4-naphthohydroquinone under mild conditions pro-

(1) This problem was assigned to the author by Dr. Louis F. Fieser.

(2) National Research Predoctoral Fellow, 1946–1947; present address: Department of Chemistry, University of California at Los Angeles, California.

(3) Spruit, *Rec. trav. chim.*, **66**, 655–672 (1947).

(4) Dimroth and Schultz, *Ann.*, **411**, 343 (1916); see also Kuhn and Wallenfels, *Ber.*, **74**, 1594 (1941).

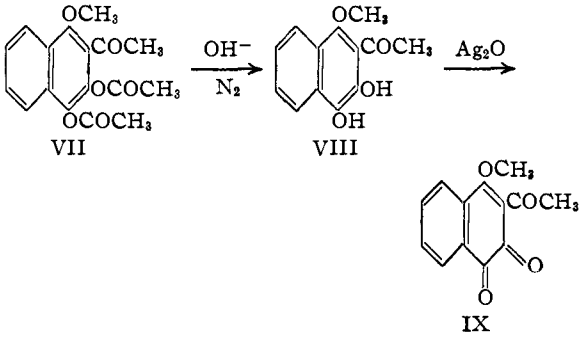
(5) The preparation of this substance is described further on in the investigation.

(6) Friedlaender, *Ber.*, **28**, 1950 (1895).

(7) This substance was obtained by Friedlaender[6] by the oxidation of 2-acetyl-4-amino-1-naphthol with ferric chloride, but the yield was poor and the product difficult to purify.

(8) This reaction has been used with sulfuric acid as catalyst for the conversion of naphthoquinone to 1,2,4-triacetoxynaphthalene [Thiele and Winter, *Ann.*, **311**, 347 (1900)], and more recently Fieser [THIS JOURNAL, **70**, 3165 (1948)] employed boron trifluoride as catalyst.

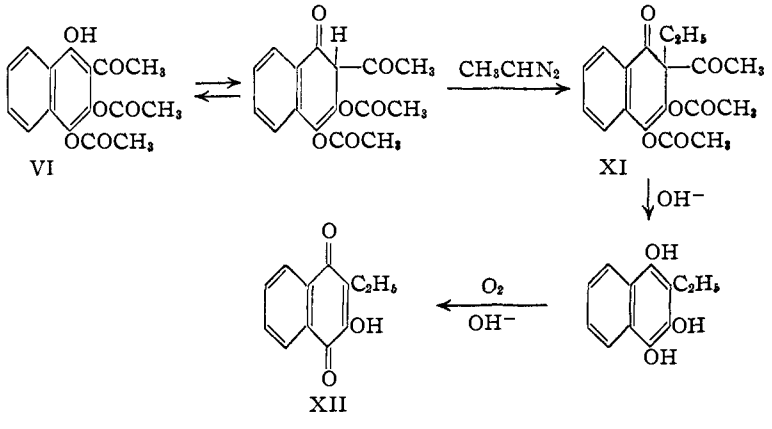
duced VI, indicating that one of the acetoxyl groups of the diacetate is in the 3-position. Methylation of VI with either dimethyl sulfate and sodium carbonate or diazomethane produced a monomethylated diacetate VII, which when hydrolyzed under carefully controlled conditions produced VIII. This substance was oxidized with silver oxide under anhydrous conditions (dry ether) to the *o*-quinone IX. Although unstable to acid or base, IX reacted with *o*-phenylenediamine to yield a diazine X.



Condensation of I with *o*-phenylenediamine produced an azine, which on methylation yielded X.

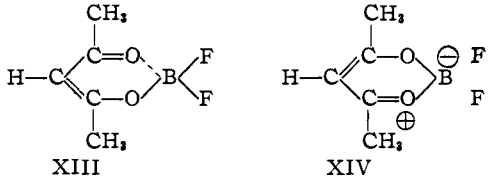
The above series of reactions proves that the diacetate VI contains two acetoxyl groups in the 3- and 4-positions and a free hydroxyl group in the 1-position.

It is interesting to note that on treating VI with diazoethane, carbon alkylation occurred to give XI, possibly *via* the ketonic tautomer of VI. The structure of XI was demonstrated by hydrolysis and oxidation to 2-ethyl-3-hydroxy-1,4-naphthoquinone (XII) which was shown to be identical with an authentic sample.[9]

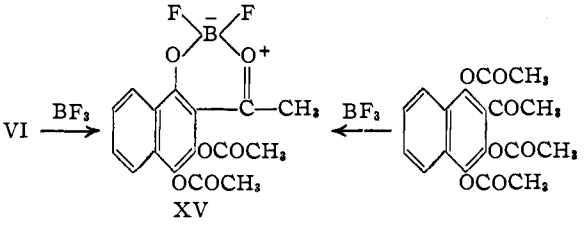


The structure of the boron fluoride containing compound V was established in the following way. The analytical values for carbon and hydrogen were high, probably owing to the passage of volatile boron fluoride compounds into the absorption train. Therefore, a method of fluorine analysis was developed, based on the conversion of fluorine to fluoride ion by fusion of the compound with alkali, and determination of the ion by the usual procedure.[10]

The analysis indicated that V contained a BF_2-group in place of a proton. There are several cases in the literature where a BF_2-group replaced a phenolic or enolic hydrogen. Morgan, *et al.*,[11] and Sugden, *et al.*,[12] prepared the boron difluoride derivative of acetylacetone by the addition of boron trifluoride to a solution of acetylacetone in benzene. The former authors assigned structure XIII to the compound, whereas the latter authors, on the basis of parachor determinations, advanced the structure XIV.



By analogy with the above observations the structure of the boron-difluoride-containing product of the Thiele reaction (V) was assigned the dipolar structure XV, which is preferred over the



alternate non-polar structure because of the strong electrophilic character of the boron atom, and because of the resonance of stabilization inherent in the dipolar form, and because of the energy gained by the formation of a new bond. Compound XV was also prepared by the addition of boron trifluoride to VI or to 2-acetyl-1,-3,4-triacetoxynaphthalene. The identity of the products of the three methods of preparation of XV was proved by (a) fluorine analysis, (b) decomposition points and (c) ultraviolet absorption spectra comparisons. To prove that the acetoxyl groups in the 3- and 4-positions of XV were not involved in the fixation of the BF_2-groups in the molecule, 2-acetyl-1-naphthol was allowed to react with boron trifluoride etherate in glacial acetic acid solution to give a com-

(9) S. C. Hooker, THIS JOURNAL, **58**, 1174 (1936).

(10) See Scott, "Standard Method of Chemical Analysis," fifth edition, Vol. I, D. Van Nostrand Co., Inc., New York, N. Y., 1939, p. 405.

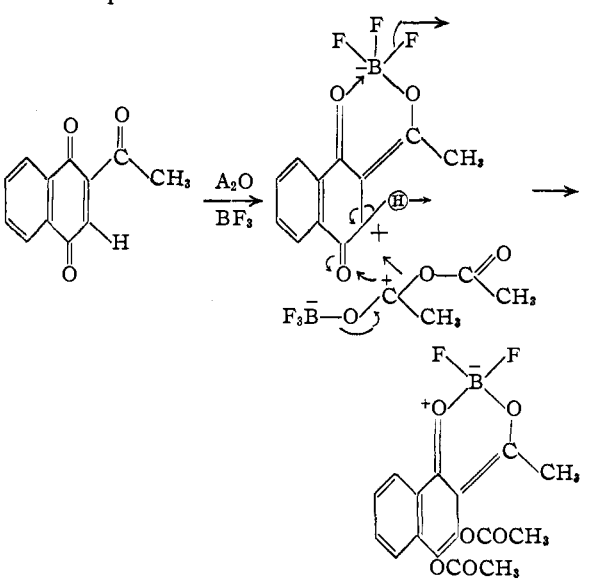
(11) Morgan and Tunstall, *J. Chem. Soc.*, **124**, 1965 (1924).

(12) Sugden, *J. Chem. Soc.*, 321 (1929); Sugden and Waloff, *J. Chem. Soc.*, 1492–1497 (1932).

pound containing a boron difluoride group in place of a hydrogen. Treatment of this substance with warm ethanol produced starting material.

Figure 1 records the ultraviolet absorption spectra of 2-acetyl-1-naphthol and its boron difluoride derivative, and Fig. 2 records the ultraviolet absorption spectra of VI and its boron difluoride derivative, XV. Examination of these spectra indicates a marked similarity between all four curves.

The elucidation of the structure of V demonstrates that 2-acyl-1,4-naphthoquinones undergo a modified Thiele reaction to give not the expected triacetate but a diacetate containing a BF_2-group on the phenolic oxygen in the 1-position. Although 1,4-naphthoquinone undergoes the normal Thiele reaction, 2-methyl-1,4-naphthoquinone does not. This fact suggests that the addition of acetic anhydride to quinone IV is a reaction involving the acetyl group in the side-chain. A possible mechanism for the reaction is presented.



The hydrolysis and subsequent oxidation of diacetate VI was carried out by procedures developed by Fieser,[13] and quinone I was the final product.

The procedures discussed above proved to be general, and were used in the present investigation for the preparation of 2-(4′-cyclohexylbutyryl)-3-hydroxy-1,4-naphthoquinone and 2-(3′-phenylpropionyl)-3-hydroxy-1,4-naphthoquinone. The substance, 2-benzalacetyl-3-hydroxy-1,4-naphthoquonine, was prepared through the base catalyzed condensation of 2-acetyl-3-hydroxy-1,4-naphthoquinone with benzaldehyde.

When compound VI was treated with a large excess of cetyl magnesium bromide in benzene solution, the two acetoxyl groups were cleaved, and the acetyl group reacted normally with the

(13) L. F. Fieser, THIS JOURNAL, **70**, 3174 (1948).

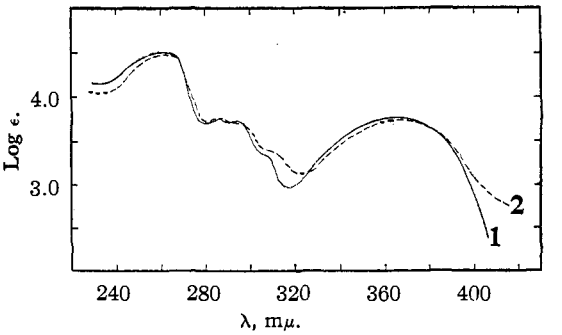


Fig. 1.—The ultraviolet absorption spectra (Beckman quartz spectrophotometer) in dioxane of: 2-acetyl-1-naphthol, curve 1; and the boron difluoride derivative of 2-acetyl-1-naphthol, curve 2.

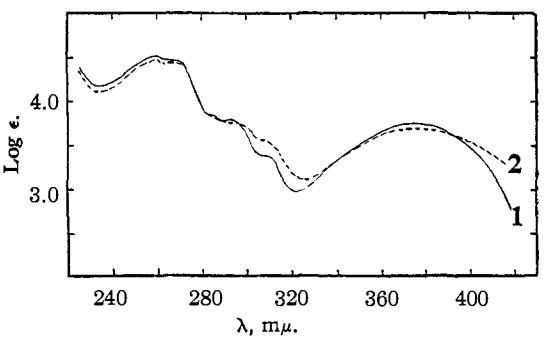
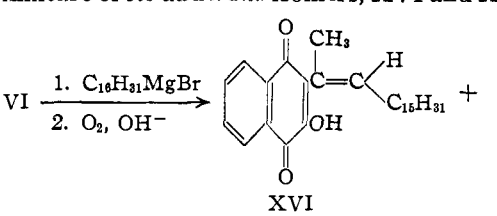
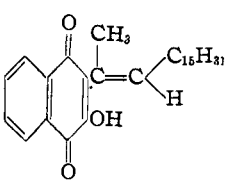


Fig. 2.—The ultraviolet absorption spectra (Beckman quartz spectrophotometer) in dioxane of: 2-acetyl-3,4-diacetoxy-1-naphthol, curve 1; and the boron difluoride derivative of 2-acetyl-3,4-diacetoxy-1-naphthol, curve 2.

Grignard reagent. When the reaction mixture was decomposed, the tertiary alcohol lost a molecule of water, and the product proved to be a mixture of *cis* and *trans* isomers, XVI and XVII.



XVI

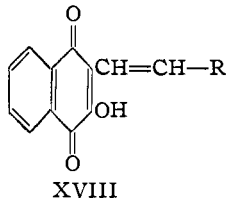


XVII

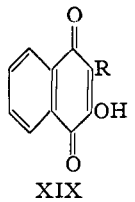
Each isomer was converted into a mixture of the two isomers when heated at 120° for half an hour. The structures of the two compounds were confirmed by oxidation to palmitic aldehyde which was identified as the *p*-nitrophenylhydrazone.

Quinones of structure XVIII give a purple color in alkaline solution, and compounds of structure XIX produce a red color.[9] Compounds

XVI and XVII both give a red color in alkaline solution.



XVIII



XIX

The steric inhibition of resonance implicit in structures XVI and XVII (the bulk of the methyl and methylene groups of the side-chain forbid coplanarity) provides an explanation for the similarity of the color reactions of these molecules and XIX.

Careful examination of Fisher–Hershfelder models of XVI indicates that the planar configuration of this molecule involves interference between the bulk of the C_{15} side-chain and the hydroxyl group in the 3-position, whereas this particular interference is absent in XVII. Determinations of the ultraviolet absorption spectra of the two isomers show that the positions of the maxima and minima as well as the extinction coefficients are all comparable, except for the maxima that occur at the longest wave length. The isomer melting at 91–92° has a maximum at 405 mμ, whereas the isomer melting at 82° has a maximum at 395 mμ. Since the isomer that presents the lesser hindrance to coplanarity of the two unsaturated systems should absorb light at the longer wave length, and since models indicate that configuration XVII gives less hindrance to coplanarity than XVI, formula XVII is assigned to the isomer melting at 91–92°, and XVI to the isomer melting at 82°.

Table I records the wave lengths and logarithms of the molecular extinction coefficients of the maxima and minima of the ultraviolet absorption spectra of isomers XVI and XVII in ethanol.

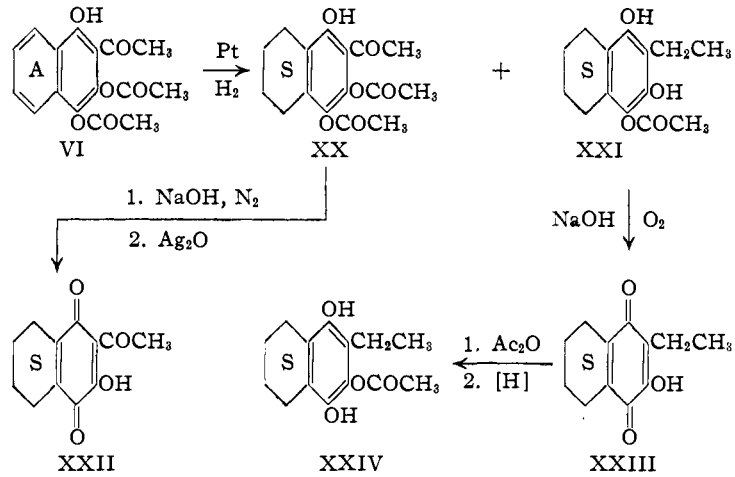
TABLE I

ULTRAVIOLET ABSORPTION SPECTRA DATA PERTAINING TO THE GEOMETRIC ISOMERS, XVI AND XVII (BECKMAN QUARTZ SPECTROPHOTOMETER) IN ETHANOL

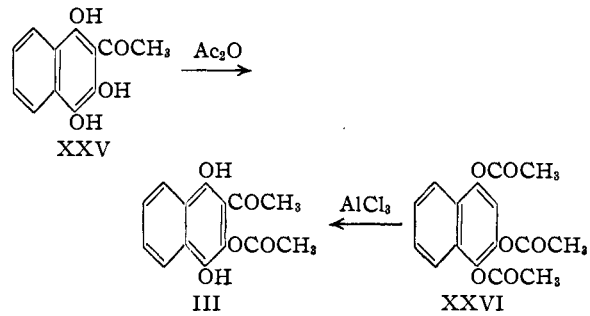
Max.		Min.		Max.		Min.	
mμ	log ε	mμ	log ε	mμ	log ε	mμ	log ε
Isomer XVI, m. p. 82°				Isomer XVII, m. p. 91–92°			
252	4.265	232	3.990	254	4.228	232	4.026
276	4.236	266	4.138	274	4.204	262	4.187
330	3.452	308	3.360	330	3.424	312	3.397
395	3.148	370	3.116	405	3.193	368	3.110

In an attempt to reduce the ketone in the side-chain of VI to the corresponding alcohol, VI was submitted to hydrogenation in a solution of glacial acetic acid with platinum oxide catalyst. Two compounds, XX and XXI, were isolated and converted to the corresponding quinones, XXII and XXIII. The position of the acetoxyl group in XXI was demonstrated by synthesis of the other possible isomer, XXIV.

The structures of these substances indicate that the reduction of VI took place in three directions: (a) ring A of the nucleus was reduced; (b) the ketonic group in the side-chain was reduced to a methylene group; (c) the acetoxyl group in the 3-position was removed by reduction. The removal by reduction of the acetoxyl group from position three of VI contrasts with the preferential acetylation of the hydroxyl group in the 3-position



of XXV, and with the selective deacetylation that must take place in the conversion of XXVI to III.



In an attempt to avoid the complications experienced in the reduction of 2-acyl-3,4-diacetoxy-1-naphthols with platinum oxide and hydrogen, compound XXVII was reduced over copper chromite catalyst in dioxane at 150° under 150 atmospheres of hydrogen. In this reduction the carbonyl group of the side-chain was reduced to a methylene group, and conversion of the substance XXVIII to quinone XXIX, a known compound,[14] confirmed the identity of the substance.

Table II records the physical properties and analyses of those of the above compounds whose detailed preparation can be adequately described by reference to the procedure used for an anal-

(14) Fieser, *et al.*, THIS JOURNAL, **70**, 3181 (1948).

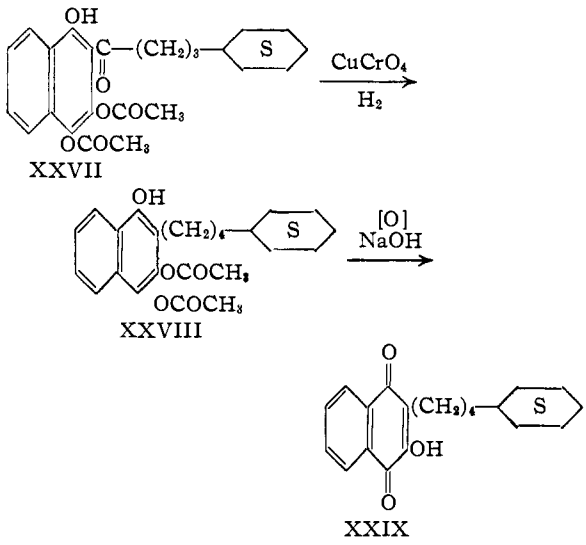
TABLE II

METHODS OF PREPARATION AND PHYSICAL PROPERTIES OF INTERMEDIATES OF, DERIVATIVES OF, AND 2-ACYL-3-HYDROXY-1,4-NAPHTHOQUINONES

N = naphthalene. NQ = 1,4-naphthoquinone. NHQ = 1,4-naphthohydroquinone. NL = 1-naphthol. PP = 3′-phenylpropionyl. CHB = 4′-cyclohexylbutryl.

Starting material	Product[1]	Prd.	Yield, %	M. p., °C.	Crys. solv.	Crys.[2] form	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
2-Acetyl-3-acetoxyNHQ	2-Acetyl-1,3,4-tri-acetoxyN	A	33	138–139	Alc.	W. pr.	$C_{18}H_{18}O_7$	62.79	62.94	4.68	4.94
2-Acetyl-3-hydroxyNQ	2-Acetyl-1,3,4-tri-acetoxyN	B	66	138–139	Alc.	W. pr.	.....	...	...	...	...
2-Acetyl-3-acetoxyNQ	2-Acetyl-3-acetoxyNHQ	C	49	196–197	Alc.	Y. n.	.....	...	...	...	...
2-Acetyl-3-hydroxyNQ	2-Acetyl-3-hydroxy-NHQ[3]	C	54	190–192	Eth.	O.-r. n.	$C_{12}H_{10}O_4$	66.05	66.25	4.62	4.85
2-Acetyl-3-hydroxyNHQ	2-Acetyl-3-acetoxyNHQ	A[4]	57	196–197	Alc.	Y. n.	.....	...	...	...	...
2-Acetyl-4-acetoxyNL	2-Acetyl-1,4-diacetoxyN	A	74	102–103	Alc.	W. pr.	$C_{16}H_{14}O_6$	67.12	66.81	4.93	5.19
2-AcetylNQ	2-Acetyl-1,4-diacetoxyN	B	74	102–103	Alc.	W. pr.	.....	...	...	...	...
2-AcetylNQ	2-AcetylNHQ[5]	C	80	216–217	Eth.	Y. n.	.....	...	...	...	...
2-AcetylNHQ	2-Acetyl-4-acetoxyNL[5]	A[4]	81	103–104	Alc.	Y. n.	.....	...	...	...	...
2-Acetyl-4-acetoxyNL	2-Acetyl-4-aminoNL	D	83	126–127[6]	Alc.	Y. pl.	.....	...	...	...	...
2-Acetyl-4-aminoNL	2-Acetyl-4-acetylamino-NL	A[7]	84	217–218[8]	Alc.	L. y. n.	$C_{14}H_{13}O_3N$	69.12	69.24	5.39	5.29
2-Acetyl-4-acetylaminoNL	2-AcetylNQ	E	88	80–81[9]	Pet.	Y. n.	.....	...	...	...	...
2-AcetylNQ	BF_2-deriv. of VI	F	82	232–236 (d.)	Acet.	Y. n.	$C_{16}H_{13}O_6BF_2$		F, 10.85		10.79
2-Acetyl-3,4-diacetoxyNL	BF_2-deriv. of VI	G	72	232–236 (d.)	Acet.	Y. n.	$C_{16}H_{13}O_6BF_2$		F, 10.85		10.87
2-Acetyl-1,3,4-tri-acetoxyNL	BF_2-deriv. of VI	G	77	232–236 (d.)	Acet.	Y. n.	$C_{16}H_{13}O_6BF_2$		F, 10.85		10.68
BF_2-deriv. of VI	2-Acetyl-3,4-diacetoxy-NL	H	85	184–185	Acet.	Y. n.	$C_{16}H_{14}O_6$	63.57	63.69	4.67	4.81
2-AcetylNL	BF_2-deriv.-2-acetylNL[10]	G	63	245–248 (d.)	Acet.	Y. p.	$C_{12}H_9O_2BF_2$		F, 16.24		16.18
2-Acetyl-3,4-diacetoxy-NL	2-Acetyl-3-hydroxyNQ	I	70	134–135	Acet.	Y. p.	.....	...	...	...	...
2-Acetyl-3-acetoxyNHQ	2-Acetyl-3,4-diacetoxy-NL	A[4]	64	184–185	Acet.	Y. n.	.....	...	...	...	...
2-Acetyl-3,4-diacetoxy-NL	2-Acetyl-1,3,4-tri-acetoxyN	A	78	138–139	Alc.	W. pr.	.....	...	...	...	...
2-Acetyl-2-ethyl-3,4-di-acetoxy-1-naphthone	2-Ethyl-3-hydroxyNQ[11]	I	93	139–140	Acet.	Y. n.	.....	...	...	...	...
2-Benzalacetyl-4-nitroNL[12]	2-(PP)-4-aminoNL[13]	D	56	140–141	Alc.	O. pl.	$C_{19}H_{17}O_2N$	78.32	78.59	5.88	5.64
2-(PP)-4-aminoNL	2-(PP)-4-acetylaminoNL	A[7]	76	184–185	Acet.	Y. n.	$C_{21}H_{19}O_3N$	75.65	75.73	5.74	5.67
2-(PP)-4-acetylaminoNL	2-(PP)NQ	E	76	94–95	Acet.	Y. n.	$C_{19}H_{14}O_3$	78.60	78.51	4.86	4.91
2-Benzal-4-nitroNL	2-(PP)NQ	J	68	94–95	Acet.	Y. n.	.....	...	...	...	...
2-(PP)NQ	2-(PP)-3,4-diacetoxyNL	F + H[14]	54	116–117	Acet.	Y. n.	$C_{23}H_{20}O_6$	70.40	70.62	5.14	5.23
2-(PP)-3,4-diacetoxyNL	2-(PP)-3-hydroxyNQ	I	71	97–98	Benz. + Pet.	Y. n.	$C_{19}H_{14}O_4$ $C_{21}H_{18}O_6$[15]	74.50 68.84	74.60 68.94	4.61 4.95	4.81 5.05
2-(CHB)-4-nitroNL	2-(CHB)NQ	J	72	52–53	Acet.	Y. n.	$C_{20}H_{22}O_3$	77.39	77.40	7.15	7.26
2-(CHB)NQ	2(CHB)-3,4-diacetoxy-NL	F + H[14]	71	171–172	Acet.	Y. n.	$C_{24}H_{28}O_6$	69.88	69.83	6.84	6.97
2-(CHB)-3,4-diacetoxy-NL	2-(CHB)-3-hydroxyNQ	I	85	134–135	Acet.	Y. pl.	$C_{20}H_{22}O_4$	73.60	73.40	6.80	6.91
2-Acetyl-3,4-diacetoxy-NL	2-Acetyl-3,4-diacetoxy-5,6,7,8-tetrahydroNL[16]	K	44	124–125	Eth.	Y. gr.	$C_{16}H_{18}O_6$	62.74	62.51	5.92	5.92
2-(CHB)-3,4-diacetoxy-NL	2-(CHB)-3,4-diacetoxy-5,6,7,8-tetrahydroNL	K	36	115–116	Alc.	Y. n.	$C_{24}H_{32}O_6$	69.21	69.44	7.75	7.67
2-Acetyl-3,4-diacetoxy-5,6,7,8-tetrahydroNL	2-Acetyl-3,4-dihydroxy-5,6,7,8-tetrahydroNL	L	89	180–182 (d.)	Eth.	Y. n.	$C_{12}H_{14}O_4$	64.85	65.11	6.35	6.53
2-Acetyl-3,4-dihydroxy-5,6,7,8-tetrahydroNL	2-Acetyl-3-hydroxy-5,6,7,8-tetrahydroNQ	M	83	87–88	Eth.	O. pl.	$C_{12}H_{12}O_4$	65.44	65.56	5.49	5.73
2-(CHB)-3,4-diacetoxy-5,6,7,8-tetrahydroNL	2-(CHB)-3-hydroxy-5,6,7,8-tetrahydroNQ	L + M[17]	75	66–67	Pet.	O. n.	$C_{20}H_{26}O_4$	72.70	73.12	7.93	8.12

[1] In all cases where two different methods of preparation of the same compound are reported, admixture of samples produced no depression of melting point. [2] y. = yellow, n. = needles, w. = white, pr. = prisms, o. = orange, r. = red, pl. = plates, gr. = granules, l = light. [3] Forms a deep purple color in alkaline sol., deep red color in concd. sulfuric acid. [4] The procedure was modified by not heating the reaction mixture, but allowing it to stand ten hours at room temp. [5] Admixture with same substance produced from Fries rearrangement (see expl.) gave no m. p. depression. [6] Friedlaender (ref. 6) prepared this compound by a different procedure but reported neither melting point nor yield. [7] The sodium acetate and heating period were unnecessary. [8] Friedlaender (ref. 6) reported a m. p. of 107° for a monoacetylated amine, and Torrey and Cardarelli [THIS JOURNAL, **32**, 1477 (1910)] reported a m. p. of 212°. [9] Friedlaender (ref. 6) reported a m. p. of 78° for this compound prepared by a different procedure. [10] This substance when warmed with ethanol reverts to the starting material. [11] Hooker reported a m. p. of 138–139° for this compound. The m. p. of a mixture of the two samples is 138–139°. [12] This substance [Torrey and Cardarelli (ref. 18) reported m. p. 202–208°] was prepared in a 92% yield, m. p. 210°. [13] The double bond in the side-chain was also reduced. [14] In this reaction the BF_2-derivative was treated directly with ethanol to give the phenol. [15] When crystallized from glacial acetic acid this quinone contains one mole of acetic acid of crystallization (yellow needles, m. p. 85–86 (dec.)). [16] 2-Ethyl-3-hydroxy-4-acetyl-5,6,7,8-tetrahydro-1-naphthol was isolated as a by-product (see expl.). [17] The intermediate hydroquinone was not isolated.



ogous reaction described in the experimental section.

Experimental

2-Acetyl-3-hydroxy-1,4-naphthoquinone (I) from Purpurin.—The reaction was run according to the procedure of Dimroth and Schultze,[4] but since the products were isolated from the reaction mixture by a method different than that reported by these workers, the procedure is repeated here.

To a cooled solution of 6 g. of purpurin in 150 cc. of water and 18 cc. of 5 *N* sodium hydroxide solution, 15 drops of a 1% cobalt sulfate solution and 10 cc. of a 30% hydrogen peroxide solution were added. The temperature rose to 40° in about three minutes and was maintained by placing the mixture in an ice-bath. After five minutes the solution turned red-brown, and 7.5 cc. of concentrated hydrochloric acid was added; the precipitate was collected and washed with water. The solid was triturated twice with saturated sodium carbonate solution and filtered. From the solid residue 2 g. of purpurin was recovered. The filtrate was acidified; the yellow precipitate was collected, dissolved in ethanol and passed through a small alumina column. The filtrate was evaporated to a small volume, and 50 mg. (11% yield) of I was obtained as yellow plates by crystallization of the oil from glacial acetic acid; m. p. 134–135°.

This quinone gives an orange color in alkaline solution, a yellow color in concentrated sulfuric acid solution, and a deep purple color in alkaline sodium hydrosulfite solution. Dimroth and Schultze[4] reported a yield of 79% and a melting point of 128–129°.

The original filtrate of the reaction mixture was extracted with ether, and the ether solution was dried and evaporated to a small volume from which yellow crystals slowly separated. Two recrystallizations from acetone and petroleum ether furnished 100 mg. of 2-(2′-carboxyacetyl)-3-hydroxy-1,4-naphthoquinone (II) in the form of orange needles; m. p. 119–120°. This substance produces a yellow color in alkaline solution, a yellow color in concentrated sulfuric acid solution and a purple color in alkaline sodium hydrosulfite solution.

Anal. Calcd. for $C_{13}H_8O_6$: C, 60.01; H, 3.10. Found: C, 60.20; H, 3.38.

The carboxylic acid II (50 mg.) was dissolved in 2 cc. of glacial acetic acid, and the solution was heated to 90° for five minutes. When cooled and diluted with water, the yellow quinone I crystallized; m. p. 134–135°. The melting point was not depressed by the addition of an authentic sample of I.

2-Acetyl-3-acetoxy-1,4-naphthohydroquinone (III).—A mixture of 1,3,4-triacetoxynaphthalene, 5 g. of anhydrous aluminum chloride and 100 cc. of *o*-dichlorobenzene was stirred at 80° for four hours, cooled, and mixed with 200 g. of ice and 50 cc. of 50% hydrochloric acid. A yellow solid was collected, and three recrystallizations (ethanol) produced 0.15 g. (3% yield) of III in the form of yellow needles, m. p. 196–197°. The compound forms an orange color changing to purple in alkaline solution, and a green color changing to yellow in an ethanol solution containing a drop of ferric chloride solution.

Anal. Calcd. for $C_{14}H_{12}O_5$: C, 64.61; H, 4.65. Found: C, 64.37; H, 4.66.

The substance 2-hydroxy-1,4-naphthoquinone[13] (2.5 g.) was recovered from the filtrate.

Procedure A. 2-Acetyl-1,3,4-triacetoxynaphthalene from 2-Acetyl-3-acetoxy-1,4-naphthohydroquinone (III).—To 25 mg. of III, 1.0 g. of acetic anhydride and a trace of sodium acetate were added. The mixture was warmed to 100° and diluted with 100 cc. of water, cooled, and two recrystallizations (ethanol) of the substance that separated afforded 10 mg. of white prisms; m. p. 138–139°.

Procedure B. 2-Acetyl-1,3,4-triacetoxynaphthalene from 2-Acetyl-3-hydroxy-1,4-naphthoquinone (I).—A mixture of 100 mg. of I, 200 mg. of zinc dust,[15] 2 g. of acetic anhydride and a trace of sodium acetate was heated on a steam-bath for one-half hour, filtered and the filtrate was stirred into 10 cc. of water. The product that separated was crystallized from ethanol; 105 mg., m. p. 138–139°.

2-Acetyl-3-acetoxy-1,4-naphthoquinone.—To 10 cc. of a solution of 2% ammonia in a 50% water–ethanol mixture 0.4 g. of I was added. The ammonium salt crystallized immediately. An excess of 50% silver nitrate solution was added to the mixture; the silver salt was filtered, digested with ethanol, and thoroughly dried. This salt was suspended in dry ether, and acetyl chloride was added drop by drop until all the quinone salt was decomposed. The precipitated silver chloride was collected; the filtrate was evaporated to a small volume in vacuum, cooled, and the quinone acetate was collected. Two recrystallizations of the product from dry ether produced 0.32 g. of light-yellow needles; m. p. 123–124°. This acetate hydrolyzes readily into the free quinone, and for this reason cannot be crystallized from ethanol.

Anal. Calcd. for $C_{14}H_{10}O_5$: C, 65.12; H, 3.90. Found: C, 65.28; H, 4.09.

Procedure C. 2-Acetyl-3-acetoxy-1,4-naphthohydroquinone (III) from 2-Acetyl-3-acetoxy-1,4-naphthoquinone.—An ether solution of 0.20 g. of 2-acetyl-3-acetoxy-1,4-naphthoquinone was shaken successively with three fresh portions of a solution of sodium hydrosulfite in water.[16] The ether solution was thoroughly washed with water, dried, and filtered through a small mat of Darco that had been washed with ether. The filtrate was evaporated to a small volume, cooled, and the product collected. Recrystallization of the substance from ethanol furnished 0.10 g. of yellow needles, m. p. 196–197°.

2-Acetyl-4-acetoxy-1-naphthol and 2-Acetyl-1,4-naphthohydroquinone.—A mixture of 3.0 g. of 1,4-diacetoxynaphthalene, 3.0 g. of anhydrous aluminum chloride and 30 cc. of nitrobenzene was heated for two hours at 70°, cooled, and decomposed with a mixture of ice and hydrochloric acid. The nitrobenzene was steam distilled, the black tar that remained was extracted into ether, and a brown insoluble precipitate was collected. The filtrate was dried, evaporated to dryness, and the residue repeatedly extracted with low-boiling petroleum ether. The extracts were combined, treated with Darco, evaporated to a small volume, and cooled. The product crystallized, and two recrystallizations (ethanol) furnished 0.25 g. (8.4% yield) of light yellow needles of 2-acetyl-4-

(15) This procedure is patterned after that described by Fieser, "Experiments in Organic Chemistry," 2nd Edition, D. C. Heath and Co., New York, N. Y., 1941, p. 399.

(16) This procedure is patterned after that developed by Fieser, *loc. cit.*, p. 190.

acetoxy-1-naphthol, m. p. 103–104°. The acetate forms a red solution with concentrated sulfuric acid, an orange solution with aqueous alkali, and a green solution with ethanol containing a drop of ferric chloride solution.

Anal. Calcd. for $C_{14}H_{12}O_4$: C, 68.84; H, 4.95. Found: C, 68.56; H, 4.71.

The material left from the petroleum ether extractions was dissolved in ether and shaken with sodium hydrosulfite solution, washed with water, dried, and filtered through a small ether-washed pad of Darco. When the filtrate was evaporated to a small volume and cooled, a solid separated, which after two recrystallizations from ether afforded 0.2 g. (8.1% yield) of 2-acetyl-1,4-naphthohydroquinone, m. p. 216–217°. The compound forms a red solution with concentrated sulfuric acid, an orange solution (which darkens) in aqueous alkali, and a green color changing to red in an ethanol solution containing a drop of ferric chloride solution.

Anal. Calcd. for $C_{12}H_{10}O_3$: C, 71.28; H, 4.99. Found: C, 71.20; H, 5.04.

Procedure D. 2-Acetyl-4-amino-1-naphthol.—A mixture of 10 g. of 2-acetyl-4-nitro-1-naphthol,[17] 0.10 g. of platinum oxide, 100 cc. of methanol and 5 cc. of concentrated hydrochloric acid was shaken under 25 lb. of hydrogen until six equivalents of hydrogen had been absorbed (four hours). The salt that separated was filtered and washed with methanol. This substance was mixed with 50 cc. of ethanol, and 10 cc. of a saturated sodium bicarbonate solution was added. The free amine was collected and recrystallized from ethanol; 7.3 g. (83% yield), m. p. 126–127°. Friedlaender prepared this substance by a different procedure, but he did not report a melting point or a yield.

Procedure E. 2-Acetyl-1,4-naphthoquinone (IV).—To a mixture of 16 g. of 2-acetyl-4-acetylamino-1-naphthol[18] and 140 cc. of glacial acetic acid at 15°, 6 g. of 70% nitric acid dissolved in 20 cc. of glacial acetic acid was added. The solid dissolved when the mixture was stirred. When 200 cc. of water was added to the solution, IV crystallized in fine yellow needles; 10.2 g. (88% yield), m. p. 80–81°.

2-Acetyl-1,4-naphthoquinone Oxide.—A solution made up of 0.1 g. of sodium carbonate, 0.4 cc. of dioxane, 2.5 cc. of dioxane, 2.5 cc. of water and 0.5 cc. of 30% hydrogen peroxide solution was added to 0.5 g. of IV dissolved in 15 cc. of ethanol. The mixture turned black. After ten minutes 100 cc. of water was added, and the precipitated solid collected. Two recrystallizations of the product from ethanol produced white needles of the oxide; 0.2 g. (37% yield), m. p. 125–126°.

Anal. Calcd. for $C_{12}H_{18}O_4$: C, 66.67; H, 3.73. Found: C, 66.52; H, 3.96.

Boron Difluoride Derivative (V) of 2-Acetyl-3,4-diacetoxy-1-naphthol (VI)

Procedure F. From 2-Acetyl-1,4-naphthoquinone (IV).—A mixture of 4.0 g. of IV, 12.0 g. of acetic anhydride and 2.0 g. of a solution of boron trifluoride in ether (45% by weight) was allowed to stand for twenty-four hours at room temperature.[19] Brilliant yellow needles of V separated, were collected and washed with cold glacial acetic acid; 6.0 g. (82% yield), m. p. 232–236° dec. Recrystallization of the substance from glacial acetic acid did not alter the melting properties.

This compound burns with a green flame and leaves a black ash; it is insoluble in water, decomposes in alkali and shows only a slight solubility in non-polar organic solvents. If heated with any organic solvent containing water, it decomposes. Solutions fluoresce strongly in the sunlight.

Procedure G. From 2-Acetyl-3,4-diacetoxy-1-naphthol (VI).—To a saturated solution of 5.0 g. of VI in glacial acetic acid, 3 g. of boron trifluoride etherate was added. A heavy precipitate of fine, yellow crystals separated immediately.[19] Recrystallization of the substance from glacial acetic acid furnished 4.2 g. of yellow needles, m. p. 232–236° dec.

Procedure H. 2-Acetyl-3,4-diacetoxy-1-naphthol (VI).—When 10 g. of V and 100 cc. of a 90% ethanol–water mixture were boiled for one-half hour, the boron fluoride compound decomposed to give orange-yellow crystals of VI. The mixture was cooled, the product collected and recrystallized from glacial acetic acid to yield 7.3 g. of lustrous yellow needles, m. p. 184–185°. This substance forms an orange solution with concentrated sulfuric acid, a yellow solution changing to deep red and finally to brown with aqueous alkali, and a green color in a solution of ethanol containing a drop of ferric chloride.

Procedure I. 2-Acetyl-3-hydroxy-1,4-naphthoquinone (I).—A solution (10 cc.) of a 30% potassium hydroxide was added to a mixture of 4 g. of VI and 40 cc. of ethanol (both mixtures had been previously flushed with nitrogen).[13] The mixture was allowed to stand for one-half hour. At the end of this time the purple solution was cooled, acidified with a cold solution of 8 cc. of concentrated hydrochloric acid in 25 cc. of water, and a cold solution of 8.7 g. of ferric chloride hexahydrate in 2.5 cc. of concentrated hydrochloric acid and 12 cc. of water was added. A crop of yellow needles separated, which crystallized from glacial acetic acid as gold-colored plates; 2.0 g. (70% yield), m. p. 134–135°. Admixture of the substance with an authentic sample of I (prepared from purpurin) did not depress the melting point.

1-Methoxy-2-acetyl-3,4-diacetoxynaphthalene (VII).—To a solution of 4.0 g. of VI in 300 cc. of dry benzene, an ether solution of diazomethane prepared from 10 g. of N-methyl-N-nitrosourea was added. The mixture after standing at room temperature for three hours, was evaporated in vacuum to an oil, which was dissolved in 30 cc. of ethanol, treated with charcoal and cooled in a Dry Ice–acetone mixture for several hours. The white solid that separated was filtered, washed with cold ethanol, and recrystallized twice from glacial acetic acid; 1.8 g. (white prisms), m. p. 106–107°.

Anal. Calcd. for $C_{17}H_{16}O_6$: C, 64.55; H, 5.10. Found: C, 64.33; H, 5.21.

Compound VII was also prepared in the usual manner by the action of dimethyl sulfate on VI, but the yield was inferior.

1-Methoxy-2-acetyl-3,4-dihydroxynaphthalene (VIII).—Solutions of 2.2 g. of VII in 30 cc. of ethanol and 7.5 cc. of 20% potassium hydroxide were flushed with nitrogen, mixed, and allowed to stand under nitrogen for two and one-half hours (the mixture was shaken frequently). Acidification with acetic acid yielded yellow crystals which, after thorough washing with water and recrystallization from glacial acetic acid afforded 0.65 g. of light yellow needles, m. p. 227–228°. The compound formed a green solution with ethanol containing a drop of ferric chloride solution, and a red solution with concentrated sulfuric acid, and an orange solution turning to brown with aqueous alkali. The substance was not identified.

Anal. Found: C, 69.84; H, 4.38.

The mother liquors of the original reaction mixture were saturated with sodium chloride, and cooled to 0° for twelve hours. The substance that separated was recrystallized twice from an ether–petroleum ether mixture; 0.4 g. of deep red-orange needles, m. p. 92–93°. The substance produced an orange solution with aqueous alkali, and a green color changing quickly to orange with an aqueous solution containing a drop of ferric chloride.

Anal. Calcd. for $C_{13}H_{12}O_4$: C, 67.23; H, 5.21. Found: C, 67.15; H, 5.38.

1-Methoxy-2-acetyl-3,4-naphthoquinone (IX).—A solution of 0.15 g. of VIII in 20 cc. of anhydrous ether was stirred for one hour with 0.25 g. of anhydrous magnesium

(17) Acetylation of 1-naphthol (Friedlaender, ref. 6, reported a quantitative yield and a m. p. of 103°) gave an 80% yield of 2-acetyl-1-naphthol, m. p. 101–102°. Nitration of this compound produced an 82% yield, m. p. 157–158°, of 2-acetyl-4-nitro-1-naphthol (Friedlaender, ref. 6, reported no yield and m. p. 157°).

(18) Torrey and Cardarelli, THIS JOURNAL, **32**, 1477 (1910).

(19) A small amount of etching of the glass of the reaction flask occurred.

sulfate and 0.25 g. of silver oxide. The solid was collected, and the quinone that had crystallized during the oxidation was dissolved in dry acetone and filtered. The combined filtrates were evaporated to a small volume under reduced pressure, and cooled. The solid when recrystallized twice from acetone formed rich orange-yellow needles; 75 mg., m. p. 166–167°. This ortho quinone is slightly soluble in ether and soluble in acetone. The substance forms a yellow solution with sulfuric acid, a deep red solution with aqueous alkali (after two minutes) and a deep purple solution with a mixture of aqueous alkali and sodium hydrosulfite, if the alkali is added first and allowed to stand for two minutes before the hydrosulfite is added. If sodium hydrosulfite is added first, and then the alkali, a deep red solution results.

Anal. Calcd. for $C_{13}H_{10}O_4$: C, 67.82; H, 4.38. Found: C, 67.72; H, 4.67.

O-Methyl-2-acetyl-1-naphtheurhodol.—A mixture of 50 mg. of IX, 35 mg. of *o*-phenylenediamine, and 1 cc. of glacial acetic acid was allowed to stand at room temperature for one-half hour. When the solution was cooled, a solid separated which was crystallized from ethanol; 20 mg. (light yellow needles), m. p. 157–158°.

Anal. Calcd. for $C_{19}H_{14}O_2N_2$: C, 75.48; H, 4.67. Found: C, 75.51; H, 4.65.

2-Acetyl-1-naphtheurhodol.—A solution of 0.5 g. of I and 0.18 g. of *o*-phenylenediamine in 2 cc. of glacial acetic acid was heated to the boiling point for one minute, and cooled. The product that separated was recrystallized twice from glacial acetic acid; 0.45 g. of orange needles, m. p. 206–207°.

Anal. Calcd. for $C_{18}H_{12}O_2N_2$: C, 74.99; H, 4.20. Found: C, 74.83; H, 3.90.

O-Methyl-2-acetyl-1-naphtheurhodol from 2-Acetyl-1-naphtheurhodol.—To a solution of 0.2 g. of 2-acetyl-1-naphtheurhodol in 20 cc. of a 50% acetone–water solution saturated with sodium carbonate, 2 cc. of dimethyl sulfate was added over a period of one-half hour. The mixture was stirred and kept basic by the addition of more sodium carbonate. Crystallization of the substance that separated (ethanol and water) produced light yellow needles; 0.15 g., m. p. alone and mixed with an authentic sample (see above), 157–158°.

2-Acetyl-2-ethyl-3,4-diacetoxy-1-naphthone (XI).—An ethereal solution of diazoethane was prepared from 15 g. of N-ethyl-N-nitrosourea, and added to a solution of 8 g. of VI in one liter of dry benzene. The reaction mixture was allowed to stand overnight at room temperature, and was concentrated under reduced pressure to a volume of 100 cc. The solution was then filtered through a heavy mat of Darco, and when the filtrate was cooled, 4 g. of starting material crystallized. The mixture was filtered, and the filtrate was concentrated to an oil, which was dissolved in a small amount of ethanol, mixed with a generous portion of Darco, and filtered; the filtrate was allowed to stand in an ice-chest for forty-eight hours. At the end of this period the substance that precipitated was crystallized twice from ethanol; 1.2 g. of white needles, m. p. 130–131°. This product forms a red color when allowed to stand in an aqueous alcoholic alkaline solution, and an orange color in concentrated sulfuric acid.

Anal. Calcd. for $C_{18}H_{18}O_6$: C, 65.45; H, 5.49. Found: C, 65.47; H, 5.68.

Procedure J. 2-(3′-Phenylpropionyl)-1,4-naphthoquinone by a Condensed Procedure.—Glacial acetic acid (200 cc.), acetic anhydride (100 cc.), 0.35 g. of platinum oxide and 34 g. of 2-benzalacetyl-4-nitro-1-naphthol were mixed and shaken under twenty-five pounds of hydrogen until eight equivalents had been absorbed (eighteen hours). To the mixture 6 g. of 70% nitric acid was then added. The suspended solid went into solution in about two minutes, and the catalyst was collected. Water (one volume) was added to the filtrate, the mixture was cooled, and a crop of fine yellow needles was collected; 21 g. (68% yield), m. p. 94–95°, not depressed by addition of an authentic sample of the quinone.

2-Benzalacetyl-3-hydroxy-1,4-naphthoquinone.—A mixture of quinone I (1 g.), 0.8 g. of benzaldehyde, 10 cc. of ethanol and 5 cc. of a 30% sodium hydroxide solution was stirred for twelve hours (the mixture turned black as soon as the components were added to one another). The solution was then acidified with acetic acid and oxidized with a solution of 1 g. of ferric chloride hexahydrate in 5 cc. of water and 1 cc. of concentrated hydrochloric acid. The oil that separated was dissolved in glacial acetic acid and set aside for several days. A small crop of crystals separated, and three recrystallizations from glacial acetic acid produced 0.1 g. of tan needles, m. p. 181–182°. The quinone formed a yellow solution with aqueous alcoholic alkali, a red-orange solution with concentrated sulfuric acid, a blue solution changing to purple and finally to red with an alkaline sodium hydrosulfite solution, and a yellow-orange solution with ethanol containing a drop of ferric chloride solution.

Anal. Calcd. for $C_{19}H_{12}O_4$: C, 74.99; H, 3.98. Found: C, 74.67; H, 4.09.

2-(4′-Cyclohexylbutyryl)-1-naphthol.—Freshly fused and ground zinc chloride (160 g.) was mixed with 100 g. of 4-cyclohexylbutyric acid and 85 g. of 1-naphthol.[20] The mixture was rapidly brought to 140–145°, held there for twenty minutes, cooled to 100°, and poured into water. The oily product was boiled with ethanol, collected, and recrystallized from glacial acetic acid; 72 g. (44% yield) of white needles, m. p. 103–104°.

Anal. Calcd. for $C_{20}H_{24}O_2$: C, 81.04; H, 8.16. Found: C, 81.30; H, 8.27.

2-(4′-Cyclohexylbutyryl)-4-nitro-1-naphthol.—Over a period of twelve hours a solution of 14 g. of 70% nitric acid in 50 cc. of glacial acetic acid was added to a mixture of 40 g. of 2-(4′-cyclohexylbutyryl)-1-naphthol and 150 cc. of glacial acetic acid at 15°.[20] The product that separated was washed with glacial acetic acid and dried; 32 g. (70% yield of nitro compound in the form of granules with a slight-yellow tinge), m. p. 121–122°.

Anal. Calcd. for $C_{20}H_{23}O_4N$: C, 70.36; H, 6.79. Found: C, 70.66; H, 6.75.

***cis* and *trans*-2-(1′-Methylheptadecen-1-yl)-3-hydroxy-1,4-naphthoquinone (XVI and XVII).**—To a stirred mixture of 6.5 g. of magnesium turnings and 50 cc. of dry ether in an atmosphere of nitrogen, 73 g. of cetyl bromide (dissolved in 200 cc. of dry ether) was added over a period of one-half hour. When the addition was complete, the mixture was refluxed for two hours, and a mixture of 7.3 g. of the diacetate VI and 300 cc. of dry benzene was added in portions. The reaction mixture was then refluxed for four hours, cooled and poured into a mixture of ice and ammonium chloride. The two layers were well shaken, separated, and the ether–benzene layer was shaken with a 5% solution of sodium hydroxide in a 50% alcohol–water mixture for about one-half hour. The solution was then acidified with acetic acid, and the layers separated. The ether–benzene layer was washed twice with water, dried, and evaporated under reduced pressure to an oil, which was dissolved in an equal volume of dry ether, and chilled for two days. The product that separated was dissolved in a small amount of boiling glacial acetic acid, and the solution was cooled as slowly as possible; care was taken not to disturb the flask during the crystallization. After twelve hours the product was carefully collected, and spread out on a piece of white paper. There were two kinds of crystals present in the mixture, relatively large dense packets of rich-orange needles and scattered light-yellow needles. The crystals of each component were separated manually, and submitted to alternate crystallization from glacial acetic acid and ethyl ether solutions until the melting points no longer changed. In this manner 1.7 g. of rich orange needles of the *trans* isomer (XVII), m. p. 91–92°, and 1.2 g. of fine yellow needles of the *cis* isomer (XVI), m. p. 82°, were obtained.

(20) These procedures are modeled after those of Friedlaender (ref. 6) in the preparation of 2-acetyl-4-nitro-1-naphthol.

Both compounds formed a red solution with an alkaline ethanol–water mixture, and an orange solution changing through brown, green and blue to a dirty purple with concentrated sulfuric acid. A mixed melting point determination of the two substances gave 86–89°.

Anal. Calcd. for $C_{28}H_{40}O_3$: C, 79.20; H, 9.50. Found for the *cis* isomer: C, 79.14; H, 9.68. Found for the *trans* isomer: C, 79.14; H, 9.50.

Ozonolysis of *cis*- and *trans*-2-(1′-Methylheptadecen-1-yl)-3-hydroxy-1,4-naphthoquinone (XVI and XVII).—Ozone was passed into a solution of 0.3 g. of the *trans* isomer in 30 cc. of ethyl acetate till the color was discharged. The solution was then dripped into boiling water; the water was cooled and extracted twice with petroleum ether. The extracts were combined, and the solution was washed once with dilute alkali, once with water, dried, and evaporated to a volume of 10 cc. This solution was run through a small column of acid-washed alumina, and the alumina was washed well with petroleum ether. The column filtrate was evaporated to a small volume and cooled to Dry-Ice temperature. The white solid that separated was crystallized from petroleum ether; 90 mg. of palmitic aldehyde[21] (white needles), m. p. 33–34°. The *p*-nitrophenylhydrazone[21] was prepared by the usual method, m. p. 95–96°.

The *cis* isomer (100 mg.) was oxidized by the same procedure, and 25 mg. of the *p*-nitrophenylhydrazone of palmitic aldehyde was isolated, m. p. 95–96°. A mixed melting point of the two samples of this substance showed no depression.

Conversion of *trans*-2-(1′-Methylheptadecen-1-yl)-3-hydroxy-1,4-naphthoquinone (XVII) into the *cis* Isomer (XVI).—The *trans* isomer (220 mg.) was heated at 120° for one-half hour. The melt was dissolved in a small amount of glacial acetic acid, and the solution was seeded with a crystal of the *cis* isomer. The product that separated was recrystallized twice from ethyl ether to give 63 mg. of the *cis* isomer, m. p. 82°. A mixed melting point with an authentic sample of XVI gave no depression. Starting material (105 mg.) was recovered from the combined filtrates.

A similar experiment, carried out on 130 mg. of the *cis* isomer (XVI), produced 30 mg. of the *trans* isomer XVII; m. p. 91–92°, not depressed by the addition of an authentic sample.

Procedure K. Reduction of 2-Acetyl-3,4-diacetoxy-1-naphthol (VI) to 2-Acetyl-3,4-diacetoxy-5,6,7,8-tetrahydro-1-naphthol (XX) and 2-Ethyl-3-hydroxy-4-acetoxy-5,6,7,8-tetrahydro-1-naphthol (XXI).—A mixture of 5 g. of the diacetate VI, 0.1 g. of platinum oxide and 100 cc. of glacial acetic acid was shaken under a pressure of twenty-five pounds of hydrogen till all the diacetate had dissolved (two hours). The mixture was filtered, and two volumes of water were added to the filtrate. The solid that precipitated was recrystallized twice (ethanol); 2.3 g. (light brown granules), m. p. 124–125°.

This substance (XX) dissolved in dilute alkali, and gave a yellow solution that turned quickly to orange, and finally to red. (Procedure K terminates here.)

The initial filtrate from the reaction mixture was extracted with ether, and the ether layer was well washed with water, dried, and evaporated to an oil. The oil was dissolved in a small amount of ether; an equal volume of petroleum ether was added, and the solution was cooled. The product that separated was crystallized from benzene; 0.7 g. (white needles), m. p. 144–145°.

This substance (XXI), when dissolved in aqueous alkali, gives a yellow solution that changes to brown, then to amber, to red, and finally to purple.

Anal. Calcd. for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25. Found: C, 67.33; H, 7.20.

(21) A melting point of 34° for palmitic aldehyde and 95.5–96.5° for the *p*-nitrophenylhydrazone is reported in Heilbron, "Dictionary of Organic Compounds," Vol. 3, Oxford University Press, New York, N. Y., 1943, p. 329.

Procedure L. 2-Acetyl-3,4-dihydroxy-5,6,7,8-tetrahydro-1-naphthol.—Diacetate XX (2.0 g.) and sodium hydroxide (20 cc. of a 5% solution) were mixed in an atmosphere of nitrogen and stirred for one-half hour. The solution was acidified, and the solid that separated was recrystallized twice from ether; 1.3 g. (canary-yellow needles), m. p. 180–182° dec. This hydroquinone gives a red solution with aqueous alkali, a yellow solution with concentrated sulfuric acid, and an orange color in an aqueous solution containing a drop of ferric chloride solution.

Procedure M. 2-Acetyl-3-hydroxy-5,6,7,8-tetrahydro-1,4-naphthoquinone (XXII).—A solution of 1.0 g. of 2-acetyl-3,4-dihydroxy-5,6,7,8-tetrahydro-1-naphthol in 25 cc. of ether was treated with 1.5 g. of silver oxide and a small amount of magnesium sulfate. The mixture was stirred for two hours and filtered; the solid was warmed with glacial acetic acid and filtered. Two parts of water were added to the combined filtrates, the solution was cooled, and a crystalline solid separated. Two recrystallizations of the quinone from ether gave 0.6 g. of orange plates of quinone XXII, m. p. 87–88°. This quinone forms an orange solution in aqueous alkali that turns red upon the addition of sodium hydrosulfite, and a yellow solution in concentrated sulfuric acid.

2-Ethyl-3-hydroxy-5,6,7,8-tetrahydro-1,4-naphthoquinone (XXIII).—Air was passed into a solution of 0.5 g. of XXI in 5 cc. of 1 *N* sodium hydroxide solution for ten minutes. The solution was acidified and the product that separated was crystallized twice from an ether–petroleum ether mixture; flat deep-orange rods, 0.3 g., m. p. 102–103°. This quinone (XXIII) forms a deep purple color in alkaline solution, as well as in concentrated sulfuric acid solution, and in ethanol solution containing a drop of ferric chloride solution. The alkaline solution turns colorless when sodium hydrosulfite is added.

Anal. Calcd. for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84. Found: C, 69.61; H, 6.91.

2-Ethyl-3-acetoxy-4-hydroxy-5,6,7,8-tetrahydro-1-naphthol (XXIV).—A mixture of 0.2 g. of XXIII, 1 cc. of acetic anhydride and a trace of sodium acetate was warmed on the steam-bath for one hour, cooled, and 3 cc. of water was added. After the excess acetic anhydride had decomposed, the mixture was extracted with ether, and the ether layer was washed with water. The ether solution was then shaken with a solution of sodium hydrosulfite in water, washed with water, dried, filtered through an ether-washed pad of Darco, and evaporated to an oil, which crystallized when cooled. Recrystallization of the solid from an ether–petroleum ether mixture gave 0.15 g. of white needles, m. p. 128–129°. The color reactions of this substance were similar to those of XXI.

Anal. Calcd. for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25. Found: C, 67.47; H, 7.48.

Reduction of 2-(4′-Cyclohexylbutyryl)-3,4-diacetoxy-1-naphthol (XXVII) to 2-(4′-Cyclohexylbutyl)-3,4-diacetoxy-1-naphthol (XXVIII).—Diacetate XXVII (10 g.) was dissolved in 50 cc. of purified dioxane and reduced at 150–160° for five hours under a pressure of 3900 lb. of hydrogen in the presence of 2.0 g. of copper chromite catalyst. The reaction mixture was then filtered, excess water was added to the filtrate, and the solution was extracted with ether. The ether layer was washed with water, dried, evaporated to a small volume and cooled. The product that separated was crystallized from glacial acetic acid; 3.0 g. of white prisms, m. p. 117–118°.

Anal. Calcd. for $C_{24}H_{30}O_5$: C, 72.33; H, 7.59. Found: C, 72.39; H, 7.73.

To the mother liquors from the original crystallization of the diacetate, 100 cc. of ethanol and 50 cc. of 1 *N* sodium hydroxide were added. Air was bubbled through this mixture for three hours, and the solution was acidified. The oily product that separated was crystallized from glacial acetic acid; 3.1 g. of quinone XXIX, m. p., alone and mixed with an authentic sample (ref. 14), 108–109°.

A small sample of the diacetate XXVIII was hydrolyzed

and oxidized by procedure I. From 500 mg. of the diacetate XXVIII, 390 mg. of the quinone was isolated; m. p., alone and mixed with an authentic sample, 108–109°.

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Summary

1. Several new methods for the preparation of 2-acyl-3-hydroxynaphthoquinones have been developed.

2. A new boron-trifluoride-catalyzed Thiele type of reaction has been found to take place between acetic anhydride and 2-acyl-1,4-naphthoquinones; the structures of the products have been elucidated.

3. The abnormal C-alkylation of a 2-acyl-1-naphthol type of compound with diazoethane has been investigated.

4. The reaction of 2-acetyl-3,4-diacetoxy-1-naphthol with a Grignard reagent has resulted in the preparation of two *cis–trans* isomeric olefins, whose ultraviolet absorption spectra were taken, and structural assignments based on these data were made.

5. The course of reduction of 2-acyl-3,4-diacetoxy-1-naphthol type compounds was investigated.

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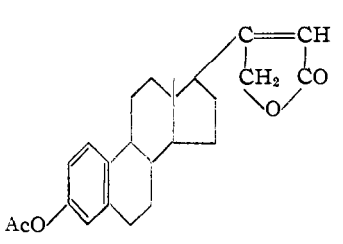
The Preparation of Two Aromatic Analogs of Desoxycorticosterone Acetate

BY CARL DJERASSI[1] AND CAESAR R. SCHOLZ

The biological testing of compounds containing both the nucleus of the estrogens and the functional side-chain of other physiologically active steroids is of considerable interest. Oettel[1a] reported on a pharmacological investigation of a cardiac aglucone derivative I, which contained an aromatic ring A, without disclosing the method of preparation, while Velluz and Muller[2] described the synthesis of an aromatic analog (II) of progesterone. The biological activity of the latter was unfortunately not indicated. The present paper summarizes our work on two independent syntheses of 3-methoxy-17-(β-acetoxyacetyl)-1,3,5-estratriene (III), as well as the preparation of the corresponding 1-methyl derivative XI. III and XI represent aromatic analogs of desoxycorticosterone acetate.



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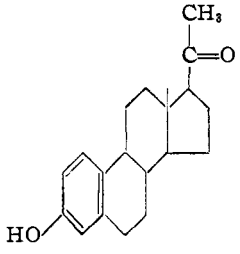

II

The starting material for the first synthesis (Flowsheet I) was 17-ethynylestradiol (IV), which has previously been converted[3] in unspecified yield by Rupe–Nickel reduction to 17-vinylestradiol (Va). The use of a palladium–calcium carbonate catalyst in pyridine solution[4] in the present instance led in 88% yield to the desired 17-vinyl derivative, which was converted into its methyl ether Vb with dimethyl sulfate. Hydroxylation of Vb with osmium tetroxide, followed by acetylation gave 50% of 3-methoxy-10-nor-1,3,5-pregnatriene-17,20,21-triol 20,21-diacetate (VI), which was subjected to a modified Serini reaction[5] in toluene solution and thus furnished directly the desired cortical hormone derivative III in 63% yield.

The aromatic analog III could also be prepared from methyl 3-ketoetiochola-1,4-dienate (VII) (Flowsheet II), which has been synthesized from cholesterol.[6] Aromatization with elimination of the angular methyl group of the dienone ester VII in tetralin solution at 650° by the general procedure of Inhoffen[7] led in 44% yield to the phenolic ester VIIIa which proved to be insoluble in 10% aqueous alkali. This methyl ester (VIIIa) as well as the 3-methyl ether 17-methyl ester (VIIIb) required drastic conditions for saponification (refluxing in 20% alcoholic potassium hydroxide solution for eighteen hours). This behavior is in marked contrast to the relative ease of saponification of the dienone ester VII or the aromatic

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(1a) Oettel, *Pharmazie*, **2**, 385 (1947).

(2) Velluz and Muller, *Compt. rend.*, **226**, 411 (1948).

(3) Inhoffen, Logemann, Hohlweg and Serini, *Ber.*, **71**, 1024 (1938).

(4) Ruzicka and Müller, *Helv. chim. acta*, **22**, 755 (1939).

(5) Fieser and Fieser, "Natural Products Related to Phenanthrene," 3rd edition, Reinhold Publishing Corporation, New York, N. Y., 1949, pp. 440–444; see Miescher and Heer, U. S. Patent 2,372,841.

(6) Djerassi and Scholz, THIS JOURNAL, **69**, 2404 (1947).

(7) British Intelligence Objectives Sub-Committee F.I.A.T. Final Report No. 996, "The Commercial Development and Manufacture of Synthetic Hormones in Germany," H. M. Stationery Office, London, 1947, pp. 20 and 79; see also Inhoffen, *Angew. Chem.*, **59**, 207 (1947), and Wilds and Djerassi, THIS JOURNAL, **68**, 2125 (1946).