To triene **5a** (500 mg) in anhydrous ether (100 ml) lithium aluminum hydride (500 mg) was added. The mixture was stirred for 2 hr, then decomposed with water. The aluminum hydroxide was dissolved with 2 *N* hydrochloric acid and the mixture was extracted with ether, washed, and dried. Removal of ether gave trihydroxytetraene **17**, which was recrystallized from ethyl acetate to mp 237–242° dec; ν_{max} 3420, 1625, 1610, 1575 cm^{-1}; λ_{max} 266 mμ (ϵ 15,400); nmr (DMSO) 449–389 (aromatic H), 363 (multiplet, W_H = 18 cps, 11-H), 312 (doublet, J = 7 cps, OH, disappeared on exchange with D_2O), 273 (multiplet, W_H = 21 cps, 6β-H), 211 (multiplet, W_H = 20 cps, 17-H), and 50 cps (18-CH_3).

Anal. Calcd for $C_{18}H_{22}O_3$: C, 75.49; H, 7.74. Found: C, 75.24; H, 7.43.

B.—A solution of **5a** (1.1 g) in methanol (100 ml) was made basic to phenolphthalein with 2 *N* sodium hydroxide, then sodium borohydride (6 g) was added, and the mixture was stored for 16 hr at room temperature. Most of the methanol was removed in a stream of nitrogen, water was added, and the steroids were recovered with ethyl acetate. The extract was washed with water, dried, and reduced to a residue to yield 549 mg of a syrup. Trituration with methanol gave **17** (237 mg) identical with the above sample.

3,6ξ,17β-Trihydroxy-6ξ-methylestra-1,3,5(10),9(11)-tetraene (18).—An ethereal solution of methyllithium (1.62 *M*, 50 ml) was added dropwise with cooing to a solution of **5a** (1000 mg) in ether–tetrahydrofuran (1:1, 50 ml). The mixture was stored for 16 hr, refluxed for 1 hr, and then terminated with a saturated aqueous solution of ammonium chloride. After a conventional work-up 1.1 g of a crude syrup was obtained and chromatographed on a silica gel column. The column was eluted with mixtures of ethyl acetate–acetone, and the various fractions were combined into four main groups according to their infrared spectra: fraction 1, starting material (78 mg); fraction 2, mainly **5b** (160 mg); fraction 3, a syrup (350 mg) which yielded **18** (78 mg) from acetone crystallization; and fraction 4, a syrup (415 mg).

Repeated recrystallizations of **18** obtained from fraction 3 gave a sample with mp 220–224°; λ_{max} 265.5 mμ (ϵ 14,200); ν_{max} 3575, 3360, 1620, 1610, 1570 cm^{-1}; nmr (in DMSO) 447–390 (aromatic H), 360 (multiplet, W_H = 13 cps, C-11 proton), 285 (singlet, C-6 OH, verified by D_2O exchange), 272 (doublet, J = 5.0 cps, C-17 OH, exchangeable with D_2O), 215 (multiplet, W_H = 20 cps, 17α-H), 84 (C-6 methyl), and 41 cps (18 methyl).

Anal. Calcd for $C_{19}H_{24}O_3$: C, 75.97; H, 8.05. Found: C, 76.05, 75.64; H, 8.28, 7.88.

3-Acetoxy-9α-hydroxyestra-1,3,5(10)-triene-6,17-dione (19).—Fraction 4 (415 mg) from the above experiment on rechromatography on tlc (silica gel, ethyl acetate) gave a residue (237 mg) which resisted crystallization: λ_{max} 258 mμ; λ_{max} (film) 3480, 1670, 1615 and 1580 cm^{-1}; nmr [$(CD_3)_2CO$] 525 (1 H, exchanges with D_2O), 452–414 (aromatic H), 224 and 173 (1 H each, exchange with D_2O), 224 (triplet, J = 8 cps, 17α-H), 49 (18-CH_3). The product (230 mg), presumably 3,9α,17β-trihydroxyestra-1,3,5(10)-trien-6-one, was treated first with Sarett's reagents [chromium trioxide (215 mg) in a total of 4.3 ml of pyridine] and then acetylated. After the recovery of the acetylated-oxidized material, it was purified by tlc to yield 90 mg of a crude solid. The solid was crystallized from ethyl acetate: mp 210–215°; λ_{max} 251 mμ (ϵ 10,000); ν_{max}^{KBr} 3530, 1760, 1735, 1665, 1600 cm^{-1}; nmr (CD_3OD) 421–478 (aromatic H), 138 (acetate) and 55 (18 CH_3), mass spectrum *m/e* 342 (M^+), 324 (M − 18), 300 (M − 42), 282 (M − 60 or 300 − 18), 267 (282 − 15).

Anal. Calcd for $C_{20}H_{22}O_3$: C, 70.15; H, 6.69. Found: C, 69.68; H, 6.69.

Registry No.—**5a**, 18181-55-0; **5b**, 18181-56-1; **5c**, 18239-03-7; **6a**, 18239-04-8; **6b**, 18181-57-2; **7**, 10006-41-4; **8c**, 18181-59-4; **9b**, 18239-05-9; **11**, 18181-60-7; **14**, 18181-61-8; **17**, 18181-62-9; **18**, 18181-63-0; **19**, 18181-64-1; ruthenium tetroxide, 14103-93-6.

Naphthoquinones. On the Oxidative Cyclization of Isolapachol to Dehydro-α-lapachone and Prototypal Studies Related to the Synthesis of Lapachol and Its Derivatives[1]

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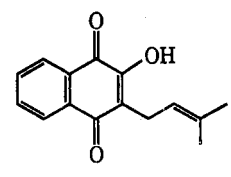
Received May 9, 1968

The reaction of isolapachol (**2**) with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) gives a mixture of dehydro-α-lapachone and dehydro-β-lapachone (*e.g.*, **3** and **4**). Treatment of the mixture with dilute acid–ethanol causes an "*ortho–para*" rearrangement of the latter compound (*e.g.*, **4**), and **3** is then isolated in an over-all 60% yield. Birch reduction (in the absence of ethanol) of **3** gives an acidic fraction (66%) comprised of a 7:3 mixture of isolapachol (**2**) and lapachol (**1**). In the presence of ethanol, Birch reduction gives an acidic fraction (33%) comprised of lapachol (**1**) and hydrolapachol (**5**) in the ratio 3:2, respectively.

Lapachol (**1**), the subject of a series of researches[2] culminating in the discovery of a new class of antimalarial agents,[3] has gained renewed interest as a consequence of its activity against the Walker carcinosarcoma 256 (intramuscular) and a favorable preclinical toxicological evaluation.[4] In view of the difficulties encountered in attempts to introduce directly



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the Δ^2-isopentenyl side chain[5] and because we had at hand a novel oxidative ring closure (note below, Scheme I, **2** → **3**), it was of interest to test the feasibility of the two-step sequence in eq 1 as a means for deconjugation

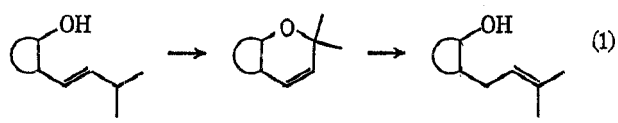
(1) This research was supported by Public Health Service Research Grant GM 13606 (Dr. Thomas C. Butler, Principal Investigator) from the National Institute of General Medical Sciences.

(2) S. C. Hooker, *J. Amer. Chem. Soc.*, **58**, 1163 (1936); see editor's note and references within.

(3) (a) L. F. Fieser, M. T. Leffler, *et al.*, *ibid.*, **70**, 3151 (1948); (b) L. F. Fieser, S. Archer, *et al.*, *J. Med. Chem.*, **10**, 513, 517 (1967).

(4) (a) Data were kindly provided by Dr. Harry B. Wood, Jr. (Cancer Chemotherapy National Service Center, National Institutes of Health). (b) A preliminary report on the pharmacology of lapachol has recently appeared: P. K. Nayak, D. Molins, F. J. Carelton, and R. K. Morrison, *Federation Proc.*, **27**, 532 (1968).

(5) (a) L. F. Fieser, *J. Amer. Chem. Soc.*, **49**, 857 (1927); (b) M. Gates and D. L. Moesta, *ibid.*, **70**, 614 (1948). (c) An unrelated synthesis of lapachol has been reported by S. C. Hooker, *ibid.*, **58**, 1181 (1936).



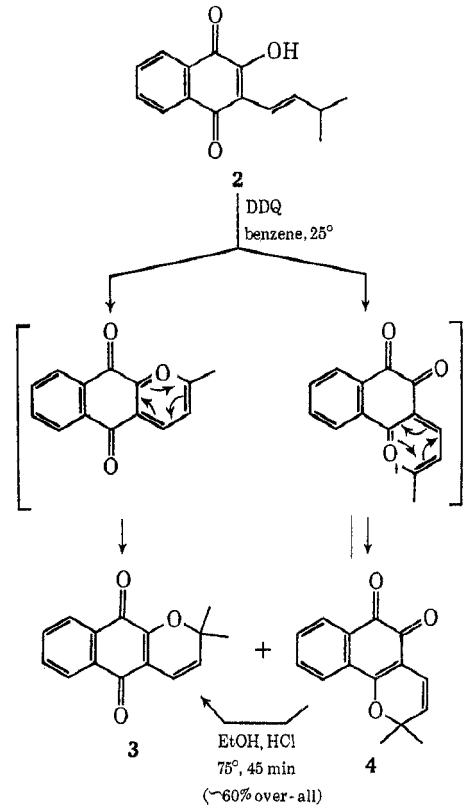
(1)

of conjugated olefin in this particular series. If successful, this approach would constitute a facile method for conversion of easily accessible isolapachol (**2**) into lapachol (**1**) and thus to analogs of **1**.

Exposure of isolapachol (**2**) to an equimolar quantity of 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ)[6a-e] in benzene resulted in oxidative cyclization of **2** to a mixture of the dehydrolapachones (*e.g.*, **3** and **4**) and proved to be a facile entry into the "lapachol series."[6e,7,8] Isolation of a single component was greatly simplified by mild treatment of the mixture with acid to effect conversion of the β form **4** to the α form **3** (over-all yield, ~60%) (Scheme I). The oxidation product **3** was identical with a sample of dehydro-α-lapachone (**3**) (DEαLN) taken from the collection of the late Dr. Samuel C. Hooker.[9]

A reductive means which leads to ring opening with "allylic migration" of the double bond (eq 1) was next sought. Prior to our investigation, an encouraging example of metal–amine reduction existed in the recent literature[10] and, during the course of our work, Birch

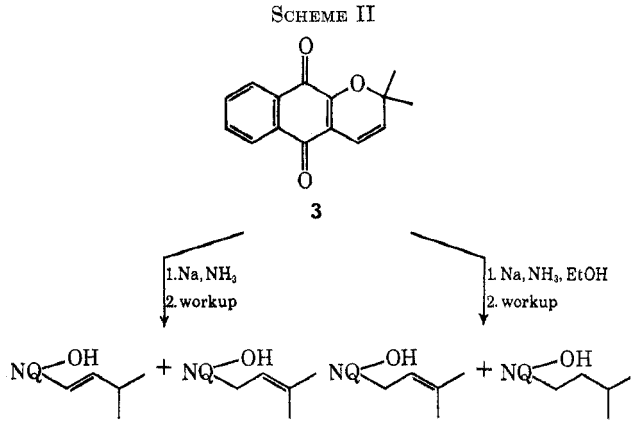
SCHEME I



and Maung[11] published a preliminary account dealing specifically with the usefulness of metal–amine procedures for the conversion of annelated chromenes (and related compounds) to ring-opened products characterized by the Δ^2-isopentenyl side chain.

Sodium–ammonia reduction of DEαLN (**3**) in the absence of alcohol donor gave a negligible neutral fraction and an acidic fraction (~66%) which was largely isolapachol (**2**) in mixture with lapachol (**1**) (Scheme II). Nmr integrals and spectrophotometric

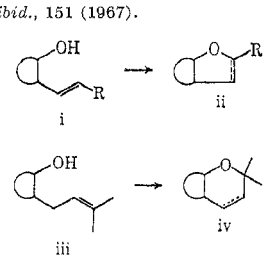
SCHEME II



analysis indicated an isolapachol–lapachol ratio of about 7:3. On the other hand, reduction of **3** in the presence of ethanol provided an acidic fraction (~33%) which was analyzed to contain lapachol (**1**) and hydrolapachol (**5**) in the approximate ratio of 3:2; a

(6) (a) L. M. Jackman, *Advan. Org. Chem.*, **2**, 329 (1960); (b) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," John Wiley & Sons Inc., New York, N. Y., 1967, p 215; (c) A. B. Turner and H. J. Ringold, *J. Chem. Soc., C*, 1720 (1967). (d) Oxidative cyclizations related to DDQ oxidation of isolapachol: R. Mechoulam, B. Yagnitinsky, and Y. Gaoni, *J. Amer. Chem. Soc.*, **90**, 2418 (1968), and G. Cardillo, R. Cricchio, and L. Merlini, *Tetrahedron*, **24**, 4825 (1968). Stimulated by the remarks of Cardillo, *et al.*, regarding the biogenesis of natural chromenes (which came to our attention during review of our manuscript), we examined the DDQ oxidation of lapachol using conditions herein employed for isolapachol; the DDQ oxidation of **1** afforded a mixture of DEαLN (**3**) and DEβLN (**4**), which was converted by mild acid treatment into **3** in about 30% over-all yield. Dehydro-α-lapachone (**3**) has been classified as a naturally occurring quinone. (e) The "elusive" dehydro-β-lapachone (**4**) has recently been isolated in pure form, and the general problem concerned with the correctness of structure of the dehydrolapachones has been reviewed, investigated, and settled: A. R. Burnett and R. H. Thomson, *J. Chem. Soc., C*, 1261 (1967).

(7) Isolapachol and its derivatives (side chain, —CH=CHR) customarily give cyclization products containing the furano system (*e.g.*, i → ii), while lapachol and its derivatives (side chain, —CH_2CH=CR_2) provide cyclization products containing the pyrano system (*e.g.*, iii → iv); see (a) S. C. Hooker, *J. Amer. Chem. Soc.*, **58**, 1202 (1936); (b) M. G. Ettlinger, *ibid.*, **72**, 3090 (1950); (c) review, R. H. Thomson, "Naturally Occurring Quinones," Academic Press, New York, N. Y., 1957, pp 59–90; (d) K. H. Dudley and H. W. Miller, *J. Org. Chem.*, **32**, 2341 (1967); (e) K. H. Dudley and H. W. Miller, *Tetrahedron Lett.*, 571 (1968); (f) A. C. Baillie and R. H. Thomson, *J. Chem. Soc., C*, 48 (1968), and references within. (g) Unrelated to the naphthoquinones, but pertinent to "*ortho–para*" rearrangements: A. Jefferson, I. Moore, and F. Scheinmann, *ibid.*, 151 (1967).



Two notable exceptions to the above generality are the acid-catalyzed cyclizations of norlomatiol (side chain, —CH=$C(CH_3)CH_2OH$) and a derivative having side chain —$CH_2C(CH_3)$=$CHCH_3$. See, respectively, S. C. Hooker, *J. Amer. Chem. Soc.*, **58**, 1181 (1936), and ref 5b.

(8) S. C. Hooker, *ibid.*, **58**, 1190 (1936).

(9) A sample of Dr. Hooker's dehydro-α-lapachone (**3**) was kindly provided by Professor Louis F. Fieser. We are also indebted to Professor Fieser for a generous sample of lapachol.

(10) (a) A. S. Hallsworth, H. B. Henbest, and T. I. Wrigley, *J. Chem. Soc.*, 1969 (1957); see footnote added in proof. Example cited by (b) A. J. Birch and H. Smith, *Quart. Rev.* (London), **12**, 17 (1958), and (c) H. O. House, "Modern Synthetic Reactions," W. A. Benjamin, Inc., New York, N. Y., 1965, p 75.

(11) A. J. Birch and M. Maung, *Tetrahedron Lett.*, 3275 (1967).

noticeable quantity of α-lapachone (**9**) was also formed. Since the ratios of lapachol (**1**) to complementary acidic product were profoundly different in the presence and absence of alcohol donor, it was of interest to investigate and then, if possible, to exploit the factors involved with product determination and/or distribution. Immediate questions stemming from the above findings concerned (1) whether product distribution of **1** and **2** involved equilibration of either **1** or **2** with sodium amide, (2) whether hydrolapachol (**5**) production stemmed from direct overreduction of isolapachol (**2**), and (3) whether intricacies related to acidities of ammonia and ammonia–alcohol systems might account for the failure to observe hydrolapachol (**5**) in the absence of alcohol donor.

Experiments listed below indicate that potential equilibrations at the three possible naphthoquinone states of **1** and **2** (*i.e.*, side chain deprotonation–protonation mediated by sodium amide) are, at most, very slow and kinetically unimportant under conditions comparable to those employed for reductions of DEαLN (**3**).

(1) Lapachol (**1**) and isolapachol (**2**) failed to equilibrate with excess sodium amide in ammonia.

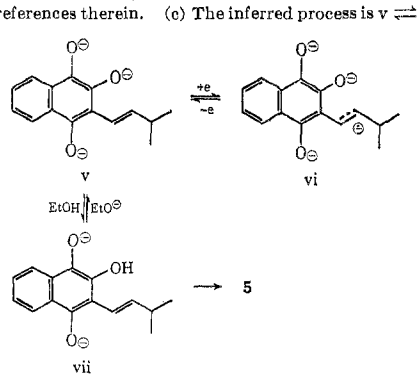
(2) Attempted sodium–ammonia reduction (absence of alcohol) of lapachol (**1**) led to recovery of pure **1**; ample time (~30 min) was given in this experiment for destruction of produced ammonium ion (from neutralization of the acidic hydroxyl group) by the sodium–ammonia agent. Similarly, attempted reduction (absence of alcohol) of *isolapachol sodium salt* resulted in recovery of pure isolapachol (**2**).

When reduction of isolapachol (**2**) or isolapachol sodium salt was conducted in the presence of ethanol and under conditions employed for DEαLN (**3**), the conversion of each to hydrolapachol (**5**) was poor (25–28%). This would seemingly indicate that isolapachol (**2**, *i.e.*, its hydroquinone) cannot serve during sodium–ammonia–ethanol reduction of DEαLN (**3**) as the principal precursor to hydrolapachol (**5**).

In light of the probable mechanism for the first stage of most metal–amine reductions,[12a,b] hydrogenolysis of isolapachol hydroquinone trianion to hydrolapachol hydroquinone trianion would require the intermediacy of a tetraanion radical in a sequence[12c] where the uptake of an electron in the side chain may be viewed as the "potential determining stage" and rate-determining step.[12a] The equilibrium between isolapachol hydroquinone trianion and its tetraanion radical apparently lies far to the left, because sodium–ammonia–ethanol reductions of **2** and its sodium salt proceeded slowly; besides sodium–ammonia reduction of isolapachol sodium salt did not occur to any measurable extent.[12d] Accordingly, the failure to observe hydrolapachol (**5**) among acidic products from sodium–ammonia reduction of DEαLN (**3**) is apparently not only owing to an unfavorable electron addition barrier but also to the poor deprotonating capacity of ammonia.

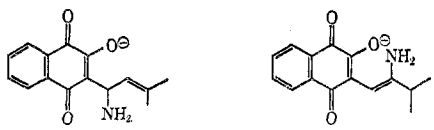
These evidences permitted construction of Scheme III as a working hypothesis for the sodium–ammonia (absence of alcohol) reduction of DEαLN (**3**).[13] It would seem that a "β-elimination" type of ring opening of trianion radical **6** to trianion radical **7** and, thence, reduction of **7** to tetraanion **8** (which may be reversible with respect to **7** as a transition state complex) are the important processes concluded by kinetically controlled, irreversible protonations. Apparently, ammonia is totally insufficient as an "acid" for trapping **6**, for only trace amounts, if any, of α-lapachone (**9**) could be detected in the relatively small neutral fraction. Commensurate with this point, we feel that protonations of trianion radicals **7** by ammonia are probably of minor consequence in product determination of **1** and **2**. The deduction that trianion radical **7** ought to be relatively less basic than **6** (which failed to deprotonate ammonia) and the fact that the reaction takes a profoundly different course when conducted in the presence of a series of alcohol donors would tend to support this view.

When reduction of DEαLN (**3**) was conducted in the presence of ethanol, a preponderant quantity of α-lapachone (**9**) was formed. It was thus hoped that measurable trends resulting from trapping of trianion radical **6** might be realized by (1) conducting sodium–ammonia reductions of **3** in the presence of a series of alcohols (of varying acidity) or by (2) carrying out a series of reductions with variable amounts of a specific donor (*e.g.*, ethanol). With a series of alcohols it was observed, in the order of increasing acidity of donor, that crude weights of acidic fractions became progressively smaller; although an appreciable neutral fraction was formed in each case, a trend for α-lapachone (**9**) production was not forthcoming. Trends for production of both acidic and neutral fractions were measurable, however, by varying the quantity of ethanol; in fact, the quantity of ethanol could be raised to the point where formation of acidic products was

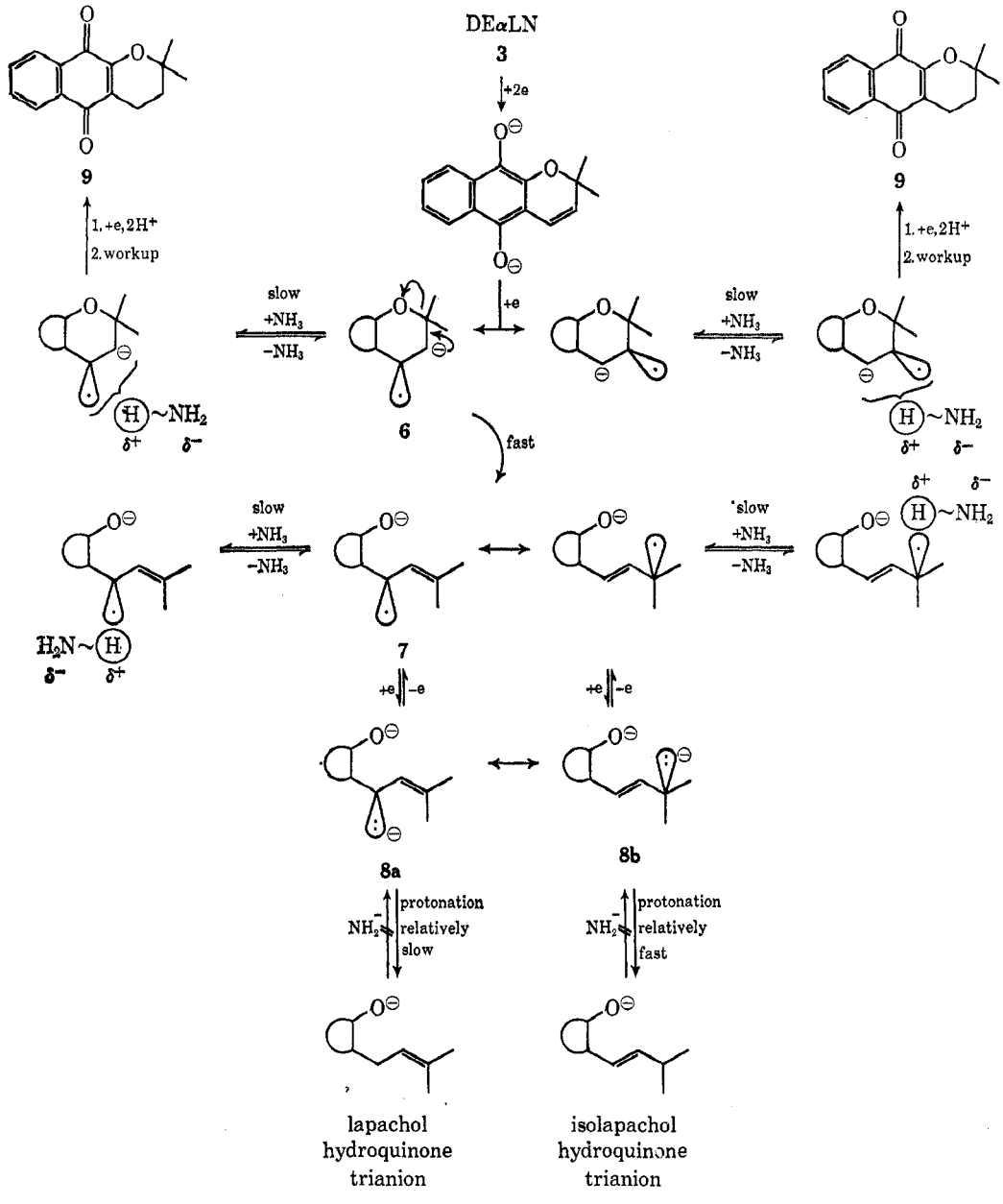


(12) (a) A. J. Birch, *Quart. Rev.* (London), **4**, 69 (1950). (b) W. A. Remers, G. J. Gibs, C. Pidacks, and M. J. Weiss, *J. Amer. Chem. Soc.*, **89**, 5513 (1967), and references therein. (c) The inferred process is v ⇄ vi. That reduction of **2** and its sodium salt to **5** will proceed (25–28%) using the sodium–ammonia–ethanol reagent may be owing to formation of dianion vii *via* protonation of v by alcohol donor. (d) In contrast to sodium–ammonia–ethanol reductions of isolapachol and isolapachol sodium salt (which gave 25–28% of **5**) and attempted sodium–ammonia reduction of isolapachol sodium salt (which resulted in isolation of pure **2**), sodium–ammonia reduction of isolapachol resulted in fair conversion to **5** (60–65%). Apparently, the NH_4^+ ion (through neutralization of the acidic hydroxyl group of **2**) is a sufficient acid for promoting reduction of **2**; it would seem in the sodium–ammonia–ethanol reduction, however, that the rate of destruction of NH_4^+ is far greater than the rate of reduction of **2**, *i.e.*, v or vii.

(13) DEαLN (**3**) appeared stable in liquid ammonia, for its solution failed to provide an intense red or purple color which characteristically should develop if **3** were being altered through ring opening of the chromeno moiety (*e.g.*, viii or ix); M. G. Ettlinger, *J. Amer. Chem. Soc.*, **72**, 3085 (1950).

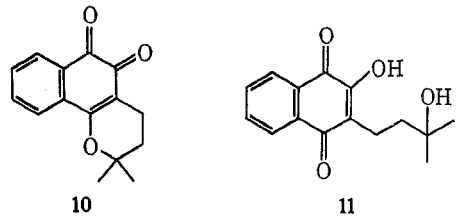


SCHEME III



almost completely suppressed (*i.e.*, almost total trapping of **6**).

By variance of the specific alcohol donor, it was found that methanol, ethanol, and *t*-butyl alcohol, respectively, led to production of approximately 30, 33, and 43% of hydrolapachol in the acidic fractions (spectrophotometric method). The approximate lapachol–hydrolapachol ratios in these preparations, as determined by nmr analysis, were 70:30 (methanol), 63:37 (ethanol), and 40:60 (*t*-butyl alcohol). In reactions where *t*-butyl alcohol was employed as donor, the discrepancy between values for hydrolapachol content (43%) and lapachol–hydrolapachol ratio (40:60) is owing to the production of a significant quantity (~28%) of a third acidic component which showed a characteristic tendency in very weakly acid solution for cyclization to β-lapachone (**10**). Other evidences also accorded with formulation of this third component as γ-hydroxyhydrolapachol (**11**), production of which is apparently derived through autoxidative ring opening of α-lapachone (**9**) (note Experimental Section).

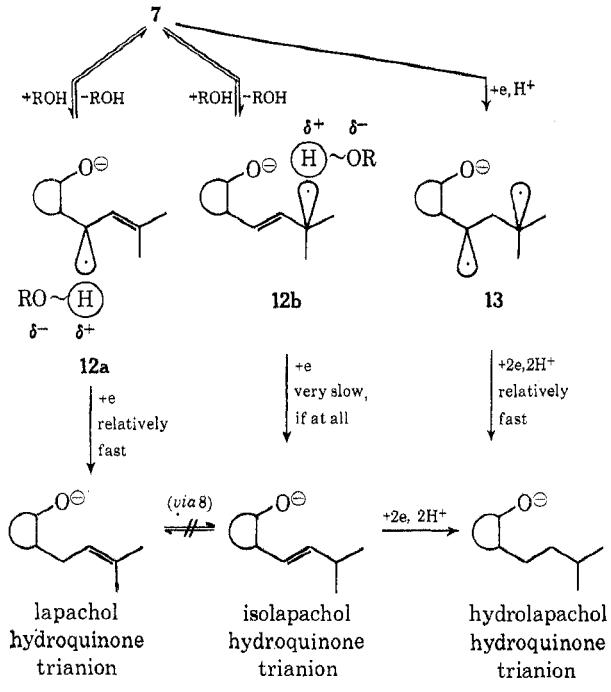


10 **11**

To explain the preponderance of lapachol (**1**) in the reduction conducted with ethanol as donor (note Scheme IV), we propose that a kinetically favored reduction of protonated anion radical **12a**[14] may be the primary factor leading to reversal of ratios (as contrasted with the reduction void of alcohol donor, Scheme III). Although hydrolapachol (**5**) content might be determined in small part, if at all, *via* protonated anion radical **12b** and then overreduction of isolapachol hydroquinone anion, the aforementioned findings on the sodium–ammonia–ethanol reductions

(14) The determining protonation factor may as well involve protonation of naphthoate oxygen.

SCHEME IV



of **2** and its sodium salt clearly indicate that the principal course of hydrolapachol production involves additional factors. A viewpoint (note Scheme IV) of trianion radical **7** competing for protonation (*e.g.*, **7** → **12a**) and a complex reduction (involving three electron–three proton uptake) (*e.g.*, **7** → **13**) is consistent with the trend observed in hydrolapachol production upon variance of proton donor, for it would be anticipated that a lesser acidic donor (*e.g.*, *t*-butyl alcohol) would favor the latter course.[15]

Experimental Section[16]

General.—Lapachol (**1**), isolapachol (**2**), and hydrolapachol (**5**) have essentially the same mobilities on tlc[16] when eluted in benzene–ethyl acetate–acetic acid (90:10:1 or 9:1:1), which as solvent systems were quite satisfactory for other derivatives reported within. Compositions of mixtures containing **1**, **2**, and **5** were conveniently approximated through measurement of nmr spectra.

Dehydro-α-lapachone (3).—A solution of 15.0 g (61.8 mmol) of isolapachol[17] in 220 ml of benzene was added in one portion to a stirred solution of 16.5 g (72.6 mmol) of 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ, Arapahoe Chem) in 220 ml of benzene and the mixture was stirred overnight at room temperature, filtered, and the collected solid (H_2DDQ) was washed thoroughly with benzene. The organic solution was shaken vigorously with *one* 50-ml portion of 1% sodium hydroxide, tlc then indicating complete removal of acidic materials and the presence of only DEαLN (orange zone) and DEβLN (purple zone). The organic solution was dried (Na_2SO_4), filtered, and evaporated under reduced pressure (T_{max} 40°) to a purplish brown crystalline solid, which was taken up in a hot mixture of 200 ml of absolute ethanol and 6 ml of concentrated hydrochloric acid and let stand, with occasional swirling, on the water bath (gentle boiling) for 45 min. Tlc then showed a more intense orange zone and a very faint lavender zone. The hot solution was filtered and let stand at 25°, and then at 4° (overnight), to give 8.8–9.2 g (59–62%) of chromatographically pure **3**, mp 143.5–146°, as dense clear orange rods. By mixture melting point, tlc, and comparison of infrared spectra, the sample was identical with DEαLN (**3**) taken from the collection of the late Dr. Samuel C. Hooker:[8,9] ir 1679, 1650 cm^{-1}; uv, $\lambda_{max}^{C_6H_{12}}$ 258 mμ (ε 14,500), 282 (16,400), 330 (2420), 418 (1630), 426 (1630), 434 (1630); λ_{sh} 233 (9350), 251 (13,700), 273 (14,500), 292 (12,700), 340 (1850), 457 (1110); nmr, δ 1.56 (s, 6 H), 5.67 [d (J = 10 cps), 1 H], 6.61 [d (J = 10 cps), 1 H], 7.64 (m, 2 H), 8.40 (m, 2 H). *Anal.* Calcd for $C_{13}H_{12}O_3$ (240.3): C, 74.98; H, 5.04. Found: C, 74.77; H, 5.01.

Dehydro-β-lapachone (4).—A mixture of **3** and **4** in benzene (minimum volume), prepared from reaction of 250 mg (1.03 mmol) of isolapachol and 230 mg (1.03 mmol) of DDQ in 16 ml of benzene and freed from DDQ and H_2DDQ, was adsorbed on a column of 15 g of silica gel (Fisher Grade 923). Partial separation was achieved by elution with 10% ethyl acetate–benzene; fractions rich in DEβLN (**4**) were combined and the solute was readsorbed on the same column; DEαLN (**3**) was eluted with benzene and DEβLN (**4**) was then eluted with 10% ethyl acetate–benzene. Eluate containing pure **4** (by tlc) was combined, evaporated, and the residue was recrystallized from ether–petroleum ether (bp 30–60°): yield, 25 mg (perfect rectangular purplish black plates); mp 104–111.5° (lit.[6e,7b] mp 102–107 and 122–123°). This sample was dried *in vacuo* for analysis. Tlc and microscopic examination indicated the compound pure; a sample (~5 mg) in warm ethanol containing 1 drop of mineral acid was converted solely into DEαLN (**3**): ir 1697 and 1638 cm^{-1} (the spectrum contained a host of bands attributable to **3**, which, however, may result through rearrangement of **4** during pressing of the pill); uv, $\lambda_{max}^{C_6H_{12}}$ 226 mμ (ε 19,800), 244 (12,300), 285 (19,300), 297 (17,800), 465 (1920); λ_{sh} 330 (19,400), 530 (830); nmr, δ 1.58, s, 5.50 [d (J = 10 cps)], 6.59 [d (J = 10 cps)]; 7.50–8.10, m. *Anal.* Calcd for $C_{15}H_{12}O_3$ (240.3): C, 74.98; H, 5.04. Found: C, 75.56; H, 4.95.

Sodium–Ammonia Reductions of Dehydro-α-lapachone (3).—Distilled ammonia was employed in all experiments. Tetrahydrofuran (THF) was of reagent grade quality and was purchased from Matheson Coleman and Bell. This solvent required special attention before use, especially *when a proton donor was concomitantly employed*. For example, runs using THF from one bottle (negative peroxide, Fe^{2+} – SCN test) gave, as reported within (ethanol as donor), acidic fractions comprised of lapachol and hydrolapachol, while runs employing another bottle (same label, negative peroxide) gave, in addition to the normal products, a significant quantity of isolapachol. When the THF from the latter bottle was distilled from lithium aluminum hydride, the acidic fractions were of the same composition as those obtained from use of the former bottle. The THF was stored under nitrogen and over Molecular Sieves (Linde, Type 5A) prior to use.

Procedure A. Sodium–Ammonia Reduction of 3 (Production of Isolapachol and Lapachol).—Freshly cut sodium (200 mg, 8.7 mmol) in 35 ml of ammonia (magnetically stirred and blanketed by nitrogen) was given 10 min to dissolve, and then a solution of 360 mg (1.5 mmol) of DEαLN (**3**) in 10 ml of THF (under nitrogen) was added dropwise over 10 min. An aerobically sensitive orange-red precipitate always separated either during or after the addition, and to aid stirring of the thick suspension it was advantageous to avoid frosting on the lower section of the apparatus by intermittently spraying with acetone. Fifteen minutes after the addition of **3** had been completed, the ammonia was allowed to evaporate (under nitrogen, 1 hr), and then 2 ml of ethanol, followed by 50 ml of water, was added. After gravity filtration (for quick aerobic oxidation), the solution was acidified to pH 3 with drops of 6 *N* hydrochloric acid and was extracted with two 50-ml portions of ether. Back-extraction of the combined ether solution with 0.5% sodium hydroxide (total volume 100 ml) gave a deep purple aqueous layer that upon acidification afforded 240–256 mg (three trials) of orange crystalline solid.

(15) A factor which may be important in the production of a diradical such as **13** is an inherent difference in the reducing capacity (or the actual metal–ammonia–alcohol species thereof) of metal–amine solutions containing alcohol.

(16) Thin layer chromatograms were prepared by coating microscope slides with silica gel H. Micro melting points were taken on a Kofler hot-stage microscope having a calibrated thermometer; where accumulation of a significant amount of moisture was observed before actual collapse of the crystals, and where the observation proved characteristic, the mp range, say 154–159° (β-lapachone), connotes the points where significant moisture begins to complete fusion. Ultraviolet and visible spectra were recorded on a Cary Model 15 spectrophotometer. Nmr spectra were recorded on Varian HA-100 (North Carolina State University) and Varian A-60 (Research Triangle Institute) instruments, using deuteriochloroform with tetramethylsilane as an internal standard. Infrared spectra were measured with a Perkin-Elmer Model 257 instrument; samples were prepared in the form of pressed KBr disks. Microanalyses were carried out by Micro-Tech Laboratories, Skokie, Ill.

(17) S. C. Hooker, *J. Chem. Soc.*, **69**, 1355 (1896).

Nmr analysis and spectrophotometric anaysis[18] indicated an isolapachol–lapachol ratio of 72:28. Isolapachol (**2**), mp 115–118.5° (lit.[17] mp 120°), was obtained by crystallization of the mixture from a small volume of methanol (25°); the mother liquor (4°) afforded a mixture of **1** and **2** in about equal parts (by nmr and ir). The ether extract contained 15–25 mg of deeply colored gummy material, which was essentially **3** by tlc.

Procedure B. Sodium–Ammonia–Alcohol Reductions of 3. Variance of Quantity of Alcohol.—The reaction was carried out as above but with the following variations. Ethanol (1 ml) was added to the DEαLN solution (360 mg in 10 ml of THF), and it is necessary that the alcohol be evenly distributed throughout the solution. When the apparatus was opened to permit evaporation (nitrogen, 1 hr), 2 ml of ethanol was added and, thereafter, work-up (completed within 2 hr) was essentially the same, except that during filtration of the aqueous THF solution a yellow precipitate (α-lapachone, **9**) was encountered; any portion of **9** trapped by the filter was eventually dissolved in ether and returned to the neutral fraction. The yellow acidic fraction (98–125 mg, mp 91–120, three trials) consisted of lapachol (**1**) and hydrolapachol (**5**). Nmr analysis indicated ~65% lapachol. Lapachol (crop A, golden yellow plates, 50 mg) of mp 130–138° [our melting point of pure **1** was 141.5–143° (lit.[19] mp 139.5–140.5°)] was the first crystallizate from absolute ethanol (1–2 ml), and the mother liquor was diluted with an equal volume of water to give crop B (neglected). The filtrate from crop B was further diluted to give crop C (homogeneous slender orange needles) which was recrystallized three times by solution in ethanol (1 ml), adding 2 drops of saturated bisulfite solution, and then dilution with water. The end product **5** was obtained as soft yellow needles: mp 87.5–89° (sharp); mmp, crystalline change at 87° and melting sharply at 93.5–95° (lit.[2] mp 94–95°). The neutral fractions (three trials) ranged from 80 to 125 mg and in all cases consisted chiefly of α-lapachone (**9**) in mixture with DEαLN (**3**) (by tlc). For isolation of **9**, a sample (165 mg) was dissolved in 10 ml of ethanol, 10 drops of 1% sodium hydroxide was added, the mixture was briefly warmed and held for 2–3 min, and was diluted with water to give soft yellow needles (100 mg) of **9**, mp 116–118°. Comparison was made with an authentic sample of **9** prepared from lapachol.[20]

In related experiments, the quantity of ethanol (evenly distributed!) was varied. When 0.5 ml of ethanol was employed, the acidic fraction amounted to 145.6 mg and consisted of lapachol (**1**), isolapachol (**2**), and hydrolapachol (**5**); nmr analysis indicated the ratio 57:30:13, respectively. The neutral fraction (brown crystals and gum) was 73.7 mg and consisted of **9** and **3**. When 3 ml of ethanol was employed, the acidic fraction (32–42 mg, two trials) consisted of **1** and **5** (nmr analysis, 67:33, respectively), while the neutral fraction (195–244 mg) was largely α-lapachone (**9**) in mixture with DEαLN (**3**).

Nearly total suppression of formation of acidic products was accomplished with the following procedure. To ~35 ml of ammonia under a blanket of nitrogen was added successively 360 mg (1.5 mmol) of finely pulverized **3** and 15 ml of ethanol (clear pale orange solution; neither bleaching nor transient color observed). After 10 min purging with nitrogen, a total of 150 mg (6.5 mmol) of sodium (in small pieces) was added all at once (rapid evolution of hydrogen) and the system was quickly closed. After 5 min the reaction mixture was poured into a large crystallizing dish and the greater portion of the ammonia was driven off within 3–5 min. Dilution of the residual liquor with water (~150 ml) gave a microcrystalline, bright yellow precipitate [pure α-lapachone (**9**), 132 mg, mp 114.5–115°], which was collected within 30 min. Remaining product was isolated from the filtrate by acidification and ether extraction; partitioning of the ether extract with alkali gave a neutral fraction (50.4 mg, mixture of **3** and **9**) and an acidic fraction (6.7 mg, essentially lapachol by tlc and ir).

Variance of Specific Alcohol Donor.—Reductions were conducted in the usual manner by dropwise addition of a solution of DEαLN (**3**) (360 mg, 1.5 mmol) in 10 ml of THF containing *25 mmol of alcohol donor* to a solution of 200 mg (8.7 mmol) of sodium in 35 ml of ammonia. After dilution and filtration, the acidified filtrate was let stand *overnight* and total product was isolated with ether and then partitioned with small volumes of 0.5% alkali. Filtration of the combined alkaline extract (charcoal avoided) and acidification (6 hr, 25°) gave a yellow-orange solid. In one series of experiments where the proton donor was methanol, ethanol, and *t*-butyl alcohol, the acidic fractions amounted to 75, 87, and 150 mg, respectively, and nmr analysis indicated lapachol–hydrolapachol ratios of 70:30, 63:37, and 40:60, respectively. The spectrophotometric method for approximation of hydrolapachol (**5**) in these mixtures is given later.

Reductions conducted under this procedure have been attended by a third acidic component, which is characterized in the nmr spectrum by a sharp singlet at δ 1.33. On tlc (benzene–ethyl acetate–acetic acid, 90:10:1), the zone remained near the origin and was easily distinguished from **1**, **2**, **5**, and β-lapachone (**10**). In reactions where methanol and ethanol were donors, the extent of formation of this product, X, was negligible (as evidenced by tlc and nmr), but in the *t*-butyl alcohol reaction, it was a significant component (~28%) in the acidic fraction. Compound X may have side chain $-CH_2CH_2C(OH)(CH_3)_2$, for it was much more hydrophilic than **1** or **5** and was identical by R_f value (tlc, two solvent systems) with authentic γ-hydroxyhydrolapachol (**11**). Weakly acidic solutions containing X (from partitioning experiments) slowly deposited β-lapachone (**10**) over a period of 4–5 days. The designation of X as **11** is further substantiated by the finding that exposure of α-lapachone (**9**) to the reduction conditions results in the formation of γ-hydroxyhydrolapachol (**11**) [note below, Birch reduction of α-lapachone (**9**)].

Product X was converted by concentrated sulfuric acid, along with lapachol, quantitatively into β-lapachone (**10**). Thus 103.4 mg of crude acidic product (mixture of **1**, **5**, and **X**) from sodium–ammonia–*t*-butyl alcohol reduction of **3** was covered with 0.5 ml of concentrated sulfuric acid and, after solution was effected, was let stand at room temperature for 20 min. The acidic and neutral fractions were obtained as described below under the analytical procedure for determination of **5**. Acidification of the alkaline extract gave 40.8 mg of bright yellow needles (homogeneous by tlc), which were recrystallized from ethanol–water to provide **5** (34.6 mg), mp 88° (sharp) (identification was achieved by tlc, mixture melting point, and ir spectrum). Drying (Na_2SO_4) and evaporation of the ether gave the neutral fraction as a bright orange solid (62.1 mg), which was chromatographically uniform and identical with **10**. Recrystallization from ethanol gave β-lapachone (**10**) (27 mg), mp 154–159.5°, which was identical with authentic material, mp 154–159.5°, prepared from α-lapachone[20] (identification was achieved by mixture melting point, tlc, and ir spectrum).

Spectrophotometric Method for Approximating Material Balance of Mixtures of Lapachol (1) and Hydrolapachol (5).—The accuracy (±3%) was determined using known mixtures of pure lapachol (**1**) and hydrolapachol (**5**). About 10 mg of mixture (*e.g.*, **1**, **5**, and X) was accurately weighed in a glass boat, 0.2 ml of concentrated sulfuric acid was deposited on top of the solid and, after complete solution had formed, the mixture was let stand for 10 min. After transfer with the aid of 5 ml of ether and 5 ml of water, the aqueous layer was extracted with successive volumes (5 ml) of ether until colorless; the combined ether extract was washed with water until neutral and was then partitioned with small volumes of 0.1 *N* alkali; the alkali extract was diluted to 50 ml with 0.1 *N* (stock solution). Absorbances were read at 275 mμ (1:25 dilution of stock) and 485 mμ (2:5 dilution of stock). Percentages calculated from the two absorbance readings agreed within 1%. Values obtained from two runs for each alcohol donor are summarized in Table I.

Sodium–Ammonia Reductions of Isolapachol (2), Isolapachol Sodium Salt, Lapachol (1), α-Lapachone (9), and γ-Hydroxyhydrolapachol (11). Isolapachol.—Sodium–ammonia reductions of **2** (360 mg, 1.5 mmol) were conducted as described under procedures A and B; the isolated acidic fractions were analyzed by nmr. During work-up, the ether solutions were virtually colorless and provided negligible residues (3–8 mg) upon evaporation. In the absence of alcohol donor (procedure A), the reduction gave an acidic fraction (312 mg, mp 81–89°) which consisted of 36.7% of **2** and 63.4% of **5**. In the presence of ethanol (procedure B), the reduction afforded acidic material (250 mg, mp 81–109°) comprised of 74.5% of **2** and 25.5% of **5**.

Isolapachol Sodium Salt.—The sodium salt[17] was washed with dilute alkali and finally with a small volume of water, and was dried for 1.5 days under vacuum at 40° prior to use. Attempted reduction (procedure A, 394 mg of salt in 10 ml of THF) resulted in isolation of a neutral fraction (25 mg, chiefly α-lapachone (**9**), by tlc) and an acidic fraction (302 mg, mp 117–122°) which

(18) Simultaneous analysis, at either 273 or 307 mμ. The nmr method is far more convenient.

(19) W. H. Greene and S. C. Hooker, *Amer. Chem. J.*, **11**, 267 (1889).

(20) S. C. Hooker, *J. Chem. Soc.*, **61**, 611 (1892).

TABLE I

Proton donor (25 mmol)	Acidic fraction, mg	Neutral fraction, mg	% Hydrolapachol in acidic fraction
MeOH	75.55	149.1	31.4
MeOH	73.30	152.0	27.1
EtOH	86.80	94.60	32.2
EtOH	87.80	122.8	33.8
t-BuOH	108.0[a]	116.5[a]	42.8
t-BuOH	108.2[a]	93.91[a]	43.9

[a] Acidic and neutral weights are corrected. Originally, each acidic fraction amounted to ~150 mg, which, however, contained ~28% of **11** from oxidative ring opening of **9**.

proved by ir and nmr to be pure **2**. Reduction in the presence of ethanol (1 ml) gave an acidic fraction comprised of 71.6% of **2** and 28.4% of **5**.

Lapachol.—Attempted reductions (procedures A and B) of **1** resulted in recovery of pure **1** (recoveries: 89 and 92%, respectively).

α-Lapachone.—A reduction was carried out using procedure B [360 mg (1.5 mmol) of **9** and 25 mmol of ethanol in 10 ml of THF] and it showed that **9** is a nonparticipant in the production of **5**. The recovery of **9** was 70% (containing a small amount of **3**); the acidic material (32 mg), which was isolated as an orange-red oil, was identified (by tlc, two solvent systems) as γ-hydroxyhydrolapachol (**11**).

α-Lapachone is converted into γ-hydroxyhydrolapachol (**11**) (of excellent quality, 45% yield) by sodium–ammonia reduction of **9** (absence of alcohol donor) and then permitting exposure of the reduced solution of **9** to air during evaporation of ammonia. Thus a solution of **9** (500 mg, 2.06 mmol) in 10 ml of THF was added dropwise to a solution of 280 mg (13.4 mmol) of sodium dissolved in ~40 ml of ammonia (under nitrogen). After addition was complete, nitrogen purging was ceased, the bluish green solution was stirred for 15 min, and the system was opened to the atmosphere to permit evaporation (without the aid of nitrogen, ~1 hr). Ethanol (2 ml) was added to the residual liquor, followed by 50 ml of water, and the clear solution was carefully acidified with drops of 6 *N* hydrochloric acid (an excess must be avoided[20]) and let stand for 15 min. Total product was isolated with ether and partitioning with dilute alkali gave a neutral fraction (38 mg, comprised of **3** and **9**) and a salt solution which was carefully acidified; the acidic product was reisolated with ether and partitioned once again with dilute alkali. Careful acidification (6 *N* HCl) of the alkaline solution gave a bright yellow turbid solution which was induced by *immediate* scratching to give bright yellow microcrystalline prisms of γ-hydroxyhydrolapachol (**11**) (201 mg), mp 124.7–125.0°. An additional 42 mg of **11** (chromatographically uniform) was obtained from the filtrate as an orange oil by isolation with ether, drying (Na_2SO_4), and evaporation; 15.25 mg of this oil was converted by concentrated sulfuric acid to 13.0 mg of chromatographically pure β-lapachone (**10**), which was recrystallized from ethanol to give orange-red needles (5.7 mg): mp 154–159°; total yield of **11**, 243 mg, 45%. The crystalline product, mp 124.7–125.0°, was identical (by mixture melting point, ir, tlc, and nmr) with a sample of γ-hydroxyhydrolapachol, mp 125.0–125.5°, prepared from α-lapachone (**9**) (alkaline hydrolysis) using essentially the same manipulations described by Hooker for the conversion of β-lapachone (**10**) into **11**.[20]

The nmr spectrum of **11** contained a sharp singlet at δ 1.33 (6 H), two four-line multiplets centered at 1.77 (2 H) and 2.80 (2 H), and aromatic proton multiplets at 7.75 (2 H) and 8.12 (2 H).

γ-Hydroxyhydrolapachol.—The reduction was conducted as described in the first paragraph for α-lapachone, using 384 mg (1.5 mmol) of **11** and 1.46 ml (25 mmol) of ethanol. Work-up followed the procedure described in the second paragraph under α-lapachone, except that nitrogen was used during the evaporation of ammonia. The recovery of γ-hydroxyhydrolapachol was 83%, and its purity was indicated by microscopic examination, its sharp mp of 124.5–125°, tlc, and its ir spectrum.

Equilibration Experiments.—Using essentially procedure A, where a solution of either **1** or **2** (360 mg) in THF was added dropwise to a solution of sodium amide in ammonia (prepared from 8.7 mmol of sodium, and then reaction vessel purged with nitrogen), the recovery of **1**, mp 140.5–142°, was 80% and the recovery of **2**, mp 116–123°, was 70%; purities were verified by nmr.

Registry No.—**1**, 84-79-7; **2**, 4042-39-1; **3**, 15297-92-4; **4**, 15297-93-5.

Acknowledgment.—We wish to thank Dr. Thomas C. Butler for his encouragement and support of this work. We gratefully acknowledge the able technical assistance of Mrs. Irma Jean Davis, who carried out multiple preparations of isolapachol and aided R. W. C. with the spectroanalytical work. We are indebted to Dr. C. G. Moreland (North Carolina State University) and Mr. C. Fenske and Mr. J. Younger (Research Triangle Institute), who kindly provided us liberal time on their nmr instruments.

Synthesis of Compounds Related to Gibberellic Acid. III. Analogs of Ring A of the Gibberellins

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Received June 28, 1968

Reductive alkylation of tetrahydronaphthoic acids **1** and **8** gave the alkylated hexahydro acids **3** and **9a**, respectively. These were lactonized under acidic conditions to the *trans* lactones **4** and **10**, and the latter was elaborated to hydroxy lactones representing the elements of ring A of most of the gibberellins. The hydroxy acid **20** was converted into an iodo lactone **21** whose deiodination led stereospecifically to a *cis*-decalin lactone. Similar reactions were used for the synthesis and elaboration of compounds containing an additional double bond or a ketone group in the second naphthalene ring. Attempted acid-catalyzed lactonization of most of these led to decarboxylation or aromatization, and the deiodination of the ketal iodo lactone **44** was not stereospecific.

In previous work in this field,[1,2] we described a synthetic path to the bicyclo[3.2.1]octane system represented by rings C and D of the gibberellins. We now turned our attention[3] to the construction of the ring A system of some of the gibberellins[4] which consists of a cyclohexane ring containing a methyl group, a γ-lactone bridge and in addition a hydroxyl group and/or a double bond, as exemplified in gibberellic acid (A), gibberellin A_4 (B), and gibberellin A_5 (C).

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