Notes

The Mercuric Acetate Oxidation of Isolapachol[1]

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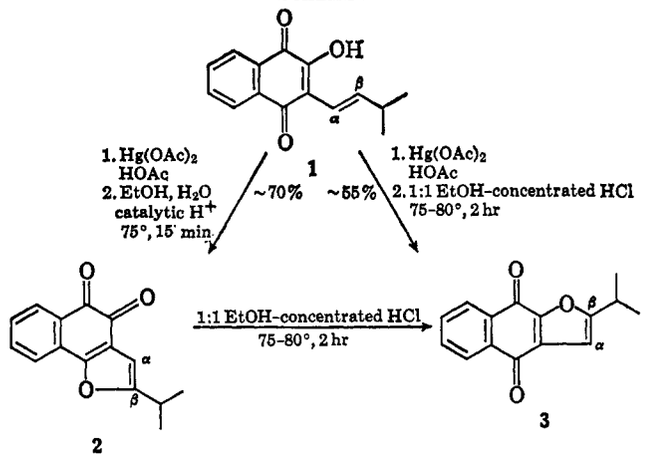
The mercuric acetate oxidation of isolapachol (**1**) has been found to be a convenient synthetic method for the preparation of β-isopropylfurano-1,2-naphthoquinone (**2**) or β-isopropylfurano-1,4-naphthoquinone (**3**), the isolation of angular or linear furanonaphthoquinone depending upon the method of work-up.[2] As seen in Scheme I, the only differences in the experimental procedures involved the time of heating and amount of mineral acid employed in the second step.

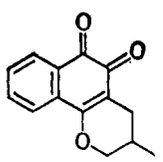
SCHEME I



When solutions of isolapachol and mercuric acetate in acetic acid were mixed, an oxidative process ensued, as evidenced by the immediate deepening of color and gradual precipitation of mercurous acetate. The oxidation could be conveniently hastened by bringing the temperature of the solution to 65–70°, after which thin layer chromatography (tlc) revealed that two principal oxidation products (**2** and product A) had been formed.[3] Having recognized by tlc that addition of a catalytic amount of hydrochloric acid to the oxidation solution caused complete conversion of the bright yellow product A (color on tlc) to the orange-red component, a procedure was readily devised for obtaining a single product. The isolated orange-red naphthoquinone proved to be identical with a sample of **2** prepared by the method of Hooker.[4]

In the light of Hooker's brilliant investigations on "*ortho–para* rearrangements" of 1,2- and 1,4-naphthoquinones,[5,6] the work-up procedure was easily modified to permit a satisfactory preparation of the furano-1,4-naphthoquinone **3**. The strong acid conditions utilized in the second step are essential for rearranging the 1,2-naphthoquinone **2** to the 1,4-naphthoquinone **3**.

We have isolated the oxidation product A, which is converted under mild acidic conditions to the furano-1,2-naphthoquinone **2**. The analytical data for the bright orange, crystalline compound, mp 128–132.5° dec,[7] were consistent with a molecular formula $C_{17}H_{16}O_5$. The presence of an acetate moiety was supported by the infrared spectrum (KBr pill), which contained ν_{CO} 1730 cm^{-1}. Bands at 1700 and 1665 cm^{-1} resembled those present in the spectrum of the furano-1,2-naphthoquinone **2**. A 1,2-naphthoquinone structure for the product was confirmed by the ultraviolet and visible light absorption data. The absorption spectrum contained λ_{max}^{MeOH} 416 mμ (log ε 3.32) and 336 mμ (log ε 3.25) and was similar to that of model compound **4** and unlike that of **5**.[6]



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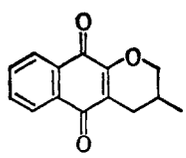

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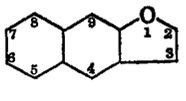
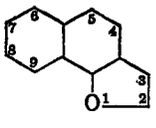
The nmr spectrum indicated that product A, mp 128–132.5° dec, was comprised of two geometrical isomers (**6** and **7**) in the ratio 78:22, respectively. As regards the principal component **6**, the spectrum contained three signals attributable to an AMX spin system. A *trans* relationship for H_x and H_m is supported by the coupling constant for the lower field proton H_x ($\Delta\nu_{H_x}$ 373 cps, $J_{H_xH_m}$ = 2.5 cps), the magnitude of which is more compatible with a dihedral angle of 120–130° than 0°. The additional very weak doublet observed in the X portion of the spectrum ($\Delta\nu_{H_{x'}}$ 398 cps, $J_{H_xH_{m'}}$ = ~7.0 cps) is attributed to

(1) (a) This investigation was carried out under Contract DA-49-193-MD-2862 with the Department of the Army and the U. S. Army Medical Research and Development Command. This paper is Contribution 155 from the Army Research Program on Malaria. (b) The nomenclature in the text follows that adopted by L. F. Fieser for continuing the clarity of S. C. Hooker's papers; see S. C. Hooker, *J. Am. Chem. Soc.*, **58**, 1168 (1936), footnote 6. The preferred nomenclature (*Chemical Abstracts*), utilized in the Experimental Section, is as follows.



naphtho[1,2-*b*]furan



naphtho[1,2-*b*]furan

(2) To our knowledge, there is but one analogous reaction in which the furan system is formed by the oxidative action of mercuric acetate, *e.g.*, the synthesis of menthofuran from isopulegone: W. Treibs, G. Lucius, H. Koegler, and H. Breslauer, *Ann.*, **581**, 59 (1953).

(3) The furano-1,4-naphthoquinone **3** is formed to a small extent (4.4%) in the oxidation reaction, but does not interfere with the isolation and purification of **2**.

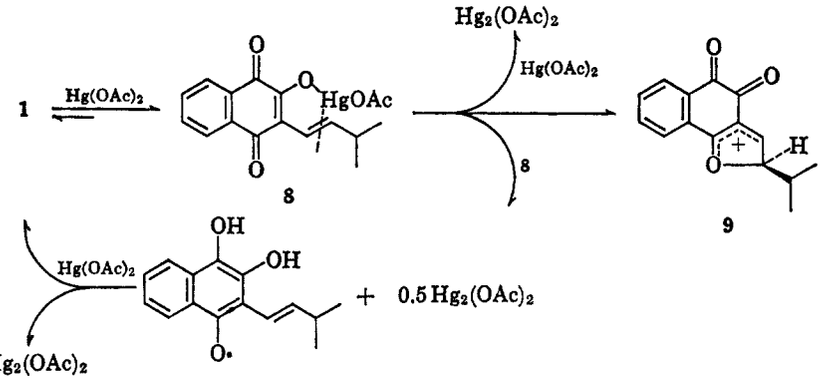
(4) S. C. Hooker, *J. Chem. Soc.*, **69**, 1355 (1896).

(5) S. C. Hooker and A. Steyermark, *J. Am. Chem. Soc.*, **58**, 1202 (1936), and references therein.

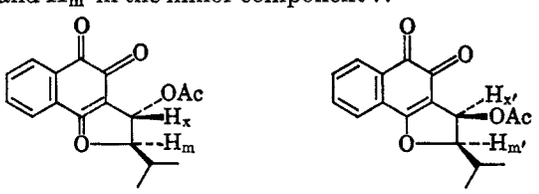
(6) M. E. Ettlinger, *ibid.*, **72**, 3090 (1950).

(7) The melting points of different preparations varied considerably. One sample, for which satisfactory analytical data were obtained, had mp 133–137.5° and proved to be identical in all respects by comparison of infrared, ultraviolet, and nmr spectra.

SCHEME II



spin–spin coupling resulting from a *cis* relationship of $H_{x'}$ and $H_{m'}$ in the minor component **7**.[8]



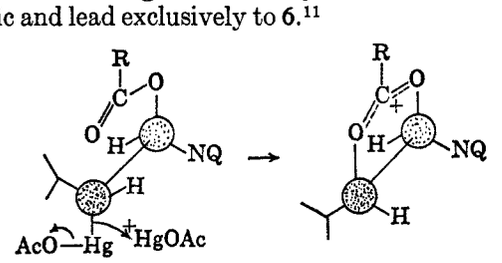
6 **7**

Complete oxidation of isolapachol to a mixture of **2**, **6**, and **7**, required 2 moles of mercuric acetate. If 1 mole of mercuric acetate was employed, a substantial quantity of isolapachol remained unaltered before and after the brief heating period. In all experiments, the inorganic product of the oxidation appeared to be solely mercurous acetate. In the cases of reactions conducted with 2:1 ratio of oxidant–substrate, the substrate could not be detected (tlc) after keeping the solution at room temperature for 30 min. At this point, substrate had been converted to **2**, **6**, **7**, and an orange intermediate observed at the origin of the chromatogram.

This latter, unidentified intermediate, which might be either a mercury chelate or oxymercuration product of **1**, was converted to **2**, **6**, and **7** products by mild warming of the solution, as evidenced by tlc and the observation that an instantaneous precipitation of a further quantity of mercurous acetate set in as the temperature of the reaction solution was raised to 60–70°. That the 2-hydroxy group of isolapachol plays an important role in the oxidative sequence was inferred by the resistance of 2-O-acetylisolapachol to react in any manner with mercuric acetate under the normal conditions of the reaction. In another experiment, hydrolapachol (2-hydroxy-3-isopentyl-1,4-naphthoquinone) also failed to react with mercuric acetate. These two experiments signify the necessity of both the 2-hydroxy group and the external double bond for the oxidative ring closure. The existing experimental data do not allow one, however, to differentiate between substrate–metal electron transfer and oxymercuration[9] as an explanation for the oxidation process.

From the viewpoint of substrate–metal electron transfer, our explanation assumes the mercury chelate **8** as a species which can disproportionate in reaction with another one-electron acceptor, such as mercury(II) or possibly **8**, to give the resonance-stabilized carbonium ion **9**. If disproportionation were concomitant with ring closure, the oxidation could be looked upon as being supported by the formation of the resonance-stabilized ion **9**. The carbonium ion **9** is a satisfactory intermediate for explaining the production of furano-1,2-naphthoquinone **2** (by proton elimination) and the ratio of products **6** and **7** (by thermodynamically controlled solvent addition)[10] (Scheme II).

The oxidation, from the viewpoint of oxymercuration, may be more complex than initially apparent, and conceivably could involve an ionic solvolysis as depicted by **10**. It is noteworthy that acetoxylanchimeric assistance in the solvolysis could preserve stereochemistry, whence ring closure may be rendered stereospecific and lead exclusively to **6**.[11]



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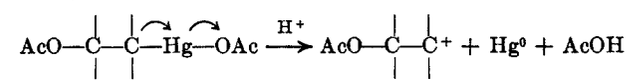
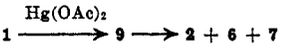
A plausible mechanism includes two steady-state approximations (eq 1) and the assumption that the solvolysis



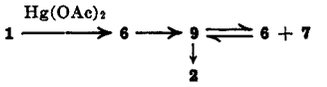
(8) The coupling constants of the H_m and H_x protons in compounds **6** and **7** are in parallelism with the Karplus theoretical "zero-order" approximations for the dependency of coupling constants upon the dihedral angle between vicinal protons.

(9) Oxymercuration is defined as the reaction of mercuric salts with olefins to yield addition products *via* a mercurinium ion; see T. G. Traylor and A. W. Baker, *J. Am. Chem. Soc.*, **85**, 2746 (1963). A dimer has recently been isolated from the oxymercuration of allylbenzene and characterized as having an Hg–Hg bond; see S. Wolfe, P. G. C. Campbell, and G. E. Palmer, *Tetrahedron Letters*, 4203 (1966).

(10) At this point, we wish to emphasize that it has not been established whether carbonium ion **9** is responsible for a concurrent formation of **2**, **6**, and **7**, *e.g.*



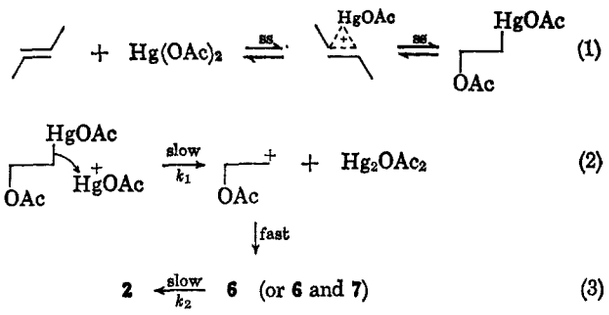
or whether **6** (or **6** and **7**) is the only "true" oxidation product of the reaction and, therefore, an intermediate which decomposes by solvolysis to **2**, *e.g.*



The fact that a mixture of **6** and **7** in acetic acid is rapidly decomposed to **2** at 70°, and more slowly at room temperature, is evidence for supporting the latter case.

(11) The ring-closure step leading to 1,2-naphthoquinone, in preference to 1,4-naphthoquinone, may be regarded as another among the many examples to which little attention has been paid for understanding the underlying causes. These examples have been cited by Ettlinger (*cf.* ref 6).

is kinetically unimportant, as contrasted with the velocity of the bimolecular decomposition denoted by k_1.[12]



Experimental Section[13]

The Isolation of the Dihydrofurano-1,2-naphthoquinones 6 and 7 from the Oxidation Reaction.—To a solution of 13.5 g (41.2 mmoles) of mercuric acetate in 175 ml of acetic acid was added 5.0 g (20.6 mmoles) of isolapachol[4] in 75 ml of acetic acid. A 25-ml portion of acetic acid was used to rinse the isolapachol container. Upon mixing, a deep red-brown reaction solution formed. This solution was kept at room temperature for 30 min, during which a lightening in color was accompanied by a steady precipitation of crystalline mercurous acetate. At this point, a thin layer chromatogram (tlc),[14] eluted in benzene–ethyl acetate–acetic acid (90:10:1), contained the following four zones (in decreasing R_f value): a faint yellow zone (furano-1,4-naphthoquinone, **3**), an orange-red zone (furano-1,2-napthoquinone, **2**), a yellow zone (the dihydrofurano-1,2-naphthoquinones, **6** and **7**), and near the origin an orange zone (a mercury chelate or oxymercuration product of isolapachol???). The temperature of the reaction solution was raised to 65–70° on the steam bath during 15 min and maintained at that temperature for approximately 5 min. A copious quantity of mercurous acetate began separating as the temperature reached 60–65°.[15] A chromatogram then contained only the first three zones mentioned above. After cooling to room temperature, the inorganic salt was filtered and washed with small portions of acetic acid, and the filtrate was evaporated under reduced pressure at 40°. The residue was dried overnight on the freeze dryer.

The orange-red solid was dissolved in a minimum volume of 10% ethyl acetate–benzene and applied to a 38.0 × 4.0 cm column of silica gel.[16] When the column was eluted with 10% ethyl acetate–benzene, the first substance to be eluted was the furano-1,4-naphthoquinone **3**. The yellow eluate was collected and all fractions which afforded a single, yellow spot (tlc) were combined and evaporated. The yellow residue was recrystallized from a small amount of absolute methanol to give **3** (13.3 mg), mp 105.5–107°.

The next fractions of eluate contained a mixture of **3** and **2**. When tlc indicated the furano-1,2-naphthoquinone **2** as principal component, the fraction of **2** was begun and continued *until eluted completely from the column with 10% ethyl acetate–benzene.* The solvent was removed under reduced pressure to yield an orange-red, crystalline residue. This product was taken into a minimum volume of warm ethanol and recrystallized as slender, soft, orange-red needles, (3.08 g), mp 93–94°, by continually adding water beyond the cloudy point, and keeping the mixture at room temperature for 1 hr. The product was identical with a sample of **2**, prepared by the method of Hooker,[4] by mixture melting point and comparison of infrared and nmr spectra.

After the furano-1,2-naphthoquinone **2** had been eluted completely, the eluent was changed to 20% ethyl acetate–benzene. The yellow-orange band was rapidly discharged from the column, and was obtained as a chromatographically uniform band (tlc). The solvent was removed under reduced pressure to give an orange syrup which crystallized slowly at room temperature, or more quickly by covering with a small amount of ether. When it was dissolved in 5.0 ml of chloroform and diluted with ether to a volume of ~20 ml, and the solution kept overnight at −12°, the mixture of **6** and **7** was obtained as heavy, bright orange prisms (0.96 g), mp 127–134° dec. A 0.3-g sample was dissolved in 2.0 ml of chloroform and filtered, and the solution was diluted with ether to a volume of 10 ml; after keeping the solution at about −12° overnight, the collected orange prisms amounted to 0.25 g: mp 128–132.5° dec; infrared, 1730 (s), 1700 (w), 1665 (s), 1620 (s), 1587 (m), and 1570 (m) cm^{-1}; ultraviolet spectrum and visible spectra, λ_{max}^{MeOH} 254 mμ (log ε 4.48), 334 (3.27), 414 (3.34); $\lambda_{inflection}^{MeOH}$ 261 mμ (log ε 4.38), 275 mμ (log ε 3.98); λ_{min}^{MeOH} 230 mμ (log ε 4.03), 313 (3.18), 363 (3.07); nmr spectrum, $\Delta\nu$ 452–497 (aromatic multiplet, 3.8 protons), 398 (doublet, J = 7.0 cps, 0.22 proton), 373 (doublet, J = 2.5 cps, 0.78 proton), 273–290 [multiplet, O>C*H*CH(CH_3)$_2$, 0.91 proton], ν 118–153 [multiplet, C*H*(CH_3)$_2$], 125 cps (singlet, $OCOCH_3$, 4.0 protons), 65.5 [triplet (two overlapping doublets, J = 6.5 cps), CH(CH_3)$_2$, magnetically nonequivalent, 6.0 protons]. The analytical sample, mp 128–132.5° dec, was dried at the boiling point of methylene chloride for 12 hr.

Anal. Calcd for $C_{17}H_{16}O_5$ (300.3); C, 67.99; H, 5.37. Found: C, 67.75; H, 5.44.

The Conversion of the Dihydrofurano-1,2-naphthoquinones 6 and 7 to the Furano-1,2-naphthoquinone 2.—A 13.75-mg sample of **6** and **7**, mp 132.5–137° dec, in 1.0 ml of ethanol was treated with 1 drop of concentrated hydrochloric acid. The solution was warmed to 65° and then kept at room temperature for 5 min. Tlc showed the conversion of **6** and **7** to **2** complete. After dilution with water to 7.0 ml, compound **2** was obtained as soft, orange-red needles (9.2 mg), mp 91.5–92.5°, mmp 92–93°.

The Preparation of 2-Isopropylnaphtho[1,2-*b*]furan-4,5-dione (2).—To a solution of 2.64 g (8.40 mmoles) of mercuric acetate in 30 ml of acetic acid was added a solution of 1.0 g (4.12 mmoles) of isolapachol in 15 ml of acetic acid. A 5-ml portion of acetic acid was used to rinse the isolapachol container. After 30 min at room temperature, the temperature of the reaction mixture was raised to 65–70°[15] (during which mercurous acetate was observed to precipitate more rapidly), and the solution was removed from the heat and allowed to cool to room temperature. The mercurous acetate was removed by filtration and washed with acetic acid, and the filtrate was evaporated under reduced pressure to yield a deep red resin. The resin was freed from a small amount of inorganic salt by solution in ether, filtration, and evaporation.

The syrup was dissolved in 50 ml of absolute ethanol, to which was added, successively, 10 ml of water and 3.0 ml of concentrated hydrochloric acid. This solution was heated at 70–75° for 10–15 min, after which tlc indicated the complete conversion of **6** and **7** to **2**. The solution was removed from the heat source and treated with activated charcoal, the filtrate was stirred magnetially, and a 200-ml portion of water was slowly added (the resulting solution was well beyond the cloudy point). The crystallization process was allowed to proceed for about 10 min and then another 100-ml portion of water was added. After 1 hr, the crop of orange-red needles was collected, washed with 1:1 ethanol–water, and vacuum dried at 40°. The yield was 0.76 g, mp 92–95°. A sample recrystallized by adding water to its ethanolic solution had mp 93.5–95° and was chromatographically pure (tlc).

The Preparation of 2-Isopropylnaphtho[2,3-*b*]furan-4,9-dione (3).—A 1.0-g sample of isolapachol was oxidized, and the mix-

(12) The steady-state approximations have been applied to the equilibria governing olefin–mercuric salt addition compounds. The reversibility of oxymercuration has been demonstrated by a crossover experiment: S. Wolfe, *et al.* (*cf.* footnote 9); see also, K. Ichikawa, H. Ouchi, and S. Araki, *J. Am. Chem. Soc.*, **82**, 3880 (1960). The assumption pertaining to the demercuration step is supported, by analogy, with the rate studies on the decomposition of aralkyl mercuric salts: K. Ichikawa and H. Ouchi, *ibid.*, **82**, 3876 (1960). More recently, the demercuration step in an allylic oxidation by mercuric acetate has been shown to be "Hg(OAc)$_2$-promoted:" Z. Rappaport, P. D. Sleezer, S. Winstein, and W. C. Young, *Tetrahedron Letters*, 3719 (1965).

(13) Melting points were determined on a Kofler hot-stage microscope using a calibrated thermometer. Ultraviolet and visible spectra were measured on a Cary Model 14 spectrophotometer. Nmr spectra were recorded in deuteriochloroform on a Varian Model A-60, using tetramethylsilane as an internal standard. Infrared spectra were measured with a Perkin-Elmer 221 spectrophotometer; samples were prepared in the form of pressed KBr disks. Microanalyses were carried out by Micro-Tech Laboratories, Skokie, Ill.

(14) Thin layer plates were prepared by coating microscope slides with silica gel H. When solutions in acetic acid were spotted, the excess acetic acid was removed before elution by evaporation in a vacuum oven at room temperature.

(15) In another experiment, an oxidation reaction was allowed to stand at room temperature over a weekend (68 hr), after which the oxidation was complete and did not require the heating process.

(16) Grace-Davidson Chemical Co., Baltimore, Md. (Grade 923, mesh size 100–200, specification Mil-D-3176).

ture was handled and worked up to the point as described by the first paragraph in the procedure for **2**.

Using an *uncovered* 250-ml erlenmeyer flask, the dark red syrup in 25 ml of ethanol was treated with an equal volume of concentrated hydrochloric acid, and the resulting solution was disgested at 75–80° for 2.0–2.5 hr, during which a lightening in color could be observed. The hot solution was treated with a small amount of charcoal and filtered, and the filtrate was allowed to stand undisturbed to yield a yellow, crystalline product. A 25-ml portion of water was then added and after 1–3 hr, the product was collected and vacuum dried. The yield was 0.65 g. When recrystallized by adding small amounts of water to the compound's hot methanolic solution, the yield of pure **3** was 0.54 g, mp 104–105 and/or 110–111° (lit.[4] mp 110–111°). The melting point of the product depended upon the crystalline form. As described by Hooker, this substance has a very characteristic crystallization pattern. When obtained as reflecting, brilliant yellow platelets, the compound had mp 104–105 and 110–111°; as canary needles the melting point was 110–111°.

The Determination of the Quantity of the Furano-1,4-naphthoquinone 3 Produced in the Oxidation Reaction.—A 1.0-g sample of isolapachol was oxidized, and the mixture was handled and worked up to the point described by the first paragraph in the procedure for **2**. After being dried overnight *in vacuo*, the residue was dissolved in a minimum amount of benzene and adsorbed on a 25 × 4.5 cm column of Woelm neutral alumina (activity III). The column was eluted with benzene, whereupon good separation of **3** and **2** was obtained. (Compounds **6** and **7** are slowly converted to **2** by the adsorbent.) The yield of crude **3** (chromatographically pure, tlc) was 44.40 mg. Recrystallization from methanol–water gave 30 mg of canary yellow needles, mp 111–112°. The furano-1,2-naphthoquinone **2** was subsequently eluted with benzene–ethyl acetate–acetic acid (90:10:1) and recrystallized from ethanol–water. The yield was 0.60 g, mp 92–95°.

An Approximate Material Balance of the Oxidation Reaction Using 1 Mole of Mercurous Acetate.—Employing 1.0 g (4.12 mmoles) of isolapachol, 1.32 g (4.12 mmoles) of mercuric acetate, and a total volume of 50 ml of acetic acid, an oxidation was carried out as described in the first paragraph for the preparation of **2**. After the oxidation solution had cooled to room temperature, the mercurous acetate was collected, washed successively with acetic acid and ether, and vacuum dried. The yield was 0.98 g (92% of theory). Tlc showed that the solution contained **2**, **6**, and **7** (as one zone), and a considerable amount of isolapachol.

The deep red oxidation solution was evaporated under reduced pressure, first at the water pump, and then using a vacuum pump to remove the last traces of acetic acid. The syrupy residue was taken up in 50 ml of ether and extracted with three 15-ml portions of 1% sodium hydroxide. The combined purple, alkaline extract was filtered and acidified with concentrated hydrochloric acid. The yellow, turbid solution deposited an orange solid, which was collected after keeping the flask in the cold for 1 hr. The vacuum-dried solid (0.38 g) was chromatographically pure (tlc) and was identical with isolapachol. Recrystallized from methanol, the compound was obtained as slender, orange needles, mp 118–122° (lit.[4] mp 120°).

The ether solution, from which the isolapachol was extracted, was washed with water and dried over anhydrous sodium sulfate. Tlc of the solution indicated three components: **2**, **3** (in low concentration), and **6** and **7** (as one zone). After removal of the ether, the syrupy mixture was converted, as previously described, but using 25 ml of ethanol, 5 ml of water, and 10 drops of hydrochloric acid, to **2**. The yield was 0.36 g, mp 91–94°.

The Attempted Oxidation of Hydrolapachol with Mercuric Acetate.—An oxidation was conducted in the usual manner, employing 0.5 g (2.05 mmoles) of hydrolapachol,[17] 1.30 g (4.10 mmoles) of mercuric acetate, and 25 ml of acetic acid. Mercurous acetate did not separate from the solution either before or after the heating period, and tlc indicated hydrolapachol as the sole reaction component. The reisolated hydrolapachol, after recrystallization from methanol–water, amounted to 0.38 g, mp 88–89°, and was identified by tlc and mixture melting point.

The Attempted Oxidation of 2-O-Acetylisolapachol with Mercuric Acetate.—A solution of 0.1 g (0.35 mmole) of isolapachol acetate[4] and 0.23 g (0.70 mmole) of mercuric acetate in 15 ml of acetic acid was kept at room temperature for 22 hr. Precipitation of mercurous acetate was not observed. A chromatogram, eluted in benzene, showed only isolapachol acetate. Brief warming of the solution did not cause oxidation.

(17) S. C. Hooker, *J. Am. Chem. Soc.*, **58**, 1163 (1936).

Registry No.—**1**, 4042-39-1; **2**, 13019-42-6; **3**, 13019-43-7; **6**, 13019-44-8; **7**, 13019-45-9; mercuric acetate, 1600-27-7.

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N-(2-Mercaptoethyl)alanine and Related Compounds[1]

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The synthesis of N-(2-mercaptoethyl)alanine (**3**) and related compounds was undertaken as a result of a general interest in ω-(2-mercaptoethylamino)alkanoic acids accruing from the reported radioprotective properties of N-(2-mercaptoethyl)glycine.[2] Synthesis of the glycine derivative was accomplished in two ways: one[2] involving ring opening of ethyl 1-aziridineacetate with hydrogen sulfide followed by hydrolysis, and the other[2b] by alkylation of 2-(benzylthio)ethylamine with ethyl chloroacetate followed by hydrolysis and debenzylation. A method based on the addition of 2-(tritylthio)ethylamine to acrylic compounds followed by detritylation was recently applied to the synthesis of mercaptoethylated β-alanine derivatives,[3] but is obviously not useful in the synthesis of the α isomers. The method selected for the present investigation was adapted from the previously reported[4] reduction of 2-substituted thiazolidines with sodium borohydride and proved to be advantageous in spite of a subsequently encountered functional group limitation. The route that evolved is outlined in Scheme I.

2-Methyl-2-thiazolidinecarboxylic acid (**1**), the precursor of both **3** and the corresponding carboxamides **6** (**a** and **b**), was prepared by the reported[5] condensation of pyruvic acid and 2-aminoethanethiol in good yields, but the preparation of **1** was later made more convenient by *in situ* neutralization of commercially available 2-aminoethanethiol hydrochloride with triethylamine. The product isolated after ring opening of **1** by sodium borohydride in 2-propanol under reflux and in methanol at room temperature was the water-insoluble N,N′-(dithiodiethylene)bisalanine (**2**), oxidation apparently occurring during the isolation process. The preferred preparation of **2**, however, involved reduction

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(2) (a) E. Felder, F. Bonati, and S. Bianchi, *Experientia*, **15**, 32 (1959); (b) E. Felder and S. Bianchi, German Patent 1,062,705 (1959).

(3) F. I. Carroll, H. M. Dickson, and M. E. Wall, *J. Org. Chem.*, **30**, 33 (1965).

(4) E. L. Eliel, E. W. Della, and M. M. Rogić, *ibid.*, **27**, 4712 (1962).

(5) E. Biekert, J. Sonnenbichler, and D. Hoffmann, *Chem. Ber.*, **95**, 1466 (1962).