the same solvent gave the furoquinoline as a white solid. Recrystallization from hexane–acetone gave 0.45 g (24%) of material, mp 103–104°. Recrystallization from the same solvent pair gave the analytical sample, mp 106–107°.

*Anal.* Calcd for $C_{17}H_{21}NO_3$: C, 71.06; H, 7.37; N, 4.87. Found:[14] C, 70.57; H, 7.20; N, 5.47.

**1-Methyl-2-isobutyl-8-methoxy-2,3-dihydrofuro[2,3-*b*]-4-quinolone.**—A solution of 0.045 g of the above quinoline in 3 ml of iodomethane was heated at reflux 10 min, cooled, and allowed to stand at room temperature for 24 hr. The precipitated solid was collected and washed with hexane to give 0.040 g of off-white solid, mp 135–136°. This material shows $\lambda_{max}$ 217 m$\mu$ (log $\epsilon$ 4.89), 254 (4.87), 258 (sh) (4.87), 303 (4.16), and 330 (3.81). Since this material decomposed on attempted recrystallization, 0.040 g was dissolved in 1 ml of pyridine and heated on the steam bath 22 hr.[15] The solvent was evaporated, the residue was taken up in methylene chloride, washed with water, and dried, and the solvent was removed *in vacuo* leaving 18 mg (66% based on methiodide[16]) of white solid. Recrystallization from ethyl acetate–hexane gave white crystals, mp 90–91°. The infrared spectrum (solution) of this compound was very similar but not identical with that of a sample of (−)-lunacrine, the ultraviolet spectrum in both neutral and acidic solution was identical with that reported for lunacrine.[4a] This compound also has the same $R_f$ value on tlc in two systems (benzene–acetone 4:1 and methanol–hydrochloric acid–water, both on silica gel G) as natural lunacrine. The mother liquors from the recrystallization of the supposed lunacrine gave a small quantity of a yellow picrate, mp 163–165°[17] (*dl*-lunacrine picrate is reported to melt at 211–212°).[4b]

The nmr spectrum of this "lunacrine" is very similar to that of lunacrine,[18] with the exception of a broad multiplet (three protons) between $\delta$ 1.3 and 2.0. The analytical sample, mp 92–93°, was recrystallized from hexane. (*dl*-Lunacrine is reported to melt at 146–148°.)[4]

*Anal.* Calcd for $C_{17}H_{21}NO_3$: C, 71.06; H, 7.37. Found: C, 70.93; H, 7.60.

**Compounds Related to "Demethoxylunacrine."**—The compounds originally reported[1] were recrystallized and resubmitted for analysis as summarized in Table I. This entire series of compounds originally gave analytical data for one less methylene unit. The nmr spectra of all the above are virtually identical with those reported for the 8-methoxy series, except for the aromatic regions and methoxyl group.

**Acknowledgments.**—This work was supported in part by Public Health Service Research Career Program Award 1-K3-GM-5433-01 from the National Institute of General Medical Sciences and in part by Grant GM-08731, also from the National Institute of General Medical Sciences. We wish to thank Dr. Sidney Goodwin for a sample of lunacrine.

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[14] There was insufficient material for reanalysis. It should be noted that calcd for $C_{16}H_{19}NO_3$ is C, 70.31; H, 7.01; N, 5.12.

[15] R. A. Corral and O. O. Orazi, *Tetrahedron*, **21**, 909 (1965). Demethylation with lithium bromide–acetonitrile[4a] also gave adequate results.

[16] Tlc of the mother liquors from formation of the methiodide indicated that this material comprised the bulk of the organic soluble residues from the quaternization.

[17] There was insufficient material for analysis.

[18] N. S. Bhacca, L. F. Johnson, and J. N. Shoolery, "NMR Spectra Catalog," Varian Associates, Palo Alto, Calif., 1962, Spectrum 325.

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# One-Step Synthesis of Polyalkyl-2-iodo-*p*-benzoquinones

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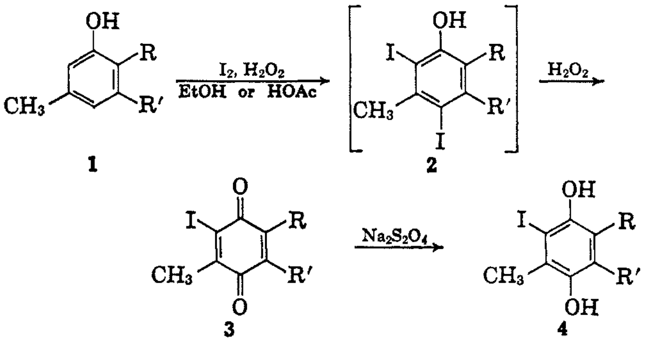
*Received October 21, 1965*

During an investigation of synthetic routes to iodopseudocumoquinone (3, R = R′ = $CH_3$) desired for other studies,[1] it was found that when the oxidative iodination procedure[2] described for the preparation of triiodophenol was applied to pseudocumenol-6 (1, R = R′ = $CH_3$) and other similarly substituted polyalkylphenols 1, it led directly to the iodinated *p*-benzoquinones 3 (Scheme I). This combined iodination and oxidative deiodination reaction proceeded at elevated temperatures in the presence of excess 30% hydrogen peroxide, thus providing a convenient one-step method for the preparation of a variety of di- and trialkyl-2-iodo-*p*-benzoquinones. In Table I are listed a number of *p*-benzoquinones prepared in this manner, and in Table II are shown the iodohydroquinones obtained by reduction of the quinones with sodium dithionite.

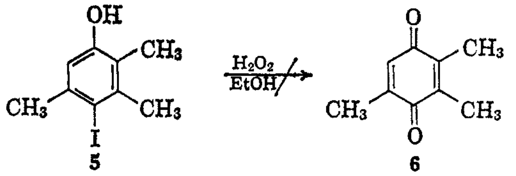
Scheme I



R = alkyl; R′ = H, alkyl

When the iodination of pseudocumenol-6 was carried out at room temperature in the presence of the theoretical amount of oxidant,[3] the diiodophenol 2 (R = R′ = $CH_3$) could be isolated from the reaction mixture. On being heated in alcohol with an excess of hydrogen peroxide, 2 (R = R′ = $CH_3$) rapidly lost iodine and yielded the benzoquinone 3 (R = R′ = $CH_3$), identical with the product obtained directly from pseudocumenol-6.

Oxidative iodination of pseudocumenol-6 with 1 equiv of iodine gave a monoiodinated product whose infrared spectrum shows[4] it to be 4-iodo-2,3,5-trimethylphenol (5). This compound, on attempted oxidation to the known pseudocumoquinone 6 under the conditions used for the conversion of 2 to 3, was recovered unchanged. The relief of steric crowding in the diiodo compound 2 (R = R′ = $CH_3$) may be the reason for



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[1] C. A. Bishop, R. F. Porter, and L. K. J. Tong, *J. Am. Chem. Soc.*, **85**, 3991 (1963).

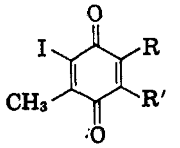
[2] J. E. Marsh, *J. Chem. Soc.*, 3164 (1927).

[3] T. D. Aldoshin and V. S. Chalykh'yan, *J. Gen. Chem. USSR*, **9**, 748 (1939); *Chem. Abstr.*, **34**, 397$^2$ (1940).

[4] Infrared spectra for 2,4-diiodo-5,6-dimethylphenol and 2,4-diiodo-3,5,6-trimethylphenol show sharp oxygen–hydrogen stretching absorptions at 2.95 and 2.9 $\mu$, respectively. The monoiodinated compound has a stronger and broader absorption near 3 $\mu$. This suggests that the hydroxyl group in the monoiodinated compound is not as sterically hindered as in those phenols with iodine in the 2-position. Therefore, we assign the iodine atom in 5 to the 4-position. The authors acknowledge with thanks the help of Miss Thelma Davis of these laboratories in the analysis of the spectrum.

TABLE I

POLYALKYL-2-IODO-*p*-BENZOQUINONES

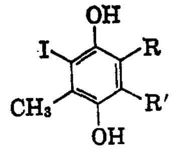


| R | R′ | Mp, °C | Yield, % | Formula | Carbon, % Calcd | Carbon, % Found | Hydrogen, % Calcd | Hydrogen, % Found | Iodine, % Calcd | Iodine, % Found |
|---|---|---|---|---|---|---|---|---|---|---|
| $CH_3$ | H | 81–82[a,b] | 47 | $C_8H_7IO_2$ | 36.7 | 37.0 | 2.7 | 2.8 | 48.3 | 48.0 |
| $CH_3$ | $CH_3$ | 71–73[a] | 48 | $C_9H_9IO_2$ | 39.2 | 39.0 | 3.3 | 3.5 | 46.0 | 45.9 |
| $CH(CH_3)_2$ | H | 62–64[a,c] | 50 | $C_{10}H_{11}IO_2$ | 41.4 | 41.4 | 3.9 | 3.8 | 43.7 | 43.6 |
| $C_{12}H_{25}$ | $CH_3$ | 65–66[d,e] | 49 | $C_{20}H_{31}IO_2$ | 55.9 | 55.8 | 7.2 | 7.0 | 29.4 | 29.0 |

[a] Recrystallized from petroleum ether (bp 66–75°). [b] C. V. Bordeianu [*Ann. Sci. Univ. Jassy,* [I] **23,** 240 (1937); *Chem. Abstr.,* **32,** 5803[2] (1938)] reported mp 79–80°. [c] The reported melting point is 61°: F. Kehrmann, *J. Prakt. Chem.,* [2] **39,** 392 (1889); *ibid.,* [2] **40,** 188 (1889); C. V. Bordeianu, *Arch. Pharm.,* **272,** 8 (1934); *Chem. Abstr.,* **28,** 2339[7] (1934). [d] Recrystallized from acetonitrile. [e] Glacial acetic acid reaction medium heated at 90–95° for 3 hr.

TABLE II

POLYALKYL-2-IODOHYDROQUINONES



| R | R′ | Mp, °C | Yield, % | Formula | Carbon, % Calcd | Carbon, % Found | Hydrogen, % Calcd | Hydrogen, % Found | Iodine, % Calcd | Iodine, % Found |
|---|---|---|---|---|---|---|---|---|---|---|
| $CH_3$ | H | 139–140[a] | 78 | $C_8H_9IO_2$ | 36.4 | 36.5 | 3.3 | 3.2 | 48.1 | 47.9 |
| $CH_3$ | $CH_3$ | 135–136[b,c] | 80 | $C_9H_{11}IO_2$ | 38.8 | 38.8 | 4.0 | 4.2 | 45.6 | 45.9 |
| $CH(CH_3)_2$ | H | 74–75[a,d] | 84 | $C_{10}H_{13}IO_2$ | 41.0 | 41.3 | 4.5 | 4.3 | 43.5 | 43.7 |
| $C_{12}H_{25}$ | $CH_3$ | 105–107[b,c] | 86 | $C_{20}H_{33}IO_2$ | 55.5 | 55.4 | 7.7 | 7.3 | 29.3 | 29.5 |

[a] Recrystallized from petroleum ether (bp 66–75°). [b] Recrystallized from benzene. [c] Melted with loss of iodine. [d] F. Kehrmann [*J. Prakt. Chem.,* [2] **39,** 392 (1889)] reported mp 74–75°.

its facile oxidation. Possible mechanisms suggested for such oxidations involve free-radical intermediates[5] and hydrolyzable quinone ketals.[6]

As already indicated, the combined iodination and oxidative deiodination reaction appears to be limited to phenols having alkyl substituents in the 2,5-position. Oxidative iodination of 3,5-dimethylphenol gave the previously reported[7] triiodophenol, even when only 2 equiv of iodine were used. Oxidants stronger than hydrogen peroxide are apparently required to convert this iodinated phenol to the quinone. When 2,4,6-triiodophenol was treated with cold, fuming nitric acid, 2,6-diiodobenzoquinone was obtained in low yield.[8]

Oxidative iodination of 2,3-dimethylphenol gave as the principal product 2,4-diiodo-5,6-dimethylphenol;[7] no iodinated *p*-benzoquinone could be isolated from the reaction mixture.

## Experimental Section[9]

**Starting Materials.**—Pseudocumenol-6 (2,3,5-trimethylphenol) and 2,3-dimethylphenol are available from Aldrich Chemicals Co., Inc. The remainder, with the exception of 3,5-dimethyl-2-dodecylphenol, were Eastman Kodak Co. products. The latter compound was prepared as follows.

**3,5-Dimethyl-2-lauroylphenol.**—Acylation[10] of 3,5-dimethylphenol (92 g, 0.75 mole) with lauric acid (100 g, 0.5 mole) and boron fluoride (93 g, 1.4 moles) led to 85 g (56%) of light yellow oil, bp 180–182° (1 mm). A portion crystallized from methanol and twice from petroleum ether (bp 30–60°) formed white crystals, mp 42–44°.

*Anal.* Calcd for $C_{20}H_{32}O_2$: C, 79.0; H, 10.5. Found: C, 79.0; H, 10.7.

**3,5-Dimethyl-2-dodecylphenol.**—Hydrogenation (200 atm, 160°) with copper chromite catalyst[11] of 3,5-dimethyl-2-lauroylphenol (60.8 g, 0.2 mole) gave 47 g (81%) of a colorless viscous oil, bp 168–170° (1 mm), which soon solidified. A portion recrystallized from methanol yielded white needles melting at 56–57°.

*Anal.* Calcd for $C_{20}H_{34}O$: C, 82.8; H, 11.8. Found: C, 82.5; H, 11.9.

The following oxidative iodination procedures illustrate the methods used.

**2-Iodo-3,5,6-trimethyl-*p*-benzoquinone. Procedure A.**—A solution of 27.2 g (0.2 mole) of pseudocumenol-6 and 50.8 g (0.2 mole) of iodine in 350 ml of ethanol was stirred at 60°, while 100 ml of 30% hydrogen peroxide (0.98 mole) diluted with 50 ml of ethanol was added, dropwise, over a 2-hr period. After the mixture had been stirred at 70–75° for an additional hour, the brownish solution was cooled to 0–5°. The solid was collected, washed successively with a 5% $NaHSO_3$ solution (150 ml), water (200 ml), and cold (0–5°) 70% aqueous methanol (50 ml), and dried. The orange crystalline powder weighed 35 g (63%), mp 70–73°. Recrystallization from 360 ml of petroleum ether (bp 66–75°) gave 26.7 g (48%) of orange flakes, mp 71–73°.

**Procedure B.**—A stirred solution of 3.8 g (0.01 mole) of 2,4-diiodo-3,5,6-trimethylphenol, prepared as described in the following paragraph, in 75 ml of ethanol was heated at reflux during the dropwise addition of 30% hydrogen peroxide (10 ml) diluted with an equal volume of alcohol. The brown solution was stirred and heated at reflux for 2 hr. The crystalline product, isolated and purified as just described, weighed 1.4 g (51%), mp 71–73°. A mixture melting point determination with the *p*-quinone obtained in the one-step process gave no depression.

**2,4-Diiodo-3,5,6-trimethylphenol.**—To a stirred solution of 27.2 g (0.2 mole) of pseudocumenol-6 and 50.8 g (0.2 mole) of iodine in 350 ml of ethanol was added, dropwise, 21.0 ml of 30%

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(5) J. Cason, *Org. Reactions,* **4,** 305 (1948).

(6) H.-D. Becker, *J. Org. Chem.,* **30,** 982 (1965).

(7) K. Heicken, *Angew. Chem.,* **52,** 263 (1939).

(8) D. E. Kvalnes, *J. Am. Chem. Soc.,* **56,** 669 (1934).

(9) All temperatures are uncorrected.

(10) W. M. McLamore, *J. Am. Chem. Soc.,* **73,** 2221 (1951).

(11) E. C. Armstrong, R. L. Bent, A. Loria, J. R. Thirtle, and A. Weissberger, *ibid.,* **82,** 1928 (1960).

hydrogen peroxide (0.21 mole), the temperature being kept below 20° by external cooling. The reaction mixture was stirred at 18–20° for 6 hr and then allowed to stand at room temperature for 18 hr. The crystalline product that separated on concentration of the reaction mixture in a rotary evaporator to a volume of about 150 ml was collected and dried. Three recrystallizations from 80% aqueous alcohol gave 8.5 g (11%) of colorless crystals, mp 85–86°. No attempt was made to isolate and purify the monoiodinated phenol; it was readily obtained as described below.

*Anal.* Calcd for $C_9H_{10}I_2O$: C, 27.9; H, 2.6; I, 65.4. Found: C, 27.8; H, 2.7; I, 65.4.

**4-Iodo-2,3,5-trimethylphenol.**—The procedure was similar to that described for the diiodophenol except that the 30% hydrogen peroxide (35 ml) was added to the alcoholic solution of 27.2 g (0.2 mole) of pseudocumenol-6 and 25.4 g (0.1 mole) of iodine at 60°. After being stirred at 60° for 1 hr, the almost colorless solution was concentrated under reduced pressure to a volume of about 150 ml and poured into an equal volume of water. The product was collected and washed with water, giving 46.1 g of nearly colorless crystals, mp 100–105°. Two recrystallizations from petroleum ether gave 35.5 g (68%) of colorless needles, mp 112–113°.

*Anal.* Calcd for $C_9H_{11}IO$: C, 41.2; H, 4.2; I, 48.4. Found: C, 41.5; H, 4.3; I, 48.6.

**Attempted Oxidation to Pseudocumoquinone. Procedure B.**—A solution of 5.2 g (0.02 mole) of 4-iodo-2,3,5-trimethylphenol and 10 ml of 30% hydrogen peroxide was heated at reflux for 3 hr and then evaporated to dryness in an air stream. The white crystalline residue (4.9 g) melted at 111–113°. A mixture melting point determination with starting iodinated phenol gave no depression.

**3,5-Dimethyl-2,4,6-triiodophenol. Procedure A.**—A solution of 12.2 g (0.1 mole) of 3,5-dimethylphenol, 25.4 g (0.1 mole) of iodine, and 50 ml of 30% hydrogen peroxide in 250 ml of ethanol was heated at 60° for 1 hr and an additional 30 min at reflux. The white crystalline product, which began to separate from the hot solution after addition of approximately one-half of the hydrogen peroxide, was collected, giving 22.1 g (67%) of white crystals, mp 177–179°, with loss of iodine. Recrystallization from ethanol gave white needles, mp 178–179° dec (lit.[7] mp 177° with brown coloration).

*Anal.* Calcd for $C_8H_7I_3O$: C, 19.2; H, 1.4; I, 76.4. Found: C, 19.4; H, 1.6; I, 76.2.

**2,4-Diiodo-5,6-dimethylphenol. Procedure A.**—A solution of 24.4 g (0.2 mole) of 2,3-dimethylphenol, 50.8 g (0.2 mole) of iodine, and 100 ml of 30% hydrogen peroxide in 450 ml of ethanol was stirred and heated at 60° for 2 hr. The crude product (44 g, 60%) that was collected from the chilled reaction mixture after three recrystallizations from 60% ethanol gave 23.2 g (31%) of almost colorless crystals, mp 82–83° (lit.[7] mp 84.5°).

*Anal.* Calcd for $C_8H_8I_2O$: C, 25.6; H, 2.2; I, 67.9. Found: C, 25.8; H, 2.5; I, 67.7.

**Polyalkyl-2-iodohydroquinones (Table II).**—To vigorously agitated ether solutions of the polyalkyl-2-iodo-*p*-benzoquinones (0.1 mole in 1200–1500 ml of diethyl ether) was added, in a thin stream, a concentrated aqueous solution of sodium dithionite (90%) until the orange color was discharged. About 60 g of $Na_2S_2O_4$ in 300 ml of water was required. The organic layer was separated, washed with water, dried over sodium sulfate, and concentrated to dryness. The residues were recrystallized to give the analyses and melting points indicated.

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# An Improved Synthesis of *dl*-Anonaine

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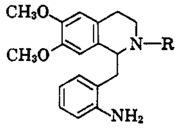
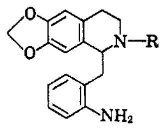
*Received November 15, 1965*

Anonaine (I) is one of the less readily available of the aporphine alkaloids. The naturally occurring base is neither a commercial product nor is it accessible in good yield from any readily available plant source. The racemic alkaloid has been synthesized;[2,3] the described procedure is of little practical utility, however, the final Pschorr cyclization step (employing diamine II) proceeding in only 2.5% yield.[2b,3]

Since we required a quantity of anonaine for other investigations an improved synthesis was devised. Yields recorded in the literature[4–7] (Table I) offer at least modest experimental support for the hypothesis that the presence of a N-alkyl substituent in the heterocyclic ring of an *o*-aminobenzyltetrahydroisoquinoline is a necessary condition for satisfactory results in the Pschorr cyclization.[8] N-Benzylanonaine (III) was therefore chosen as our key synthetic intermediate.

TABLE I

APORPHINE YIELDS IN THE PSCHORR SYNTHESIS

| Aporphine precursor | Yield (%) of corresponding aporphine<br>R = H | <br>R = $CH_3$ | <br>R = $CH_2C_6H_5$ |
|---|---|---|---|
|  | 3.3[a] | 10–15[b] | 20[a] |
|  | 2.5[c] | 24[d] | (31)[e] |

[a] Reference 4. [b] Reference 5. [c] References 2 and 3. [d] Reference 6. [e] Reference 7.

An attempt to synthesize *dl*-N-benzylanonaine by a route strictly parallel to the recently reported synthesis of *dl*-N-benzylnornuciferine (IV)[4] failed. Thus repeated attempts to treat the readily prepared[3] imine V with benzyl bromide did not afford the expected immonium salt VI; after work-up imine V was recovered unchanged in high yield.[9]

The necessary hitherto unreported precursor for the Pschorr cyclization, 1-(*o*-aminobenzyl)-2-benzyl-1,2,3,4-tetrahydro-6,7-methylenedioxyisoquinoline (VII) was prepared, albeit in low yield, by sodium borohydride reduction of V to the corresponding 1-(*o*-nitrobenzyl)-1,2,3,4-tetrahydro-6,7-methylenedioxyisoquinoline (VIII), followed by benzoylation to yield IX, followed by reduction of the aromatic nitro group of IX with hydrazine in the presence of palladium[10] to provide amine X, and, ultimately, further reduction of this amine to VII with lithium aluminum hydride.

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(1) To whom correspondence should be addressed: Department of Chemistry, Wayne State University, Detroit, Mich. 48202.

(2) (a) G. Barger and G. Weitnauer, *Helv. Chim. Acta*, **22**, 1036 (1939); (b) L. Marion, L. Lemay, and R. Ayotte, *Can. J. Res.*, **B28**, 21 (1950).

(3) Barger and Weitnauer[2a] claimed to have synthesized anonaine, obtaining a 22% yield in the last step. This yield represents, however, only a crude hydrochloride; as Marion, *et al.*,[2b] have pointed out, Barger and Weitnauer's *dl*-anonaine was not obtained crystalline. Under these circumstances, the validity of the 22% yield in the Pschorr step is highly questionable.

(4) J. A. Weisbach and B. Douglas, *J. Org. Chem.*, **27**, 3738 (1962).

(5) J. M. Gulland and R. D. Haworth, *J. Chem. Soc.*, 581 (1928).

(6) L. Marion and V. Grassis, *J. Am. Chem. Soc.*, **66**, 1920 (1944).

(7) This work; see Experimental Section.

(8) The theoretical explanation for this phenomenon probably lies in the known effect of N substitution on the conformation of benzyltetrahydroisoquinolines: D. R. Dalton, M. P. Cava, and K. T. Buck, *Tetrahedron Letters*, 2687 (1965).

(9) An investigation is currently under way to determine the cause of the unusual behavior of V toward alkylation.

(10) L. P. Kuhn, *J. Am. Chem. Soc.*, **73**, 1510 (1951).