Preparation of 7*H*-Dibenzo[*de,g*]quinol-7-ones ("7-Oxoaporphines") (1)

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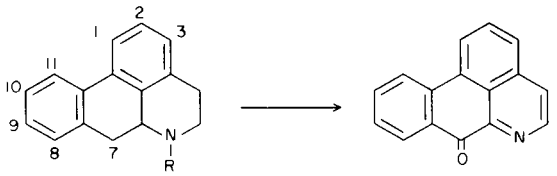
In the course of a continuing study, it was desired to convert a number of alkoxylated aporphines **1** into 7-oxoaporphine systems **2**. Cava and Dalton (2) have con-



1

1a 10,11-diethoxy; R = CH_3
1b 1,2-dimethoxy; R = benzyl
1c 9,10-dimethoxy; R = CH_3
1d 2,3-dimethoxy; R = CH_3
1e no substituents; R = CH_3

2

2a 10,11-diethoxy
2b 1,2-dimethoxy
2c 9,10-dimethoxy
2d 2,3-dimethoxy
2e no substituents

verted noraporphines (**1**; R = H) into 7-oxoaporphines by air oxidation; this procedure, when applied to *N*-alkylaporphines in the present study, resulted in essentially quantitative recovery of starting material. Tomita, *et al.* (3) reported conversion of a short series of alkoxylated aporphines to **2** with Sarrett's reagent (chromium trioxide in pyridine). In those instances where a yield was reported, it was of the order of 10%. Attempts to utilize the Tomita procedure in this laboratory resulted in occasional trace (1%) yields of impure products, and gave extremely erratic results. The method could not be adapted to gram-scale preparative reactions. A disadvantage in the procedure was the difficulty in attaining complete removal of pyridine from the crude reaction mixture prior to the column chromatographic treatment which was essential for isolation of the products. Traces of pyridine hindered the chromatographic separation.

Taylor (4) oxidized 6,7-methylenedioxy-1-benzyl-3,4-dihydroisoquinoline to 6,7-methylenedioxy-1-benzoyl-3,4-dihydroisoquinoline with chromium trioxide in glacial acetic acid (Fieser's reagent). The isoquinoline nucleus was reported not to have been aromatized in the reaction. Application of the Taylor procedure to a variety of aporphines (**1a-e**) permitted isolation of pure 7-oxoaporphines (**2a-e**) in yields of the order of 10%. Some of these products (as indicated in Table I) are new chemical entities. The method is illustrated in some detail for one oxidation.

While the Tomita method (3) seems adequate for very small-scale reactions, such that, as performed by Smith and Sood (5), the product is isolated by preparative thin layer chromatography, the acetic acid method seems to be superior for gram-size lots. In addition, the chromium trioxide-acetic acid reactions are cleaner and the workup is much less tedious than those with pyridine.

Infrared and nuclear magnetic resonance spectra for the 7-oxoaporphine products were consistent with the proposed structures. A mass spectrum of compound **2a** indicated a parent ion of molecular weight 319, corresponding to $C_{20}H_{17}NO_3$, the proposed molecular formula. One of the alkoxylated aporphines utilized in this study (**1d**) has not been previously reported in the literature; it was prepared by variation of literature procedures, and will be the subject of a future communication.

EXPERIMENTAL

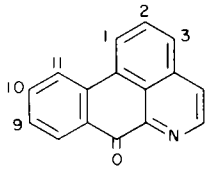
Melting points were determined in open glass capillaries on a Thomas-Hoover Uni-Melt apparatus, and are corrected. Infrared spectra were recorded with Beckman IR-5A and IR-10 instruments, and nuclear magnetic resonance spectra were recorded on a Varian Associates T-60 instrument. Elemental analyses were performed by the Microanalytical Service, College of Pharmacy, The University of Iowa. The mass spectrum was obtained from the Mass Spectrometry Center, Purdue University.

10,11-Diethoxybenzo[*de,g*]quinolin-7-one (2a).

A mixture of 31 g. (0.0947 mole) of 10,11-diethoxyaporphine (prepared by treatment of the hydrochloride salt of **1a** with excess concentrated ammonium hydroxide), 31 g. (0.31 mole) of chromium trioxide, and 310 ml. of glacial acetic acid was gently warmed on a steam bath for 1-4 minutes, until a vigorous exothermic reaction was initiated. The reaction mixture was removed from the steam bath and was permitted to stand at room temperature for 23 hours. The internal temperature of the mixture rose to 119° before subsiding. The dark reaction mixture was diluted with 500 ml. of water and after chilling, the mixture was filtered and the dark yellow solid which was collected was reserved. The filtrate was extracted with 500 ml. of chloroform. The reserved solid was dissolved in the chloroform extract and this solution

TABLE I

Oxoaporphines



Compound	Substituents	Starting Material	Yield %	M.p., °C	Formula	Analysis Calculated	Found
2a	10,11-diethoxy	**1a**	10	175-178 (a)	$C_{20}H_{17}NO_3$	C, 75.20 H, 5.36 N, 4.41	C, 75.44 H, 5.39 N, 4.35
2b	1,2-dimethoxy	**1b**(e)	5	213-216.5 (decompose) (a,b)	$C_{18}H_{13}NO_3$	C, 74.20 H, 4.50 N, 4.83	C, 74.00 H, 4.41 N, 4.65
2c	9,10-dimethoxy	**1c**(f)	9	255-256 (d)	$C_{18}H_{13}NO_3$	C, 74.20 H, 4.50 N, 4.83	C, 74.15 H, 4.50 N, 4.76
2d	2,3-dimethoxy	**1d**	9	190-191 (c)	$C_{18}H_{13}NO_3$	C, 74.20 H, 4.50 N, 4.83	C, 74.55 H, 4.50 N, 4.50
2e	none	**1e**(g)	6	222-222.5 (a)	$C_{16}H_{19}NO$	C, 83.10 H, 3.92 N, 6.05	C, 82.80 H, 4.07 N, 5.85

(a) From benzene. (b) Literature m.p. 208-210° (3) and 210-211° (11). (c) From methanol-water. (d) From methanol. (e) Prepared by the method of Vavrek, *et al.*, (9). (f) Prepared by the method of Cannon and Aleem (10). (g) Prepared by the method of Gadamer, *et al.*, (12).

was washed with two 400 ml. portions of saturated sodium chloride solution then with two 400 ml. portions of water. The organic solution was dried over anhydrous potassium carbonate, filtered, and the filtrate was evaporated under reduced pressure at room temperature to give a dark oily residue which was chromatographed on neutral alumina (80-120 mesh) and eluted with chloroform. A clean yellow band was eluted and was taken to dryness under reduced pressure (room temperature) to leave a yellow semi-solid which was recrystallized to afford yellow needles (see Table I); ir (potassium bromide) 1650 cm^{-1} (conjugated C=O); nmr (deuteriochloroform) δ 1.35-1.65 (sextet, 6H; C-CH_3); 3.93-4.38 (overlapping quartet, 4H; OCH_2); 7.10 (d, 1H, Ar-*H*); 7.35-7.97 (m, 3H, Ar-*H*); 8.38 (d, 1H, Ar-*H*); 9.00 (d, 1H, Ar-*H*); and 9.57 (q, 1, Ar-*H*).

An oxime was prepared by refluxing a mixture of 0.2 g. (0.000626 mole) of **2a**, 0.0735 g. (0.00106 mole) of hydroxylamine hydrochloride, 0.0735 g. (0.0005 mole) of potassium carbonate, 3.5 ml. of methanol, and 0.3 ml. of water on a steam bath for 13 hours. The hot solution was filtered and the filtrate was evaporated under reduced pressure (steam bath) to give a yellow semi-solid which was recrystallized twice from methanol (charcoal) to afford 0.182 g. of a fluffy yellow solid, m.p. 173-175°. Mixture melting point determination of this product and **2a**, 162-164°.

Anal. Calcd. for $C_{20}H_{18}N_2O_3$: C, 71.84; H, 5.43; N, 8.38. Found: C, 72.08; H, 5.40; N, 8.20.

dl-10,11-Diethoxyaporphine Hydrochloride (**1a**) Hydrochloride.

This was prepared by a combination of methods of Skaletzky, *et al.* (6) and of Cannon, *et al.* (7). To a stirred suspension of 18 g. (0.428 mole) of 57% oil suspension of sodium hydride in 500 ml. of dimethylsulfoxide was added 40 g. (0.13 mole) of apomorphine hydrochloride, then 60 g. (0.299 mole) of ethyl *p*-toluenesulfonate in 300 ml. of anhydrous ether was slowly added. The mixture was stirred for 13 hours and was permitted to stand at room temperature for 10 hours. After addition of 700 ml. of water to the reaction mixture, it was extracted with three 800 ml. portions of ether. The combined extracts were washed with two 700 ml. portions of water and dried over anhydrous magnesium sulfate. Filtration and evaporation of the filtrate under reduced pressure (steam bath) gave an oily residue which was dissolved in 70 ml. of concentrated hydrochloric acid and 80 ml. of water. This solution was extracted with three 300 ml. portions of chloroform, and the combined extracts were dried over anhydrous magnesium sulfate. Filtration and evaporation of the filtrate under reduced pressure (steam bath) afforded a semi-solid residue which was recrystallized from ethanol-ether (charcoal) to give 36.07 g. (94%) of white needles, m.p. 255-259.5° (decompose), literature (8) m.p. 250-251°.

Anal. Calcd. for $C_{21}H_{26}ClNO_2$: C, 70.08; H, 7.28; N, 3.89. Found: C, 70.09; H, 7.29; N, 3.76.

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