afford **7a** as an oil (360 mg, 89%). An analytical sample was obtained after chromatography on a silica gel column eluting with chloroform as a colorless oil, $n^{20}D$ 1.5163.

Anal. Calcd for $C_9H_{14}O$: C, 78.21; H, 10.21. Found: C, 78.27; H, 10.15.

5-Oxahomobrendane (6).—Catalytic hydrogenation of **2** (1.70 g, 10.0 mmol) with 5% Pd/C (1.7 g) in 4% (w/v) methanolic sodium hydroxide solution (50 ml) at room temperature and under atmospheric pressure afforded a colorless oil (1.02 g, 74%) after work-up as usual. Sublimation of the oil at 80° gave **6** as colorless crystals: mp 92–96° (sealed tube); ir (KBr) 2925, 1456, 1085, 1056, 1038, and 1017 cm^{-1}.

Anal. Calcd for $C_9H_{14}O$: C, 78.21; H, 10.21. Found: C, 78.40; H, 10.02.

Conversion of 4 to Bicyclo[3.3.1]nonane (8).—To a mixture of liquid ammonia (50 ml) and sodium metal (1.0 g, 43 g-atoms) was added an ethanol (0.1 ml) solution of **4** (0.30 g, 1.3 mmol). After the mixture was stirred for 8 hr at −78° and ammonia was removed, the work-up afforded a colorless syrup (40 mg) which revealed ir absorption at 1638 cm^{-1} ($CHCl_3$). Catalytic hydrogenation of this syrup with 5% Pd/C (50 mg) in ethanol afforded **8** as a major product on glpc analysis. An authentic sample of **8**[16] prepared from $NaBH_4$ reduction of bicyclo[3.3.1]nonane-2,6-dione bistosylhydrazone (**9**)[19] had the same retention time on two different columns (10% silicone SE-30 on Chromosorb W and 10% Apiezon on Chromosorb W).

3-Bromo-5-oxatricyclo[5.2.1.0^{4,8}]dec-2-ene (10).—To a vigorously stirred mixture of 50% potassium hydroxide (500 g), benzene (30 ml), benzyltriethylammonium chloride (500 mg, 2.2 mmol), and **1** (2.4 g, 20 mmol) was added bromoform (101 g, 0.40 mol) in 10 hr at 20°. After stirring was continued for a further 12 hr, work-up as above gave a dark brownish oil (4.13 g) which was purified on an alumina column eluting with methylene chloride to give an oily mixture (2.25 g) of **10** (relative yield 58%, total yield 31%) and five other minor products (*ca.* 42%) on glpc analysis. Further purification of this oil on an alumina column eluting with *n*-hexane–benzene afforded **10** as a colorless oil (865 mg, 20%): $n^{28.5}D$ 1.5552; ir (neat) 2930, 2855, 1620, 1032, 796, 765, and 692 cm^{-1}; nmr (CCl_4) τ 3.65 (d, 1, $J_{1,2}$ = 7.3 Hz, H_2), 5.53 (d, 1, $J_{4,5}$ = 6.6 Hz, H_4), 5.91 (t, 1, $J_{5,6}$ = $J_{6,7}$ = 8.8 Hz, H_{6x}), 6.70 (d of d, 1, $J_{6,6}$ = 8.8, $J_{6,7}$ = 3.8 Hz, H_{6n}), 7.00–7.72 (m, 3, H_1, H_7, and H_8), and 7.75–8.80 (m, 4, 2 H_9 and 2 H_{10}).

Anal. Calcd for $C_9H_{11}OBr$: C, 50.26; H, 5.15. Found: C, 50.41; H, 5.00.

On catalytic hydrogenation with 5% Pd/C in methanolic sodium hydroxide solution at room temperature and under atmospheric pressure, **10** afforded **6** (97%).

5-Oxaprotoadamantane (12).—To a solution of mercuric acetate (1.152 g, 3.61 mmol) and sodium acetate (295 mg, 0.360 mmol) in water (10 ml) was added a solution of **7a** (414 mg, 3.00 mmol) in methanol (1.5 ml). After the mixture was stirred for 1 hr at room temperature, the mixture was diluted with water (30 ml) and extracted with chloroform (3 × 10 ml). The combined extracts were dried (Na_2SO_4) and evaporated to afford an oily product (**11**) (1.20 g, 100%), which was treated with sodium borohydride (150 mg, 3.95 mmol) in 3.4% aqueous sodium hydroxide (24 ml) for 6 hr at room temperature. Work-up in the usual way afforded **12** as crystals which were sublimed at 120° (25 mm) to give analytically pure **12** (355 mg, 83%): mp 175–178° (sealed tube); ir (KBr) 2925, 1184, and 1092 cm^{-1}.

Anal. Calcd for $C_9H_{14}O$: C, 78.21; H, 10.21. Found: C, 78.36; H, 10.06.

10-Acetoxy-5-oxaprotoadamantane (13).—A mixture of **7a** (138 mg, 1.00 mmol) and lead tetraacetate (886 mg, 2.00 mmol) in chloroform (40 ml) was refluxed for 1 day. The cooled mixture was washed with 5% aqueous sodium hydroxide (2 × 10 ml) and water (10 ml) successively. The dried (Na_2SO_4) organic layer was evaporated to give **13** as an oil (175 mg, 89%). An analytical sample was obtained by preparative tlc (silica gel, 50% benzene–methylene chloride) as an oil: $n^{23.5}D$ 1.5035; ir (neat) 2940, 1730, 1240, and 1195 cm^{-1}; mass spectrum *m/e* 196 (M^+); nmr ($CDCl_3$) τ 5.24 (m, 1, H_{10}), 5.77–6.47 (m, 3, $2H_4$ and H_6), 7.17–9.06 (m, 9, other ring protons), and 7.95 (s, 3, $COCH_3$).

Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 67.31; H, 8.23.

Registry No.—*endo*-**1**, 15507-06-9; *exo*-**1**, 13360-81-1; **2**, 39833-55-1; **3**, 39833-56-2; **4**, 39833-57-3; **5**, 39833-58-4; **6**, 39837-56-4; **7a**, 39837-57-5; **10**, 39837-58-6; **11**, 39837-59-7; **12**, 39837-60-0; **13**, 39837-61-1; dichlorocarbene, 1605-72-7; dibromocarbene, 4371-77-1.

(19) H. Musso and U. Biethan, *Chem. Ber.*, **100**, 119 (1967).

Notes

Chemistry of Heterocyclic Compounds. 8. A One-Step Synthesis of 2-Hydroxy-4*H*-quinolizin-4-ones[1]

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In connection with a current project related to construction of heteromacrocycles, we needed large quantities of substituted ethyl 2-pyridylacetates. The simplest preparation of ethyl 2-pyridylacetate is the condensation[2] of 2-picolyllithium with diethyl carbonate under very mild conditions.[3] After prolonged extraction with petroleum ether (bp 30–60°), the major side product, 1,3-di(2-pyridyl)acetone, was recovered in trace amounts, as indicated by analysis of its dipicrate.[2]

Repetition of this procedure is easily accomplished. However, in an initial attempt to isolate increased yields of **1** and **5**, during the work-up procedure the strongly alkaline aqueous solution was neutralized to a pH of 7.5–8 by addition of dilute hydrochloric acid; extraction with chloroform afforded additional quantities of **1** and **5**, as well as the previously undetected 1-carboethoxy-2-hydroxy-3-(2-pyridyl)-4*H*-quinolizin-4-one (**4**). Structural assignment[4] of **4** was based

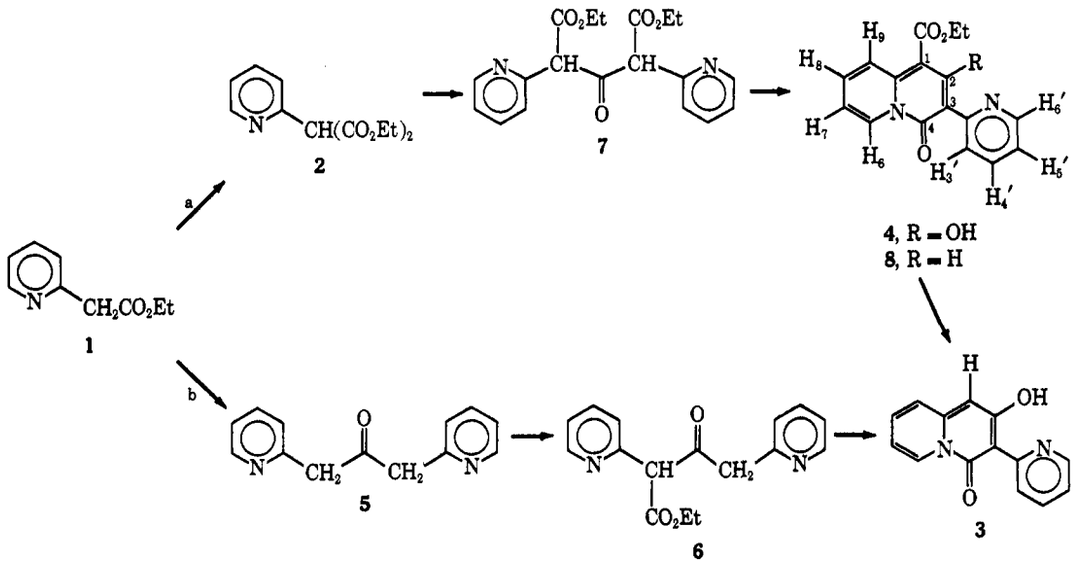
(1) (a) This research has been supported by Public Health Service Grant No. 5-RO1-MS-09930 from the National Institute of Neurological Diseases and Stroke, the donors of the Petroleum Research Fund, administered by the American Chemical Society, and the Research Corporation. (b) Presented in part at the 28th Southwest Regional Meeting of the American Chemical Society, Baton Rouge, La., Dec 1972.

(2) N. N. Goldberg, B. M. Perfetti, and R. Levine, *J. Amer. Chem. Soc.*, **75**, 3843 (1953).

(3) Alternate routes are known; see references in ref 2, as well as K. Winterfeld and K. Flick, *Arch. Pharm. (Weinheim)*, 448 (1956), and K. Winterfeld and K. Nonn, *Pharmazie*, **29**, 337 (1965).

(4) The infrared spectral data of related compounds have been previously assigned.

SCHEME I



upon degradation[5] to 2-hydroxy-3-(2-pyridyl)-4*H*-quinolizin-4-one (**3**)[6] and upon nmr analysis. The nmr spectral comparison of **3** and **4** is particularly important in establishing the structure **4**. In **3** and **4**, the most downfield absorptions at δ 18.3 and 19.75, respectively, indicate the presence of a hydroxyl group proton that is strongly hydrogen bonded to the pyridyl ring nitrogen atom. Occurrence of the unusually low-field resonance at δ 9.34 and 9.29 for the pyridyl H-3′ proton in **3** and **4** is possible only if the pyridyl ring exists in a planar conformation with the quinolizinone ring; thus proton H-3′ is subjected to the close proximity of the C-4 carbonyl function. The signals at δ 9.00 and 9.11 in **3** and **4**, respectively, are assigned to H-6.[7] The low-field position is attributed to a combination of a long-range deshielding peri effect due to the C-4 carbonyl function and an α effect of the amido nitrogen atom. In **4**, the H-9 proton experiences a similar peri effect from the C-1 carboethoxy group; however, in **3**, the absence of this long-range interaction causes the H-9 resonance to shift upfield by ~0.5 ppm. The remaining chemical shifts and coupling constants are in excellent accord with the assigned structures.

Self-condensation of ethyl 2-pyridylacetate (**1**) has been demonstrated[6,8] to afford **3** *via* the pathway **1** → **6** → **3**. Similarly, the preparation of 1-carboethoxy-3-(2-pyridyl)-4*H*-quinolizin-4-one (**8**) has been accomplished utilizing ethyl orthoformate as the source of the C-3 ring atom.[9] Unexpected formation of the major isolated quinolizinone **4**, which possesses both the 1-carboethoxy group and functionality in the 2 position, has been envisaged as proceeding through two possible routes (Scheme I). Alterations in reaction conditions permit the distinction between the two routes. More vigorous conditions result in (a) isolation of the intermediate diethyl 2-pyridylmalonate (**2**) along with **4**, and (b) the absence of detectable quantities of ketone **5**, which by further carboethoxylation and subsequent cyclization would generate **3**. These results suggest that the formation of quinolizinone **4** involves carboethoxylation of **1** and then nucleophilic substitution by the carbanion of **1** or **2** forming **7**, which cyclizes to give **4** (route a). The alternative of further carboethoxylation of **6** to give **7** was deemed unlikely under the reaction conditions.

Isolation of **4** is uncomplicated since the major impurities are easily removed by distillation. No attempt has been made to optimize the reaction conditions.

Experimental Section[10]

Ethyl 2-pyridylacetate was prepared by the method of Goldberg, *et al.*,[2] from 2-picolyllithium and diethyl carbonate. Work-up procedure deviated slightly from the literature procedure. The reaction mixture was poured into 200 g of ice water and extracted with several 200-ml portions of ether. The combined ethereal phases were dried with anhydrous magnesium sulfate, concentrated *in vacuo* to remove starting 2-picoline, and distilled to afford 13.4 g (41%) of ethyl 2-pyridylacetate: bp 110–116° (6 mm) [lit.[2] bp 110–113° (6 mm)]; ir (Nujol) 1738 (C=O), 1597, 1160 (CO), 1036 cm^{-1}; nmr ($CDCl_3$) δ 1.23 ($-CH_2CH_3$, t, J = 7 Hz), 3.83 ($-CH_2CO$, s), 4.17 ($-CH_2CH_3$, q, J = 7 Hz), 7.0–7.8 (pyr H, m), and 8.45–8.65 (6-pyr H, m). The residue chromatographed on silica gel G [cyclohexane–ethyl acetate (1:1)] affording an additional 459 mg of ethyl 2-pyridylacetate and 3.0 g (7.1%) of di-2-picolyl ketone: bp 170–180° (0.7 mm) [lit.[4] bp 130–135° (0.05 mm)]; picrate (recrystallized with ethanol) mp 210° (lit.[11] mp 191–191.5°).

Anal. Calcd for dipicrate ($C_{25}H_{18}N_8O_{15}$): C, 44.78; H, 2.71; N, 16.72. Found: C, 44.98; H, 2.62; N, 16.77.

The aqueous layer was then adjusted with dilute acid to pH 7.5–8 and extracted with chloroform. Chromatography of the dried (magnesium sulfate) chloroform extract gave 100 mg of

(5) T. Kappe, *Monatsh. Chem.*, **98**, 874 (1967).

(6) K. Winterfeld, W. Zengerling, and M. Rink, *Justus Liebigs Ann. Chem.*, **597**, 104 (1955).

(7) K. T. Potts and M. Sorm, *J. Org. Chem.*, **36**, 8 (1971).

(8) K. Winterfeld, G. Wald, and M. Rink, *Justus Liebigs Ann. Chem.*, **588**, 125 (1955).

(9) (a) G. R. Clemo, W. M. Morgan, and R. Raper, *J. Chem. Soc.*, 1025 (1936); (b) N. J. Leonard and R. E. Beyler, *J. Amer. Chem. Soc.*, **70**, 2298 (1948); (c) *ibid.*, **72**, 1316 (1950); (d) S. I. Goldberg and A. H. Lipkin, *J. Org. Chem.*, **37**, 1823 (1972).

(10) Melting points were recorded in sealed capillary tubes on a Thomas-Hoover melting point apparatus and are uncorrected. Infrared spectra were determined on a Perkin-Elmer 621 spectrophotometer. Nmr spectra were determined on either a Varian Associates Model HA-100 or Perkin-Elmer Model R12-B spectrometers; chemical shifts are given in parts per million relative to TMS as an internal standard. Analyses were performed by Mr. R. Seab in these laboratories.

(11) R. Bodalski, J. Michalski, and B. Mlotkowska, *Rocz. Chem., Ann. Soc. Chim. Polonorum*, **43**, 677 (1969); *Chem. Abstr.*, **71**, 61159w (1969).

ethyl 2-pyridylacetate, 1.11 g of di-2-picolyl ketone, and 24 mg of 1-carboethoxy-2-hydroxy-3-(2-pyridyl)-4*H*-quinolizin-4-one (**4**): mp 166–167°; nmr[12] ($CDCl_3$) δ 1.44 (t, J = 7 Hz, $-CH_2CH_3$), 4.47 (q, J = 7 Hz, $-CH_2CH_3$), 6.82 (ddd, J = 7.5, 6.5, 1.5 Hz, H_7), 7.22 (ddd, J = 7.5, 6.5, 1.2 Hz, H_5'), 7.37 (ddd, J = 9.2, 6.5, 1.4 Hz, H_8), 7.71 (ddd, J = 9.2, 1.5, 0.9 Hz, H_9), 7.92 (ddd, J = 8.6, 7.5, 1.9 Hz, H_4'), 8.29 (ddd, J = 5.3, 1.9, 1.0 Hz, H_6'), 9.11 (ddd, J = 7.5, 1.4, 0.9 Hz, H_6), 9.29 (ddd, J = 8.6, 1.2, 1.0 Hz, H_3'), and 19.75 (broad s, -OH); ir (Nujol) 1700 (ester), 1652, 1630, 1602, 1557, and 1231 cm^{-1}; mass spectrum m/e 310 (M^+), 309, 264 ($M^+ - C_2H_6O$), 237 ($M^+ - C_3H_5O_2$), 181, 146, 91, 78 (C_5H_4N).

Anal. Calcd for $C_{17}H_{14}N_2O_4$: C, 65.78; H, 4.55; N, 9.03. Found: C, 65.56; H, 4.46; N, 8.99.

Reaction of 2-Picolyllithium with Diethyl Carbonate. 1-Carboethoxy-2-hydroxy-3-(2-pyridyl)-4*H*-quinolizin-4-one (**4**).—To a solution of phenyllithium (Alfa Chemical Co., 0.6 mol, 2.2 *M* in benzene–ether) in 500 ml of ether, 2-picoline (bp 128–129°, 56 g, 0.6 mol) was added over a 10-min period. The solution was refluxed for 30 min, and then diethyl carbonate (47 g, 0.4 mol) in 50 ml of ether was added rapidly. Reflux was maintained for an additional 30 min. The mixture was cooled, poured into ice water, adjusted with acid to pH ~8, and extracted with chloroform. After removal of the solvents, as well as unreacted 2-picoline, the residue was fractionally distilled, affording 2.0 g of ethyl 2-pyridylacetate, bp 110–113° (6 mm).

The distillation residue (11.7 g) was chromatographed, affording 917 mg of ethyl 2-pyridylacetate, 6.0 g (14%) of **4** (mp 166–167°), and 150 mg (1%) of 3-hydroxy-3-(2-pyridyl)-4*H*-quinolizin-4-one (**3**): mp 175–177° (lit.[6] mp 181–182°); nmr ($CDCl_3$) δ 6.30 (d, J = 0.75 Hz, H_1), 6.73 (five lines), 7.21 (ddd, J = 6.0, 5.0, 1.0 Hz, H_5'), 7.21 (m, H_8 and H_9), 7.89 (ddd, J = 8.5, 6.0, 1.0 Hz, H_4'), 8.36 (ddd, J = 5.0, 1.9, 1.0 Hz, H_6'), 9.00 (broad d, H_6), 9.34 (ddd, J = 8.5, 1.0, 1.0 Hz, H_3'), and 18.3 (broad s, -OH); ir (Nujol) 3500–3100 (broad, OH), 1667, 1641, 1613, and 1589 cm^{-1}.

2-Hydroxy-3-(2-pyridyl)-4*H*-quinolizin-4-one (**3**).—The ester **4** (1.00 g, 3.22 mmol) suspended in 100 ml of a 5% sodium hydroxide solution was refluxed for 8 hr. After cooling to ambient temperature, the pH was adjusted to 7.5–8. The solution was extracted with chloroform, dried with anhydrous sodium sulfate, and concentrated *in vacuo*, affording 630 mg (82%) of 2-hydroxy-3-(2-pyridyl)-4*H*-quinolizin-4-one, mp 174.5–176°. Recrystallization from ethanol gave a sample of pure **3**, mp 176.5–178°.

Reaction of 2-Picoline with Diethyl Carbonate and Sodium Hydride.—Sodium hydride (50% dispersion, 2.15 g, 0.05 mol) in 1,2-dimethoxyethane (DME, 25 ml) was stirred under nitrogen with addition of a solution of 2-picoline (4.65 g, 0.05 mol), diethyl carbonate (11.8 g, 1.10 mol), and DME (20 ml). After the mixture was refluxed for 8 hr, it was poured into ice water. The pH of the aqueous layer was adjusted with dilute acid to 7.5–8 and the layer was extracted with chloroform. The extract was dried with sodium sulfate and concentrated *in vacuo*, removing all solvents and unreacted starting materials. Chromatography of the remaining yellow oil afforded 322 mg (2.7%) of diethyl 2-pyridylmalonate: bp 130–132° (1 mm); nmr ($CDCl_3$) δ 1.21 ($-CH_2CH_3$, t, J = 7 Hz), 4.22 ($-CH_2CH_3$, q, J = 7 Hz), 5.04 (CHCO, s), 7.05–7.88 (pyr H, m), and 8.44–8.65 (6-pyr H, m).

Anal. Calcd for $C_{12}H_{15}NO_4$: C, 60.76; H, 6.38. Found: C, 61.06; H, 6.40.

Further elution afforded 1.099 g (13.3%) of ethyl 2-pyridylacetate [bp 110–117° (6 mm)], 131 mg (1.7%) of 1-carboethoxy-2-hydroxy-3-(2-pyridyl)-4*H*-quinolizin-4-one (**4**, mp 166–168°), and only traces of **3**.

Registry No.—**2**, 39541-69-0; **3**, 39541-70-3; **4**, 39541-71-4; **5** dipicrate, 39541-72-5; 2-picolyllithium, 39541-73-6; diethyl carbonate, 105-58-8; 2-picoline, 109-06-8; sodium hydride, 7646-69-7.

(12) The nmr spectrum of **4** will appear following these pages in the microfilm edition of this volume of the journal. Single copies may be obtained from the Business Operations Office, Books and Journals Division, American Chemical Society, 1155 Sixteenth St., N.W., Washington, D. C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JOC-73-2234.

Unambiguous Synthesis of a Monocyclic 5,6-Dihydro-1,2-oxazine[1]

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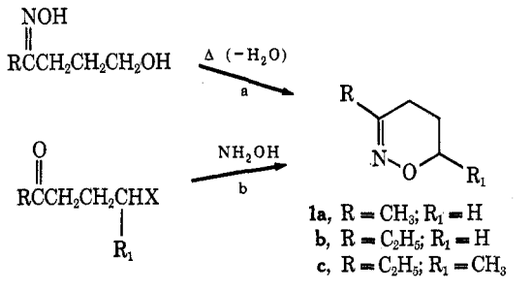
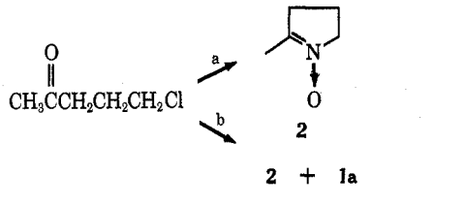
Recent review articles[2] to the contrary, considerable ambiguity exists regarding the published procedures[3,4] for the synthesis of monocyclic 4*H*-5,6-dihydro-1,2-oxazines. Neither Marshall and Perkin's cyclodehydration of a γ-hydroxy oxime (eq 1, path a) nor Wohlgemuth's oximation of a γ-halo ketone unequivocally produces the desired oxazine (eq 1, path b).[5,6]



(1)

Utilizing the procedure of Wohlgemuth,[4] 5-chloro-2-pentanone was treated with hydroxylamine hydrochloride–potassium carbonate in the molar ratio 1.0:1.1:0.5 (eq 2, path a). A compound, **2**, was obtained which analyzed for C_5H_9NO and which possessed all the physical properties previously described.[6] If this were 3-methyl-4*H*-5,6-dihydro-1,2-oxazine (**1a**), it would not be expected to show any significant uv absorption above 220 nm.[8] However, a maximum was observed at 227 nm (ϵ 8700). This, together with the ir data presented in Table I, led us to assign the structure 2-methylpyrroline 1-oxide (**2**) to this material.



(2)

(1) Work done at Seton Hall University, South Orange, N. J. 07079.

(2) (a) R. L. McKee in "Heterocyclic Compounds," Vol. 17, A. Weissberger, Ed., Interscience, New York, N. Y., 1962, p 329; (b) N. H. Cromwell in "Heterocyclic Compounds," Vol. 6, R. E. Elderfield, Ed., Wiley, New York, N. Y., 1957, p 559.

(3) J. R. Marshall and W. H. Perkin, *J. Chem. Soc.*, 861 (1891).

(4) H. Wohlgemuth, *Ann. Chim. (Paris)*, **2**, 403 (1914).

(5) Attempts to reproduce Marshall and Perkin's work have met with conflicting results.[7] Our own attempts to prepare **1a** by the author's procedure were unsuccessful.

(6) Wohlgemuth reported only that the compounds obtained were "water soluble, reduced ammoniacal silver nitrate in the cold and Fehling's solution when boiled."[4]

(7) (a) H. E. Glynn and W. H. Linnell, *Quart J. Pharmacol.*, **5**, 496 (1932); (b) M. Carmack, O. H. Bullitt, Jr., G. R. Handrick, L. W. Kissinger, and I. Von, *J. Amer. Chem. Soc.*, **68**, 1220 (1946).

(8) C. N. R. Rao, "Ultraviolet and Visible Spectroscopy," Butterworths, London, 1961, pp 31–32.