with 10% hydrochloric acid and extracted with ether. From the bicarbonate extract of the ethereal solution, an oily acidic substance with the characteristic odor of a fatty acid was isolated. The oily substance was identified as isobutyric acid by glpc.

5,7-Dihydroxy-4-phenylcoumarin (VII).—The ethereal layer left after washing with bicarbonate was washed and dried. The oil obtained after removal of the solvent, was crystallized from aqueous alcohol as colorless needles: mp 234–235° (lit.[8] mp 235–237°); uv 260 mμ (log ε 4.07), 340 (4.01); ir (KBr) 3200, 1681, 1626, 1556, and 704 cm^{-1}. Owing to paucity of the material, the analysis of this compound was not possible.

The above degraded product was identical with that of synthetic specimen of 5,7-dihydroxy-4-phenylcoumarin[9] in all respects (mixture melting point, uv, ir, and tlc).

Deacylation of II.—To a solution of II (25 mg) in glacial acetic acid (5 ml) was added concentrated sulphuric acid (2 ml) and the mixture was kept on a water bath for 1 hr. After the reaction was over the mixture was poured into crushed ice (50 g). The precipitate was filtered and crystallized from ethyl acetate as pale yellow needles: mp 244–245° (12 mg); uv 283 mμ (log ε 4.33); ir (Nujol) 3125, 1703, 1617, 1370, and 698 cm^{-1}. A similar deacylation reaction using mammeigin (III) as a substrate was carried out. The reaction product after working up in the above way gave the compound identical with VIII.

Anal. Calcd for $C_{20}H_{16}O_4$: C, 74.99; H, 5.03. Found: C, 74.63; H, 4.87.

(8) J. Polonsky, *Bull. Soc. Chim., Fr.*, 541 (1955).

(9) Synthetic specimen prepared in our laboratory by Pechmann condensation of phloroglucinol and benzoyl ethylacetate using acetic acid and bronotrifluoride dietherate complex as the condensing agent.

Registry No.—II, 21721-08-4; III, 2289-11-4; V, 21721-10-8; VI, 21721-11-9.

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The Chemistry of Aporphines. IV. Synthesis of Aporphines *via* Reissert Alkylation, Photochemical Cyclization, and the Pschorr Cyclization Route[1a]

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Nitrobenzyl- (**4b**) and iodobenzylisoquinoline (**4a**) derivatives have been synthesized by the condensation of Reissert compounds (**1**) with nitrobenzyl (**2b**) and iodobenzyl chlorides (**2a**). Subsequent reduction and Pschorr cyclization of the nitrobenzylisoquinoline resulted in a facile route to the synthesis of aporphines (**4b** → **5b** → **6c** → **7**). Photochemical cyclization of 1-(2-iodobenzyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline (**6a** → **7**) also resulted in the isolation of aporphine, but in considerably lower yields.

Aporphine and the naturally occurring aporphine alkaloids have a long and interesting chemical history. One of the shortcomings in this field of chemistry is due in large measure to the fact that the methods generally used for the synthesis are very poor in yields. Toward this end we have investigated promising new approaches to the synthesis of the aporphine ring system, which can be similarly applied to the synthesis of the related aporphine alkaloids.

In a preliminary communication[2] from our laboratories we have reported the synthesis of aporphine (**7**) by the generation of 1-(*o*-nitrobenzyl)isoquinoline (**4b**) by the reaction of a Reissert compound **1a** with *o*-nitrobenzyl chloride (**2b**) with subsequent reduction and Pschorr cyclization (**5b** → **6c** → **7**). In this report we wish to further expand the utility of the Reissert alkylation procedure for the generation of 1-(2-iodobenzyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline (**6a**), an aporphine precursor which when subjected to photolysis effects cyclization to the aporphine **7**. The advantages and experimental details of the two methods will be discussed.

The reaction of Reissert compounds with aldehydes or alkyl halides has proved a valuable method for the synthesis of a number of benzylisoquinoline alkaloids.[3] Alkylation of a Reissert compound with *o*-nitrobenzaldehyde has yielded *o*-nitrophenyl-1-isoquinolylmethyl benzoate, but the attempted base hydrolysis to *o*-nitrophenyl-1-isoquinolylmethanol failed to yield the desired product.[4] We have attributed this failure to the vigorous basic hydrolysis conditions used, which by analogy to similar systems studied in our laboratories[5] probably yields the anthranil **8**.

The generation of 1-cyano-1-(2-nitrobenzyl)-2-benzoyl-1,2-dihydroisoquinoline (**3b**) from **1a** and **2b** in 80% yield and further careful hydrolysis has yielded the desired benzylisoquinoline **4b** in 73% yield. The details of the conversion of **3b** → **4b** → **5b** → **6c** → **7** in excellent yields are described in the Experimental Section of this paper. The limiting step in this sequence of reactions was still the Pschorr cyclization step, since yields of better than 50% could not be obtained.

In our previous study[1] we discussed the borohydride reduction products of a number of nitrobenzylisoquinolinium salts and the unusual carbon–carbon cleavage which occurred when these salts were subjected to a borohydride reduction. It thus became necessary to resort to a catalytic reduction (Adams catalyst) for the conversion of **5b** → **6c**. As expected, the reduction of **5a** → **6a** with sodium or preferably potassium borohydride proceeded smoothly.

Condensation of **2a** (prepared in two steps by the diborane reduction of *o*-iodobenzoic acid to the alcohol followed by conversion into the chloride **2a** with thionyl chloride) with the Reissert compound (**1**, R′ =

(1) (a) Paper III: J. L. Neumeyer, M. McCarthy, K. K. Weinhardt, and P. L. Levins, *J. Org. Chem.*, **33**, 2890 (1968). (b) To whom inquiries should be addressed: The Department of Medicinal Chemistry, School of Pharmacy, Northeastern University, Boston, Mass. 02115

(2) J. L. Neumeyer, B. R. Neustadt, and J. W. Weintraub, *Tetrahedron Lett.*, 3107 (1967).

(3) F. D. Popp, *Advan. Heterocycl. Chem.*, **9**, 1 (1968).

(4) H. W. Gibson and F. D. Popp, *J. Chem. Soc., C*, 1860 (1966).

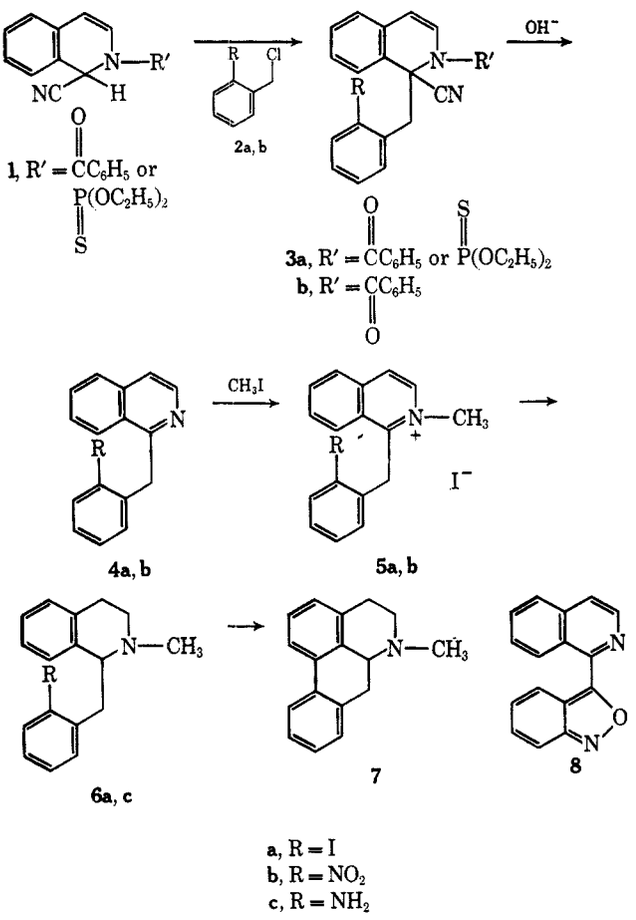
(5) C. B. Boyce and J. L. Neumeyer, unpublished results.

COC_6H_5) using sodium hydride in DMF at 5° yielded crude **3a** in 90% yield. Hydrolysis of **3a** with potassium hydroxide in ethanol afforded 1-(2-iodobenzyl)-isoquinoline (**4a**) in 80% yield. An alternative procedure in which the phosphorus Reissert compound [**1**, R′ = P(=S)$(OC_2H_5)_2$][6] was alkylated with **2a** in sodium hydride and DMF, followed by alkaline hydrolysis, also yielded **4a** but in a considerably lower yield.

Initial attempts at the photochemical cyclization of **4a** to the dehydronoraporphine system by irradiation for 24 hr at room temperature with a Hanovia-type 7420 (253.7 mμ) uv lamp in a Rayonet photochemical reactor failed to yield any identifiable products.

Formation of the methiodide **5a** from **4a** followed by reduction with potassium borohydride in ethanol smoothly afforded **6a** in 96% yield. Irradiation of **6a** hydrochloride in methanol–water for 12 hr at 70° gave the aporphine **7** as the hydrochloride in 10–16% yields (Scheme I). A number of recent communications have

SCHEME I



reported on the photocyclization of either a benzylidene tetrahydroisoquinoline to dehydroaporphanes[7,8] or the photocyclization of iodobenzyltetrahydroisoquinoline derivatives to noraporphines and aporphines.[9] The details of these reactions have not yet appeared, however.

It has been our experience that the Pschorr cyclization route **1a** → **4b** → **6c** → **7** is a superior method in both overall yields obtained and in the ease of preparation of the desired aporphine precursor. Yields in the photochemical cyclization have been disappointing and attempts to optimize the reaction conditions have not been successful, even though the iodoaromatic precursor can now be synthesized from readily available starting materials. We can only conclude that the photocyclization techniques are of little preparative value for such systems.

Experimental Section[10]

2-Benzoyl-1,2-dihydroisoquinaldonitrile [1, R = C(=O)C_6H_5].—This compound was prepared according to the method of Weinstock and Boekelheide,[11] mp 125–127° (70% yield) (lit.[11] mp 125–126°).

1-Cyano-1-(2-nitrobenzyl)-2-benzoyl-1,2-dihydroisoquinoline (3b).—A mixture of 7.80 g (33 mmol) of 2-benzoyl-1,2-dihydroisoquinaldonitrile [**1**, R′ = C(=O)C_6H_5] and 5.62 g (33 mmol) of *o*-nitrobenzyl chloride (**2b**, mp 50–52°, Aldrich Chemical Co.) in a flame-dried, round-bottom flask equipped with magnetic stirrer and nitrogen inlet tube was dissolved in 75 ml of spectro-quality N,N-dimethylformamide. A dispersion of 54% sodium hydride in mineral oil (1.9 g, 43 mmol of hydride) was added to the stirred reaction mixture. After 1.5 hr of stirring at room temperature the reaction mixture was poured into 250 ml of chloroform, and 250 ml of water was added cautiously. The layers were separated and the chloroform layer was extracted twice with 250 ml of water each time. The three aqueous layers were combined and extracted with 50 ml of chloroform, which was added to the principal extract. The chloroform solution was evaporated almost to dryness and the product eluted from a 150-g column of silicic acid with benzene. The yellow product obtained was recrystallized from absolute ethanol to yield 10.4 g (80% yield) of **3b**, mp 143–144°. The infrared spectrum (KBr) showed bands at 2250 cm^{-1} (w), 1670 (s), 1640 (s), 1530 (s), 1340, 1330 (s). The ultraviolet spectrum showed bands at λ_{max}^{MeOH} 228 mμ (ε 26,000), 281 (10,000), 312 (9300).

Anal. Calcd for $C_{24}H_{17}N_3O_3$: C, 72.90; H, 4.33; N, 10.63. Found: C, 72.82; H, 4.27; N, 10.53.

1-(2-Nitrobenzyl)isoquinoline (4b).—To a solution of 6.7 g (26 mmol) of **3b** in 110 ml of methanol was added 5.65 g (0.1 mol) of potassium hydroxide. The mixture turned dark and was warmed on a steam bath for 5 min and then poured over 200 g of crushed ice and stirred. The mixture was then successively extracted with ether, chloroform, and again ether. The combined extracts were then washed with water and dried over sodium sulfate, and the solvents removed under reduced pressure to yield 4.8 g (70%) of a dark oil. Without further purification the product **4b** was converted into the methiodide **5b**.

A sample of crude **4b** was purified by chromatography on silicic acid and benzene. The white plates were obtained from ether: mp 110–111°; picrate mp 182°; uv λ_{max}^{MeOH} 261 mμ (ε 9200), 268 (8900), 278 (s) (6900), 307 (4300), 321 (4200).

Anal. Calcd for $C_{16}H_{12}N_2O_2$: C, 72.71; H, 4.58; N, 10.60. Found: C, 72.59; H, 4.70; N, 10.51.

1-(2-Nitrobenzyl)isoquinoline Methiodide (5b).—The preparation of this compound from (**4b**) has been previously described.[1]

1-(2-Aminobenzyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline (6c).—The reduction of 1.11 g of **5b** in 50 ml of ethanol and 200 mg of platinum oxide in a Parr hydrogenator proceeded until the calculated amount of hydrogen was absorbed. The product was filtered and hydrogen chloride gas bubbled through the ethanol mixture. The formed white precipitate yielded 0.79 g (70%) of a colorless solid which was recrystallized in methanol–ether to give **6c**·2HCl: mp 257–258°; λ_{max}^{EtOH} 261 mμ (ε 6300), 287 (1900) (lit.[12] mp 272–273°).

Aporphine Hydrochloride (7). A. Pschorr Cyclization Pro-

(6) D. M. Spatz and F. D. Popp, *J. Heterocycl. Chem.*, **5**, 497 (1968).

(7) M. P. Cava, S. C. Havlicek, A. Lindert, and R. J. Spangler, *Tetrahedron Lett.*, 2937 (1966).

(8) N. C. Yang, G. R. Lenz, and A. Shari, *ibid.*, 2941 (1966).

(9) S. M. Kupchan and R. M. Kanoja, *ibid.*, 5353 (1966).

(10) All melting points were recorded on a Thomas–Hoover melting point apparatus unless otherwise specified and were uncorrected; the microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. The infrared spectra were recorded on a Perkin-Elmer grating spectrophotometer, Model 521; ultraviolet spectra were recorded with a Beckman Model DK-1A.

(11) J. Weinstock and V. Boekelheide, "Organic Syntheses," Coll. Vol. IV, John Wiley & Sons, New York, N. Y., p 641, 1963.

(12) J. Gadamer, M. Oberlin, and A. Schoeler, *Arch. Pharm.*, **263**, 81 (1925).

cedure.—The amine **6c** was converted into **7** hydrochloride by the procedure described by Weisbach, *et al.*[13] The product **7**·HCl was obtained in 40–50% yield, mp 255° dec, lit. mp 286°.[14]

o-**Iodobenzyl Alcohol.**—To 24.8 g (0.1 mol) of *o*-iodobenzoic acid in 100 ml of dry tetrahydrofuran was slowly added 200 ml of 1 *M* diborane in tetrahydrofuran (Ventron Metal Hydride Division) in an atmosphere of nitrogen. A color change from colorless to yellow to colorless was observed in the reaction mixture. The reaction mixture was stirred for 2 hr at room temperature and the excess diborane was decomposed by the careful addition of water. The reaction mixture was liberally diluted with water and allowed to stand for several hours. The precipitate was then filtered and dried to yield 17.4 g (75%) of the alcohol, mp 89.5–92° (lit.[15] mp 81.5–90°).

o-**Iodobenzyl Chloride** (**2a**).—*o*-Iodobenzyl alcohol (16 g, 0.0684 mol) was converted into the chloride with thionyl chloride in pyridine. The product, 12.5 g (73%), was distilled at 78.5° (1 mm) and solidified on standing, mp 28–29° (lit.[15] mp 28.5–29.5°).

Anal. Calcd for C_7H_6ClI: C, 33.30; H, 2.40; Cl, 14.04; I, 50.26. Found: C, 33.49; H, 2.40; Cl, 13.84; I, 50.46.

1-Cyano-1-(2-iodobenzyl)-2-benzoyl-1,2-dihydroisoquinoline (**3a**).—A mixture of 5.22 g (20 mmol) of the Reissert compound **1** [R′ = C(=O)C_6H_5] and 6 g (24 mmol) of the chloride **2a** in a flame-dried, round-bottom flask equipped with stirrer was dissolved in 60 ml of spectro-quality N,N-dimethylformamide. The reaction mixture was cooled to −5 to −10° and dispersion of 54% sodium hydride in mineral oil (1.6 g, 43 mmol) was added to the stirred reaction mixture. The mixture was stirred for 1.5 hr at −5 to 5°, for 1 hr at 5–10°, and at room temperature for an additional hour. The mixture was then poured on ice and the yellow precipitate which formed was filtered and washed with water to yield 9.5 g of crude **3a**. A small portion of this precipitate was recrystallized from ethanol and benzene–hexane to give pure **3a**, mp 150.5–151°, and the balance of the precipitate was used directly from hydrolysis to **4a**.

Anal. Calcd for $C_{24}H_{17}IN_2O$: C, 60.52; H, 3.60; N, 5.88; I, 26.64. Found: C, 60.72; H, 3.72; N, 5.86; I, 26.91.

1-(2-Iodobenzyl)isoquinoline (**4a**). **A.**—To a suspension of 9.4 g (19.7 mmol) of **3a** described above in 250 ml of ethanol was added a solution of 2.64 g (47 mmol) of potassium hydroxide in 10 ml of water. After 0.5 hr of reflux the solvent was evaporated to one-third the volume and the residue poured onto ice. The beige precipitate (6.8 g) which formed was collected and washed with water. A small sample was recrystallized from ethanol, mp 119–120°.

Anal. Calcd for $C_{16}H_{12}IN$: C, 55.64; H, 3.48; N, 4.06. Found: C, 55.94; H, 3.30; N, 4.11.

B.—A mixture of 2.9 g (10 mmol) of 2-(diethoxythiophosphono)-1,2-dihydroisoquinaldonitrile [**1**, R′ = P(=S)$(OC_2H_5)_2$][6] and 2.8 g (11 mol) of *o*-iodobenzyl chloride (**2a**) in 50 ml of dimethylformamide was cooled to −15° and treated with 0.43 g (10 mmol) 54% sodium hydride in mineral oil. The mixture was stirred for 1.5 hr and at 0° for an additional hour. The mixture was then poured into 0.5 liter of water and extracted into ether. On work-up the isolated yellow oil could not be induced to crystallize and was directly converted into **4a** by hydrolysis with 6 g of sodium hydroxide in 40 ml of ethanol and 15 ml of water. The black residue which was extracted with ether was dried to yield 31% of **4a**, mp 120–122°, identical with the sample prepared by method A.

1-(2-Iodobenzyl)isoquinoline Methiodide (**5a**).—A mixture of 6.6 g of **4a** in 65 ml of methyl iodide was stirred and heated under reflux for 20 hr. The mixture was cooled and the yellow crystals that separated were washed with dry ether and dried under vacuum to yield 8.2 g, 84% yield based on **1** [R′ = C(=O)C_6H_5], of the quaternary salt **5a**, mp 238.5–240°.

Anal. Calcd for $C_{17}H_{15}NI_2$: C, 41.92; H, 3.10; N, 2.87; I, 52.10. Found: C, 42.03; H, 2.83; N, 2.76; I, 52.41.

1-(2-Iodobenzyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline (**6a**).—To a suspension of **5a** (1 g, 2.05 mmol) in 50 ml of absolute ethanol was added 0.216 g (4 mmol) of potassium borohydride and stirred for 40 min at room temperature. 1.6 ml of water was added and the reaction mixture was stirred at room temperature for an additional 12 hr. The temperature of the reaction mixture was then gradually raised to reflux and 100 mg of potassium borohydride was added three times at 30-min intervals. The solvent was removed and the white precipitate which remained dissolved in water and extracted with ether. On evaporation of the ether a pale yellow oil remained which when treated with ethanolic hydrogen chloride yielded 0.82 g (96%) of **6a**·HCl (recrystallized from ethanol–ether), mp 203–204° (EtOH–ether).

Anal. Calcd for $C_{17}H_{19}ClNI$: C, 51.09; H, 4.79; N, 3.50; Cl, 8.90; I, 31.75. Found: C, 51.31; H, 4.85; N, 3.56; Cl, 8.84; I, 31.71.

Photochemical Cyclization. Aporphine Hydrochloride (**7**·**HCl**).—To 1 g (2.5 mmol) of **6a**·HCl dissolved in 120 ml of methanol was added a solution of 0.26 g (2.5 mmol) of sodium bisulfite in 30 ml of water. The mixture was photolyzed at 257.3 mμ in a Rayonet photochemical reactor in a 250-ml quartz cylinder with nitrogen being bubbled through the reaction mixture. The solvent was evaporated and the resulting yellow solution was made basic with 5% ammonium hydroxide, extracted with chloroform and washed several times with water. The chloroform extract was dried over magnesium sulfate and the solvent removed to give a brownish oil (0.83 g) which was treated with ethanolic hydrogen chloride. A white crystalline product (0.37 g) was isolated. The hydrochloride was fractionated (as the free base) by preparative tlc (silica gel G, 10–40 μ) using 20% benzene in ethyl acetate to develop the plates. Three fractions were obtained, fraction A in trace quantities (R_f 0.80), fraction B (R_f 0.47), and fraction C (R_f 0.21). Fraction B when eluted from the tlc plate was identified as the isoquinoline **6a**. Fraction C was identified as the aporphine **7** when eluted from the tlc plate with methanol and converted into the hydrochloride to give 0.11 g (16.2%) of **7**·HCl, mp 251–254° dec.

The recrystallized sample (methanol–ethyl acetate), mp 252–254°, mp 285°[14] (lit.[13] mp 255° dec), was identical with that obtained from the Pschorr cyclization of **6c**.

Anal. Calcd for $C_{10}H_{13}ClN$: C, 75.13; H, 6.68. Found: C, 74.93; H, 6.54.

Registry No.—**3a**, 21876-56-2; **3b**, 17750-44-6; **4a**, 21899-36-5; **4b**, 17750-45-7; **5a**, 21876-58-4; **6a** (HCl), 14528-40-6; **6c** (2HCl), 17750-48-0; **7** (HCl), 21876-61-9.

(13) J. A. Weisbach, C. Burns, E. Macho, and B. Douglas, *J. Med. Chem.*, **6**, 91 (1963).

(14) Determined on a Du Pont 900 differential thermal analyzer under nitrogen.

(15) S. C. J. Olivier, *Rec. Trav. Chim. Pays-Bas*, **42**, 516 (1923).