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.

An Improved Synthesis of *dl*-Anonaine

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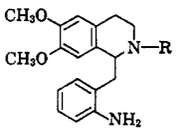
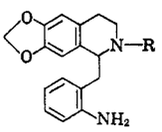
Anonaine (I) is one of the less readily available of the aporphine alkaloids. The naturally occurring base is neither a commercial product nor is it accessible in good yield from any readily available plant source. The racemic alkaloid has been synthesized;[2,3] the described procedure is of little practical 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 R = H	R = CH_3	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.

(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).

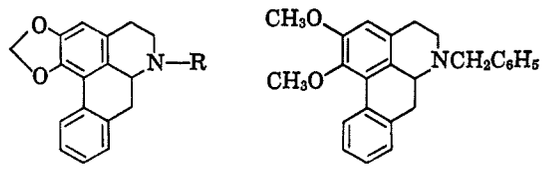
(6) L. Marion and V. Grassis, *J. Am. Chem. Soc.*, **66**, 1920 (1944).

(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).

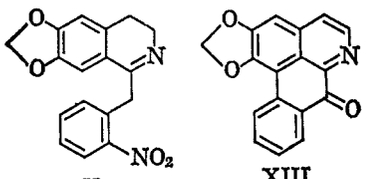
(9) An investigation is currently under way to determine the cause of the unusual behavior of V toward alkylation.

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



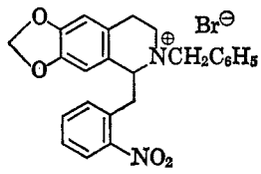
I, R = H
III, R = $CH_2C_6H_5$

IV

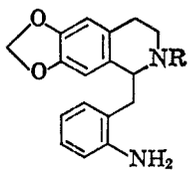


V

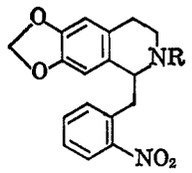
XIII



VI



VII, R = $CH_2C_6H_5$
X, R = COC_6H_5
II, R = H
XI, R = $CH(OH)C_6H_5$



VIII, R = H
IX, R = COC_6H_5
XII, R = $CH_2C_6H_5$

The reduction of X with lithium aluminum hydride in refluxing tetrahydrofuran for periods of as long as 24 hr resulted in the recovery of starting material (*ca.* 50%) and the formation of small quantities (12–15%) of 1-(*o*-aminobenzyl)-1,2,3,4-tetrahydro-6,7-methylenedioxyisoquinoline[3] (II); the latter diamine presumably arose through partial reduction of X to the carbinolamine XI which, on hydrolysis during work-up, generated II. Treatment of X under similar reducing conditions for 4 days, however, did result in total consumption of the starting amide and the generation of the desired VII (5–10%) along with large quantities (60–70%) of II.

In order to circumvent the low yield of VII as well as the difficulties involved in the separation of amines VII and II, use was made of the recently reported diborane reduction of amides.[11] Thus, IX on treatment with diborane[12] in refluxing tetrahydrofuran yielded XII which could be further reduced to VII with hydrazine and palladium. The conversion of IX to VII was accomplished in excellent (76%) over-all yield.

dl-N-Benzylanonaine (III) was obtained from VII in 31% yield by a modification of the procedure of Weisbach and Douglas[4] and was then almost quantitatively debenzylated (97%) to *dl*-anonaine (I).

Solutions of *dl*-anonaine were observed to undergo air oxidation very easily. Indeed, passage of a stream of air through a *t*-butyl alcohol solution of *dl*-anonaine resulted in the formation of the completely oxidized and aromatized product, liriodenine (XIII), in yields as high as 30%.

This observation is of interest in regard to the suggestion which was made that liriodenine and similar bases may be artifacts produced by aerial oxidation of noraporphines.[13]

(11) H. C. Brown and P. Hein, *J. Am. Chem. Soc.*, **86**, 3566 (1964).
(12) Obtained as a 1 *M* solution in tetrahydrofuran from Metal Hydrides, Inc., Beverly, Mass.
(13) W. I. Taylor, *Tetrahedron*, **14**, 42 (1961).

Experimental Section

All melting points were taken on a Fisher-Johns melting point apparatus and are uncorrected. Infrared spectra were taken on a Perkin-Elmer Infracord (Model 137B) and in chloroform solution or as potassium bromide pellets. Ultraviolet spectra were taken on a Perkin-Elmer spectrophotometer (Model 202) and are in 95% ethanol. Analyses were performed by Midwest Microlab, Inc., Indianapolis, Ind.

Attempted Reaction of 1-(*o*-Nitrobenzyl)-3,4-dihydro-6,7-methylenedioxyisoquinoline (V) with Benzyl Bromide.—A solution of nitroimine V[6] (1 mmole) in dry benzene was treated with benzyl bromide (4 mmoles) and the solution was then allowed to reflux (nitrogen atmosphere) with stirring for 6 hr. The deep red solution was then allowed to remain at room temperature overnight and, since no crystals had deposited, evaporated to dryness *in vacuo*. Crystallization of the basic product yielded starting material (V), mp 167–168°, in about 50% yield. In another attempted benzylation under similar conditions, the reaction mixture was treated directly with excess sodium borohydride. Acidification with 6 *N* hydrochloric acid afforded, in 90% yield, the hydrochloride of amine VIII (mp 238–243°), identified by its infrared spectrum and by mixture melting point with authentic material (see below).

1-(*o*-Nitrobenzyl)-1,2,3,4-tetrahydro-6,7-methylenedioxyisoquinoline (VIII).—1-(*o*-Nitrobenzyl)-3,4-dihydro-6,7-methylenedioxyisoquinoline[5] (3.12 g, 10 mmoles) was dissolved in methanol (50 ml). Sodium borohydride (0.40 g, 10.6 mmoles) was added portionwise, with stirring, during 15 min. After stirring an additional 30 min, hydrochloric acid (6 *N*) was added dropwise until the solution was distinctly acidic. On cooling, light yellow crystals, mp 238–243° (3.39 g, 97%) of the hydrochloride of VIII were deposited. Recrystallization from methanol gave an analytical sample, mp 243–245° dec.

Anal. Calcd for $C_{17}H_{17}N_2O_4Cl$: C, 58.53; H, 4.92; N, 8.03; Cl, 10.17. Found: C, 58.91; H, 5.31; N, 7.75; Cl, 10.24.

The free base (mp 98°) was generated by basification of a stirred aqueous suspension of the hydrochloride and extraction of the resulting mixture with chloroform. It was unstable to air and was routinely generated from the hydrochloride immediately prior to use.

1-(*o*-Nitrobenzyl)-2-benzoyl-1,2,3,4-tetrahydro-6,7-methylenedioxyisoquinoline (IX).—1-(*o*-Nitrobenzyl)-1,2,3,4-tetrahydro-6,7-methylenedioxyisoquinoline hydrochloride (3.50 g, 10 mmoles) was shaken with aqueous sodium hydroxide (10%, 100 ml) and chloroform until all of the solid had dissolved. The chloroform solution was withdrawn and the aqueous phase was washed with a fresh portion of chloroform (50 ml). The combined chloroform extracts were washed once with water, dried, and evaporated to yield, as a yellow oil, 1-(*o*-nitrobenzyl)-1,2,3,4-tetrahydro-6,7-methylenedioxyisoquinoline (3.14 g, 10 mmoles, 100%). The oil was taken up in dry pyridine (50 ml) and treated with benzoyl chloride (1.50 g, 10.6 mmoles). After standing overnight at room temperature, the reaction mixture was poured into a slurry of ice and concentrated hydrochloric acid and, when the ice had melted, the resulting suspension was extracted with three 150-ml portions of chloroform. The combined chloroform extracts were washed with aqueous sodium hydroxide (10%), dilute hydrochloric acid (6 *N*), and water, dried, and evaporated to yield, after crystallization from methanol, hard white crystals of IX, mp 178–180° (4.10 g, 98%).

Anal. Calcd for $C_{24}H_{20}N_2O_5$: C, 69.22; H, 4.84; N, 6.73. Found: C, 69.23; H, 4.94; N, 6.77.

1-(*o*-Aminobenzyl)-2-benzoyl-1,2,3,4-tetrahydro-6,7-methylenedioxyisoquinoline (X).—1-(*o*-Nitrobenzyl)-2-benzoyl-1,2,3,4-tetrahydro-6,7-methylenedioxyisoquinoline (IX, 2.09 g, 5 mmoles) was dissolved in methanol (200 ml). Palladium on carbon (10%, 0.50 g) was added cautiously (nitrogen atmosphere) and the solution was stirred and heated at reflux while hydrazine hydrate (12 ml of a solution prepared by dilution of 3 ml of 85% hydrazine hydrate to a volume of 12 ml with methanol) was added dropwise. The mixture was allowed to reflux with stirring overnight and the warm solution was filtered through a thin Celite mat. Removal of the solvent *in vacuo* afforded white needles of X; recrystallization from methanol afforded pure X (92% yield), mp 193°.

Anal. Calcd for $C_{24}H_{22}N_2O_3$: C, 74.59; H, 5.74; N, 7.25. Found: C, 74.38; H, 5.52; N, 7.14.

Attempted Lithium Aluminum Hydride Reduction of 1-(*o*-Aminobenzyl)-2-benzoyl-1,2,3,4-tetrahydro-6,7-methylenedioxy-

isoquinoline. A. For 24 hr.—The amine X (389 mg, 1 mmole) was added, in small portions, to a solution of lithium aluminum hydride (380 mg, 10 mmoles) in tetrahydrofuran. Addition was effected at such a rate that the tetrahydrofuran refluxed. Heating at reflux was continued for 24 hr, after which the reaction mixture was cooled to room temperature and the remaining lithium aluminum hydride was destroyed by addition of water. The resulting suspension was made strongly alkaline with 10% sodium hydroxide and continuously extracted with ether. Chromatography of the extract on alumina (Woelm III, neutral) gave, with 1:1 chloroform–benzene eluent, crystalline amine X (204 mg, 53% recovery); on elution with chloroform–methanol (99:1) 1-(*o*-aminobenzyl)-1,2,3,4-tetrahydro-6,7-methylenedioxyisoquinoline (II, 51 mg, 13%), identical with that prepared by the reduction[5] of 1-(*o*-nitrobenzyl)-3,4-dihydro-6,7-methylenedioxyisoquinoline with zinc and hydrochloric acid, was removed.

B. For 4 days.—The above reaction was repeated on the same scale and the reaction mixture was refluxed for 4 days. Chromatography of the resultant products yielded, after crystallization from methanol (chloroform–benzene eluent, 1:1), 20.3 mg (5.23%) of white crystals of diamine VII, mp 137–138°. The analytical sample, mp 141–142°, was obtained by recrystallization from methanol.

Anal. Calcd for $C_{24}H_{24}N_2O_2$: C, 77.39; H, 6.50; N, 7.52. Found: C, 77.11; H, 6.65; N, 7.33.

Continued elution of the column with chloroform–methanol (99:1) yielded diamine II (258 mg, 68%).

1-(*o*-Nitrobenzyl)-2-benzyl-1,2,3,4-tetrahydro-6,7-methylenedioxyisoquinoline (XII).—A solution of nitroamide IX (500 mg, 1.20 mmoles) in dry tetrahydrofuran (30 ml) was added dropwise (nitrogen atmosphere) with stirring during 10 min to a cooled solution (ice bath) of diborane in tetrahydrofuran (15 ml, 15 mmoles).[12] When the addition was complete, the solution was allowed to warm to room temperature and was then refluxed for 12 hr. After cooling to room temperature, 6 *N* hydrochloric acid (50 ml) was added cautiously. The reaction mixture was warmed on the steam bath until evolution of hydrogen ceased and the solvent was removed *in vacuo*. The solid residue was suspended in chloroform and shaken with dilute sodium hydroxide solution (10%) until all of the solid had dissolved. The aqueous phase was washed with fresh chloroform and the combined chloroform extracts were washed with water and evaporated to dryness. Crystals of nitroamine XII (424 mg, 87.5%), mp 82–83°, were obtained from methanol–chloroform.

Anal. Calcd for $C_{24}H_{22}N_2O_4$: C, 71.62; H, 5.51; N, 6.96. Found: C, 72.36; H, 5.50; N, 6.70.

1-(*o*-Aminobenzyl)-2-benzyl-1,2,3,4-tetrahydro-6,7-methylenedioxyisoquinoline (VII).—1-(*o*-Nitrobenzyl)-2-benzyl-1,2,3,4-tetrahydro-6,7-methylenedioxyisoquinoline (XII, 4.05 g, 1 mmole) was suspended in methanol (500 ml) and 10% palladium on carbon (2.5 g) was added (nitrogen atmosphere). Hydrazine hydrate (2 ml of 85%, diluted to 8 ml with methanol, 8 mmoles) was added dropwise to the stirred and refluxing mixture, and refluxing was continued overnight. The warm solution was filtered through a thin Celite mat and evaporation of the filtrate afforded 3.26 g (86.6%) of VII as white needles, mp 141–142°. The product was identical with that (melting point, mixture melting point, and infrared spectrum) produced in low yield from X through the action of lithium aluminum hydride. Continuous extraction of the catalyst in a Soxhlet apparatus yielded an additional 63 mg of oil which could not be induced to crystallize. Treatment of a methanolic solution of the oil with 6 *N* hydrochloric acid yielded needles, mp 238–240°, identical with authentic 1-(*o*-nitrobenzyl)-1,2,3,4-tetrahydro-6,7-methylenedioxyisoquinoline hydrochloride by melting point, mixture melting point, and infrared spectrum.

N-Benzyl-*dl*-anonaine (III).—1-(*o*-Aminobenzyl)-2-benzyl-1,2,3,4-tetrahydro-6,7-methylenedioxyisoquinoline (VII, 1.33 g, 3 mmoles) was dissolved in a mixture of glacial acetic acid (10 ml) and concentrated sulfuric acid (1 ml) and the clear, colorless solution was cooled to 10°. A solution of sodium nitrite (221.6 mg, 3.19 mmoles) in water (2 ml) was added dropwise for several minutes The resulting bright orange solution was stirred at 10° for an additional 15 min and a few crystals of sulfamic acid were then added, followed by acetone (50 ml), cuprous chloride (50 mg), and freshly prepared metallic copper (2 g). Nitrogen was evolved vigorously from the stirred solution for several minutes, after which it was warmed on the steam bath and then refluxed for 30 min. The acetone was removed by distillation and the residual suspension was cooled to room temperature and then made basic with ammonium hydroxide. The blue aqueous solution was continuously extracted with ether for 24 hr and the ethereal extract was evaporated to dryness. The residue was chromatographed on a 1 in. × 10 in. column of Woelm grade I neutral alumina. Elution with benzene afforded 1-benzyl-1,2,3,4-tetrahydro-6,7-methylenedioxyisoquinoline: mp 102–104°; λ_{max} 214 mμ (log ε 4.52), 295 (4.02).

Anal. Calcd for $C_{24}H_{23}NO_2$: C, 80.64; H, 6.49; N, 3.92. Found: C, 80.52; H, 6.30; N, 3.92.

Further elution with benzene afforded N-benzyl-*dl*-anonaine (crystals from chloroform–methanol, 332 mg, 31%): mp 129° and second mp 146°; λ_{max} 211 mμ (log ε 4.48), 270 (4.13), 318 (3.49).

Anal. Calcd for $C_{24}H_{21}NO_2$: C, 81.10; H, 5.96; N, 3.94. Found: C, 80.70; H, 6.00; N, 3.66.

***dl*-Anonaine (I).**—N-Benzyl-*dl*-anonaine (III, 826.9 mg, 2.32 mmoles) was placed in a Parr bottle together with 10% palladium on carbon (1.0 g), concentrated hydrochloric acid (5 ml), and ethyl alcohol (95%, 100 ml). Hydrogenolysis was carried out at 49 psi for 24 hr. The catalyst was removed by filtration and was extracted with ethanol in a Soxhlet apparatus. The extract was combined with the filtrate and evaporated to dryness to yield 690 mg (97%) of crystalline *dl*-anonaine hydrochloride, mp 285° dec (lit.[2b] mp 295°).

Anal. Calcd for $C_{17}H_{10}NO_2$: C, 67.66; H, 5.31; N, 4.66. Found: C, 67.68; H, 5.48; N, 4.56.

Neutralization of the above hydrochloride afforded *dl*-anonaine, which crystallized readily (ether) as small prisms, mp 114.5–115° (lit.[2b] mp 116.5°).

Liriodenine (XIII).—*dl*-Anonaine (I, 47.5 mg, 0.127 mmole) was dissolved in *t*-butyl alcohol (25 ml) and filtered air was passed through the solution for a period of 5 days. At the end of this time, the solution was evaporated to dryness *in vacuo*. The residue, in chloroform solution, was transferred to neutral alumina preparative chromatography plates. The plates were developed with chloroform and liriodenine was recovered from the bright yellow band (R_f 0.32) by extraction of the stationary phase with methanol–chloroform (1:10). The sample (14.7 mg, 31%), mp 275–280° dec, was identical (melting point, mixture melting point, and infrared spectrum) with an authentic sample from natural sources.[14]

Acknowledgment.—This investigation was supported by a Public Health Service Fellowship (7-F2-GM-14, 470-01A1) from the National Institute of General Medical Sciences.

(14) This material was kindly supplied by Professor J. Beal, College of Pharmacy, The Ohio State University.

Friedel–Crafts Acylation of Thiophene with Mixed Acetic Anhydrides[1a]

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An earlier paper[2] described the behavior of a number of mixed acetic anhydrides, when these reacted with limited quantities of benzene in the presence of aluminum chloride, and gave particular attention to the molar ratios of the two possible ketonic products. The relative ketone-forming proficiencies of the competing acyl groups appeared to be influenced substantially by their electronic qualities, and to a lesser extent by their steric characteristics. Marked dif-

(1)(a) From the M.S. Thesis of Robert J. Eckert, Jr., Louisiana State University, June 1962. (b) Cities Service Honor Fellow, 1961–1962.

(2) W. R. Edwards, Jr., and E. C. Sibille, *J. Org. Chem.*, **28**, 674 (1963).