[CONTRIBUTION FROM THE CHEMICAL AND BIOLOGICAL RESEARCH SECTION, LEDERLE LABORATORIES DIVISION, AMERICAN CYANAMID COMPANY]

AN ANTIMALARIAL ALKALOID FROM HYDRANGEA. XXIII. SYNTHESIS BY THE PYRIDINE APPROACH. II

B. R. BAKER AND FRANCIS J. McEVOY

Received October 11, 1954

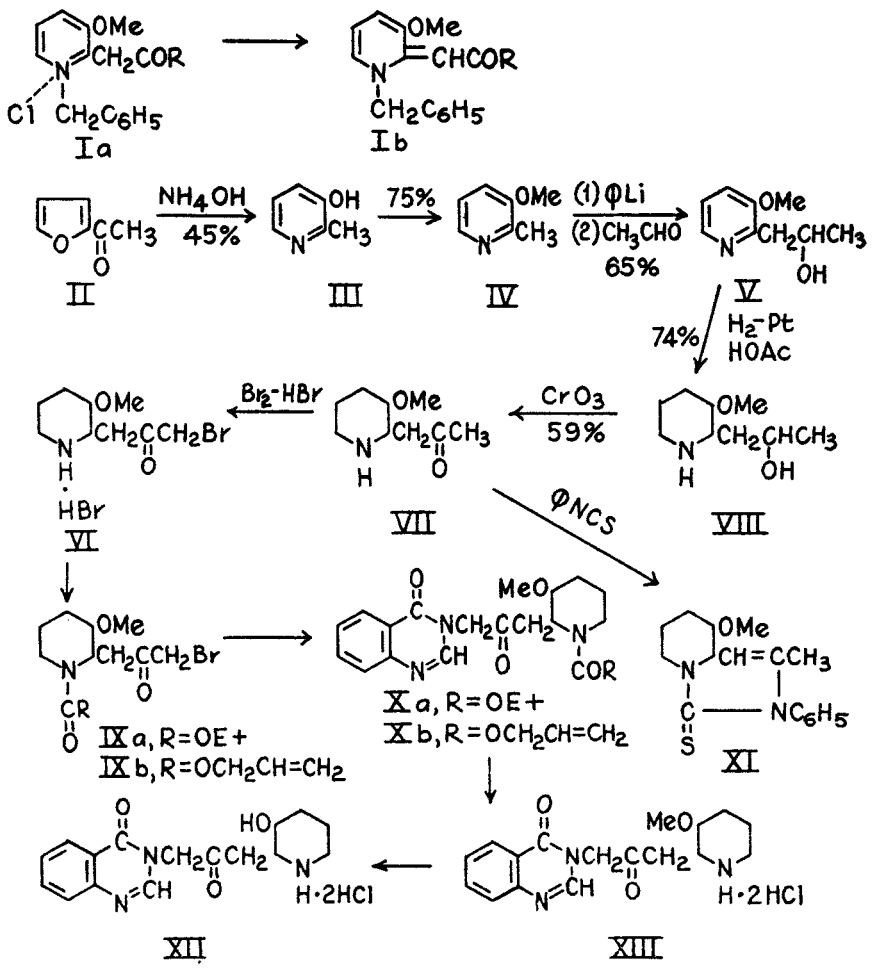
In the accompanying paper XXII of this series it was demonstrated that the pyridine approach to the Hydrangea alkaloid (XII) was not feasible with a system such as a 1-benzyl-2-(β-ketoalkyl-3-methoxypyridinium chloride (Ia) or its relatively unstable methylene base (Ib). It was pointed out that a synthesis by the pyridine approach should proceed through the key intermediate 2-(β-hydroxypropyl)-3-methoxypyridine (V). The latter has now been synthesized in three steps from 2-acetofuran (II) and converted, in turn, to the Hydrangea alkaloid (XII) in an additional seven steps.

2-Methyl-3-pyridol (III), which is readily obtained in 45% yield by reaction of 2-acetofuran (II) with ammonium hydroxide under pressure (1), was O-methylated to IV in 75% yield by heating its trimethylphenylammonium salt in dimethylformamide.[1] Since the product distilled at about the same temperature as the by-product dimethylaniline, these two compounds could not be readily separated by distillation. The use of insoluble salts (4) also failed. However, these two compounds were quantitatively separated by conversion of the 2-methyl-3-methoxypyridine (IV) to its insoluble cadmium chloride complex.[2] The pyridine base was regenerated by treatment of the complex with aqueous sodium hydroxide. Treatment of IV with phenyllithium in ether gave 2-lithiummethyl-3-methoxypyridine which was reacted with acetaldehyde to form a 65% yield of the key intermediate, 2-(β-hydroxypropyl)-3-methoxypyridine (V).

Hydrogenation of V in acetic acid at 70° in the presence of Adams catalyst proceeded smoothly to give a 74% yield of the piperidine, VIII, as a distillable oil which solidified on standing. Although this structure has three asymmetric centers and can theoretically exist as four racemates, two *cis* and two *trans*, no difficulty was anticipated in obtaining the correct *cis*-racemate. Firstly, the number of racemates is reduced to two, one *cis* and one *trans*, when the hydroxyl group is oxidized to ketone (VII). Secondly, the reaction product should be almost exclusively *cis* since hydrogenation of aromatic rings with platinum oxide in acetic acid usually gives mainly *cis*-racemates due to simultaneous addition of two hydrogens at a time from the same side of the molecule. The proof of configuration would follow by completion of the synthesis of the Hydrangea

[1] This type of methylation has been employed for a number of phenolic nitrogen bases in order to avoid N-methylation caused by the usual reagents such as methyl halides, sulfate, or sulfonates. Thus morphine has been converted to codeine (2), methyl 2-methyl-3-hydroxypyridine-4,5-dicarboxylate to its methyl ether (3), and 2-iodo-3-pyridol to 2-iodo-3-methoxypyridine (4). The pyrolysis of the trimethylphenylammonium salt of III without solvent (2) gave only 53% yield of IV.

[2] The formation of the cadmium chloride complex of pyridine has been described by Lang (5).



alkaloid where both the natural *cis* and the unnatural *trans* configurations have been synthesized (6). That the racemates of VIII obtained were indeed almost exclusively *cis* was demonstrated by completion of the synthesis.

Oxidation of 2-(β-hydroxypropyl)-3-methoxypiperidine (VIII) with chromium trioxide in acetic acid (7) at 100° to the corresponding ketone (VII) proceeded in 59% yield.[3] Later it was found unnecessary to isolate the intermediate alcohol, VIII, and the combination reduction, then oxidation with chromate in dilute sulfuric acid proceeded to give the same yield of pure ketone (VII) from V.

To this point the synthesis proceeded smoothly in a very satisfactory over-all yield of 10% of 2-acetonyl-3-methoxypiperidine (VII) from 2-acetofuran. However, the subsequent steps required considerable study to obtain satisfactory yields, since the intermediates VI and IXa were oils and the sequence could only

[3] This β-aminoketone was characterized by reaction with phenyl isothiocyanate in boiling ethylene dichloride. The resultant phenylthiocarbamyl derivative spontaneously cyclized to XI.

be evaluated by conversion to the crystalline blocked alkaloid derivative (Xa) (8). There are two orders in which these reactions may be carried out, (a) the NH group of VII can be blocked by carbethoxylation followed by bromination or (b) the hydrobromide salt of VII can be brominated to VI followed by carbethoxylation. Method (b) suffers from the disadvantage that cyclization of the side chain on the nitrogen may be a competing reaction during acylation of VI to IXa, a difficulty avoided by method (a). However, method (a) suffers from the disadvantage that bromination of the intermediate 1-carbethoxy-2-acetonyl-3-methoxypiperidine would proceed mainly on the methylene carbon adjacent to the ketone rather than the methyl (9) whereas bromination of the salts of Mannich bases causes an orientation of the bromine predominately to the methyl group (10). Method (b) was found to give a negligible amount of blocked alkaloid (Xa) although bromination of the intermediate 1-carbethoxy-2-acetonyl-3-methoxypiperidine proceeded rapidly. No appreciable yield of Xa was obtained when the methyl group of 1-carbethoxy-2-acetonyl-3-methoxy-piperidine was activated by condensation with ethyl oxalate followed by iodination or bromination of the glyoxalic acid as described for selective iodination of the 21-position of a 20-keto steroid nucleus (11). Method (a) was therefore investigated thoroughly since it had the most possibilities for variation of experimental conditions.

After more than twenty runs it was found that the optimum conditions for the conversion of 2-acetonyl-3-methoxypiperidine (VII) to the blocked alkaloid (Xa) were (a) bromination of VII in 3 moles of 15% hydrogen bromide in acetic acid for 2 hours at room temperature and (b) acylation of VI to IXa with ethyl chlorocarbonate in chloroform-water using sodium bicarbonate as the acid acceptor. The yield of Xa from VII was 33% or an average yield of 69% per step. This compared to an over-all yield in the first run of 3% when the bromination was run in the usual fashion for Mannich bases (10) and the usual sodium carbonate (4) was used for the acid acceptor during the conversion of VI to IXa. The change from carbonate to bicarbonate doubled the yield.

One of the final two steps of the Hydrangea alkaloid synthesis proceeds in only 35% yield, namely, the hydrolysis of Xa to the alkaloid methyl ether, XIII. In a previous extensive study this yield was the optimum and it was shown that this low yield was due to the inherent instability of the blocked alkaloid, Xa, to aqueous hydrochloric acid since the product (XIII) was stable to this acid (8). Thus, the yield of XIII from X should be roughly proportional to the ease with which the N-blocking group is removable. Three other blocking groups for IX have now been investigated: benzoyl, carbobenzoxy, and carboallyloxy. Since the intermediates X did not crystallize in each case, the over-all yields from 2-acetonyl-3-methoxypiperidine (VII) to the alkaloid methyl ether (XIII) were compared. The base-line used was the carbethoxy blocking group which afforded 11% over-all yield for these four steps. The benzoyl blocking group gave a disappointing 5% over-all yield, but the carbobenzoxy gave a more than double yield, 25%, and finally the carboallyloxy afforded four times the yield, an excellent 46%. This 46% yield averages to 82% for each of the four steps and the carboallyloxy is obviously the blocking group of choice in this synthesis. The

difference in yields between the carbobenzoxy and carboallyloxy groups appears to be mainly in the yield obtained in acylation step of VI to IX.[4]

Thus, the over-all yield of the *dl*-form of the Hydrangea alkaloid (XII) from 2-acetofuran in this 10-step synthesis is 2.1%. In addition to the elimination of the diazomethane used in the earlier syntheses of the alkaloid, the over-all yield is eight times higher than the 14-step first synthesis starting with ethyl malonate (8) and fifteen times higher than the 16-step second synthesis starting with furfural (6).

Acknowledgement. The authors are grateful to W. Fulmor and staff for the spectrophotometric data and to L. Brancone and staff for the microanalyses.

EXPERIMENTAL

2-Methyl-3-methoxypyridine (IV). A solution of 72.6 g. of 2-methyl-3-pyridol (1), 40 g. of sodium methoxide (Mathieson), and 128 g. of phenyltrimethylammonium chloride in 726 cc. of dimethylformamide was refluxed for 2½ hours. The cooled solution was filtered from salt, acidified with 726 cc. of saturated absolute alcoholic hydrogen chloride, and evaporated to dryness *in vacuo*. The residue was dissolved in 470 cc. of water, basified with 950 cc. of 10% sodium hydroxide, and then extracted with two 600-cc. portions of ether. The combined extracts were shaken with 480 cc. of 10% cadmium chloride solution.[3] The pasty mass was diluted with 620 cc. of water and slurried with 80 g. of Celite. The filtered precipitate was washed with two 310-cc. portions of water and two 310-cc. portions of ether. The ether-free, but still moist filter cake, suspended in 1800 cc. of 5% sodium hydroxide, was stirred on the steam-bath under a condenser for 1 hour. The cooled mixture was filtered and the filter cake was washed with three 470-cc. portions of chloroform. Each washing was used successively to extract the filtrate. Dried with magnesium sulfate, the combined extracts were evaporated on the steam-bath under a 12″ Vigreaux column. Distillation of the residue afforded 69 g. (75%) of product as a colorless oil, b.p. 84–86° (15 mm.).

Anal. Calc'd for C_7H_9NO: C, 68.3; H, 7.32; N, 11.4.

Found: C, 67.5; H, 8.18; N, 11.3.

This compound formed a *picrate* from ethanol as yellow crystals, m.p. 167–168°. When the reaction time was 1 hour, the yield dropped to 63%. Pyrolysis (2) of the trimethylphenylammonium salt at 17 mm. pressure and a bath temperature of 120–140° until no more product distilled gave a 53% yield of product, b.p. 82° (14 mm.), after separation *via* the cadmium chloride complex, and 53% of dimethylaniline, b.p. 77–79° (17 mm.).

2-(β-Hydroxypropyl)-3-methoxypyridine (V). To a refluxed and stirred solution of phenyllithium (12a) from 15 g. of lithium wire and 113 cc. of bromobenzene in 870 cc. of dry ether was added a solution of 66.7 g. of IV over a period of 45 minutes. After being refluxed and stirred for an additional hour, the red-brown mixture was cooled to 5° with an ice-salt bath in an atmosphere of dry nitrogen. A solution of 61 cc. of freshly distilled acetaldehyde in 78 cc. of dry ether was added at such a rate that the temperature was 5–7° (40 minutes). The colorless solution was processed as described for 2-(β-hydroxypropyl)pyridine (12b); yield, 60 g. (66%) of a pale yellow oil, b.p. 105–125° (0.1 mm.), suitable for the next step. A similar preparation was redistilled in a modified Claisen flask, b.p. 143–146° (10 mm.), $\lambda_{max.}^{pH7-14}$ 279 mμ (ε 5670), $\lambda_{max.}^{pH1}$ 290 mμ (ε 8520). In the infrared (chloroform solution) this compound showed OH absorption at 2.96 μ, C=N absorption at 6.27 and 6.33 μ, aromatic C—O—C absorption at 7.82 and 9.76 μ and aromatic (pyridine) absorption at 12.47 μ.

Anal. Calc'd for $C_9H_{13}NO_2$: C, 64.7; H, 7.78; N, 8.38.

Found: C, 63.8; H, 8.45; N, 7.93.

[4] The direct condensation of VI with 4-quinazolone in methanol containing 2 equivalents of sodium methoxide failed to give an appreciable amount of the alkaloid methyl ether (XIII) probably because the predominant reaction of VI free base was intramolecular cyclization.

A *hydrochloride* could be obtained as white crystals, m.p. 159–160°, by addition of a slight excess of absolute alcoholic hydrogen chloride to an ethereal solution of the base.

Anal. Calc'd for $C_9H_{13}NO_2 \cdot HCl$: C, 53.0; H, 6.89; N, 6.87.

Found: C, 53.2; H, 7.11; N, 7.06.

2-(β-Hydroxypropyl)-3-methoxypiperidine (VIII). A solution of 4.3 g. of redistilled V in 25 cc. of acetic acid was shaken with hydrogen at 2–3 atm. at 70° in the presence of 0.30 g. of platinum oxide. Reduction stopped in 2⅔ hours with 3.0 mole-equivalent uptake of hydrogen. The filtered solution was evaporated to dryness *in vacuo* (bath 50°). The residue was dissolved in 15 cc. of water and made basic with 10 cc. of 50% potassium hydroxide solution. An oil separated which was collected by extraction with three 25-cc. portions of ether. Dried with magnesium sulfate, the combined extracts were evaporated *in vacuo* (bath 40°). Distillation of the residue afforded 3.3 g. (74%) of a colorless oil, b.p. 126–130° (15 mm.), which partially solidified to a hygroscopic solid on standing. This compound showed OH—NH absorption at 3.0 μ, NH absorption at 6.10 μ, and aliphatic C—O—C absorption at 9.20 μ in the infrared in chloroform. The analysis indicated some hydration had occurred prior to determination.

Anal. Calc'd for $C_9H_{19}NO_2$: C, 62.4; H, 11.0; N, 8.08; MeO, 1.0.

Found: C, 61.0; H, 10.9; N, 7.98; MeO, 0.84.

2-Acetonyl-3-methoxypiperidine (VII). (*A*). To a solution of 3.1 g. of VIII in 18 cc. of acetic acid at 80° was added in portions a solution of 1.35 g. of chromium trioxide in 1.35 cc. of water at such a rate that the temperature was 100–103°. After being heated on the steam-bath for an additional 30 minutes, the solution was evaporated to dryness *in vacuo*. The residual gum was dissolved in 3 cc. of water and treated with 30 cc. of 50% potassium hydroxide. The mixture was extracted with two 30-cc. portions of ether, filtration through Celite being used to break the emulsion formed. The combined extracts were dried with magnesium sulfate and evaporated *in vacuo* (bath 25°). Distillation of the residue in a modified Claisen flask gave 1.83 g. (59%) of a colorless oil, b.p. 110–118° (15 mm.).

Anal. Calc'd for $C_9H_{17}NO_2$: C, 63.1; H, 9.94; N, 8.18.

Found: C, 63.3; H, 10.4; N, 7.72.

This compound showed NH absorption at 2.98, 3.15, and 6.10 μ, C=O at 5.82 μ and aliphatic C—O—C at 9.20 μ in the infrared in chloroform. This compound gradually darkens in air and is best stored in a sealed container under nitrogen.

A similar oxidation has been used by Meisenheimer and Mahler (7) for the preparation of 2-acetonylpiperidine.

(*B*). The following procedure was superior to (*A*) on a preparative scale. A solution of 48 g. of once-distilled V in 200 cc. of acetic acid was shaken with hydrogen at 2–3 atm. at 70° in the presence of 2 g. of platinum oxide until reduction was complete (6 hours). The filtered solution was evaporated to dryness *in vacuo* (bath 50°) leaving a residue of VIII acetate.

The residual syrup was dissolved in 325 cc. of water and 46 cc. of 96% sulfuric acid. Then 41.7 g. of potassium dichromate was added in one portion with stirring. The temperature was maintained at 30–35° with occasional cooling until the reaction was no longer exothermic (about 30 minutes). Thirty minutes later the solution was seeded with hydrated chromic sulfate, then allowed to stand for 20 hours. The filtered solution was diluted with 270 cc. of water and basified with 590 cc. of 50% potassium hydroxide with cooling. After addition of 40 g. of Celite and 270 cc. of ether, the slurry was filtered and the filter cake was washed with ether. The separated aqueous layer was extracted with four more 270-cc. portions of ether, then with two 270-cc. portions of chloroform. The combined extracts, dried with magnesium sulfate, were evaporated *in vacuo* (bath 50°). Distillation of the residue gave 30.3 g. of crude product, b.p. 55–78° (0.2 mm.). Redistillation in a modified Claisen flask gave, after a forerun, 21.4 g. (44%) of a colorless oil, b.p. 68–76° (0.1 mm.).

Reaction of VII with an equimolal quantity of phenyl isothiocyanate in boiling ethylene dichloride gave XI, m.p. 118–119°, when crystallized from 60% methanol. Recrystallization from heptane gave white crystals of unchanged m.p.

Anal. Calc'd for $C_{16}H_{20}N_2OS$: C, 66.7; H, 6.94; N, 9.76.
Found: C, 66.7; H, 7.23; N, 9.76.

3-[β-Keto-γ-(1-carbethoxy-3-methoxy-2-piperidyl)propyl]-4-quinazolone (Xa). To a solution of 500 mg. of VII in 2 cc. of acetic acid and 2 cc. of 30% hydrogen bromide in acetic acid was added 0.15 cc. of bromine in 0.5 cc. of acetic acid. After 2 hours the solution was evaporated to dryness *in vacuo* (bath 45–50°). The residual VI was dissolved in 10 cc. of chloroform and cooled in an ice-bath. After the addition of 10 cc. of saturated sodium bicarbonate solution and 0.32 cc. of ethyl chlorocarbonate, the mixture was stirred for ½ hour at 0°. Then 3 cc. of saturated sodium bicarbonate and 0.32 cc. of ethyl chlorocarbonate was added and the mixture again was stirred for ½ hour in the ice-bath. The separated chloroform solution was washed with two 10-cc. portions of 1 *N* hydrochloric acid. Dried with magnesium sulfate, the organic solution was evaporated to dryness *in vacuo* (bath 45–50°) leaving 910 mg. (97%) of crude IXa.

A solution of the 910 mg. of crude bromoketone in 9.1 cc. of methanol was added to a solution of 410 mg. of 4-quinazolone in 2.8 cc. of 1 *N* methanolic sodium methoxide. After 1 hour the solution was processed as previously described (8). Crystallization of the crude residue (840 mg.) from 8 cc. of benzene by the addition of 14 cc. of heptane gave 400 mg. (33% from VII) of product, m.p. 135–136°, which was identical with an authentic sample (8).

The use of sodium carbonate instead of sodium bicarbonate for the conversion of VI to IXa gave about ½ the over-all yield. Bromination in acetic acid contaning 1 mole of hydrogen bromide (10) gave about 10% over-all yield. The above bromination time was near optimum since longer or shorter times before processing gave lower yields.

3-[β-Keto-γ-(3-methoxy-2-piperidyl)propyl]-4-quinazolone dihydrochloride (XIII). The crude VI obtained from 1.42 g. of VII as described in the preceding experiment was dissolved in 28 cc. of chloroform. The stirred solution was cooled in an ice-bath and neutralized with 28 cc. of saturated aqueous sodium bicarbonate. Immediately 0.91 cc. of allyl chlorocarbonate was added. The mixture was stirred in the ice-bath for 1½ hours, more sodium bicarbonate being added if necessary to keep the solution from becoming acidic. The separated chloroform layer was washed with 28 cc. of 1 *N* hydrochloric acid, dried with magnesium sulfate, and evaporated to dryness *in vacuo*; yield, 2.52 g. of crude IXb.

This crude bromo ketone was dissolved in 23 cc. of methanol and added to a solution of 1.1 g. of 4-quinazolone in 7.5 cc. of 1 *N* methanolic sodium methoxide. After 1 hour the solution was processed as usual (8) to give 2.57 g. of crude Xb.

A solution of this crude Xb in 26 cc. of 6 *N* hydrochloric acid was refluxed for 15 minutes when carbon dioxide evolution was complete, then evaporated to dryness *in vacuo*. The residue was dissolved in 26 cc. of absolute alcohol and the evaporation was repeated. Crystallization from 10 cc. of saturated absolute alcoholic hydrogen chloride was complete after about 15 hours at 3°. The product was collected and washed with 3:1 acetone-absolute alcohol; yield, 1.47 g. (46% from VII), m.p. 200–202° dec. A similar preparation was recrystallized from methanol by addition of absolute alcoholic hydrogen chloride to give white crystals of the dihydrate, m.p. 159–160° dec. This gave an infrared spectrum (KBr window) identical with that of an authentic sample (8) and the m.p. data also corresponded.

A solution of 65 mg. of the high-melting form in 0.6 cc. of water was treated with a solution of 39 mg. of potassium cyanate. The filtered solution was allowed to stand for 1½ hours during which time the N-carbamyl derivative was deposited. The product was collected and washed with water; white crystals, m.p. 203–204° dec.

Anal. Calc'd for $C_{18}H_{22}N_4O_4$: C, 60.3; H, 6.15; N, 15.6.
Found: C, 60.2; H, 6.40; N, 15.6.

Similarly, an authentic sample of XIII, prepared as previously described (8), gave an N-carbamyl derivative as white crystals, m.p. 200–201° dec. A mixture with the above preparation gave no depression in m.p. and both had identical infrared spectra.

Anal. Found: C, 60.2; H, 6.35; N, 15.5.

SUMMARY

A synthesis of the Hydrangea alkaloid, 3-[β-keto-γ-(3-hydroxy-2-piperidyl) propyl]-4-quinazolone (XII), has been described which requires ten steps from 2-acetofuran and proceeds through the key intermediates 2-(β-hydroxypropyl)-3-methoxypyridine and 2-acetonyl-3-methoxypiperidine.

PEARL RIVER, NEW YORK

REFERENCES

(1) DUNLOP AND SWADESH, U. S. Patent 2,636,882.
(2) RODIONOW, *Bull. soc. chim.*, [4] **39**, 305 (1926).
(3) COHEN, HAWORTH, AND HUGHES, *J. Chem. Soc.*, 4374 (1952); Brit. Patent 629,423.
(4) BAKER AND McEVOY, Paper XXII of this series, *J. Org. Chem.*, **20**, this issue (1955).
(5) LANG, *Ber.*, **21**, 1578 (1888).
(6) BAKER, McEVOY, SCHAUB, JOSEPH, AND WILLIAMS, *J. Org. Chem.*, **18**, 153 (1953).
(7) MEISENHEIMER AND MAHLER, *Ann.*, **462**, 301 (1928).
(8) BAKER, SCHAUB, McEVOY, AND WILLIAMS, *J. Org. Chem.*, **17**, 132 (1952).
(9) CATCH, ELLIOTT, HEY, AND JONES, *J. Chem. Soc.*, 272 (1948); JANETZKY AND VERKADE, *Rec. trav. chim.*, **65**, 691 (1946).
(10) LAND, ZIEGLER, AND SPRAGUE, *J. Am. Chem. Soc.*, **69**, 125 (1947).
(11) SARETT AND CO-WORKERS, *J. Am. Chem. Soc.*, **74**, 4974 (1952); ADDINALL, FIAT Final Report, 996, Jan. 29, 1947.
(12) (a) WOODWARD AND KORNFELD, *Org. Syntheses*, **29**, 44 (1949); (b) WALTER, *Org. Syntheses*, **23**, 83 (1943).