The product failed to give an enol test with ferric chloride solution indicating the absence of the unalkylated starting material.

This compound (b.p. 130–133° at 48 mm.) has previously been prepared in unreported yield by methylating 2-acetylcyclohexanone by means of sodium in benzene.[11]

Alkaline cleavages of β-diketones X *and* XII. Samples of these β-diketones were cleaved by alkali according to the procedure for the unalkylated β-diketones.

There was obtained from 2-acetyl-2-methylcyclopentanone a 65% yield of δ-acetylcaproic acid, b.p. 127–128° at 1.5 mm. Neut. equiv. Calcd. 158. Found: 159. The ethyl ester, prepared in 92% yield by the Fisher method, boiled at 77–79° at 0.6 mm.

Anal. Calcd. for $C_{10}H_{18}O_3$; C, 64.47; H, 9.74; Found: C, 64.23; H, 9.72.

There was obtained from 2-acetyl-2-methylcyclohexanone a 25% yield of ε-acetylheptylic acid, b.p. 128–129° at 0.7 mm. Neut. equiv. Calcd. 172. Found: 173. The ethyl ester, prepared in 93% yield by the Fisher method, boiled at 84–85° at 0.6 mm.

Anal. Calcd. for $C_{11}H_{20}O_3$; C, 65.96; H, 10.06. Found: C, 65.82; H, 10.06.

Also there was obtained from the cleavage of 2-acetyl-2-methylcyclohexanone a 54% yield of 2-methylcyclohexanone boiling at 165–167°; reported b.p. 166°.[12]

DURHAM AND WINSTON-SALEM, N. C.

(11) H. K. Sen and U. Bose, *J. Indian Chem. Soc.*, **4**, 62 (1927).

(12) A. Skita, *Ber.*, **56**, 1016 (1923).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF CINCINNATI]

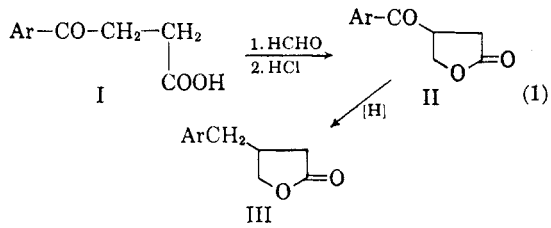
Substituted γ-Lactones. III. A General Route to β-Substituted γ-Butyrolactones[1]

JOHANNES ROTHE[2a] AND HANS ZIMMER[2b]

Received November 7, 1958

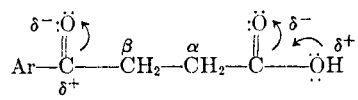
The reaction of β-aroylpropionic acids I with equimolecular amounts of formaldehyde in alkaline solution leads to β-aroylbutyrolactones II. This reaction appears to be a general one; with acetaldehyde, the corresponding β-aroyl-γ-valerolactones are obtained. A small yield of β-acetylbutyrolactone is formed from levulinic acid and formaldehyde. Catalytic hydrogenations and Meerwein-Ponndorf reductions of the II are described.

We were interested in preparing substituted β-benzylbutyrolactones as starting materials for further synthetic work. The hydroxymethylation of β-benzoylpropionic acid (Ia) or substituted β-benzoylpropionic acids, respectively, followed by lactonization and reduction of the carbonyl group, seemed to be a possible way:

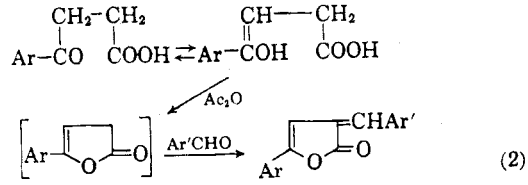


a: Ar = C_6H_5 *b*: Ar = 3,4-$(CH_3O)_2C_6H_3$

According to theoretical considerations, the β-methylene group in I should be more reactive than the α-methylene group:



It is a well known fact that the nucleophilic character of a keto-carbonyl-C-atom is stronger than that of a carboxyl-C-atom. Hence aldol-like condensations of aldehydes with I should preferably occur in the β-position. The reaction[3] of β-aroylpropionic acids with aldehydes under the influence of acetic anhydride to give α-arylidene-γ-arylcrotonolactones provides no argument against this assumption because, under the reaction conditions, enolization and lactonization seem to occur first, followed by condensation with the aldehyde:



(2)

In fact, reaction of ethyl β-benzoylpropionate and benzaldehyde with sodium ethylate in ethanolic solution yields up to 90% of β-benzylidene-β-benzoylpropionic acid.[3b]

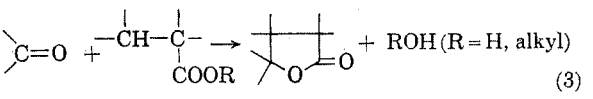
There are two classic examples for the preparation of lactones based on the principle of an aldol-like condensation of a carbonyl compound

(1) Paper II of this series, see H. Zimmer and J. Rothe, *J. Org. Chem.*, **24**, 100 (1959).

(2) (a) Chattanooga Medicine Company Post-doctorate Research Fellow 1956–58. Recipient of a Fulbright Travel Grant. Present address: Department of Chemistry, Harvard University, Cambridge, Mass. (b) To whom inquiries concerning this paper should be directed.

(3) (a) *e.g.*, J. Thiele, *Ann.*, **306**, 145 (1899); W. Borsche, P. Hofmann, and H. Kuhn, *Ann.*, **554**, 23 (1943); F. W. Schueler and C. Hanna, *J. Am. Chem. Soc.*, **73**, 3528 (1951); C. Hanna and F. W. Schueler, *J. Am. Chem. Soc.*, **75**, 741 (1953). (b) W. Borsche, *Ber.*, **47**, 1108 (1914).

with an activated β-CH-group of a carboxylic acid derivative according to the scheme:



(3)

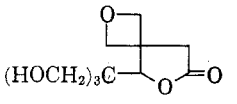
(1) The preparation of α-ketolactones (aldehyde or ketone with substituted pyruvic acids or esters,[4] (2) The Fittig paraconic acid synthesis (aldehydes with Na-succinate).[5,6]

Besides these well known reactions, we found surprisingly few examples[7-10] for the preparation of lactones according to Scheme 3. Haworth and Sheldrick[7] as well as Drake and Tuemmler[9] condensed substituted benzoylpropionic acids with formaldehyde but obtained partly the bis-hydroxymethylated products. Ladd and Paxton[8] prepared β-acylparaconic esters from α-acylsuccinic esters and aldehydes. Mikhlina and Rubtsov[10] obtained β-hydroxymethyl-β-4-pyridyl-γ-butyrolactone from ethyl β-(4-pyridyl)-propionate and an excess of formaldehyde.

In order to avoid any di-hydroxymethylation,[7,9,10] we regarded it as essential to apply only stoichiometric amounts of formaldehyde and to work under rather mild conditions. After several days standing at room temperature in alkaline solution [*p*H 8–10] we obtained from equimolecular amounts of Ia and 40% aqueous formalin a 45% yield of β-benzoyl-γ-butyrolactone (IIa). Similarly, from β-veratroylpropionic acid (Ib), up to 69% of β-veratroyl-γ-butyrolactone (IIb) was obtained. These neutral products are easily separated from unreacted starting material which can be recovered; the isolation and purification is simple. When the reaction with Ib was tried at a lower *p*H (7–8), the yield dropped to 2%, and 90% of the starting material was recovered. In one experiment, an excess of formalin was used; the m.p. of the product was lower in this case, and by fractional crystallization a low yield of the bis-hydroxymethylated product, β-hydroxymethyl-β-veratroyl-γ-butyrolactone, was isolated.

Using acetaldehyde instead of formaldehyde, we obtained the corresponding β-acyl-γ-valerolactones; this fact indicates that the reaction is not limited to formaldehyde, but that with other aldehydes a variety of β-acyl-γ-substituted butyrolactones may be synthesized.

In order to investigate further the limitations of the reaction, the simplest aliphatic α-keto acid, levulinic acid, was condensed with formaldehyde. This reaction has previously been investigated by Rave and Tollens[11] who worked with a large excess of the aldehyde and consequently obtained a poly-hydroxymethylated product which they formulated as IV. In our hands, with a 1:1 molar



IV

ratio, a small yield of β-acetyl-γ-butyrolactone was isolated. We believe, however, that the yield could be improved by a more suitable isolation technique. β-Acetyl-γ-butyrolactone is, to our knowledge, only described in form of its 2.4-dinitrophenylhydrazone.[12,*]

The second step of the intended synthesis (II→III) involves the reduction -CO- → -CH_2-. It was decided not to apply the Clemmensen reaction in this case, because of a possible cleavage of the methoxy groups in IIb, and also because the lactonic ring might be affected.[13] Wolff-Kishner reduction seems to be applicable, but the method of choice is hydrogenation according to the method of Zelinsky.[14] The catalyst used by Zelinsky consisted of platinum-on-carbon, activated with palladium chloride solution. We applied palladium chloride without a carrier and obtained practically

(4) *e.g.*, W. Wislicenus and A. Jensen, *Ber.*, **25**, 3448 (1892); E. Erlenmeyer Jr., and co-workers, *Ann.*, **333**, 160 (1904); R. Kuhn and T. Wieland, *Ber.*, **75**, 121 (1942); H. Schinz and M. Hinder, *Helv. Chim. Acta*, **30**, 1349 (1947); B. Puetzer, C. H. Nield, and R. H. Barry, *J. Am. Chem. Soc.*, **67**, 832 (1945); H. Gault and co-workers, *Ann. chim.*, [12], **6**, 220 (1951); G. W. Stacy and G. D. Wagner, *J. Am. Chem. Soc.*, **74**, 909 (1952).

(5) R. Fittig and co-workers, *Ann.*, **216**, 26 (1882); **227**, 79 (1885); **255**, 1, 257 (1889).

(6) About the occurrence of paraconic esters in the Stobbe condensation (aldehyde or ketone with succinic esters), *cf.* W. S. Johnson and G. H. Daub, *Org. Reactions*, **6**, 1 (1951).

(7) R. D. Haworth and G. Sheldrick, *J. Chem. Soc.*, 289 (1941).

(8) E. C. Ladd and H. W. Paxton, U. S. Pat. **2,598,803** (1952) [*Chem. Abstr.*, **46**, 10194d (1952)].

(9) N. L. Drake and W. B. Tuemmler, *J. Am. Chem. Soc.*, **77**, 1204 (1955).

(10) E. E. Mikhlina and M. V. Rubtsov, *Zhur. Obshchet Khim.*, **27**, 691 (1957); [*Chem. Abstr.*, **51**, 16463f (1957)].

(11) P. Rave and B. Tollens, *Ann.*, **276**, 69 (1893).

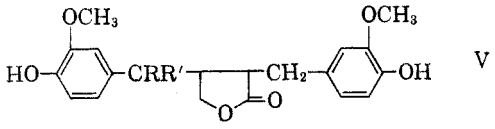
(12) (a) B. R. Baker, R. E. Schaub, and J. H. Williams, *J. Org. Chem.*, **17**, 116 (1952); (b) L. Birkofer and I. Storch, *Ber.*, **87**, 571 (1954).

(13) E. L. Martin, *Org. Reactions*, **1**, 155 (1942); *J. Am. Chem. Soc.*, **58**, 1438 (1936).

(14) N. D. Zelinsky, K. Packendorff, and L. Leder-Packendorff, *Ber.*, **66**, 872 (1933); **67**, 300 (1934).

* NOTE ADDED IN PROOF: After submitting this manuscript our attention was directed to an article by S. Olsen [*Acta chem. scand.*, **9**, 101 (1955)] who experimentally disproved structure IV. He condensed levulinic acid with an excess of paraformaldehyde in acidic medium and obtained, among other products, a compound $C_6H_8O_3$ (b.p. 153°) which decolorized bromine in chloroform, gave a positive Baeyer reaction and which he assumed to be either β- or δ-methylenelevulinic acid or β-acetylbutyrolactone. Our analytical sample reacted neutral in aqueous solution and neither decolorized bromine in chloroform nor a dilute potassium permanganate solution in 5% sodium bicarbonate. Its IR-spectrum is in agreement with our assumed structure. It shows peaks at 5.62μ and 5.82μ resp., indicating the presence of a lactonic and a ketonic carboxyl groups. There is no peak between 5.82μ and 6.75μ indicating the absence of C=C unsaturation. In addition it shows no evidence for COOH absorption.

quantitative yields of IIIa and IIIb, respectively. After these experiments were completed, we learned that Freudenberg[15] had used the same catalyst for the reduction of (+)-oxo-matairesinol (*V*, R=O) to (−)-matairesinol (*V*,R′=R=H). Freu-



V

denberg[15] also reports that under milder conditions (palladium-on-kieselguhr) the hydrogenation stops at the carbinol stage (*V*, R=H, R′=OH). In our experiments, the desired β-benzyl-γ-butyrolactones were definitely obtained, as was shown by analytical results and IR spectra.

Meerwein-Ponndorf reduction of II led to the corresponding carbinols. With IIb, the yield was moderate, probably due to the fact that only one of the two possible racemic diastereoisomers was obtained as a crystalline solid; attempts to isolate the other isomer in crystalline form were so far unsuccessful. The reduction product of IIa was an oil, probably a mixture of the two isomers.

EXPERIMENTAL

The infrared spectra were obtained with a Baird double beam spectrophotometer and measured in nujol mull (solids) or neat (liquids). Melting points are not corrected. Analysis by A. Bernhardt, Max Planck Institute, Mulheim/Ruhr, Germany.

DL-*β-Benzoyl-γ-butyrolactone* (IIa). Twenty g. (0.145 mole) of potassium carbonate were dissolved in 100 cc. of water, and 35.6 g. (0.2 mole) of β-benzoylpropionic acid (Ia) were cautiously added, followed by 18 cc. (0.2 mole) of a solution of 36–38% formalin. The solution was kept at room temperature for 8 days. After the addition of 30 cc. of concentrated hydrochloric acid to effect lactonization, the mixture was warmed on a boiling water bath for 30 min., then cooled and repeatedly extracted with methylene chloride. The extracts were washed several times with 10% sodium carbonate solution, then with water, dried over sodium sulfate, and the solvent was evaporated. An oily residue was left which in the first experiment did not solidify until it had been redistilled several times. In all the following experiments, the oil was dissolved in hot methanol and precipitated upon cooling; no difficulty in crystallization was encountered. The analytical sample (b.p. 176–176.5°/4.5 mm.) melted at 60–61.5°. In later experiments, melting points of 65–66° were observed. The yield was 17.0 g. (45%).

Anal. Calcd. for $C_{11}H_{10}O_3$: C, 69.46; H, 5.30. Found: C, 69.30; H, 5.43. Infrared spectrum: 5.66 μ (5-membered lactone-CO) and 5.97 μ (ketone-CO). 5.9 g. of Ia were recovered from the sodium carbonate washings; the yield based on consumed Ia is 53%.

2,4-Dinitrophenylhydrazone, m.p. 223.5–224°, orange-yellow microcrystalline powder from dioxane-methanol.

Anal. Calcd. for $C_{17}H_{14}N_4O_6$: C, 55.13; H, 3.81; N, 15.13. Found: C, 55.37; H, 3.92; N, 15.02.

Phenylhydrazone, m.p. 168–169°, short needles from methanol.

Anal. Calcd. for $C_{17}H_{16}N_2O_2$: N, 9.99. Found N, 10.10.

Semicarbazone, m.p. 144–145°, leaflets from methanol-water.

Anal. Calcd. for $C_{12}H_{13}N_3O_3$: N, 17.00. Found: N, 17.04.

Similarly, the following compounds were prepared: DL-*β-(3,4-Dimethoxybenzoyl)-γ-butyrolactone* (IIb), from Ib and 40% formalin (15 days; 69%). Plates from CH_3OH, m.p. 116–117°. Infrared spectrum: 5.65 μ and 6.00 μ.

Anal. Calcd. for $C_{13}H_{14}O_5$: C, 62.39; H, 5.64. Found C, 62.34; H, 5.80.

2,4-Dinitrophenylhydrazone, m.p. 212–213°, orange microcrystalline powder from dioxane.

Anal. Calcd. for $C_{19}H_{18}N_4O_8$: C, 53.02; H, 4.22. Found: C, 53.27; H, 4.49.

DL-*β-Benzoyl-γ-valerolactone*, from Ia and acetaldehyde (12 days). Yellowish oil, b.p. 157–160°/5 mm., n_D^{26} 1.5455.

Anal. Calcd. for $C_{12}H_{12}O_3$: C, 70.57; H, 5.92. Found: C, 70.27; H, 6.03.

2,4-Dinitrophenylhydrazone, m.p. 210–211°, small orange leaflets from ethanol.

Anal. Calcd. for $C_{18}H_{16}N_4O_6$: C, 56.25; H, 4.20; N, 14.58. Found: C, 56.21; H, 4.16; N, 14.74.

DL-*β-(3,4-Dimethoxybenzoyl)-γ-valerolactone*, m.p. 114–115° (from methanol-ether).

Anal. Calcd. for $C_{14}H_{16}O_5$: C, 63.62; H, 6.10. Found: C, 63.48; H, 6.00.

2,4-Dinitrophenylhydrazone, m.p. 214.5–215.5°, orange flakes from dioxane-methanol.

Anal. Calcd. for $C_{20}H_{20}N_4O_8$: C, 54.05; H, 4.54. Found: C, 54.02; H, 4.53.

DL-*β-Hydroxymethyl-β-(3,4-dimethoxybenzoyl)-γ-butyrolactone*. Veratroylpropionic acid (95.3 g.), 48 g. of potassium carbonate, 32 cc. of 36–38% formalin, and 300 cc. of water were kept at room temperature for 15 days. After this time, 10 more g. of potassium carbonate and 30 cc. of 40% formalin were added and the mixture was stored for 13 more days. After the usual working up and one recrystallization from methanol, 59.9 g. of a product, m.p. 106–108°, were obtained. Another recrystallization from the same solvent gave 56.8 g. (56%) of IIb, m.p. 109–110.5°. The filtrates of these two recrystallizations were combined and evaporated to a small volume; 3.6 g. of crystals, m.p. 131–136°, were collected. After 6 further recrystallizations from methanol, the analytical sample of DL-β-hydroxymethyl-β-(3,4-dimethoxybenzoyl)-γ-butyrolactone melted at 145–146°.

Anal. Calcd. for $C_{14}H_{16}O_6$: C, 59.99; H, 5.75. Found C, 60.18; H, 5.88.

2,4-Dinitrophenylhydrazone, m.p. 201–202° (from dioxane-methanol).

Anal. Calcd. for $C_{20}H_{20}N_4O_9$: C, 52.17; H, 4.38; N, 12.17. Found: C, 52.33; H, 4.47; N, 12.20.

DL-*β-Acetyl-γ-butyrolactone*. Fifty-five g. of levulinic acid (once distilled), 47.5 g. of potassium carbonate, 38 cc. of 40% formalin, and 100 cc. of water were kept at room temperature for 2 weeks. The mixture was then acidified, heated on a boiling water bath for 30 min., cooled, saturated with potassium sulfate, and extracted 3 times with 100-cc. portions of chloroform. The combined chloroform extracts were washed twice with 50-cc. portions of saturated sodium carbonate solution, and the alkaline layer once again extracted with 100 cc. of chloroform. The extracts were eventually washed with saturated potassium sulfate solution, dried (sodium sulfate), and the solvent evaporated. A yellowish liquid remained which upon distillation gave 5.2 g. (8.6%) of the lactone, b.p. 114–122°/5 mm. After 2 more distillations, a center cut (b.p. 118–120°/5 mm.; n_D^{19} 1.4630) was analyzed.

Anal. Calcd. for $C_6H_8O_3$: C, 56.24; H, 6.29. Found: C, 56.37; H, 6.30.

2,4-Dinitrophenylhydrazone, orange-yellow leaflets from dioxane, m.p. 193.5–194° (lit. m.p.: 191–192°[12a], 193°[12b]).

Anal. Calcd. for $C_{12}H_{12}N_4O_6$: C, 46.76 H, 3.92 N, 18.18. Found: C, 46.81 H, 4.04 N, 18.29.

DL-*β-Benzyl-γ-butyrolactone* (IIIa). Five and seven tenths g. of IIa in 250 cc. of methanol were hydrogenated with 0.3 g. of palladium chloride in a Parr apparatus at 50 p.s.i. initial pressure. After about 2 hr., the pressure had dropped

(15) K. Freudenberg and L. Knof, *Ber.*, **90**, 2857 (1957).

to 44.5 p.s.i. and then remained constant. After removal of the catalyst and solvent, the product was distilled, yielding 5.2 g. (98%) of DL-β-benzyl-γ-butyrolactone, b.p. 161–163°/6 mm. The analytical sample, a center cut from a second distillation, had b.p. 162–163°/6 mm. Colorless liquid, n_D^{20} 1.5373.

Anal. Calcd. for $C_{11}H_{12}O_2$: C, 74.97 H, 6.86. Found: C, 74.69; H, 6.68. Infrared spectrum: 5.64 μ (lactone-CO); a weak band appeared at 2.83 μ (indicating that the compound was contaminated by a trace of OH-containing material).

DL-β-(*3,4-Dimethoxybenzyl*)-γ-*butyrolactone* (IIIb) was similarly prepared from IIb, yield 95–97%. Slightly yellowish, rather viscous oil, b.p. 220°/6 mm., n_D^{20} 1.5519.

Anal. Calcd. for $C_{13}H_{16}O_4$: C, 66.08; H, 6.83. Found: C, 66.08; H, 6.81. Infrared spectrum: 5.58 μ (lactone-CO); no absorption between 2 μ and 3.2 μ (no OH-containing impurity).

DL-β-(α-*Hydroxy-3,4-dimethoxybenzyl*)-γ-*butyrolactone.* A mixture of 10.1 g. of IIb, 8.2 g. of aluminum isopropoxide,[16] and 50 cc. of isopropanol (previously distilled over calcium oxide) was placed in a 500-cc. two-necked, round-bottom flask which was fitted with a Widmer column. The mixture was gently refluxed for 1 hr., then heated at such a rate that acetone distilled as it was formed. After 3 hr., 50 cc. of isopropanol were added. The reaction proceeded slowly, but after 8 hr. the distillate gave a negative test with 2,4-dinitrophenylhydrazine. The reaction mixture was then concentrated nearly to dryness, decomposed with 100 cc. of 10% hydrochloric acid, and kept overnight in the refrigerator. It was then extracted twice with chloroform, the chloroform layers dried over sodium sulfate, and the solvent evaporated. A yellowish oil remained which solidified partly after digestion with a large amount of ether and standing for several weeks. 4.8 g. (48%) of crude product, m.p. 77–81°, was obtained. One recrystallization from methanol-ether gave 2.2 g. of a product, m.p. 91–93°. Three more recrystallizations raised the m.p. to 96.5–97.5°.

Anal. Calcd. for $C_{13}H_{16}O_5$: C, 61.89; H, 6.39. Found: C, 61.95; H, 6.50. Infrared spectrum: 5.65 μ and 5.75 μ (double band) and 2.95 μ. Various attempts to isolate more crystalline material from the oily residues of the evaporated mother liquors were unsuccessful. Further investigation of this oil is in progress.

DL-β-(α-Hydroxybenzyl)-γ-butyrolactone was obtained similarly from 9.5 g. of IIa. The reaction product was a slightly yellowish oil which did not crystallize, and hence was distilled (b.p. 160–205°/5 mm., 7.3 g., 76%). After two more distillations, a fraction (4.1 g., 43%) with b.p. 195–197°/5 mm., n_D^{26} 1.5461, was analyzed.

Anal. Calcd. for $C_{11}H_{12}O_3$: C, 68.73; H, 6.29. Found: C, 68.36; H, 6.31. Infrared spectrum: 5.65 γ and 2.90–2.95 μ (broad band).

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(16) The authors are indebted to Chattem Chemicals, Division of the Chattanooga Medicine Co., Chattanooga, Tenn., for a generous gift of this compound.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, DUKE UNIVERSITY]

Aromatic Cyclodehydration. XLI.[1,2] *Meso*-substituted Acridiziniúm Benzologs

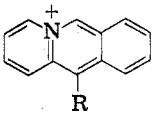
C. K. BRADSHER AND T. W. G. SOLOMONS

Received October 17, 1958

Benzacridizinium derivatives with a substituent in the central nucleus have been prepared by the acid-catalyzed cyclization of quaternary salts obtained by reaction of (1) 1-bromomethylnaphthalene with 2-pyridyl ketones or (2) benzyl (or naphthylmethyl) halides with 1-benzoylisoquinoline.

Only a single, highly activated, 1-benzoyl-2-benzylisoquinolinium salt (VIII) was found to cyclize in liquid hydrogen fluoride, but the remainder of the isoquinolinium salts could be cyclized in hot polyphosphoric acid.

In the preceding communication of this series it was shown that salts obtained by the quaternization of 2-pyridyl ketones could be cyclized to yield the first 11-substituted acridizinium salts I. It appeared interesting to examine the usefulness of



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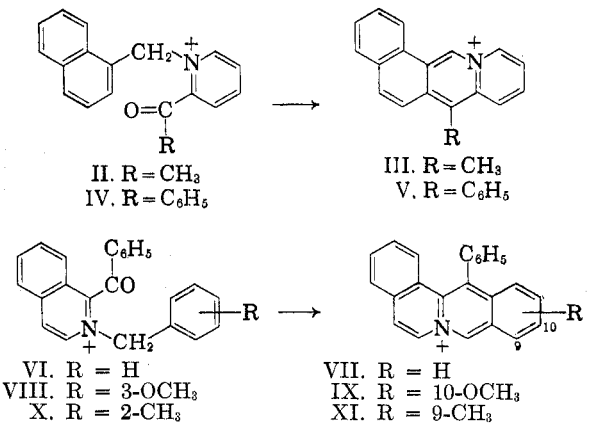
this approach in the synthesis of some acridizinium benzologs, since at least one of these would be isosteric with a known carcinogen and further information could be gained about the importance of steric and electronic effects on the ease of cyclization. For the synthesis of the monobenzologs two general approaches have been used, both involving the cyclization of quaternary salts. In the first, a



II. R = CH_3
IV. R = C_6H_5
III. R = CH_3
V. R = C_6H_5
VI. R = H
VIII. R = 3-OCH_3
X. R = 2-CH_3
VII. R = H
IX. R = 10-OCH_3
XI. R = 9-CH_3

(1) For the preceding communication of this series, see *J. Am. Chem. Soc.*, in press.

(2) Taken in part from a thesis to be submitted in partial fulfillment of the requirements for the Ph.D. degree, Duke University. This research was supported by a research grant (NSF-G2364) of the National Science Foundation.