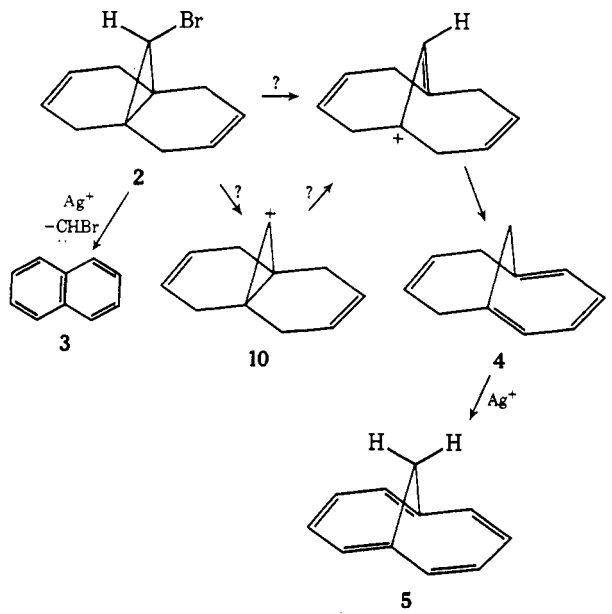
Scheme II



stituent on the stability of the cyclopropyl cation formed from **6** will be negligible.[12,13]

One might thus expect to observe a larger difference in rate between **2** and **6** since the larger bromine substituent should increase the ground-state energy of **6** due to increased steric strain. In fact molecular mechanics indicate a difference in ground-state strain energy between **2** and **6** of 3.78 kcal/mol. This would correspond to a relative rate $k_6/k_2 = 600$.[14] However, it is risky to put too much faith in the absolute difference in strain energy between compounds of this type calculated in this manner.[15]

In addition, the low yields of isolable products preclude an unambiguous interpretation of the rate and product data. We offer a mechanistic scheme (Scheme II) as a suggested mode for the formation of **3–5**. Whether or not a cyclopropyl cation (*e.g.*, **10**) is in fact an intermediate in the solvolysis of **2** awaits further experimentation.[16]

Experimental Section[17]

11-Bromotricyclo[4.4.1.0^{1,6}]undeca-3,8-diene (2). To a refluxing solution of compound **6** (7.9 g, 0.026 mol) and a small amount of AIBN in 125 ml of absolute ether was added dropwise with stirring and under a nitrogen atmosphere 7.6 g (0.33 mol) of tri-*n*-butyltin hydride dissolved in 8 ml of absolute ether. After the addition was complete (2 hr) the reaction mixture was refluxed an additional 5 hr and then stirred at room temperature for 18 hr. The solvent was removed under reduced pressure and the resulting solution was then distilled. The fraction boiling between 90 and 100° (0.5 mm) was collected and then sublimed. Recrystallization of the sublimate from methanol afforded 3 g (56%) of material, mp 50–51° (lit.[18] mp 51°). The nmr spectrum of **2** was identical with that reported by Paquette.[19]

Silver Ion Assisted Methanolysis of 2. Compound **2** (3.0 g, 0.013 mol) and silver nitrate (22.5 g, 0.13 mol) were dissolved in 100 ml of methanol and heated for 25 hr at 100° in a glass pressure flask. After the usual work-up the crude reaction mixture was subjected to gas chromatographic analysis on an 8 ft × ¼ in. Hi-EFF (DEGS) 15% column. Three major components (**3–5**) were shown to be present. These were collected and identified (see text).[20] The absolute yields of **3–5** were determined using standard gas chromatographic techniques. α-Methylnaphthalene was employed as the internal standard.

Kinetic procedures as previously outlined[8] were employed. Eight points were taken for each run and 1,3-diphenylpropane was employed as an internal standard.

Acknowledgment. We wish to thank the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research.

Registry No.—**2**, 4622-37-1; **4**, 38795-15-2; **5**, 2443-46-1; **6**, 4578-96-5.

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(10) (a) All attempts to free the sample of naphthalene met with no success. The spectra reported contain ~10% naphthalene as an impurity. This precluded a correct elemental analysis for compound **4**. (b) E. Vogel, *et al.*, *Justus Liebigs Ann. Chem.*, **759**, 1 (1972).
(11) The infrared spectrum of **4** exhibits absorption at 1630, 1597, and 1490 cm^{-1}, while **8** has absorption at 1494 and 1600 cm^{-1}.[10]
(12) V. Buss, P. v. R. Schleyer, and L. C. Allen, *Top. Stereochem.*, **7**, 253 (1973).
(13) Hine has demonstrated that the SN1 reactivities of benzal and benzyl bromides in aqueous acetone at 25° are essentially identical. See J. Hine and D. E. Lee, *J. Amer. Chem. Soc.*, **73**, 22 (1951).
(14) We thank Professor Paul Schleyer and Diane Khoury for performing the force field calculations mentioned above.
(15) For a critical review of molecular mechanics see E. M. Engler, J. D. Andose, and P. v. R. Schleyer, *J. Amer. Chem. Soc.*, **95**, 8005 (1973), and references contained therein.
(16) In a typical run for 25 hr at 100° the ratio of **4:3** was 1. However, when the reaction was carried out at 90° for approximately 15 hr, the ratio of **4:3** was 5. Starting material was still present and no detectable amounts of **5** were observed. Vogel has studied the thermal behavior of **4** extensively.[9] He has demonstrated that **4** is stable at temperatures below 250°. At temperatures above 250° **4** rearranges exclusively to benzocycloheptatriene. It thus seems unlikely that **4** is converted to **3** at 100°.
(17) Infrared spectra were determined with a Perkin-Elmer 457 recording spectrophotometer. The nmr spectra were measured at 60 MHz with an Hitachi Perkin-Elmer R20 spectrometer using tetramethylsilane as the internal reference. All spectra were measured in CCl_4 unless otherwise stated. A Hewlett-Packard 5750B gas chromatograph was used for all vpc analyses. All peak areas were integrated with a planimeter. Magnesium sulfate was employed as the drying agent. All reactions involving air- or moisture-sensitive compounds were carried out under a nitrogen atmosphere.
(18) E. Vogel, *et al.*, *Tetrahedron Lett.*, 3625 (1965).
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(20) It was found advantageous in subsequent experiments to separate the volatile materials from polymeric material by chromatographing the crude reaction mixture on a silica gel column eluted with ligroin before final isolation of the components *via* gas chromatography.

Steroids and Related Natural Products. 90. 15β-Hydroxydigitoxigenin[1]

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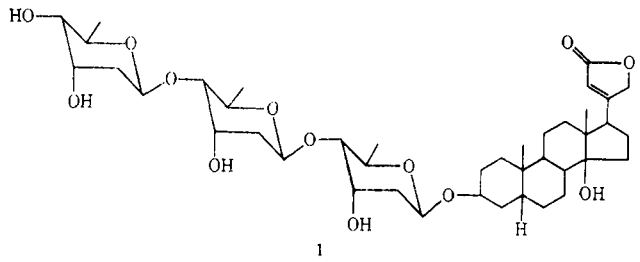
Biologically active steroids of the cardenolide type generally occur in plants[2] as glycosides and have also been isolated from butterflies[2] and toad venoms.[3] Isolation of the parent aglycone by acid hydrolysis of the corresponding glycoside is most useful with sugar attachments of the 2-deoxy type (*cf.* ref 1). If the aglycone is bound to a 2-hydroxy sugar such as D-glucose, acid hydrolysis is much less practical. In such cases enzymatic hydrolysis is considerably more useful.[4] One of the earliest procedures for acid-catalyzed cleavage of cardiac glycosides utilized a mixture of hydrochloric acid in aqueous acetic acid.[5] Another early procedure was based on alcoholysis with 2% hydrogen chloride in methanol.[6] The Reichstein[7] modification of these methods utilized an equal volume mixture of 0.1 *N* sulfuric acid–methyl alcohol to hydrolyze odoroside A and we have



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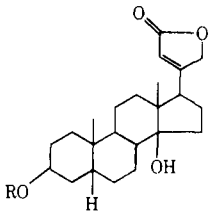
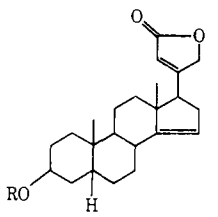
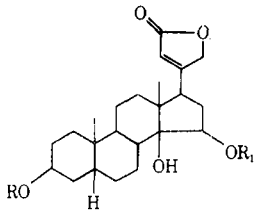


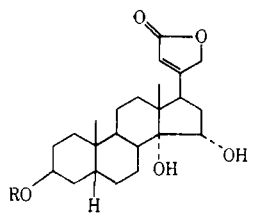
2a, R = H
b, R = $COCH_3$



3a, R = H
b, R = $COCH_3$



4a, R = R_1 = H
b, R = $COCH_3$; R_1 = H
c, R = R_1 = $COCH_3$



5a, R = H
b, R = $COCH_3$

routinely employed the same reagent for hydrolysis of digitoxin (**1**) to digitoxigenin (**2a**).[8]

The four-step (**1** → **2a** → **2b** → **3b**) conversion of digitoxin (**1**) to 3β-acetoxy-14-dehydrodigitoxigenin (**3b**) has been carried out many times in our laboratory.[1,9] Initially, we employed thionyl chloride in pyridine for dehydration of the tertiary alcohol **2b**, but later concentrated hydrochloric acid in methanol (2 hr at reflux) was found more satisfactory.[10] Principal objectives of the present investigation involved finding a more efficient route for conversion of digitoxin (**1**) to olefin **3b** and exploring Woodward[11] cis hydroxylation of the latter substance as a method of synthesizing 15β-hydroxydigitoxigenin (**4a**).[12] To begin with, digitoxin (**1**) was subjected to hydrolysis with concentrated hydrochloric acid in methanol. Brief warming led to a mixture of olefin **3a** as major product accompanied by digitoxigenin (**2a**). By extending the reaction period to 90 min, good conversion to 14-dehydrodigitoxigenin (**3a**) as the only product was realized. Substitution of an acidic ion exchange resin for the hydrochloric acid gave digitoxigenin as major product accompanied by a lesser amount of olefin **3a**.

Attention was next directed to one-step conversion of digitoxin to 3β-acetoxy-14-dehydrodigitoxigenin (**3b**). The most efficient method found involved heating glycoside **1** with *p*-toluenesulfonic acid in acetic acid–acetic anhydride. Good conversion to olefin **3b** was routinely experienced and the presence of alcohol **2b** was not detected. Shorter reaction periods gave either alcohol **2b** or mixtures of both products (**2b** and **3b**). The *p*-toluenesulfonic acid–acetic anhydride reagent also proved very effective for the transformation of diol **2a** and alcohol **2b** to olefin **3b**.

Minimum reaction conditions necessary for partial dehydration of digitoxigenin (**2a**) and its acetate derivative (**2b**) to give a good yield of olefin **3a** were also evaluated. Hydrochloric acid–methanol treatment[10] of digitoxigenin (**2b**) required 1 hr at reflux and with acetate **2b** approximately 1.5 hr at reflux. In both cases good yields of olefin **3a** were obtained. Extension of the reaction period to 2 hr and use of an acidic ion exchange resin in place of hydrochloric acid gave comparable yields of olefin **3a**. As expected, both methods were quite suitable for transformation of acetate **3b** to alcohol **3a**. After completion of these model hydrolysis experiments and the practical procedure for one-step conversion of digitoxin to olefin **3b**, the synthesis of 15β-hydroxydigitoxigenin (**4a**) was undertaken.

The very specific steric requirements of cis hydroxylation with osmium tetroxide would suggest that attack on olefin **3b** would proceed from the less hindered α side and produce triol **5a**. The very careful study of this reaction by Tamm[13] nicely showed α-side approach to be preferred. Formation of α-*cis*-diol **5a** was favored over that of the β-*cis*-diol **4a** in a ratio of 10:1. The lactone olefin system could also be hydroxylated by allowing diol **5a** to react with osmium tetroxide. The stereochemistry of diols **4** and **5** was determined by degradation to the corresponding 17β-carboxylic acids and interpretation of spectral data.

In our hands osmium tetroxide hydroxylation of olefin **3b** gave α-diol **5b** as major product (42%) and only a minor amount (6.5%) of β-diol **4b**. However, treatment of olefin **3b** with iodine and silver acetate in aqueous acetic acid[11] afforded a good route to diacetate **4c**. After purification by column chromatography and recrystallization, a 38% yield of the β product (**4c**) was recovered. Compelling evidence for structure **4c** was provided by comparison with the diacetate obtained by acetylating the minor product (**4b**) of osmium tetroxide hydroxylation. Acid hydrolysis of acetate **4c** at room temperature with, for example, hydrochloric acid in methanol completed the route to 15β-hydroxydigitoxigenin (**4a**).

Experimental Section[14]

Acid Hydrolysis of Digitoxin (1). Method A. With Hydrochloric Acid. A solution of digitoxin (**1**, 40 mg)[8] in methanol (1.4 ml) containing 35% hydrochloric acid (0.09 ml) was heated at reflux 90 min. The solution was poured into ice–water and extracted with chloroform and the solvent extract was washed with water and evaporated to dryness. The residue was subjected to column chromatography and the fraction eluted by 5:1 hexane–acetone was recrystallized from methanol–hexane to yield 16 mg of 14-dehydrodigitoxigenin (**3a**) melting at 199–202° (lit.[15,16] mp 198–204 and 202°).

With a 25-min period at reflux reaction of digitoxin (**1**, 80 mg) and 35% hydrochloric acid (0.18 ml) in methanol (2.8 ml) gave 30 mg of olefin **3a**, mp 201–203°. A more polar fraction was recrystallized from 80% ethyl alcohol to yield 8 mg of digitoxigenin (**2a**) melting at 248–251°. Essentially the same yields of both products were obtained with ethyl alcohol as solvent.

Method B. With Amberlite CG-120 (H^+). A mixture prepared from digitoxin (**1**, 60 mg) in methanol (6 ml)–water (1.2 ml) and Amberlite CG-120 (H^+, 0.30 g) was heated at reflux for 1 hr. After filtration the solution was evaporated to a 47-mg residue which was purified as described in method A above to provide 8 mg, mp 200–202°, of olefin **3a** and 14 mg, mp 250–252°, of digitoxigenin (**2a**). Substitution of Dowex-50W-X80 (H^+, 0.25 g) for the Amberlite resin led to 6 mg of olefin **3a** and 14 mg of digitoxigenin.

Method C. With *p*-Toluenesulfonic Acid–Acetic Anhydride. A solution of digitoxin (**1**, 0.10 g) in acetic acid (5 ml)–acetic anhydride (1 ml) containing *p*-toluenesulfonic acid (50 mg) was allowed to remain at room temperature 7 hr. The crude product was isolated as noted in method A above except for washing the chloroform extract with dilute sodium bicarbonate. Recrystallization from acetone–hexane afforded 34 mg of olefin **3b** melting at 182–184° (lit.[17] mp 182–183° and lit.[16] mp 192–193°). When the preceding reaction was terminated after 25 min, only 12 mg of 3β-acetoxydigitoxigenin (**2b**, mp 224–226° from acetone–hexane) was isolated. Substitution of acetic acid (5 ml) containing 5 drops of water for the acetic acid–acetic anhydride mixture and use of a 30-min period reflux led to 10 mg of olefin **3b**, mp 183–185°, as the only hydrolysis product from 50 mg of digitoxin (**1**). The same reaction at room temperature with 0.10 g of digitoxin gave 21 mg, mp 249–251°, of digitoxigenin (**2a**) and 13 mg of olefin **3a** melting at 198–202°.

The specimens of olefin **3b** prepared by the above procedures

were found identical with a sample obtained by acetylating and dehydrating digitoxigenin (see following experiment).

3β-Acetoxy-5β-carda-14,20(22)-dienolide (3b). Method A. From Digitoxigenin. A solution of digitoxigenin (**2a**, 50 mg) and *p*-toluenesulfonic acid (5 mg) in acetic acid (2.5 ml) was heated at reflux for 30 min. The product **3b** was isolated as already outlined in the preceding experiment and found to weigh 46 mg and melt at 181–183° (after crystallization from methylene chloride–ethyl ether).

In another experiment digitoxigenin (**2a**, 50 mg) was allowed to react with the reagent prepared from *p*-toluenesulfonic acid (5 mg) and acetic acid (2.5 ml)–acetic anhydride (0.5 ml). The reaction was allowed to proceed at room temperature for 6 hr. After chromatographic purification of the product as described above, 44 mg of olefin **3b** (mp 181–184°) was isolated.

Method B. From 3β-Acetoxydigitoxigenin (2b). A solution of acetate **2b** (25 mg) and *p*-toluenesulfonic acid (2.5 mg) in acetic acid (6 ml) was allowed to remain at room temperature 6 hr. Olefin **3b** (21 mg, mp 180–183°) was isolated as just summarized.

14-Dehydrodigitoxigenin (3a). Method A. From Digitoxigenin (2a). Procedure 1. With Hydrochloric Acid. A solution composed of digitoxigenin (**2a**, 80 mg), 35% hydrochloric acid (0.18 ml), and either 3 ml of methanol or ethanol was heated at reflux 1 hr. Purification of the product by column chromatography and recrystallization of the product from methanol–hexane afforded 69 mg of olefin **3a** melting at 199–203°.

Procedure 2. With an Acidic Ion-Exchange Resin. The preceding dehyration reaction was repeated employing 30 mg of digitoxigenin in ethanol (3 ml)–water (0.6 ml) and either Amberlite CG-120 (H^+ form) or Dowex 50W-X80 (H^+ form). Here the period at reflux was 2 hr and 24 mg of olefin **3a** (mp 198–203°) was obtained.

Method B. From 3β-Acetoxydigitoxigenin (2b). The method A, procedure 1 (see above) hydrolysis reaction was repeated with acetate **2b** (0.10 g) and hydrochloric acid (2.2 ml) in ethanol (5 ml) at relux for 1.5 hr. After recrystallization the specimen of olefin **3a** amounted to 94 mg and melted at 200–204°.

When the preceding reaction was allowed to proceed only 25 min, a complex mixture of products resulted. The fractions eluted by 5:1 hexane–acetone were recrystallized to provide 28 mg of olefin **3b** (mp 182–185° from methylene chloride–ethyl ether), 54 mg of olefin **3a** (mp 199–203° from methanol–hexane), and 14 mg of digitoxigenin (mp 246–250° from methanol–hexane). The same mixture (16 mg of **3b**, 20 mg of **3a**, and 9 mg of **2a**) resulted from dehydrating 50 mg of digitoxigenin acetate (**2b**) with 0.25 g of Amberlite CG-120 (H^+ form). The reaction was conducted in methanol at reflux for 1 hr.

Acid-Catalyzed Hydrolysis of 3β-Acetoxy-5β-carda-14,20-(22)-dienolide (3b). A solution of acetate **3b** (20 mg) in methanol (2 ml) containing 3 drops of water and 0.05 ml of 35% hydrochloric acid was heated at reflux 1 hr. After chromatographic purification and recrystallization, the yield of alcohol **3a** was 14 mg, mp 198–202°. Substitution of 0.10 g of Amberlite CG-120 (H^+ form) or the same amount of Dowex 50W-X80 (H^+ form) for the hydrochloric acid and extension of the reaction time to 2 hr led to 15 mg of alcohol **3a** melting at 199–201°.

Reaction of Osmium Tetroxide with 3β-Acetoxy-5β-carda-14,20(22)-dienolide (3a). The selective hydroxylation of olefin **3b** (0.5 g) was carried out with osmium tetroxide (0.5 g) in dry ethyl ether (70 ml)–pyridine (7 ml) during 8 hr (10°) essentially as described by Tamm and coworkers.[13] In this experiment the product was purified by column chromatography on silica gel. Elution with 3:1 hexane–acetone gave a mixture (0.26 g) of diols **4b** and **5b**. Rechromatography and elution with 5:1 hexane–acetone led (after recrystallization) to 34 mg of β-diol **4b** (mp 253–255° from methanol, lit.[13] mp 250–259°) and 0.21 g of α-diol **5b** (mp 201–203° from methanol, lit.[13] mp 202–203°).

3β,15β-Diacetoxy-14β-hydroxy-5β-card-20,22-enolide (4c, 15β-Hydroxydigitoxigenin Diacetate). Iodine (0.4 g) and silver acetate (0.4 g) were added to a solution of olefin **3b** (0.2 g) in acetic acid (12 ml)–water (0.6 ml). The mixture was stirred at room temperature 12 hr and the solution was filtered. Solvent was removed and the yellow residual solid was subjected to column chromatography. The fraction eluted by 9:1 hexane–acetone was recrystallized from methanol–hexane to afford 76 mg of diacetate **4c** as needles melting at 125–128° (lit.[13] mp 123–130°): λ_{max} 218 nm (log ε 4.21); ν_{max} 3580 (OH), 1780, 1740, 1728, 1620 (butenolide ring and ester CO), 1240, 1220 cm^{-1} (C–O); pmr (10% solution in deuteriochloroform) δ 0.94 (3 H, s, 18-CH_3), 0.96 (3 H, s, 19-CH_3), 2.05 (3 H, s, 3-OAc), 2.09 (5 H, s, 15-OAc), 2.77 (1 H, d, J = 7 Hz, 17-H), 4.8 and 5.1 (2 H, a narrow AB-type quartet, J = 2 Hz, 22-H); mass spectrum *m/e* 474 (M^+), 456 ($M^+ - H_2O$), 414 (M^+ – AcOH), 396 ($M^+ - H_2O$ – AcOH), 354 (M^+ – 2AcOH), 336 (M^+ – 2AcOH – H_2O).

Anal. Calcd for $C_{27}H_{38}O_7$: C, 68.33; H, 8.07. Found: C, 68.45; H, 8.09.

A 20-mg sample of diol **4b** was acetylated with acetic anhydride (0.3 ml)–pyridine (0.5 ml) at room temperature during 20 hr. The resulting diacetate **4c** was recrystallized from methanol–hexane to afford needles weighing 16 mg and melting at 123–127°. Diacetate **4c** originating from the osmium tetroxide approach was found identical with the product **4c** obtained by the iodine–silver acetate method.

15β-Hydroxydigitoxigenin (4a, 3β,14β,15β-Trihydroxy-5β-card-20(22)-enolide). A solution of diacetate **4c** (50 mg) in 80% ethanol (30 ml) containing sulfuric acid (0.2 ml) was allowed to stand at room temperature 3–5 days. The solution was poured into water, neutralized with dilute sodium bicarbonate, and extracted with chloroform. The combined extract was washed with water and the solvent was removed. The residue (46 mg) was chromatographed on a column of silica gel and a fraction eluted with hexane–acetone (3:1) was recrystallized from acetone–hexane to afford 28 mg of diol **4a** melting at 247–250° (lit.[13] mp 248–252 and 245–247°): λ_{max} 218 nm (log ε 4.20); ν_{max} 3540, 3480 (OH), 1780, 1745, 1625 cm^{-1} (butenolide ring); pmr (10% solution in deuteriochloroform) δ 0.91 (3 H, s, 18-CH_3), 0.97 (3, H, s, 19-CH_3), 2.78 (1 H, d, J = 7 Hz, 17-H), 4.10 (1 H, broad peak, 3α-H), 4.8 and 5.1 (2 H, a narrow AB-type quartet, J = 2 and 17 Hz, 21-CH_2), 5.88 (1 H, d, J = 2 Hz, 22-H); mass spectrum *m/e* 390 (M^+), 372 ($M^+ - H_2O$), 354 ($M^+ - 2H_2O$).

Anal. Calcd for $C_{23}H_{34}O_5$: C, 70.74; H, 8.78. Found: C, 70.89; H, 8.76.

The preceding reaction was repeated employing diacetate **4c** (25 mg) in 80% ethanol (30 ml) or methanol containing 35% hydrochloric acid (0.15 ml). The yield of triol **4a** melting at 245–248° was 14 mg. The yield of 15β-hydroxydigitoxigenin (**4a**) was slightly lowered by employing the acidic ion exchange resin method. For example, stirring diacetate **4c** (25 mg) in 80% ethanol (15 ml) with 0.125 g of Amberlite CG-120 (H^+ form) or Dowex 50W-X80 (H^+ form) for 5 hr at 45° gave 13 mg of triol **4a** melting at 245–249°.

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Registry No.—**1**, 71-63-6; **2a**, 143-62-4; **2b**, 808-19-5; **3a**, 4321-20-4; **3b**, 4240-51-1; **4a**, 13265-07-1; **4c**, 35596-51-1.

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Reactions of 3,4-Benzopyrrolidinones with β-Keto Esters

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As part of a synthetic study directed toward camptothecin and camptothecin analogs,[1,2] we had occasion to synthesize the tricyclic lactam **1** and to investigate its utility as a starting material for various annelation schemes.[3] Our route to lactam **1**, which we believe to be simpler than the three[4-6] which have been described in the interim, is set forth below.

The required 2-carbomethoxy-3-methylquinoline (**2**) was prepared by the Friedlander condensation of 2-oxobutyric acid with *o*-aminobenzaldehyde followed by esterification of the intermediate acid[7] with methanolic HCl. Compound **2** (87%) was treated with *N*-bromosuccinimide and dibenzoyl peroxide in carbon tetrachloride. The intermediate 2-carbomethoxy-3-bromomethylquinoline (**3**), assumed to be present but not characterized, was treated with ammonia to give an 86% yield of **1**. This method[8] was extended to the preparation of phthalimidine (**5**). Treatment of methyl *o*-toluate with *N*-bromosuccinimide gave methyl-2-bromomethylbenzoate (**4**). Reaction of **4** with ammonia gave **5** in 60% yield.

Sugasawa had reported that heating of **1** with diethyl acetone-1,3-dicarboxylate (**6**) gave the acylated product **7**[9] in 95% yield. Before the experimental procedure became available, we attempted to achieve this result, based on our reading of the preliminary report,[9] by heating **1** + **6** at 160–165° at atmospheric pressure. No product corresponding to **7** was isolated. In fact, the starting material, **1**, was recovered largely unchanged.[10] However, when the actual experimental conditions of Sugasawa[6,11] (**1** + **6** (excess), 160–165° (15–20 mm)) were employed, a 94% yield of **7** was obtained. The reason for the dramatic effect achieved by conducting the reacton under vacuum is not clearly understood.

When the reactants **5** + **6** were heated neat at 160–165° for 2 hr at atmospheric pressure, a 77% yield of a crystalline product, mp 138–139°, was obtained. Both its mass spectrum and combustion analysis indicated it to be a product corresponding to **5** + **6** − H_2O. This information, in addition to that obtained from its nmr spectrum, defines its structure as the enamide **8**,[12] rather than the expected **9**.

When the reaction of **5** + **6** was carried out under the Sugasawa conditions (15–20 mm, 160–165°, 0.5 hr), a mixture of **8** (24%) and another crystalline product, mp 94–95° (59%), was obtained. The mass spectrum and combustion analysis of the compound melting from 94 to 95° establish it to be the product of **5** + **6** − C_2H_6O. These data plus its nmr spectrum define its structure to be imide **9**, *i.e.* the analog of **7**.

Similarly, reaction of **5** with methyl acetoacetate at 200° for 18 hr gave a 46% yield of the crystalline enamide **10**,[11] mp 120–121°, whereas comparable conditions involving heating **1** with methyl acetoacetate up to 200–210° for 24 hr gave essentially recovered starting material and decomposition products. Also, Sugasawa had reported that cyclodehydration of **7** (formation of **11**) could be achieved (89%) using piperidine in acetonitrile. We were able to achieve the same result for compund **7**. However, attempts to extend the reaction to imide **9**, in the phthalimidine series (attempted formation of **12**), led to recovered starting material.

The greater nucleophilicity of the lactam nitrogen of **5** relative to **1** (enamide formation from β-keto esters *vs.* no reaction at atmospheric pressure) correlates logically with the greater electrophilicity of the carbonyl group of **7** relative to **9** with respect to internal aldolization (*cf.* **7** → **11**; **9** → **12**). Both presumably arise from the electron-withdrawing effect of the quinoline (inductive effect plus formal α-azomethine linkage) ring. The effect of the vacuum conditions in promoting imide relative to enamine formations is not understood.

The results of further studies involving annelations of **1** will be described shortly.

Experimental Section[13]

Preparation of 2-Carbomethoxy-3-methylquinoline (2). A solution of 2-oxobutyric acid (7.5 g; 0.074 mol), *o*-aminobenzalde-