Heterocyclic Studies. 46. Reaction Pathways of the 2-Acyl-1,2-diazabicyclo[3.2.0]-3-hepten-6-one System

James A. Moore* and Ben Staskun[1]

Department of Chemistry, University of Delaware, Newark, Delaware 19711

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The 2,6-diazabicyclic carbinolamine **17** has been isolated from the reaction of the 1,2-diazabicyclic ketone **1** in methanol plus Et_3N; **17** gives the same products (**13** and **14**) on further reaction in methanol as does **1**. The reaction of ketone **1b** with base gives the enamino ketone **30** plus glycine, indicating attack at the carbonyl group. Four reaction pathways of **1** are summarized.

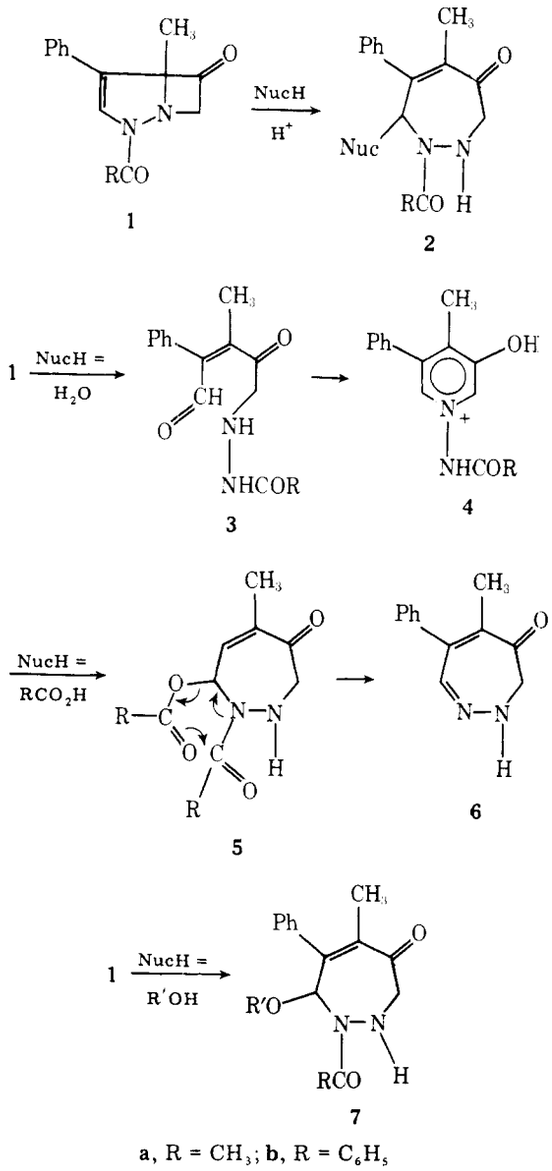
The chemistry of the bicyclic ketones **1** (Scheme I) is unusually rich and varied. Thus, different products are obtained on warming the compounds in methanol, methanol plus acid, methanol plus base, and in methanol–benzene mixtures. Moreover, the product mixtures in higher alcohols differ significantly at reaction temperatures of 60 and 70 °C.[2] In an earlier paper,[3] we described a number of the reactions in methanol and offered some speculation on their pathways. We now report further work on the reactions of **1** in alcohols which confirms some of the earlier ideas, disproves others, and clarifies the situation considerably.

Taking together the previous findings and new results, the chemistry of **1** can be discussed in terms of four groups of reactions, each arising by a different primary event.

Group 1. Acid-Catalyzed Reactions. These reactions are summarized in Scheme I. The products can be accounted for in each case by protonation of N-1 and attack of a nucleophile at C-3. In aqueous media the final product is the pyridinium system **4**.[4] In acetic acid the dihydrodiazepinone **6** is obtained, probably by cyclic elimination of an anhydride. In methanol containing a small amount of a carboxylic acid, the 7-methoxytetrahydrodiazepinones **7** (R′ = Me) are produced.[4] In the present work we have found that the corresponding 7-ethoxydiazepine (**7a**; R′ = Et) can be obtained from the acetyl ketone in ethanol under comparable conditions, but not from the benzoyl ketone. Nucleophilic addition is slower, apparently due to steric factors, and the reactions of Group 3 occur (vide infra). However, the 1-benzoyl-7-ethoxy compound **7b** (R′ = Et) can be readily isolated after warming the benzoyl ketone in ethanol in the presence of magnesium sulfate.

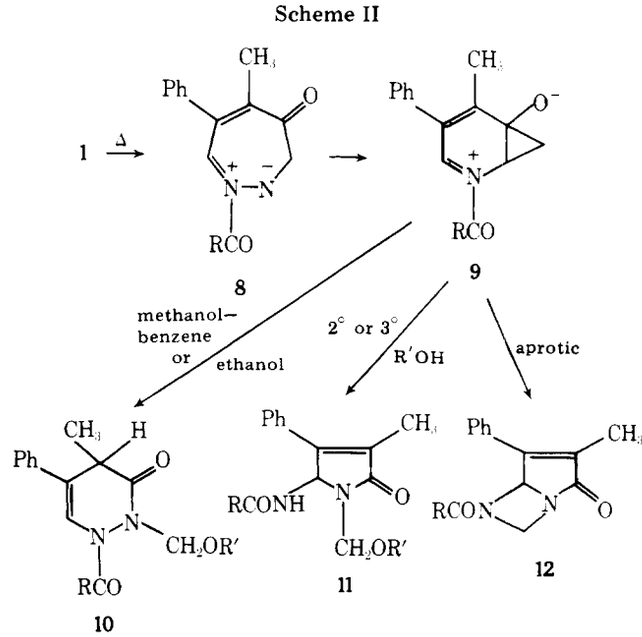
Group 2. Thermal Reactions. The initial step in these reactions is opening of the bicyclic system to the diazepinium betaine **8** (Scheme II), followed by recyclization to the dipolar valence isomer **9**.[2] Further reactions of **9** lead to **12** in benzene or to the pyridazinones **10** or pyrrolinones **11** in alcohols. This sequence is the major pathway followed in reactions of **1** in anhydrous ethanol at temperatures above 70 °C and in higher alcohols. With methanol the formation of **10** is observed only

Scheme I



a, R = CH_3; b, R = C_6H_5

Scheme II



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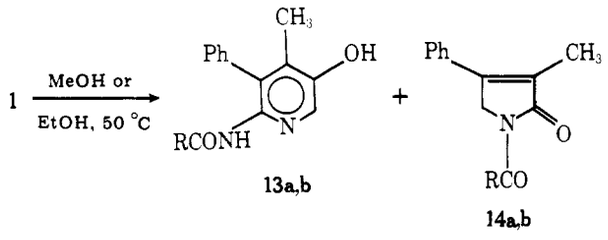
if the polarity of the medium is reduced (and the temperature is increased) by diluting the methanol with benzene; otherwise the reactions of Group 3 occur.

Group 3. Alcoholysis Reactions. The main products in this group are the 6-acylamidopyridines **13** and 1-acylpyrrolinones **14.** When a solution of the benzoyl ketone in methanol is warmed to 50 °C for 1.5 h, **13b** and **14b** are obtained in a



a, R = CH_3; b, R = C_6H_5

ratio of about 2:1 in a total yield of 80%; ammonia and trimethyl orthoformate are byproducts in the formation of **14.**[3] Partial deacylation of **14b** occurs on prolonged reaction time.

By NMR examination of product mixtures from numerous small-scale experiments, we have obtained information on the boundaries for the reaction conditions leading to **13** + **14** and products from Groups 1 and 2. In ethanol solution, **13** and **14** are produced together with the "thermal product" **10** (R′ = Et; Scheme II). The proportion of **10** increases steadily from 50 to 75 °C, and only minor amounts of **13** and **14** are formed in refluxing absolute ethanol. The presence of 1% of water in ethanol causes a marked decrease in the amount of **10,** and the disappearance of **1** is more rapid.

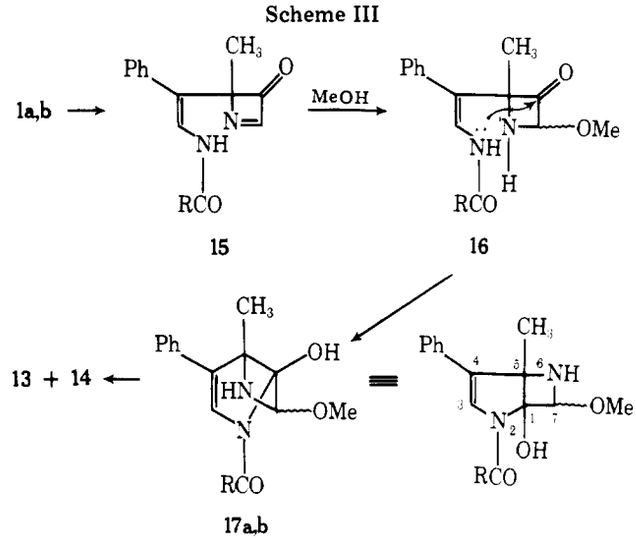
Addition of a trace of acetic acid to the alcohol causes a marked increase in the proportion of the pyrrolinone **14** relative to pyridine **13;** with the acetyl ketone **1a** the 7-alkoxydiazepinone **7** (Scheme I) then becomes a major coproduct. Correspondingly, the addition of a trace of tertiary amine suppresses the formation of **14** relative to **13.**

To summarize, the distribution of products arising from **1a** and **1b** in alcohols depends on both the temperature and the reaction medium. In a given solvent, e.g., ethanol, an increase in temperature favors the thermal reaction (Group 2). On the other hand, an increase in the polarity of the solvent (methanol vs. ethanol and wet ethanol vs. anhydrous ethanol) promotes the process of Group 3, leading to **13** and **14.** The addition of acetic acid effects both the partitioning of **1** between Groups 1 and 3 and also the ratio of products within Group 3, indicating that a step subsequent to the initial reaction in the Group 3 sequence is susceptible to acid.

The pathway to **13** and **14** was previously postulated[3] to involve elimination in the acylhydrazino ketone system of **1** to give the azetinone **15** and subsequent addition of methanol to give **16** (Scheme III). We have now isolated this latter intermediate in the form of bicyclic carbinolamine **17.**

When the reaction of the benzoyl bicyclic ketone **1b** was followed by NMR spectroscopy in CD_3OD–$CDCl_3$ solution, peaks due to an intermediate appeared and then subsided to give the spectrum of **13** + **14.** After adjusting the conditions, **17b** was obtained in large colorless crystals by a 15-min treatment of **1b** at 36 °C with a solution of methanol and chloroform containing a trace of triethylamine. The IR (3550 cm^{-1} for OH and 3360 cm^{-1} for NH), ^1H NMR, and ^{13}C NMR spectra all support structure **17b.** The proton-decoupled ^{13}C NMR spectrum contained a peak at 92.8 ppm, which in a SFORD spectrum was resolved into a singlet at 92.9 ppm due to C-5 and a doublet at 92.7 ppm due to C-7. The configuration of the methoxy group in **17b** is not assigned. Acetylation of **17b** gave an *N*-acetyl derivative. The ethoxy compound analogous

Scheme III



to **17b** was obtained by treatment of **1b** with ethanol and triethylamine in chloroform.

The bicyclic carbinolamine **17b** is a highly reactive compound, and it rapidly decomposes in solution to give the 6-benzamidopyridine **13b** and benzoylpyrrolinone **14b.** In methanol, ethanol, or benzene, the pyridine is the major product. In C_6D_6 solution at 55 °C, $t_{1/2}$ for the conversion of **17b** to **13b** plus methanol is about 45 min; a small amount (<10%) of the pyrrolinone **14b** can be detected by NMR. Addition of a trace of acetic acid to the benzene results in a large increase in the amount of **14b.** Thus, it seems quite clear that **17b,** arising via **15b** as previously suggested, is an intermediate in the low temperature alcoholysis reactions of **1b.**

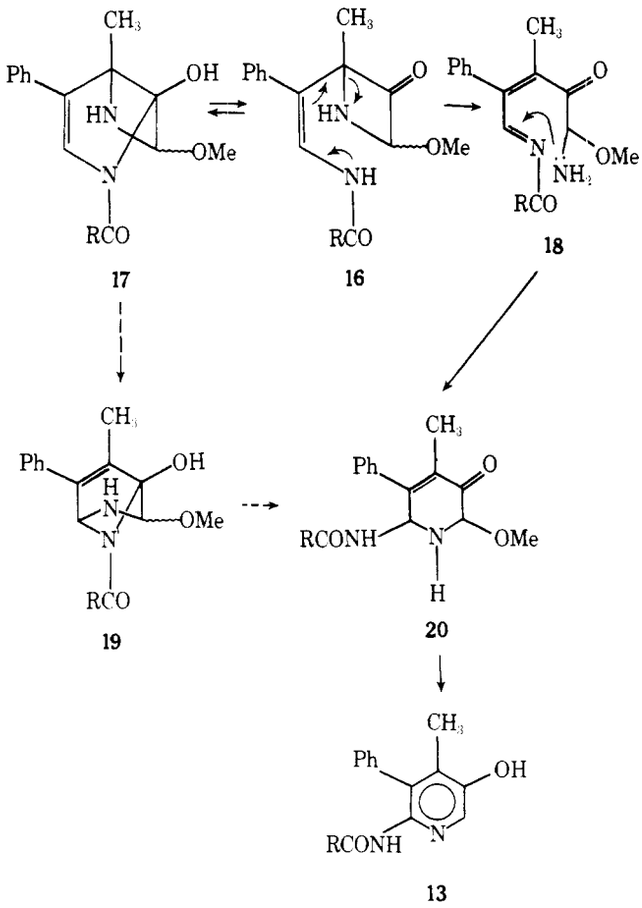
For the subsequent steps leading from **17** to the pyridine **13,** we originally suggested[3] an elimination from the ketone **16** to an acyclic structure followed by ring closure. An alternative which might be considered for the thermal reaction of **17** is a 1,3-sigmatropic rearrangement to the bicyclo[2.2.1] structure **19** (Scheme IV). Although an analogous [3.2.0] → [2.2.1] process is observed in carbocyclic systems at 300 °C,[5] there is no precedent for such a rearrangement of nitrogen and the elimination–cyclization path, perhaps modified as shown in Scheme IV, seems as satisfactory a rationalization as any.

The formation of the pyrrolinone **14** also involves breaking the C_5–N bond. This reaction can be depicted as in Scheme V, with the cation **21** as an intermediate. Loss of methyl formimidate then leads to the hydroxypyrrole which can tautomerize to the Δ^4-pyrrolinone **23** and finally to the more stable Δ^3-pyrrolinone **14.** When the carbinolamine **17b** was treated with aqueous methanolic HCl under conditions such that the product precipitated directly from solution, a mixture was obtained whose NMR spectrum showed the presence of the Δ^4 isomer **23b** [δ 1.45 (d, J = 7 Hz), 3.78 (q, J = 7 Hz), 6.80 (s)]. Further treatment of the mixture with acid converted **23b** to **14b.**

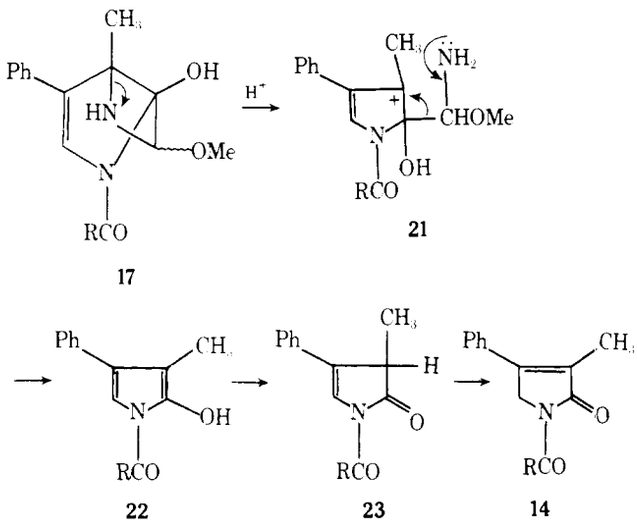
The reaction of **17b** in base takes a different course. The compound dissolved rapidly in 2 N aqueous NaOH, and after standing at 25 °C for 2 h the benzamido ketone **25** was isolated in 41% yield. This compound, previously[3] identified among the products of **1b** in aqueous base, may arise by attack of hydroxide at the carbonyl group of the ketonic tautomer **1b** to give the enamine **24** followed by hydrolysis to **25** and methoxyglycine (Scheme VI).

In the acetyl series, a compound assigned the carbinolamine structure **17a** was obtained from **1a** under the same conditions used for **17b.** The ^1H NMR spectrum at 25 °C of the initial crystalline product showed two sets of peaks of approximately equal intensities for the CH_3CO, OCH_3, H-7 and H-3 signals.

Scheme IV



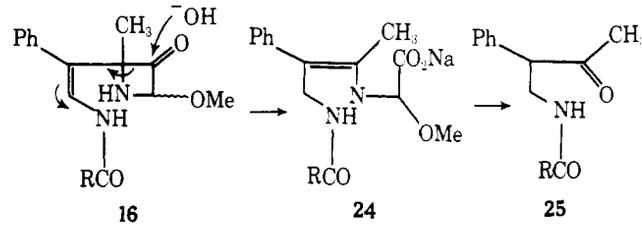
Scheme V



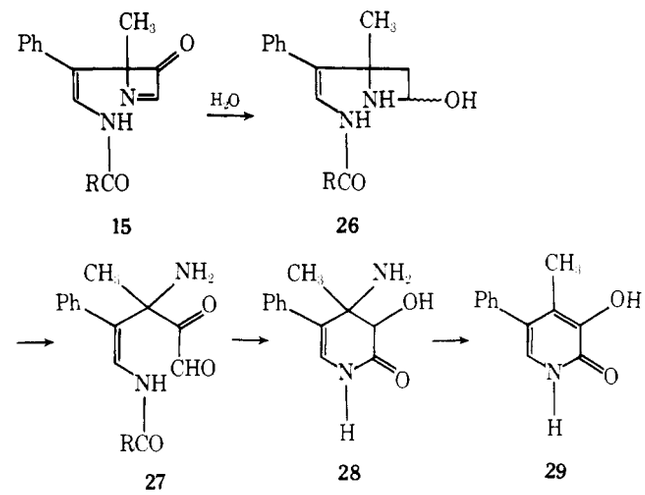
At 35 °C these peaks began to coalesce; at 45 °C coalescence was complete. The NMR observations and the fact that **17a** redissolved quite slowly in organic solvents suggest that the compound may be in equilibrium with a dimeric or higher oligomeric form. At 40 °C peaks due to the pyrrolinone **14a** began to appear; after 1 h about 40% of the mixture was **14a.**

The pyrrolinone **14a** was the main product (from NMR of total reaction mixtures) in the reactions of **17a** in methanol and in benzene; pyridine **13a** was present in smaller amounts. These reactions were not as clean as those of the benzoylcarbinolamine **17b,** and significant quantities of decomposition products were also present. Surprisingly the pyrrolinone was

Scheme VI



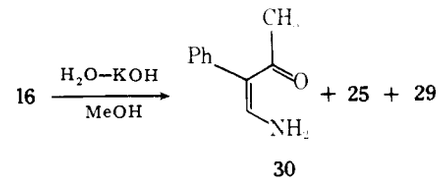
Scheme VII



also obtained from the reaction of **17a** in aqueous base, and there was no indication of ketone **25.** The relatively larger proportion of pyrrolinone to pyridine in the acetyl series was also observed in the reaction of the ketone **1a** in methanol,[3] and the data are thus consistent with **17a** being an intermediate in the reactions of **1a** in alcohol. However, the picture with the acetyl compounds is less clear than that in the benzoyl series, and the reason for the differences in product composition is obscure.

Group 4. Reactions in Base. In aqueous KOH the acetyl ketone **1a** gives the aminopiperidone **28** with a trace of the pyridone **29,** which is formed by loss of ammonia from **28.**[3] These products are presumed to arise by addition of water to the azetinone **15** with subsequent ring opening, deacylation, and recyclization (Scheme VII); their isolation provided the major basis for the original suggestion of azetinone **15** as an intermediate in reactions of the bicyclic ketones.

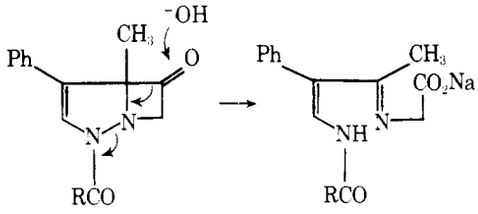
In the benzoyl series, the reaction of **1b** in aqueous methanolic base gave a complex mixture from which traces of the pyridone **29** and the benzamido ketone **25** (Scheme VI) were isolated.[3] The product obtained in largest amount (35%) was the enamino ketone **30.** Pathways were proposed with **27** (R



= Ph) as an intermediate for all three products.[3] In view of the isolation of **25** from the methoxy intermediate **17b** ⇄ **16b,** the route **1b** → **16b** → **24** (Scheme VI) now seems a more likely source of **25** in the product mixture from **1b** in H_2O–CH_3OH–KOH.

The question of the origin of the major product **30** remains. The pathway suggested[3] via **27** requires the elimination of $(CHOHCO_2H)^-$ and poses several difficulties. An alternative was suggested by the reaction of **17b** ⇄ **16b** to give **25** with loss

Scheme VIII



31

⟶ 30 + $NH_2CH_2CO_2H$

of a two-carbon fragment (Scheme VI). Similar attack by hydroxide at the carbonyl group of **1b** would lead to the intermediate **31** by heterolytic fragmentation,[6] and the final products would be the enamino ketone **30** and glycine (Scheme VIII). To test this possibility, the aqueous solution from the reaction of **1b** in aqueous methanolic base was subjected to amino acid analysis, and glycine was found in 24% yield. Thus, carbonyl attack appears to represent still another mode of reaction of the bicyclic ketone.

In summary, evidence now indicates that the diverse products obtained to date from the diazabicycloheptenones **1a,b** involve four different initial reactions rather than the two types proposed previously.[3] These four pathways occur under conditions which differ only slightly from one to another, and their rates are very delicately balanced, as seen in the concurrence of reactions in Groups 1, 2, and 3 and Groups 3 and 4.

Experimental Section

NMR spectra designated FT 90 MHz were recorded on a Bruker HFX 90 instrument; other NMR spectra were obtained on a Perkin-Elmer R-12B instrument.

1-Acetyl-7-ethoxy-5-methyl-6-phenyl-1,2,3,7-tetrahydro-4*H*-1,2-diazepin-4-one (7a; R′ = Et). A solution of 240 mg of **1a** in 20 mL of ethanol containing about 0.5 mL of acetic acid was allowed to stand for 2 days at 25 °C. After evaporation to a gum and reevaporation of added solvent to remove AcOH, crystallization from ether gave 130 mg of **7a** (R′ = Et) as a white solid which was recrystallized from ethanol: mp 129–130 °C; NMR δ 1.05 (t, 3, J = 7 Hz), 1.83 (s, 3), 2.28 (s, 3), 3.48 (q, 2, J = 7 Hz), 3.7–4.0 (m, 2, CH_2), 5.0 (brd, NH), 6.45 (s, 1, H-7), 7.35 (brd s, 5).

Anal. Calcd for $C_{16}H_{20}N_2O_3$: C, 66.64; H, 6.99. Found: C, 66.85; H, 6.72.

Under the same conditions, the benzoyl ketone **1b** gave mainly **14b** with a small amount of **13b** and no **7b** (based on NMR).

1-Benzoyl-7-ethoxy-5-methyl-6-phenyl-1,2,3,7-tetrahydro-4*H*-1,2-diazepin-4-one (7b; R′ = Et). A solution of 110 mg of **1b** in 10 mL of absolute ethanol plus 330 mg of anhydrous $MgSO_4$ was kept at 50 °C for 22 h. After filtration, the solution was evaporated to a gum which crystallized from ethanol–water to give 60 mg of **7b** (R′ = Et): mp 117–118 °C; NMR δ 1.05 (t, CH_3CH_2, J = 6.6 Hz), 1.84 (s, CH_3), 3.55 (q, $-CH_2-$, J = 6.6 Hz), 3.90 (brd s, CH_2), 5.0 (v brd, NH), 6.4 (brd s, H-7), 7.3–8.0 (m, Ar) (similar broadening of peaks at ambient probe temperature is also seen in the NMR spectrum of the 1-benzoyl-7-methoxytetrahydrodiazepinone[4]).

Anal. Calcd for $C_{21}H_{22}N_2O_3$: C, 71.98; H, 6.33. Found: C, 71.92; H, 6.38.

The corresponding 1-benzoyl-7-methoxytetrahydrodiazepinone was similarly formed, together with traces of **13b** and **14b**, in methanol with $MgSO_4$.

2-Benzoyl-5-methyl-4-phenyl-7-methoxy-2,6-diazabicyclo-[3.2.0]-3-hepten-1-ol (17b). A 200-mg amount of the benzoyl bicyclic ketone **1b** was dissolved by stirring in 4 mL of a mixture of chloroform, methanol, and triethylamine (5:10:0.1 v/v). After standing for 15 min in a 36 °C water bath, the solution was evaporated in vacuo to a pale yellow oil. CCl_4 (2 mL) was added, and the solution was again evaporated; this step was repeated, and the residue, after evaporation, was a pale cream foam. The addition of ether and brief stirring caused the crystallization of **17b** as dense colorless prisms: 120 mg (60%); 90–93 °C decomposes; IR ν ($CHCl_3$) 3550 (OH), 3360 (NH), 1620, 1640 cm^{-1} [after shaking the $CHCl_3$ solution with D_2O, small peaks appeared at 2620 and ~2500 cm^{-1}, indicating OD and ND]; ^1H NMR δ 1.60 (s, 3), 3.56 (s, 3), ~4.0–4.6 (v brd; in D_2O → O), 5.08 (s, 1, H-7), 7.02 (s, 1, H-3), 7.3 and 7.6 (brd, Ar); ^{13}C NMR (FT 90 MHz, 8% in $CDCl_3$) δ 19.3 (q, CCH_3), 54.9 (q, OCH_3), 70.3 (s, C-5), 92.7 (d, C-7), 92.9 (s, C-1), 125.8 (d, C-2 (ortho) of 4-Ph group), 127.2 (d, C-4 of 4-Ph plus C-3), 128.0 (d, C-2 of PhCO ring), 128.7 (d, C-3 (meta) of both Ph), 129.0 (s, C-4), 131.4 (d, C-4 of PhCO), 131.8 (s, C-1 of 4-Ph), 134.0 (s, C-1 of PhCO), 167.2 (C=O).

Anal. Calcd for $C_{20}H_{20}N_2O_3$: C, 71.41; H, 5.99; N, 8.33. Found: C, 71.58; H, 5.97; N, 8.43.

Reaction of 17b in Acid. A. In Methanol. To a solution of 80 mg of **17b** in 0.8 mL of methanol plus 0.2 mL of H_2O was added 0.4 mL of 1.0 N HCl. A mass of colorless crystals separated within a few seconds. The mixture was extracted with CH_2Cl_2, and the organic solution was washed, dried, evaporated, and reevaporated with CCl_4. The NMR spectrum of the solid residue contained predominant peaks at δ 2.08 (t, J ~ 1 Hz), 4.84 (q, J ~ 1 Hz), and 7.54 (brd), corresponding to the Δ^3-pyrrolinone **14b,** and a very small doublet at δ 1.43 ($J \cong 7$ Hz) due to the Δ^4 isomer **23b.** Crystallization of the product from ether gave 34 mg of **14b** as colorless prisms, mp 145–147 °C (lit.[3] mp 145–146 °C), and 11 mg of a lower melting material.

B. In Water. To a suspension of 110 mg of **17b** in 2 mL of water was added 0.5 mL of 1 N HCl. The mixture immediately became milky; a yellow oil separated and partially crystallized on stirring. After 30 sec, the mixture was extracted with CH_2Cl_2; the residue, after evaporation with CCl_4, showed peaks for the Δ^3-pyrrolinone (as above) and the Δ^4 isomer **23** in a ratio of roughly 2:1. The complete spectrum of the Δ^4 isomer was δ 1.45 (d, J = 7 Hz), 3.78 (q, J = 7 Hz), 6.80 (s), and 7.45 (s). Several crops of low melting crystals were obtained, the NMR spectra of which indicated mixtures.

A solution of the pyrrolinone mixture in $CDCl_3$ containing a drop of CF_3CO_2H and CH_2Cl_2 as an internal standard was allowed to stand for 14 h, and the NMR spectrum was recorded. The peaks due to **23** were no longer present, and the intensity of the peaks due to **14b** had increased relative to the CH_2Cl_2 peak, establishing the conversion **23** → **14b.**

Acetylation of 17b. To a solution of 500 mg of **17b** in 6 mL of CH_2Cl_2 was added 1 mL of acetic anhydride and 1 mL of pyridine. After 40 min, the CH_2Cl_2 was evaporated and the oily residue was triturated with water to give a solid which was washed and air-dried, 560 mg (mp 147–150 °C). Recrystallization from methanol–water gave colorless crystals of the *N*-acetyl derivative: mp 155–156 °C, IR ν ($CHCl_3$) 3530 (OH), 1660, 1610 cm^{-1}; NMR δ ($CDCl_3$) 1.76 (s, 3), 2.06 (s, 3), 3.75 (s, 3), 5.40 (s, 1), 5.7 (brd, s; in D_2O → O), 7.08 (s, 1), 7.4, 7.6 (m, Ar).

Anal. Calcd for $C_{22}H_{22}N_2O_4$: C, 69.82; H, 5.86; N, 7.40. Found: C, 69.85; H, 5.88; N, 7.25.

7-Ethoxy Analogue of 17b. A solution of 200 mg of **1b** in 4 mL of EtOH–$CHCl_3$–Et_3N (10:5:0.1) was kept at 36 °C for 15 min and then evaporated. After addition and removal of CCl_4, addition of ether gave white crystals: mp 60–70 °C; NMR δ 1.30 (t, 3), 1.58 (s, 3), 3.78 (q, 2), 5.15 (s), 7.05 (s, 1), 7.4 (m).

Thermal Reaction of 17b. A. A solution of 128 mg of **17b** in 2 mL of benzene was kept at 50 °C for 3.5 h and then evaporated to give 63 mg of the benzamido pyridine **13b:** mp 210–211 °C; NMR 1.9 (s, CH_3), 7.4 (m, Ar), 8.0 (s, H.2). The NMR spectrum of the mother liquor showed peaks for **13b** and the pyrrolinone **14b.**

B. A solution of **17b** in benzene-d_6 containing Me_4Si was placed in a 55 °C bath, and the NMR spectrum was scanned at 15-min intervals. Peaks due to the pyridine **13b** and methanol were present after 15 min. After 45 min, the CH_3O peaks due to starting material **17b** and methanol were of equal intensity. After 75 min at 55 °C and 12 h at 25 °C, the spectrum showed peaks due to **13b** and methanol and a trace (~5%) of the pyrrolinone **14b.**

C. A solution of **17b** in benzene containing 0.5% acetic acid was allowed to stand at 25 °C for 150 min and then evaporated. The NMR spectrum showed roughly equal amounts of **13b** and **14b** and no **17b.**

Reaction of 17b in NaOH. A 100-mg sample of **17b** was added to 1 mL of 2 N NaOH. The solid dissolved rapidly to give a clear pale yellow solution. After 90 min, the solution was diluted with 2 mL of water, giving an oily precipitate which became crystalline on addition of a few drops of methanol. Acid was then added to neutralize part of the base, and after standing for 2 h the solid was collected, washed, dried, and recrystallized from ether to give 36 mg (45%) of the benzamido ketone **25,** mp 125–126 °C (lit.[3] mp 125–126 °C); semicarbazone, mp 172–175 °C (lit.[3] mp 172–174 °C).

2-Acetyl-5-methyl-4-phenyl-7-methoxy-2,6-diazabicyclo-[3.2.0]-3-hepten-1-ol (17a). A solution of 400 mg of **1a** in 4.5 mL of $CHCl_3$–MeOH–Et_3N (5:10:0.1) was kept at 31 °C for 12 min and then evaporated. The white solid residue was stirred with ether, and 213

mg (47%) of white crystals was collected. The melting point was 93–100 °C with decomposition and partial resolidification. The compound was recrystallized by dissolving it in CH_2Cl_2 (several minutes of warming required); the solution was filtered to clarify and then evaporated at reduced pressure to a solid which was rinsed with ether. This material decomposed with softening and slight darkening at 95–100 °C.

Anal. Calcd for $C_{15}H_{18}N_2O_3$: C, 65.67; H, 6.61. Found: C, 65.67; H, 6.42.

The 90 MHz FT proton NMR ($CDCl_3$) spectrum at 25 °C showed the following: δ 1.51 (s, 5-CH_3), 2.19 and 2.25 (two s, CH_3CO), 3.45 and 3.47 (two s, CH_3O) 4.86 and 4.94 (two s, H-7), 6.87 and 7.52 (two s, H-3), 7.26 and 7.28 (two s, C_6H_5). At 45 °C, the spectrum showed peaks due to **17a** at δ 1.50, 2.20, 3.45, 4.90, and 7.27 (the coalesced peaks due to H-3 were merged with the large C_6H_5 peak at δ 7.27) and peaks due to pyrrolinone **14a** at δ 2.10 (t, 3-CH_3), 2.61 (CH_3CO), 4.59 (CH_2), and 7.47 (s, C_6H_5) [lit.[3] δ 2.08 (t), 2.60 (s), 4.58 (q), 7.48 (s)]. After 20 min at 45 °C, integration of the CH_3 peaks indicated 23% of **14a**, after 30 min, 30% of **14a**, and after 1 h, 42% of **14a**.

Identification of Glycine from Reaction of 1b and KOH. A 30-mg (100-μmol) amount of the benzoyl bicyclic ketone **1b** was dissolved in 0.2 mL of 10% aqueous KOH containing a drop of methanol. After 2 h, the solution was diluted with water, and 10.5 mg of serine plus 11.7 mg of valine (100 μmol) were added as standards. The pH was adjusted to 6, causing a yellow gum to separate. After filtration through Darco, the solution was further diluted and analyzed on a Beckman 120C amino acid analyzer.[7] The ratio of standards/glycine was 4.15, indicating a 24% yield of glycine based on **1b**.

Registry No.—**1a**, 5109-37-5; **1b**, 5109-45-5; **7a** (R′ = Et), 67350-78-1; **7b** (R′ = Et), 67350-77-0; **13b**, 10137-10-7; **14a**, 10147-13-4; **14b**, 10137-11-8; **17a**, 67328-94-3; **17b**, 67328-95-4; **17b** *N*-acetyl derivative, 67328-96-5; **17b** 7-ethoxy analogue, 67328-97-6; **23b**, 67328-98-7; **25b**, 10137-17-4.

References and Notes

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(7) We thank Professor J. Wriston and Mrs. Jean Denis for this determination.

^{13}C-Labeled Benzo[a]pyrene and Derivatives. 1. Efficient Pathways to Labeling the 4, 5, 11, and 12 Positions[1,2]

Richard S. Bodine, Mark Hylarides, Guido H. Daub,* and David L. VanderJagt

Department of Chemistry, University of New Mexico, Albuquerque, New Mexico 87131

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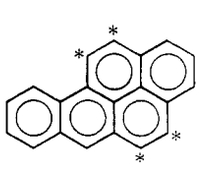
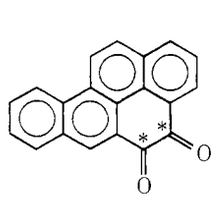
Efficient pathways leading to the synthesis of benzo[a]pyrene labeled with ^{13}C in the 4, 5, 11, or 12 positions are described. A method of synthesis of the benzo[a]pyrene-4,5- and -11, 12-quinones leading to labeling in the 4 or 5 and 11 or 12 positions, respectively, is also presented, allowing ready access to the labeled 4,5- and 11,12-oxides. The values of the ^{13}C NMR chemical shifts for C_4, C_5, C_{11}, and C_{12} of benzo[a]pyrene were determined using the labeled compounds.

Discussion

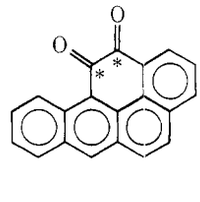
As part of a program to develop efficient syntheses of the potent carcinogen benzo[a]pyrene labeled with ^{13}C (90%) at each one of the peripheral carbon atoms of the ring system we have successfully developed such routes to the 4-, 5-, 11-, and 12-labeled benzo[a]pyrenes (**1a, 1b, 1c,** and **1d**). In addition, the benzo[a]pyrenequinones **2** and **3** have been prepared as intermediates for the synthesis of the corresponding arene oxides **4** and **5.**



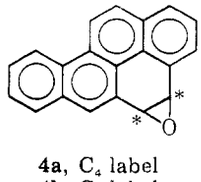
1a, label at C_4
1b, label at C_5
1c, label at C_{11}
1d, label at C_{12}



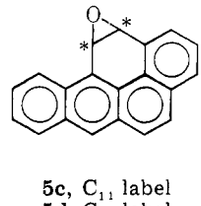
2a, C_4 label
2b, C_5 label



3c, C_{11} label
3d, C_{12} label



4a, C_4 label
4b, C_5 label



5c, C_{11} label
5d, C_{12} label

The synthesis of benzo[a]pyrene (1) from 1,2-dihydrochrysen-4(3*H*)-one (**6**)[3a] and from 3,4-dihydrobenz[a]anthracen-1(2*H*)-one (**7**)[4] was studied (Scheme I), since these ketones are relatively easily synthesized and have been shown previously to undergo the Reformatsky reaction[3b,4] in moderate yield. Furthermore, these two approaches would allow the introduction of the ^{13}C label at the 4 or 5 and the 11 or 12 positions, respectively, late in the synthesis depending on the position of the label in the starting ester. It was felt that the Reformatsky reaction as carried out earlier[3b,4a] would be unsuitable for labeling studies, since an excess of bromo ester was used, and in the case at hand this would contain the label. Attempts to prepare the hydroxy esters **8** and **9** via the Reformatsky reaction failed to give satisfactory yields using equimolar ratios of the ketones **6** or **7** and ethyl bromoacetate even under conditions reported to give excellent yields for selected ketones.[5-7] However, when the ketone **6** or **7** was allowed to react with the lithium enolate of ethyl acetate[8] in THF at −78 °C, the hydroxy ester **8** or **9** was obtained in 82% yield. The hydroxy esters **8** and **9** rapidly revert to the respective ketones if the reaction mixture is allowed to warm to room temperature before acidification; thus, acidification of the reaction mixtures had to be carried out at −78 °C in order for the hydroxy esters to survive.

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