of colorless needles: mp 125–126 °C; ^{1}H NMR δ 8.44 (2 H, d), 5.37 (1 H, br s), 1.30 (9 H, s) inter alia; IR (KBr) 1678, 1521 (amide), 3400 cm^{-1} (OH); mass spectrum, *m/e* 315, 208, 109.

Anal. Calcd for $C_{17}H_{21}N_3O_3$: C, 64.74; H, 6.71; N, 13.32. Found: C, 64.34; H, 7.10; N, 13.35.

***N*-*tert*-Butyl-2-hydroxy-2-(2-pyridyl)ethanamide (10a).** To a mixture of 30 g (0.28 mol) of pyridine-2-carboxaldehyde and 10.5 g (0.12 mol) of *tert*-butyl isocyanide in 100 mL of $CHCl_3$ cooled to −5 °C (dry ice–acetone) was added dropwise with stirring at −5 to +5 °C 30 g (0.26 mol) of trifluoroacetic acid. The mixture was warmed to room temperature and stirred with 300 mL of 1 N aqueous NaOH for 2 h, and the layers were separated. The $CHCl_3$ layer was extracted with 1.2 N aqueous HCl, and the aqueous layer was basified with Na_2CO_3 and extracted with ether. The combined ether extracts were washed with aqueous $NaHSO_3$ until the starting aldehyde was removed (as indicated by TLC) and then with 3 N aqueous HOAc. The ether extract was dried (Na_2SO_4), filtered, and concentrated under vacuum to give 23 g of a dark oil which deposited 8.0 g (32%) of crude amide, mp 105–109 °C. An analytical sample was obtained by recrystallization from $CH_3CO_2C_2H_5$ to give pure *N*-*tert*-butyl-2-hydroxy-2-(2-pyridyl)ethanamide (**10a**), mp 114–115 °C.

Anal. Calcd for $C_{11}H_{16}N_2O_2$: C, 63.44; H, 7.75; N, 13.45. Found: C, 63.69; H, 7.92; N, 13.36.

Modified Passerini Reaction: *N*-*tert*-Butyl-2-(3,4-dichlorophenyl)-2-hydroxyethanamide (10c). (A) Preferred Procedure. A mixture of purified 3,4-dichlorobenzaldehyde (8.75 g, 0.050 mol), *tert*-butyl isocyanide (2.08 g, 0.035 mol), and pyridine (3.96 g, 0.050 mol) in 25 mL of CH_2Cl_2 was cooled to −5 °C (dry ice–acetone) under N_2 and treated dropwise with stirring at −5 to +5 °C with 2.9 g of CF_3CO_2H (0.025 mol). The mixture was warmed to room temperature for 1 h, after which TLC (2% CH_3OH–$CHCl_3$, silica gel) showed little conversion to **10c**. The mixture was treated dropwise with an additional 2.9 g of CF_3CO_2H at 20–30 °C (ice cooling); after 30 min, TLC showed significant conversion to **10c**. The mixture was stirred 2 h at room temperature and then treated with a solution of 15 g of $NaHSO_3$ in 100 mL of H_2O for 2 h at room temperature. The mixture was filtered to give 9.0 g of the $NaHSO_3$ adduct of the starting aldehyde (mp 164–165 °C), and the CH_2Cl_2 layer obtained from the filtrate was dried (Na_2SO_4) and concentrated to give crude **10c**. Recrystallization from *n*-C_4H_9Cl gave pure **10c**: mp 116–117 °C; 2.90 g (60% based on recovered $NaHSO_3$ adduct of starting aldehyde); ^{1}H NMR δ 7.42 (1 H, d, *J* = 1 Hz), 7.35 (1 H, d, *J* = 7 Hz), 7.13 (1 H, dd, *J* = 1, 7 Hz), 4.82 (1 H, d, *J* = 4 Hz, exchangeable), 4.72 (1 H, d, *J* = 4 Hz), 1.28 (9 H, s).

Anal. Calcd for $C_{12}H_{15}Cl_2NO_2$: C, 52.19; H, 5.48; N, 5.07. Found: C, 52.18; H, 5.62; N, 5.03.

(B) Pyridinium Trifluoroacetate Procedure. To a solution of pyridine (3.96 g, 0.050 mol) and trifluoroacetic acid (3.8 mL, 5.62 g, 0.049 mol) in 25 mL of CH_2Cl_2 was added 3,4-dichlorobenzaldehyde (8.75 g, 0.050 mol) and *tert*-butyl isocyanide (2.08 g, 0.035 mol) with stirring at room temperature under N_2. The mixture was stirred 42 h at room temperature and refluxed 6 h. An NMR spectrum of the reaction mixture showed no unreacted isocyanide (characteristic *tert*-butyl triplet at δ ($CDCl_3$) 1.43). The mixture was diluted to 100 mL with CH_2Cl_2 and stirred 2 h at room temperature with a solution of 15 g of $NaHSO_3$ in 100 mL of water. The mixture was worked up as in procedure A (except that CH_2Cl_2 was evaporated after mixing with aqueous $NaHSO_3$). There was obtained 9.6 g of the $NaHSO_3$ adduct of the starting aldehyde and 1.95 g (66% of procedure A) of pure **10c**, mp 116–117.5 °C (isolated by alumina chromatography and crystallization from *n*-C_4H_9Cl).

Reduction of Hydroxy Amides: *N*-*tert*-Butyl-2-hydroxy-2-methyl-3-phenoxy-1-propanamine (13e) Hydrogen Maleate. To a cooled, stirred solution of 2.51 g (10.0 mmol) of *N*-*tert*-butyl-2-methyl-2-hydroxy-3-phenoxypropanamide (**10e**) in 40 mL of tetrahydrofuran (dried by percolating through activity I Al_2O_3) under N_2 was added 3.2 mL of borane–dimethyl sulfide from a syringe. The stirred mixture was heated to reflux for 4 h, treated with an additional 1 mL (total 44 mmol) of BH_3·$(CH_3)_2S$, and refluxed 1 h longer. The mixture was stirred overnight at room temperature, cooled to 0 °C, and treated with 8 mL of glacial CH_3CO_2H dropwise. After gas evolution ceased, water (2 mL) was added and the solvent removed by distillation. The residual suspension was diluted with water, basified with NaOH, and extracted with CH_2Cl_2. The combined CH_2Cl_2 extracts were washed with saturated aqueous NaCl, dried (Na_2SO_4), filtered, and concentrated under vacuum to give crude **13e** which was converted to the hydrogen maleate salt with a solution of 1.5 g maleic acid in 33 mL of CH_3CN: yield 1.9 g (54%); mp 161–161.5 °C.

Anal. Calcd for $C_{14}H_{23}NO_2$·$C_4H_4O_4$: C, 61.17; H, 7.70; N, 3.96. Found: C, 61.42; H, 7.55; N, 4.01.

Acknowledgment. The author is grateful to Dr. John J. Baldwin for his helpful suggestions, to Mr. W. McGaughran and Ms. J. Murphy for determining NMR spectra, and Mr. R. Rhodes for determining mass spectra.

Registry No. 7a, 1121-60-4; **7b**, 123-08-0; **7c**, 17763-69-8; **7d**, 6287-38-3; **8**, 7188-38-7; **9**, 78167-17-6; **10a**, 78167-18-7; **10b**, 78167-19-8; **10c**, 78167-20-1; **10d**, 78167-21-2; **10e**, 78167-22-3; **10f**, 74953-47-2; **13a**, 78167-23-4; **13b**, 78167-24-5; **13c**, 59630-55-6; **13d**, 78167-25-6; **13e**, 78167-26-7; **13f**, 64980-40-1.

Methods for Converting *N*-Alkyl Lactams to Vinylogous Urethanes and Vinylogous Amides via (Methylthio)alkylideniminium Salts

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Received April 1, 1981

Treatment of enolizable (methylthio)alkylideniminium salts with active methylene compounds under basic conditions gives Knoevenagel-type adducts in excellent yields. Attempts to convert several of these adducts to vinylogous urethanes and vinylogous amides met with varied success. One-pot preparations of vinylogous urethanes and vinylogous amides from (methylthio)alkylideniminium salts and selected active methylene compounds are also described.

During the course of studies directed toward the synthesis of nitrogenous natural products we needed to convert enolizable *N*-alkyl lactams **1** to vinylogous amides and vinylogous urethanes **3**. A survey of the literature revealed that an established method for accomplishing this transformation was via the derived thiolactam **2** by use of the elegant sulfide-contraction procedure developed by the Eschenmoser group.[1-3] It also appeared that existing methods for performing Knoevenagel-type reactions on

(1) Roth, M.; Dubs, P.; Götschi, E.; Eschenmoser, A. *Helv. Chim. Acta* **1971**, *54*, 710.

(2) For the first application of the "sulfide-contraction" procedure to *N*-alkyl lactams see: Yamaguchi, H. *Chem. Abstr.* **1973**, *78*, 29617.

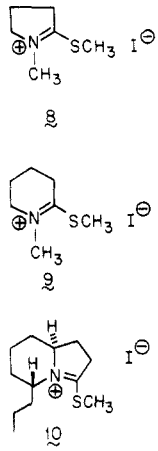
0022-3263/81/1946-3671$01.25/0

Table I. Reactions of Salts 8–10 with Active Methylene Compounds

entry	salt	active methylene	product	conditions	rxn time[a]	% yield[b]
1	8	11	18	A[c]	5.5	53
2	8	12	19	A	5	85
3	8	12	19	C[d]	8	83
4	9	12	20	A	46	71
5	8	13	21	A	2	80
6	8	14	22 + 23	A	1.5	74 (22), 23 (23)
7	8	14	22 + 23	C	16	84 (22), 2 (23)
8	10	14	24 + 25	A	2	57 (24), 32 (25)
9	8	15	26 + 27	A	6	64 (26), 21 (27)
10	8	15	26 + 27	C	18	84 (26), 2 (27)
11	8	16	28 + 29	A	4	53 (28), 23 (29)
12	8	17	30 + 31	A	5	67 (30), 14 (31)
13	8	17	30 + 31	B[e]	23	68 (30), 1 (31)
14	8	17	30 + 31	C	6	74 (30), 2 (31)

[a] Hours. [b] Isolated, purified products. [c] 2.0 equiv of K_2CO_3, DMF, 25 °C. [d] 2.0 equiv. of Et_3N, CH_2Cl_2, 25 °C. [e] 2.0 equiv of Et_3N, DMF, 25 °C.

Chart I



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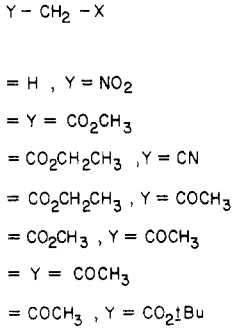
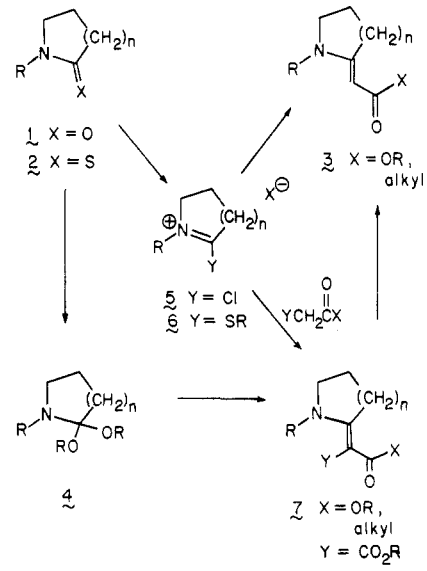
10

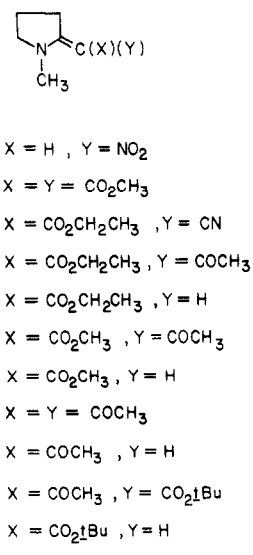


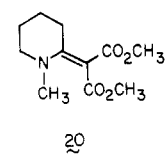
Scheme I



lactam-derived acetals **4**[4,5], iminium chlorides **5**,[6] and (alkylthio)alkylideniminium salts **6**[7] might be adapted to suit our needs (Scheme I) and provide an alternative to the Eschenmoser procedure.[8] The long shelf life of salts of type **6** and the ease with which they can be prepared from *N*-alkyl lactams prompted us to examine their use in the conversion of **1** to **3**.[9,10] The details of this inves-

Chart II





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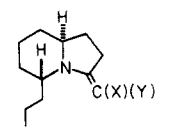


24 X = $CO_2CH_2CH_3$, Y = $COCH_3$
25 X = $CO_2CH_2CH_3$, Y = H

(3) For other applications of the "sulfide-contraction" procedure to *N,N*-dialkyl amides and *N*-alkyl lactams see: Gerrans, G. C.; Howard, A. S.; Orlek, B. S. *Tetrahedron Lett.* **1975**, 4171. Ireland, R. E.; Brown, F. R., Jr. *J. Org. Chem.* **1980**, *45*, 1868.

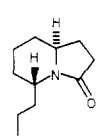
(4) (a) Meerwein, H.; Florian, W.; Schon, N.; Stepp, G. *Justus Liebigs Ann. Chem.* **1961**, *641*, 1. (b) Shvo, Y.; Shanan-Atidi, H. *J. Am. Chem. Soc.* **1969**, *91*, 6683, 6689. (c) Kostyuchenko, N. P.; Granik, V. G.; Zhidkova, A. M.; Glushkov, R. G.; Sheinker, Y. N. *Khim. Geterotsikl. Soedin.* **1974**, *10*, 1053. (d) Virmani, V.; Murti, A. V.; Jain, P. C.; Anan, N. *Indian J. Chem.* **1975**, *13*, 1355. (e) Oishi, T.; Ochiai, M.; Nakayama, T.; Ban, Y. *Chem. Pharm. Bull.* **1969**, *17*, 2314. (f) Oishi, T.; Ochiai, M.; Nagai, M.; Ban, Y. *Tetrahedron Lett.* **1968**, *491*, 497. (g) For a relevant review see: Brinkmeyer, R. S.; Abdulla, R. F. *Tetrahedron* **1979**, *35*, 1675.

(5) For a related reaction see: Howe, R. K. *J. Org. Chem.* **1969**, *34*, 230.

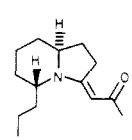
(6) Bredereck, H.; Bredereck, K. *Chem. Ber.* **1961**, *94*, 2278.

(7) (a) To our knowledge, the only reported intermolecular reactions between enolizable (alkylthio)alkylideniminium salts and active methylene compounds were reported in a Japanese patent: Yamaguchi, H. *Chem. Abstr.* **1965**, *63*, 18321. (b) For other reactions between nonenolizable (alkylthio)alkylideniminium salts and active methylene compounds see: Restle, S.; Wermuth, C. G. *Tetrahedron Lett.* **1979**, 4837.

(8) For a method of converting *N*-alkyl lactams to vinylogous ureas, see: Rathke, M. W.; Woodbury, R. P. *Tetrahedron Lett.* **1978**, 709. This method gave only trace amounts of vinylogous urea with lactam i.



i



ii

(9) For a review of the synthesis and reactions of (alkylthio)-methyleniminium salts, see: Kantlehner, K. *Adv. Org. Chem.* **1979**, *9*, 279.

tigation are described herein.

We began by examining the generality of the known conversion of (alkylthio)alkylideniminium salts **6** to enamines **7** upon treatment with active methylene compounds.[7] Salts **8–10**[11-14] (see Chart I) were treated with active methylene compounds **11–17** in *N,N*-dimethylformamide with either anhydrous potassium carbonate[15] or triethylamine as base or in dichloromethane with triethylamine as the base. The results are presented in Table I. In most cases, high yields of condensation products were obtained. No complications due to base mediated *S,N*-ketene acetal formation were encountered.[16] It was noticed, however, that treatment of salts **8–10** with β-keto esters or β-diketones with use of potassium carbonate in *N,N*-dimethylformamide gave substantial amounts of deacylated products (e.g., **23**; see Chart II) in addition to the normal condensation products (e.g., **22**; see Table I, entries 6, 8, 9, 11, 12).[7b] The yield of deacylation product could be suppressed by using triethylamine as the base in either dichloromethane (see entries 7, 10, 14) or *N,N*-dimethylformamide (see entry 13). Control experiments showed that the normal condensation products were not intermediates in the formation of the deacylation products (**22** ↛ **23**). Although the exact origin of the deacylation products remains uncertain, we speculate that a carbonate- or hydroxide-mediated deacylative elimination of methyl mercaptan is involved in their formation.

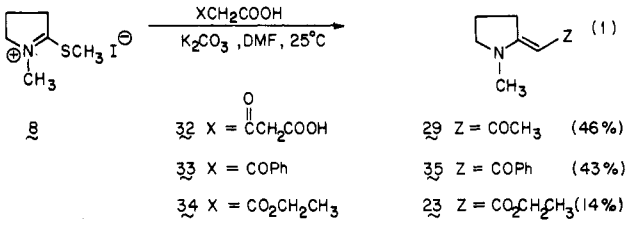
With a reliable route to enamines having the general structure **7** in hand, the conversion of these compounds to the desired vinylogous amides and vinylogous urethanes **3** was examined. At least two examples of basic hydrolysis and decarboxylation of similar enamino esters had been reported.[17] We found, however, that treatment of esters **21** and **22** with aqueous potassium hydroxide merely effected a retrograde condensation to give *N*-methylpyrrolidone (79–90%) and in one case the corresponding active methylene compound.[18] Attempts to convert methyl ester **26** to vinylogous amide **29** via *O*-alkyl cleavage followed by decarboxylation were also unsatisfactory.[19] Thus, treatment of **26** with sodium cyanide in *N,N*-dimethylformamide (150 °C, 4 h) gave **29** and **27** in 28% and 8% yields, respectively, along with 30% of recovered **26**. Treatment of *tert*-butyl ester **30** with neat trifluoroacetic acid, however, did give vinylogous urethane **29** in a 90% yield.[20] Thus, iminium salt **8** could be converted to **29** in a 67% overall yield.[21]

Table II. Reactions of (Methylthio)alkylideniminium Salts with 36

entry	salt	product	temp,[a] °C	rxn time, h	% yield
1	**8**	**23**	60	0.75	87
2	**9**	**37**	60	1	89
3	**10**	**25**	65	2	82
4	**38**	**39**[b]	60	2	75

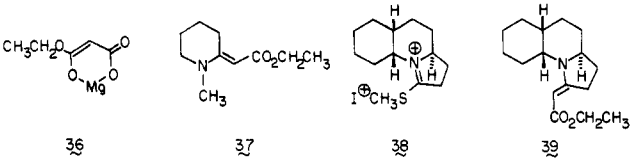
[a] DMF and 2.0 equiv of **36** were used in all reactions. [b] A trace of the corresponding lactam was also detected.

We next examined reactions of β-keto acids with (methylthio)alkylideniminium salts with the hope of directly producing vinylogous amides and vinylogous urethanes. Treatment of **8** with acetonedicarboxylic acid (**32**) gave vinylogous amide **29** in 46% yield (1.0 equiv of **32**, DMF, 2.0 equiv of K_2CO_3, 25 °C, 8 h). Similar treatment of **8** with benzoylacetic acid (**33**) and ethyl hydrogen malonate (**34**) gave **35** and **23** in 43% and 14% yields, respectively (eq 1). Attempts to improve the yields by



varying reactant concentrations, bases, and solvents met with failure. Product analysis revealed that β-keto acid decarboxylation, S-demethylation, and iminium salt hydrolysis were all taking place.[22]

In an attempt to eliminate the decarboxylation problems, we examined the use of magnesium salts of active methylene compounds. Although salts derived from β-keto acids were unsuccessful,[23] we did find that the dibasic magnesium salt of ethyl hydrogen malonate (**36**)[25] reacted



with (methylthio)alkylideniminium salts to give high yields of vinylogous urethanes in a one-pot procedure. The results are summarized in Table II.

To summarize, our original objective of converting *N*-alkyl lactams to vinylogous urethanes and amides can be accomplished via the sequence outlined in Scheme I (**1** → **2** → **6** → **3**). The procedures for preparing vinylogous amides proceed in only modest yields. The procedure for preparing vinylogous urethanes, however, proceeds in a high overall yield and provides an alternative to the excellent procedure of Eschenmoser[1] with the operational

(10) For other uses of (alkylthio)alkylideniminium salts, see: Harada, T.; Tamuro, Y.; Yoshida, Z. *Chem. Lett.* **1979**, 1353. Raucher, S.; Klein, P. *Tetrahedron Lett.* **1980**, 4061.

(11) Salts **8–10** were prepared by treating the parent lactams with the dimer of (*p*-methoxyphenyl)thionophosphine sulfide[12] followed by alkylation of the resulting thiolactams with methyl iodide in diethyl ether. The overall yields of **8**,[13] **9**,[13] and **10**[14] from the corresponding lactams were 84%, 89%, and 82%, respectively.

(12) Schiekze, S.; Pederson, B. S.; Lawesseon, S.-O. *Bull. Soc. Chim. Belg.* **1978**, *87*, 229.

(13) Gompper, R.; Elser, W. *Justus Liebigs Ann. Chem.* **1969**, *725*, 64.

(14) NMR ($CDCl_3$) δ 0.80–2.90 (m, H), 2.96 (s, 3 H, SCH_3), 3.5–4.8 (m, 4 H, NCH and $=CCH_2$); mp 110–114 °C.

(15) White, D. A. *Synth. Commun.* **1977**, *7*, 559.

(16) One might have anticipated competition between ketene S,N-acetal formation[18] and iminium ion addition under the basic conditions used throughout this study.

(17) Howard, A. S.; Gerrans, G. C.; Michael, J. P. *J. Org. Chem.* **1980**, *45*, 1713. Yamada, Y.; Miljkovic, D.; Wehrli, P.; Gelding, B.; Löliger, P.; Keese, R.; Müller, K.; Eschenmoser, A. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 343.

(18) Methyl acetoacetate was isolated in a 40% yield from the attempted hydrolysis of ester **26** with aqueous potassium hydroxide.

(19) McMurray, J. *Org. React.* **1976**, *24*, 187.

(20) For a related reaction, see: Wenkert, E. *Acc. Chem. Res.* **1968**, *1*, 78.

(21) For a hydrogenolysis–decarboxylation procedure which may be suitable for converting compounds of type **7** to vinylogous amides, see: Horii, Z.; Morikawa, K.; Ninomiya, I. *Chem. Pharm. Bull.* **1969**, *17*, 2230.

(22) For example, treatment of **10** with **32** gave vinylogous amide ii (13%) and lactam i (51%). Sequential treatment of **33** with magnesium methoxide and **8** in DMF gave substantial amounts of *N*-(methylthio)-pyrrolidone.

(23) Sequential treatment of several methyl ketones with methyl magnesium carbonate[24] in DMF followed by salt **8** gave less than 10% of the desired condensation product.

(24) (a) Stiles, M. *J. Am. Chem. Soc.* **1959**, *81*, 2598. (b) Finkbeiner, H. L.; Wagner, G. W. *J. Org. Chem.* **1963**, *28*, 215.

(25) Braum, G.; Vilkas, M. *Bull. Soc. Chim. Fr.* **1964**, 945. McMurry, J. E.; Andrus, W. A.; Musser, J. H. *Synth. Commun.* **1978**, *8*, 53.

advantage that phosphines need not be employed.

Experimental Section

All melting points were taken with a Thomas-Hoover melting point apparatus and are uncorrected. ^1H magnetic resonance spectra were recorded on a Varian Associates EM-390 or EM-360 spectrometer and are reported in parts per million from internal tetramethylsilane on the δ scale. Data are reported as follows: chemical shift [multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, qu = quintet, br s = broad singlet), coupling constants (in hertz), integration, interpretation]. Infrared spectra were taken with a Perkin-Elmer 457 instrument. Mass spectra were recorded on an AEI-MS9 instrument. Samples on which exact masses were measured exhibited no significant peaks at m/e values greater than that of the parent.

Solvents and reagents were dried and purified prior to use: *N,N*-dimethylformamide, distilled from calcium hydride; dichloromethane, passed through activity I alumina. Reactions requiring inert atmosphere were run under a blanket of nitrogen or argon. Analytical thin-layer chromatography was performed by using EM laboratories 0.25 mm precoated silica gel 60F-254 plates. Column chromatography was performed over EM laboratories silica gel (70–230 mesh).

Starting materials were either purchased [nitromethane (**11**),[26] dimethyl malonate (**12**),[27] ethyl cyanoacetate (**13**),[28] ethyl acetoacetate (**14**),[28] methyl acetoacetate (**15**),[27] 2,4-pentandione (**16**),[27] *tert*-butyl acetoacetate (**17**),[27] acetone-1,3-dicarboxylic acid (**32**)[27]] or prepared according to known procedures [2-(methylthio)-*N*-methylpyrrolideniminium iodide (**8**),[11] 2-(methylthio)-*N*-methylpiperideniminium iodide (**9**),[11] 9-(methylthio)-(*rel*-2*R*,6*S*)-2-propyl-1-azabicyclo[4.3.0]non-9-enyl iodide (**10**),[11] benzoylacetic acid (**33**),[24a] ethyl hydrogen malonate (**34**),[29] magnesium salt **36**,[25] 1-(methylthio)-(*rel*-3a*S*,5a*R*,9a*R*)-dodecahydropyrrolo-[1,2-*a*]quinolin-1-ylideniminium iodide (**39**)[30]].

Reactions of 8–10 with Active Methylene Compounds (Table I). Method A. To a mixture of the appropriate (methylthio)alkylideniminium salt (1.0 equiv) and potassium carbonate (2.0 equiv) under argon was added a 1.0 M solution of the active methylene compound (1.0 equiv) in dry *N,N*-dimethylformamide in one portion. The resulting mixture was stirred at room temperature, and the reaction progress was monitored by thin-layer chromatography (methanol–ethyl acetate, 1:5, as eluant). When the reaction was complete, the mixture was partitioned between water and dichloromethane. The aqueous phase was extracted with dichloromethane, and the combined organic phases were dried (Na_2SO_4) and concentrated in vacuo. The DMF was removed at 1.0 mm, and the residue was chromatographed over silica gel with a suitable methanol–ethyl acetate pair as eluant to give the desired product.

Method B. To the appropriate salt (1.0 equiv) under argon was added a solution of the active methylene compound (1.0 equiv) in dry DMF (1.0 mL mmol^{-1}) followed by the addition of 2.0 equiv of triethylamine. The resulting solution was stirred at room temperature, and the reaction progress was monitored by thin-layer chromatography. When the reaction was complete, it was worked up as described in method A.

Method C. To the appropriate salt (1.0 equiv) under argon was added a solution of the active methylene compound (1.0 equiv) in dichloromethane (1.0 mL mmol^{-1}) in a single portion followed by 2.0 equiv of triethylamine. The resulting solution was stirred at room temperature, and the reaction progress was monitored by thin-layer chromatography. When the reaction was complete, it was worked up as described in method A.

Reaction of (Methylthio)alkylideniminium Salts with 36 (Table II). A solution of the appropriate salt (1.0 equiv) and magnesium salt **36** (2.0 equiv) in DMF (1.0 mL/mmol of **36**) was warmed in an oil bath at 60–65 °C. The progress of the reaction was monitored by thin-layer chromatography. When the reaction was complete, the mixture was diluted with dichloromethane and washed several times with water. The organic phase was dried (Na_2SO_4) and concentrated in vacuo, and the residue was chromatographed over silica gel to afford the desired product.

1-(Methyl-2-pyrrolidinylidene)-2-propanone (29) from *tert*-Butyl Ester 30. To 202 mg (0.84 mmol) of ester **30** was added 1.2 mL of trifluoroacetic acid in a single portion. The resulting solution was stirred at room temperature for 1 h and concentrated in vacuo. The residual oil was dissolved in 20 mL of dichloromethane and washed with 5 mL of aqueous sodium bicarbonate solution. The aqueous phase was extracted with 5 mL of dichloromethane, and the combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. The residual oil was chromatographed over 8 g of silica gel (eluted with methanol–ethyl acetate, 1:10) to give 104 mg (90%) of vinylogous amide **29** as a pale yellow oil.

Characterization of Compounds. 1-Methyl-2-(nitromethylidene)pyrrolidine (18):[4b] mp 154.0–155.0 °C (lit.[4d] mp 154 °C); ^1H NMR ($CDCl_3$) δ 2.07 (qu, J = 8, 2 H, CH_2), 2.92 (s, 3 H, CH_3), 3.53 (q, J = 8, 4 H, NCH_2), 6.67 (s, 1 H, =CH); ^{13}C NMR ($CDCl_3$) 20.41 (t), 33.94 (q), 34.47 (t), 55.98 (t), 108.82 (d), 164.51 (s).

Dimethyl (1-methyl-2-pyrrolidinylidene)propanedioic acid (19):[4b] ^1H NMR ($CDCl_3$) δ 2.00 (qu, J = 7.5, 2 H, CH_2), 2.88 (s, 3 H, NCH_3), 3.18 (t, J = 7.5, 2 H, NCH_2), 3.55 (t, J = 7.5, 2 H, NCH_2), 3.75 (s, 6 H, OCH_3); ^{13}C NMR ($CDCl_3$) 20.58 (t), 35.30 (t), 36.75 (q), 51.22 (q), 57.34 (t), 88.55 (s), 167.40 (s), 168.56 (s).

Dimethyl (1-methyl-2-piperidinylidene)propanedioic acid (20): mp 48.5–52 °C; IR ($CHCl_3$) 1555, 1670 cm^{-1}; NMR ($CDCl_3$) δ 1.47–2.00 (m, 4 H, CH_2), 2.70–3.10 (br t with s at 2.90, 5 H, NCH_3, $=CCH_2$), 3.10–3.50 (br t, 2 H, NCH_2), 3.67 (s, 6 H, OCH_3); mass spectrum, m/e (relative intensity) 227 (69), 196 (92), 195 (62), 168 (87), 164 (79), 138 (17), 137 (17), 136 (25), 113 (100), 112 (42), 101 (52), 96 (42); exact mass calcd for $C_{11}H_{17}NO_4$ m/e 227.1157, found m/e 227.1163.

Ethyl cyano(1-methyl-2-pyrrolidinylidene)acetate (21):[6] mp 122–123.5 °C (lit.[6] mp 123–124 °C); NMR ($CDCl_3$) δ 1.27 (t, J = 7, 3 H, CH_3), 1.97 (qu, J = 8, 2 H, CH_2), 3.27 (t, J = 8, 2 H, $=CCH_2$), 3.40 (s, 3 H, NCH_3), 3.58 (t, J = 8, 2 H, NCH_2), 4.13 (q, J = 7, 2 H, OCH_2).

Ethyl 2-(1-methyl-2-pyrrolidinylidene)-3-oxobutanoate (22):[4d] ^1H NMR ($CDCl_3$) δ 1.32 (t, J = 7, 3 H, CH_3), 2.07 (qu, J = 7, 2 H, CH_2), 2.35 (s, 3 H, $COCH_3$), 2.88 (s, 3 H NCH_3), 3.25 (t, J = 7, 2 H, CCH_2), 3.68 (t, J = 7, 2 H, NCH_2), 4.25 (q, J = 7, 2 H, OCH_2); ^{13}C NMR ($CDCl_3$) δ 14.36 (q) 20.55 (t), 30.56 (q), 36.39 (t), 38.81 (q), 57.44 (t), 59.57 (t), 99.02 (s), 169.23 (s), 172.57 (s), 195.14 (s).

Ethyl α-(1-methyl-2-pyrrolidinylidene)acetate (23): IR ($CHCl_3$) 1600, 1675 cm^{-1}; NMR ($CDCl_3$) δ 1.25 (t, J = 7, 3 H, CH_3), 1.93 (qu, J = 7, 2 H, CH_2), 2.80 (s, 3 H, NCH_3), 3.13 (t, J = 7, 2 H, $=CCH_2$), 3.37 (t, J = 7, 2 H, NCH_2), 4.10 (q, J = 7, 2 H, OC H_2), 4.47 (s, 1 H, =CH); mass spectrum, m/e (relative intensity) 168 (8), 124 (24), 97 (17), 88 (10), 86 (66), 85 (10), 84 (100), 83 (13); exact mass calcd for $C_9H_{15}NO_2$ m/e 169.1103, found m/e 169.1107.

Ethyl 2-[(*rel*-2*R*,6*S*)-2-propyl-1-azabicyclo[4.3.0]nonan-9-ylidene]-3-oxobutanoate (24): IR ($CHCl_3$) 1510, 1600, 1670 cm^{-1}; NMR ($CDCl_3$) δ 0.57–2.20 (m with t, J = 7, at 1.27, 18 H), 2.25 (s, 3 H, $COCH_3$), 2.83–3.27 (m, 2 H, $=CCH_2$), 3.43–4.07 (m, 2 H, NCH), 4.13 (q, J = 7, 2 H, OCH_2); mass spectrum, m/e (relative intensity) 293 (5), 250 (15), 208 (20), 181 (7), 140 (100); exact mass calcd for $C_{17}H_{27}NO_3$ m/e 293.1991, found m/e 293.1999.

Ethyl [(*rel*-2*R*,6*S*)-2-propyl-1-azabicyclo[4.3.0]nonan-9-ylidene]acetate (25): IR ($CHCl_3$) 1590, 1675 cm^{-1}; NMR ($CDCl_3$) δ 0.70–3.83 (m with t, J = 7, at 1.23, 22 H), 4.07 (q, J = 7, 2 H, OCH_2), 4.50 (br s, 1 H, =CH).

Methyl 2-(1-methyl-2-pyrrolidinylidene)-3-oxobutanonate (26): IR ($CDCl_3$) 1550, 1610, 1675 cm^{-1}; NMR (CCl_4) δ 1.80–2.20 (qu, J = 7.5, with s at 2.13, 5 H, $COCH_3$ and CH_2), 2.75 (s, 3 H, NCH_3), 3.10 (t, J = 7.5, 2 H, $=CCH_2$), 3.50–3.73 (t with s at 3.65, 5 H, NCH_2 and OCH_3); mass spectrum, m/e (relative intensity) 197 (67), 182 (100), 180 (11), 178 (13), 166 (24), 165 (24), 164 (6), 155 (15), 151 (47), 138 (11), 137 (6), 125 (69), 124 (11), 123 (14); exact mass calcd for $C_{10}H_{15}NO_3$ m/e 197.1052, found m/e 197.1057.

(26) Purchased from Fisher.
(27) Purchased from Aldrich Chemical Co.
(28) Purchased from Eastman Chemical Co.
(29) Strube, R. E. "Organic Syntheses"; Wiley: New York, 1963; Collect. Vol. IV, p 417.
(30) Prepared in a 90% yield from the corresponding lactam as described in ref 11: mp 165–170 °C; NMR ($CDCl_3$) δ 0.80–3.00 (m, 15 H), 3.00 (s, 3 H, SCH_3), 3.61–4.95 (m, 4 H, NCH and $=CCH_2$).

Methyl 2-(1-methyl-2-pyrrolidinylidene)acetate (27): mp 50.5–51.5 °C; IR ($CHCl_3$) 1595, 1670 cm^{-1}; NMR (CCl_4) δ 1.93 (qu, J = 7.5, 2 H, CH_2), 2.80 (s, 3 H, NCH_3), 3.07 (t, J = 7.5, 2 H, $=CCH_2$), 3.33 (t, J = 7.5, 2 H, NCH_2), 3.50 (s, 3 H, OCH_3), 4.32 (s, 1 H, =CH); mass spectrum, m/e (relative intensity) 155 (42), 124 (100), 97 (18), 96 (18); exact mass calcd for $C_8H_{13}NO_2$ m/e 155.0946, found m/e 155.0952.

Anal. Calcd for $C_8H_{13}NO_2$: C, 61.91; H, 8.44. Found: C, 62.14; H, 8.51.

3-(1-Methyl-2-pyrrolidinylidene)-2,4-pentanedione (28):[4d] NMR ($CDCl_3$) δ 2.03 (qu, J = 7.5, 2 H, CH_2), 2.27 (s, 6 H, $COCH_3$), 2.82 (s, 3 H, NCH_3), 3.17 (t, J = 7.5, 2 H, $=CCH_2$), 3.63 (t, J = 7.5, 2 H, NCH_2).

1-(1-Methyl-2-pyrrolidinylidene)-2-propanone (29):[2] NMR (CCl_4) δ 1.70–2.10 (q, J = 7, with s at 1.90, 5 H, $COCH_3$ and CH_2), 2.83 (s, 3 H, NCH_3), 3.07 (t, J = 7, 2 H, $=CCH_2$), 3.33 (t, J = 7, 2 H, NCH_2), 4.80 (s, 1 H, =CH).

***tert*-Butyl 2-(1-methyl-2-pyrrolidinylidene)-3-oxobutanoate (30)**: mp 65.5–66.5 °C; IR ($CHCl_3$) 1545, 1615, 1670 cm^{-1}; NMR (CCl_4) δ 1.52 (s, 9 H, O-*t*-Bu), 2.00 (qu, J = 7.5, 2 H, CH_2), 2.17 (s, 3 H, $COCH_3$), 2.77 (s, 3 H, NCH_3), 3.07 (t, J = 7.5, 2 H, $=CCH_2$), 3.60 (t, J = 7.5, 2 H, NCH_2); mass spectrum, m/e (relative intensity) 239 (3), 238 (18), 182 (16), 167 (30), 165 (23), 164 (23), 149 (21), 118 (19), 103 (100); exact mass calcd for $C_{13}H_{21}NO_3$ m/e 239.1521, found m/e 239.1516.

Anal. Calcd for $C_{13}H_{21}NO_3$: C, 65.24; H, 8.85. Found: C, 65.25; H, 8.99.

***tert*-Butyl 2-(1-methyl-2-pyrrolidinylidene)acetate (31)**: IR ($CHCl_3$) 1590, 1670 cm^{-1}; NMR (CCl_4) δ 1.43 (s, 9 H, O-*t*-Bu), 1.93 (qu, J = 7.5, 2 H, CH_2), 2.78 (s, 3 H, NCH_3), 3.03 (t, J = 7.5, 2 H, $=CCH_2$), 3.30 (t, J = 7.5, 2 H, NCH_2), 4.27 (s, 1 H, =CH); mass spectrum, m/e (relative intensity) 197 (31), 96 (100); exact mass calcd for $C_{11}H_{19}NO_2$ m/e 197.1416, found 197.1418.

α-(1-Methyl-2-pyrrolidinylidene)acetophenone (35): mp 100–101 °C; IR ($CHCl_3$) 1540, 1580, 1620 cm^{-1}; NMR (CCl_4) δ 1.97 (qu, J = 6, 2 H, CH_2), 2.90 (s, 3 H, NCH_3), 3.33 (q, J = 6, 4 H, NCH_2, allyl), 5.53 (s, 1 H, =CH), 7.20–7.50 (m, 3 H, ortho and para Ar H), 7.63–7.90 (m, 2 H, meta Ar H); mass spectrum, m/e (relative intensity) 201 (64), 200 (55), 184 (30), 124 (100), 115 (8), 105 (26), 96 (44); exact mass calcd for $C_{13}H_{15}NO$ m/e 201.1154, found m/e 201.1158.

Acknowledgment. We thank Dr. Chuck Cottrell and Richard Weisenberger for their assistance in obtaining ^{13}C NMR and mass spectra, respectively. Financial support from the National Institutes of Health is gratefully acknowledged.

Registry No. 8, 25355-40-2; 9, 25355-41-3; 10, 78167-63-2; 11, 75-52-5; 12, 108-59-8; 13, 105-56-6; 14, 141-97-9; 15, 105-45-3; 16, 123-54-6; 17, 1694-31-1; 18, 26171-05-1; 19, 26924-97-0; 20, 53583-61-2; 21, 21985-16-0; 22, 60624-10-4; 23, 78167-64-3; 24, 78167-65-4; 25, 78167-66-5; 26, 78167-67-6; 27, 78167-68-7; 28, 60624-11-5; 29, 39178-30-8; 30, 78167-69-8; 31, 78167-70-1; 32, 542-05-2; 33, 614-20-0; 34, 1071-46-1; 35, 39178-28-4; 36, 64679-38-5; 37, 78167-71-2; 38, 78167-72-3; 39, 75533-98-1; i, 78167-73-4; ii, 78167-74-5; 1-methyl-2-pyrrolidinone, 872-50-4; 1-methyl-2-piperidone, 931-20-4; *rel*-(3a*S*,5a*R*,9a*R*)-dodecahydropyrrolo[1,2-*a*]quinolin-1-one, 75533-96-9.

Synthesis of Dihydrodiol and Other Derivatives of Benz[*c*]acridine

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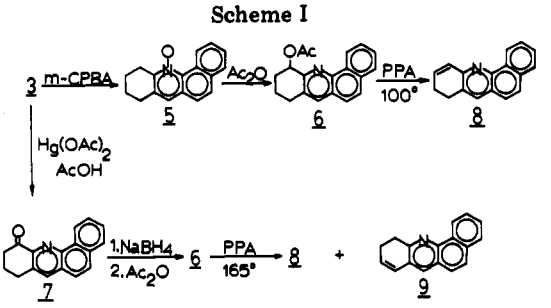
Received March 30, 1981

The K-region and non-K-region *trans*-dihydrodiols and the cis and trans bay-region diol epoxides of benz[*c*]acridine have been synthesized. Regiospecific oxygenation at C-11 of 8,9,10,11-tetrahydrobenz[*c*]acridine and at C-4 of 1,2,3,4-tetrahydrobenz[*c*]acridine with mercuric acetate in acetic acid afforded intermediates that were converted to the 10,11- and 3,4-dihydrodiols, respectively. The 1,2- and 8,9-dihydrodiols were prepared by routes involving separation of their precursors from analogous precursors of the 3,4- and 10,11-dihydrodiols. The K-region *trans*-dihydrodiol was prepared by acid-catalyzed hydration of the K-region oxide. The *cis*- and *trans*-3,4-diol 1,2-epoxides, which are structurally analogous to the most mutagenic and tumorgenic of the benzo[*a*]anthracenediol epoxides, were prepared from the 3,4-dihydrodiol in good yields by base-catalyzed bromotriol cyclization and direct epoxidation with *m*-chloroperoxybenzoic acid, respectively.

It is well established that metabolism of polycyclic aromatic hydrocarbons to dihydrodiols and diol epoxides is an important event in the activation of these molecules to ultimate mutagens and carcinogens.[1] The analogous aza aromatics, which are also environmental contaminants and which include a number of known carcinogens,[2] have received scant attention. Kitahara et al.[3] prepared K-region oxides of several aza aromatics and have observed mutagenicity levels in *S. typhimurium* TA 100 insufficient to support their involvement as likely bioactivated forms of the molecules. Reports of the preparation of dihydrodiols and other derivatives of dibenzo[*c*,*h*]acridine[4] and of the K-region oxide of 7-methylbenz[*c*]acridine[5] have appeared recently, but the biological data reported for these molecules has been fragmentary.

Scheme I



Benz[*c*]acridine (1) was chosen as the initial target for the several reasons. The analogous polycyclic aromatic hydrocarbon, benz[*a*]anthracene (BA, 2) has been exten-

(1) For a recent review, see M. Nordqvist, D. R. Thakker, H. Yagi, R. E. Lehr, A. W. Wood, W. Levin, A. H. Conney, and D. M. Jerina in "Molecular Basis of Environmental Toxicity", R. S. Bhatnagar, Ed., Ann Arbor Science Publishers, Ann Arbor, MI, 1980, pp 329–357.

(2) A. Dipple in "Chemical Carcinogens", C. E. Searle, Ed., American Chemical Society, New York, 1976, p 245.

(3) Y. Kitahara, H. Okuda, K. Shudo, T. Okamoto, M. Nagao, Y. Scino, and T. Sugimura, *Chem. Pharm. Bull. Jpn.*, 26, 1950 (1978).

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(5) L. J. Boux, H. T. A. Cheung, G. M. Holder, and L. Moldovan, *Tetrahedron Lett.*, 21, 2923 (1980).

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