Heterocyclic Syntheses *via* the Intramolecular Acylation of Enamines Derived from Amino Acids[1]

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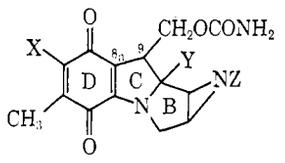
A general heterocyclic synthesis using enamines derived from amino acids is described. The use of salts of amino acids in the enamine-forming step is developed. The preparations of dihydroorcinol and dehydroproline, potential starting materials for the heterocyclic synthesis, are described. Asymmetric induction, ultimately observed in the heterocycle, caused by the chiral amino acids, is discussed.

Enamine derivatives of amino acids have been used as blocking groups[2] and as asymmetric catalysts for alkylations.[3] There is a great deal of literature on the acylation of enamines.[4] In this report, we wish to describe the incorporation, into heterocyclics, of enamines derived from the reaction of natural amino acids with cyclic diketones. The key step in this synthesis is an intramolecular acylation reaction. Of particular interest to us was the accessibility of frameworks related to the mitomycins (**1**). Removal of the bond between 8a and 9 generates structure **2**;



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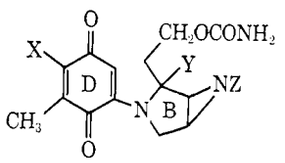

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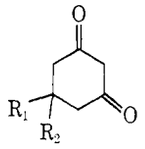
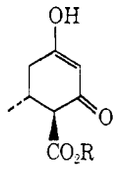
thus the conceptual basis of this program was the preparation of intermediates of this type and the reformation of the bond in question.[5]

Results and Discussion

The carbonyl compounds used in this study are the cyclohexane-1,3-diones known as dihydroresorcinol (**3**), dihydroorcinol (**4**), and dimedone (**5**). Compounds **3** and **5** are commercially available and there is a well-known preparation of **4**, namely, condensation of ethyl crotonate with ethyl acetoacetate to form diketo ester **6**. Finally, alkaline saponification and decarboxylation afford the desired diketone.[6] However, the penultimate saponification, plagued with reverse Claisen and Dieckmann reactions, is highly irreproducible. We found it convenient to circumvent this problem by employing the expedient of using *tert*-butyl acetoacetate, thus affording diketo ester **7**. Cleavage and decarboxylation of this intermediate



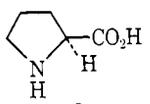
3, $R_1 = R_2 = H$
4, $R_1 = H$; $R_2 = CH_3$
5, $R_1 = R_2 = CH_3$



6, R = CH_2CH_3
7, R = $C(CH_3)_3$

can be done entirely in dilute aqueous acid, affording a reproducible 52% overall yield of **4**.

Of the amino acids used in this work, L-proline (**8**) and L-hydroxyproline (**9**) were commercial samples. *N*-Benzylglycine (**10**) and 4-chloroproline (**11**) were



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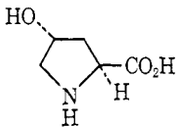

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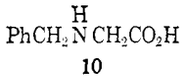

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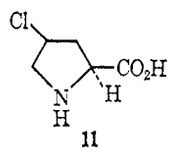

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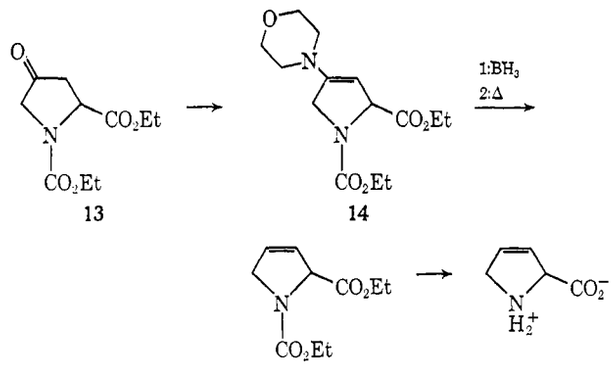
prepared using modifications of literature procedures.[7] Racemic dehydroproline (**12**) was obtained as a gift from Ravizza S. A. Milan. Prior to the availability of **12** from this source, a route to this amino acid was developed as outlined in Scheme I. The key step

SCHEME I



13 **14** **15** **12**

(1) (a) Portions of this article are taken from the Ph.D. Theses of R. J. F and J. M. G., Fordham University, 1970 and 1972, respectively, and the undergraduate report of R. P. S., 1971. (b) A preliminary communication of some of this research has been published: R. W. Franck, R. J. Friary, and J. F. Tobin, *Chem. Commun.*, 283 (1969). (c) The support of the National Cancer Institute, Grant 11421, is gratefully acknowledged.

(2) (a) B. Halpern and L. James, *Aust. J. Chem.*, **17**, 1282 (1964); (b) B. Halpern, *ibid.*, **18**, 417 (1965); (c) B. Halpern and L. James, *Nature (London)*, **202**, 592 (1964); (d) P. Crabbe, B. Halpern, and E. Santos, *Tetrahedron*, **24**, 4299 (1968); (e) *ibid.*, **24**, 4215 (1968).

(3) (a) K. Hiroi, K. Achiwa, and S.-I. Yamada, *Chem. Pharm. Bull.*, **20**, 246 (1972). An intramolecular cyclization such as our work describes is mentioned in this paper. (b) K. Hiroi and S.-I. Yamada, *ibid.*, **21**, 47 (1973).

(4) A. G. Cook, Ed., "Enamines: Their Synthesis, Structure, and Reactions," Marcel Dekker, New York, N. Y., 1969.

(5) This analysis of the problem was reported previously: L. Mandell and E. C. Roberts, *J. Heterocycl. Chem.*, **2**, 479 (1965).

(6) (a) A. Crossley and N. Renouf, *J. Chem. Soc.*, **107**, 605 (1915); (b) R. V. Schilling and D. Vorlander, *Justus Liebigs Ann. Chem.*, **308**, 192 (1899); (c) D. Vorland and F. Kalkow, *Ber.*, **30**, 1801 (1897); (d) E. Knoevenagel, *Justus Liebigs Ann. Chem.*, **289**, 170 (1896).

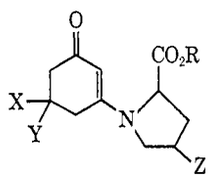
(7) (a) J. A. King and F. McMillan, *J. Amer. Chem. Soc.*, **72**, 1236 (1950); (b) J. Kerwin, G. Hall, F. Milnes, I. Witt, R. McLean, E. Macko, E. Fellows, and G. Ullyot, *ibid.*, **73**, 4162 (1951); (c) R. H. Andreatta, V. Nair, A. V. Robertson, and W. R. J. Simpson, *Aust. J. Chem.*, **20**, 1493 (1967).

TABLE I
DATA FOR ENAMINE ESTERS, YIELDS, ANALYSES, AND UV DATA

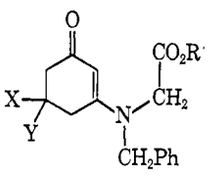
Compd	Mp, °C	Yield, %	Formula	Calcd (found), % C	H	N	Uv, λ_{max}, nm (ε)
16a	58.5–59	70	$C_{14}H_{21}NO_3$	66.9 (67.0)	8.4 (8.5)	5.6 (5.5)	310 (14,700)
17a	Oil	76					
18a	55.5–57.5	91					
19a	98.5	76	$C_{18}H_{23}NO_3$	71.7 (71.6)	7.7 (7.6)	4.7 (4.6)	214 (6960), sh 290 (13,800), 306 (16,100)
20a	94	37	$C_{19}H_{25}NO_3$	72.4 (72.5)	8.0 (8.0)	4.4 (4.4)	208 (4800), 298 (16,000)

was the one-pot conversion of a ketone to an alkene in the presence of ester and urethane functions in 53% yield using the method of Lewis and Pearce.[8]

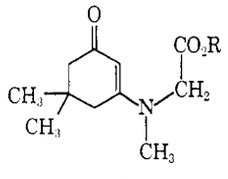
Previous workers[2,3] had used esters of amino acids in the enamine-forming reaction to circumvent the problems presented by the zwitterionic nature of the free acids, *viz.*, insolubility in aprotic organic solvents and lack of basicity of the protonated amino group. Although the technique was satisfactory for enamine formation, the desired synthons were the acids **18–21b**. Thus, we were in the uneconomic position of having to esterify our commericial amino acids so as to synthesize enamines **16–21a** (Table I) and then treat these intermediates under carefully defined hydrolysis conditions so as to remove the ester group. With this in mind, a direct method was developed using the sodium salts of the desired amino acids, formed by treating the free acid with NaH. These salts were sparingly soluble in DMF at room temperature. However, upon heating the mixture of DMF, diketone, and acid salt, a clear solution developed. In most cases, the salt of the enamino acid was less soluble in DMF than its precursors. Thus, the desired products usually crystallized from the hot DMF. The salts **16c**, **17c**, **22c**, **23c**, and **24c** (Table II) were simply



16, X = CH_3; Y = Z = H
17, X = Y = CH_3; Z = H
22, X = CH_3; Y = H; Z = OH
23, X = CH_3; Y = H, Z = Cl



18, X = Y = H
19, X = CH_3; Y = H
20, X = Y = CH_3



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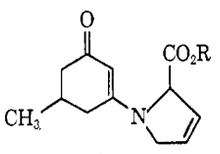

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a, R = CH_2CH_3
b, R = H
c, R = Na

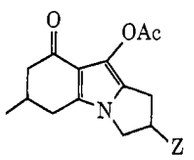
characterized by their identifiable ir bands. Then they were either converted to free acids by protonation to be compared with samples prepared from the ester pathway which were more carefully characterized

(8) J. W. Lewis and A. A. Pearce, *J. Chem. Soc. B*, 863 (1969).

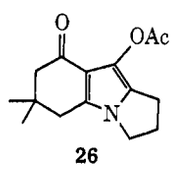
TABLE II
YIELDS AND INFRARED SPECTRAL DATA FOR THE ENAMINE ACID SALTS

Salt	Yield, %	ν_{max}, cm^{-1} −COO⁻	NC=CC=O
16c	59	1541, 1393	1603
17c	71	1529, 1391	1587
21c	72	1538, 1391	1603
22c	97	1524, 1416	1592
23c	76	1530, 1400	1605
24c	64	1525, 1430	1600

or, more usefully, they were directly cyclized in hot acetic anhydride to the desired ketotetrahydroindoles **25–30** (Table III). We speculate that first formed



25, Z = H
29, Z = OAc
30, Z = Cl



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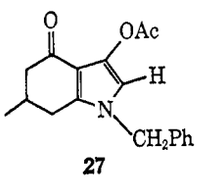

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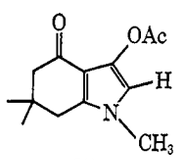

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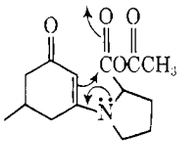
TABLE III
YIELDS, MELTING POINTS, AND ANALYSES FOR ACETOXYTETRAHYDRO- AND ACETOXYHEXAHYDROPYRROLOOXINDOLES[a]

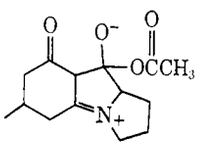
Compd	Mp, °C	Yield, %	Formula	Calcd (found), % C	H	N	Cl
25	113–114.5	40	$C_{14}H_{17}NO_3$	68.0 (67.9)	6.9 (6.8)	5.7 (5.5)	
26	117–118	57	$C_{15}H_{19}NO_3$	68.9 (69.1)	7.3 (7.3)	5.4 (5.4)	
27	124–124.5	85	$C_{18}H_{19}NO_3$	72.7 (72.7)	6.4 (6.4)	4.7 (4.6)	
28	121–122.5	63	$C_{13}H_{17}NO_3$	66.4 (66.5)	7.3 (7.3)	6.0 (5.9)	
29	110–111	38	$C_{15}H_{19}NO_5$	62.9 (63.0)	6.3 (6.2)	4.6 (4.6)	
30	123–124	10	$C_{14}H_{15}ClNO_3$	59.7 (59.6)	5.7 (5.7)	5.0 (5.0)	12.6 (12.5)

[a] At the request of the editor and referees, the tables of nmr and ir assignments have been omitted. They are all consistent with those reported for **25** in the Experimental Section.

is a mixed anhydride intermediate A which acylates the enamine carbon to form B. Subsequently, elim-



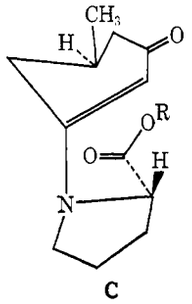
A



B

ination of water or acetic acid results in the formation of the tetrahydroindole. Experiments using isopropenyl acetate or dicyclohexylcarbodiimide failed to produce cyclization. Most disappointing to our program was the failure of salt **24** to afford cyclized product when subjected to hot acetic anhydride. An examination of models suggests that the two trigonal carbons in the dehydroproline ring of the salt confer rigidity to the amino acid framework. Thus, the carboxyl carbon cannot approach the enamine double bond so as to overlap well with the π bond.

The tricyclic **25** was examined by CD to determine if any detectable asymmetric induction had taken place, either in the formation of **16c** or in the cyclization. A rotation at λ_{max} 305 nm ($\Delta\epsilon$ +0.33) and a broad, noisy maximum centered at 265 nm ($\Delta\epsilon$ −0.24) were observed. That this rather small rotation was not due to contamination by the precursor **16c** was demonstrated by its CD spectrum, λ_{max} 292 nm ($\Delta\epsilon$ −9.1) and 214 (+3.3), which is behavior expected for these derivatives of amino acids.[9] Spectra of appropriate model compounds do not seem to be available for assignment of absolute configuration. Use of the chiral nmr shift reagent, trisheptafluorobutyrylcamphoratoeuropium (Regis Chemical Co.) revealed an optical purity of 10%. One can speculate that the asymmetric induction involves preferred cyclization of the diastereomer C depicted so as to minimize repulsions between the methyl and the mixed anhydride. Thus, the absolute configuration of the product should be *R* as illustrated. It is interesting to note that the CD of pulegone (**31**) is λ_{max} 330 nm ($\Delta\epsilon$ +0.38).[10]



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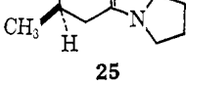

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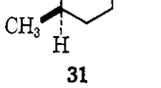

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In the cases of the tricyclics derived from hydroxyproline and chloroproline, one expects the formation of diastereoisomeric mixtures. In fact, single isomers seem to have been isolated. The nmr spectrum of **29** at 60 MHz revealed a doubling of the A portion of the ABX spectrum assigned to protons at carbon 3. However, spectra at 100 and 220 MHz[11] showed the splitting unchanged. Thus, the doubling of lines is simply long-range spin–spin coupling to a proton at C-5. We cannot identify hydrogens at C-5 in the spectrum. We are able to observe protons at C-1 and are thus able to discount them as the partners in the long-range coupling. If one assumes the same sense of asymmetric induction of methyl stereochemistry at C-6, owing to the identical chirality of the carboxyl portions of both proline and hydroxyproline, and also takes into account the trans relationship of the hydroxyl and carboxyl, then one is able to predict that the absolute configuration and relative stereochemistry of **29** (Table IV) are as drawn.

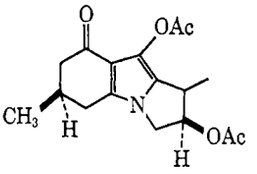

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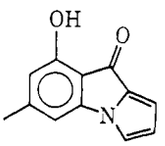
TABLE IV

SOME NMR DATA FOR 29

Assignment	δ_A	δ_B	J_{AB}	J_{AX}	J_{BX}
H_A' | NCCH$_X$(OAc)CH$_2$ | H_B'	4.23[a]	3.90	12.3	5.85	2.65
H_A | >NCH$_2$CH$_X$(OAc)C– | H_B	3.21	2.88	17.0	6.80	2.80

[a] Further long-range splitting, J = 1.9 Hz; *cf.* M. Barfield, *J. Chem. Phys.*, **48**, 4463 (1968); G. J. Karabatsos and S. S. Lande, *Tetrahedron*, **24**, 3907 (1968).

Although the cyclization yields in this work were not high, it was thought that this rather direct preparation of tricyclics could be applied to the synthesis of aromatic substrates for use in other mitomycin schemes underway in these laboratories. There are several reports of catalytic dehydrogenations of keto-tetrahydroindoles.[12] In the event, **25** afforded the completely aromatized **32** in variable yields when



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treated with palladium on carbon in refluxing mesitylene. The structural assignment was made by comparison of data to those of similar 9-keto-9*H*-pyrrolo[1,2-*a*]-indoles that had been prepared in this laboratory.[13]

(9) P. Crabbe, "Optical Rotatory Dispersion and Circular Dichroism in Organic Chemistry," Holden-Day, San Francisco, Calif., 1965, p 311.

(10) L. Velluz, M. Legrand, and M. Grosjean, "Optical Circular Dichroism, Principles, Measurements, and Applications," Academic Press, New York, N. Y., 1965, p 207.

(11) We are indebted to the Analytical Laboratory of Ciba-Basel for these spectra.

(12) (a) S. Hauptmann, G. Clume, G. Hartmann, D. Haendel, and P. Franke, *Z. Chem.*, **6**, 183 (1966); (b) H. Plieninger and K. Klinge, *Chem. Ber.*, **101**, 2605 (1968); (c) W. A. Remers, R. H. Roth, G. J. Gibbs, and M. J. Weiss, *J. Org. Chem.*, **36**, 1232 (1971).

(13) V. J. Mazzola, K. F. Bernady, and R. W. Franck, *J. Org. Chem.*, **32**, 486 (1967).

Experimental Section[14,15]

5-Methylcyclohexane-1,3-dione (4).—A solution of 34.2 g (0.300 mol) of ethyl crotonate, 47.8 g (0.303 mol) of *tert*-butyl acetoacetate (Aldrich Chemical Co.), and 0.306 mol of sodium ethoxide, prepared from sodium hydride mineral oil dispersion and 105 ml of absolute ethanol, was refluxed for 2.5 hr, when a precipitate was deposited. After an additional 1 hr at reflux, the precipitate was collected and washed thoroughly with anhydrous ether to afford 59 g (79%) of the sodium enolate of 4-carbo-*tert*-butoxy-5-methylcyclohexane-1,3-dione (**7**) as a chalk-colored powder: ir ν_{max} 1701, 1639, 1248, 1220 cm^{-1}; nmr (D_2O) δ 1.03 (d, J = 6 Hz, 3 H), 1.47 (s, 9 H), 1.72–2.66 (br envelope, 3 H), 2.95 (d, J = 10 Hz, 1 H), 5.10 ppm (s, 1 H).

A solution of 14.2 g of salt in 50 ml of water was filtered and acidified with 5 ml of concentrated hydrochloric acid. The resulting white precipitate was washed with water and air dried to give 11.1 g (86%) of 4-carbo-*tert*-butoxy-5-methylcyclohexane-1,3-dione (**7**): mp 130–131.5°; ir ν_{max} 3484–3311, 2778–2128, 1718, 1590, 1242, 1198 cm^{-1}; nmr (DMSO-d_6) δ 1.02 (d, J = 6 Hz, 3 H), 1.45 (s, 9 H), 2.00–2.66 (br envelope, 3 H), 2.94 (d, J = 11 Hz, 1 H), 5.28 ppm (s, 1 H). Two recrystallizations of a specimen of **3** from ethyl acetate containing a little acetone gave the analytical sample, mp 138.5–141.5°.

Anal. Calcd for $C_{12}H_{18}O_4$: C, 63.70; H, 8.02. Found: C, 63.55; H, 7.94.

To 160 ml of vigorously stirring and boiling 0.05 N sulfuric acid was added 20.8 g of the *tert*-butyl ester **7** in small portions over 22 min. Slow addition was necessary to avoid material loss due to extensive foaming. Residual ester was rinsed into the reaction mixture with 35 ml of 0.05 N sulfuric acid and 15 ml of water. The mixture was refluxed for 50 min, when the evolution of gas had nearly ceased. The resulting hot solution was decolorized with charcoal, filtered, seeded, and refrigerated overnight at −5° to afford 8.76 g of **4**, identified by comparison of its ir spectrum with that of an authentic sample.[6] Recrystallization of a sample from ethyl acetate gave a 78% return of long, white needles of **4**, mp 125.5–127° (lit.[6] mp 126–127°). The yield of **4** was found to decrease with increasing acid concentration.

1,2-Dicarbethoxypyrrolidinone-4 (13).—Previously reported methods[16] were modified as follows: 29.8 g of ethyl N-carbethoxyglycinate in 10 ml of benzene was added dropwise over 30 min to a suspension of 7.9 g of 50% NaH mineral oil dispersion (prewashed with anhydrous benzene) in 450 ml of benzene. This was stirred vigorously for 14 hr under an inert atmosphere. At the end of this period, 29.4 g of diethyl maleate in 40 ml of benzene was added over a 20-min period. After an additional 6 hr the reaction mixture was diluted with 100 ml of ether and extracted with ice water (4 × 100 ml). The combined aqueous layers were backwashed with 100 ml of ether and carefully added to a mixture of 20 ml of concentrated H_2SO_4 in about 100 ml of ice. This was extracted with ether (5 × 100 ml), and the combined ether layers were washed with 100 ml of brine, dried over $MgSO_4$, and evaporated to yield 40.5 g (82% if pure) of 1,2,3-tricarbethoxypyrrolidinone-4 as an orange oil. This material was refluxed for 30 min in a mixture of 125 ml of concentrated HCl and 125 ml of water. The water was evaporated and the resultant red-brown oil was dissolved in 250 ml of absolute ethanol. After the addition of 1 ml of concentrated HCl this mixture was allowed to reflux for 8 hr and the volatile materials were removed on a rotary evaporator. The resultant oil was dissolved in 250 ml of chloroform, washed with 100 ml of water, 100 ml of saturated $NaHCO_3$ solution, and 100 ml of brine, dried over $MgSO_4$, and evaporated. Distillation yielded 22.5 g (57%) of a water-white liquid, bp 120–124° (0.05 mm) [lit.[16] bp 116–122° (0.02 mm)].

1,2-Dicarbethoxy-3-pyrroline (15).—A mixture of 5.17 g (22.6 mmol) of 1,2-dicarbethoxypyrrolidinone-4 (**13**), 1.96 g (22.6 mmol) of morpholine, and 10 mg of *p*-toluenesulfonic acid was dissolved in 50 ml of benzene and the mixture was refluxed under an inert atmosphere for 2 hr, during which time 1 equiv of water was collected in a Dean–Stark trap. After solvent was removed, the resultant enamine was dissolved in 25 ml of dry THF. The solution was transferred to a round-bottom flask equipped with septum and gas valve. After introduction of an inert atmosphere, the flask was immersed in an ice bath and 22.6 ml of 1 M BH_3–THF (Alfa Inorganics) was injected while the mixture was stirred with a magnetic stirring bar. The ice bath was removed and the mixture was stirred for 7 min; 6.0 g of ethanol was injected; and the mixture was stirred for an additional 15 min. The solvents were removed under vacuum without detaching the flask from the gas supply apparatus. An inert atmosphere was reintroduced and 50 ml of benzene was added through the septum. The mixture was refluxed for 1 hr, cooled, diluted with 100 ml of ether, washed with 100 ml of water, 100 ml of $NaHCO_3$ (saturated solution), and 100 ml of brine, and dried over $MgSO_4$, and the solvents were evaporated. Distillation yielded 2.01 g (42%) of a water-white liquid: bp 87° (0.10 mm); ir (CCl_4) 1748, 1712 cm^{-1}; nmr (CCl_4) δ 4 (m), 5.90 (2 H), 4.93 (1 H), 4.22 (6 H), 1.20 (6 H).[17]

Anal. Calcd for $C_{10}H_{15}O_4N$: C, 56.33; H, 7.09; N, 6.57. Found: C, 56.25; H, 6.93; N, 6.72.

3,4-Dehydroproline (12).—A sample of 268 mg of 1,2-dicarbethoxy-Δ^3-pyrrolidine (**15**) was dissolved in 15 ml of 57% HI in H_2O and the solution was refluxed under an inert atmosphere for 2 hr. The HI solution was removed under reduced pressure (0.3 mm) at room temperature until only a gummy residue remained. This was taken up in 2 ml of distilled water and passed through a 2-g column of Dowex 50 W-X8 ion exchange resin in the H^+ form. The column was washed with distilled water until the eluent became neutral and then the dehydroproline was eluted with 25 ml of 0.5 N NH_4OH. This was evaporated at room temperature and reduced pressure to give 112 mg (73%) of light brown material identified as 3,4-dehydroproline by means of its identical mobility on paper chromatography, characteristic and unusual color reaction with ninhydrin, and its ir, which was superimposable on that of a small sample of 3,4-dehydroproline graciously supplied by Ravissa S. A.

Typical Preparation of an Enamine Ester. 3-(2-Carboethoxypyrrolidino)-5-methylcyclohex-2-en-1-one (16a).—To a hot solution of 5.00 g (3.97 × 10^{-2} mol, 10% excess) of 5-methylcyclohexanedione-1,3 (**4**) (freshly recrystallized from ethyl acetate), mp 128–129.5, in 114 ml of benzene was added, rapidly in 1–2-ml portions, a solution of 5.16 g (3.61 × 10^{-2} mol) of ethyl prolinate in 30 ml of benzene. The resulting solution became yellow; a Dean–Stark trap was attached, and a condenser was affixed to it. The reaction mixture was magnetically stirred under reflux for 2.25 hr, after which the separation of water had ceased. The cooled solution was washed twice with one-half saturated aqueous sodium bicarbonate solution and twice with water. The aqueous layers were back-extracted with ether, and the combined organic layers were washed with brine, dried, filtered, and evaporated. A light yellow oil was obtained which, when seeded and scratched, exothermically crystallized to afford 6.39 g (70%) of bright yellow crystals of **16a**, mp 54.5–59°, homogeneous to tlc in chloroform–acetic acid, ethyl acetate–acetic acid, and acetone–acetic acid. Crude **16a**, whether crystalline or oily, from various runs always showed a single component to tlc in the foregoing solvent pair Exemplary melting points of such samples were 54.5–58, 55.5–57.5, and 54.5–59°. On one occasion, the nmr spectrum in $CDCl_3$ of oil, crude **16a** was found, with the exception of slight solvent shifts and the presence of a trace of benzene, to be identical with that of the analytical sample in pyridine.

Recrystallization of a sample of crude **16a**, mp 54.5–58°, from ether gave pale yellow crystals (89% recovery), mp 46–54°, homogeneous to tlc in the aforementioned solvent pairs. Recrystallization from the same solvent gave a 67% return of solid, mp 57–60°. Two additional recrystallizations from ether gave

(14) Commercially available starting materials were used as supplied, except where noted. Liquids were distilled through a vacuum-jacketed, 4-in. Vigreux column; melting points were determined on a Fisher-Johns block, and, like boiling points, are uncorrected. Thin layer chromatograms (tlc) in at least two different solvents or solvent pairs were performed on microscope slides coated with silica gel or alumina, and were visualized with iodine vapor. Merck acid-washed alumina and Fisher 100–200 mesh silica gel were used for elution chromatography. Woelm fluorescent alumina and silica gel (activity II–III) were used for dry-column chromatography. Solutions were dried by washing with saturated sodium chloride solution (brine), followed by treatment with anhydrous sodium sulfate. Solvents were removed by rotary evaporation. Where noted, an atmosphere of dry nitrogen was maintained by use of the apparatus described by W. S. Johnson and W. P. Schneider, *Org. Syn.*, **30**, 18 (1954). We thank the Fisher Scientific Co. for a generous gift of chemicals.

(15) Only representative examples of enamine formation and cyclization are included. For the details of each preparation, *in extenso*, the reader is referred to the experimental sections of the Ph.D. Theses of R. J. F. and J. M. G., Fordham University, 1970 and 1972, respectively.

(16) (a) R. Kuhn and C. Osswald, *Ber.*, **89**, 1423 (1956); (b) H. Rapoport and C. Willson, *J. Amer. Chem. Soc.*, **84**, 630 (1962).

(17) *Cf.* A. Cambrella, P. Gariboldi, and G. Jommi, *Chem. Ind.* (*London*), 583 (1969).

material (73% recovery), mp 58.5–59.5°, and the analytical sample (74% return) as fine white needles: mp 58.5–60.5°; ir ν_{max} (KBr) 1715 and 1608 ($CHCl_3$), 1733, and 1600 cm^{-1}; nmr (C_5H_5N) δ 0.97 (br m, $W_{1/2}$ = 9 Hz) and 1.09 (t, J = 7 Hz) (total 6 H), 1.58–2.76 (br envelope, 9 H), 3.08–3.42 (br, 2 H), 4.19 (q, J = 7 Hz) and 4.47 (s) (total 3 H), 5.19 ppm (s, 1 H); uv λ_{max} 310 nm (ϵ 14,700).

Anal. Calcd for $C_{14}H_{21}NO_3$: C, 66.91; H, 8.42; N, 5.57. Found: C, 66.96; H, 8.45; N, 5.52.

Typical Preparation of Enamine Acid. 3-(2-Carboxypyrrolidino)-5-methylcyclohex-2-en-1-one (16b).—A mixture of 2.75 g (1.05×10^{-2} mol) of crystalline **16a** and 25 ml of 10% (w/w) aqueous sodium hydroxide solution was magnetically stirred at 27° for 5 min. The mixture was then warmed over 15 min to 47°; at the end of this time, all of the solid had dissolved to give a reddish yellow solution. The solution was cooled during 5–8 min to room temperature, diluted with 40 ml of water, and extracted with ether, which was discarded. The vigorously stirred basic aqueous layer, admixed with 50 ml of dichloromethane, was acidified with cold, concentrated hydrochloric acid to pH 2. The layers were separated, and the aqueous layer was extracted with two 50-ml portions of dichloromethane. The combined organic layers were washed twice with 50-ml portions of water, dried, filtered, and evaporated to give 0.901 g (37%) of creamy powder, mp 220–221° (gas evolution at the melting point), homogeneous to tlc in methanol. The infrared spectrum (ν_{max} 1698, 1536–1502 cm^{-1}) of this material was identical with that of a sample of **16a**, mp 225.5–227°, prepared by condensation of sodium prolinate with 5-methylcyclohexanedione-1,3 in 1,2-dimethoxyethane, followed by acidification.

Typical Preparation of Enamine Acid Salt. 3-(Sodium pyrrolidino-2-carboxylate)-5-methylcyclohex-2-en-1-one (16c).—To a solution of 5.70 g (4.25×10^{-2} mol, 10% excess) of 5-methylcyclohexanedione-1,3 (**4**) and 30 ml of *N*,*N*-dimethylformamide in a 125-ml erlenmeyer flask was added 5.62 g (4.11×10^{-2} mol) of sodium prolinate (from L-proline and sodium hydride in 1,2-dimethoxyethane). The flask was tightly stoppered and heated for several minutes on the steam bath, when most of the solid dissolved. The remaining lumps of solid were crushed with the aid of a spatula, whereupon they dissolved, and the resulting orange solution was heated on the steam bath for 20 min, when crystals were deposited. After an additional 12 min on the steam bath, the mixture was allowed to cool over about 30 min to room temperature. The light yellow powder was collected by filtration, washed with *N*,*N*-dimethylformamide, acetone, and finally ether, and dried at reduced pressure at 100° for 20 min. In this manner there was secured 5.93 g (59%) of the desired **16c**, ir ν_{max} 1603, 1541, 1393 cm^{-1}. Without purification, this material was used in the next step.

Typical Cyclization. 9-Acetoxy-6-methyl-8-oxo-1,2,5,6,7,8-hexahydro-3*H*-pyrrolo[1,2-*a*]indole (25).—To 38 ml of hot (80°) acetic anhydride was added 3.80 g (1.55×10^{-2} mol) of the salt **16c**, prepared as described above. The resulting light yellow suspension was stirred in an atmosphere of dry nitrogen at 80–83° for 3.75 hr, and thereafter at 25° for 21 hr. After 20 min at 80–83°, the supernatant liquid had become orange. A small amount of solid adhering to the walls of the vessel above the reaction mixture was washed into it with 10 ml of acetic anhydride.

Thin layer chromatography (ethyl acetate–acetic acid) after 1 hr at 80–83° revealed that the mixture contained the desired **25** as the major component, as well as lesser amounts of a more mobile impurity, and two nearly immobile impurities. After 2.67 hr one of the nearly immobile constituents appeared to have been consumed, and after 3.75 hr at 80–83° and 21 hr at 25°, the composition of the mixture was essentially unchanged.

The reaction mixture was diluted with 200 ml of toluene, and the solvents were evaporated. Two repetitions of this process gave a semisolid residue which was partitioned between ether and water. The organic layer was washed with water, and the aqueous phase was back-extracted with ether. The combined organic layers were washed with one-half saturated aqueous sodium bicarbonate solution, water, and brine. The solution was dried, filtered, and evaporated to give a crystalline residue. A solution of this residue in ether–hexane was refrigerated to afford 1.55 g (40% from **16c**) of light brown prisms, mp 107.5–111.5°, homogeneous to tlc in ethyl acetate–acetic acid.

In another experiment, the suspension of **16c** was heated at gentle reflux for 0.75 hr. After processing as described above, light brown prisms of **25**, mp 107.5–109°, were obtained in 34% yield from **16c**. The crude product was homogeneous to tlc in dichloromethane–acetic acid and in ethyl acetate–acetic acid; its ir spectrum was sufficiently indistinguishable from that of a sample of **25** which had been repeatedly recrystallized.

Several recrystallizations of a specimen of crude **25** gave fine, tan needles: mp 108–109°; ir ν_{max} 1767, 1640 cm^{-1}; uv λ_{max} 255 nm (ϵ 12,300); nmr δ 1.00–1.23 (br, $W_{1/2}$ = 7 Hz, 3 H), 2.27 (s), and *ca.* 2.34–2.97 (br envelope) (total of 12 H), 3.86 ppm (t, J = 7 Hz, 2 H). Several additional recrystallizations from ether containing a little dichloromethane gave the analytical sample as diamond-shaped white prisms, mp 113–114.5°. The medium-resolution mass spectrum of material of this quality exhibited the correct molecular ion at m/e 247.

Anal. Calcd for $C_{14}H_{17}NO_3$: C, 68.00; H, 6.93; N, 5.66. Found: C, 67.92; H, 6.79; N, 5.51.

6-Methyl-8-hydroxy-9-keto-9*H*-pyrrolo[1,2-*a*]indole (32).—9-Acetoxy-6-methyl-8-oxo-1,2,5,6,7,8-hexahydro-3*H*-pyrrolo[1,2-*a*]-indole (**25**) (0.146 g, 0.59 mol) in 20 ml of purified mesitylene was refluxed in the presence of 0.20 g of 30% palladium on carbon catalyst in an atmosphere of dry nitrogen. The reaction was followed by ir. After 13.5 hr of reflux, it appeared that the absorbances due to the acetate carbonyl and to the ketone carbonyl had almost completely disappeared. The reaction was allowed to continue at reflux for an additional 5 hr, and was subsequently stirred for 48 hr at room temperature. The ir at the end of this length of time revealed the complete disappearance of the two aforementioned bands. The reaction mixture was filtered through a Celite 545 pad and the latter was washed thoroughly with hot mesitylene. The filtrate was distilled to a small volume under reduced pressure. Thin layer chromatography revealed the presence of three components having mobilities exhibiting R_f values of 0.3, 0.5, and 0.7. The crude reaction products were absorbed on 1.0 g of Woelm dry column silica gel and subjected to descending column chromatography over a 14.5 × 1.5 in. column of 90.0 g of silica gel, dry packed in nylon tubing. The column was developed with chloroform. A distinct 6.25-in yellow band was apparent followed closely by a 1-in. deep red-brown band. In order to effect better separation of these two bands, elution was continued until the aforementioned yellow band reached the bottom of the column. It was sectioned and extracted with approximately 250 ml of chloroform by means of a Soxhlet extraction apparatus over an 18-hr period. Drying over sodium sulfate, filtering, and evaporation of the solvent yielded 0.06 g (50.4%) of 6-methyl-8-hydroxy-9-keto-9*H*-pyrrolo[1,2-*a*]-indole. Sublimation at 115° afforded material of analytical purity: ir (CCl_4) 1254, 1644, 1689, and 3399 cm^{-1}; nmr (chloroform-d_3) δ 2.32 (s, 3 H) and 6.21–7.43 ppm (m, 6 H); uv max (95% C_2H_5OH) 212 mμ (log ϵ 3.69), 251 (3.83), 286 (3.29), 297 (3.70), and 360 (3.25).

Anal. Calcd for $C_{12}H_9NO_2$: C, 72.35; H, 4.55; N, 7.03. Found: C, 72.17; H, 4.68; N, 6.91.

Registry No.—**3**, 504-02-9; **4**, 4341-24-6; **5**, 126-81-8; **7**, 41263-40-5; **7** Na salt, 41263-41-6; **12**, 3395-35-5; **13**, 41263-42-7; **15**, 41263-43-8; **16a**, 41263-45-0; **16b**, 41263-46-1; **16c**, 41263-47-2; **17a**, 41263-48-3; **17c**, 41263-49-4; **18a**, 41263-50-7; **19a**, 41263-51-8; **20a**, 41263-52-9; **21c**, 41263-53-0; **22c**, 41263-54-1; **23c**, 41263-55-2; **24c**, 412-56-3; **25**, 41263-57-4; **26**, 41263-58-5; **27**, 41312-36-1; **28**, 41312-37-2; **29**, 41263-59-6; **30**, 41312-38-3; **32**, 41263-60-9; *tert*-butyl acetoacetate, 1694-31-1; ethyl *N*-carboethoxyglycinate, 999-30-4; 1,2,3-tricarbethoxypyrrolidinone-4, 41263-63-2; ethyl prolinate, 5817-26-5; sodium prolinate, 33006-43-8; ethyl *N*-benzylglycinate, 6436-90-4.