Cyclol (1,2) Derivatives Related to Ergocornine

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Novel cyclol derivatives (Table I, **15**, **16**) similar in structure to the peptide portion of ergocornine were synthesized. Detailed experimental procedures are given for the preparation of the *cis*-**13a** and the unknown *trans*-**14a** cyclol esters.

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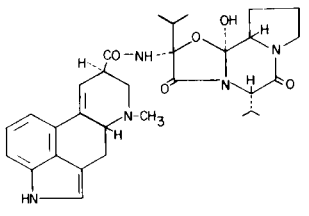
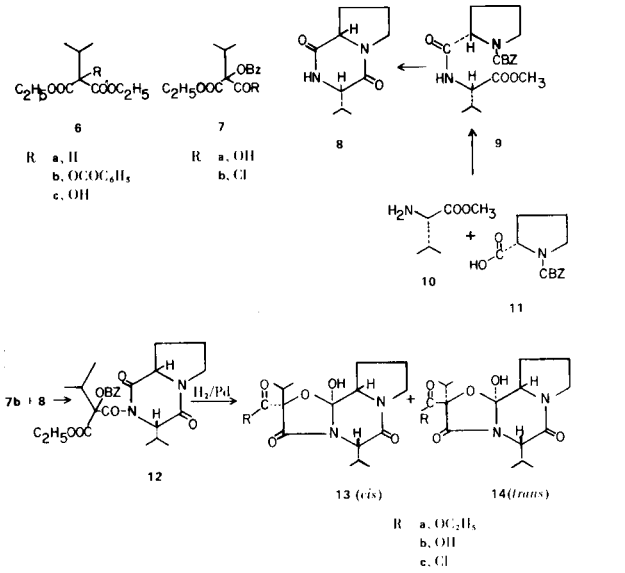
Ergot alkaloids display a wide variety of pharmacological properties including a pronounced effect on the central nervous system (CNS) (3). A few compounds of this class are used as therapeutic agents in the treatment of migraine and in the control of postpartum hemorrhage. Recent reports on the reduction of systemic levels of prolactin and antitumor activity in rats by ergocornine and 2-bromo-α-ergocryptine have focused attention on this class of ergot alkaloids (3b,4). Both compounds belong to the Ergotoxin-group which are cyclic peptides of lysergic acid (5). It is interesting to note that thus far most of the structural modifications in the ergot field have been carried out in the ergoline part of the molecule. Much less attention has been paid to the peptide portion even though it has been observed that the peptide-type ergot alkaloids generally possess more potent pharmacological activity compared to the clavine-type (6).

We therefore carried out the synthesis of novel cyclol compounds **13d** through **14f** (Table I) as part of our ongoing program to prepare potential CNS antineoplastic agents. All of these compounds have the same cyclol part as in ergocornine.



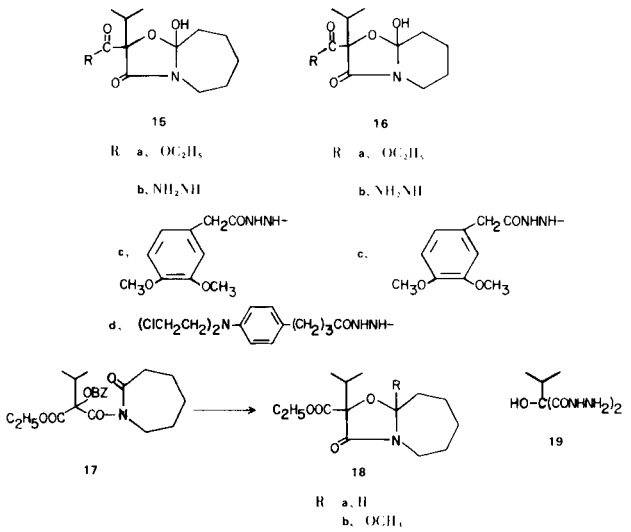
Ergocornine

As a part of this study, two new cyclols **15** and **16** were prepared. Unlike the cyclol **13** or **14**, these new cyclols proved to be unstable as the free acid (**15** and **16**, R = OH). Thus their hydrazides **15b** and **16b** were prepared which provided the amides **15c** and **16c**. In addition, a chlorambucil derivative **15d** was prepared from **15b** for comparison purposes. The synthesis and the anticancer activity of these compounds are described in this paper.



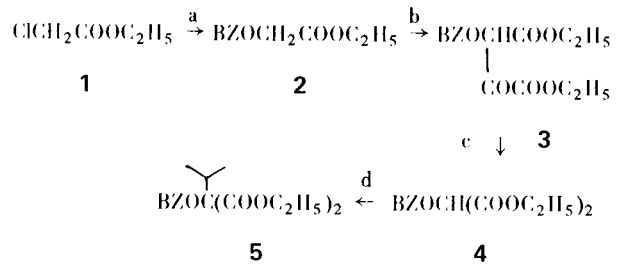
Chemistry.

In preparing the cyclol tripeptide ring system initial effort was made to develop a satisfactory procedure for the preparation of the α-benzyloxyacid chloride **7b** and the diketopiperazine **8**, which are the two basic precursors used to synthesize the cyclols **13a** and **14a**. Although the synthesis of the *cis*-cyclol acid **13b**, and the precursors **7b** and **8** were outlined in the literature by the Sandoz group (7,8) the specific experimental details were lacking in these publications. Much effort was therefore required in finding



the correct experimental conditions for these reactions. In our experience, the reactions used in the preparation of these compounds are quite sensitive to impurities and proceed reproducibly only if the intermediates are carefully purified as outlined in the experimental section. The synthesis of compound **5** which is the key intermediate for the preparation of **7b** was approached by two routes. In the first method (Scheme I), chloroethyl acetate **1** was

Scheme I



(a) Benzyl alcohol/potassium hydroxide in xylene. (b) Sodium hydride/ethyl oxalate. (c) Heat *in vacuo*. (d) Isopropyl iodide/-sodium ethoxide.

transformed into **4** by a literature procedure (9), but it was found necessary to modify the conditions for the preparation of **2** from **1**. Finally **4** was alkylated with isopropyl-iodide to yield **5** (8) in an overall yield of 8% (from **1**). The alternate procedure (8) was carried out from the commerically available diester **6a** by oxidation with dibenzoyl peroxide to the triester **6b**. This triester was converted to the diester alcohol **6c** with sodium ethoxide; the separation of this from ethyl benzoate requires careful fractional distillation. The alcohol **6c** was treated with sodium hydride and benzyl bromide to obtain the benzyl ether **5**. The overall yield for the three steps was 44% and this procedure was preferred to the first method. The ester **5** was saponified to **7a** in ethanolic potassium hydroxide and converted to the acid chloride **7b** using purified thionyl chloride (distilled from quinoline, then boiled linseed oil) in absolute DMF. Careful distillation of the product was carried out, otherwise it tended to decompose. This racemic mixture of acid chlorides (**7b**; overall yield 28%) was used for further transformations.

A modified procedure for the synthesis of the diketopiperazine **8** (7c) was developed. It was prepared by DCC coupling of L-valine methyl ester **10** as the hydrochloride with *N*-carbobenzoxy-L-proline **11** in the presence of triethylamine in dichloromethane at room temperature to give the dipeptide **9**, which was catalytically debenzylated in acetic acid-ethyl acetate with hydrogen on 10% palladium/carbon. Then decarboxylation and cyclization with elimination of methanol was effected by heating in benzene, to give **8** in 71% overall yield. The diketopiperazine is very sensitive to base and epimerizes readily (7a).

The diketopiperazine **8** was acylated by the acid chloride **7b** in dioxane in the presence of diisopropylethylamine. This reaction proceeds *via* *O*-acylation followed by rearrangement to the *N*-acyl product **12** (7b). On catalytic debenzylation in 70% acetic acid by hydrogen on 10% palladium/carbon, spontaneous cyclization occurred stereospecifically (7a) to give the diastereomeric cyclol esters, **13a** and **14a** in 50% yield from **8**.

In that the racemic acid chloride had been employed, a diastereomeric mixture of "*cis*" and "*trans*" cyclols was obtained. The Sandoz group (8) had resolved the acid **7a** and thus had obtained only the *cis*-cyclol ester **13a**. As far as we are aware, the *trans* ester **14a** has not been reported.

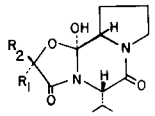
The *cis-trans* ester mixture was easily separated on a silica gel column by chromatography due to the difference in polarity attributed to the hydrogen bonding in the *cis*-compound **13a**, which is not possible in the *trans*-compound **14a**. The *cis*-cyclol ester **13a** was found to be identical in all respects with an authentic sample generously provided by Sandoz, Ltd.

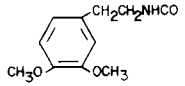
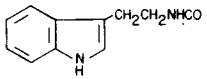
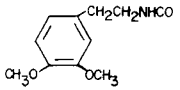
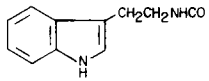
Each cyclol ester was saponified in cold 1*N* sodium hydroxide to give the corresponding acids **13b** and **14b**, (the proton in the proline ring is no longer sensitive to base) which were converted to their acid chlorides on reaction with phosphorus pentachloride. They appeared to be stable and resistant to rapid atmospheric hydrolysis.

From the *cis* and *trans*-cyclol acid chlorides, **13c** and **14c**, the amides of phenethylamine, 3′,4′-dimethoxyphenethylamine and tryptamine (Table I) were prepared by reaction with the appropriate amine in the presence of triethylamine in anhydrous dioxane for 43 hours to 7 days and purified by column chromatography and recrystallization

Table I

Amides from **13b** and **14b**



Compound Number	R_1	R_2	Reaction Time	M.p. °	Crystn. Solvent	Yield %	Mass Spec m/e ($M.^+$)	Mol. Formula	*Anal.* Calcd. Found	
13d	Ph-CH_2CH_2NHCO-	-$CH(CH_3)_2$	7 days	(a)	–	78	443	$C_{24}H_{33}N_3O_5$	C, 65.01; 65.14;	H, 7.45; 7.51; N, 9.48; 9.70.
13e		-$CH(CH_3)_2$	3.5 days	139.5-140.5	isopropyl ether/ethyl acetate	76	503	$C_{26}H_{37}N_3O_7$	C, 62.01; 62.05;	H, 7.44; 7.47; N, 8.35; 8.36.
13f		-$CH(CH_3)_2$	46 hours	104-105	isopropyl ether	40	482	$C_{26}H_{34}N_4O_5$	C, 64.73; 65.21;	H, 7.05; 7.84; N, 11.62; 11.45.
14d (b)	-$CH(CH_3)_2$	Ph-CH_2CH_2NHCO-	4 days	164-166	isopropyl ether/chloroform (3:1)	78	443	$C_{24}H_{33}N_3O_5$	C, 65.01; 65.04;	H, 7.45; 7.60; N, 9.48; 9.42.
14e	-$CH(CH_3)_2$		4 days	(a)	–	63	503	$C_{26}H_{37}N_3O_7$	C, 62.01; 62.06;	H, 7.44; 7.71; N, 8.35; 8.65.
14f (b)	-$CH(CH_3)_2$		43 hours	230-233	C_2H_5OH	82	482	$C_{26}H_{34}N_4O_5$	C, 64.73; 64.81;	H, 7.05; 7.38; N, 11.62; 11.55.

The material after chromatography failed to crystallize and was obtained as a foam. (b) No chromatographic purification was necessary.

The new cyclols **15a** and **16a** were similarily prepared from **7b** and the appropriate lactam (2). The acylations proceeded smoothly in a mixture of pyridine/benzene at 0° which on catalytic debenzylation in 60% acetic acid by hydrogen on 10% palladium/carbon furnished the racemic cyclol esters **15a** and **16a**. In the preparation of **15a**, when the catalytic debenzylation of **17** was carried out either in 90% acetic acid or allowed to absorb 2 moles of hydrogen in 60% acetic acid, the reduced cyclol **18a** was formed. The same compound was obtained by hydrogenation of **15a** in glacial acetic acid. Confirmation of the structure of **15a** was obtained by methylation of the hydroxy group with silver oxide/methyliodide to give **18b**. Although the presence of tautomeric forms in cyclols (2,7a) is well known, the nmr or ir data did not show the presence of ring opened tautomeric forms in either **15a** or **16a**. However, the preparation of the acid (**15**, R = OH) from **15a** under a variety of hydrolytic conditions was unsuccessful. In every case the hydrolysis was accompanied by decarboxylation to give a high molecular weight compound m/e 390 ($M.^{+}$), 196, 194. The difference in the behavior of the cyclol **15a** compared to **13a** or **14a** in the presence of base is noteworthy. It could be attributed to the difference in the various amounts of tautomeric forms in **15** compared to the more rigid cyclol **13** or **14**.

Nevertheless, **15a** and **16a** were converted to the hydrazides **15b** and **16b** on careful treatment with 1 mole of hydrazine. Treatment with excess hydrazine resulted in the cleavage of the cyclol **15a** to yield **19**. The structure of **19** was confirmed by its synthesis from **6c**.

Treatment of **15b** with 3,4-dimethoxyphenyl acetic acid and DCC gave **15c**, whereas **16c** was obtained by acylation of **16b**. Similarly, the acid chloride of chlorambucil (oxalyl chloride/benzene) on treatment with **15b** in pyridine/benzene furnished **15d** as a *cis/trans* mixture which was readily separated by thick layer chromatography to give the two isomers.

Ergocornine, all compounds listed in Table I, **15c**, **15d** and **16c** were tested in the lymphoid leukemia L1210 system by standard NCI protocol (10). Evaluations were made as mean survival time and compounds showing percent/control (T/C) > 125 are considered active in this test system.

Ergocornine was found inactive in this test (L1210) even when the regimen was changed to a daily injection for nine doses. However, in P388 leukemia test system, it was marginally active showing a T/C of 125 at 100 mg./kg. All the other compounds except **15d** were found inactive. The chlorambucil derivative **15d** was active (P388) with a T/C of 220 (2 cures, *i.e.*, 30 day survivors) and 175 at 100 and 50 mg./kg. respectively. In the same tumor system

EXPERIMENTAL

All melting points are uncorrected and were determined on a Thomas-Hoover apparatus. The ir spectra were recorded on a Perkin-Elmer Model 700 instrument and the nmr spectra were measured on a Varian T-60 spectrometer. A Varian Aerograph Model 1440 equipped with a 6 ft. x 1/8 in. stainless steel column packed with a 2% OV-17 on 100-200 mesh Gas Chrom Q and a flame ionization detector was used for glc analysis. Where spectral data is not given compounds showed ir and nmr consistent with the assigned structures. Tlc used silica gel (Adsorbosil-2) on microscope slides and visualized in iodine. Microanalyses were performed by Spang Microanalytical Laboratories, Ann Arbor, Michigan.

Compounds **13** and **14** and those listed in Table I are optically active and have the stereochemistry as shown wehreas cyclols **15** and **16** are racemic mixtures of *cis* and *trans* isomers and consequently their derivatives are also *cis/trans* mixtures.

Ethyl Benzyloxyacetate (**2**).

The method described by Hammond, *et al.*, (9) was followed. However, the use of 10 *N* sodium hydroxide for hydrolysis as given in their procedure resulted in a very poor yield of **2**. The following modified procedure was therefore used.

A mixture of 220 g. (2.03 mole) of benzyl alcohol, 112 g. (2.0 mole) of potassium hydroxide and 1.4 l. of xylene was refluxed until azeotropic removal of water was complete (overnight). The reaction was cooled to 60° and 260 g. (2.13 mole) of ethyl chloroacetate (**1**) was added at a controlled rate to keep the reaction temperature below 110°. Refluxing at 110-120° was continued until the reaction mixture was almost neutral (about 2 hours).

After cooling the product was poured into water and 200 ml. of ether was added. The organic layer was separated and the aqueous layer was acidified with hydrochloric acid and reextracted with 2 x 100 ml. of ether. The combined ether layer was washed with water, dried and concentrated to give an oil which was hydrolyzed by heating with 2*N* sodium hydroxide for 8 hours. The product was cooled, acidified with hydrochloric acid and extracted with ether. Evaporation of the organic solvent left an oil, which was reesterified by refluxing with 500 ml. of ethanol and a few drops of sulfuric acid. After workup, the residue was distilled to give 108 g. (28%) of **2**.

Diethyl Isopropylbenzoyloxymalonate (**6b**).

To a four liter reaction kettle were added 50.5 g. (1.2 moles) of a 57% mineral oil dispersion of sodium hydride and 1 l. of benzene (dried by prolonged standing over molecular sieve). The slurry was stirred and cooled with an ice bath, and 202.0 g. (1.0 mole) of diethyl isopropylmalonate (**6a**) was added at a rapid drop-rate. When addition was complete, the slurry was warmed to 50° for 1 hour. The reaction mixture was then cooled with an ice-bath (below 10°) and a solution of 242.9 g. (1.0 mole) of dibenzoylperoxide in 2.4 l. of dry benzene was added over a period of 3 hours. The mixture was warmed to 40° for 1 hour, cooled with an ice bath again, and 20 g. of activated charcoal added in several portions to decompose any unreacted peroxide. The mixture was then again warmed to 40° for 1 hour, cooled, 300 ml. of water added, and filtered. The charcoal residue was washed with 300 ml. of benzene. The layers were separated and the benzene phase washed with 250 ml. of water, dried (sodium sulfate), and concentrated. The resultant oil was further concentrated warming to 75° for 1 hour. The remaining light yellow oil, which weighed

Diethyl Isopropyltartronate (**6c**).

A 2 l., three-necked flask was flushed with dry nitrogen and 22.3 g. of sodium was added in small pieces. Absolute ethanol (444 ml.) was added at such a rate to maintain a slow reflux. When the reaction was complete, the nitrogen was stopped and the solution heated to 35-40°. The crude mixture of **6b** was added rapidly and the resulting mixture stirred for 8 minutes at 35-40° (cooling may be necessary). The mixture was then cooled in an ice bath and 58.5 g. of glacial acetic acid added slowly keeping the temperature below 15° followed by the addition of 800 ml. of water and 200 ml. of ether. The layers were separated and the aqueous phase extracted with three 250 ml. portions of ether. The ether layer was washed with 100 ml. of saturated sodium bicarbonate solution and 150 ml. of water. The ether layer was dried (sodium sulfate) and concentrated to afford a yellow oil. This oil was carefully distilled through a six inch column wrapped with glass wool to yield at first ethylbenzoate b.p. 24-25°/0.01-0.003 mm, oil bath temperature 42-45° (it is essential to keep the oil bath below 45° until all the ethyl benzoate has distilled) followed by **6c** as a colorless oil, b.p. 48-51°/0.01-0.003 mm, oil bath temperature 55-63° (lit. (8) 64-67°/0.3 mm). The yield was 135 g. (62% from **6a**) and the material was pure by glc; ir (neat): 3520 (OH) and 1740 (CO) cm^{-1}.

Diethyl Isopropylbenzyloxymalonate (**5**) (8).

In a 3 l. reaction kettle, 54.7 g. (1.3 moles) of a 57% mineral oil dispersion of sodium hydride was added followed by the addition of 800 ml. of dry *N,N*-dimethylacetamide. With stirring and cooling in an ice bath, 218.2 g. (1.0 mole) of **6c** was added dropwise keeping the temperature below 30°. When addition was complete, the slurry was warmed to 70°. Heating was then discontinued and 205.0 g. (1.2 moles) of benzyl bromide was added at a rate sufficient to maintain the temperature at 70-75°. When addition was complete, the mixture was warmed to 75° for 2 hours. After this time, 130 ml. of absolute ethanol were added dropwise to decompose excess sodium hydride and benzyl bromide. The temperature was then maintained at 75° for an additional 30 minutes and the reaction mixture cooled to room temperature. At this time 78 g. (1.3 moles) of glacial acetic acid was added dropwise followed by the addition of 1.5 liters of water. The mixture was stirred well for 30 minutes and then 200 ml. of ether were added. The layers were separated and the aqueous layer extracted with four 200 ml. portions of ether. The ether layer was finally washed with 200 ml. of saturated sodium bicarbonate solution, 200 ml. of water, and dried (sodium sulfate). After filtration and concentration, the semi-viscous orange oil was distilled through a seven inch Vigreux column. After a small forerun, the product (220 g., 71%) distilled at 113-118°/0.015-0.010 mm/-oil bath 152-155° and was pure by glc; ir (neat): 1738 cm^{-1}.

Racemic Ethyl Isopropylbenzyloxymalonic Acid (**7a**) (8).

To a 2 l. flask, a solution of 154.0 g. (0.50 mole) of **5** in 400 ml. of absolute ethanol was added. After cooling in an ice-bath, 733 ml. (1.03 moles) of a 1.4*N* solution of potassium hydroxide in absolute ethanol was added slowly with stirring and the solution was allowed to stir slowly overnight. Ice (500 g.) was then added and the *p*H was adjusted to 8 by the addition of approximately 15 ml. of concentrated phosphoric acid. The ethanol was then removed keeping the temperature below 40°. The remaining oil was diluted with 500 ml. of water and the *p*H again adjusted to 8-9 by the addition of approximately 30 ml. of 4*N* sodium hydroxide. This solution was washed three times with 200 ml. portions of ether. The aqueous phase was then cooled by means of a dry ice-acetone bath to -5°. Ether (500 ml.) was added and with vigorous stirring, the *p*H was adjusted to 2 by the addition of approximately 100 ml. of concentrated phosphoric acid. The layers were separated and the aqueous phase extracted twice with 200 ml. portions of ether. The combined ether layer was washed with four 150 ml. portions of water and then dried (sodium sulfate). After concentration (bath temperature <50°) a viscous oil remained, which on further concentration by evacuation on the vacuum pump for 24 hours yielded 105 g. (74%) of a light yellow oil. It showed one spot on tlc (methanol:chloroform; 3:7), R_f = 0.48 and was stored at 0°; ir (neat): 1743 and 1710 cm^{-1}.

Racemic Ethyl Isopropylbenzyloxymalonyl Chloride (**7b**) (8).

Solutions of 24.53 g. (0.0875 mole) of racemic **7a** in 40 ml. of dry (molecular sieve) dichloromethane and 8.2 ml. (0.1138 mole) of purified thionyl chloride in 10 ml. of dry dichloromethane were cooled to -20° in separate flasks. The malonate half-ester solution was then vigorously stirred and 14 ml. of dry (molecular sieve) DMF added. Next the thionyl chloride solution was added slowly. The resultant clear solution was allowed to stir overnight at room temperature. The light yellow solution was then flash evaporated (water bath at room temperature) and finally freed of volatile components by stirring under high vacuum. The resultant solution was allowed to stand at -10° overnight. After this time the light yellow mixture was filtered through glass wool into a 50 ml. flask containing a 1 inch stir bar and attached to a distillation head connected to a vacuum system. The flask was stirred until a good vacuum (~0.05 mm) was attained. Then the flask was immersed into an oil bath heated to ~70° until all of the low boiling liquid is distilled. The flask was then allowed to reach room temperature and the receiver changed. When maximum vacuum was again attained, the flask was immersed into an oil bath set at 120-130° and a clear distillate soon came over, b.p. 115-118°/0.20-0.05 mm, oil bath ~135°. The colorless distillate was then redistilled in a clean apparatus, b.p. 105-109°/0.005-0.003 mm, oil bath ~135°, yield 22 g. (85%). The product was stored in a dessicated amber bottle at 0°; nmr (deuteriochloroform): δ 7.58-7.18 (m, 5H, Ar), 4.80 (s, 2H, CH_2), 4.29 (q, 2H, CH_2), 2.98-2.40 (m, 1H, CH), and 1.44-0.92 (m, 9H, CH_3); ir (neat): 1745 and 1790 cm^{-1}.

(3S,8aS)-1,4-Dioxo-3-isopropyloctahydropyrrolo[1,2-*a*]pyrazine (**8**).

To a stirred suspension of 55 g. (0.22 mole) of carbobenzoxy-L-proline (**11**), 33.5 g. (0.20 mole) L-valine methyl ester hydrochloride and 21.2 g. (0.21 mole) of dry triethylamine in dry dichloromethane (350 ml.) was added a solution of 40.9 g. (0.20 mole) of DCC in dry dichloromethane (150 ml.). After 16 hours at room temperature, the mixture was filtered, washed consecutively with water, 1*N* hydrochloric acid saturated, sodium bicarbonate, saturated brine and dried over sodium sulfate. Concentration *in vacuo* afforded a yellowish oil which was dissolved in 100 ml. of ethyl acetate and cooled at -10° overnight. The mixture containing **9** was filtered and added to a stirred suspension of 5 g. of palladium/carbon in 250 ml. of acetic acid and 150 ml. of ethyl acetate. Hydrogenolysis was carried out overnight with a slow stream of hydrogen. When no presence of **9** was observed on tlc (R_f = 0.43, 5% methanol/chloroform), the mixture was filtered through Celite and concentrated *in vacuo*. The resulting oil was taken up in 500 ml. of benzene and refluxed overnight protected from moisture. Concentration *in vacuo* afforded a colorless solid which was recrystallized in two crops from hot ethyl acetate to give **8** (28 g., 71%) as colorless needles, m.p. 190-192°, lit. (7c) m.p. 190-192°; nmr (deuteriochloroform): δ 0.98 (d, 3H), 1.05

(d, 3H), 1.80-2.83 (m, 5H), 3.41-3.78 (m, 2H), 3.82-4.25 (m, 2H), 7.00 (s, 1H); ir (potassium bromide): 1660 cm^{-1}; m/e 196 ($M.^+$), 181 (M -CH_3), 154 (M -C_3H_6); $[\alpha]_D^{28}$ -133° (C 0.7, ethanol), lit. (7c) $[\alpha]_D^{20}$ -159° (C 0.7, ethanol).

(2*R* and 2*S*,3*S*,8a*R*)-2-(2-Benzyloxy-2-ethoxycarbonyl-3-methylbutyryl)-1,4-dioxo-3-isopropyloctahydropyrrolo[1,2-*a*]pyrazine (**12**).

To a 500 ml. flask with a magnetic stirrer, were added 7.35 g. (37.50 mmoles) of **8** and 200 ml. of dry (molecular sieve) dioxane. The flask was protected from moisture by a drying tube and cooled in an ice-bath; the contents were stirred under a blanket of dry nitrogen and 9.70 g. (75.0 mmoles) of specially purified (treated with phenyl isocyanate and distilled four times after filtration) diisopropylethylamine were added. Finally, 11.20 g. (37.50 mmoles) of **7b** were added and the colorless frozen mixture allowed to stir for 15 minutes. The ice-bath was then removed and stirring continued for 1 hour. The colorless mixture was then immersed into an oil bath warmed to 70°. After 1.5 hours the faintly yellow solution was cooled in an ice-bath for 10 minutes and 250 ml. of ether were added. After stirring for 15 minutes, 200 ml. of ice-cold 2*N* hydrochloric acid was added and the mixture shaken for 30 minutes with intermittent cooling in an ice-bath. The layers were separated and the aqueous layer washed 3 x 150 ml. of ether. The combined ether layer was washed with 150 ml. of ice-cold saturated aqueous sodium bicarbonate solution and dried with a mixture of sodium sulfate and 50-200 mesh activated decolorizing charcoal. The mixture was filtered and flash evaporated (water-bath at room temperature) to afford a light yellow mixture of oil and solid. It shows one main spot on tlc, 5% methanol:chloroform, R_f = 0.64. This product was used immediately without further purification in the subsequent reaction.

(2*R* and 2*S*,5*S*,10a*S*,10b*S*)-2-Ethoxycarbonyl-2,5-diisopropyl-10b-hydroxy-3,6-dioxooctahydrooxazolo[3,2-*a*]pyrrolo[2,1-*c*]pyrazine (**13a** and **14a**).

To a 500 ml. 3-necked flask carrying a magnetic stirrer and an addition funnel, 5 g. of palladium/carbon and 100 ml. of 70% acetic acid were added (making sure all the catalyst was wet). Crude **12** was dissolved in 300 ml. of 70% acetic acid and added to the addition funnel which was then connected to a volumetric buret filled with hydrogen. The catalyst mixture was stirred for 1 hour and then the solution of **12** was added. After 24 hours, 935 ml. of hydrogen was absorbed (theoretical 840 ml.). The mixture was filtered through Celite and the residue washed well with ethyl acetate. The very light yellow filtrate was evaporated (water-bath <35°) to afford a light yellow oil. This oil was dissolved in 500 ml. of ethyl acetate and washed with 4 x 75 ml. of ice cold saturated sodium chloride solution. After drying (sodium sulfate) and concentration *in vacuo* at room temperature, a viscous light yellow oil was obtained, which weighed ~8 g. (58% yield from **7b**) and showed two spots on tlc; 5% methanol/chloroform, R_f = 0.42 and 0.53; ir (neat): 1740 and 1660 cm^{-1}. It was dissolved in 20 ml. of diisopropyl ether and the resulting solution stored at 0° for 48 hours. After this time, the clear crystals were filtered and dried to give 1.82 g. of **14a**, which after two recrystallizations from ethyl acetate/diisopropyl ether gave colorless needles, m.p. 150-151°; $[\alpha]_D^{28}$ -47.2° (C2, ethanol); nmr (deuteriochloroform): δ 0.52-1.15 (m, 12H, CH_3), 1.28 (t, 3H, CH_3), 1.52-3.12 (m, 6H), 3.18-4.35 (m, 5H), 4.55 (d, 1H, CH), and 5.32 ppm (s, 1H, OH); ir (potassium bromide): 1737 and 1619 cm^{-1}; m/e 368 ($M.^+$), 326 (M -C_3H_6); 295 (M -COOEt); one spot on tlc (5% methanol:chloroform), R_f = 0.42.

Anal. Calcd. for $C_{18}H_{28}N_2O_6$: C, 58.67; H, 7.67; N, 7.60. Found: C, 58.67; H, 7.59; N, 7.53.

The filtrate was concentrated to afford ~6 g. of an oil, which was then column chromatographed through 120 g. of Woelm silica gel (0.05-0.20 mm) with chloroform. A total of sixty-five 50 ml. fractions were collected. Fractions 24-29 contained the faster moving cyclol **13a** (2.85 g.) and fractions 45-64 contained **14a** (0.63 g.). This sample of **13a** was identical in all respects (m.p., ir, nmr, ms, glc) to an authentic sample kindly provided by Sandoz.

(2*R*,5*S*,10a*S*,10b*S*)-2-Carboxy-2,5-diisopropyl-10b-hydroxy-3,6-dioxooctahydrooxazolo[3,2-*a*]pyrrolo[2,1-*c*]pyrazine (**13b**).

A mixture of 2.04 g. (5.54 mmoles) of **13a** and 5.82 ml. (11.63 mmoles) of ice cold 2.0*N* sodium hydroxide was stirred well for 5 hours at room temperature under nitrogen. The *p*H was adjusted to 8.5-9.0 with cold 2*N* hydrochloric acid and the solution stirred at 0° for 15 minutes. It was extracted with 100 ml. of ethyl acetate. The remaining aqueous layer was then cooled with an ice-bath and 100 ml. of ethyl acetate added. Enough cold 2*N* hydrochloric acid was then added to bring the *p*H to 2. The layers were separated and the aqueous layer extracted with 100 ml. of ethyl acetate. The combined organic phase was dried (sodium sulfate) and concentrated *in vacuo* (<35°) to give **13b** as a white solid (12) (91% yield) m.p. ~145° (gas evolution) (lit., (8) as monohydrate m.p. 162-164°); ir (potassium bromide): 1725, 1608 cm^{-1}; mass spectrum m/e 340 ($M.^+$), 298 (M -C_3H_6), 278 (M -H_2O, CO_2).

(2*R*,5*S*,10a*S*,10b*S*)-2-Chloroformyl-10b-hydroxy-2,5-diisopropyl-3,6-dioxooctahydro-8*H*-oxazolo[3,2-*a*]pyrrolo[2,1-*c*]pyrazine (**13c**).

To a flask was added 496 mg. (2.38 mmoles) of phosphorus pentachloride (freshly sublimed and ground to a fine powder) and 20 ml. of absolute ether. The white slurry was stirred under a blanket of nitrogen for 1 hour. The clear solution was cooled in an ice-bath and 584 mg. (1.72 mmoles) of **13b** (freshly dried under vacuum at room temperature for 3 hours) was added. After *ca.* 5 minutes, the ice-bath was removed and the resulting solution stirred for 3 hours. Forty ml. of dry (molecular sieve) petroleum ether was added dropwise and the resulting mixture cooled in a dry ice-2-propanol bath for 1 hour. The white solid was then filtered under a dry nitrogen cap and washed with 40 ml. of dry petroleum ether. After drying in the vacuum oven for 1 hour, the white solid weighed 474 mg. (77% yield); ir (chloroform): 1790, 1735, and 1630 cm^{-1}; m/e 358 ($M.^+$) and 316 (M -C_3H_6). This material was used immediately without further purification.

(2*S*,5*S*,10a*S*,10b*S*)-2-Carboxy-2,5-diisopropyl-10b-hydroxy-3,6-dioxooctahydrooxazolo[3,2-*a*]pyrrolo[2,1-*c*]pyrazine (**14b**).

This compound was prepared from **14a** as described for **13b** (79% yield), m.p. 162-164° (gas evolution); nmr (DMSO-d_6): δ 0.80-1.33 (m, 12H, CH_3), 1.73-2.87 (m, 6H), 3.27-4.27 (m, 3H), 4.27-4.57 (d, 1H, NCHCO), 5.23-6.00 (broad s, 3H, 1 Ph, deuterium oxide exchangeable), and 8.40 ppm (s, 1H, deuterium oxide exchangeable); ir (potassium bromide): 1720, 1680, and 1618 cm^{-1}; mass spectrum: m/e 340 ($M.^+$), 297 (M -C_3H_7), and 278 (M -H_2O, CO_2).

(2*S*,5*S*,10a*S*,10b*S*)-2-Chloroformyl-10b-hydroxy-2,5-diisopropyl-3,6-dioxooctahydro-8*H*-oxazolo[3,2-*a*]pyrrolo[2,1-*c*]pyrazine (**14c**).

This compound was prepared as **13c** in 98% yield; ir (neat): 1790, 1730 and 1635 cm^{-1}; mass spectrum: m/e 358 ($M.^+$), 343 (M -CH_3), 340 (M -H_2O), 322 (M -HCl) and 316 (M -C_3H_6).

The various amides in the *cis* and the *trans* series are listed in Table I. They were prepared according to the method described for **13e**.

(2*R*,5*S*,10*aS*,10*bS*)-10b-Hydroxy-2,5-diisopropyl-2-[2-(3,4-dimethoxyphenyl)ethyl]carbamoyl-3,6-dioxooctahydro-8*H*-oxazolo-[3,2-*a*]pyrrolo[2,1-*c*]pyrazine (**13e**).

Under nitrogen, a solution of 433 mg. (2.39 mmoles) of β-3,4-dimethoxyphenylethylamine (freshly distilled) in 25 ml. of dry (molecular sieve) dioxane was added to a solution of 347 mg. (3.44 mmoles) of triethylamine in 25 ml. of dry dioxane. To this mixture, 474 mg. (1.32 mmoles) of **13c** was added followed by 25 ml. of dry dioxane. The resulting white slurry was allowed to stir at room temperature under nitrogen for 3.5 days. The reaction was quenched by the addition of ice cold 0.5*N* hydrochloric acid to give a clear solution, which was extracted with 200 ml. of chloroform. After separation of the layers, the aqueous layer was extracted with an additional 100 ml. of chloroform. The combined organic layer was dried (sodium sulfate) and concentrated (<40°) to give a viscous pale yellow oil, which was chromatographed through 0.05-0.20 mm Woelm silica gel (35 g.) with chloroform. Thirty-50 ml. fractions were collected. Fractions 13-29 upon concentration gave a viscous oil which crystallized upon trituration with isopropyl ether. The white powder, 503 mg. (76% yield), was recrystallized from isopropyl ether/ethyl acetate, m.p. 139.5-140.5°; nmr (deuteriochloroform): δ 0.67-1.27 (m, 12H, CH_3), 1.63-3.03 (m, 8H), 3.33-3.80 (m, 5H), 3.97 (s, 6H, OCH_3), 4.47 (d, 1H, CH), and 6.00-7.13 (m, 5H, 3 aromatic and 2 deuterium oxide exchangeable); ir (potassium bromide): 3380, 1720 and and 1640 cm^{-1}; mass spectrum: m/e 503 ($M.^+$), 485 ($M-H_2O$), and 472 ($M-OCH_3$).

N-(2-Benzyloxy-2-ethoxycarbonyl-3-methylbutyryl)-ε-caprolactam (**17**).

A solution of 0.316 g. (0.004 mole) of ε-caprolactam in 0.316 g. (0.004 mole) of pyridine and 10 ml. of benzene was cooled until frozen. To the resulting solidified material, 0.298 g. (0.001 mole) of **7b** was added in portions and the mixture was kept overnight at 0°. The mixture was then refluxed for 12 hours. It was cooled and treated with 20 ml. of ice-water and 20 ml. of benzene. The organic layer was separated and the aqueous layer reextracted with 3 x 50 ml. of benzene. The combined benzene solution was washed with ice cold 10% sodium bicarbonate and again with water. After drying (magnesium sulfate), the solution was concentrated *in vacuo*. The resulting oil solidified on keeping and yielded 0.362 g. (97%) of **17**. It was recrystallized from hexane/ether as colorless crystals, m.p. 60-62°; ir (nujol): 1753, 1722 and 1680 cm^{-1}; mass spectrum: m/e 375 ($M.^+$).

Anal. Calcd. for $C_{21}H_{29}NO_5$: C, 67.20; H, 7.73; N, 3.73. Found: C, 67.22; H, 7.55; N, 3.64.

Octahydro-9a-hydroxy-2-isopropyl-3-oxooxazolo[3,2-*a*]azepine-2-carboxylic Acid, Ethyl Ester (**15a**).

A solution of 3 g. (0.008 mole) of **17** in 80 ml. of 60% acetic acid was hydrogenated under atmospheric pressure over 0.5 g. of 10% palladium/carbon. After 1 mole of hydrogen was absorbed the reaction was stopped, the product was filtered from Celite, and the filtrate was concentrated *in vacuo*. The resulting oil was dissolved in chloroform. After washing with 5% sodium bicarbonate followed by water, the organic layer was dried (magnesium sulfate) and concentrated *in vacuo* to give **15a** as a colorless oil 2.1 g. (92% yield). It showed a single spot on tlc (50:50 petroleum ether/ether); ir (neat): 3450, 1720 cm^{-1}; nmr (deuteriochloroform): δ 0.96, 0.99 (2d, 6H, $C(CH_3)_2$), 1.35 (t, 3H, OCH_2CH_3), 1.6-2.5 (br, m, 8H), 2.86 (heptet, 1H, $CH(CH_3)_2$), 3.08 (br, 1H), 3.91 (br, d, 1H), 4.4, 4.42 (q, 2H, OCH_2CH_3), 5.53 (br, 1H, deuterium oxide exchangeable); mass spectrum: m/e 285 ($M.^+$).

Anal. Calcd. for $C_{14}H_{23}NO_5$: C, 58.90; H, 8.07; N, 4.90. Found: C, 58.93; H, 8.06; N, 4.98.

When 0.8 g. (2.13 mmoles) of **17** in 40 ml. of 60% acetic acid was hydrogenated with 1.2 g. of 10% palladium/carbon until no more hydrogen was absorbed or alternatively the reduction was carried out in 90% acetic acid, the product obtained after workup as in **15a** was **18a**, 0.52 g. (91% yield); ir (dichloromethane): 1745 and 1715 cm^{-1}; nmr (deuteriochloroform): δ 0.92, 0.93 (2d, 6H, $C(CH_3)_2$), 1.3 (t, 3H, OCH_2CH_3), 1.46-2.13 (br, m, 8H), 2.68 (m, 1H, $CH(CH_3)_2$), 2.98 (br, 1H), 3.76 (br, 1H), 4.27, 4.29 (q, 2H, OCH_2CH_3), 5.41 (m, 1H, O-CH-N); mass spectrum: m/e 269 ($M.^+$).

Anal. Calcd. for $C_{14}H_{23}NO_4$: C, 62.40; H, 8.50; N, 5.20. Found: C, 62.23; H, 8.46; N, 5.18. Similarly, reduction of **15a** in glacial acetic acid gave **18a** (identical in all respects).

On treatment of 1 g. (3.5 mmoles) of **15a** with excess freshly prepared silver oxide, 10 ml. of methyl iodide and refluxing the mixture for 3 hours followed by filtration and extraction with chloroform gave **18b** as a colorless oil, 0.95 g. (91%); nmr (deuteriochloroform): δ 3.33 (s, 3H, OCH_3); mass spectrum: m/e 299 ($M.^+$).

Anal. Calcd. for $C_{15}H_{25}NO_5$: C, 60.20; H, 8.30; N, 4.60. Found: C, 60.09; H, 8.11; N, 4.68.

Octahydro-9a-hydroxy-2-isopropyl-3-oxooxazolo[3,2-*a*]azepine-2-carboxylic Acid, Hydrazide (**15b**).

A mixture of 2.85 g. (0.01 mole) of the cyclol ester **15a** and 0.36 g. of 97% hydrazine hydrate in 10 ml. of ethanol was refluxed for 1 hour. The mixture was concentrated *in vacuo* to give an oily residue which was crystallized from chloroform/benzene, m.p. 145-146° (1.8 g., 66% yield); ir (nujol): 3400, 3350, 1722 cm^{-1}; nmr (deuteriochloroform and deuterium oxide): δ 0.91 (d, 6H, $C(CH_3)_2$), 1.60 (br, s, 6H), 2.27 (br, 2H), 2.5 (m, 1H, $CH(CH_3)_2$), 3.11 (br, 1H), 3.75 (br, 1H); mass spectrum: m/e 271 ($M.^+$).

Anal. Calcd. for $C_{12}H_{21}N_3O_4$: C, 53.10; H, 7.70; N, 15.50. Found: C, 53.08; H, 7.60; N, 15.35.

Similar treatment of 0.2 g. (0.7 mmoles) of **15a** with 0.5 ml. of 65% hydrazine hydrate in 3 ml. of ethanol gave after chromatography on silica gel and eluted with graded mixtures of chloroform/methanol (75:25), compound **19** which was crystallized from ethanol/ether, m.p. 140-141°; mass spectrum: m/e 190 ($M.^+$) and was identical in all respects with a sample similarly prepared (using 97% hydrazine hydrate) from **6c**.

Anal. Calcd. for $C_6H_{14}N_4O_3$: C, 37.80; H, 7.30; N, 29.4. Found: C, 37.83; H, 7.21; N, 29.3.

1-(3,4-Dimethoxyphenylacetic)-2-(octahydro-9a-hydroxy-2-isopropyl-3-oxooxazolo[3,2-*a*]azepine-2-carbonyl)hydrazine (**15c**).

To a solution of 136 mg. (0.5 mmoles) of **15b** and 100 mg. (0.51 mmoles) of 3,4-dimethoxyphenylacetic acid (Aldrich) in 6 ml. of dry dichloromethane, 115 mg. (0.55 mmole) of dicyclohexyldicarbodiimide (DCC) in 4 ml. of dichloromethane was added with stirring. A white precipitate appeared after a few minutes. Stirring was continued for 5 hours and the reaction mixture was left overnight after filtration of the solid, 10 ml. of dichloromethane were added to the filtrate which was washed with sodium bicarbonate solution followed by water. After drying the solvent was removed *in vacuo* and the residue was dissolved in a minimum quantity of methanol. The solution was filtered and on addition

of isopropyl ether with cooling gave 135 mg. (66%) of **15c** as a solid. It was recrystallized from ether, m.p. 134-135°; ir (nujol): 3250, 1730, 1710 cm^{-1}; mass spectrum: m/e 431 ($M.^+ - H_2O$).

Anal. Calcd. for $C_{22}H_{31}N_3O_7$: C, 58.50; H, 6.92; N, 9.37. Found: C, 58.68; H, 6.94; N, 9.41.

1-(4-[Di(2-chloroethyl)amino]phenylbutyryl)-2-(octahydro-9a-hydroxy-2-isopropyl-3-oxooxazolo[3,2-*a*]azepine-2-carbonyl)-hydrazine (**15d**).

To a cooled solution of 0.32 g. (1.05 mmoles) of chlorambucil in 20 ml. of benzene was added 0.5 ml. of oxalylchloride. After standing for 2 hours at room temperature the mixture was concentrated *in vacuo*. To remove excess acid, 30 ml. of benzene was added and the mixture was again concentrated *in vacuo*. The brownish oil was dissolved in 20 ml. of benzene and added to a cooled solution of 0.28 g. (1 mmole) of **15c** in 4 ml. of dry pyridine. After keeping the mixture for 3 days at room temperature it was gently warmed for 10 minutes and then concentrated *in vacuo*. The residue was dissolved in 30 ml. of chloroform and successively washed with cold water, 1*N* hydrochloric acid, 10% sodium bicarbonate solution and water. After drying the chloroform was removed *in vacuo* to give an oily brown material 0.28 g. (50%) which solidified on keeping; nmr (deuteriochloroform): δ 0.93 (d, 6H, $C(CH_3)_2$), 3.63 (t, 8H, $N(CH_2\text{-}CH_2Cl)_2$), 6.6, 7.1 (A_2B_2, 4H, J = 8 Hz, aromatic).

Anal. Calcd. for $C_{26}H_{38}Cl_2N_4O_5$: C, 56.01; H, 6.87; N, 10.05. Found: C, 56.15; H, 6.81; N, 9.85.

Tlc of this material (95:5 chloroform/methanol) showed two close spots which were separated by preparative tlc on 2-mm thick silica gel (Merck, 95:5 chloroform/methanol). Both materials showed very similar ir, nmr and mass spectra.

Hexahydro-8a-hydroxy-2-isopropyl-3-oxooxazolo[3,2-*a*]pyridine-2-carboxylic Acid, Ethyl Ester (**16a**).

By following exactly the same procedure as in the preparation of **15a** and using valerolactam and the acid chloride **7b** gave **16a** as an oil (80% overall yield); nmr (deuteriochloroform): δ 0.87, 1.0 (2d, 6H, $C(CH_3)_2$), 1.35 (t, 3H, OCH_2CH_3), 1.5-2.33 (br, 4H), 2.37 (m, 2H), 2.77 (heptet, 1H, $CH(CH_3)_2$), 3.17 (br, 1H), 4.03 (br, 1H), 4.4, 4.42 (q, 2H, OCH_2CH_3), 5.0 (br, s, 1H, deuterium oxide exchangeable); mass spectrum: m/e 253 ($M.^+ - H_2O$).

Anal. Calcd. for $C_{13}H_{21}NO_5$: C, 57.60; H, 7.76; N, 5.17. Found: C, 57.72; H, 7.68; N, 5.09.

Hexahydro-8a-hydroxy-2-isopropyl-3-oxooxazolo[3,2-*a*]pyridine-2-carboxylic Acid, Hydrazide (**16b**).

As in the preparation of the hydrazide **15b**, **16a** gave **16b**, m.p. 145-146° (recrystallized from chloroform-methanol-ether mixture; 75% yield); ir (nujol): 3350, 1720 cm^{-1}; mass spectrum: m/e 239 ($M.^+ - H_2O$).

Anal. Calcd. for $C_{11}H_{19}N_3O_4$: C, 51.35; H, 7.40. Found: C, 51.18; H, 7.39.

1-(3,4-Dimethoxyphenylacetyl)-2-(hexahydro-8a-hydroxy-2-isopropyl-3-oxooxazolo[3,2-*a*]pyridine-2-carbonyl) Hydrazine (**16c**).

By following the same procedure as in the preparation of **15d**, treatment of **16b** with the acid chloride of 3,4-dimethoxyphenylacetic acid (prepared from the acid with oxalychloride) in pyridine/-benzene gave **16c** as a solid (90% yield) which on trituration with ether had m.p. 150-151°. It showed a single spot on tlc (90:10 chloroform:methanol); ir (nujol): 3350, 1740, 1725 cm^{-1}; mass spectrum: m/e 417 ($M.^+ - H_2O$).

Anal. Calcd. for $C_{21}H_{29}N_3O_7$: C, 57.92; H, 6.67; N, 9.66. Found: C, 57.78; H, 6.60; N, 9.59.

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(12) Attempted recrystallization of **13b** from dioxane/water resulted in decarboxylation to give a white solid, m.p. 180-181°; nmr and ir were consistent with the structure (**13b** $-CO_2$); m/e 296 ($M.^+$); *Anal.* Calcd. for $C_{15}H_{24}N_2O_4$: C, 60.79; H, 8.16; N, 9.45. Found: C, 60.75; H, 8.24; N, 9.41.