Experimental Section[5]

The procedure described for the synthesis of IV is general and was used to prepare the condensation products described in this work.

Cyclopentanecarboxylic Acid 5-Oxo-2,3-diphenyl-*n*-hexyl Ester (IV).—In a 2-l. three-necked flask fitted with a stirrer and a reflux condenser carrying a drying tube, there was placed 23 g (1 g-atom) of sodium. After finely dividing the sodium by rapid stirring in hot xylene and decanting the xylene, the flask was half-filled with dry ether. To the flask, from a separatory funnel, there was added 116.2 g (0.50 mole) of *n*-hexylcinnamate in 100 ml of dry ether, slowly with stirring, at such a rate that gentle reflux was maintained. After the addition, the reaction mixture was refluxed for 14 hr longer. The excess sodium was destroyed by the careful addition of 100 ml of 37% sulfuric acid through the condenser, while the reaction mixture was cooled and stirred. The sodium sulfate was separated by filtration, and the water was removed from the ether layer in a separatory funnel. The sodium sulfate was triturated with two 75-ml portions of ether and the ether washings were added to the ether layer in the separatory funnel. The ether solution was washed successively with four 75-ml portions of 20% sodium carbonate followed by washing with four 75-ml portions of distilled water and dried over anhydrous sodium sulfate. The ether was removed under reduced pressure with a water pump, and the residue, a brown syrup, was placed in the freezer. A solid product formed. The product was recrystallized from petroleum ether (bp 30–60°). A pure dried sample melted at 59–60°. The product weighed 14.7 g, a yield of 16.2% of theory based on the ester.

Registry No.—I, 10498-72-3; Ia, 10498-73-4; Ib, 10498-74-5; II, 10498-75-6; IIa, 10498-76-7; III, 10498-77-8; IV, 10498-78-9; IVa, 10498-79-0; V, 10498-80-3; Va, 10498-81-4; Vb, 10498-82-5; VI, 10498-83-6; VIa, 13090-95-4; VIb, 10498-84-7.

Acknowledgment.—The authors wish to express their appreciation to Dr. R. H. Eastman of Stanford University, Stanford, Calif., for the infrared spectra in this work.

(5) (a) Melting points were taken on a Fisher-Johns apparatus. (b) Analyses were performed by Micro-Tech Laboratories, Skokie, Ill.

Reaction of Methyl and Ethyl 2-Cyclopentanonecarboxylates with Amines to Give Carbinolamines, Enamines, and Adipamides

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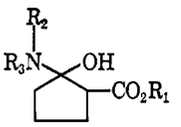
Our interest in the reaction of amines with esters of 2-cyclopentanonecarboxylic acid was stimulated by a study of the reactions of chlorophyll with amines.[1] Chlorophyll and many chlorophyll derivatives have a β-keto ester cyclopentenone ring which is readily opened by both primary and secondary amines to give ester amides.[1,2] It was desirable to study an analogous cyclic β-keto ester, to compare the relative ease of ring cleavage, and to observe what other reactions with amines might be expected.

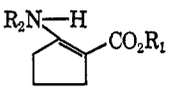
(1) F. C. Pennington, S. D. Boyd, H. Horton, S. W. Taylor, D. G. Wulf, J. J. Katz, and H. H. Strain, in preparation; A. Weller and R. Livingston, *J. Am. Chem. Soc.*, **76**, 1575 (1954).

(2) H. Fischer and G. Spielberger, *Ann.*, **510**, 156 (1934); H. Fischer and S. Goebel, *ibid.*, **524**, 269 (1936); H. Fischer and Gibian, *ibid.*, **550**, 208 (1942); H. Fischer, F. Balav, F. Gerner, and M. Koniger, *ibid.*, **557**, 163 (1948).

Dieckmann was the first to study systematically the reactions of ethyl 2-cyclopentanonecarboxylate. He noted that ammonia added to the carbonyl group to give a white, crystalline solid which he suggested might be the carbinolamine or an ammonium salt.[3] More recently, Treibs, Mayer, and Madejski found that ethyl 2-cyclopentanonecarboxylate readily gave a precipitate with benzylamine and proposed that a carbinolamine (Ia) was formed.[4] These products were both relatively unstable. They decomposed in air to give back the starting ester and base, and they were dehydrated by heating or standing to give enamines. Dieckmann also reported that the predominant product on heating the ester with ammonia was adipamide.



Ia, $R_1 = CH_3CH_2$; $R_2 = H$; $R_3 = C_6H_5CH_2$
b, $R_1 = CH_3$; $R_2 = H$; $R_3 = CH_3CH_2CH_2$
c, $R_1 = CH_3$; $R_2 = H$; $R_3 = (CH_3)_2CHCH_2$
d, $R_1 = CH_3$; $R_2 = H$; $R_3 = (CH_3)_3C$
e, $R_1 = CH_3$; $R_2, R_3 = (CH_2)_5$



IIa, $R_1 = CH_3CH_2$; $R_2 = C_6H_5CH_2$
b, $R_1 = CH_3$; $R_2 = CH_3CH_2CH_2$
c, $R_1 = CH_3$; $R_2 = (CH_3)_2CHCH_2$
d, $R_1 = CH_3CH_2$; $R_2 =$ α-naphthyl
e, $R_1 = CH_3CH_2$; $R_2 =$ 8-quinolinyl
f, $R_1 = CH_3$; $R_2 = (CH_3)_2N$

We have found that many amines give comparable products with the 2-cyclopentanonecarboxylates. Our titration data clearly indicate a 1:1 complex or carbinolamine. An infrared spectrum as a mineral oil mull supports the carbinolamine structure since there is evidence of a chelated ester carbonyl. But when these products are dissolved in carbon tetrachloride, their infrared spectra exhibit a ketone carbonyl absorption and appear to be simply a mixture of ester and amine.

Mayer[5] reviewed the reactions of ethyl 2-cyclopentanonecarboxylate with amines and concluded that dehydration of the carbinolamines led to ketimines. Although Treibs, Mayer, and Madejski had earlier proposed that an enamine was formed by heating the carbinolamine Ia, Mayer assigned the ketimine structure to the product, preferring an exocyclic double bond because of steric factors.

Our data support an enamine structure rather than the ketimine structure for the dehydrated benzylamino product (IIa). We have also found that enamines (II) are readily formed at room temperature when methyl 2-cyclopentanonecarboxylate is treated with benzylamine, propylamine, isobutylamine, and *unsym*-dimethylhydrazine in solvents such as tetrahydrofuran and methanol.

Ultraviolet, infrared, and nmr spectra establish the structure of the enamines unequivocally. Our ultraviolet molar absorptivities and λ_{max} values are comparable with those reported by Hay and Caughley for

(3) W. Dieckmann, *ibid.*, **317**, 37 (1901).

(4) W. Treibs, R. Mayer, and M. Madejski, *Ber.*, **87**, 356 (1954).

(5) R. Mayer, "Newer Methods of Preparative Organic Chemistry," Vol. II, W. Foerst, Ed., Academic Press Inc., New York, N. Y., 1963, pp 101–131.

an enamine derived from ethyl acetoacetate and ethylenediamine[6] and those reported by Sanchez and Del Pina for enamines derived from ethyl acetoacetate and glycosylamines.[7] Furthermore, our frequencies assigned to the chelated ester carbonyl as well as the imine group are consistent with those reported for the enamines derived from ethyl acetoacetate.

The formation of the enamine rather than the ketimine is apparently favored by chelation. Even when aromatic amines are used, the most stable tautomer may have the double bond conjugated with the ester carbonyl rather than the aromatic system. For example, Clemo and Mishra[8a] condensed α-naphthylamine with ethyl 2-cyclopentanonecarboxylate, and Bew and Clemo[8b] condensed 8-aminoquinoline with the same ester. They reported that the products have the ketimine structure. We prepared the products which they reported, and nmr and infrared spectra clearly indicate that their compounds are enamines. Steric factors may also play a significant part in determining the most stable tautomer.

All enamines exhibited a chelated ester carbonyl absorption at about 1650 and evidence of N–H at about 3300 cm^{-1} in carbon tetrachloride solution. In the same solvent nmr spectra confirmed the presence of N–H and the two protons on the 4 carbon of the cyclopentene ring gave rise to a characteristic multiplet at about 1.8–1.9 ppm.

Both tetrahydrofuran and methanol were used as solvents. The reaction is much faster in methanol. A reaction that takes 4 days at room temperature in tetrahydrofuran at a concentration of 0.14 *M* may take as little as 1 day in methanol.

Secondary amines gave only trace amounts of enamine under conditions that readily give enamines with the 2-cyclopentanonecarboxylates and primary amines. This may indicate that the primary amines first form ketimines which then tautomerize to give the enamine although in following the reaction in nmr spectra we did not see any spectral evidence of the presence of ketimines. Secondary amines would have to form enamines by another mechanism and appear to require much different conditions. Schmutz has reported the synthesis of an enamine from ethyl 2-cyclopentanonecarboxylate and diethylamine.[9] He used a 33% alcoholic amine solution for 12 hr at 20° and obtained the enamine after fractional distillation.

Ring opening was much slower than that observed with chlorophyll[1] and occurred when the 2-cyclopentanonecarboxylates were allowed to stand for several days in a large excess of propylamine or isobutylamine. Only low yields (1–2%) of the diamides of adipic acid were obtained[10] under conditions that gave nearly quantitative opening of ring V in chlorophyll.[1] Thin layer chromatography was used to follow the reaction. We found no indication of the formation of an ester amide, the analogous structure obtained from chlorophyll and its derivatives.

(6) R. W. Hay and B. P. Caughley, *Chem. Commun.*, 58 (1965).

(7) A. G. Sanchez and J. V. Del Pina, *Carbohydrate Res.*, **1**, 421 (1966).

(8) (a) G. R. Clemo and L. K. Mishra, *J. Chem. Soc.*, 192 (1953); (b) D. G. Bew and G. R. Clemo, *ibid.*, 1775 (1955).

(9) J. Schmutz, *Helv. Chim. Acta*, **38**, 1712 (1955).

(10) In the nmr spectra of both the amides and the enamines the nitrogen protons split the adjacent alkyl protons. G. Dudek and H. Holm [*J. Am. Chem. Soc.*, **84**, 2691 (1962)] have reported a comparable splitting for α,β-unsaturated ketoamines.

Experimental Section

Methyl and Ethyl 2-Cyclopentanonecarboxylate (I).—Commercially available[11] ethyl 2-cyclopentanonecarboxylate is a mixture of the methyl and ethyl esters containing about 20% methyl ester. Although separation was possible by means of a spinning-band fractionating column, it was more convenient to prepare the pure methyl and ethyl esters from adipic acid diesters using Dieckmann's procedure.[12]

General Method for Preparing the Carbinolamines (I).—Methyl 2-cyclopentanonecarboxylate (2.0 g, 0.014 mole) was dissolved in ether (100 ml), and the resulting solution was cooled to 0°. The amine (0.14 mole) was added to the cooled solution, and a white precipitate formed. In the case of *t*-butylamine and piperidine the precipitate formed after 2 days. The precipitate was collected and washed with a large volume of cold ether. The white solid was stored in an evacuated flask in a freezer until it was used.

Titration of the carbinolamines (Table I) was carried out in glacial acetic acid using 0.1158 *N* perchloric acid in glacial acetic acid. The end point was determined potentiometrically. All melting points except that of the reported benzylamino compound (Ia) were determined in evacuated, sealed capillaries.

TABLE I
CARBINOLAMINES

Compd	Mp, °C	Formula	Equiv wt Calcd	Equiv wt Found
Ia[a]	64–64[b]	$C_{15}H_{21}NO_3$	263.4	264
Ib	73–74	$C_{10}H_{19}NO_3$	201.2	204
Ic	68–69	$C_{11}H_{21}NO_3$	215.3	207
Id	65–67	$C_{11}H_{21}NO_3$	215.3	213
Ie	61–62.5	$C_{12}H_{21}NO_3$	227.3	222

[a] ν_{max}^{mull} 3100 (broad shoulder, OH, NH), 1660 cm^{-1} (chelated C=O). [b] Lit.[4] mp 56–57°.

General Method for Preparing Enamines (II).—Methyl 2-cyclopentanonecarboxylate (2.0 g, 0.014 mole) was dissolved in tetrahydrofuran (50 ml) and cooled to 0°. The amine (0.014 mole) was added to the cooled solution, and the solution was allowed to stand at room temperature for 4 days or more. The tetrahydrofuran was evaporated *in vacuo*, and the residual oil was distilled at reduced pressure.

Ethyl 2-Benzylamino-1-cyclopentenecarboxylate (IIa).—This compound was prepared in tetrahydrofuran and also by Treibs' procedure: mp 26–27° (lit.[4] mp 26–27°); $\nu_{max}^{CCl_4}$ 3300 (m, NH), 1650 (s, chelated C=O), 1600 cm^{-1} (s, conjugated C=C); nmr (CCl_4) δ 1.79 (q, splitting = 7 cps, 4-CH_2 in cyclopentene), 4.09 (q, J = 7 cps, CH_2O), 4.32 (d, J = 7 cps, CH_2N), 8.85 (broad singlet, NH).

Methyl 2-Propylamino-1-cyclopentenecarboxylate (IIb).—This compound (67%) distilled at 95° (3 mm); $\lambda_{max}^{95\%EtOH}$ 296.6 mμ (log ε 4.20); $\nu_{max}^{CCl_4}$ 3306 (m, NH), 1650 (s, chelated C=O), 1595 cm^{-1} (s, conjugated C=C); nmr (CCl_4) δ 3.13 (q, J = 6.5 cps, CH_2N), 3.58 (s, OCH_3), 7.47 (s, NH). *Anal.* Calcd for $C_{10}H_{17}NO_2$: C, 65.54; H, 9.35; N, 7.64. Found: C, 65.34; H, 9.52; N, 7.65.

Methyl 2-Isobutylamino-1-cyclopentenecarboxylate (IIc).—This compound (68%) distilled at 95° (2 mm); $\lambda_{max}^{95\%EtOH}$ 296 mμ (log ε 4.13); $\nu_{max}^{CCl_4}$ 3306 (m, NH), 1647 (s, chelated C=O), 1592 cm^{-1} (s, conjugated C=C); nmr (CCl_4) δ 1.80 (q, splitting = 6.5 cps, 4-CH_2 in cyclopentene), 2.95 (q, J = 6.5 cps, CH_2N), 3.56 (s, OCH_3), 7.52 (s, NH). *Anal.* Calcd for $C_{11}H_{19}NO_2$: C, 66.97; H, 9.77; N, 7.10. Found: C, 66.85; H, 9.62; N, 7.31.

Ethyl 2-(α-Naphthylamino)-1-cyclopentenecarboxylate (IId).—This compound was prepared by the method reported by Clemo and Mishra;[8a] mp 73–74° (lit.[8a] mp 73°); $\nu_{max}^{CCl_4}$ 3280 (m, NH), 1648 cm^{-1} (chelated C=O); nmr (CCl_4) δ 9.88 (broad singlet, NH), 1.87 (q, splitting = 6.5 cps, 4-CH_2 in cyclopentene).

Ethyl 2-(8-Quinolinylamino)-1-cyclopentenecarboxylate (IIe).—This compound was prepared by the method of Bew and Clemo:[8b] mp 86–87° (lit.[8b] mp 86–87°); $\nu_{max}^{CCl_4}$ 3220 (m, NH), 1644 cm^{-1} (chelated C=O); nmr (CCl_4) δ 11.3 (broad singlet, NH), 1.93 (q, splitting = 6.5 cps, cyclopentene 4-CH_2).

(11) Aldrich Chemical Co., Milwaukee, Wis., and Arapahoe Chemicals, Inc., Boulder, Colo.

(12) W. Dieckmann, *Ber.*, **27**, 965 (1894); see also A. R. Vogel, "A Textbook of Practical Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1956, p 856.

Methyl 2-(*unsym*-Dimethylhydrazino)-1-cyclopentenecarboxylate (IIf).—This compound distilled at 72–73° (4 mm); $\lambda_{max}^{95\%\,EtOH}$ 291 mμ; $\nu_{max}^{CCl_4}$ 3250 (m, NH), 1653 cm^{-1} (s, chelated C=O); nmr (CCl_4) δ 1.81 (q, splitting = 7 cps 4-CH_2 in cyclopentene), 2.51 [s, $(CH_3)_2$], 3.60 (s, CH_3O). *Anal.* Calcd for $C_9H_{16}N_2O_2$: C, 58.66; H, 8.77; N, 15.21. Found: C, 58.75; H, 8.65; N, 15.22.

Cleavage of the Ring to Form Adipic Acid Diamides.—Methyl 2-cyclopentanonecarboxylate (Ia, 2.0 g, 0.014 mole) was placed in a flask, and a large excess (10 ml) of propylamine or isobutylamine was added. A white precipitate formed. The mixture was allowed to stand for 4 days and was then poured into hexane. The amide precipitated and was recrystallized from tetrahydrofuran. Identification of dipropyladipamide and diisobutyladipamide was positively established by analysis and comparison with amides prepared from adipic acid chloride.

N,N′-Dipropyladipamide.—This compound was obtained in 2% yield, mp 181°; ν_{max}^{mull} 3300 (NH), 1628 cm^{-1} (C=O). *Anal.* Calcd for $C_{12}H_{24}N_2O_2$: C, 63.12; H, 10.59; N, 12.29. Found: C, 63.02; H, 10.74; N, 12.21.

N,N′-Diisobutyladipamide.—This compound was obtained in 3% yield, mp 188°; ν_{max}^{mull} 3300 (NH), 1623 cm^{-1} (C=O); nmr (pyridine) δ 3.03 (t, J = 6.5 cps, CH_2N). *Anal.* Calcd for $C_{14}H_{28}N_2O_2$: C, 65.58; H, 11.01; N, 10.93. Found: C, 65.69; H, 10.85; N, 11.02.

Chromatographic Procedures.—The enamines were chromatographed on silica gel[13] using a 20% mixture of acetone dissolved in hexane. This system was effective for analysis using thin layer chromatography (tlc) or for separations using column chromatogaphy. Columns were packed dry and a water pump vacuum was used to assure even packing. An ultraviolet lamp was used for observing column fractionations since both ester and enamine fluoresced strongly.

On tlc plates the enamines gave light brown-purple colors when they were sprayed with methanolic ferric chloride. Amides were best detected by using bromine vapors. The relative rates of reaction as determined by tlc of the amines with methyl 2-cyclopentanonecarboxylate were as follows: benzylamine > propylamine > isobutylamine > isopropylamine > *t*-butylamine. The reaction may also be followed by means of nmr, infrared, and ultraviolet spectra.

Registry No.—Ia, 10472-13-6; Ib, 10472-14-7; Ic, 10472-15-8; Id, 10472-16-9; Ie, 10472-17-0; IIa, 10412-92-7; IIb, 10472-19-2; IIc, 10472-20-5; IId, 10472-21-6; IIe, 10472-22-7; IIf, 10472-23-8; methyl 2-cyclopentanonecarboxylate, 10472-24-9; ethyl 2-cyclopentanonecarboxylate, 611-10-9; N,N′-dipropyladipamide, 10263-96-4; N,N′-diisobutyladipamide, 10472-27-2.

Acknowledgment.—This research was supported by a National Science Foundation Research Grant (GB-3091) and by a National Science Foundation Undergraduate Research Grant (GE-6199). We are indebted to J. E. Keiser for his helpful suggestions and to J. G. Murphy for tlc analyses.

(13) Kieselgel, Camag, and Eastman Kodak silica gel coated plastic.

Investigation of the Claimed Synthesis of 1,1′-(Oxydiethylene)bisaziridine

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Manecke and Heller[1] claim to have synthesized 1,1′-(oxydiethylene)bisaziridine (I) by treating bis-2-chloroethyl ether with ethylenimine (Scheme I). They state that reaction of the presumed bisaziridine I with hydrobromic acid leads to the formation of 1,4-bis(2-{2-[(2-bromoethyl)amino]ethoxy}ethyl)piperazine tetrahydrobromide (II). They further claim that rigorous treatment of the bispiperazine II with hydriodic acid, followed by subsequent reaction with strong alkali, produces 1,4-piperazinediethanol (III), which they isolate as the known dipicrate.[2]

We have repeated the work of Manecke and Heller and have isolated products which have the same melting points and elemental analyses as were cited by them for compounds I and II. Instrumental analyses and an alternate method of synthesis revealed that the presumed compound I was really 4-[2-(1-aziridinyl)-ethyl]morpholine (IV). The synthesis of IV by the two methods shown in Scheme II was accompanied in each case with the production of a small amount of 4-(2-methoxyethyl)morpholine (V). The presumed compound II was found to be 4-[2-(2-bromoethyl)aminoethyl]morpholine dihydrobromide (VI). Treatment of IV with hydrobromic acid should not affect the morpholine ring; a normal opening of the aziridine ring should be expected.[3]

Samples of IV, prepared by the two different methods, had identical nmr spectra and gave the known derivative 2-[(2-morpholinoethyl)amino]ethanethiol dihydrochloride (VII) upon treatment with hydrogen sulfide and subsequently with hydrochloric acid.[4]

The treatment of the haloethylamine VI with hydriodic acid, under the vigorous conditions cited by Manecke and Heller, could easily lead to the formation of 1,4-piperazinediethanol (III).

That morpholine derivatives can result from the treatment of bis-2-chloroethyl ether with amines is not surprising. Farrar[5] has reported his inability to form 1,1′-(oxydiethylene)bishydrazine by treating bis-2-chloroethyl ether with hydrazine. Instead, his major reaction product was 4-aminomorpholine. Rappaport[6] and Cerkovnikov and Stern[7] have reported the synthesis of 4-phenylmorpholine from aniline and bis-2-chloroethyl ether. Cerkovnikov, *et al.*,[8] also has reported that treatment of benzylamine with the bis-halo ether resulted in 4-benzylmorpholine.

An alternate approach to the bisaziridine I, involving reaction of the tosylate of 1-(2-hydroxyethyl)aziridine with the alkoxide of the same amino alcohol, was investigated. The reaction product gave evidence of being the desired compound [nmr studies of the crude reaction product (Figure 1), together with the quantitative recovery of the expected by-products, sodium *p*-toluenesulfonate and sodium chloride]. Unfortunately, the product has repeatedly undergone violent decomposition soon after removal of the reaction solvent. Attempts to prepare stable derivatives of this product have been unsuccessful.

(1) G. Manecke and H. Heller, *Ber.*, **95**, 2700 (1962).

(2) F. L. Pyman, *J. Chem. Soc.*, **93**, 1802 (1908).

(3) G. Benoit and A. Funke, *Bull. Soc. Chim. France*, 946 (1955).

(4) R. J. Wineman, M. H. Gollis, J. C. James, and A. Pomponi, *J. Org. Chem.*, **27**, 4222 (1962).

(5) W. V. Farrar, *J. Chem. Soc.*, 782 (1956).

(6) G. Rappaport, J. A. Szaruga, and J. Wall, U. S. Patent 2,895,926 (July 21, 1959).

(7) E. Cerkovnikov and P. Stern, *Arkiv Kemi*, **18**, 12 (1946); *Chem. Abstr.*, **42**, 1938*f* (1948).

(8) E. Cerkovnikov, N. Skarica, and P. Stern, *Arkiv Kemi*, **18**, 37 (1946); *Chem. Abstr.*, **42**, 1942*h* (1948).