The Synthesis of Cyclopentane Derivatives. I

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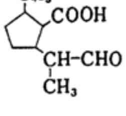
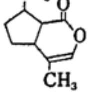
Recently, several methylcyclopentane derivative from natural sources have been reported. Among them, nepetalic acid (I) and nepetalactone (II) from the oil of cat-nip (Nepeta cataria)[1], matatabilactone (III) from the oil of the wormseed of matatabi (Actinidia poligama Miq.,)[2] and iridolactone (IV) from ant (Iridomyrmex species)[3] are particularly interesting because of their close relationship concerning both physiological activities and chemical structures.



(I)



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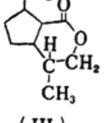

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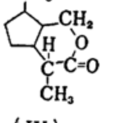

(IV)

The determination of conformations of these compounds[4] in relation to their physical and chemical properties seems worthy of further considerations. Now, synthesis of several cyclopentane derivatives was attempted with a view to obtain some informations about conformational problems and to find out a new synthetic route.

In the present experiment, *cis*- and *trans*-lactones of 2-α-carboxyethylcyclopentanol were prepared as the first step in a series of this investigation attempted, which lead to the compounds having no methyl substituent in the ring, and thus alleviating stereochemical difficulties. The condensation of carbethoxycyclopentanone (V) with ethyl α-bromopropionate, reported by Šorm et al.[5] and Sen et al.[6], respectively, was re-examined and some new results were obtained. The condensation was conducted by use of either sodium metal in toluene[5,7] or sodium ethoxide in absolute alcohol[8]. 2-Carbethoxy-2-α-carbethoxyethyl cyclopentanone (VII) was obtained

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[1] S. M. McElvain, R. D. Bright and P. R. Johnson, *J. Am. Chem. Soc.*, **63**, 1558 (1941); E. J. Eisenbraun and S. M. McElvain, ibid., **77**, 1599 (1955).

[2] T. Sakan, A. Fujino, F. Murai, Y. Butsugan and A. Suzui, This Bulletin, **32**, 315 (1959).

[3] G. W. K. Cavill, D. L. Ford and H. D. Locksley, *Chem. & Ind.*, **75**, 465 (1956).

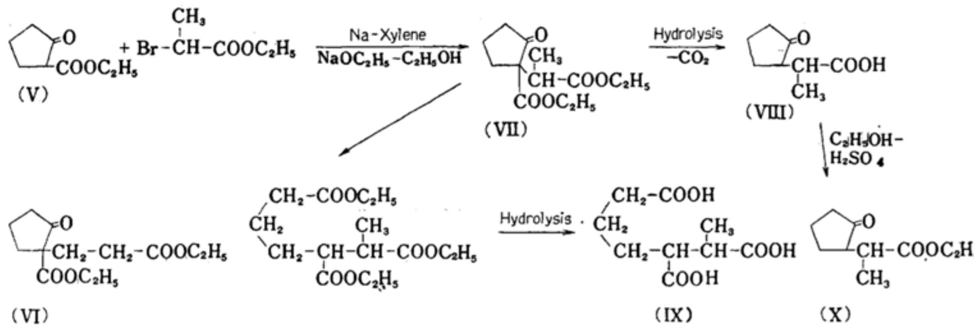
[4] R. B. Bates, E. J. Eisenbraun and S. M. McElvain, *J. Am. Chem. Soc.*, **80**, 3420 (1958); ibid., **80**, 3413 (1958).

[5] F. Šorm, Z. Šormová and L. Šedivý, *Collection Czechoslov. Chem. Communs.*, **12**, 554 (1947); *Chem. Abstr*, **42**, 7742*c* (1948).

[6] K. Sen and P. Bagchi, *Science and Culture* (*India*), **20**, 254 (1954); *Chem. Abstr.*, **49**, 14652*e* (1955).

[7] W. Herz. *J. Am. Chem. Soc.*, **78**, 1485 (1956).

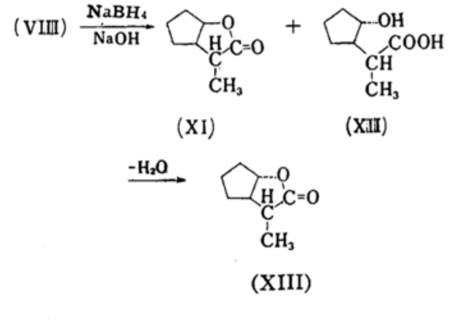
[8] (a) E. D. Bergmann and R. Ikan, ibid., **80**, 3135 (1958). (b) A. Kötz, *Ann.*, **350**, 235 (1906).



in 70 and 60% yield, respectively. Here, in the latter case, an acid, m. p. 147°C, was newly detected as the by-product of the cleavage of the ring in VII[9,8b] followed by hydrolysis of the ester group. The acid was identified as hexane-tricarboxylic acid-1, 4, 5 (IX) obtained by Sen et al.[10] from 2-methyl-2, 3-dicarbethoxy-cyclohexanone; the formation substantiates structure VII for the condensation product.

2-Carbethoxy-2-β-carbethoxyethyl-cyclopentanone (VI) which might be the product of dehydrobromination and Michael addition[11] of ethyl α-bromopropionate to carbethoxycyclopentanone (V) could not be detected. The ketoester (VII) was converted into 2-α-carboxyethyl-cyclopentanone (VIII), m. p. 66°C, which on esterification yielded ethyl ester (X), as indicated in the formulation.

On the other hand, VIII was treated with sodium borohydride, when a selective reduction of the keto group[12] was realized;



from the reduction product a lactone of possibly *cis*-2-α-carboxyethyl-cyclopentanol (*cis*-lactone) (XI) and a hardly lactonized one, possibly *trans*-hydroxyacid (XII) were obtained. Structure XII was ascertained by analysis and also by the comparison of the absorption spectrum of the reduction product with that of keto-acid (VIII). 288 mμ band in the ultraviolet spectrum and 5.80 μ peak in the infrared spectrum of the keto-acid were not observed in the spectrum of the reduction product as illustrated in Figs. 1 and 2, respectively.

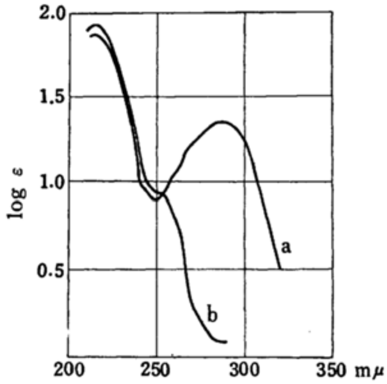


Fig. 1. Ultraviolet spectra of 2-α-carboxyethyl-cyclopentanone (a) and *trans*-2-α-carboxyethyl-cyclopentanol (b) in alcoholic solutions.

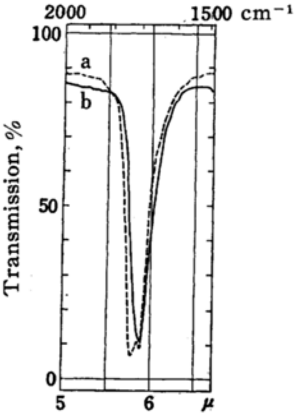


Fig. 2. Infrared spectra of 2-α-carboxyethyl-cyclopentanone (a) and *trans*-2-α-carboxyethyl-cyclopentanol (b).

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[9] A. H. Cook and R. P. Linstead, *J. Chem. Soc.*, **1934**, 964.

[10] K. Sen and P. Bagchi, *Science and Culture* (*India*)., **19**, 312 (1953); *Chem. Abstr.*, **49**, 2338*f* (1955).

[11] P. B. Talukdar and P. Bagchi, *J. Org. Chem.*, **20**, 25 (1955).

[12] E. B. Reid and J. R. Siegel, *J. Chem. Soc.*, **1954**, 520; R. P. Zelinski, B. W. Turnquest and E. C. Martin, *J. Am. Chem. Soc.*, **73**, 5521 (1951).

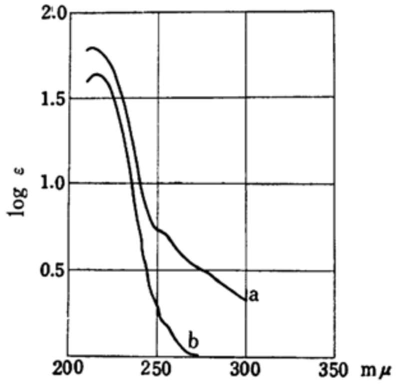
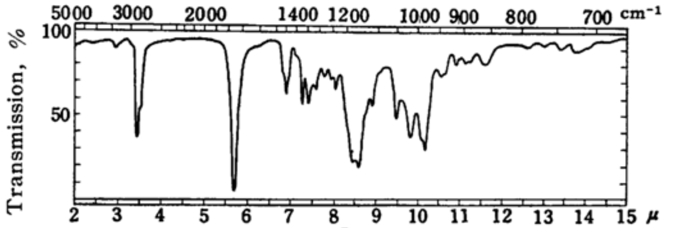
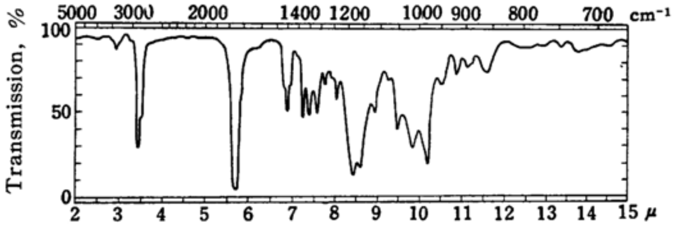


Fig. 3. Ultraviolet spectra of *trans*-lactone (a) and *cis*-lactone (b) in alcoholic solutions.



trans-Lactone



cis-Lactone

Fig. 4. Infrared spectra of *trans*-lactone and *cis*-lactone.

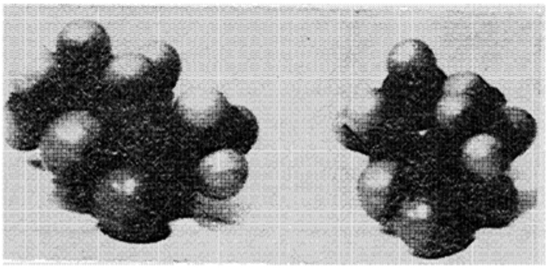
The reduction of 2-carboxymethyl-cyclopentanone with sodium amalgam in sodium hydroxide solution was reported by Linstead et al.[13] to yield *cis*-lactone in 28% yield. The lactonization of XII gave a sweet smelling *trans*-lactone (XIII) (heated under diminished pressure); a trace of concentrated sulfuric acid facilitated the reaction. In this way the reduction of keto-acid (VIII) yielded 37% of *cis*-lactone and 38% of *trans*-lactone (consult Table I).

TABLE I. PHYSICAL CONSTANTS OF *cis*- AND *trans*-LACTONES

	Density $d_4^{13.5}$	Refractive index $n_D^{13.5}$	b. p., °C
cis-Lactone	1.08462	1.4712	73∼74/2 mm.
trans-Lactone	1.09688	1.4725	67/2 mm.

Some differences between these lactones were also revealed in the ultraviolet (Fig. 3) and infrared (Fig. 4) spectra of them. In the ultraviolet spectra, the extinction coefficient of *trans*-lactone is a little higher than that of *cis*-lactone particularly at longer wavelengths.

In the infrared spectra, comparison of relative intensity of absorption peaks 8.44 μ (a) and 8.60 μ (b) (C–O stretching) gives a convenient method of characterizing these lactones. In the spectra of *cis*- and *trans*- lactones, a>b and b>a are recognized, respectively. And the singlet absorption peaks 10.50 μ, 11.13 μ in the spectrum of *cis*-lactone, appear as doublet peaks 10.50, 10.64 μ; 11.13, 11.25 μ respectively in that of *trans*-lactone. By the examination of the molecular models in Fig. 5, it is ascertained that *cis*-lactone is a staggered molecule having *cis*-orientation at C_1 and C_2, while *trans*-lactone is a planar molecule having a *gauche*-orientation at C_1 and C_2.



trans-Lactone *cis*-Lactone

Fig. 5. The molecular models of *trans*-lactone and *cis*-lactone.

Experimental[14]

2-Carbethoxy-2-α-carbethoxyethyl-cyclopentanone.—(a) The Condensation of 73 g. of ethyl α-bromopropionate with 62 g. of 2-carbethoxy-cyclopentanone by use of 9.2 g. of sodium in 500 ml. of toluene was completed by refluxing the mixture for ten hours. The reaction product, being treated in the usual way, yielded 61 g. of fraction b. p. 128∼129°C/2.5 mm., 7 g. of fraction b. p. 123∼128°C/2.5 mm. The latter was also used for further work. Yield, 70%. λ_{max} 249 mμ log ε 3.09; ν_{max} 5.74 μ, 5.82 μ (C=O).

Anal. Found: C, 60.30; H, 7.85. Calcd. for $C_{12}H_{20}O_5$: C, 59.00; H, 8.25%.

2-α-Carboxyethyl-cyclopentanone. — Forty-five grams of 2-carbethoxy-2-α-carbethoxyethyl-cyclo-

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[13] R. R. Linstead and E. M. Mead, *J. Chem. Soc.*, **1934**, 935.

[14] Infrared spectra were measured with Perkin Elmer Model 21 spectrophotometer and ultraviolet spectra in alcoholic solutions with Beckman E. P. U. spectrophotometer.

TABLE II. PHYSICAL CONSTANTS OF 2-α-CARBOXYETHYL-CYCLOPENTANONE AND ITS DERIVATIVES

	b. p., °C	m. p., °C	Melting point of semicarbazone °C	Melting point of 2,4-dinitrophenylhydrazone °C	Boiling point of ethylester °C
Šorm et al.	154/15 mm.	—	188	—	81∼83/0.5 mm.
Sen et al.	150/3 mm.	—	—	220	—
Experiment	118∼119/0.4 mm.	66	189	220	93.5∼94/3 mm.

pentanone was gently refluxed with 100 ml. of concentrated hydrochloric acid for sixteen hours at 135∼145°C in an oil bath. The reaction mixture was cooled and extracted with ether. Benzene was added to the ether solution and the solvents were evaporated and the residue was vacuum-distilled. A portion (18.4 g.) of the acid b. p. 118∼119°C/0.4 mm. was obtained. Yield, 64%. On standing in the ice box, it gradually crystallized; m. p. 45°C. Recrystallized from benzene-petroleum ether as feathery needles; m. p. 66°C, $\lambda_{\max}$ 214 mμ log ε 1.86, 288 mμ log ε 1.34; $\nu_{\max}$ 5.80 μ, 5.90 μ (C=O).

Anal. Found: C, 60.72; H, 7.84. Calcd. for $C_8H_{12}O_3$: C, 61.52; H, 7.75%.

An additional amount (ca. 1 g.) was obtained by evaporating the hydrochloric acid solution in vacuum and extracting the residual tar with ether. Physical constants by three different authors are listed in Table II.

(b) To a solution of 7.6 g. of sodium in 120 ml. of absolute alcohol was added 54 g. of carbethoxycyclopentanone in twenty minutes at 20°C with efficient stirring. Sixty-four grams of ethyl α-bromopropionate was added to the mixture and refluxed for four hours. A clear red solution resulted. Fifty milliliters of alcohol was distilled off from it and the residue was diluted with 250 ml. of ice water and extracted with ether. The ether solution, after washing with water, dried with sodium sulfate and the ether was evaporated and the residue vacuum-distilled. Fifty and a half grams of fraction boiling 126.5∼130°C/2.5 mm. was obtained. Yield, 60%.

2-α-Carboxyethyl-cyclopentanone and Hexanetricarboxylic Acid-1, 4, 5.—Hydrolysis was effected in the same way as in a) by using 47.5 g. of ketodiester b. p. 126.5∼130°C/2.5 mm. and 105 ml. of concentrated hydrochloric acid. On evaporation of ether and redissolving the residue in a small amount of dry ether, 850 mg. of colorless crystals which were difficult to solve in ether, separated, which on crystallization from ethyl acetate-petroleum ether melted at 147°C. Analysis and titration conformed to hexane-tricarboxylic acid-1, 4, 5.

Anal. Found: C, 49.40; H, 6.71. Calcd. for $C_9H_{14}O_6$: C, 49.54; H, 6.47%. Titration. 9.00 mg. required 12.4 ml. of 0.010 N sodium hydroxide. Calcd. for $C_6H_{11}(COOH)_3$: 12.4 ml. From the ether solution after distillation in vacuum was obtained 14 g. of 2-α-carboxyethyl-cyclopentanone b. p. 119∼120°C/0.4 mm. Yield, 46%.

2-α-Carbethoxyethyl-cyclopentanone. — Seven grams of 2-α-carboxyethyl-cyclopentanone was dissolved in 20 ml. of absolute alcohol containing 0.7 ml. of concentrated sulfuric acid and refluxed for six hours in a water bath. Twelve milliliters of ethanol was distilled off from the reaction mixture and the residue was poured into 120 ml. of ice water.

The product was extracted with ether and the ether solution was washed with 5% aqueous sodium carbonate solution and with water successively, and dried with sodium sulfate. Evaporation of ether and vacuum-distillation of the residue produced 5.8 g. of 2-α-carbethoxyethyl-cyclopentanone b. p. 93.5∼94°C/3 mm. Yield, 70%. $\lambda_{\max}$ 214 mμ log ε 2.02, 288 mμ log ε 1.36; $\nu_{\max}$ 5.80 μ (C=O).

Anal. Found: C, 64.91; H, 9.21. Calcd. for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75%.

***cis*-Lactone, *trans*-2-α-Carboxyethyl-cyclopentanol and *trans*-Lactone.**—The aqueous sodium hydroxide solution (4.2 g. of sodium hydroxide in 94 ml. of water) of 14.4 g. of 2-α-carboxyethyl-cyclopentanone was gradually (in one hour) added to a solution of 2.3 g. of sodium borohydride in 35 ml. water. The mixture was well shaken after each addition and left to stand for two days at room temperature after the addition was over. It was cooled in an ice bath, and 50 ml. of concentrated hydrochloric acid was added to it with stirring. After the addition was over, it was warmed on a water bath for fifteen minutes, cooled in an ice bath and extracted three times with benzene followed by four times with ether. The combined benzene solution after washing three times with water was dried with sodium sulfate. Benzene was evaporated under reduced pressure and the residue vacuum-distilled. Four and four-fifth grams of *cis*-lactone (3.8 g. of fraction b. p. 73∼74°C/2 mm., 1 g. of fraction b. p. 71∼72.5°C/2 mm.) was obtained. The latter fraction was also used for further work. Yield, 37%. $\lambda_{\max}$ 215 mμ log ε 1.65; $\nu_{\max}$ 5.70 μ (C=O) 8.44 μ, 8.60 μ (C–O).

Anal. Found: C, 67.96; H, 8.89. Calcd, for $C_8H_{12}O_2$: C, 68.54; H, 8.63%.

To the combined ether solution was added 100 ml. of benzene. Ether and moisture were azeotropically distilled. And the residue was vacuum-distilled. *trans*-2-α-Carboxyethyl-cyclopentanol b. p. 125∼126°C/0.4 mm., m. p. 58°C, was obtained. $\lambda_{\max}$ 215 mμ log ε 1.93; $\nu_{\max}$ 5.90 μ (C=O).

Anal. Found: C, 61.37; H, 9.21. Calcd. for $C_8H_{14}O_3$: C, 60.74; H, 8.92%.

***trans*-Lactone Prepared from *trans*-2-α-Carboxyethyl-cyclopentanol.** — In the usual procedure the residue of the ether extract was directly lactonized by heating it at 180~195°C under 30 mm. pressure from thirty minutes to three hours. *trans*-Lactone mixed with water slowly distilled out. But when one drop of concentrated sulfuric acid was added to the hydroxyacid, lactonization was completed in a few minutes. The product was dissolved in benzene, dried with sodium sulfate. Benzene was evaporated and the residue vacuum-distilled. Four and nine-tenths grams of *trans*-lactone b. p. 67°C/2 mm. was obtained. Yield, 38%. $\lambda_{\max}$ 213.5 mμ log ε 1.81; $\nu_{\max}$ 5.70 μ (C=O) 8.44 μ, 8.60 μ (C–O).

Anal. Found: C, 68.52; H, 8.80. Calcd. for $C_8H_{12}O_2$: C, 68.54; H, 8.63%.

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