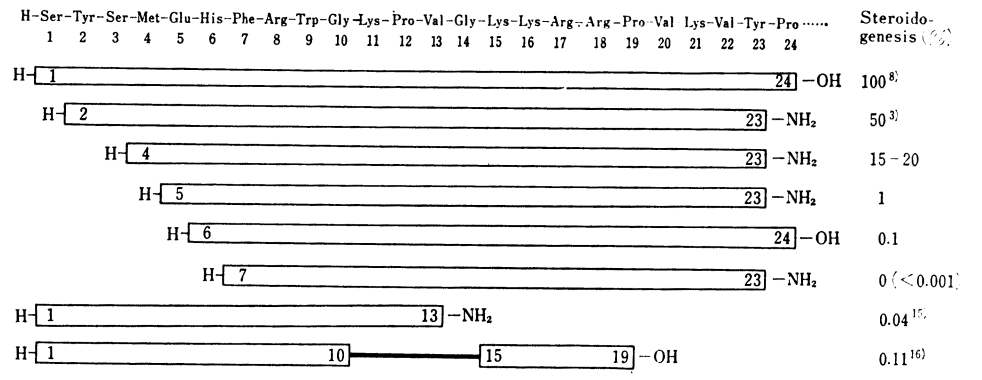
TABLE I. Relationship between Activity and Chain Length of ACTH



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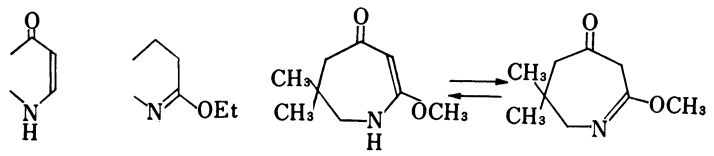
Imine-enamine Tautomerism and Ring Contraction of 2-Methoxy-4,5,6,7-tetrahydro-1H-azepin-4-ones

Recent investigations have established that enamineketone (I) and lactim ether (II) are in imine-enamine tautomeric equilibrium, and that the enamine form predominates in the former case[1] and the imine form does in the latter case.[2] However, there has been no information on imine-enamine tautomerism of β-alkoxy-enamineketone.[3] In the present work, it is shown that 6,6-dimethyl-2-methoxy-4,5,6,7-tetrahydro-1H-azepin-4-one (III), prepared by Curtius-type rearrangement of 3-azido-5,5-dimethyl-2-cyclohexen-1-one, exists as enamine form (IIIA) in polar solvent such as ethanol and dimethyl sulfoxide, as imine form (IIIB) in non-polar solvent such as carbon tetrachloride and as a mixture of both forms in chloroform. The result would show that the enamine and imine forms of III have comparable stabilities in solution. It is also shown that the azepinone (III) undergoes ring contraction by treatment with dilute acid to give methyl 4,4-dimethyl-2-pyrrolidylideneacetate (V). It

1) V.G. Granik, B.M. Pyatin, J.V. Persianova, E.M. Peresleni, N.P. Kostyuchenko, R.G. Glushkov, and Y. N. Sheinker, *Tetrahedron*, **26**, 4367 (1970).
2) J. Dabrowski and J. Terpinski, *Tetrahedron Letters*, **1965**, 1363.
3) T. Oishi, M. Ochiai, T. Nakayama, and Y. Ban, *Chem. Pharm. Bull.* (Tokyo), **17**, 2314 (1969).

has recently been reported that the azepine derivatives undergo ring contractions with acid and base to give pyrroles, pyridines[4] and γ-lactones.[5] The present ring contraction provides a novel type of example and also a facile synthetic route to V and its analogues.



I II IIIA IIIB

Chart 1

Treatment[6] of 3-chloro-5,5-dimethyl-2-cyclohexen-1-one with sodium azide in methanol (containing small amount of water) followed by refluxing a methanolic solution of the resulted 3-azido-5,5-dimethyl-2-cyclohexen-1-one for 4 hr gave a 36% yield of III, mp 146—146.5° (from acetone–pet.ether). The structure of III was proved by hydrolysis of III to 6,6-dimethylhexahydroazepine-2,4-dione (IV)[6,7] [with 10% $HClO_4$ (67% yield), with 10% KOH (59% yield)] and by the following spectral analyses.

The ultraviolet (UV), infrared (IR), and nuclear magnetic resonance (NMR) spectra of III in carbon tetrachloride show that III exists solely as the imine tautomer (IIIB) in this solvent; UV: no observed absorption maximum between 250 and 340 mμ. IR ν_{max} cm^{-1}: 1720 (C=O) and 1665 (C=N). NMR τ: 8.98 (6H, s, di-CH_3), 7.78 (2H, s, $COCH_2$), 6.86 (4H, s, CH_2N and $COCH_2C{=}N$) and 6.34 (3H, s, OCH_3). Spectra in polar solvent show that III exists solely as the enamine tautomer (IIIA); UV λ_{max} (EtOH) mμ: 290 (log ε 4.42). NMR (DMSO-d_6) τ: 9.08 (6H, s, di-CH_3), 7.83 (2H, s, $COCH_2$), 7.13 (2H, d, CH_2N), 6.40 (3H, s, OCH_3), 5.65 (1H, d, CH=) and 2.1—2.7 (1H, b-s, NH). The spectra in chloroform show that III exists as a 3:2 mixture of IIIA and IIIB; IR ν_{max} cm^{-1}: 1710 (C=O), 1660 (C=N) and 1570 [CO–C=C(OCH_3)–N]. NMR τ: signals due to IIIA, 8.92 (3/5×6H, s, di–

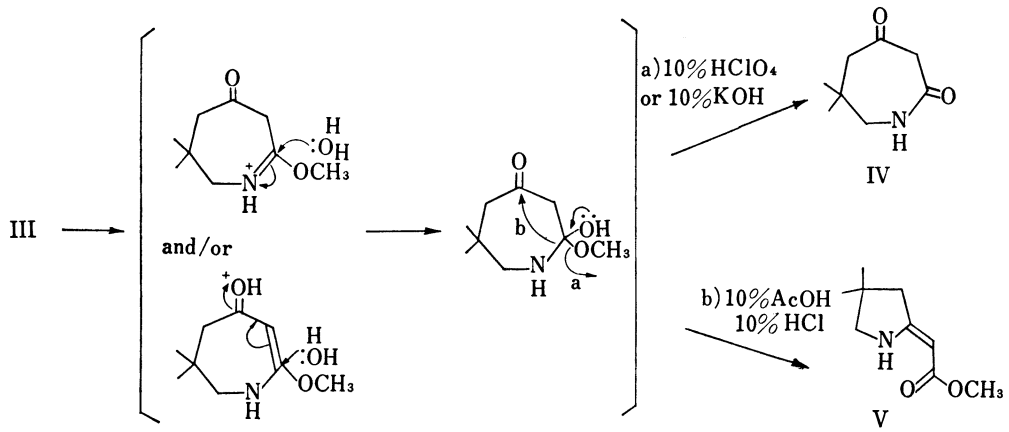


Chart 2

4) P.J. Brignell, E. Bullock, U. Eisner, B. Gregory, A.W. Johnson, and H. Williams, *J. Chem. Soc.*, **1963**, 4819; M. Anderson and A.W. Johnson, *ibid.*, **1965**, 2411; R.F. Childs and A.W. Johnson, *ibid.* (*C*), **1966**, 1950; R.F. Childs, R. Grigg, and A.W. Johnson, *ibid.* (*C*), **1967**, 201.
5) Leo A. Paquette, *J. Am. Chem. Soc.*, **85**, 3288 (1963).
6) S. Sato, *Bull. Chem. Soc. Japan*, **41**, 2524 (1968).
7) Y. Tamura, Y. Kita, Y. Matsutaka, and M. Terashima, *Chem. & Ind.*, **1970**, 1350.

CH_3), 7.58 (3/5×2H, s, $COCH_2$), 6.98 (3/5×2H, d, CH_2N), 6.33 (3/5×3H, s, OCH_3), 5.36 (3/5×1H, d, CH=) and 4.5—4.9 (3/5×1H, b-s, NH), signals due to IIIB, 8.96 (2/5×6H, s, di-CH_3), 7.67 (2/5×2H, s, CH_2CO), 6.77 (2/5×2H, s, CH_2N), 6.71 (2/5×2H, s, $COCH_2C{=}N$) and 6.28 (2/5×3H, s, OCH_3).

Treatment of III with 10% acetic acid or 10% hydrogen chloride brought about a ring contraction to give methyl 4,4-dimethyl-2-pyrrolidylideneacetate (V), mp 85° (from water), in 71% or 63% yield; UV λ_{max} (EtOH) mμ: 282 (log ε 4.24). IR ν_{max} ($CHCl_3$) cm^{-1}: 3380 (NH hydrogen-bonded with ester carbonyl), 1660 and 1600 ($N{-}C{=}C{-}CO_2CH_3$). NMR ($CDCl_3$) τ: 8.88 (6H, s, di-CH_3), 7.66 (2H, s, $CH_2C{=}$), 6.76 (2H, s, CH_2N), 6.38 (3H, s, OCH_3), 5.50 (1H, s, CH=) and 2.1—2.3 (1H, b-s, NH).

A similar series of the reactions employed for V converted 3-chloro-2-cyclohexen-1-one to ethyl 2-pyrrolidylideneacetate,[8] mp 63° (lit.[8] 63—63.5°), *via* 2-ethoxy-4,5,6,7-tetrahydr - 1H-azepin-4-one. The ring contraction and hydrolysis of III may be reasonably explained by the mechanism as shown in Chart 2.

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8) Z. Horii, K. Morikawa and I. Ninomiya, *Chem. Pharm. Bull.* (Tokyo), **17**, 2230 (1969).

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A New Trichloro-depsidone from a Lichen of the Genus *Caloplaca*

Very recently, Santesson[1] has reported an extensive phytochemical study on the anthraquinone components in *Caloplaca* spp. (Caloplacaceae), where he has covered 230 species of the genus, while shortly before that Bohman surveyed the anthraquinones in some lichens of the same genus.[2] On the other hand, during the course of the investigations on the lichen phenolic products[3] we have been aware of the rich phenolic components of an orange crustose lichen[4] belonging to the genus *Caloplaca* collected at Settsu-kyō in Osaka prefecture. Since no work has been done on the metabolic products other than anthraquinones of *Caloplaca* spp., we have performed the structural study on the phenolic products of the lichen and reached a conclusion leading the structures I and II to the depsidones as described below.

Successive extraction of the lichen using ether and acetone followed by silica gel chromatography (column and thin-layer chromatography (TLC)) furnished four anthraquinone derivatives, *i.e.* parietin (III) (0.80%), fallacinal (IV) (0.15%), fallacinol (V) (trace), and emodin (VI) (trace), in addition to two chlorine-containing depsidones tentatively designated Ca-III (1.78%) and Ca-II (0.45%).

1) J. Santesson, *Phytochemistry*, **9**, 2149 (1970).
2) G. Bohman, *Phytochemistry*, **8**, 1829 (1969); **9**, 461 (1970).
3) *a*) I. Yosioka, H. Yamauchi, K. Morimoto, and I. Kitagawa, *Tetrahedron Letters*, **1968**, 1149; *b*) *Idem*, *ibid.*, **1968**, 3749; *c*) *Idem*, *Journ. Jap. Bot.* (Tokyo), **43**, 343 (1968); *d*) I. Yosioka, T. Nakanishi, S. Izumi, and I. Kitagawa, *Chem. Pharm. Bull.* (Tokyo), **16**, 2090 (1968); *e*) I. Yosioka, Y. Morita, and K. Ebihara, *ibid.*, **18**, 2364 (1970).
4) The identification of the lichen is in progress.