The Synthesis of dl-Nepetalactone

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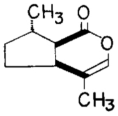
The authors wish to report the synthesis of *dl*-nepetalactone, the levorotatory form of which was first isolated in 1941 from the oil of catnip plant, *Nepeta cataria* L., by S. M. McElvain et al.(1), and was later shown clearly to be I(2,3).



I

Ethyl 3-methyl-2-oxocyclopentanecarboxylate(4) (II) was condensed with 3-bromobutyne(5) to give III, b. p. 99°C/1 mmHg ($\nu_{C\equiv C}$ 4.72 μ, $\nu_{C=O}$ 5.72 μ, 5.86 μ), which was, after hydration, hydrolyzed to diketone IV, b. p. 86°C/1 mmHg (Found : C, 70.97 ; H, 9.44. Calcd. for $C_{10}H_{16}O_2$: C, 71.39 ; H, 9.59%) ($\nu_{C=O}$ 5.78 μ, 5.86 μ). IV was converted through intramolecular condensation into bicyclic α, β-unsaturated ketone V, b. p. 66~70°C/1 mmHg (λ_{max}^{EtOH} 240 mμ, ε=21,000; $\nu_{C=O}$ 5.88 μ, $\nu_{C=C}$ 6.01 μ). Semicarbazone : m. p. 188~189°C ; 2, 4-dinitrophenylhydrazone : m. p. 213°C. Catalytic hydrogenation of V afforded saturated ketone VI, b. p. 72~75°/ 2 mmHg (Found: C, 78.57 ; H, 10.57. Calcd. for $C_{10}H_{16}O$: C, 78.89; H, 10.59%) ($\nu_{C=O}$

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1) S. M. McElvain, R. D. Bright and P. R. Johnson, *J. Am. Chem. Soc.*, **63**, 1558 (1950).

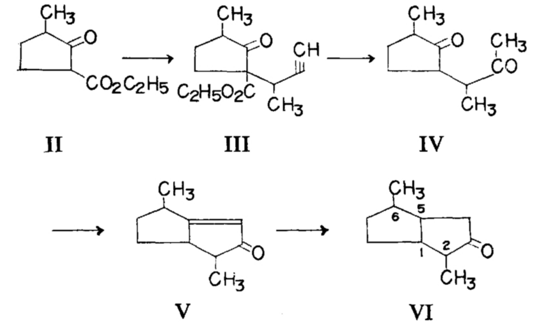
2) J. Meinwald, ibid., **76**, 4571 (1954).

3) R. B. Bates, E. J. Eisenbraun and S. M. McElvain, ibid., **80**, 3420 (1958).

4) W. Dieckmann, *Ann.*, **317**, 37 (1903).

5) M. T. Rogers and M. B. Panish, *J. Am. Chem. Soc.*, **77**, 3684 (1955).

5.78 μ), likely fulfilling the stereochemical requirements ($H_{(C-1)}-H_{(C-5)}-H_{(C-6)}$: cis-trans). 2, 4-Dinitrophenylhydrazone of VI: m. p. 87∼88°C.

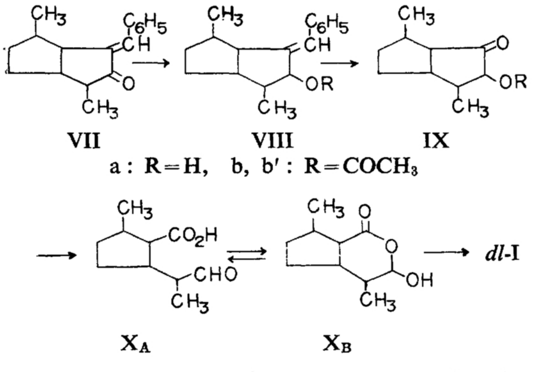


II III IV

V VI

To make sure the above stereospecificity, the benzylidene derivative (VII), b. p. 110∼120°C/0.005 mmHg (λ_{max}^{EtOH} 303 mμ, $\varepsilon=13{,}000$; $\nu_{C=O}$ 5.86 μ, $\nu_{C=C}$ 6.18 μ) (2, 4-dinitrophenylhydrazone: m. p. 181∼182°C), of VI was ozonolyzed. A dicarboxylic acid, $C_{10}H_{16}O_4$ (Found: C, 60.29; H, 8.29. Calcd.: C, 59.98; H, 8.05%), m. p. 124.5∼126°C, was obtained as an oxidation product. As the IR spectrum of this compound in carbon disulfide was in good accord with that of one (m. p. 85°C[3]) of nepetalinic acids, the acid in hand was distinctly racemic *cis-trans*-nepetalinic acid (m. p. in lit.[6]: 127°C).

Then VII was reduced with sodium borohydride to unsaturated alcohol VIIIa, b. p. 110∼128°C/0.015 mmHg (ν_{OH} 2.98 μ). Acetylation of VIIIa yielded a crystalline acetate (VIIIb), m. p. 120∼121°C (Found: C, 79.90; H, 8.55. Calcd. for $C_{19}H_{24}O_2$: C, 80.24; H, 8.51%) and an oily one (VIIIb′), b. p. 105∼108°C/0.025 mmHg (Found: C, 80.09; H, 9.00%) ($\nu_{C=O}$ 5.77 μ), the latter predominating much over the former.



VII VIII IX

a : R=H, b, b′ : R=$COCH_3$

X_A X_B

dl-I

When VIIIb was, after ozonolysis and hydrolysis, oxidized with permanganate, a dicarboxylic acid, $C_{10}H_{16}O_4$ (Found: C, 60.11; H, 8.26%), m. p. 158∼159°C, was the only product, which showed an IR absorption undoubtedly different from that given by either of the nepetalinic acids (m. p. 85°C and m. p. 117∼118°C). Therefore, the crystalline acetate might result from the ketone of cis-cis-series corresponding to VI, formed in a small quantity in the process IV → V → VI.

VIIIb′ was ozonolyzed to α-acetoxyketone IXb, b. p. 70∼73°C/0.05 mmHg (Found: C, 68.17; H, 8.84. Calcd. for $C_{12}H_{18}O_3$: C, 68.54; H, 8.63%). On treatment with diluted alkali, IXb afforded α-ketol IXa (ν_{OH} 2.89 μ, $\nu_{C=O}$ 5.80 μ), which was too unstable to be distilled, and was immediately oxidized with periodate to aldehyde carboxylic acid X_A. The product, with some charactor of lactol X_B, was dehydrated to *dl*-nepetalactone (*dl*-I), b. p. 135°C (bath temp.)/7 mmHg ($\nu_{C=O}$ 5.68 μ, $\nu_{C=C}$ 5.93 μ) by heating at about 200°C. The synthesized lactone accorded in all respects with the natural lactone in their IR charts except only a slight difference of the absorption intensities near 11.4 and 12.2 μ.

The authors are grateful to Professor S. M. McElvain for his kind offer of the spectrum chart of nepetalactone for the identification.

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[6] K. J. Clark, G. I. Fray, R. H. Jaeger and Sir R. Robinson, *Tetrahedron*, 6, 217 (1959).