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93\ Hisao Tsukamoto*2 and Minoru Yoshimura*3 : Metabolism of Drugs. XXIV.*1 Biotransformation of Drugs having Cyclohexene Ring. (1). Synthesis of Cyclohexenylglutarimide Derivatives.

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The majority of synthetic organic compounds used as sedative and hypnotic possess two structural similarities, a tertiary or quaternary carbon atom and a peptide unit, such as barbiturates or glutarimides. The introduction of cyclohexene ring into them has an important effect upon their pharmacological activity and on their metabolism.

On the metabolism of barbiturates having a cyclohexene ring, it has been demonstrated by Tsukamoto, *et al.*[1~5] that a metabolite isolated from the urine of rabbits receiving 5-ethyl-5-(1-cyclohexenyl)barbituric acid or 1,5-dimethyl-5-(1-cyclohexenyl)barbituric acid was identical with an oxidation product of these drugs with chromium trioxide and that the cyclohexene ring was selectively oxidized. In the metabolism of cyclohexenylglutarimides, it is also expected that the cyclohexene ring would be preferentially oxidized in animals to the oxo and hydroxyl compounds.

Various derivatives of glutarimides were prepared by Hoffmann, *et al.*[6] but the glutarimide derivative having a cyclohexene ring was only 2-cyclohexenyl-2-phenylglutarimide. A series of cyclohexenylglutarimides was, therefore, prepared in order to investigate their metabolic fate in animals.

The synthesis of glutarimides (VIa~VId) was accomplished by converting the corresponding glutaronitriles (Va~Vd) which were synthesized by the Michael condensation.[7] Cyclohexylidenecyanoacetate (II) prepared by the method of Cope[8] was alkylated to alkylcyclohexenylcyanoacetate (III) and then (III) was converted to alkylcyclohexenylacetonitrile (IV) by the hydrolysis, acidification, and decarboxylation. On the other hand, phenyl-1-cyclohexenylacetonitrile (VIII) was synthesized from phenylacetonitrile (VII), cyclohexanone, and sodium ethoxide by the method of Harding.[9] The cyanoethylation of alkyl- or phenyl-1-cyclohexenylacetonitrile (IV or VIII) in the presence of methanolic potassium hydroxide

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5) H. Yoshimura : *Ibid.*, **5**, 561 (1957).
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7) A. Michael, J. Ross : J. Am. Chem. Soc., **52**, 4598 (1930).
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9) V.J. Harding, W.N. Haworth, W.H. Perkin : J. Chem. Soc., **1910**, 486.

solution or potassium ethoxide gave alkyl- or phenyl-1-cyclohexenylglutaronitrile (Va~Vc or Vd), respectively. This synthetic pathway is summarized in Chart 1. 2-Methyl-, -ethyl-, -propyl-, and -phenyl-2-(1-cyclohexenyl) glutarimides were synthesized.

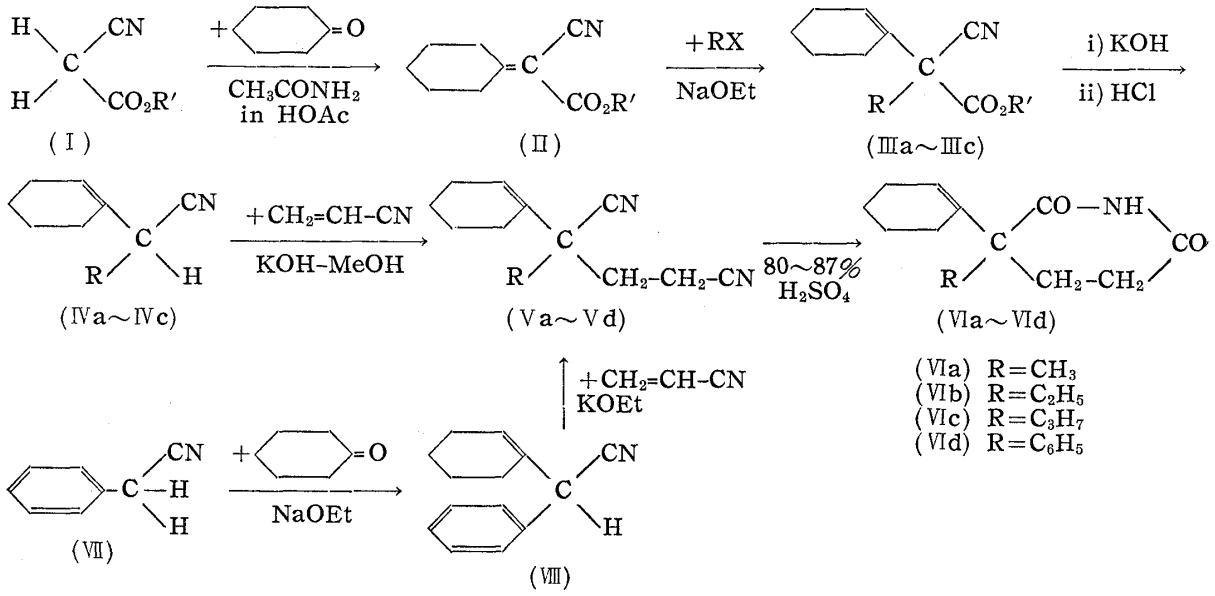


Chart 1. The Synthetic Pathway of 2-Alkyl- or 2-Phenyl-2-(1-cyclohexenyl)glutarimides

Experimental*4

Ethyl 1-Cyclohexenylalkylcyanoacetate (III)——The following general procedure was used for the alkylation of ethyl cyclohexylidenecyanoacetate (II) which was prepared by the method of Cope.[8] To a stirred solution of 0.1 mole of Na in 70 cc. of dehyd. EtOH, 0.1 mole of (II) was added and 0.12 mole of alkyl bromide was added dropwise at 15~20° during 0.5~1.0 hr. The reaction mixture was maintained on a boiling water bath for 0.5 hr. After cool, the reaction mixture was acidified with dil. HCl and extracted twice with Et_2O. The extract was washed with 2% Na_2CO_3 solution and water, and dried over Na_2SO_4. Removal of Et_2O gave a crude red-brown oily substance, which was repeatedly distilled *in vacuo*. The boiling point and yield of products are shown in Table I.

Alkyl-1-cyclohexenylacetonitrile (IV)——(IV) was prepared by the hydrolysis, acidification, and decarboxylation from (III) by the method of Perkin, *et al.*[9] Ethyl 1-cyclohexenylalkylcyanoacetate (III) was warmed with excess of 15% EtOH-KOH solution at 34~35° for 3 hr., water was then added, EtOH was distilled off in a reduced pressure, the alkaline solution was acidified with H_2SO_4, and repeatedly extracted with Et_2O. The Et_2O solution was dried over Na_2SO_4, Et_2O was evaporated, and the residue was distilled at 80~90 mm. Hg at 120~130°. Decarboxylation occurred and (IV) was obtained as a colorless oil after repeated fractional distillation below 90 mm. Hg. The distillate was redistilled *in vacuo*. The boiling point and yield of (IV) are shown in Table I.

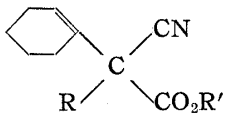
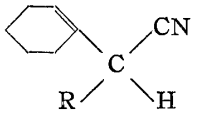
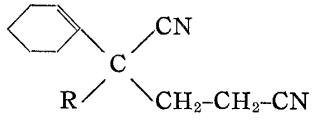
Phenyl-1-cyclohexenylacetonitrile (VIII)——To a stirred solution of 6.6 g. of Na in 150 cc. of dehyd. EtOH, 34 g. of phenylacetonitrile (VII) was added, followed by dropwise addition of 29 g. of cyclohexanone at 20° during 2 hr. The reaction mixture was kept on a boiling water bath for 0.5 hr. and stirring at room temperature was continued for 1 hr. The mixture was extracted with Et_2O, the Et_2O solution was washed with water and 5% Na_2CO_3 solution, and dried over Na_2SO_4. After removal of Et_2O, the brown residue was distilled *in vacuo* and (VIII) was obtained as a pale yellow viscous substance, $b.p_3$ 167~168°; yield, 30 g. (ca. 55%).

2-Alkyl-2-(1-cyclohexenyl)glutaronitrile (V)——To a stirred solution of 0.1 mole of acetonitrile (IV) in 30 cc. of *tert*-BuOH, 3 cc. of 30% MeOH-KOH solution was added, followed by dropwise addition of a solution of 0.12 mole of the freshly distilled acrylonitrile in 20 cc. of *tert*-BuOH at 10~15° during 40 min. Stirring at room temperature was continued for 2 hr. and the mixture was allowed to stand overnight. The reaction mixture was submitted to vacuum distillation at room temperature to remove BuOH, the residue was acidified with AcOH, and extracted repeatedly with Et_2O. Et_2O solution was washed with water, 5% Na_2CO_3 solution, and water, and dried over Na_2SO_4. After removal

*4 All melting points are uncorrected.

of Et_2O, the brown residue was distilled *in vacuo*. The distillate was repeatedly fractionated and refined. The yield of (V) is shown in Table I.

Table I. Boiling Point and Yield of Each Product

Compound			 (IIIa~IIIc)		 (IVa~IVd)		 (Va~Vd)	
	R	R′	b.p. (°C/mm. Hg)	Yield (%)	b.p. (°C/mm. Hg)	Yield (%)	b.p. (°C/mm. Hg)	Yield (%)
a	CH_3	CH_3	140~142/10	60	129~132/12	62	180~181/12	22
b	C_2H_5	C_2H_5	135~140/6	63	93~94/7	50	144~145/2	20
c	C_3H_7	C_2H_5	143~146/6	68	87~90/3	49	103~105/3	26
d	C_6H_5	—	——	—	167~168/3	55	197~199/3	52

2-Alkyl-2-(1-cyclohexenyl)glutarimide (VI)——A mixture of 0.1 mole of glutaronitrile (V), 0.25 mole of H_2SO_4, 30 cc. of glacial AcOH, and 5 cc. of water was refluxed for 1 hr. After cool, the reaction mixture was distilled *in vacuo* to remove AcOH.

The reddish brown residue having green fluorescence was extracted with benzene-water (3:1) mixture. The benzene layer was washed with saturated $NaHCO_3$ solution and water, and dried over Na_2SO_4. After removal of benzene, a brown viscous residue was obtained, which crystallized from MeOH on standing. It was repeatedly recrystallized from MeOH or iso-PrOH. These imides decolorize $KMnO_4$ solution, and color purple with 1% $Co(NO_3)_2$ solution-dil.NH_4OH, and are soluble in NaOH solution, but not in $NaHCO_3$ solution. The data of glutarimides prepared according to the general procedure are shown in Table II.

Table II. Data of 2-Substituted 2-(1-Cyclohexenyl)glutarimides

Compound (VI)	R	Appearance	Solvent	m.p. (°C)	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N	Yield (%)
a	CH_3	leaflets	iso-PrOH	134	$C_{12}H_{17}O_2N$	69.56	8.21	6.76	69.58	8.11	7.02	50
b	C_2H_5	leaflets	MeOH	101~102	$C_{13}H_{19}O_2N$	70.55	8.65	6.33	70.53	8.64	6.32	52
c	C_3H_7	leaflets	iso-PrOH	105	$C_{14}H_{21}O_2N$	71.45	9.00	5.96	71.49	8.63	6.28	47
d	C_6H_5	prisms	iso-PrOH	176	$C_{17}H_{19}O_2N$	75.81	7.11	5.20	75.59	6.93	5.08	56

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Summary

In order to investigate the metabolism of glutarimides having a cyclohexene ring, 2-methyl-, -ethyl-, -propyl-, and -phenyl-2-(1-cyclohexenyl)glutarimide were synthesized by the conversion of the corresponding glutaronitriles prepared by the Michael condensation. The introduction of a cyclohexene ring into cyanoacetate was accomplished by the method of Cope.

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