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Toshiro Murata : The Metabolic Fate of 1-Ethynylcyclohexyl Carbamate. Ⅲ.[*2] Synthesis of 1-Ethynylcyclohexane-1,2-diol.

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It was reported in the previous papers[1,2] that the chief metabolite of 1-ethynylcyclohexyl carbamate (ECC) in man was 1-ethynyl-4-hydroxycyclohexyl carbamate (OH-ECC) and that a small amount of glucuronide of OH-ECC was excreted in human urine. In human experiments, however, the amount of OH-ECC excreted for 8 hours was very small, about 1%,[1] while intact ECC was not recovered. Since the presence of other metabolites of ECC was supposed from these findings, their detection was attempted.

OH-ECC was isolated from dichloromethane-soluble metabolite by passing through alumina column and eluting with benzene + dichloromethane. After isolation of OH-ECC, the column was eluted with methanol and a substance having ethynyl group and reacting with sodium periodate reagent[*2] on paper chromatogram was found in the methanol-soluble fraction. This finding suggested the presence of 1,2-diol. This 1,2-diol was extracted from the paper and isolated as an oily compound. In order to have the authentic synthetic sample of 1-ethynylcyclohexane-1,2-diol, the synthesis of this compound was attempted.

The synthesis was carried out by the route shown in Chart 1.

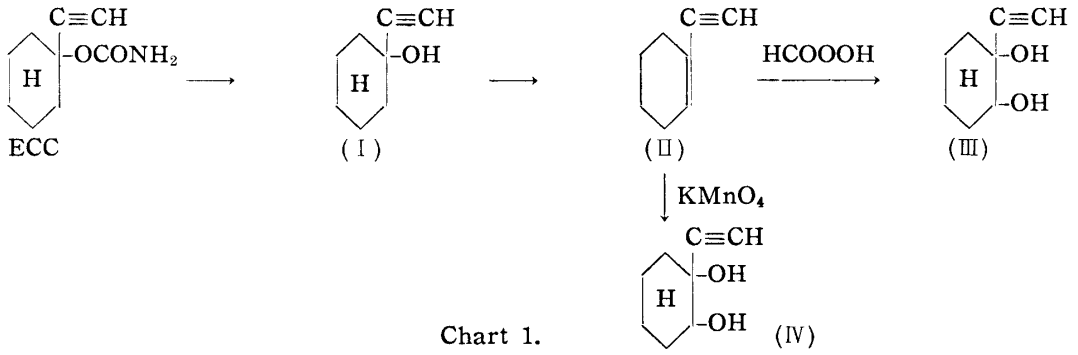

Chart 1.

1-Ethynylcyclohexanol (I) was readily prepared by hydrolysis of ECC. Dehydration of (I) was successfully effected with phosphoryl chloride,[2] but the product (Ⅱ) was not identified chemically as 1-ethynylcyclohexene, because of its instability. Its oxidation was carried out with performic acid or with potassium permanganate.

Price and Berti[3] reported that cyclohexene was oxidized to the corresponding epoxy compound by treating with performic acid and *trans*-1,2-cyclohexanediol was prepared by treatment with alkali. Thus, (Ⅱ) was oxidized according to their procedure and a crystalline compound (Ⅲ), m.p. 73.5~74.5°, was obtained. The compound was consistent with the structure of 1-ethynylcyclohexanediol from its analysis and infrared spectrum, and the structure of 1-ethynylcyclohexane-*trans*-1,2-diol was supposed from its synthetic method. Catalytic hydrogenation of (Ⅲ) gave 1-ethylcyclohexane-*trans*-1,2-diol.[4]

The corresponding *cis*-isomer of (Ⅲ) was prepared according to the method described by Clarke and Owen.[5] The product (Ⅳ) was liquid and could not be identified as 1-ethynyl-

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*2 Part Ⅱ : This Bulletin, **9**, 146 (1961).

1) T. Murata : This Bulletin, **8**, 629 (1960).
2) J. C. Hamlet, H. B. Henbest, E. R. H. Jones : J. Chem. Soc., **1951**, 2656.
3) C. C. Price, G. Berti : J. Am. Chem. Soc., **76**, 1211 (1954).
4) P. R. Jefferies, B. Milligan : J. Chem. Soc., **1956**, 4384.
5) M. Clarke, L. Owen : *Ibid.*, **1949**, 318.

cyclohexane-*cis*-1,2-diol, because of its instability. (IV) was further hydrogenated and the analysis and melting point of the crystalline product were identical with those of 1-ethylcyclohexane-*cis*-1,2-diol.

Experimental

Hydrolyzation of ECC—In the flask fitted with a reflux condenser, 77.8 g. of ECC was heated with 1875 cc. of 3% KOH-EtOH solution for 12 hr. The reaction mixture was neutralized with 10% HCl and filtered. The filtrate was concentrated under a reduced pressure and the product, a yellow oily substance, was extracted with Et_2O. The extract was dried over anhyd. Na_2SO_4 and the solvent was evaporated. The residual pale yellow liquid was distilled in a reduced pressure and the fraction of $b.p_7$ 61～63° was collected. The product crystallized in a refrigerator; m.p. 30°. Yield, 46.1 g. *Anal.* Calcd. for $C_8H_{12}O$: C, 77.37; H, 9.74. Found: C, 77.02; H, 9.62.

Dehydration of (I)—In a three-necked flask fitted with a reflux condenser, stirrer, and a separatory funnel, 46 g. of (I) was dissolved in 69 cc. of dehyd. pyridine, and 25.3 cc. of $POCl_3$ was added with heating the reaction mixture to boil and constant stirring for 1 hr. After the reaction was over, the content of the flask was poured on ice and the separated organic layer was extracted with pentane. The extract was distilled in a reduced pressure and the distillate (II) of $b.p_{30}$ 47～48° was collected. Yield, 33.6 g. The product (II), which was supposed to be 1-ethynylcyclohexene, was very labile and colored soon in air. Further studies on the property of (II) were hard to carry out.

Oxidation of (II) with Performic Acid—In the flask fitted with a condenser, 105 g. of 95% HCOOH, 13 g. of 30% H_2O_2, and 10.35 g. of (II) were well mixed and the mixture was heated in a boiling bath for 2 hr. After oxidation was over, excess HCOOH was distilled off and 50 cc. of 20% NaOH was added to the content of the flask. The flask was heated again at 100° for 45 min., the reaction mixture was cooled, and neutralized with HCl. The neutral product was distilled in a reduced pressure and the distillate of $b.p_{12}$ 77～78° was collected. This pale yellow liquid crystallized by storage in a desiccator for a few days. Recrystallization from benzene gave 1-ethynylcyclohexane-*trans*-1,2-diol (III), m.p. 73.5～74.5°. Yield, 3.4 g. *Anal.* Calcd. for $C_8H_{12}O_2$: C, 68.5; H, 8.50. Found: C, 68.11; H, 8.44. IR ν_{max}^{Nujol} cm^{-1}: 3340 (C≡C), 3220 (-OH), 2110 (-C≡CH); δ, 1388 (C-O tert.), 1302 (C-O sec.), 1154 (C-O tert.), 1065 (C-O sec.).

Catalytic Hydrogenation of (III)—One-half g. of 1-ethynylcyclohexane-*trans*-1,2-diol was converted quantitatively to the corresponding 1-ethylcyclohexane-*trans*-1,2-diol by hydrogenation at atmospheric pressure using Pd-$CaCO_3$ as a catalyst. The product was recrystallized on refrigeration for some days and formed prisms (from hexane), m.p. 47～48° (reported[4] m.p. 47°). *Anal.* Calcd. for $C_8H_{16}O_2$: C, 66.63; H, 11.18. Found: C, 66.35; H, 11.05.

Oxidation of (II) with Potassium Permanganate—A solution of 25 g. of $KMnO_4$ and 20 g. of anhyd. $MgSO_4$ dissolved in 500 cc. of H_2O was added gradually to a suspension of 16.5 g. of (II) in 300 cc. of EtOH with vigorous stirring. After addition was over, the reaction mixture was stirred for 1.5 hr., the temperature being kept between −15° and −20°, during all the procedure. After filtration, the solution was concentrated to small volume, saturated with NaCl, and extracted with $CHCl_3$ to yield a brown liquid. The liquid was distilled in a reduced pressure and the fraction boiling above 95°/6 mm. Hg was collected. The distillate (IV) did not solidify by refrigeration, but reacted with Tollens and $NaIO_4$ reagents.*2

Catalytic Hydrogenation of (IV)—(IV) was hydrogenated over Pd-$CaCO_3$ catalyst and the product was crystallized from petr. ether; m.p. 82～83° (reported[4] m.p. 81°). *Anal.* Calcd. for $C_8H_{16}O_2$: C, 66.63; H, 11.18. Found: C, 66.21; H, 10.95.

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Summary

One of metabolites of ECC in human urine was assumed to be 1-ethynylcyclohexane-1,2-diol from its color reaction. For confirmation, 1-ethynylcyclohexane-*trans*-1,2-diol and its isomer were synthesized from ECC and the two products prepared were confirmed as the same 1,2-diols by catalytical reduction.

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