

Formation of Cyclohexano[c]1, 2, 5-oxadiazole from 1, 2-Cyclohexanedione Dioxime. An Attempted Beckmann Rearrangement with Thionyl Chloride in Liquid Sulfur Dioxide^{1,2)}

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It has already been shown by the present authors^{2,3)} and also by other writers⁴⁾ that the direction of the migratory aptitude in the Beckmann rearrangement was often changed by the circumstances, by the reagents or for other reasons. A transannular rearrangement

was observed when 1,6-cyclodecanedione dioxime was subjected to the rearrangement with thionyl chloride in place of sulfur trioxide in liquid sulfur dioxide³⁾.

1) The Beckmann rearrangement in liquid sulfur dioxide. Part VII.

2) Part VI; R. Tada, Y. Masubuchi and N. Tokura, This Bulletin, in press.

3) N. Tokura, R. Tada and K. Suzuki, *ibid.*, **32**, 654 (1959).

4) Y. Yukawa, "Jikken Kagaku Koza", Vol. 18, Maruzen, Tokyo (1958), p. 426; A. D. McLaren and R. E. Schat, *J. Org. Chem.*, **14**, 254 (1959); R. F. Brown, N. M. van Gulick and G. H. Schmid, *J. Am. Chem. Soc.*, **77**, 1094 (1955); R. Huisgen, J. Witte and I. Ugi, *Ber.*, **90**, 1844 (1957).

Tada, Masubuchi and Tokura²⁾ carried out the Beckmann rearrangement of the geometrical isomers of cyclohexyl phenyl ketoximes in liquid sulfur dioxide without any appreciable difference of the migratory aptitude by a variety of reagents at -70°C .

The Beckmann rearrangements of 1,2-diketone dioximes have scarcely been reported at all, but those of 1,2-diketone monoximes have been examined extensively to yield nitriles and carboxylic acid as the result of cleavage^{5,6)} of the dione monoximes. A number of trials of the Beckmann rearrangement on benzil dioximes have been reported since the turn of the last century⁷⁻⁹⁾ but the result were subjects of controversy¹⁰⁾ and the presence of geometrical isomers in the dioxime led the direction of the rearrangement to various products, for example, 3,5-diphenyl-1,2,4-oxadiazole, oxanilide and so on, among which the derivation of the 1,2,4-oxadiazole was ascribed to the Beckmann rearrangement of one of the two oximino groups, followed by dehydration. The reagents used were phosphorus pentachloride, phosphorus pentoxide, phosphoryl chloride and sulfuric acid. Of the three isomers, only the γ -isomer was reported to yield oxanilide, a product of the double Beckmann rearrangement, whereas the α - and β -isomers gave the diphenyl-1,2,4-oxadiazole. Recently, Conley and Mikulski⁶⁾ have obtained the same oxadiazole with polyphosphoric acid as the reagent.

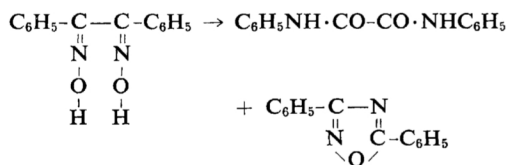


Chart 1.

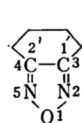
The present paper describes the experiments which have been undertaken to throw light upon the nature and the migratory tendency of 1,2-cyclohexanedione dioxime in sulfur dioxide. The preparation of the 1,2-cyclohexane dioxime has been reported in a number of papers, of which the method of Belcher, Hoyle and West¹¹⁾ has been adopted. This method, consisting in the oximation of 2-bromocyclohexanone (Ia), is essentially similar

to that of Tokura and Oda¹²⁾ which was published earlier in 1943 and uses 2-chlorocyclohexane (Ib) as the starting material. The former method is however more convenient for laboratory work. To our regret, however, neither method was satisfactory enough to be a standard method of preparation owing to the formation of many resinous matters and unavoidable fluctuation in the yields.

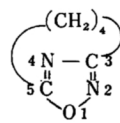
1,2-Cyclohexanedione dioxime (II) was obtained in yields of 10~34% as crystals of m.p. $185\sim186^{\circ}\text{C}$ (literature¹¹⁾, $186\sim187^{\circ}\text{C}$), from which it was impossible further to separate the possible isomers by repeated crystallization or by repeated precipitation. Since the various reagents examined on this material have given no symptom of the geometrical isomers which will be reported in the following paper, the problem of the possible isomers was shelved in this project.

In this light of such a consideration, it is interesting to examine the direction of the Beckmann rearrangement, but contrary to expectation, the rearrangement was not caused by thionyl chloride in liquid sulfur dioxide. When thionyl chloride was used as the reagent, a low melting material III, m.p. 26°C , was obtained in a yield of 70% by ether extraction of the residue obtained on evaporation of sulfur dioxide from the reaction mixture. Although the elementary analysis was consistent with the anhydride of the dioxime II, there still remained another possibility of the presence of isomeric matters such as those produced by single and/or double rearrangement followed by dehydration. As cited above, benzil dioxime gave in such a case 3,4-diphenyl-1,2,4-oxadiazole and oxanilide, products of single and double rearrangement, respectively.

If the anhydride was formed by a simple dehydration without rearrangement, the structure must be a 1,2,5-oxadiazole derivative A, and not a 1,2,4-oxadiazole derivative B.



(A)



(B)

The I. R. spectrum of III showed the characteristic absorption of a 1,2,5-oxadiazole(furazan)¹³⁾ at 1630 and 1588 cm^{-1} . This substance was very stable and resisted hydrolysis on refluxing with concentrated hydrochloric acid for 5 hr., with aqueous 25% caustic soda for 6.5 hr., with aqueous 40% sulfuric acid for 7 hr. and

5) D. Murakami and N. Tokura, *This Bulletin*, **31**, 1044 (1958).

6) K. J. Conley and F. A. Mikulski, *J. Org. Chem.*, **24**, 97 (1959).

7) K. Awers and V. Meyer, *Ber.*, **21**, 810 (1888).

8) E. Beckmann and A. Koster, *Ann.*, **274**, 18 (1893).

9) A. Günther, *Ber.*, **21**, 517 (1888); *Ann.*, **257**, 46 (1889).

10) J. Meisenheimer and W. Lamparter, *Ber.*, **57**, 276 (1924).

11) R. Belcher, W. Hoyle and T. S. West, *J. Chem. Soc.*, **1958**, 2743.

12) N. Tokura and R. Oda, *Sci. Papers Inst. Phys. Chem. Research (Tokyo)*, **22**, 8501 (1943).

13) R. J. Gaughran et al., *J. Am. Chem. Soc.*, **76**, 2233 (1954).

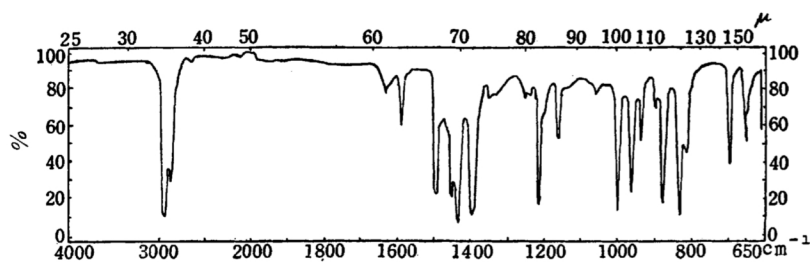


Fig. 1. I. R. spectrum of III.

heating with concentrated sulfuric acid for 5 hr. on a steam bath. Oxidation with chromic anhydride in acetic acid or with ozone in 50% acetic acid and reduction with tin and hydrochloric acid were all ended in the recovery of the starting compound. The compound underwent an oxidation only with potassium permanganate in dilute sulfuric acid to yield a dicarboxylic acid, $C_6H_6O_5N_2$, m. p. 147~148°C (decomp.), which showed no coloration with a nickel salt and is assigned to the structure of IVa. Another possible structure IVb is ruled out because the cleavage of this sort may be more difficult than the cleavage to afford IVa.

The exhaustive oxidation of the compound with the same oxidant gave a dicarboxylic acid, m. p. 178°C (decomp.), 1,2,5-oxadiazole-3,4-dicarboxylic acid (V), (literature¹⁴), m. p. 178°C, the structure being proved as V by elementary analysis and mixed melting point.

Bower^{17b}) and by Smith¹⁶). Wallach^{17a}) prepared the compound VII from II by reduction with zinc and alkali and a structure of decahydrophenazine was assigned, but recently^{17b}) it was found to be octahydrophenazine.

It was reported as early as in 1886 that 3,4-diphenyl-1,2,5-oxadiazole¹⁸) was synthesized from benzil dioxime by the reaction with potassium ferricyanide. The present authors have devised a method of synthesis of compound III in a low yield by refluxing II in aqueous 10% sodium hydroxide. The coincidence of the melting point and the mixed melting point, and the I. R. spectra of the two materials confirmed the structure III unequivocally.

Thionyl chloride is one of the most powerful reagents to effect the Beckmann rearrangement. The failure of the rearrangement of II with thionyl chloride in liquid sulfur dioxide in contrast to benzil dioxime suggests some meaning. Benzil dioxime has presumably a coplanar structure favorable for a Beckmann rearrangement at least in one moiety of the molecule, whereas cyclohexanedione dioxime will prefer dehydration rather than a Beckmann rearrangement since it is sterically more restricted than benzil dioxime to build an intermediate azilinium cation¹⁹) (aza-cyclopropenyl cation). In addition, the formation of the intermediate cation of benzil dioxime may be facilitated by the presence of phenyl ring participation in the rearrangement.

Gillis²⁰) recently reported that a cyclic sulfite derived from tetramethylene glycol and thionyl chloride gave tetrahydrofuran without stopping at the stage of a cyclic sulfone via the Bissinger rearrangement²¹). The formation of the anhydride III may likely proceed through cyclic sulfite IIa and sulfone IIb (Chart 3).

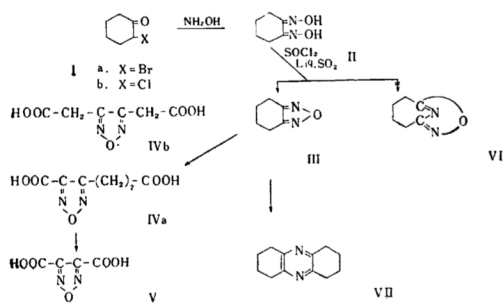


Chart 2.

Another evidence of structure III as the anhydride of the unrearranged dioxime was attained by reduction with sodium in ethanol. The use of lithium aluminum hydride was avoided because of the possible rearrangement¹⁵) by this reagent. The reduction of III gave a basic compound, the analysis and the melting point corresponding to octahydrophenazine, $C_{12}H_{16}N_2$ (VII), m. p. 108~109°C, which was prepared by Wallach^{17a}), by Baumgarten and

14) L. Wolff, *Ber.*, **28**, 69 (1895); A. Quilico and M. Freri, *Gaz. chim. Ital.*, **76**, 3 (1946), *Chem. Abstr.*, **41**, 382d (1947).

15) A. T. Blomquist, B. F. Hallam and A. D. Josey, *J. Am. Chem. Soc.*, **81**, 678 (1959).

16) P. A. S. Smith, *ibid.*, **70**, 323 (1948).

17) a. A. Wallach, *Ann.*, **437**, 177 (1924); b. H. E. Baumgarten and F. A. Bower, *J. Am. Chem. Soc.*, **76**, 4561 (1954).

18) R. Koreff, *Ber.*, **19**, 176 (1886).

19) R. Huisgen, J. Witte and I. Ugi, *Ber.*, **90**, 1844 (1957).

20) R. G. Gillis, *J. Org. Chem.*, **25**, 651 (1960).

21) W. E. Bissinger, F. E. King and C. W. Hamilton, *J. Am. Chem. Soc.*, **70**, 3940 (1948).

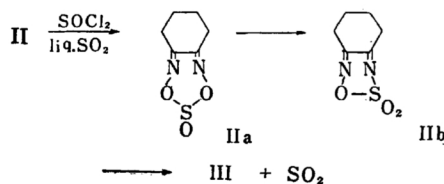


Chart 3.

A variety of products have also been obtained as the results of the attempted Beckmann rearrangement with some other reagents. The results will be reported elsewhere in near future.

Experimental

Material.—Commercial sulfur dioxide was dried with concentrated sulfuric acid and distilled. A commercial thionyl chloride was redistilled.

Apparatus and General Procedure.—The procedure and manipulation for the Beckmann rearrangement were essentially the same as described earlier^{1,2)}.

1,2-Cyclohexanedione Dioxime (II).—To a refluxed mixture of hydroxylamine hydrochloride (227 g.), sodium acetate (45 g.), methanol (400 ml.) and water (460 ml.) was added 128 g. of 2-bromocyclohexanone (Ia) gradually. After the mixture was refluxed for 45 min., it was condensed and diluted with water. The crystals were recrystallized from water, m. p. 186–187°C. Yield, 31 g. (34%).

Found: N, 19.66. Calcd. for $\text{C}_6\text{H}_{10}\text{O}_2\text{N}_2$: N, 19.71%.

Reaction of II with Thionyl Chloride in Liquid Sulfur Dioxide.—A mixture of the dioxime II (7.1 g.), thionyl chloride (13.0 g.) and 150 ml. of liquid sulfur dioxide was allowed to stand for an hour at room temperature. The solution was then poured into ice water, sulfur dioxide was evaporated and the residue was extracted with ether. The ether solution was washed with water, dried and condensed to give 5 g. (70%) of colorless crystals III, m. p. 26°C (recrystallized from ethanol), b. p. 99–101.5°C (13 mmHg). The substance was later identified as cyclohexano[c]1,2,5-oxadiazole.

Found: C, 58.19; H, 6.16; N, 22.10. Calcd. for $\text{C}_6\text{H}_5\text{ON}_2$: C, 58.05; H, 6.50; N, 22.57%. Mol. wt. Found: 139.5 (benzene). Calcd.: 124.

I. R. $\nu_{\text{max}}^{\text{liq}}$ 1588(m) (C=N-), and 2960(s), 2880(s) (CH_2), cm^{-1} , U. V. $\lambda_{\text{max}}^{\text{MeOH}}$ 220 μ ($\log \epsilon = 3.56$). No significant amount of any other material was found in the residual solution after the ether extraction.

Synthesis of III with Alkali.—With 20 ml. of 10% aqueous sodium hydroxide, 3 g. of II was refluxed for 1.5 hr. The reaction mixture was extracted with ether. After the distillation of the ether, a small quantity of crystals was obtained as the residue. This was recrystallized from ethanol, m. p. 25.5–26.0°C, b. p. 180–196°C (18 mmHg), 0.3 g. (10%). This material showed no depression of melting point when mixed with III from II and thionyl chloride and gave an I. R. spectrum com-

pletely identical with that given by the specimen obtained from II and thionyl chloride.

Oxidation of III with Potassium Permanganate.

—To 10 ml. of 10% aqueous solution of sulfuric acid was added 1.5 g. of III and the mixture was stirred and heated on a water bath. About 2.0 g. of potassium permanganate was added to the mixture bit by bit till the permanent red color remained. The precipitate of manganese dioxide was dissolved by introducing sulfur dioxide gas, and the mixture was extracted with ether, and the extract was condensed to give 1.3 g. (86.7%) of colorless fine crystals IVa, m. p. 147–148°C (decomp.) (from acetone-ligroin), IVa was soluble in hot water, alkali, alcohol and acetone, but insoluble in benzene.

Structure of 4-ethyl-1,2,5-oxadiazole-3,2'-dicarboxylic acid (IVa) was assigned.

Found: C, 38.08; H, 3.62; N, 14.78. Calcd. for $\text{C}_6\text{H}_6\text{O}_5\text{N}_2$: C, 38.72; H, 3.25; N, 15.02%. Acid value, Found: 628. Calcd. for 2-COOH: 617.0. I. R. $\nu_{\text{max}}^{\text{KBr}}$ 3400–3540 (–OH) and 1695 ($>\text{CO}$) cm^{-1} . White precipitates with Ag^+ and Ba^{2+} ions. No red coloration with Ni^{2+} .

Exhaustive Oxidation of IVa.—A mixture of 0.5 g. of IVa, 1.0 g. of potassium permanganate and 10 ml. of 10% sulfuric acid was stirred and warmed for two days on a water bath. The precipitate of manganese dioxide was dissolved by passing sulfur dioxide gas. Extraction of the mixture with ether followed by condensing the ether solution yielded 0.1 g. of fine crystals V, m. p. 178°C (decomp.). (repeated recrystallization from alcohol.)

Found: N, 17.78. Calcd. for $\text{C}_4\text{H}_2\text{O}_5\text{N}_2$: N, 17.72%.

V was mixed with an authentic specimen of 1,2,5-oxadiazole-3,4-dicarboxylic acid prepared by the method of Wallach^{17a)} to show no melting point depression.

Reduction of III with Sodium and Ethanol.

—To a solution of 2.0 g. of III in 100 ml. of ethanol was added 5 g. of metallic sodium with stirring. The mixture was further refluxed for 1.5 hr. and then a half of the ethanol was evaporated. The residual mixture was acidified with concentrated hydrochloric acid and was extracted with ether. Evaporation of the ether extract gave 0.4 g. of a product which was identified as the starting material III. The residual solution was again made alkaline with soda ash and the mixture was again extracted with ether. Evaporation of the ether extract gave colorless needles VII contaminated with a brown resinous matter. The needles sublimed at 60–80°C (15 mmHg). The needles were repeatedly recrystallized from ethanol to m. p. 108–109°C. Picrate, yellow needles, m. p. 155°C (decomp.).

Base: Found: C, 75.89; H, 8.10; N, 14.46. Calcd. for $\text{C}_{12}\text{H}_{16}\text{N}_2$: C, 76.55; H, 8.57; N, 14.88%. Picrate: Found: N, 16.83. Calcd. for $\text{C}_{18}\text{H}_{19}\text{N}_5\text{O}_7$: N, 16.78%.

The material VII was proved to be octahydro-phenazine by admixing with an authentic sample prepared by reduction of II by the method of Wallach. No depression of the melting point^{17a)} was observed.

Summary

An attempted Beckmann rearrangement of 1,2-cyclohexanedione dioxime with thionyl chloride in liquid sulfur dioxide resulted in the formation of cyclohexano[c]1,2,5-oxadiazole in 70% yield. The structure of the oxadiazole was established by oxidation, reduction, and synthesis. The reason why the condensation was predominant over the rearrangement

was discussed in comparison with the case of benzil dioxime.

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