23. Studies on Tropolone Derivatives. III. On Methyl Ethers of Tropolone and Its Halogen Derivatives.

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Nozoe et al.^{1a)} found that the ether (II) of hinokitiol (I), i. e. m-isopropyltropolone, was more similar to the esters of carboxylic acids or enolic ethers than the ethers of aliphatic alcohols and of aromatic phenols, in point of the ease of hydrolysis by acids or alkalis. They assumed that the ease of the hydrolysis of (II) might be caused by the strong inclination of returning to the more stable original state (I), due to the increase in basicity and decrease of stability in (II) resulting from the restriction of resonance by fixation of acidic hydrogen atom which is responsible for the hydrogen bond resonance in (I)²⁾. It was supposed that in contrast with the case of (I), the easy reduction^{1a)} of (II) to saturated cyclic diol by metallic sodium and alcohol was also due to the decreased stability of (II) compared to (I) and especially its salt or anionoid form. Dewar³⁾ assumed for C-ring in colchicine a structure (IIIa) corresponding to methyl ether of tropolone and, moreover, he proposed a resonance with the ionic form (IIIb) to explain its unusually high solubility in water.

As to the ethers of tropoloid compounds, methyl ethers of purpurogallin and stipitatic acid have been reported⁴⁾, but their properties have not been described in detail.

The present paper describes the properties of methyl ethers of tropolone (IV), the mother substance of this series, and its bromo derivatives, considering the characteristic structure and properties of tropoloid compounds, as well as the unique biological action of colchicine.

Nozoe, et al.^{1b)} previously obtained methyl, ethyl and isopropyl ethers of (I) by the action of alkyl halides with Na and Ag salt of (I), but in the case of (IV), due to the very high water-solubility

of the reaction product, this method was found disadvantageous. However, the reaction of (IV) with diazomethane in ether easily gave its methyl ether in crystalline form (Va), m. p. 41°. By drying in vacuum desiccator, or by distillation, it changed to an oily form (Vb), which on standing in the air, returned to crystals, rapidly absorbing 1/2 mole of water, and subsequently absorbed more water slowly (Fig. 1).

This fact and the analytical values of (Va) showed that methyl ether of tropolone is stabilized especially by taking 1/2 mole of water of crystallization. (Va) and (Vb) are soluble in water in any proportions are stable on boiling with water and give no coloration with FeCl_3 . (Va) however, is readily hydrolyzed to (IV), by boiling with dil. acid or dil. alkali (Table I).

Fig. 1. Increase in the weight of (Vb) on standing in the air.

Table I. Hydrolysis of Tropolone Methyl Ether at 100°C. %.

Conc. of Sample (M)	0.0621	0.0296	0.0293
Reagent	H ₂ O	HCl	NaOH
Time (min.)		N/20 × 1.029	N/20 × 0.892
10	0	3.75	51.00
30	0	17.75	89.06
60	0	—	96.29
80	0	31.14	
150	0	45.04	

Hinokitiol and tropolone were previously postulated by Nozoe²⁾ to have three types (A, B and C) of resonance structures with a large number of non-ionic and ionic forms, to explain their remar-

kable characters. From the results of measurements of their dipole moments and magnetic susceptibilities carried out by his co-workers, Kubo, Hazato, et al., it was established that the structure of this system in normal state can be well explained mainly by the resonance of type B^{vi)}. Further, type C can be assumed as the activated structure of fundamental type A in the case of reaction with electrophilic reagents. It is suggested that, in methyl ether of tropolone, due to the substitution of methyl group for acidic hydrogen atom of (IV) which is responsible for the hydrogen bond resonance in tropoloid system, contribution of type A (Vb) in the normal state becomes smaller, while both the basicity of dipolar type (Vc) and the affinity for water are increased. The fact that (Vb) stabilizes by absorbing 1/2 mole of water may be explained by a resonance structure such as (Va). These points will probably be ascertained by the measurements of dipole moments and other physical properties.

The hydrolysis by acid and alkali may be illustrated by the following scheme.

The fact that (VIa) can stabilize itself more easily than (VIIa) is enough to show that this ether is more stable against acid than to alkali.

As in the case of (II), b. p. of (Vb) is higher than that of (IV), contrary to the case of normal ethers, showing the larger contribution of ionic forms in the ether than in tropolone itself.

The coupling of (Vb) with diazonium salt in water does not occur even when alkali is added to pH 8. Bromination of (Vb) in water gives precipitation of tribromotropolone, m. p. 125–126°. (Vb) also does not react with phenylhydrazine, semicarbazide and aniline.

Nozoe, Kitahara, et al.⁹⁾ reported that o-bromotropolone, having an asymmetric structure, gave two kinds of isomeric methyl ethers (m. p. 91.5° and 50°). In the present work, three kinds of bromo derivatives, — i. e. p-monobromotropolone (VIII), o, o'-dibromo-

tropolone (IX) and *o*, *p*, *o'*-tribromotropolone (X) -- each gave only one kind of methyl ether ((VIIIa), m. p. 135–136°; (IXa), 132–132.5°; (Xa), 110–111°), as was expected from their symmetric structures.

These ethers have higher solubility in water than the original substances and are readily hydrolyzed by acid or alkali.

Their infrared and ultraviolet absorption spectra, magnetic susceptibility and other physical properties and their effect on Yoshida sarcoma⁷⁾ as well as on mitotic cells of animals and plants will be reported in the future.

Experimental⁹⁾.

Methyl Ether (Vc) of Tropolone (IV):—Addition of ether soln. of diazomethane to (IV) in ether precipitated pale yellow needles (Vc), m. p. 41°, with evolution of N₂. The crystals (Vc) contain 1/2 mole crystal water. On distilling at 128°/5 mm., or drying in vacuum desiccator, it lost its crystal water and turned into an oil. (Tropolone, b. p. 85°/5 mm.) (Vc): Anal. Calcd. for (C₈H₅O₃)₂H₂O; C, 66.19; H, 6.25. Found: C, 65.89; H, 5.89.

Methyl Ethers (VIIIa, IXa, Xa, respectively) of *p*-Bromotropolone (VIII), *o*, *o'*-Dibromotropolone (IX) and *o*, *p*, *o'*-Tribromotropolone (X):—Obtained in the similar manner as above. (VIIIa), pale yellow needles, m. p. 135–136°. Anal. Calcd. for C₈H₇O₃Br: C, 44.68; H, 3.28. Found: C, 44.01; H, 2.84. (IXa), pale yellow needles, m. p. 132–132.5°. Anal. Calcd. for C₈H₅O₃Br₂: C, 32.68; H, 2.06. Found: C, 32.72; H, 1.87. (Xa), pale yellow microneedles, m. p. 110–111°. Anal. Calcd. for C₈H₃O₃Br₃: C, 25.69; H, 1.35. Found: C, 25.52; H, 1.48.

Bromination of (Vc):—Brown crystalline precipitate separated on the addition of 1 mole of Br₂ to (Vc) in water. After recrystallizations, it was identified as *o*, *p*, *o'*-tribromotropolone⁹⁾, by mixed fusion.

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