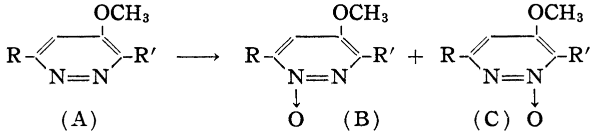
TABLE I.



Compounds (A)	Oxidizing agents	N-Oxides (%) 1-Oxide (B)	2-Oxide (C)	Other products (%)	Recovery (%)
(III) R=R′=Cl	a)	(IV) 12	(V) 5	MeO-Cl-pyridazine 0.7	45
(VIII) R=R′=H	b)	(IX) 11	(X) 8	4(1*H*)-Pyridazinone 2	54
(XIII) R=Cl, R′=OMe	a)	(XVI) 50	—	—	—

a) Monoperphthalic acid. *b*) H_2O_2-AcOH at 70°

catalytic hydrogenation in an alkaline medium, the structure of (XVI) was shown to be 1-oxide of 6-chloro-3,4-dimethoxypyridazine.

Table I summarized the above-mentioned experimental results. The N-oxidation reactions of (III) and (VIII) do not give so preferentially 1-oxide to 2-oxide in both cases as expected, while in the case of (XIII), the oxidizing agent seems to attack almost selectively to 1-nitrogen as observed in the N-oxidation of 3-methoxy-6-chloropyridazine.[5,6] Thus, it may be concluded that the methoxyl group in 4-position of the pyridazine ring exhibits only a weak polar effect to the ring nitrogen.

National Institute of Hygienic Sciences,
Tamagawa-yoga, Setagaya-ku, Tokyo.

Takanobu Itai (板井孝信)
Sachiko Natsume (夏目幸子)

May 21, 1962.

UDC 547.92

Preparation of 3β-Acetoxy-14β,15β-epoxy-5β-card-20(22)enolide

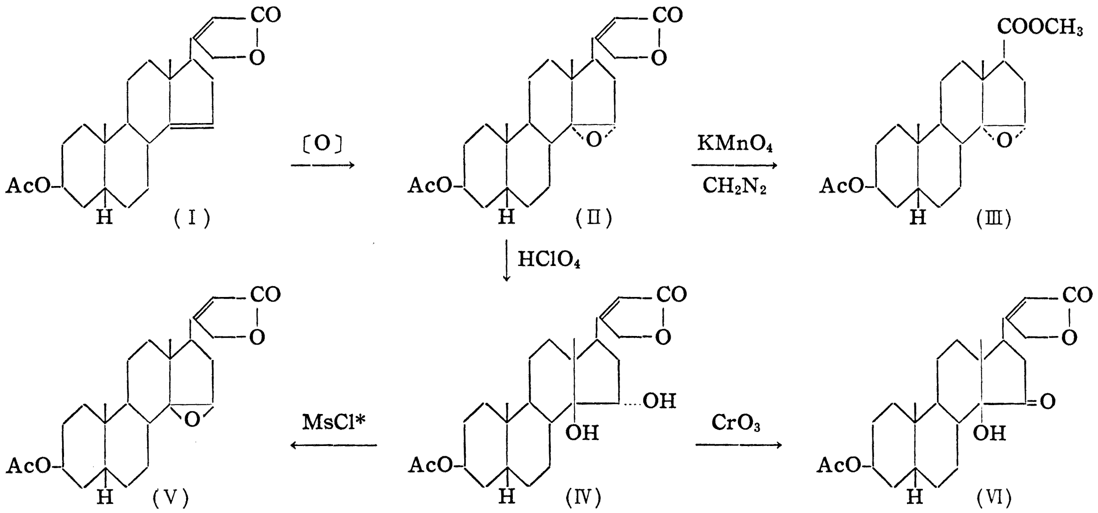
It has been reported that resibufogenin possessed a stimulating effect of respiratory center.[1] In order to compare the pharmacological action of the corresponding cardenolide derivative with that of resibufogenin, partial synthesis of the 14β,15β-epoxide of cardenolide was made using "β"-anhydrodigitoxigenin acetate as the starting material.

"β"-Anhydrodigitoxigenin acetate (I) was oxidized with monoperphthalic acid to give 3β-acetoxy-14α,15α-epoxy-5β-card-20(22)-enolide (II), m.p. 199~206°, $[\alpha]_D^{21}$ +12.0°($CHCl_3$), UV : λ_{max}^{EtOH} 216 mμ (log ε 4.20). Hydrolytic cleavage of (II) with perchloric acid afforded a *trans*-glycol, 15α-hydroxydigitoxigenin 3-acetate (IV), m.p. 247~250°, $[\alpha]_D^{26}$ +35.6°($CHCl_3$). Treatment of (IV) with mesyl chloride in pyridine and purification of the resulting product by chromatography on alumina gave a sulfur-free compound (V), $C_{25}H_{34}O_5$, m.p. 180~181°, $[\alpha]_D^{24}$ +34.4°($CHCl_3$). Since (V) showed no hydroxyl band in its infrared spectrum and gave a negative reaction with hydroxylamine, this compound (V) was assumed to be 14β,15β-epoxide isomeric with (II).

The structures of the compounds (II), (IV) and (V) were proved by the following experiments : (a) The configuration of the 14,15-epoxy group of (II) was α, since (II) was converted into the known methyl 3β-acetoxy-14α,15α-epoxy-5β-etianate[2] (III) by oxidation

---

1) M. Okada : Nippon Yakurigaku Zasshi, **57**, 160 § (1961).
2) A. Lardon, H.P. Sigg, T. Reichstein : Helv. Chim. Acta, **42**, 1457 (1959).



* MsCl : methylsulfonyl chloride

with potassium permanganate and esterification of the acid so obtained with diazomethane. (b) Oxidation of (IV) with chromic acid gave a 15-ketone derivative (VI), m.p. 236~240°. This compound showed a negative Cotton effect in the rotatory dispersion curve, indicating that (VI) was a 14β-15-oxo-steroid.[3] Hence the configuration of the *trans*-glycol group in (IV) was considered to be 14β,15α. (c) Quite recently, Meyer *et al*[4] have reported on the preparation of two isomeric 3β-acetoxy-14,15-epoxy-5β-card-20(22)-enolides. In their experiments, they obtained 14β,15β-epoxy derivatives by treatment of Δ^{14}-steroids with N-bromoacetamide in acetone. Comparison of (V) with the authentic specimen kindly supplied from Prof. K. Meyer through mixed melting point and infrared spectra established that (V) was 3β-acetoxy-14β,15β-epoxy-5β-card-20(22)-enolide.

The authors express their gratitude to Prof. T. Reichstein of the Organisch-chemische Anstalt der Universität Basel and to Prof. K. Meyer of the Pharmazeutische Institut der Universität Basel, for their kind donation of valuable samples. They are grateful to Prof. M. Ishikawa of the Tokyo Medico-Dental University for his helpful advice.

Shionogi Research Laboratory
Shionogi & Co., Ltd.
Fukushima-ku, Osaka.

Hiroshi Ishii (石井 宏)
Takehiko Tozyo (東条武彦)
Daisuke Satoh (佐藤大助)

May 22, 1962.

---

[3] C. Djerassi, "Optical Rotatory Dispersion," 41, 111 (1960). McGraw-Hill Book Co., New York.
[4] P. Hofer, H. Linde, K. Meyer : Helv. Chim. Acta, **45**, 1041 (1962).