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THE STRUCTURE OF KROMIN

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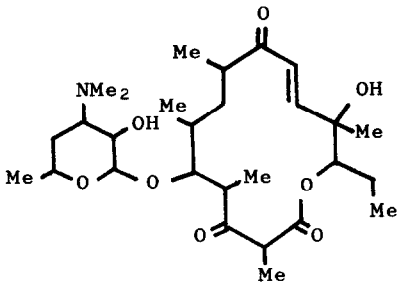
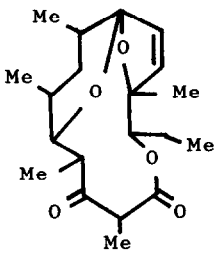
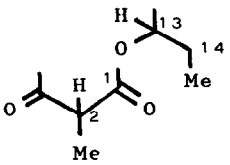
Amaromycin is an antibiotic isolated from Streptomyces flavochromogenes by Hata et al.,[1] and was considered to be the same compound as pikromycin from the comparison of hydrolyzed products.[2] Pikromycin was hydrolyzed under the condition at pH 6.5 to give kromycin,[3,4] and the structure of kromycin was confirmed by Muxfeldt et al.,[5,6] and Rickards et al.[7] On the other hand, pikromycin (I) was treated with 5N hydrochloric acid yielded an unknown compound "kromin" by Brockman.[3]



I



II



III

We now wish to report evidences that kromin has the structure of foumula II and the stereoformula IV, on the basis of ir, nmr, and mass spectra. Kromin (mp 200.5-202°, $[\alpha]_D^{26}$ +80.6° in $CHCl_3$) showed a molecular ion at m/e 350 (Calcd for $C_{20}H_{30}O_5$, 350.209. Found: 350.206). Ir spectrum of II has an absorption for lactonic carbonyl group at 1732 cm^{-1}, a strong absorption at

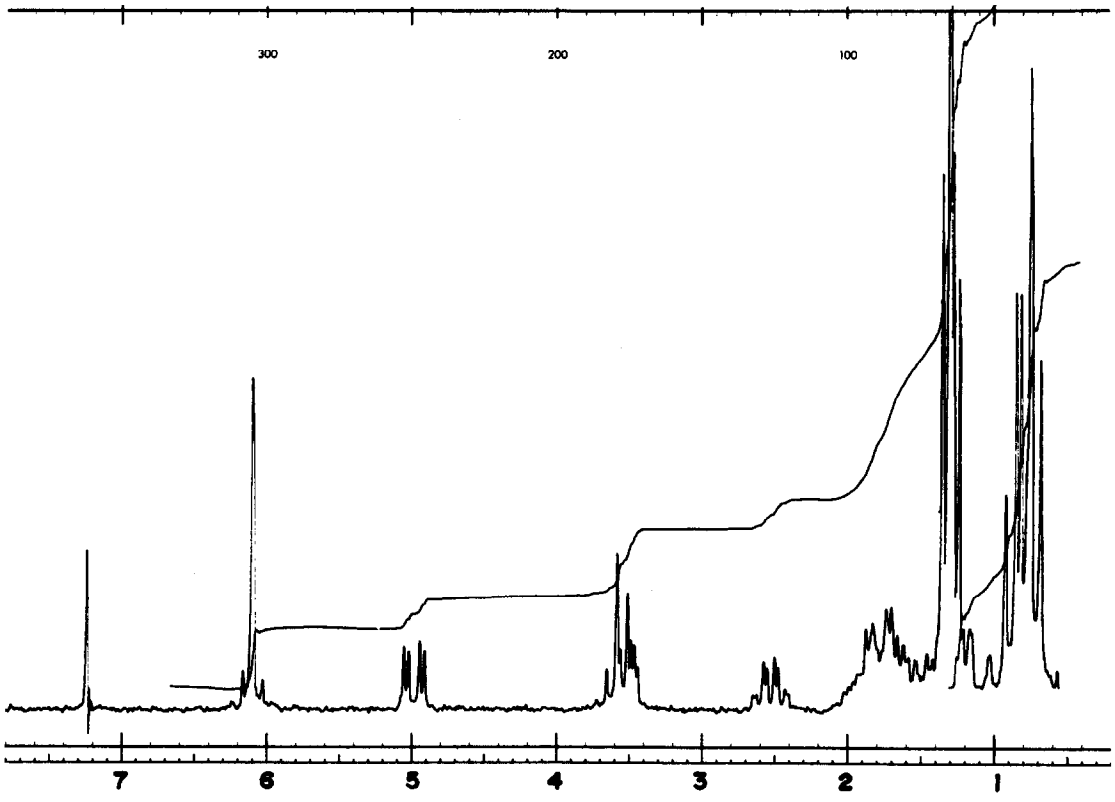
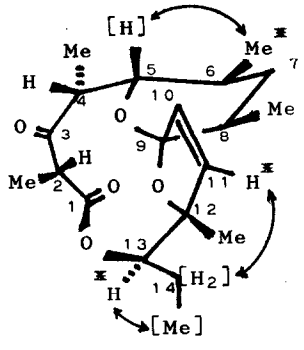


Fig. 1 Nmr Spectrum of Kromin (δ: ppm, $CDCl_3$ 100 MHz)

815 cm^{-1} (oxide). Although II has not hydroxyl band at 3000-3500 cm^{-1} region, and II has a saturated carbonyl group from uv spectrum λ_{max}^{EtOH} 294 nm (log ε 2.91). The nmr spectrum (Fig. 1) of II shows bands at 0.88 (3H, t, J=7.0 Hz, 14-CH_3), 1.34 (3H, d, J=7.2 Hz, 2-CH_3), 3.57 (1H, q, J=7.2 Hz, 2-H), and 5.00 (1H, dd, J=3.5 and 11.0 Hz, 13-H) corresponding to a part of structure (III), and peaks at 6.09 (1H, d, J=6.5 Hz) and 6.16 (1H, d, J=6.5 Hz) which correspond to a cis-olefinic structure.[8] These data indicate that kromin (II) is an acid-catalyzed elimination product of pikromycin (I) which is formulated as II and not a true aglycone. This acid-catalyzed elimination reaction has already been reported in the macrolide antibiotics, erythromycins,[9] methymycin,[10] and neomethymycin.[11]

Table 1. Nmr Data of Kromin ($CDCl_3$ 100 MHz) and Aromatic Solvent Induced Shifts ($\delta CDCl_3$-δC_6D_6)

2-H	4-H	5-H	6-H	8-H	10-H	11-H	13-H	2-Me	4-Me	6-Me	8-Me	12-Me	14-Me
3.57	2.55	3.55	1.6-1.9	1.6-1.9	6.09	6.16	5.00	1.34	1.30	0.81	0.75	1.33	0.88
0.05	0.13	0.30	0.4 ±0.2	—	0.39	0.44	-0.12	-0.09	-0.08	0.35	0.06	0.28	0.13



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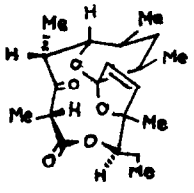
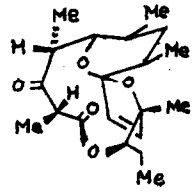
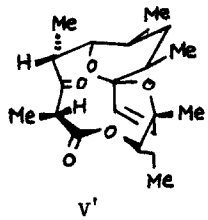


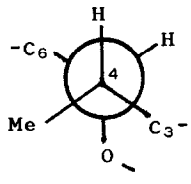
IV'



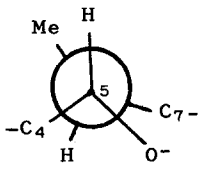
V



V'



VI



VII

Stereochemistry of kromin (II) was confirmed by means of nmr spectra. The conformational structure was shown as IV from the nmr data as shown in Table 1 and nuclear Overhauser effect[12] was observed between 5-H and 6-Me (11%), 14-Me and 13-H (10%), and 14-H_2 and 11-H (20%). From these results, tetrahydropyranyl ring has to be a twist form and a furyl ring is fixed in an axial position. This conclusion is supported by the coupling constant of 5-H ($J_{4,5}$=2.5 Hz, $J_{5,6}$=9.8 Hz) (VI and VII).

There is another possibility that configuration (12R) and conformation as indicated V and V', but there is not observed the nuclear Overhauser effect between H-11 and H-13. This suggest that C-12 should have a S-configuration. There is also a possibility that the conformation may be as indicated by IV', although solvent shifts of nmr spectrum in deuteriobenzene (Table 1) and CD spectrum, 208 nm ([θ] -10185) and 290 nm ([θ] +7528)[13]

strongly supported the conformation as indicated IV. In conclusion, the configuration of kromin (II) was formulated as 2R,4R,5S,6S,8R,12S,13R-10,11-cis-13-ethyl-5,9:9,12-diepoxy-2,4,6,8,12-pentamethyl-3-oxo-10-tridecenolide.

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