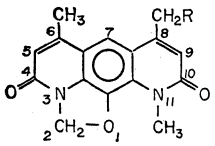
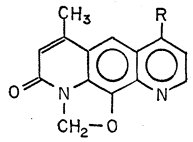
NYBOMYCIN. V TOTAL SYNTHESIS OF NYBOMYCIN[1]

Sir:

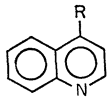
The antibiotic nybomycin was isolated several years ago in two laboratories from streptomyces cultures.[2,3] It has strong antibacterial activity against Gram-positive and some Gram-negative organisms, as well as antifungal and antiphage activity, but its insolubility hinders its *in vivo* utility.[2,4] We very recently assigned structure **1** to nybomycin[5], revising a previously assigned formula[6]. We report here an unambiguous total synthesis of 6,11-dimethyl-8-hydroxymethyl-4, 10-dioxo-2H, 4H, 10H, 11H-pyrido [3,2-g]-oxazolo[5,4,3-ij]quinoline (**1**) and its complete identity with nybomycin.



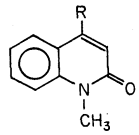
1 : R=OH
3 : R=H
14 : R=$OCOCH_3$



2 : R=CH_3
11 : R=CHO
12 : R=CH_2OH
13 : R=CH_2OCOCH_3



4 : R=CH_3
5 : R=CHO
8 : R=CH_2OH
9 : R=CH_2OCOCH_3



6 : R=CH_3
7 : R=CH_2OH
10 : R=CH_2OCOCH_3

The key intermediate in our synthetic scheme was deemed to be **2**, with its disparate terminal rings, a compound prepared earlier in our recently reported total synthesis of deoxynybomycin (**3**)[1]. If the pyridine γ-methyl group (8-methyl of **2**) could be oxidized selectively in the presence of the pyridone γ-methyl group (6-methyl of **2**), then the procedure employed for the synthesis of deoxynybomycin could be adapted readily to the preparation of nybomycin. Accordingly, studies with model compounds were initiated. These revealed that the methyl group in lepidine (**4**) could be oxidized to an aldehyde by freshly prepared selenium dioxide in refluxing dioxane[7], giving **5** ($C_{10}H_7NO$,*,† m.p. 48~50°C) in 52 % yield. Under the same conditions the methyl group of **6** was unaffected and to oxidize it to an aldehyde required fusion with selenium dioxide at 175°C for 1.25 hours[8].

Conversion of **4** to the model quinolone **7** continued with the reduction of **5** by sodium borohydride[9] in ethanol to **8** ($C_{10}H_9NO$, m.p. 93~95°C, 86 %).*,† Methylation of **8** with an equivalent amount of dimethyl sulfate in refluxing benzene gave its methosulfate salt, which was oxidized in aqueous media with potassium hydroxide and potassium ferricyanide[10] at 3°C for 6 hours; however, the product mixture gave a positive test with 2,4-dinitrophenylhydrazine, indicating that oxidation of the hydroxymethyl group of **8** to an aldehyde had occurred. The hydroxyl group of **8** was, therefore, protected by acetylation in glacial acetic acid containing a trace of sulfuric acid at 100°C. The acetate, **9** ($C_{12}H_{11}NO_2$, m.p. 55~58°C, 72 %),*† was then converted by methylation to its methosulfate and oxidized as before, to give **10** ($C_{13}H_{13}NO_3$, m.p. 157~159°C)*,† in 31 % yield. The quinolone ester **10** was hydrolyzed in 0.5 N ethanolic potassium hydroxide at reflux for 0.5 hour to afford **7** ($C_{11}H_{11}NO_2$, m.p. 185~187°C, 74 %).*,†

Employing the reaction sequence and reagents developed for preparation of the model compound **7**, **2** was selectively oxidized to the formyl derivative **11** ($C_{15}H_{10}N_2O_3$, m.p. 278~280°C, 53 %),*,†,†† which was reduced to the hydroxymethyl analog **12** ($C_{15}H_{12}N_2O_3$, m.p. 224~226°, 93 %).*,†,†† The latter compound was subsequently acetylated to give **13** ($C_{17}H_{14}N_2O_4$, m.p. 248~250°, 63 %),*,†,†† which was methylated then oxidized with potassium hydroxide and potassium ferricyanide to give **14** ($C_{18}H_{16}N_2O_5$)*,†,†† in 18 % yield (from **13**).

The synthetic sample of **14** was identical with an authentic sample of nybomycin acetate, prepared from nybomycin by the method of EBLE, *et al.*[3], in m.p. (234~236°C),

* Microanalyses agree with the molecular formula shown.
† Low resolution mass spectral data agree with the molecular formula shown.
†† High resolution mass spectral data agree with the molecular formula shown.

thin-layer chromatographic behavior, infrared spectrum (KBr), nmr spectrum (trifluoroacetic acid), and mass spectrum. An intimate mixture of the synthetic and authentic samples of **14** melted at 233~235°C. Basic hydrolysis of synthetic **14** was effected in 73 % yield. The product (**1**, $C_{16}H_{14}N_2O_4$, m.p. >350C°),*,† was identical with authentic nybomycin in thin-layer chromatographic behavior, as well as infrared (KBr), nmr (trifluoroacetic acid), and mass spectra.

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References

1) Preceding paper in this series: Forbis, R. M. & K. L. Rinehart, Jr.: Nybomycin. IV. Total synthesis of deoxynybomycin. J. Amer. Chem. Soc. 92 : 6995, 1970
2) Strelitz, F.; H. Flon & I. N. Asheshov: Nybomycin, a new antibiotic with antiphage and antibacterial properties. Proc. Natl. Acad. Sci. U. S. 41 : 620~624, 1955
3) Eble, T. E.; G. A. Boyack, C. M. Large & W. H. DeVries: Nybomycin: isolation, properties, and derivatives. Antibiot. Chemotherapy 8 : 627~630, 1958
4) Brock, T. D. & W. T. Sokolski: Biological studies on the antibiotic nybomycin. Antibiot. Chemotherapy 8 : 631~636, 1958
5) Rinehart, Jr., K. L.; G. Leadbetter, R. A. Larson & R. M. Forbis: Nybomycin. III. A revised structure. J. Amer. Chem. Soc. 92 : 6994, 1970
6) Rinehart, Jr., K. L. & H. B. Renfroe: The structure of nybomycin. J. Amer. Chem. Soc. 83 : 3729~3730, 1961
7) Kaplan, H.: The use of selenium dioxide in the preparation of quinoline aldehydes. J. Amer. Chem. Soc. 63 : 2654~2655, 1941
8) Cook, D. J. & M. Stamper: 1-Methyl-4-carbostyrilcarboxaldehyde and certain condensation products. J. Amer. Chem. Soc. 69 : 1467~1468, 1947
9) Chaikin, S. W. & W. G. Brown: Reduction of aldehydes, ketones and acid chlorides by sodium borohydride. J. Amer. Chem. Soc. 71 : 122~125, 1949
10) Prill, E. A. & S. M. McElvain: 1-Methyl-2-pyridone. pp. 419~421
In A. H. Blatt (ed.), Organic Syntheses, Coll. Vol. II, John Wiley & Sons, Inc., New York, 1943