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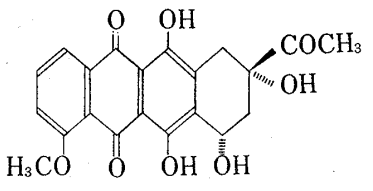
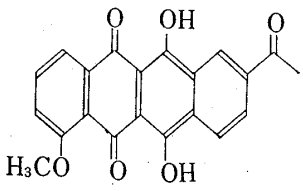
Synthesis of Bisanhydrodaunomycinone

Daunomycin, an antibiotic isolated from *Streptomyces peucetius*[1] and *S. coeruleorubidus*,[2,3] was found to have antitumour activity.[2,4] Arcamone, *et al.*[5] obtained daunomycinone (I), the aglycone of daunomycin, and bisanhydrodaunomycinone (II), the dehydration product of I, and proposed their structures by the degradative and physical methods. We have now synthesized 8-acetyl-6,11-dihydroxy-1-methoxynaphthacenequinone (II) and identified it with bisanhydrodaunomycinone, which corroborates its structure.

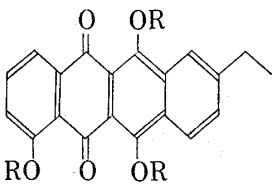
8-Ethyl-1,6,11-trihydroxynaphthacenequinone (III)[6–8] was acetylated to avoid nuclear bromination[9] in the next step to afford the triacetate (IV), mp 249—253° (IR ν_{max}^{KBr} cm^{-1}: 1777sh, 1768(OAc), 1673(quinone). Mass Spectrum *m/e*: 460(M^+)). Benzylic bromination of IV with N-bromosuccinimide in the presence of benzoyl peroxide in carbon tetrachloride, followed by heating with potassium acetate in acetic anhydride–acetic acid afforded the tetra-



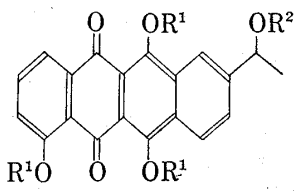
I



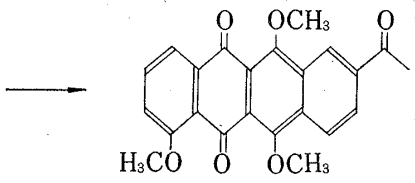
II



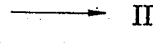
III : R=H
IV : R=Ac



V : $R^1=R^2=Ac$
VI : $R^1=CH_3$, $R^2=H$



VII



1) A. Grein, C. Spalla, A. Di Marco, and G. Canevazzi, *Giorn. Microbiol.*, **11**, 109 (1963).
2) G.F. Gause, *Chem. Ind.* (London), **1966**, 1506.
3) G.L. Tong, P. Lim, and L. Goodman, *J. Pharm. Sci.*, **56**, 1691 (1967).
4) A. Di Marco, M. Gaetani, P. Orezzi, B.M. Scarpinato, R. Silvestrini, M. Soldati, T. Dasdia, and L. Valentini, *Nature*, **201**, 706 (1964).
5) F. Arcamone, G. Franceschi, P. Orezzi, G. Cassinelli, W. Barbieri, and R. Mondelli, *J. Am. Chem. Soc.*, **86**, 5334 (1964); F. Arcamone, G. Franceschi, P. Orezzi, and S. Penco, *Tetrahedron Letters*, **1968**, 3349; R.H. Iwamoto, P. Lim, and N.S. Bhacca, *ibid.*, **1968**, 3891; F. Arcamone, G. Franceschi, G. Cassinelli, R. Mondelli, P. Orezzi, and S. Penco, *Gazz. Chim. Ital.*, **100**, 949 (1970).
6) H. Brockmann, R. Zunker, and H. Brockmann, Jr., *Ann.*, **696**, 145 (1966).
7) We have synthesized this compound (III) *via* another route, which will be published in the full paper.
8) All compounds mentioned in this paper gave satisfactory elemental analyses.
9) K. Ueda and I. Yosioka, *Chem. Pharm.Bull.* (Tokyo), **16**, 1521 (1968).

acetate (V), mp 205—205.5° (IR ν_{max}^{KBr} cm^{-1}: 1772(aromatic OAc), 1747 (aliphatic OAc), 1678 (quinone). NMR ($CDCl_3$) τ: 8.41 (3H, d, J=7 Hz, AcO–CH–CH_3), 7.38, 7.44, 7.58, 7.91 (each 3H, s, $OCOCH_3$), 3.98 (1H, q, J=7 Hz, AcO–CH–CH_3). Mass Spectrum m/e: 518(M^+)). The tetraacetate (V) was hydrolyzed with potassium hydroxide in aqueous methanol and subsequently methylated with dimethyl sulfate to give the trimethyl ether (VI), mp 91—94° (IR ν_{max}^{KBr} cm^{-1}: 3470(OH), 1670(quinone). NMR ($CDCl_3$) τ: 8.40 (3H, d, J=7 Hz, HO–CH–CH_3), 5.97, 5.91, 5.86 (each 3H, s, OCH_3), 4.84 (1H, q, J=7 Hz, HO–CH–CH_3). Mass Spectrum m/e: 392(M^+)).

Ball oxidation of VI with manganese dioxide in benzene yielded the ketone (VII), mp 224—226° (IR ν_{max}^{KBr} cm^{-1}: 1680(aromatic ketone), 1674, 1660(quinone). NMR ($CDCl_3$) τ: 7.22 (3H, s, $COCH_3$), 5.95 (6H), 5.80 (3H) (each s, OCH_3). Mass Spectrum m/e: 390(M^+)), which was identical with bisanhydrodaunomycinone dimethyl ether in mp, mixed mp, thin-layer chromatography, infrared(KBr) and mass spectra.

Demethylation of VII with ten molar equivalents of boron tribromide in methylene chloride at −60° gave selectively 8-acetyl-6,11-dihydroxy-1-methoxynaphthacenequinone (II), mp 320—325° (IR ν_{max}^{KBr} cm^{-1}: 1683(aromatic ketone), 1615, 1605(chelated quinone). NMR (CF_3COOD) τ: 7.11 (3H, s, $COCH_3$), 5.98 (3H, s, OCH_3). Mass Spectrum m/e: 362(M^+)), which was identical with bisanhydrodaunomycinone in mp, mixed mp, thin-layer chromatography, infrared(KBr) and mass spectra.

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Isolation of 2,2,6,6-Tetramethylpiperidone-(4) from Pronase Lysate of Ox Brain as a Hypotensive Principle

Martini and his coworkers reported that acetone extracts obtained from brains of different animals show depressor activities on the mean arterial blood pressure of cat or guinea pig.[1–3]

Later, the same workers indicated that an extract obtained from tryptic or chymotryptic lysate of brains possesses a clearly hypertensive effect, whereas that from papain lysate retains a hypotensive effect[4], and they assumed that a certain substance showed hypertensive effect in reduced state and hypotensive effect in oxidized state and it might be interconvertible under

1) E. Martini, A. Marzorati, and E. Morpurgo, *Experientia*, **8**, 225 (1952).
2) F. Chiesa, *Ist. Lombardo* (*Rend. Sc.*), **93**, 7 (1959).
3) F. Chiesa, *Ist. Lombardo* (*Rend. Sc.*), **93**, 26 (1959).
4) E. Martini, F. Chiesa, A. Spiga, and R. Oberosler, *Enzymologia*, **29**, 1 (1965).