

VARIATION OF SKELETONS OF ANTITUMOR ANTIBIOTICS I.

SIMPLE SYNTHESIS OF NAPHTHO[2,3-*g*]QUINOLINES AND A NAPHTHO[2,3-*g*]QUINOXALINENoriichi Oda, Kazuhiro Kobayashi, Taisei Ueda, and Isoo Ito*Faculty of Pharmaceutical Sciences, Nagoya City UniversityTanabe-dori, Mizuho-ku, Nagoya, Japan.

Abstract—Simple synthesis of naphtho[2,3-*g*]quinolines (III,VI,IX) and a naphtho[2,3-*g*]quinoxaline (XII), which are a novel heterocyclic ring system, was carried out by the Diels-Alder reaction of 1,2-dimethylenecyclohexane (I) with quinoline-5,8-quinone (II,V,VIII) or quinoxaline-5,8-quinone (XI). Air oxidation of these adducts (III,VI,IX) in alcoholic alkaline solution gave tetrahydronaphtho[2,3-*g*]quinolines (IV,VII,X).

The anthracycline antibiotics such as adriamycin¹ and daunomycin² are of current interest as promising antitumor agents. We thought some variation of the skeletons of these anthracyclines also might exhibit interesting biological activity and we have interested in the syntheses of naphtho[2,3-*g*]quinolines (III,IV,VI,VII,IX,X) and a naphtho[2,3-*g*]quinoxaline (XII) as novel linear polycyclines. This paper describes simple syntheses of these polycyclines by the Diels-Alder reaction of 1,2-dimethylenecyclohexane (I)³ with quinoline-5,8-quinones (II,V,VIII) or quinoxaline-5,8-quinone (XI).

The Diels-Alder reaction of the diene (I) with quinoline-5,8-quinone (II)⁴ or 2,4-dimethylquinoline-5,8-quinone (V)⁵ in refluxing ethanol under nitrogen gave the corresponding adducts (III or VI). [III; colorless prisms, 97% yield, mp 222-223°, ir (KBr) cm^{-1} 1683 (C=O), nmr (CDCl_3) δ 3.45 (2H, m, methine protons), 2.26 (4H, m, methylene protons on B-ring), mass m/e 267 (M^+). VI; yellow needles, 82% yield, mp 204-205°, ir (KBr) cm^{-1} 1660 (C=O), nmr (CDCl_3) δ 3.74 (2H, m, methine protons), 2.27 (4H, m, methylene protons on B-ring), mass m/e 295 (M^+)].

The similar cycloaddition of carbostyrylquinone (VIII)⁶ with I was carried out in refluxing ethyl acetate under nitrogen to give 2,5,12-trioxo-5a,6,7,8,9,10,11,11a-

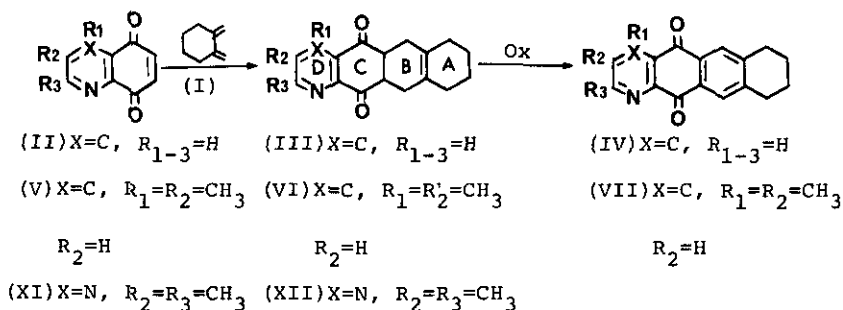
octahydro-1H-naphtho[2,3-*g*]quinoline (IX) in 93% yield, and another possible isomer octahydronaphtho[2,3-*c*]quinoline was not isolated. The confirmation of the structure of IX was carried out by the nmr, ir and mass spectra; mp $>300^\circ$, nmr (CF_3COOD) δ 8.41 (1H, d, $J=9\text{Hz}$, H-4), 7.30 (1H, d, $J=9\text{Hz}$, H-3); ir (KBr) cm^{-1} 1655 (C=O); mass m/e 283(M^+).

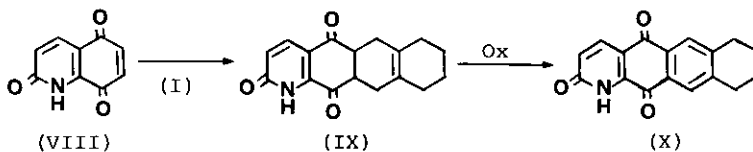
The reaction of 2,3-dimethylquinoxaline-5,8-quinone (XI)⁷ with I proceeded smoothly in refluxing ethanol under nitrogen to give 2,3-dimethyl-5,12-dioxo-5a,6,7,8,9,10,11,11a-octahydronaphtho[2,3-*g*]quinoxaline (XII) in 84% yield, mp $210-211^\circ$, whose skeleton has not been reported in the literature and appears to be a novel ring system. The structural confirmation of XII was carried out by the nmr and ir spectra; nmr (CDCl_3) δ 3.46 (2H, m, methine protons), 2.29 (4H, m, methylene protons on B-ring), ir (KBr) cm^{-1} 1710 (C=O), mass m/e 296(M^+).

These Diels-Alder adducts (III, VI, IX) were easily oxidized by passing through the air into the ethanolic sodium hydroxide solution to give the corresponding tetrahydronaphtho[2,3-*g*]quinolines (IV, VII, X) [IV; mp $265-266^\circ$, 51% yield, ir (KBr) cm^{-1} 1670 (C=O), nmr (CF_3COOD) δ 8.25 (2H, s, aromatic protons), mass m/e 263(M^+); VII; mp $253-254^\circ$, 85% yield, ir (KBr) cm^{-1} 1655 (C=O), nmr (CDCl_3) δ 7.87, 7.99 (each 1H, each s, aromatic proton), mass m/e 291(M^+); X; mp $>300^\circ$, 96% yield, ir (KBr) cm^{-1} 1635 (C=O), nmr (CF_3COOD) δ 8.04 (2H, s, aromatic protons), mass m/e 279(M^+)].

The absorption maxima of the uv spectra of these compounds (IV and VII) [$\lambda_{\text{max}}^{\text{EtOH}}$ nm IV; 271, VII; 269] shifted to the longer wave region compared to those of the Diels-Alder adducts (III and VI) [$\lambda_{\text{max}}^{\text{EtOH}}$ nm III; 242, VI; 245], and this fact indicated the B-ring was aromatized. The attempted aromatization of XII, however was failure, giving only intractable powder.

Further chemical modifications of the above described novel polycyclines to 6,10,11-trihydroxynaphtho[2,3-*g*]quinoline-5,12-quinones are currently under investigation.





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Received, 1st September, 1980