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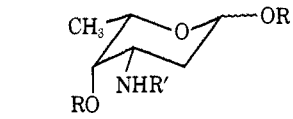
Communications to the Editor

Total Synthesis of the Antitumor Antibiotic Daunorubicin. Coupling of the Sugar and Aglycone

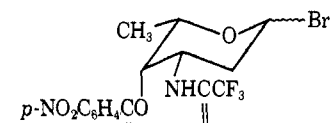
Sir:

The antibiotics daunorubicin†[1,2] (**7**) and especially adriamycin[3] (**7**, with $COCH_3$=$COCH_2OH$) show promise in the clinical treatment of a broad spectrum of human cancers. Adriamycin was recently described as the "most promising new agent under investigation" among anticancer drugs.[4] Daunosamine (**1**, common to both antibiotics) was synthesized previously in these laboratories,[5] and a synthesis of daunomycinone (**5**, the aglycone of **7**) was recently reported.[6] Conversion of daunorubicin (**7**) to adriamycin has been described,[7] so that total synthesis of **7** also constitutes a formal synthesis of adriamycin.

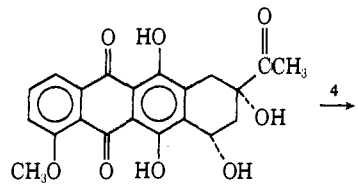
Total synthesis of daunorubicin has now been completed by coupling the suitably protected sugar and aglycone and deblocking the product. Unexpectedly, the coupling was completely stereospecific in that only the natural α-L anomer was formed. *N*-Trifluoroacetyldaunosamine (**2**), mp 146.5–147.0° from ethyl acetate, was obtained from daunosamine hydrochloride. The 1,4-bis(*O*-*p*-nitrobenzoate) **3**, mp 197.0–198.5° from ether–acetone, was suspended in CH_2Cl_2 at 0° and saturated with anhydrous HBr to form a clear solution, from which *p*-nitrobenzoic acid precipitated. Filtration and evaporation afforded the residual 1-bromo sugar **4**. Daunomycinone (**5**), with mercuric cyanide, mercuric bromide, and powdered molecular sieve 3A in anhydrous THF at reflux, was treated with **4** in three portions, each freshly generated from 1 molar equiv of **3** after 0, 22, and 31 hr. After 47 hr the product was detected by tlc on silica gel in ethyl acetate–benzene–methanol (50:50:1) as a red spot under uv or visible light, R_f 0.85, contaminated with **5** (R_f 0.55) and sugar impurities mainly at R_f 0.75 and 0.92. Column chromatography on silica gel separated 22% of unreacted **5**. A second column separated sugar impurities and afforded **6**, estimated to be 80% pure by extinction coefficients in visible and uv spectra. Recrystallization from 95% ethanol gave pure **6** in two crops (50% yield): uv λ_{max} (95% EtOH) 234 nm ($\epsilon \times 10^{-3}$, 43.7), 253 (39.4), 481 (12.5), 496 (12.7), 532 (7.12); fmr ($CDCl_3$, ppm upfield from internal $CFCl_3$) 76.60 (singlet); cmr ($CDCl_3$, ppm from TMS) δ 211.8 (s, MeC=O), 100.3 (d, C-1′), 17.0 (q, C-6′). The pmr spectrum was nearly identical with that[8] for *N*-acetyldaunorubicin, except for downfield shifts of C-4′-H expected from the *p*-nitrobenzoyl groups. The mother liquor residue was purified by preparative tlc on silica gel in ethyl acetate–benzene (1:2) and then by high-pressure liquid chromatography to yield an additional 3%, identical with previous crops in tlc, ir, cmr, pmr, and fmr. Thus, all of the coupling product was isolated and characterized as homogeneous **6** (53% yield), and there was no evidence for any of the β anomer of **6**.



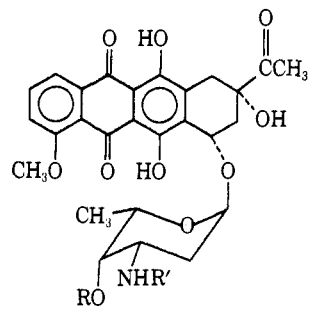
1, R = R′ = H
2, R = H; R′ = CF_3CONH
3, R = *p*-$NO_2C_6H_4CO$; R′ = CF_3CO



4



5



6, R = *p*-$NO_2C_6H_3CO$; R′ = CF_3CO
7, R = R′ = H

Deblocking was accomplished by treating a THF solution of **6** (1 g/120 ml) with an equal volume of 0.1 *N* NaOH at 0° for 4.5 hr. The pH was adjusted to 6, THF was evaporated, and after readjustment to pH 9–10, the product was extracted with $CHCl_3$ to yield (94%) daunorubicin free base[9] (**7**), homogeneous on silica gel in acetone–methanol (1:1), R_f 0.55, 90–98% pure by uv and visible extinctions. A $CHCl_3$ solution treated with an equivalent of HCl in ethanol afforded **7**·HCl, precipitated with ether (61% yield): mp 176–181° dec; R_f 0.5 in acetone–methanol (1:1) on silica gel; uv λ_{max} (95% EtOH) 234 nm ($\epsilon \times 10^{-3}$, 37.5), 252 (25.1), 289 (9.24), 480 (12.0), 496 (12.4), 532 (6.54); cmr (D_2O, dioxane internal standard,

†The name daunorubicin has replaced the synonyms daunomycin and rubidomycin. However, the aglycone has retained the name daunomycinone.

ppm from TMS) δ 215.8 (s, MeC=O), 99.6 (d, C-1′), 16.6 (q, C-6′); CD (EtOH) 269 nm ([θ], (deg cm²)/mol, 0), 287 (−12.1), 303 (0), 320 sh (+5.22), 344 (+7.60). It was identical with natural daunorubicin hydrochloride[10] on direct comparison by these methods and by bioassay as an inhibitor of DNA and RNA synthesis in cultured L1210 murine lymphoid leukemia cells.

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Book Reviews

Protein Turnover. Ciba Foundation Symposium 9 (new series). American Elsevier, New York, N. Y. 1973. Aspects of protein metabolism with 14 contributors. viii + 319 pp. 16 × 24 cm. $16.50.

The Ciba Foundation sponsored a Symposium on Protein Turnover held at the Ciba Foundation, London, May 9-11, 1972. The 14 papers presented with their discussions report experimental results of clinical significance as well as observation on patients with renal, hepatic, or other disorders. The topics included in this Symposium dealt with cell surface receptors in immunoglobulin transport and catabolism; the role of kidney in serum protein metabolism; new two-tracer techniques for plasma protein turnover; acute phase plasma proteins in wound healing; mass balance measurement of fibrinogen synthesis; disappearance time-curve analyses for labeled proteins; amino acid and hepatotoxic agents on albumin synthesis, polysomal aggregation, and RNA turnover; regulatory factors in plasma protein synthesis; neuraminadase (IV) effects on fibrinogen turnover; labeled plasmin generation and venous injury; factors affecting albumin, fibrinogen, and transferrin synthesis; IgM turnover in man; complement in membranoproliferative glomerulonephritis; complement and properdin systems disorders; a contributors list and subject index are included as well as a general discussion of criteria of viability in perfused livers.

All of the papers are well documented and allow the nonexpert in these areas to attain a feeling of the significance of these works. The individual papers vary in length but all are clearly presented and offer many graphic presentations of data. Each paper is preceded by an abstract and the discussion sessions with questions, answers, and comments follow each article.

The intended purpose of the Symposium was to bring together clinicians and scientists interested in different aspects of protein turnover and this objective has been achieved. The book contains considerable material of interest to clinicians and offers stimulating presentations which could be useful to individuals studying biosynthesis and metabolism of proteins and their intracellular biochemistry.

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