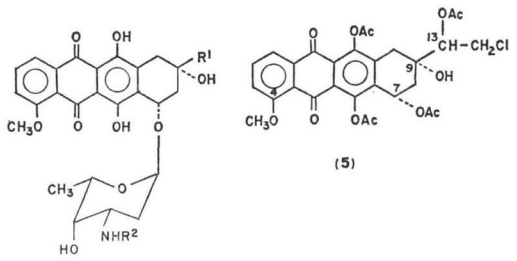
SYNTHESIS OF [14-^{14}C] DAUNORUBICIN AND DOXORUBICIN

Sir:

Tritium-labelled daunorubicin and doxorubicin have already been synthesized by tritium catalytic exchange[1] and used for a variety of biochemical and medical studies. These products, however, due to exchange of tritium in body fluids, are of limited use. We wish to report herein a new process leading to [14-^{14}C] daunorubicin and [14-^{14}C] doxorubicin with high specific radioactivity. This synthesis is based on the use of ^{14}C-labelled diazomethane for introduction of the label at C-14 in daunomycin and doxorubicin.

The selective periodate oxidation of the C-13 diol in 13-dihydro-N-trifluoroacetyldoxorubicin (**1**), obtained by treatment of 13-dihydro-doxorubicin[2] with trifluoroacetic anhydride followed by hydrolysis of O-trifluoroacetyl groups with methanol, gave the corresponding aldehyde **2**, purified by chromatography on a column of silicic acid using chloroform - acetone (10: 1 by vol.) as eluting agent; m.p. 175°C (dec.); anal.: calcd. for $C_{28}H_{26}F_3NO_{11}$, C 55.17, H 4.30, N 2.29; found C 55.29, H 4.79, N 2.34 (65% yield after crystallization by acetone). In a typical oxidation 1.28 g (2.1 mmoles) of **1** in *t*-butyl alcohol (160 ml) was treated with the stoichiometric amount (0.42 g) of sodium metaperiodate dissolved in water (125 ml) at room temperature for 90 minutes. Intermediate **2** (0.118 g, 0.193 mmoles) in methylene chloride (10 ml) was treated with an ethereal solution (10 ml) of diazomethane, generated from N-nitroso-methylurea obtained from 0.032 g (0.477 mmoles) of methylamine hydrochloride[3]. The reaction mixture, containing N-trifluoroacetyldaunorubicin (**3**) and epoxide **4** in approximately the ratio 3: 2, was chromatographed on 2 mm thick silicagel plates using the mixture chloroform - acetone (4: 1 by vol.) giving pure compounds **3** and **4**. On the other hand mainly compound **4** was obtained when the reaction was carried out in protic solvents, such as methanol or 2-methoxyethanol.

Compound **3** was identical with an authentic sample of N-trifluoroacetyldaunorubicin obtained by treatment of daunorubicin with trifluoroacetic anhydride[4]. Determination of the structure of **4** was based on the pmr spectrum study of tetraacetyl derivative **5**, *m/e* 602 (M^+), *m/e* 560 ($M-CH_2CO$), *m/e* 518 ($M-2CH_2CO$), *m/e* 416 ($M-3CH_2CO-CH_3COOH$); anal. calcd. for $C_{29}H_{27}ClO_{12}$, C 57.76, H 4.52; found C 57.35, H 4.69.



(5)

(1) R^1 = CHOH−CH_2OH ; R^2 = $COCF_3$

(2) R^1 = CHO ; R^2 = $COCF_3$

(3) R^1 = $COCH_3$; R^2 = $COCF_3$

(4) R^1 =  ; R^2 = $COCF_3$

(6) R^1 = $COCH_3$; R^2 = H

(7) R^1 = $COCH_2Br$; R^2 = H

(8) R^1 = $COCH_2OH$; R^2 = H

Compound **5** was obtained as major product by the acid hydrolysis with 0.1 N HCl of **4**, followed by acetylation with acetic anhydride and pyridine. The pmr spectrum (60 MHz, $CDCl_3$) of **5** showed signals at δ 2.08 and 2.16 (two s, CH_3COO at C-7 and C-13), δ 2.43 and 2.51 (two s, CH_3COO at C-6 and C-11), δ 3.78 and 4.07 (two dd, J_{gem} = 12.0 Hz, CH_2Cl), δ 4.00 (s, CH_3O), δ 5.20 (dd, C-13 H), δ 6.44 (m, C-7 H), δ 7.2~7.9 (m, 3 aromatic protons).

Mild alkaline treatment (0.1 N NaOH 60 minutes at 0°C) of **3** afforded daunorubicin (**6**), isolated as the hydrochloride in quantitative yield. By this method we have synthesized 0.044 g of [14-^{14}C]daunorubicin hydrochloride (specific activity 19.18 mCi/mmol) from 10.00 mCi of $NH_2{}^{14}CH_3{\cdot}HCl$ (specific activity 19.27 mCi/mmol) and 0.150 g of aldehyde **2** (15.0% radiochemical yield).

Conversion of [14-^{14}C]daunorubicin (0.054 g, specific activity 14.18 mCi/mmol) to [14-^{14}C]-doxorubicin (**8**), was performed *via* the 14-bromo-derivative (**7**)[5], to give 0.029 g (specific activity 14.04 mCi/mmol) and 0.01 g (specific activity 6.54 mCi/mmol) with 60.4% over-all radiochemical yield.

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