Tetrahedron Letters,Vol.25,No.42,pp 4837-4840,1984 0040-4039/84 $3.00 + .00
Printed in Great Britain

INTERACTION OF ANTHRALIN WITH CYSTEINE : A NEW ENTRY INTO THE CHEMISTRY OF BIOLOGICALLY ACTIVE ANTHRONES.

M. d'Ischia, A. Privitera and G. Prota*

Dipartimento di Chimica Organica e Biologica dell'Università di Napoli
Via Mezzocannone 16, 80134 Napoli, Italy.

Abstract:Evidence is reported that under physiological conditions anthralin (I), an antipsoriatic drug, reacts with cysteine to give an ether-insoluble adduct which was formulated as 1,8-dihydroxy-10-(2-amino-2-carboxyethylthio)-9-anthrone (III) by model studies and unambiguous synthesis.

Although it is well recognized that the pharmacological activity of most natural or synthetic anthraquinones involves the corresponding anthrones, their mode of action is not yet understood. Among these, anthralin (1,8-dihydroxy-9-anthrone, I) is of particular interest as it is one of the mainstays in the topical treatment of psoriasis and related skin diseases characterized by epidermal hyperplasia and severe scaling.[1] One of the models currently reported points to the generation by autoxidation of highly reactive radical species[2] capable of interfering with the keratinization processes.

In the course of a study on the effect of antioxidants on the stability of anthralin it was found that in the presence of excess cysteine the normal course of autoxidation is markedly affected owing to the formation of an ether-insoluble product with an anthracene-type chromophore (Fig. 1).

In further experiments evidence was obtained that catalytic amounts of t-butylhydroperoxide, azobisisobutyronitrile and other radical initiators increase the rate of formation of the chromophore, whereas complete inhibition occurs in the absence of oxygen. Attempts to isolate the compound from the reaction mixture were hampered by its marked facility to autoxidation, particularly at neutral or alkaline pH, leading to 1,8-dihydroxy-9,10-anthraquinone. However, the close similarity of the chromophore with that of the anthralin anion (generated anaerobically at pH above 8) together with the polar character and mechanistic considerations suggested for the product the structure III which could arise by trapping of the anthralin radical II[3] by the thiyl radical of cysteine (Fig. 2).

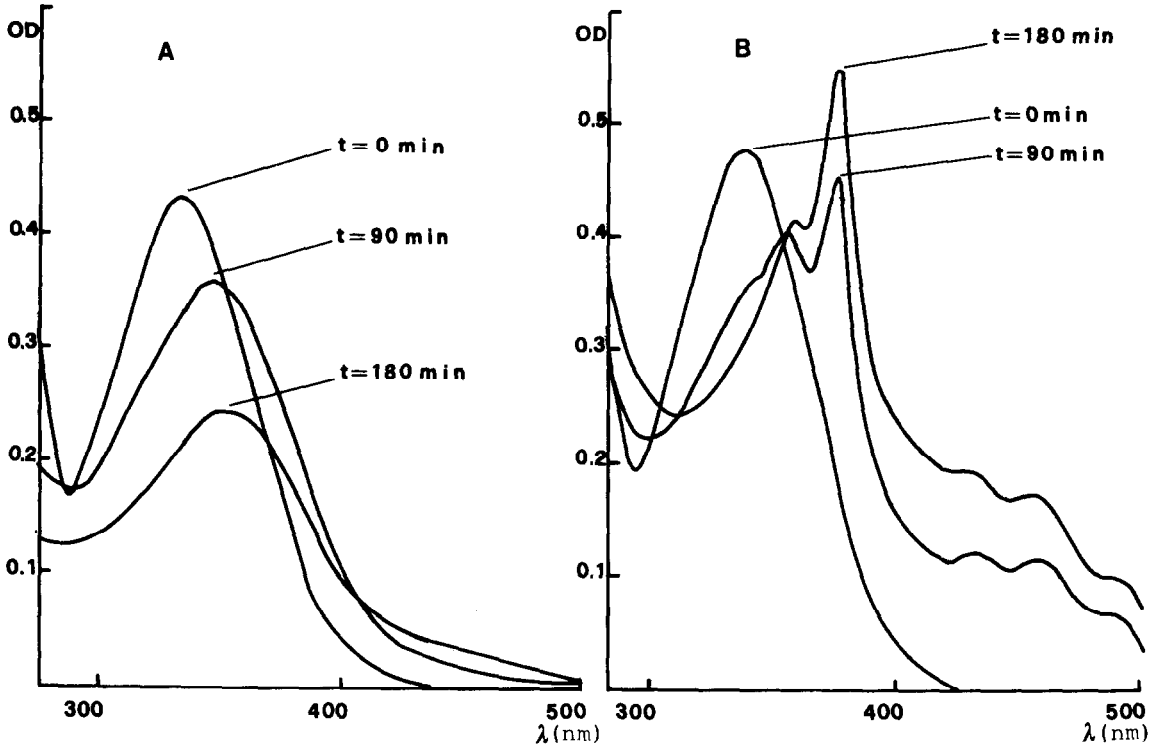


Fig. 1. Spectrophotometric course of autoxidation of $5 \cdot 10^{-5}$M anthralin at 37°C in 0.05 M phosphate buffer, pH=6.0 (75%)-acetonitrile (25%) in the absence (A) and in the presence (B) of 3 mM cysteine.

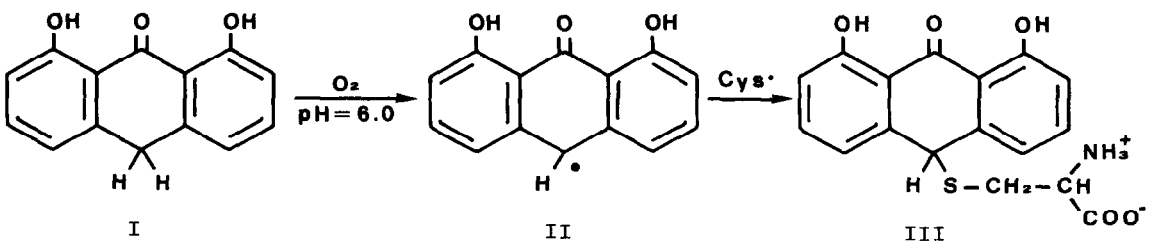
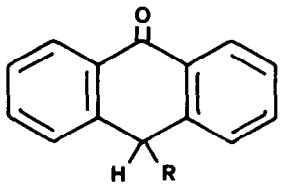


Fig. 2

To support this view, the autoxidation of the parent compound 9-anthrone IV in the presence of excess cysteine ethyl ester was then investigated. As expected, the reaction led to the formation, besides the corresponding 9,10-anthraquinone, of an ether-extractable product (20% yield) which was purified by column chromatography on silica gel (benzene-methanol 9:1) and identified as V by straightforward spectral analysis.[4] The proposed structure was secured by synthesis via reaction of 10-bromo-9-anthrone[5] (VI) with cysteine ethyl ester (4 eq) in methanol under nitrogen and in the presence of triethylamine (1.5 eq), which gave the desired product in 52% yield.



IV : R = H

V : R = $SCH_2CH(COOEt)NH_2$

VI : R = Br

Unexpectedly, attempts to obtain the compound III by analogous reaction of 10-bromo-1,8-dihydroxy-9-anthrone[6] (VII) with cysteine or cysteine ethyl ester were unsuccessful, the starting material being recovered unchanged or partly converted into 1,8-dihydroxy-9,10-anthraquinone. An alternative route was therefore developed, involving acid-catalyzed reaction of cysteine with 1,8,10-trihydroxy-9-anthrone[7] (VIII) (Fig.3).

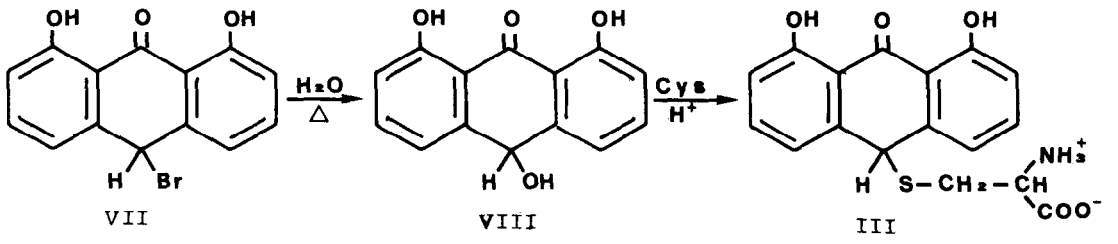


Fig. 3

Crystallization of the crude reaction product from ethanol-0.1 N HCl gave pure 1,8-dihydroxy-10-(2-amino-2-carboxyethylthio)-9-anthrone hydrochloride (III) in 51% yield, yellow prisms decomposing at 176-180°C, $[\alpha]_D^{20}$=-31.7° (c=0.8, 0.1 N ethanolic HCl); ms(FAB) m/e 346 ($M+H^+$),225; UV (EtOH,H^+) λmax (ε) 261

(9700) , 286 (6350) , 375 (10850);(EtOH , OH^-) 366 (8150) , 385 (19400) ,438(7000) , 462 (7650) ,491(4300)nm; ^1H NMR (CF_3COOD)δ3.04 (2H ,m , CH_2) , 3.82(1H ,m ,CH) , 5.54 (1H ,s ,H-10) , 7.14 (1Hx2 , d , J=7.7 Hz ,H-2 ,H-7) , 7.36 (1Hx2 ,d ,J=7.7 Hz ,H-4 ,H-5) , 7.71 (1Hx2 ,t ,J=7.7 Hz , H-3 ,H-6).

Apart from the chemical interest connected with the reactivity of anthrone systems , the observed reaction of anthralin with cysteine opens a new entry into the mechanism of action of this antipsoriatic drug since it provides the first evidence for a covalent binding between the drug and a biological target. Further experiments on the relevance of this reaction for the antipsoriatic activity of anthralin are now in progress.

ACKNOWLEDGEMENTS

This work was partly supported by a grant from CNR-P.F. Chimica Fine e Secondaria. Thanks are due to Mr. R.Ferracane for the drawing of the figures.

References and notes.

1) B.Shroot , H.Schaefer , L.Juhlin , M.W.Greaves , Br. J. Dermatol. ,105 , suppl. 20 , 3 , 1981.

2) K.K.Mustakallio , Br. J. Dermatol. , 105 , suppl. 20 , 23, 1981.

3) A.G.Davies , J.A.A. Hawari , M.Whitefield , Tetrahedron Letters ,24 ,4465 ,1983.

4) V: oil ,ms m/e 341 (M^+) , 340 , 193; UV (hexane) λmax 250 ,260 ,302 nm; IR ($CHCl_3$) ν max 3400 ,1730 ,1670 cm^{-1}; ^1H-NMR ($CDCl_3$) δ1.16 (3H ,t ,J=7.3 Hz ,CH_3) , 1.80 (2H , bs , NH_2) , 2.27 and 2.41 (1H ,dd ,J=7.8 ,13.2 Hz and 1H ,dd , J=4.3 , 13.2 Hz , S-CH_2) , 3.03 (1H , dd , J=4.3 ,7.8 Hz , CH) , 4.02 (2H ,q ,J=7.3 Hz ,O-CH_2) , 5.38 (1H ,s , H-10) , 7.48 (1Hx2 ,t ,J=7.8 Hz , H-2 ,H-7) , 7.64 (1Hx2 ,t ,J=7.8 Hz , H-3 ,H-6) , 7.77 (1Hx2 ,d , J=7.8 Hz , H-4 ,H-5) , 8.28 (1Hx2 ,d ,J=7.8 Hz , H-1 ,H-8).

5) C. Lieberman , Ber. Dtsch.Chem. Ges. 38 , 1797 , 1905

6) O.E Schultz and H.HSchultze-Mosgau , Archiv der Pharmazie , 298 , 273,1965

7) B.L.Van Duuren , A.Segal , S.S.Tseng , G.M.Rusch , G.Loewengart , U.Maté , D.Roth , A.Smith , S.Melchionn , I.Seidman , J.Med. Chem. , 21 , 26 , 1978.

(Received in UK 23 July 1984)