Tetrahedron Letters No. 38, pp 3313 - 3316, 1977. Pergamon Press. Printed in Great Britain.

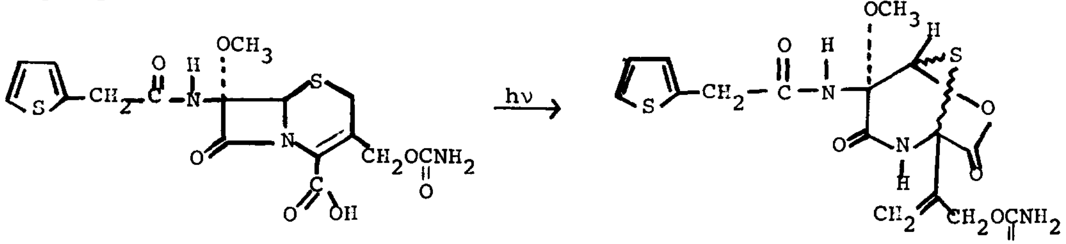
# THE PHOTOLYSIS OF 7-ACYLAMIDO-7-METHOXYCEPHALOSPORINS

N. L. Abramson, A. W. Douglas,
E. J. J. Grabowski and R. F. Czaja*
Merck Sharp and Dohme Research Laboratories
Division of Merck & Co., Inc.
Rahway, New Jersey 07065

(Received in USA 23 June 1977; received in UK for publication 28 July 1977)

The dearth of information regarding the photoreactivity of cephalosporins[1,2] and specifically 7-acylamido-7-methoxy cephalosporins, prompted us to examine the effect of uv light on CEFOXITIN® (1a) and related derivatives.

CEFOXITIN® (1a), on irradiation in methanol,[3] was converted to essentially a single product. Isolation of the product (50% yield as an amorphous powder) was achieved by concentrating the photomixture in vacuo and chromatographing the residue on silica gel (chloroform:ethyl acetate).

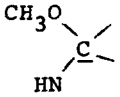
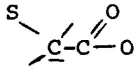


1a 5a

The following spectral data indicate that this photoproduct posseses isomeric structure 5a:[4,5] $C_{16}H_{17}N_3O_7S_2$ (m/e, $M^+$, Calcd. 427.0529; Observed, 427.0502); $^{13}C$ nmr (Table 1); $^1H$ nmr (Acetone-$d_6$, TMS) $\delta$ = 3.20 ppm (3H, s, $OCH_3$), 3.95 (2H, s, thienyl-$CH_2$-), 4,75 (2H, s, -$CH_2OCONH_2$), [5.76, s and 5.83, s; 2H, C = $CH_2$], 6.2 (2H, $OCONH_2$, deut. exch.), 6.8-7.4 (3H, m, thienyl), 7.15 (1H, s, $S\text{-}\overset{O}{C}\text{-}H$). 7.95 (1H, s, $N\text{—}\overset{CH_3O}{C}\text{-}\overset{O}{C}\text{-}NH$, deut. exch.) 9.0 (1H, broad s, thienyl $CH_2\text{-}\overset{O}{\overset{\|}{C}}\text{-}NH$, deut. exch.); ir $\nu_{max}^{THF}$ ($cm.^{-1}$) 1792, 1743, 1705, 1694; uv $\lambda_{max}^{CH_3OH}$ nm ($\varepsilon$) = 234 (9,930).

We propose that 1a is converted to 5a via PATH A wherein the primary photoprocess is S-C homolysis (i.e. formation of 2). The process is completed by the

TABLE 1. C-13 NMR[a,b] FOR PHOTOPRODUCT 5a

| CARBON | CHEM. SHIFT (PPM) | CARBON | CHEM. SHIFT (PPM) |
|---|---|---|---|
| $CH_2\text{-}\overset{O}{\overset{\|}{\underline{C}}}\text{-}\overset{H}{\overset{\mid}{N}}\text{-}$ | 171.8 | $>C=\underline{C}H_2$ | 121.8 |
| Lactone $\overset{O}{\overset{\|}{\diagup C \diagdown}}$ | 170.2[c] |  | 85.7 |
| Lactam $\overset{O}{\overset{\|}{\diagup C \diagdown}}$ | 168.3 | Bridgehead $\underline{C}H$ | 78.5[d] |
| Carbamate $\overset{O}{\overset{\|}{\diagup C \diagdown}}$ | 158.9 |  | 67.0 |
| $>\underline{C}=CH_2$ | 136.9 | $CH_2=C\text{-}\underline{C}H_2\text{-}O$ | 64.1 |
| Thienyl 2' | 137.0 | $\text{-}O\underline{C}H_3$ | 52.5 |
| " 3' | 127.6 | | |
| " 4' | 127.6 | | |
| " 5' | 126.1 | Thienyl $\text{-}\underline{C}H_2\text{-}\overset{O}{\overset{\|}{C}}\text{-}$ | 38.1 |

a. Acetone-$d_6$, ppm relative to TMS=0.

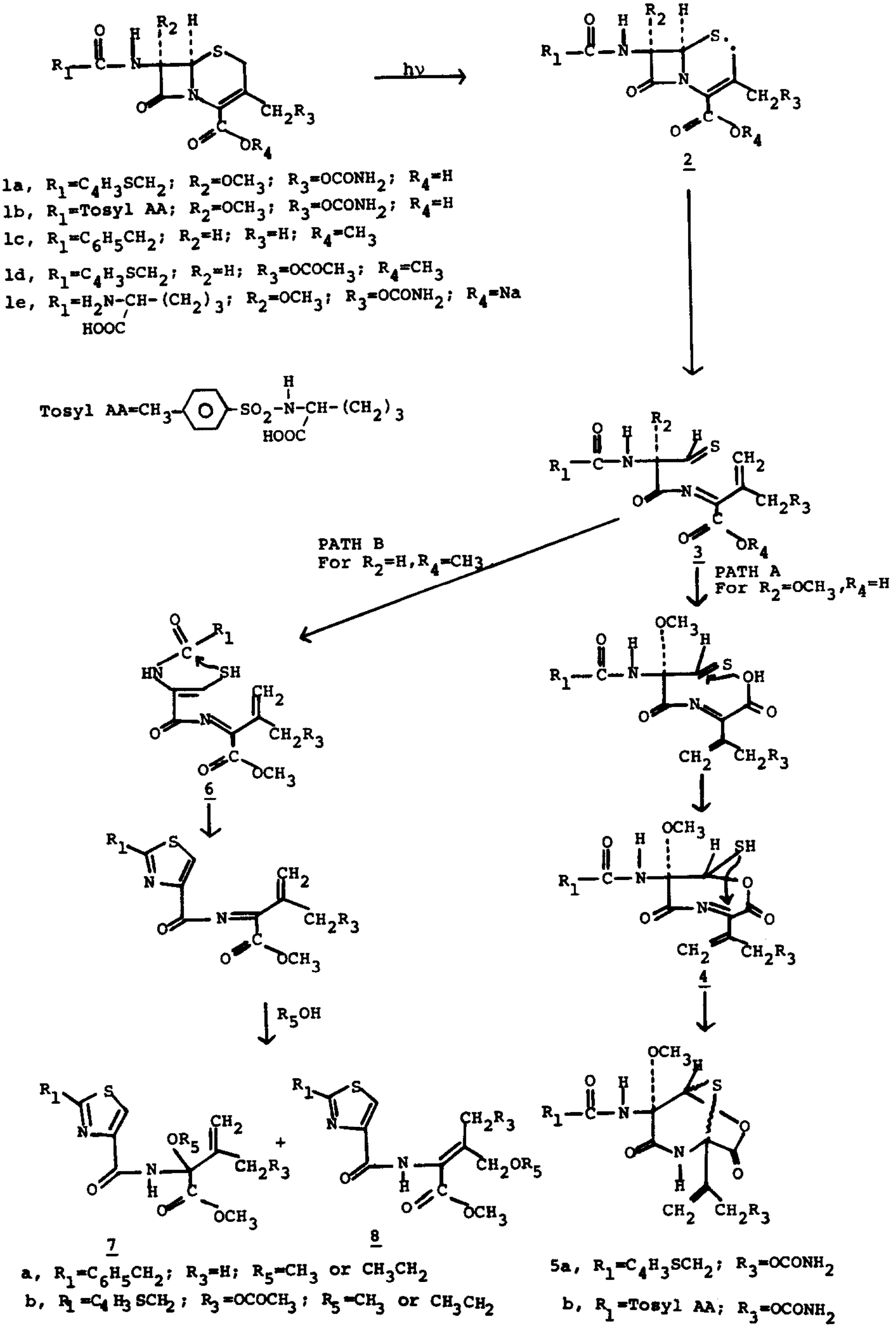
b. Observed using a Varian CFT-20 spectrometer.

c. $^3J_{CH}$ = 8.5 Hz $(\text{-}\overset{O}{\overset{\|}{\underline{C}}}\text{-}O\text{-}C\text{-}\underline{H})$.

d. $^1J_{CH}$ = 181 Hz.

tautomerism of 2 to thioaldehyde 3 followed by the intramolecular cyclizations of the thioaldehyde, acid and imine, as shown, to give 5b.

Recently Maki and Sako[2] reported the photoconversion of either cephalosporins 1c or 1d to a mixture of thiazoles 7 and 8 under essentially the same reaction conditions and suggested 3 as an intermediate (PATH B) in their formation. Clearly, an important factor influencing the products obtained upon photolysis of cephalosporins is the type of substitution in the 7-position and the availability of the free acid function. In our case, the 7-methoxy group prevents the thioaldehyde 3 $\rightleftharpoons$ thioenol 6 tautomerization. Thus, 5a becomes the favored product. Moreover, this reaction sequence may be general for 7-acylamido-7-methoxy cephalosporins containing a 4-carboxy functionality. 1b also underwent this rearrangement to 5b[6] in methanol as well as acetonitrile. The sodium salt of cephamycin C (1e) decomposed, and the methyl ester of 1a and the methoxy methyl ester of 1b gave multicomponent product mixture when similarly photolyzed. These results emphasize further the role that the 4-carboxy group plays in this reaction sequence.



1a, $R_1$=$C_4H_3SCH_2$; $R_2$=$OCH_3$; $R_3$=$OCONH_2$; $R_4$=H
1b, $R_1$=Tosyl AA; $R_2$=$OCH_3$; $R_3$=$OCONH_2$; $R_4$=H
1c, $R_1$=$C_6H_5CH_2$; $R_2$=H; $R_3$=H; $R_4$=$CH_3$
1d, $R_1$=$C_4H_3SCH_2$; $R_2$=H; $R_3$=$OCOCH_3$; $R_4$=$CH_3$
1e, $R_1$=$H_2N$-CH(COOH)-$(CH_2)_3$; $R_2$=$OCH_3$; $R_3$=$OCONH_2$; $R_4$=Na

Tosyl AA=$CH_3$-$C_6H_4$-$SO_2$-NH-CH(HOOC)-$(CH_2)_3$

7
a, $R_1$=$C_6H_5CH_2$; $R_3$=H; $R_5$=$CH_3$ or $CH_3CH_2$
b, $R_1$=$C_4H_3SCH_2$; $R_3$=$OCOCH_3$; $R_5$=$CH_3$ or $CH_3CH_2$

5a, $R_1$=$C_4H_3SCH_2$; $R_3$=$OCONH_2$
b, $R_1$=Tosyl AA; $R_3$=$OCONH_2$

## References and Notes

1. A. L. Demain, *Nature* (London), 210,426 (1966).
2. Y. Maki and M. Sako, *J. Am. Chem. Soc.*, 97, 7168 (1975).
3. The irradiation of 1a (1.5 g. in 310 ml. methanol) was achieved by using a 450 watt medium pressure mercury arc lamp (Pyrex filter) under nitrogen. The conversion required less than 2 hours (35°) and could be followed by either tlc (silica gel, benzene:methanol:acetic acid, 80:18:2; 1a, Rf 0.1; 5a. Rf 0.6.) or disappearance of uv absorption at 268 nm.
4. The relative stereochemistry of the methoxy and sulfur groups has not been determined. The nmr spectrum of the crude photomixture indicates a stereospecificity of $\geq$ 90% for the overall process.
5. 1-β-[(2-Hydroxy-1-methylene)ethyl]-5-methoxy-7-oxo-5-[2-(2-thienyl)acetamide]-6-oxa-8-thia-2-aza-bicyclo[3.2.1]octane carbamate ester.
6. Included in the characteristic H-nmr (acetone-$d_6$, TMS) chemical shifts for 5b were δ 5.73 and 5.80, 2H, s, $C = \underline{CH_2}$) and δ 7.05 (1H, s, $S\text{-}\overset{O}{\underline{C}}\text{-}H$).