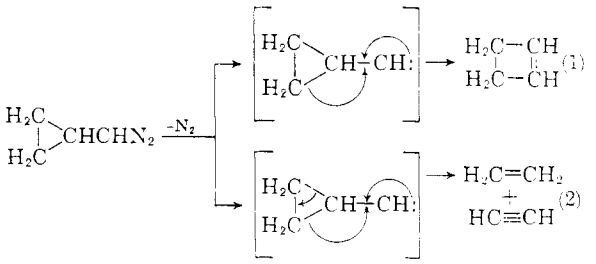
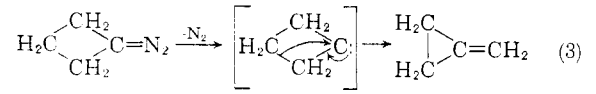


composition of cyclopropyldiazomethane to ethylene and acetylene can occur by requisite shifts of electrons and bond breaking. It has not been established whether butadiene is formed directly in decomposition of the tosylhydrazone or by subsequent decomposition of cyclobutene. The ability of a cyclopropylcarbenyl system to undergo ring-expansion is also illustrated in the base-catalyzed reaction of cyclopropyl methyl ketone tosylhydrazone in diethyl Carbitol to give 1-methyl-1-cyclobutene (92%); vinylcyclopropane (1%), isoprene (2%), methylacetylene (3%) and ethylene (3%) also were formed.

Carbenoid decomposition of cyclobutanone tosylhydrazone[4] in diethyl Carbitol or N-methylpyrrolidone is of significance in that *ring-contraction* (Equation 3) to give methylenecyclopropane (79, 80%) occurs[8]; *hydrogen-migration* to yield cyclobutene (18, 20%) and formation of 1,3-butadiene (2, 1%) are minor reactions. These results are to be contrasted with that from cyclopentanone tosylhydrazone[4] in which cyclopentene (94%) is the major product.



We wish to acknowledge the assistance of Dr. R. R. Hopkins, Whiting Research Laboratories, Standard Oil Company (Ind.).

(8) The yields of the principal carbenic products from cyclopropanecarboxaldehyde and cyclobutanone tosylhydrazones as reported in Abstracts of Papers, 136th Meeting of the American Chemical Society, Atlantic City, N. J., 1959, p. 4, are in error and should be reversed.

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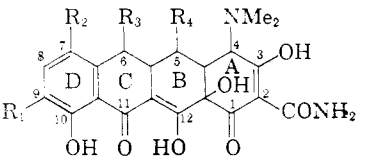
FURTHER 6-DEOXYTETRACYCLINE STUDIES: EFFECT OF AROMATIC SUBSTITUENTS ON BIOLOGICAL ACTIVITY

Sir:

The stability of 6-deoxytetracyclines[1] to acid has made feasible, for the first time, chemical substitution of the phenolic D-ring in the tetracycline series. Interesting structure-activity relationships have been observed with the derivatives thus obtained.

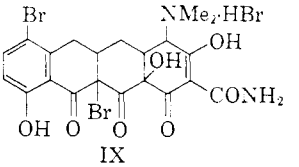
6-Demethyl-6-deoxytetracycline[1] [I, m.p. of the hydrochloride, 224–225°, dec.; $[\alpha]^{25}D$ (C = 1 in 0.01N HCl) −102°; *Anal.* Found for $C_{21}H_{22}N_2O_7 \cdot HCl$: C, 55.64; H, 5.35; N, 6.35; Cl, 7.79] was

(1) C. R. Stephens, K. Murai, H. H. Rennhard, L. H. Conover and K. J. Brunings, THIS JOURNAL, **80**, 5324 (1958).



I, $R_1 = R_2 = R_3 = R_4 = H$
II, $R_2 = Br$, $R_1 = R_3 = R_4 = H$
III, $R_1 = NO_2$, $R_2 = Br$, $R_3 = R_4 = H$
IV, $R_2 = NO_2$, $R_1 = R_3 = R_4 = H$
V, $R_1 = NO_2$, $R_2 = R_3 = R_4 = H$
VI, $R_1 = NH_2$, $R_2 = R_3 = R_4 = H$
VII, $R_2 = NH_2$, $R_2 = R_3 = R_4 = H$
VIII, $R_1 = NO_2$, $R_3 = CH_3$, $R_2 = H$, $R_4 = OH$

chosen for initial studies in this area. Compound I shows *in vitro* antibacterial activity[2] (Table I) essentially equivalent to that of tetracycline. Bromination of I (bromine in trifluoroacetic acid) results in the *substance* IX.



IX

[λ_{max}^{KBr} 5.72 μ; *Anal.* Found for $C_{21}H_{20}N_2O_7Br_2 \cdot HBr$: N, 4.15; Br, 38.0] which on heating in the reaction solution is converted to *7-bromo-6-deoxy-6-demethyltetracycline* [II, m.p. of the hydrobromide, 241–243°, dec.: $\lambda_{max}^{(MeOH-0.01N\ HCl)}$ 268 mμ, log ϵ 4.30; 345 mμ, log ϵ 4.12; 365 mμ, log ϵ 4.12; $\lambda_{max}^{(MeOH-0.01N\ NaOH)}$ 243 mμ, log ϵ 4.23; 382 mμ, log 4.10. *Anal.* Found for $C_{21}H_{21}N_2O_7Br \cdot HBr \cdot H_2O$: C, 42.59; H, 4.21; N, 4.90; Br, 27.10] a compound with somewhat enhanced *in vitro* antimicrobial activity. Nitration of II (70% HNO_3-concd. H_2SO_4) yields *7-bromo-9-nitro-6-demethyl-6-deoxytetracycline*[3] [III, $\lambda_{max}^{(MeOH-0.01N\ HCl)}$ 263 mμ, 370 mμ, $\lambda_{max}^{(MeOH-0.01N\ NaOH)}$ 239 mμ, 285 mμ, 446 mμ] which is relatively inactive.[2]

Direct nitration[4] of I (70% HNO_3-concd. H_2SO_4) results in a mixture from which a *7-nitro compound*[3] [IV, m.p. 218°, dec., λ_{max}^{KBr} 6.54, 7.46 μ; $\lambda_{max}^{(MeOH-0.01N\ HCl)}$ 263 mμ, log ϵ 4.30; 354 mμ, log ϵ 4.11; $\lambda_{max}^{(MeOH-0.01N\ NaOH)}$ 243 mμ, log ϵ 4.17; 255 mμ, log ϵ 4.16; 280 mμ, log ϵ 4.07; 385 mμ, log ϵ 4.17; *Anal.* Found for $C_{21}H_{21}N_3O_9 \cdot HCl \cdot 2H_2O$: C, 47.27; H, 5.00; N, 7.80] and a *9-nitro compound*[3] [V, m.p. 215°, dec., λ_{max}^{KBr} 6.62, 7.42 μ; $\lambda_{max}^{(MeOH-0.01N\ HCl)}$ 263 mμ, log ϵ 4.42; 360 mμ, log ϵ 4.26; $\lambda_{max}^{(MeOH-0.01N\ NaOH)}$ 242 mμ, log ϵ 4.30; 283 mμ, log ϵ 4.16; 352 mμ, log ϵ 4.02; 424 mμ, log ϵ 4.05; *Anal.* Found for $C_{21}H_{21}N_3O_9 \cdot HCl \cdot 2H_2O$: C, 47.63; H, 4.60; N, 7.96] have been isolated.

(2) Activity comparisons herein are based on the standard oxytetracycline biological assay (*cf.* R. C. Kersey, *J. Am. Pharm. Assoc.*, **39**, 252 (1950), against *Klebsiella pneumoniae*. The same relationships do not necessarily hold with other microörganisms.

(3) Structural assignments rest on interpretation of absorption spectra, polarographic studies, oxidative degradation, etc. The 9-nitro tetracyclines show characteristic ultraviolet absorption at unusually long wave length in alkaline solution—a phenomenon which greatly facilitates their identification. We wish to express our gratitude to L. L. Ciaccio and associates for the polarographic investigation.

(4) A preliminary report on a similar nitration has appeared in the patent literature without structural assignment of the products (*cf.* South African Patent Application No. 1415/59).

The 7-nitro compound, IV, is an exceedingly active substance (Table I), showing *in vitro* activity at least four times that of I against the assay organism.[2] The 9-nitro isomer, V, on the contrary, shows only a fraction of the activity[2] of I. Catalytic hydrogenation of the two nitro isomers yields the corresponding amino compounds (VI and VII), which exhibit *in vitro* activity quite comparable to each other and to I.

TABLE I

Compound	Biological assay *versus Klebsiella pneumoniae* in oxytetracycline units per mg.[2]
I	900
II	1300
III	25
IV	4600
V	200
VI	760
VII	975
VIII	<10

Nitration of 6-deoxy-5-oxytetracycline[1] yields the *9-nitro compound*[3] [VIII, $\lambda_{max}^{(MeOH-0.01N\ HCl)}$ 263 mμ, 358 mμ; $\lambda_{max}^{(MeOH-0.01N\ NaOH)}$ 241 mμ, 280 mμ, 352 mμ, 420 mμ] which like III and V is relatively inactive.[2]

These data suggest that the phenolic hydroxyl group in the tetracycline molecule plays an essential role in the microbial inhibition process which is inhibited by hydrogen bonding with an ortho nitro substituent.

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RECEIVED JANUARY 14, 1960

CONVERSION OF ALKYLMERCURIC SALTS TO DIALKYLMERCURY COMPOUNDS WITH RETENTION OF CONFIGURATION IN BOTH ALKYL GROUPS[1]

Sir:

This report concerns the finding that stereoisomeric alkylmercuric salts are reduced stereospecifically by magnesium to give dialkylmercury compounds with retention (85–97%) of configuration (1). The mechanism of the reaction has been investigated.

$$R^*HgBr + Mg \longrightarrow R^*\text{–}Hg\text{–}R^* + MgBr_2 + Hg \quad (1)$$

The reduction has been carried out with *cis*- and *trans* - 4 - methylcyclohexylmercuric bromides[2] to yield di-4-methylcyclohexylmercury with, respectively, 89% retention of configuration (96% yield) and 97% retention of configuration (93% yield). The reaction with L-(−)-*sec*-butylmercuric bromide[3,4] gives di-L-(−)-*sec*-butylmercury with 89–93% retention of configuration (yields to 98%). In a typical experiment, L-(−)-*sec*-butylmercuric bromide, $[\alpha]^{25}D$ −5.05°, gave di-L-(−)-*sec*-butylmercury, $[\alpha]^{25}D$ −7.57°, which upon cleavage with mercuric bromide (equation 2) gave L-

$$R_2^*Hg + HgBr_2 \longrightarrow 2R^*HgBr \quad (2)$$

(−)-*sec*-butylmercuric bromide, $[\alpha]^{25}D$ −4.60°. Although evidence has been given previously which indicates that reaction (2) occurs with retention of configuration,[4,5] the results of cleaving the above compounds provide additional proof of the correctness of the assigned stereochemical course.

In previous related work, α-bromomercuricamphor and *l*-menthyl α-bromomercuriphenylacetate were converted stereospecifically to the corresponding optically active dialkylmercury compounds by the addition of certain complexing agents.[6,7] For these compounds reaction (2) is reversible and the complexing agent acts on the mercuric bromide. No example of the reversal of reaction (2) where R- is a simple alkyl group has been reported.

Evidence relating to the mechanism of reaction (1) is given: (a) when the reaction is conducted in a carbon dioxide atmosphere or in the presence of 1-butanol no carboxylic acid or hydrocarbon is produced; (b) the reaction may be carried out in the presence of styrene and the styrene may be recovered unchanged from the reaction mixture; (c) the reactions with *cis*- and *trans*-2-methoxycyclohexylmercuric bromide yield only cyclohexene and no dialkylmercury compound; and (d) the stereochemical course is retention of configuration. The above evidence eliminates possible intervention of R^-, RMgBr, and R· as reaction intermediates. The simplest intermediate which would lead to olefin in a compound containing an adjacent methoxyl group (item c) is RHg^-.

The mechanism proposed to account for the results is given below; however, possible intervention of RHg in a chain reaction is not rigorously excluded. In order to give retention of configuration, the alkyl group in the organomercurous compound[8] must migrate with retention of configuration.

$$RHgBr + Mg \longrightarrow RHg^- + {}^+MgBr \quad (3)$$

$$RHg^- + RHgBr \longrightarrow RHgHgR + Br^- \quad (4)$$

$$RHgHgR \longrightarrow \underset{\displaystyle R}{\overset{\displaystyle |}{RHgHg}} \quad (5)$$

$$\underset{\displaystyle R}{\overset{\displaystyle |}{RHgHg}} \longrightarrow RHgR + Hg \quad (6)$$

The reverse of reactions (6) and (5) represent an attractive mechanism for the exchange of Hg^{203} with organomercurials, which is known to proceed with retention of configuration.[9] Other reactions which might involve intermediates having Hg–Hg bonds and involve alkyl migrations on mercury, analogous to reaction 5, are the cleavage of di-

(1) Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research.

(2) F. R. Jensen and L. H. Gale, THIS JOURNAL, **81**, 1261; **82**, 145 (1960).

(3) H. B. Charman, E. D. Hughes and C. K. Ingold, *Chem. and Ind.*, 1517 (1958).

(4) F. R. Jensen, L. D. Whipple, D. K. Wedegaertner and J. A. Landgrebe, THIS JOURNAL, **81**, 1262 (1959).

(5) H. B. Charman, E. D. Hughes and C. K. Ingold, *J. Chem. Soc.*, 2530 (1959).

(6) O. A. Reutov and L. Tszin-Chzhu, *Doklady Akad. Nauk S.S.S.R.* (English translation), **110**, 593 (1956).

(7) O. A. Reutov, I. P. Beletskaya and E. E. Mardaleishvili, *ibid.*, **116**, 901 (1957).

(8) J. Sand, *Ber.*, **34**, 2913 (1901).

(9) O. A. Reutov, P. Knoll and Yan-Tsei U, *Doklady Akad. Nauk S.S.S.R.*, **120**, 1052 (1958) (*C. A.*, **52**, 20003 (1958)); O. A. Reutov, *Izvest. Akad. Nauk S.S.S.R., Otdel. Khim. Nauk*, 684 (1959) (*C. A.*, **52**, 20004 (1958)).