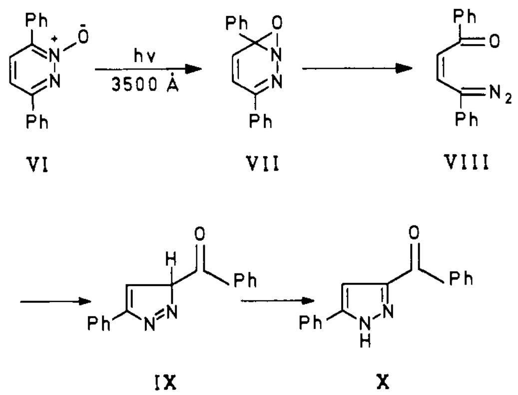
expected to result in formation of 2,5-diphenylfuran, by analogy with the behavior of the phthalazine N-oxide I.

Photolysis[6] of the pyridazine N-oxide in acetone, followed by preparative layer chromatography of the reaction mixture on silica gel, resulted in the isolation of 3-benzoyl-5-phenylpyrazole (X) in 75% yield. The substance was identical (melting point, mixture melting point, infrared spectrum) with an authentic sample of 3-benzoyl-5-phenylpyrazole.[7] Other products were formed during the irradiation, but only one, a colorless crystalline solid containing nitrogen, mp 221–222°, has been isolated in sufficient yield (~10%) for investigation.

A tentative mechanism to account for the formation of the benzoylpyrazole X from the pyridazine N-oxide VI is presented in Scheme II.

Scheme II



We believe that photolysis of the amine oxide leads initially to the oxaziridine VII[8] which is converted, in either a photochemical or a thermal process, to the diazo compound VIII. Conversion of the oxaziridine to the diazo compound is analogous to the formation of phenylnitrene from 2,3,3-triphenyloxaziridine observed by Splitter and Calvin.[9] Isomerization of the diazo compound VIII to 3-benzoyl-5-phenylpyrazole (X) *via* the tautomeric 3H-pyrazole IX, involving an intramolecular 1,3-dipolar cycloaddition that should be faster than the long-known isomerization of vinyldiazomethane to pyrazole,[10] seems wholly reasonable.

The intermediacy of the diazo compound VIII was suggested by the appearance during irradiation of a persistent, intense yellow color ($\lambda_{max}^{CH_3OH}$ 410 mμ) which faded in the dark and by the appearance of absorption at 2070 cm^{-1} in the infrared spectrum of 10% chloroform solutions of the pyridazine N-oxide immediately after irradiation. This absorption, which disappeared along with the yellow color when solutions were kept in the dark, is in the region 2040–2120 cm^{-1} where diazo compounds absorb.[11]

(5) (a) M. Ogata and K. Kano, *Chem. Commun.*, 1176 (1967); (b) H. Igeta, T. Tsuchiya, M. Yamada, and H. Arai, *Chem. Pharm. Bull.* (Tokyo), **16**, 767 (1968).

(6) The light source for all photolyses was the RUL-3500 lamps of a Rayonet reactor, Type RPR-208.

(7) D. G. Farnum and P. Yates, *J. Am. Chem. Soc.*, **84**, 1399 (1962). We thank Dr. Yates for a sample.

(8) For discussion of the photochemical formation of oxaziridines from aromatic amine N-oxides see earlier papers in this series.

(9) J. S. Splitter and M. Calvin, *Tetrahedron Letters*, 1445 (1968).

(10) (a) C. D. Hurd and S. C. Lui, *J. Am. Chem. Soc.*, **57**, 2656 (1935); (b) D. W. Adamson and J. Kenner, *J. Chem. Soc.*, 286 (1935).

It seems reasonable to assume that loss of nitrogen occurs from the diazo compound III because the thermal cyclization (analogous to the process VIII → IX) is energetically very unfavorable. It is possible that some of the minor products observed in the photolysis of 3,6-diphenylpyridazine N-oxide arise by loss of nitrogen from the diazo compound or the 3H-pyrazole derivative IX.[12]

Further attempts to elucidate the detailed mechanisms operating in the photolyses of aromatic 1,2-diazine N-oxides are currently in progress. Such experiments are primarily directed toward detection of the diazo compound III or the carbene IV during photolysis of 1,4-diphenylphthalazine N-oxide (I). These results, together with the photochemical behavior of other aromatic 1,2-diazine N-oxides, will be reported in the full paper.

Acknowledgment. We wish to acknowledge the financial support of the Carlsberg Foundation (purchase of the Rayonet reactor) and the North Atlantic Treaty Organization (NATO postdoctoral fellowship to P. L. K.).

(11) A. Foffani, C. Pecile, and S. Ghersetti, *Tetrahedron*, **11**, 285 (1960).

(12) The thermal loss of nitrogen from diazo compounds and pyrazolines is well documented. It is also known that 3H-pyrazoles can lose nitrogen in a photochemical reaction,[13] with ring opening preceding nitrogen elimination. In some cases transient diazoalkenes have been detected.[13c]

(13) (a) G. L. Closs and W. Böll, *Angew. Chem.*, **75**, 640 (1963); (b) G. L. Closs and W. A. Böll, *J. Am. Chem. Soc.*, **85**, 3904 (1963); (c) G. L. Closs, W. A. Böll, H. Heyn, and V. Dev, *ibid.*, **90**, 173 (1968).

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Total Synthesis of Anthramycin

Sir:

Recently we reported on the isolation and characterization of anthramycin,[1] a new antitumor antibiotic to which we assigned structure **1** primarily on spectroscopic evidence.[2,3] We now wish to record the total synthesis of anthramycin by methods which confirm this unique structure.

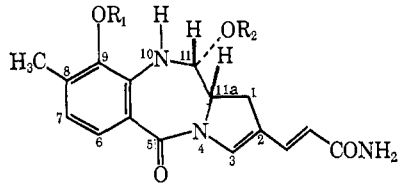
We have shown previously that anthramycin (**1**) can be obtained by partial synthesis from anthramycin methyl ether (**2**) *via* anhydroanthramycin (**5**).[1] The problem of the total synthesis was therefore reduced to the task of synthesizing anthramycin methyl ether (**2**), a comparatively stable and well-characterized derivative which had been obtained in the course of our isolation work by crystallization of the antibiotic from methanol–water.[1]

We selected as our first synthetic objective compound **17**, the structure of which differs from that of anthramycin only by the absence of two hydrogen atoms. It appeared particularly attractive to attempt the synthesis of this compound from a naturally occurring amino acid.

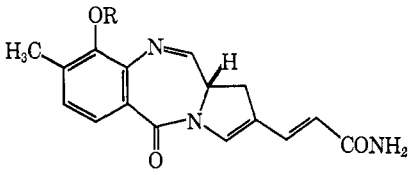
(1) W. Leimgruber, V. Stefanović, F. Schenker, A. Karr, and J. Berger, *J. Am. Chem. Soc.*, **87**, 5791 (1965).

(2) W. Leimgruber, A. D. Batcho, and F. Schenker, *ibid.*, **87**, 5793 (1965).

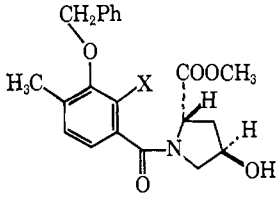
(3) W. Leimgruber, A. D. Batcho, and F. Schenker, 4th International Symposium on the Chemistry of Natural Products, IUPAC Congress, Stockholm, 1966, Abstracts, p 106.



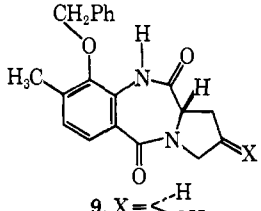
1, $R_1 = R_2 = H$
2, $R_1 = H; R_2 = CH_3$
3, $R_1 = Bz; R_2 = CH_3$
4, $R_1 = Bz; R_2 = H$



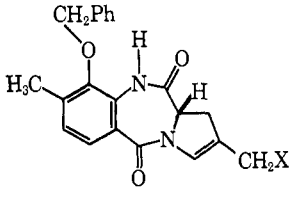
5, R = H
6, R = Bz



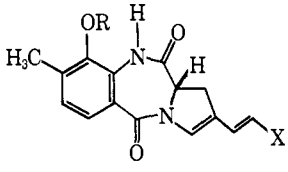
7, X = NO_2
8, X = NH_2



9, X =
10, X = O



11, X = $COOC_2H_5$
12, X = CHO
13, X = CH(OH)CN
14, X = CH(OMs)CN



15, R = CH_2Ph; X = CN
16, R = H; X = CN
17, R = H; X = $CONH_2$
18, R = Bz; X = $CONH_2$
19, R = Bz; X = CN

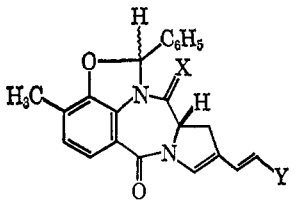
Acylation of L-hydroxyproline methyl ester[4] with 3-benzyloxy-4-methyl-2-nitrobenzoyl chloride[5] in the presence of triethylamine gave the amide **7**[6] (94%; mp 160–162°). Reduction with sodium dithionite in tetrahydrofuran–water produced the amine **8** which, on treatment with aqueous hydrochloric acid, cyclized to the lactam **9** [86%; $[\alpha]^{25}D$ +256° (*c* 0.5, CH_3OH)]. Oxidation of the secondary alcohol with Jones reagent yielded the ketone **10** (73%; $\nu_{max}^{CHCl_3}$ 1770, 1705, and 1645 cm^{-1}) which was condensed with the sodium salt of triethyl phosphonoacetate[7] in tetrahydrofuran at 0° to give as the major product the β,γ-unsaturated ester **11** [74%; δ^{CDCl_3} 6.85 ppm (1 H, singlet)]. Reduction with diisobutylaluminum hydride in toluene at −60° produced the labile aldehyde **12** which was converted *in situ* to the sodium bisulfite adduct and then, by reaction with potassium cyanide, to a mixture of epimeric cyanohydrins **13**. The product was allowed to react with methanesulfonyl chloride in pyridine at 5° to give the corresponding epimeric mesylates **14** which, on treatment with triethylamine in boiling benzene, afforded a *trans–cis* mixture of conjugated nitriles (*cf.* **15**) in the ratio 4:1 (30% over-all yield from **11**). For characterization, the crystalline isomers were separated by preparative thin layer chromatography on silica gel. Since the *trans* compound **15** [δ^{DMSO} 5.54 ppm (1 H, doublet, J = 16 Hz)] and the corresponding *cis* compound [δ^{DMSO} 5.44 ppm (1 H, doublet, J = 11.5 Hz)] thus obtained were found to be very susceptible to isomerization, the original mixture of isomers was used in the sequel. Debenzylation in trifluoroacetic acid[8] at room temperature in the presence of boron trifluoride etherate gave a mixture of phenolic *trans*- and *cis*-nitriles (*cf.* **16**; 70%) which can be separated if desired. When heated in aqueous trifluoroacetic acid at reflux temperature, the mixture afforded as the major product the desired *trans*-amide **17** [mp 324–325° dec (*in vacuo*); $[\alpha]^{20}D$ +843° (*c* 0.1, DMSO); $\lambda_{max}^{2\text{-propanol}}$ 223 (ϵ 26,600), and 332 mμ (36,900); δ^{DMSO} 5.90 and 7.25 ppm (two 1 H doublets, J = 15.5 Hz); *m/e* 313].

The same compound could also be made by partial synthesis from anthramycin methyl ether (**2**) by the following sequence of reactions. Benzoylation with benzoic anhydride in hot triethylamine gave the O-benzoyl derivative **3** which, on treatment with boiling isopropenyl acetate in the presence of a catalytic amount of acetic acid, was converted to O-benzoylanhydroanthramycin (**6**). Dissolution of the Schiff base in aqueous acetone produced a mixture of epimeric carbinolamines (*cf.* **4**) which were oxidized with chromium trioxide in pyridine[9] at room temperature to give the lactam **18**. Subsequent treatment with boiling methanol in the presence of triethylamine afforded the *trans*-amide **17**, identical in every respect (mixture melting point undepressed) with material obtained by total synthesis from L-hydroxyproline. This establishes the absolute configuration of anthramycin (**1**) for which the *S* configuration has to be assigned to the asymmetric center at C_{11a}.[10]

The remaining problem in our total synthesis consisted formally of the task of effecting the specific reduction of the secondary amide group of compound **17**. It was obvious from the outset, however, that this compound would have to be modified structurally if the desired transformation were to be achieved.[11] Thus, we envisaged for our purposes a compound corresponding to structure **21** as a suitable derivative, especially since the amide function to be reduced is tertiary.[12]

Attempts to prepare the benzoxazoline **21** from compound **17** failed. However, we were able to produce the desired intermediate **21** from the totally synthetic *trans*-nitrile **16** which in turn could be conveniently made from the amide **18**. Thus, dehydration of com-

(4) E. L. Smith and M. Bergmann, *J. Biol. Chem.*, **153**, 627 (1944).
(5) H. Brockmann and H. Muxfeldt, *Chem. Ber.*, **91**, 1242 (1958).
(6) All new substances have been characterized by infrared, ultraviolet, nmr, and, in some instances, mass spectra confirmatory of the structures presented. Satisfactory elementary analyses have been obtained for all compounds except those utilized without isolation.
(7) W. S. Wadsworth, Jr., and W. D. Emmons, *J. Am. Chem. Soc.*, **83**, 1733 (1961).
(8) J. P. Marsh, Jr., and L. Goodman, *J. Org. Chem.*, **30**, 2491 (1965).
(9) G. I. Poos, G. E. Arth, R. E. Beyler, and L. H. Sarett, *J. Am. Chem. Soc.*, **75**, 422 (1953).
(10) Correspondingly, anthramycin should be designated as (11*R*,-11a*S*)-5,10,11,11a-tetrahydro-9,11-dihydroxy-8-methyl-5-oxo-1H-pyrrolo[2,1-*c*][1,4]benzodiazepine-2-*trans*-acrylamide.
(11) Compound **17** remains unchanged upon treatment with an excess of lithium aluminum hydride in boiling tetrahydrofuran.
(12) The prospects of reducing this tertiary amide to a carbinolamine function appeared to be promising because N-methylanilides are converted in good yields to aldehydes by reduction with lithium aluminum hydride. See F. Weygand, G. Eberhardt, H. Linden, F. Schäfer, and I. Eigen, *Angew. Chem.*, **65**, 525 (1953).



20, X = O; Y = CN
21, X = O; Y = $CONH_2$
22, X =  ; Y = $CONH_2$

pound **18** with *p*-toluenesulfonyl chloride in pyridine at 50° yielded the *trans*-nitrile **19** [17% over-all yield from **2**; δ^{DMSO} 5.58 ppm (1 H, doublet, J = 16 Hz)] which, when heated in boiling methanol in the presence of triethylamine, afforded the phenol **16** [98%; δ^{DMSO} 5.54 and 7.43 ppm (two 1 H doublets, J = 16 Hz)]. Condensation of the latter compound with benzaldehyde dimethyl acetal[13] at 200° under nitrogen gave the benzal derivative **20** [60%; mp 194–195° (*in vacuo*)] which was converted to the amide **21** [67%; mp 281–282° dec (*in vacuo*)] upon treatment with hot (95°) polyphosphoric acid followed by aqueous work-up.

Reduction of compound **21** with lithium aluminum hydride in tetrahydrofuran at −60° *or* with sodium borohydride in methanol at 5° (preferred method), followed by hydrolysis of the resulting carbinolamine **22** [δ^{DMSO} 4.85 (1 H, doublet, J = 9 Hz; singlet after exchange)[2]] with 0.01 *N* aqueous hydrochloric acid in methanol, afforded a 70% over-all yield of anthramycin methyl ether (**2**), identical in every respect (including microbiological activity) with an authentic sample.

Acknowledgment. The authors wish to thank Mr. K. Hiltpold and Mr. R. Philion for their experimental assistance in certain phases of this work.

(13) E. Fischer and G. Giebe, *Chem. Ber.*, **31**, 545 (1898).

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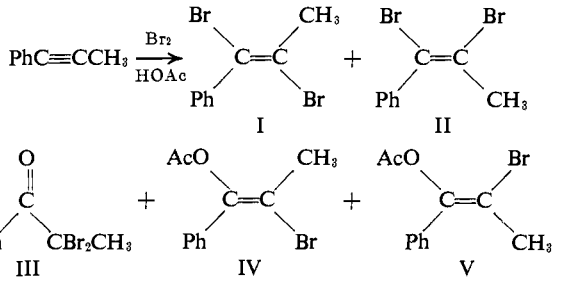
On the Mechanism of Bromination of Acetylenes

Sir:

Although the electrophilic addition of bromine to olefins has been extensively studied and the main details of the reaction are well understood,[1] very little is known about the mechanism of the corresponding reaction with acetylenes. The only kinetic work available is an early study by Robertson[2] on the bromination of a series of substituted acetylenes in acetic acid indicating that the reaction is an electrophilic addition and that the rate expression involves first- and second-order bromine terms similar to those observed for olefins. However, no systematic study of the products and stereochemistry in relation to the kinetics is available, and consequently we wish to report our preliminary results here.

The bromination of methylphenylacetylene in acetic acid yields five products: *trans*-1,2-dibromo-1-phenylpropene (I), *cis*-1,2-dibromo-1-phenylpropene (II), 1,1-dibromoethyl phenyl ketone (III), and *trans*- and *cis*-1-acetoxy-2-bromo-1-phenylpropenes (IV and V).



The products were isolated from the reaction mixture by extraction with pentane and separated by a combination of column and preparative-scale gas chromatography. The stereochemistry of I and II was established from their dipole moments, the *trans* isomer having a value of 0.1 D and the *cis* isomer a value of 2.2 D. The dibromo ketone III is identical with the product of an acid-catalyzed bromination of propiophenone and could also be obtained by the bromination of the mixture of IV and V in acetic acid. This establishes that III is a secondary reaction product and also that the bromoacetates are the 1-acetoxy compounds rather than the isomeric 2-acetoxy forms. The bromoacetates obtained could not be separated by vpc, but an nmr spectrum of the mixture indicated the two isomeric compounds were present in the ratio of 2.6:1. However, no assignment of their stereochemistry could be made on the basis of the nmr spectrum alone.

In control experiments under the reaction conditions no isomerization of the dibromides or reaction to give bromoacetates was observed. The results of product studies in pure acetic acid and in the presence of added salts are shown in Table I. Of particular interest is the

Table I. Products of Bromination of Methylphenylacetylene (MPA) in Acetic Acid at 25°

(MPA), 10^2 *M*	(Br_2), 10^3 *M*	Added salt, *M* LiBr	$LiClO_4$	Product composition, %[a] I	II	III	IV + V
3.34	3.78			59.2	13.7	6.1	21.0
8.85	4.56			55.5	12.4	13.9	18.1
10.3	10.3			59.4	13.9	8.9	17.7
10.1	5.82		0.10	47.8	10.3	15.2	26.6
7.90	3.96		0.10	53.3	9.6	12.9	24.1
3.37	3.78	0.10		98	0.2	0.5	1.5
3.77	3.78	0.06	0.04	98	0.2	0.5	1.5
3.56	3.78	0.02	0.08	92.5	1.0	2.0	4.5

[a] Evaluated by vpc from peak areas.

result that although the reaction is only selective in the pure solvent (*trans*:*cis* 4.2:1 for dibromide formation) it occurs with virtually 100% *trans* stereospecificity in the presence of lithium bromide. An interpretation of this result requires a knowledge of the kinetic processes occurring under the conditions studied.

The kinetics of the addition reaction follow the general equation

$$-\frac{d(Br_2)_T}{dt} = k_2(MPA)(Br_2) + k_3(MPA)(Br_2)^2 + k_{Br^-}(MPA)(Br_2)(Br^-) \quad (1)$$

where (MPA) is the concentration of methylphenyl-

(1) P. B. D. de la Mare and R. Bolton, "Electrophilic Addition to Unsaturated Systems," Elsevier Publishing Co., New York, N. Y., 1966, Chapter 7.
(2) P. W. Robertson, W. E. Dasent, R. M. Milburn, and W. H. Oliver, *J. Chem. Soc.*, 1628 (1950).