polarizability, are predictable, and will be subsequently discussed.[17]

The relatively large fraction of aromatic amino acids[5] contained in rhodopsin leads us to speculate that the protonated imine chromophore (analogous to **1**) bound in opsin has, in its immediate environment, aromatic side-chain groups oriented in such a way as to make the binding site highly polarizable, resulting in significant red shifts of the λ_{max} of the visual pigments and initial photoproducts. Changes in the conformation of opsin would certainly change the orientation of the polarizable groups and hence alter the local polarizability of the binding site. Thus genetic differences (with animal species) in the absorption maxima of the visual pigments, and the spectral shifts observed upon their photolysis[1] may be rationalized on the basis of the proposed model for the spectral behavior of the pyrrolidiniminium perchlorate **1**.

Acknowledgments. The authors are indebted to several of our Wesleyan colleagues and to Drs. R. S. Cooke and E. M. Kosower for stimulating discussion. Financial support was provided by the National Institutes of Health, the National Science Foundation, the Connecticut Research Commission, and the Petroleum Research Fund, administered by the American Chemical Society.

(17) Because of space limitations, this discussion is very compact. A more quantitative discussion of this general phenomenon will appear at a later date: C. S. Irving, G. W. Byers, W. C. Pringle, and P. A. Leermakers, to be published.

(18) National Science Foundation Undergraduate Research Participant, summer 1968.

(19) Alfred P. Sloan Fellow.

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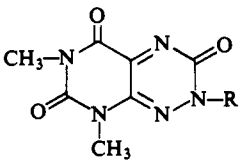
Structure and Total Synthesis of the Pyrimido[5,4-*e*]-*as*-triazine Antibiotic, 2-Methylfervenulone[1]

Sir:

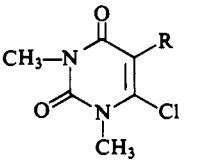
We wish to report the structure and total synthesis, by two independent routes, of the antibiotic 2-methylfervenulone (MSD-92) (2,6,8-trimethylpyrimido[5,4-*e*]-*as*-triazine-3,5,7(2H,6H,8H)-trione, **1**).

2-Methylfervenulone, previously designated as MSD-92, was isolated from the fermentation broth of an unidentified actinomycete and shown to have broad *in vitro* antibiotic activity.[2] It was correctly identified as a trimethylpyrimidotriazinetrione, although the specific structures proposed have proven to be incorrect.[2] Our results show this antibiotic to be the third member of a triad of pyrimido[5,4-*e*]-*as*-triazine antibiotics which includes toxoflavin[3] and fervenulin.[4] Both of the latter compounds have been synthesized[5-9] by routes which unequivocally establish their structures. We now report the unequivocal synthesis of **1**.

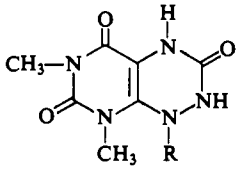
Heating 5-carbethoxyamino-1,3-dimethylbarbituric acid[10] with phosphorus oxychloride in the presence of 4–5% of added water, followed by concentration *in vacuo*, addition of ice, and filtration, gave 6-chloro-1,3-dimethyl-5-isocyanatouracil (**2**),[11] mp 145–146° (65%). Addition of methylhydrazine in acetonitrile solution then gave 4-(6-chloro-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)-2-methylsemicarbazide (**3**), mp 199–200° (46%) (benzylidene derivative, mp 182–183°), which upon stirring in aqueous solution at 65–70° with 1 equiv of sodium acetate over a 7-hr period, while the reaction solution was diffused with air, gave 2-methylfervenulone (MSD-92) (**1**), mp 181–182° (41% yield). The product was identical with the naturally occurring antibiotic both in physical (melting point, mixture melting point; nmr, uv, and ir spectra; tlc) and in biological properties.[12]



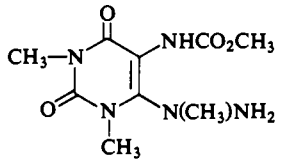
1, R = CH_3
4, R = H



2, R = N=C=O
3, R = $NHCON(CH_3)NH_2$
5, R = $NHCONHNH_2$
8, R = $NHCO_2CH_3$



6, R = H
7, R = CH_3



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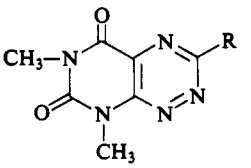
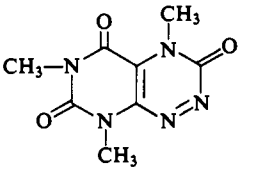


10, R = Cl
11, R = OCH_3



12

An alternate and more convenient synthesis of **1** was achieved as follows. Addition of diethyl azodicarboxyl-

(1) This investigation was supported by the U. S. Army Medical Research and Development Command (Contract No. DA-49-193-MD-2777) and is Contribution No. 530 in the Army research program on malaria. We also acknowledge partial support of this work by a grant from Eli Lilly and Co.

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(11) Satisfactory microanalytical and spectral data were obtained for all compounds reported.

(12) We are indebted to Dr. Frank J. Wolf of the Merck, Sharp and Dohme Research Laboratories, Rahway, N. J., for an authentic sample of the naturally occurring antibiotic and for the bioassay of synthetic **1**.

ate to 1,3-dimethyl-6-hydrazinouracil has been shown to give 1,3-dimethyl-5-(1,2-dicarbethoxyhydrazino)-6-hydrazinouracil.[8] Cyclization of this compound with sodium ethoxide in absolute ethanol gave the sodium salt of 6,8-dimethylpyrimido[5,4-*e*]-*as*-triazine-3,5,7(2H,-6H,8H)-trione[8] (**4**) (fervenulone), which was filtered, suspended in fresh absolute ethanol, and treated with methyl iodide. Stirring for 2 hr at 50° then gave 2-methylfervenulone (**1**) in 60% yield. Alternatively, **4** was prepared by treatment of **2** with hydrazine in chloroform solution to give 4-(6-chloro-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)semicarbazide (**5**), mp 178–179° (33%). Pyrolysis of **5** at 135–140° (0.01 mm) afforded 1,4-dihydro-6,8-dimethylpyrimido[5,4-*e*]-*as*-triazine-3,5,7(2H,6H,8H)-trione (**6**), mp 250–251° (27%), which was oxidized to **4** in 88% yield by stirring with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone in refluxing chloroform solution.

In the course of the above work an interesting rearrangement was observed upon pyrolytic cyclization of **3**. Heating **3** at 135° (0.01 mm) for 6 hr gave 1,4-dihydro-1,6,8-trimethylpyrimido[5,4-*e*]-*as*-triazine-3,5,7-(2H,6H,8H)-trione (**7**), mp 241–242° dec (66%). This compound is isomeric with dihydro-**1** but is incapable of dehydrogenation and thus provides independent evidence for the absence of a methyl group on N-1 in MSD-92. An independent, unequivocal synthesis of **7** was achieved by heating **2** in methanol solution to give the urethan **8**, mp 169–170° (80%), which upon treatment with methylhydrazine for 2 hr in acetonitrile solution at room temperature gave 1,3-dimethyl-5-carbomethoxyamino-6-(1-methylhydrazino)uracil (**9**), mp 179–180° dec (46%) (benzylidene derivative, mp 159–160°). Cyclization of **9** by heating in ethanol with sodium ethoxide then gave **7** in 38% yield.

2-Methylfervenulone (MSD-92) (**1**) is one of the three possible methyl derivatives of fervenulone (**4**). We also report at this time the synthesis of both remaining methyl isomers. 3-Methoxy-6,8-dimethylpyrimido[5,4-*e*]-*as*-triazine-5,7(6H,8H)-dione (**11**), mp 144–145° (85%), was formed by treating 3-chloro-6,8-dimethylpyrimido[5,4-*e*]-*as*-triazine-5,7(6H,8H)-dione[8] (**10**) with sodium methoxide for 15 min at room temperature. Finally, treating a solution of **4** in methanol with diazomethane gave the only remaining methyl isomer, 4,6,8-trimethylpyrimido-[5,4-*e*]-*as*-triazine-3,5,7-(4H,6H,8H)-trione (**12**), mp 218–220° dec (5%), along with smaller amounts of both **1** and **11**.

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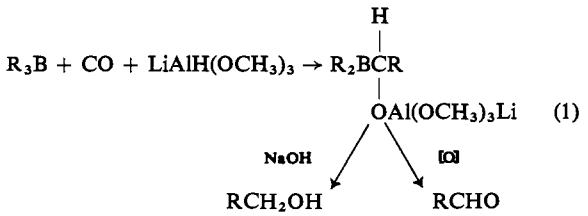
Reaction of B-Alkyl-9-borabicyclo[3.3.1]nonanes with Carbon Monoxide in the Presence of Lithium Trimethoxyaluminohydride. A Convenient Procedure for the Conversion of Olefins into Aldehydes *via* Hydroboration

Sir:

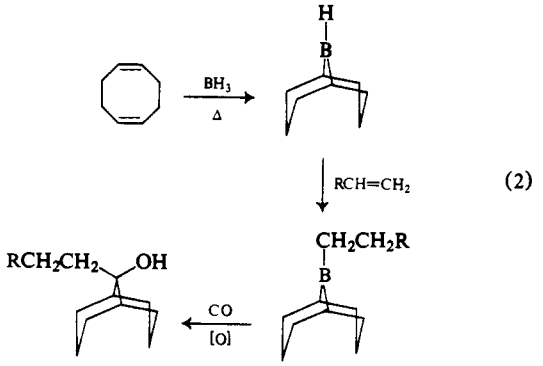
We previously reported that carbon monoxide reacts rapidly and essentially quantitatively with trialkylboranes in the presence of lithium trimethoxyaluminohydride, providing a highly useful synthetic route to the corresponding aldehyde or methylol derivative[1] (1).



(1)

Based on the equation as written, the yields were essentially quantitative. However, since only one of the three groups on boron participates in the desired reaction, the conversion of alkyl groups to the desired product is a maximum of 33%. This represents a considerable difficulty for many of the new reactions of organoboranes[2] in cases where a valuable intermediate is to be converted into the desired product.

1,5-Cyclooctadiene undergoes cyclic hydroboration with remarkable ease.[3a] The resulting bibyclic borane, 9-borabicyclo[3.3.1]nonane (9-BBN), exhibits unusual stability in air, but is a very active hydroborating agent, converting olefins into the corresponding B-alkyl derivatives.[3b] Carbonylation readily converts these B-alkyl derivatives into the corresponding tertiary alcohols[3c] (2).



(2)

We now wish to report that the use of 9-BBN solves the above problem for the new aldehyde synthesis. B-Alkyl-9-borabicyclo[3.3.1]nonanes react rapidly at 0° with carbon monoxide in the presence of lithium trimethoxyaluminohydride. The resulting intermediate can be hydrolyzed to the methylol derivative or oxidized to the aldehyde. High yields are realized, indicating that the B-alkyl group migrates in preference to the ring–boron bonds (3). (It is convenient to use the symbol shown in eq 3 for 9-BBN.)

The usual range of olefin structures can evidently be accommodated, as indicated by the following examples (4–6).

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