The reaction of sodium naphthalene (50 mmol) in tetrahydrofuran with deuterium gas (Union Carbide Corp.) at 40° was conducted in a three-necked round-bottomed flask. Reaction was followed by assaying the radical anion concentration.[1] After 36 hr the solid product was separated by centrifugation. The liquid layer was treated with water and extracted with ether. After drying and solvent removal, 6.2 g (95% recovery) of naphthalene was obtained.

A sample of the naphthalene was purified by preparative-scale glpc and analyzed by mass spectrometry. From the ratio of the intensities of the *m/e* peaks at 128 and 129 the amount of deuterated naphthalene was established as 6.0 ± 0.5%.[10]

Since the sodium deuteride is produced in an exceedingly active form,[1] a control experiment, to demonstrate the absence of exchange by the path illustrated in eq 6, was required. Such exchange would obscure

$$C_{10}H_8 + NaD \longrightarrow C_{10}H_7D + NaH \qquad (6)$$

the significance of the above results. Accordingly, naphthalene was brought into contact with the sodium deuteride prepared above in THF at 40° for 51 hr under a nitrogen atmosphere. The recovered naphthalene was analyzed by mass spectrometry and showed no deuterium incorporation. Therefore, the results in the presence of deuterium gas are not complicated by this conceivable artifact.

The results indicate that, even though naphthalene is recovered quantitatively, the mechanism involves addition to sodium naphthalene radical anion and not solely electron transfer. If mechanism II were uniquely operative and if there were no kinetic isotope effect for step 5, then a maximum value of 25% of the recovered naphthalene would be deuterated.[11] Our value is substantially less than this maximum and probably indicates that both mechanisms are operative. Such a conclusion is in accord with the conclusions regarding the reaction of alkyl radicals and sodium naphthalene.[8,9]

These mechanistic conclusions are supported by the results of Tamaru and coworkers,[3] who find a peak appearing at 435 mμ when hydrogen gas is introduced into an EDA complex solution of sodium naphthalene in THF which might be attributed to the monohydro anion. We have prepared this anion by an independent route and find the maximum to occur at 437 mμ.

When considered together, the results of Tamaru and coworkers[3] and those reported in this communication present strong support for the intermediacy of the monohydro anion.

Acknowledgment. We gratefully acknowledge support by the National Science Foundation. We wish to thank Professor Kevin T. Potts (Rensselaer Polytechnic Institute) for his assistance in obtaining some of the mass spectra.

(10) There was no evidence for naphthalene-d_2 within the limits of experimental accuracy (±0.5%).

(11) This value is obtained by assuming that 50% of the hydride is formed in an initial step that does not give exchange. With no isotope effect for the potential exchange step (eq 5), then 25% of the recovered naphthalene would be deuterated.

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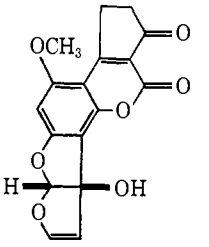
The Total Synthesis of Racemic Aflatoxin-M_1 (Milk Toxin)

Sir:

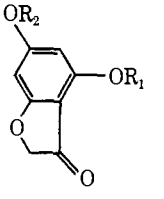
Aflatoxin-M_1 was first detected in the milk of aflatoxin-B_1-fed cows.[1,2] Metabolites with similar properties were subsequently isolated from the urine of sheep[3,4] and the livers of rats[5] dosed with aflatoxin-B_1. Subsequent work established the identity of the milk factor and the urinary metabolite.[4,6] Structural investigations led to the conclusion that aflatoxin-M_1 is a hydroxyaflatoxin-B_1 as represented by structure **1**.[4]



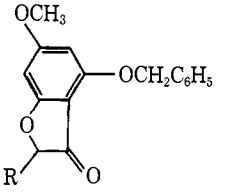
1

Although the acute toxicity[7] of M_1 seems established, the more important question concerning its carcinogenicity remains unanswered because hitherto only minute quantities of the metabolite have been available for biological studies. We wish to describe a total synthesis which makes racemic aflatoxin-M_1 (**1**) a relatively accessible substance.

Methylation of 4,6-dihydroxycoumaran-3-one (**2**)[8] in refluxing glyme with dimethyl sulfate in the presence of potassium carbonate gave the dimethyl ether **3**, mp 138–140° (78% yield).[9] Partial ether cleavage with 2 equiv of aluminum chloride in hot methylene chloride afforded the monomethyl ether **4**, mp 140–142°,[10] which in its crude form was transformed into the benzyl ether **5**, mp 172–173° (45% from **3**), by alkylation with benzyl bromide in refluxing glyme–dimethylformamide containing suspended potassium carbonate.



2, $R_1 = R_2 = H$
3, $R_1 = R_2 = CH_3$
4, $R_1 = H$; $R_2 = CH_3$
5, $R_1 = CH_2C_6H_5$; $R_2 = CH_3$



6, R = Br
7, R = $OCH_2C_6H_5$

(1) R. Allcroft and R. B. A. Carnaghan, *Vet. Rec.*, **75**, 259 (1963).
(2) H. De Iongh, R. O. Vles, and J. G. van Pelt, *Nature*, **202**, 466 (1964).
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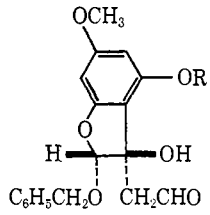
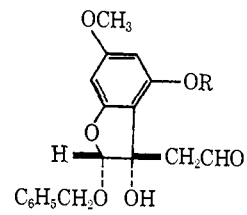
(8) T. A. Geissman and E. Hinreiner, *J. Amer. Chem. Soc.*, **73**, 782 (1951).
(9) The method of T. P. C. Mulholland and G. Ward, *J. Chem. Soc.*, 1642 (1953), using dimethyl sulfate in aqueous sodium hydroxide, in our hands, led to a substantial portion of the carbon-methylated product.
(10) A much less efficient but structurally unambiguous synthesis of **4** was described by L. A. Duncanson, J. F. Grove, J. MacMillan, and T. P. C. Mulholland, *ibid.*, 3555 (1957).

The bromoketone **6**, mp 170–172° (86%), prepared from the ketone **5** and phenyltrimethylammonium perbromide[11] in tetrahydrofuran on treatment with hot benzyl alcohol in the presence of calcium carbonate, gave the dibenzyl ether **7**, mp 45–47° (70%). Addition of allylmagnesium bromide in ether to a solution of the ketone **7** in tetrahydrofuran produced a mixture of epimeric allyl carbinols. When the latter was submitted to the action of sodium periodate–osmium tetroxide[12] in aqueous dioxane, a mixture of epimeric aldehydes (60% from **7**) containing 12 parts of the oily *trans* epimer **10** and one part of the *cis* isomer **8**, mp 90–91°, was formed.

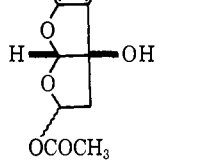


8, R = $CH_2C_6H_5$
9, R = CH_3CO

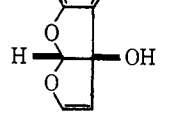


10, R = $CH_2C_6H_5$
11, R = CH_3CO

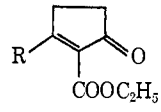
Catalytic hydrogenolysis of **8** or **10** over a 10% Pd–C catalyst in benzene–acetic anhydride containing sodium acetate eliminated one of the two benzyl groups and produced the diastereomeric acetates **9** or **11**. A second reduction of either **9** or **11** over the same catalyst, but in ethyl acetate solution followed by acetylation of the crude product with acetic anhydride in pyridine at −30°, furnished the tricyclic diacetate **12**, mp 129–131° (35% from either **8** or **10**). Pyrolysis of a toluene solution of the diacetate **12**, in a short-contact continuous-flow system at 450°, afforded the vinyl ether **13**, mp 118–120° (75%). The corresponding oily phenol **14** (94%) prepared by hydrolysis of the acetate **13** with sodium bicarbonate in methanol–water could not be condensed with 2-carbethoxycyclopentane-1,3-dione (**15**)[13] although a variety of catalysts were explored. The more electrophilic chloride **16** (80%), prepared from the enol **15** and oxalyl chloride in benzene solution at 0°, however, condensed rapidly with the phenol **14** in methylene chloride in the presence of zinc carbonate to give the coumarin **1** (20%). Identity with natural, optically active aflatoxin-M_1 was established by comparison of infrared, ultraviolet, and mass spectra as well as by thin layer chromatographic behavior.[14]



12



13, R = $COCH_3$
14, R = H



15, R = OH
16, R = Cl

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(14) We are much indebted to Drs. A. C. Keyl and A. C. Waiss, Western Regional Research Laboratory, Agricultural Research Service, U. S. Department of Agriculture, Albany, Calif., for a sample of natural aflotoxin-M_1.

The biological properties of racemic aflatoxin-M_1 will be discussed in forthcoming papers by Professor G. N. Wogan, Department of Food Science and Nutrition, Massachusetts Institute of Technology.

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(15) National Institutes of Health Postdoctoral Fellow, 1967–1968.

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Arabinonucleotides. II. The Synthesis of O²,2′-Anhydrocytidine 3′-Phosphate, a Precursor of 1-β-D-Arabinosylcytosine

Sir:

We have recently described a thermal rearrangement of polynucleotidic 2′,3′,5′-cyclic triesters obtained from oligouridylic acid, which provides a convenient route to the synthesis of oligoarabinouridylic acid.[1] A related idea proved to be useful for the synthesis of O²,2′-anhydrocytidine 3′-phosphate, which is a precursor[2] of 1-β-D-arabinosylcytosine,[3] an antiviral[4] and carcinostatic[5] agent. The cyclic trimethylsilyl ester moiety in fully trimethylsilylated cytidine 2′,3′-cyclic phosphate (**1**) was expected and found to be a good intramolecular leaving group in a sense as outlined in Scheme I. The structure of the intermediates **1** and **2** has not yet been firmly established.

The preparation can be very simply performed at any scale ranging from 0.1 to 20 mmol. Dry tri-*n*-butylammonium cytidine 2′,3′-cyclic phosphate[6] was suspended in a mixture of 50 equiv of anhydrous pyridine and 2 equiv of tri-*n*-butylamine to which 6–10 equiv of trimethylsilyl chloride was added dropwise at room temperature. The reaction mixture was kept for 1 hr at 80° and then concentrated *in vacuo* to a gum, which was shaken with ice and chloroform. The pH of the aqueous phase should be around 4.5. Colorless needles of pure O²,2′-anhydrocytidine 3′-phosphate (**3**) were obtained directly from the aqueous solution or upon the addition of 10–20% acetone (yield over 50%). Further addition of acetone precipitated a slightly contaminated material, which could be purified by passing through a small column of Dowex 1-X2 (formate) resin in water. Total isolated yield of O²,2′-anhydrocytidine 3′-phosphate was consistently between 70 and 80%.

The analytical sample was obtained on recrystallization from water–acetone and after drying 12 hr at 0.02 mm over P_2O_5.

(1) J. Nagyvary, *Fed. Proc.*, **26**, 292 (1967); paper I of this series: J. Nagyvary and R. G. Provenzale, submitted for publication.
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