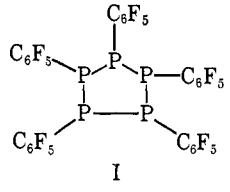
made by treatment of PBr_3 with an equimolar quantity of C_6F_5MgBr and by HI cleavage of $C_6F_5P[N(CH_3)_2]_2$,[6b] respectively. Mercury acted upon $C_6F_5PBr_2$ (2-day shaking in a sealed flask at 25°) to produce a yellow oil. The reaction was completed by extraction of the oil with ether, followed by shaking with an additional portion of mercury (1 day at 25°). Isolation and evaporation of the ether solution, followed by recrystallization from 9:1 *n*-hexane–ether, resulted in a 91% yield of a white crystalline solid, mp 156–161°. *Anal.* Calcd for C_6F_5P: C, 36.38; F, 47.49; P, 15.64. Found: C, 36.61; P, 15.16. The mercury coupling reaction of $C_6F_5PI_2$ closely resembled that of CF_3PI_2.[7]

The molecular formula $(C_6F_5P)_5$ agrees with the observed molecular weight in CH_2Br_2 solution: found, 1005; calcd, 990. The ring structure I would be consistent with mass spectral fragments bearing more than



I

one phosphorus atom such as $(C_6F_5P)_2P_2^+$ (0.3%), $(C_6F_5P)_2P^+$ (0.2%), $(C_6F_5P)_2^+$ (13.2%), and $C_6F_5PP^+$ (70.3%), and also with infrared frequencies which could be assigned to phosphorus ring stretching.[8] The presence of C_6F_5P groups was demonstrated by both the infrared and the nmr spectra of I, the latter (in diethyl ether solution) showing *ortho*, *meta*, and *para* ^{19}F resonances at ϕ = 126.41, 160.06 (triplet plus fine structure), and 149.47 ppm (approximately a triplet), respectively, relative to CCl_3F as internal standard. The *ortho* resonance was wider (~150-cps width) and more complex than the others owing to coupling with the ring ^{31}P nuclei. The π bonding situation in $(C_6F_5P)_5$ would appear to be about the same as in $C_6F_5P(C_6H_5)_2$ in terms of the recently published relationship[9] between the chemical shift of the *para* ^{19}F resonance and π bonding in pentafluorophenylphosphine derivatives.

Dissolution and subsequent evaporation of an ether solution (or sublimation) of I led to an apparently different polymorph (see X-ray powder data in Table I). The melting behavior of I is also consistent with polymorphism. The form from *n*-hexane–ether (form A) melted at 156–161° when placed in a bath which had been preheated to 145°. However, the form from the ether solution (form B) melted immediately in the 145° bath. Upon cooling and remelting form B, it melted at 159–162°, the same range as form A. It is apparent that subsequent investigation of the C_6F_5–P ring system may prove it to be as complex as its phenyl counterpart.

(7) W. Mahler and A. B. Burg, *J. Am. Chem. Soc.*, **80**, 6161 (1958).

(8) R. L. Amster, N. B. Colthup, and W. A. Henderson, *Spectrochim. Acta*, **19**, 1841 (1963), and *Can. J. Chem.*, **42**, 2577 (1964), have assigned the symmetric phosphorus ring stretch in the range 390–410 cm^{-1} and the asymmetric ring stretch in the range 465–490 cm^{-1}. We found medium intensity peaks at 390 and 508 cm^{-1} in the infrared spectrum of I (Nujol mull). The strong bands which we observed at 974 and 1480 cm^{-1} seem to be characteristic of C_6F_5P compounds; see, *e.g.*, ref 6b.

(9) M. G. Hogben, R. S. Gay, and W. A. G. Graham, *J. Am. Chem. Soc.*, **88**, 3457 (1966).

Table I. X-Ray Diffraction Data

$(C_6F_5P)_5$, form A		$(C_6F_5P)_5$, form B	
d, A	I/I_0	*d*, A	I/I_0
11.05	0.6	11.79	0.1
10.16	0.8	9.46	0.3
9.36	0.1	8.76	0.2
7.73	0.1	8.08	0.1
6.86	0.1	6.84	0.1
6.30	0.2	6.44	0.1
5.81	0.2	6.03	0.1
5.50	0.5	5.72	0.1
5.20	0.5	5.36	0.1
4.90	0.4	5.14	0.2
4.77	0.7	4.80	1.0
4.48	0.3	4.63	0.5
4.33	0.1	4.18	0.3
4.19	0.1	4.07	0.2
4.07	1.0	4.00	0.2
3.91	0.2	3.85	0.8
3.61	0.1	3.47	0.4
3.46	0.2	3.70	0.5
3.34	0.1	3.37	0.3
3.29	0.5		

The electron-withdrawing effect of the C_6F_5 group manifested itself chemically in terms of the lack of reactivity of I toward CH_3I. However, like all cyclopolyphosphines the phosphorus ring structure was ruptured by elemental chlorine.[1] Interestingly, we were unable to isolate the phosphorane, $C_6F_5PCl_4$, from this reaction, even when excess chlorine was employed. In fact, attempts to chlorinate $C_6F_5PCl_2$ resulted in an unstable yellow solid (presumably $C_6F_5PCl_4$) which decomposed *in vacuo* by Cl_2 evolution.[10] As expected[11] SbF_3 fluorination of $C_6F_5PCl_2$ led to $C_6F_5PF_2$ (vapor tension = 2.5 mm at 25°, P–F stretching modes at 838 and 850 cm^{-1} in the infrared. *Anal.* Calcd for $C_6F_5PF_2$: C, 30.51; F, 56.36. Found: C, 30.17; F, 56.19.

Acknowledgment. This work was supported by the Robert A. Welch Foundation and the U. S. Public Health Service (Grant GM 12437-02). It is also a pleasure to acknowledge the help of Dr. Stanley L. Manatt of the Jet Propulsion Laboratory, Pasadena, California, who both recorded and interpreted the nmr spectra.

(10) Emeleus and Millar[8d] have managed to prepare the phosphorane $(C_6F_5)_3PCl_2$. The reason for the apparent instability of $C_6F_5PCl_4$ is not known. There would be a certain amount of structural interest in $C_6F_5PCl_4$, since the C_6F_5 group, being the more electronegative ligand, should occupy an axial site if the molecular geometry is trigonal bipyramidal; see an excellent review on pentacoordination by E. L. Muetterties and R. A. Schunn, *Quart. Rev.* (London), **20**, 245 (1966), on this point.

(11) The available evidence indicates that fluorination stops at the phosphinous fluoride stage when electronegative groups are attached to the phosphorus atom: *e.g.*, A. B. Burg and G. Brendel, *J. Am. Chem. Soc.*, **80**, 3198 (1958); J. F. Nixon, *J. Chem. Soc.*, 777 (1965); R. Schmutzler, *Chem. Ber.*, **96**, 2435 (1963); R. Schmutzler, *Inorg. Chem.*, **3**, 415 (1964); J. F. Nixon, *J. Inorg. Nucl. Chem.*, **27**, 1281 (1965).

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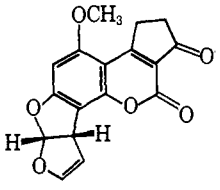
The Total Synthesis of Racemic Aflatoxin B_1

Sir:

The aflatoxins are a group of acutely toxic and extremely carcinogenic metabolites produced by some

strains of *Aspergillus flavus*. Their discovery in animal and human foodstuffs emphasized their potential public health hazard and stimulated much biological research.[1] The molecular structures of aflatoxins B_1 (**1**) and G_1 (**2**) were elucidated in these laboratories[2] and were subsequently confirmed by X-ray analyses.[3,4] We now wish to describe the total synthesis of aflatoxin B_1 (**1**).



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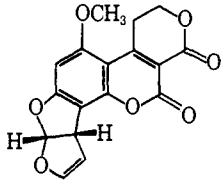
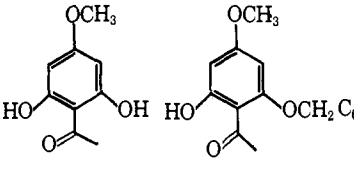


2

Phloroacetophenone 4-methyl ether[5] (**3**) was transformed to the benzyl ether **4**, mp 110–111.5°, by the action of benzyl bromide and anhydrous potassium carbonate in acetone. Wittig condensation of this ketone with carbethoxymethylenetriphenylphosphorane at 170° gave the coumarin **5**, mp 142–143°. This intermediate could be prepared more conveniently by an alternate route. Thus, crystallization of the water-insoluble portion of the precipitate formed on treatment of an acetone–tetrahydrofuran solution of 5,7-dihydroxy-4-methylcoumarin with 1 equiv of benzyl bromide in the presence of anhydrous potassium carbonate gave the monobenzyl ether **6**, mp 221–223°. Methylation with methyl iodide produced the methyl ether **5** which very recently[6] has been obtained by a third route (lit.[6] mp 138–141°). The 4-methylcoumarin **5** was oxidized with selenium dioxide[7] in hot xylene to the yellow aldehyde **7**, mp 189–190° (lit.[6] mp 189–191°), $\lambda_{max}^{CH_3CN}$ 244 (s), 341 mμ (ε 8500, 9520), which on treatment with zinc in glacial acetic acid was reduced to the lactone **8**, mp 166–167°, ν_{max}^{Nujol} 1786 cm^{-1}. Catalytic hydrogenation of the latter over a carbon-supported palladium catalyst in acetic anhydride solution furnished the acetate **9**, 126–127.5°, $\nu_{max}^{CHCl_3}$ 1795, 1965 cm^{-1}.

Von Pechmann condensation of both the acetate **9** and the corresponding phenol **10**, mp 166–167.5°, with ethyl methyl β-oxoadipate[8] in 86% sulfuric acid followed by methylation with diazomethane gave mainly the substituted allobergapten **12**, mp 152–160°, λ_{max}^{EtOH} 215, 253, 258 (s), 308, 340 mμ (ε 25,600, 19,650, 18,000, 8150, 10,450), and only minor amounts of the substituted isobergapten **13**, mp 154–155°, λ_{max}^{EtOH} 223, 230 (s), 247 (s), 253, 269, 309 mμ (ε 18,900, 17,100, 14,850, 18,600, 14,850, 10,010), and the lactone **14**, mp 210–213°, λ_{max}^{EtOH} 251, 259, 321 mμ (ε 7150, 8090, 10,800). It seemed likely that the allobergapten **12**



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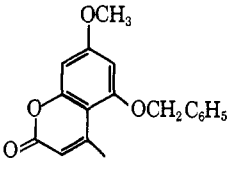

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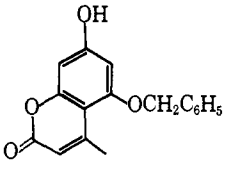

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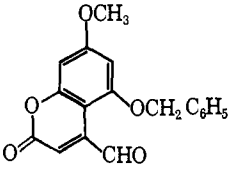

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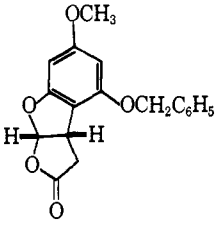

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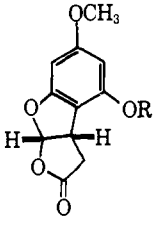
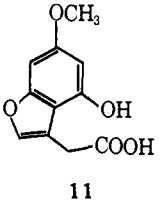
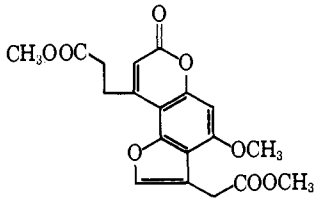


9 R = $COCH_3$
10 R = H



11

was not derived from the lactone **10** directly but rather from the isomeric benzofurancarboxylic acid **11**. To avoid the formation of this latter intermediate the condensation was performed in methanol solution containing anhydrous hydrogen chloride. Under these conditions the methoxy acetal **15**, mp 129–131°, with *trans*-oriented substituents was formed (acetal proton doublet at 5.54 ppm, J = 2 cps). The structure of this important intermediate was easily ascertained by conversion to the isobergapten **13** brought about by



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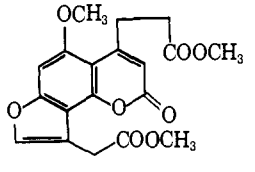

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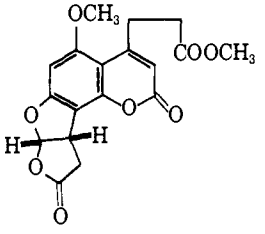

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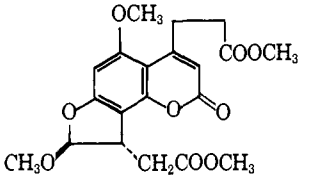

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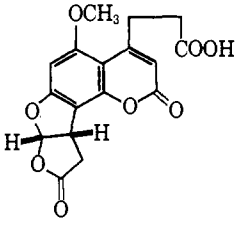
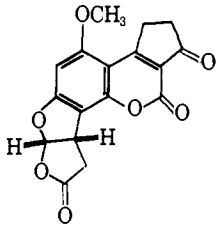


16

(1) For a summary, *cf.* G. N. Wogan, *Bacteriol. Rev.*, **30**, 460 (1966).
(2) T. Asao, G. Büchi, M. M. Abdel Kader, S. B. Chang, E. L. Wick, and G. N. Wogan, *J. Am. Chem. Soc.*, **85**, 1706 (1963); **87**, 882 (1965). The absolute configurations of the two metabolites are those indicated (S. Brechbühler, G. Büchi and G. Milne, to be published.)
(3) K. K. Cheung and G. A. Sim, *Nature*, **201**, 1185 (1964).
(4) T. C. van Soest and A. F. Peerdeman, *Proc. Koninkl. Ned. Akad. Wetenschap.*, **B67**, 469 (1964).
(5) A. Sonn and W. Bülow, *Ber.*, **58**, 1691 (1925).
(6) J. A. Knight, J. C. Roberts, and P. Roffey, *J. Chem. Soc., Sect. C*, 1308 (1966).
(7) Method of A. Schiavello and E. Cingolani, *Gazz. Chim. Ital.*, **81**, 717 (1951).
(8) D. K. Banerjee and K. M. Sivanandaiah, *J. Org. Chem.*, **26**, 1634 (1961).

brief exposure to polyphosphoric acid. Hydrolysis of the acetal **15** in aqueous hydrochloric–acetic acid solution gave the lactone carboxylic acid **16**, mp 245–254° dec; ν_{max}^{Nujol} 1787, 1739, 1711 cm^{-1}, with *cis*-fused five-membered rings (acetal proton doublet at 6.79 ppm, J = 6 cps).

Cyclodehydration of this carboxylic acid **16** was effected in methylene chloride solution by consecutive treatments with oxalyl chloride (20°; 24 hr) and aluminum chloride (−15°; 4 hr). Crystallization of the nonacidic portion of the reaction product from chloroform furnished the pentacyclic lactone **17**, mp >320° dec; ν_{max}^{Nujol} 1788, 1760, 1688 cm^{-1}; λ_{max}^{MeOH} 220, 239 (s), 263, 355 mμ (ε 19,400, 12,200, 10,600, 17,700). When the lactone **17** was treated with disiamylborane[9] in



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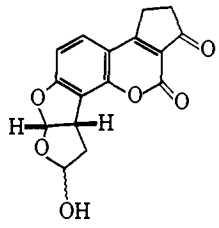

18

diglyme solution it was reduced to a mixture of at least two products from which the desired hemiacetal **18** could be isolated by chromatography. Infrared ($\nu_{max}^{CHCl_3}$ 3580, 3400, 1760, 1685 cm^{-1}) and ultraviolet spectra (λ_{max}^{EtOH} 215, 237 (s), 260, 364 mμ; $\lambda_{max}^{0.01N\ NaOH}$ 248, 292, 407 mμ) of this hemiacetal were identical with those of a sample, mp 223–225°, prepared by trifluoroacetic acid catalyzed addition of water to natural aflatoxin B_1. Treatment of the racemic hemiacetal with acetic acid–acetic anhydride in the presence of toluenesulfonic acid produced the corresponding acetate which without further purification was pyrolyzed (240°) to racemic aflatoxin B_1 identical with natural material **1** in thin layer chromatographic behavior and infrared, ultraviolet, and mass spectra.

Acknowledgment. We are indebted to the National Cancer Institute for financial support and to Dr. Elizabeth Weisburger for encouragement. Drs. J. Berger and A. Brossi kindly provided us with an aflatoxin concentrate which was prepared by Mr. B. Tabenkin in the microbiology pilot plant of Hoffmann-La Roche Inc., Nutley, N. J.

(9) H. C. Brown and D. B. Bigley, *J. Am. Chem. Soc.*, **83**, 486 (1961).
(10) National Science Foundation, Cooperative Graduate Fellow 1964–1966.

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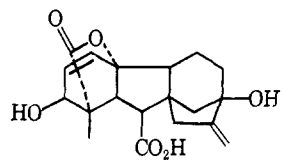
A Model Study of the Synthesis of the A Ring of Gibberellic Acid[1]

Sir:

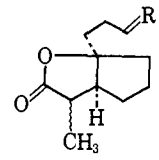
A number of natural products such as gibberellic acid[2] (**1**) and rosenolactone[3] contain a bridged γ-lactone



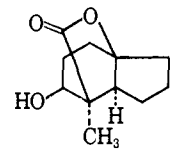
1

as part of their structures. The synthesis of this structural feature is rendered more difficult because the carbonyl group is attached to a quaternary carbon atom. We wish to report a useful synthesis of this structural feature in which the lactone ring is completed before the carbocyclic ring. This synthesis also places a hydroxyl group as found in gibberellic acid.

The action of homoallylmagnesium bromide on ethyl 2-(2-ketocyclopentyl)propionate[4] affords the desired olefinic lactone, bp 135–138° (6 mm) (**2**), in 56% yield after saponification of the crude reaction mixture and lactonization by distillation. It seems quite certain that the lactone ring is fused *cis* to the cyclopentane ring because of the ease of lactone formation, in contrast to the difficulty in obtaining such compounds with *trans* ring junctures.[5] Whereas the olefinic lactone is undoubtedly a mixture of epimers at the carbon atom bearing the methyl group[6], the material shows the expected carbonyl absorption (carbon tetrachloride solution) at 1770 cm^{-1}.



2, R = CH_2
3, R = O



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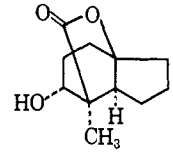

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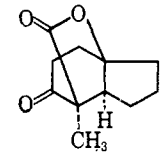

6

Oxidation of the olefinic lactone **2** with osmium tetraoxide–sodium periodate[7] gave the lactone aldehyde **3** after treatment of the crude oxidation product with hydrogen sulfide to remove osmium species. The infrared spectrum (carbon tetrachloride solution) of the lactone aldehyde shows the expected absorption at 2731, 1770, and 1730 cm^{-1}.

Cyclization of the lactone aldehyde **3** with potassium *t*-butoxide in *t*-butyl alcohol afforded a mixture of liquid hydroxy lactones **4** and **5** in 30% yields based on the olefinic lactone **2**. The major hydroxy

(1) The authors gratefully acknowledge financial support from the National Science Foundation (Grant 1266 GP3822) and a Public Health Service career program award (1-K3-NB-28,105) from the National Institute of Neurological Diseases and Blindness.

(2) F. M. McCapra, A. I. Scott, G. A. Sim, and D. W. Young, *Proc. Chem. Soc.*, 1851 (1962); J. A. Hartruck and W. N. Lipscomb, *J. Am. Chem. Soc.*, **85**, 3414 (1963).
(3) A. Harris, A. Robertson, and W. B. Whalley, *J. Chem. Soc.*, 1799 (1958); W. B. Whalley, B. Green, D. Arigoni, J. J. Britt, and C. Djerassi, *J. Am. Chem. Soc.*, **81**, 5520 (1959).
(4) F. Šorm, Z. Šormova, and L. Sedivy, *Collection Czech. Chem. Commun.*, **12**, 554 (1947).
(5) W. Hückel and W. Gelmroth, *Ann.*, **514**, 233 (1934); W. E. Grigsby, J. Hind, J. Chanley, and F. H. Westheimer, *J. Am. Chem. Soc.*, **64**, 2606 (1942).
(6) The nmr spectrum of the olefinic lactone shows four peaks in the region of τ 8.6–9 indicating two epimeric methyl compounds.
(7) R. Pappo, D. S. Allen, Jr., R. U. Lemieux, and W. S. Johnson, *J. Org. Chem.*, **21**, 478 (1956).