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# The Structure of Fumagillin ; Formation of Tetrahydrofuran Rings by Methoxyl Cleavage and the Synthesis of a Dehydrogenation Product, 2-Isoamyl-3,4-dimethylbenzofuran

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tion and the removal of most of the solvent followed by the addition of *n*-hexane, the adduct separated in form of a yellow-red layer which subsequently crystallized. Bisacrylonitrile nickel bis-triphenylphosphine,  $\text{Ni}(\text{CH}_2=\text{CH}-\text{CN})_2 \cdot 2\text{P}(\text{C}_6\text{H}_5)_3$  (II) forms yellow, somewhat fluorescent diamagnetic<sup>7</sup> crystals. When heated in a closed tube, II decomposes above  $140^\circ$  into nickel, triphenylphosphine and acrylonitrile. It is soluble in ether, benzene, acetone and alcohol but only sparingly soluble in *n*-hexane. It can be recrystallized from a concentrated ethereal solution upon addition of *n*-hexane. II is sensitive to oxygen though not pyrophoric; solutions, however, are almost instantaneously decomposed when brought into contact with air. *Anal.* Calcd. for II Ni, 8.52; P, 8.99; N, 4.06. Found; Ni, 8.69; 8.63; P, 9.03; 9.20; N (Kjeldahl), 3.85%. Molecular weight calcd. 689.4; found (cryoscopic in benzene under nitrogen) 600 and 632. Dipole moment in benzene solution at  $25^\circ$ :  $6.00 \pm 0.07 D$ . The nitrile stretch is found at  $2167 \text{ cm}^{-1}$  (Nujol). The slight shifts in comparison to the 1:1 triphenylphosphine adduct (CN:  $2180 \text{ cm}^{-1}$ ) and to I (CN:  $2220 \text{ cm}^{-1}$ ) can be attributed to an increasing positivation of the nitrile groups. The positivation of the nitrile groups can be the result of a decrease of electron back-donation into the double bonds due to the coordination of the nickel atom with triphenylphosphine. Bisacrolein nickel,  $\text{Ni}(\text{CH}_2=\text{CH}-\text{CHO})_2$  (*Anal.* Calcd. Ni, 34.37; acrolein, 65.63. Found: Ni, 34.5; acrolein, 63.2) appears to have a structure similar to I. It also forms adducts with triphenylphosphine.  $\text{Ni}(\text{CH}_2=\text{CH}-\text{CHO})_2 \cdot 2\text{P}(\text{C}_6\text{H}_5)_3$  forms yellow-red, air-sensitive crystals which start to decompose above  $140^\circ$ . *Anal.* Calcd. Ni, 8.44; P, 8.91; found Ni, 8.34; P, 8.47. Details concerning these compounds will be reported later together with a description of further catalytic applications and reactions of representative members of this new class of nickel complexes.

(7) Bisacrylonitrile nickel has a small paramagnetic moment of 0.68 Bohr magneton. Anomalous magnetic moments also were observed in the case of similar complexes (unpublished data). I am indebted to Mr. H. Olf of the Technische Hochschule at Munich for the magnetic measurements.

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THE STRUCTURE OF FUMAGILLIN; FORMATION OF TETRAHYDROFURAN RINGS BY METHOXYL CLEAVAGE AND THE SYNTHESIS OF A DEHYDROGENATION PRODUCT, 2-ISOAMYL-3,4-DIMETHYLBENZOFURAN<sup>1</sup>

Sir:

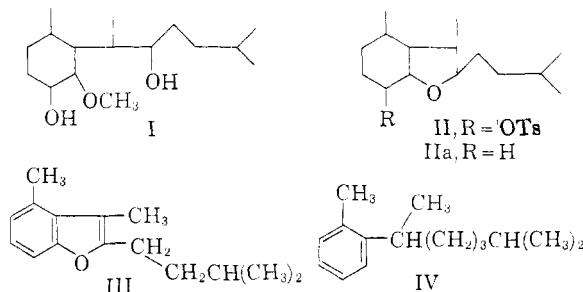
The preceding communication reported evidence allowing assignment of structures to fumagillin and its derivatives.<sup>2</sup> The present paper describes

(1) Supported in part by Grant E-1138 of the U. S. Public Health Service. Compounds described in this and the preceding communication have been characterized by elementary and group analysis, infrared spectra, optical rotation, ultraviolet absorption where applicable, and n.m.r. spectra in most cases.

(2) D. S. Tarbell, R. M. Carman, D. D. Chapman, K. R. Huffman and N. J. McCorkindale, *THIS JOURNAL*, **82**, 1005 (1960).

the conversion of a fumagillin derivative to a benzofuran, and proof of structure of the latter by synthesis.

Treatment of the desoxyhexahydroalcohol (I) with tosyl chloride-pyridine gives in good yield the perhydrobenzofuran II, with loss of methanol and cyclization; reduction of II with lithium aluminum hydride gives IIa, and this on selenium dehydrogenation gives a good yield of a mixture of the benzofuran III and the hydrocarbon IV.



We have observed four other cases of cyclization similar to that above with different conditions and different derivatives related to I. The secondary hydroxyl group adjacent to the methoxyl in I is not involved in the cyclization, because a compound related to I, in which the secondary hydroxyl is etherified with tetrahydropyran, also cyclizes.<sup>3</sup> The formulation of II and related compounds is consistent with the n.m.r. spectra showing two protons on carbon adjacent to oxygen at  $\tau 6.2-6.5$ ; in one derivative of II, where R is carbonyl, one proton has  $\tau 5.68$ , indicating that it is adjacent to the carbonyl and to the heterocyclic oxygen.

The proof of the perhydrobenzofuran ring in IIa by dehydrogenation to III and synthesis of the latter supports the structures suggested previously.

The structure of III was apparent from its analysis, ultraviolet, infrared and n.m.r. spectra. It was synthesized from 3-methyl-4,6-dichlorophenol (V) by alkylation with 3-bromo-6-methyl-2-heptanone to give VI, with subsequent cyclization by cold sulfuric acid, to give the crystalline 2-isoamyl-3,4-dimethyl-5,7-dichlorobenzofuran (m.p.  $52^\circ$ ) in 43% over-all yield. The chlorines were removed by hydrazine 5% palladium on carbon in refluxing methyl cellosolve,<sup>4</sup> giving III in 94% yield. The bromo ketone was prepared by formation of the enol acetate<sup>5</sup> from 6-methyl-2-heptanone<sup>6</sup> with subsequent bromination and decomposition in methanol.<sup>7</sup>

The identity of synthetic III with that obtained by degradation was demonstrated by the complete

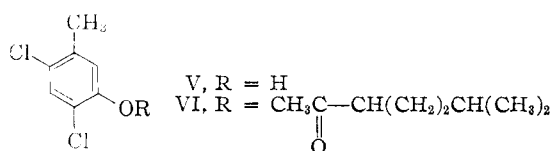
(3) Analogy for this cyclization is provided by the formation of 2-methyltetrahydrofuran by lithium aluminum hydride treatment of  $\text{CH}_3\text{O}(\text{CH}_2)_3\text{CH}(\text{OBS})\text{CH}_3$  and  $\text{CH}_3\text{CH}(\text{OCH}_3)(\text{CH}_2)_3\text{OBS}$ : E. L. Allred, Ph.D. Dissertation, University of California, Los Angeles, 1959, pp. 146-160. We are indebted to Professor S. Winstein for communicating these results prior to publication. Other cyclizations accompanied by methoxyl cleavage are reported by S. Winstein, E. Allred, R. Heck and R. Glick, *Tetrahedron*, **3**, 1 (1958); cf. D. S. Noyce and H. I. Weingarten, *THIS JOURNAL*, **79**, 3093, 3098 (1957).

(4) W. L. Mosby, *Chem. and Ind.*, 1348 (1959).

(5) Cf. E. H. Man, F. C. Frostick, Jr., and C. R. Hauser, *THIS JOURNAL*, **74**, 3228 (1952).

(6) D. H. Hey and D. S. Morris, *J. Chem. Soc.*, 48 (1948).

(7) Cf. P. Z. Bedoukian, *THIS JOURNAL*, **67**, 1430 (1945).



correspondence of infrared, and n.m.r. spectra, and by identical retention times in vapor phase chromatography. Synthetic and "natural" III showed a single peak when a mixture was examined by v.p.c. An isomer of III, 2-isoamyl-3,7-dimethylbenzofuran, prepared from *o*-cresol and the above bromo ketone, showed marked differences from III in its infrared, ultraviolet and n.m.r. spectra and in its retention time.

The structure of IV is assigned on the basis of analysis and the similarity of its ultraviolet and infrared spectra to those of 1-methyl-2-isopropylbenzene.<sup>8</sup>

Although alcohol-I contains fifteen carbon atoms, plus methoxyl, its structure, as deduced here,<sup>2</sup> does not follow the isoprene rule completely. Stereochemical and synthetic studies are now under way.<sup>9</sup>

(8) Infrared spectrum of methylisopropylbenzene: A.P.I. Project 44, Catalog of Infrared Spectra, 1585 and 1640; the spectrum of 1-methyl-2-*n*-propylbenzene (*ibid.*, no. 1964) is markedly different from that of IV.

(9) We are indebted to Abbott Laboratories for supplies of fumagillin, for fellowship support, and for many microanalyses by Mr. E. F. Shelberg and his staff. Other analyses are by Micro-Tech, W. Manser, and Thomas Montzka of this laboratory. Dr. D. J. Wilson and Mr. Y. Kawazoe supplied n.m.r. spectra and helped in their interpretation. Ultraviolet spectra were determined by Mr. Carl Whitteman. We are particularly grateful to many colleagues, from this and other laboratories, for stimulating discussions during the progress of this work.

(10) Abbott Laboratories Fellow, 1959-1960.

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# RACEMIZATION, ACETOLYSIS AND RADIO-CHLORIDE EXCHANGE OF TWO ALKYL CHLORIDES<sup>1</sup> Sir:

In rearrangement, exchange and solvolysis reactions of neutral organic substrates proceeding by way of carbonium ions, it is important to distinguish between ionization and dissociation and to consider explicitly the role of different ionic intermediates representing various stages of ionization-dissociation.<sup>2,3</sup> This situation is best understood with certain rearranging systems.<sup>2,3</sup> More recently, ion pairs also have been considered or invoked in the interpretation of solvolysis and exchange reactions of halides of the benzhydryl<sup>4</sup>

(1) Research supported by the National Science Foundation.

(2) (a) W. G. Young, S. Winstein and H. L. Goering, *THIS JOURNAL*, **73**, 1958 (1951); (b) S. Winstein, *et al.*, *ibid.*, **7**, 1154, 2165, 2171 (1952); (c) C. A. Grob and S. Winstein, *Helv. Chim. Acta*, **35**, 782 (1952).

(3) S. Winstein, *et al.*, *THIS JOURNAL*, **76**, 2597 (1954); **78**, 328, 2763, 2767, 2784 (1956); **80**, 169, 459 (1958); *Chemistry and Industry*, 664 (1954); *Helv. Chim. Acta*, **41**, 807 (1958).

(4) (a) S. Winstein, A. H. Fainberg and E. Grunwald, *THIS JOURNAL*, **79**, 4146 (1957); (b) G. Kohnstam and B. Schillaker, *J. Chem. Soc.*, 1915 (1959).

TABLE I  
RATE CONSTANTS IN ACETIC ACID AT 25.0°

M	[MOAc] 10 <sup>2</sup> M	[MCl] 10 <sup>2</sup> M	$\frac{k}{10^5 k_a}$ Values (sec. <sup>-1</sup> )			Rate ratios $(k_a/k_t)$ $(k_a/k_e)$	
			$10^5 k_a$	$10^5 k_t$	$10^5 k_e$		
$\text{ClC}_6\text{H}_4\text{CHClC}_6\text{H}_5$							
Bu <sub>4</sub> N	1.25	..	21	0.30	..	70	..
Bu <sub>4</sub> N	1.25	1.27	60	.87	0.52	69	115
Li	1.20	..	6.8	.21	..	32	..
Li	1.25	2.12	7.2	.25	0.32	29	23
$(\text{CH}_3)_3\text{C}_6\text{H}_2\text{CHClCH}_3$							
Bu <sub>4</sub> N	2.50	..	57	5.5	..	10	..
Li	2.54	..	57	4.4	..	13	..
Li	2.51	2.40	63	5.5	7.8	11	8

or trityl<sup>5</sup> type. With these systems, no clear measure of ionization rate and the importance of ion pair return has been available. However, extra information about ionization rate would be provided by rates of racemization of optically active substrates.

We have now compared first order rate constants for racemization<sup>2,3</sup> ( $k_a$ ), solvolysis<sup>2,3</sup> ( $k_t$ ) and radio-chloride exchange<sup>6</sup> ( $k_e$ ) for both *p*-chlorobenzhydryl<sup>7</sup> and  $\alpha$ -mesitylethyl<sup>8</sup> chlorides in anhydrous acetic acid solvent and for chlorobenzhydryl chloride in 80% aqueous acetone. The various rate constants in acetic acid containing lithium or tetrabutylammonium acetate and chloride (MY) are summarized in Table I, along with the corresponding ( $k_a/k_t$ ) and ( $k_a/k_e$ ) ratios. With *p*-chlorobenzhydryl chloride it is clear that racemization is faster than acetolysis by factors of *ca.* 30-70. Also, racemization is more rapid than radio-chloride exchange by similarly large factors, rate of exchange being comparable to that of acetolysis. With  $\alpha$ -mesitylethyl chloride in acetic acid solvent, acetolysis and exchange also occur at comparable rates. The ( $k_a/k_t$ ) ratios of polarimetric and acetolysis rates are 10-13, somewhat smaller than those for chlorobenzhydryl chloride.

With chlorobenzhydryl chloride at 25° in 80% acetone instead of acetic acid solvent, the ( $k_a/k_t$ ) ratio has decreased to 4.9, and rate of exchange in the presence of 0.0155 *M* Bu<sub>4</sub>NCl has dropped to *ca.* one-tenth of the solvolysis rate.

In contrast with rearranging systems such as norbornyl<sup>2b</sup> or *threo*-3-anisyl-2-butyl<sup>3</sup>, the polarimetric rate in the present cases is not equal, but instead represents a lower limit, to the rate of ionization. This is because considerable ion pair return may occur with retention of configuration. However, the present results shed considerable light on the behavior of the ionic intermediates involved. The observed polarimetric:titrimetric and titrimetric:exchange ratios show that there are carbonium ion pairs from ionization of both organic chlorides in acetic acid, or chlorobenzhydryl chloride even in 80% acetone, which lose configuration and return to the covalent condition

(5) (a) R. F. Hudson and B. Saville, *Chemistry and Industry*, 1423 (1954); *J. Chem. Soc.*, 4130 (1955); (b) C. G. Swain and M. M. Kreevoy, *THIS JOURNAL*, **77**, 1122 (1955); (c) E. D. Hughes, C. K. Ingold, S. F. Mok, S. Patai and V. Pocker, *J. Chem. Soc.*, 1265 (1957); (d) C. G. Swain and E. B. Pegues, *THIS JOURNAL*, **80**, 812 (1958).

(6) *E.g.*, L. J. LeRoux and E. R. Swart, *J. Chem. Soc.*, 1475 (1955).

(7) S. Winstein and J. S. Gall, *Tetrahedron Letters*, in press.

(8) J. C. Charlton and E. D. Hughes, *J. Chem. Soc.*, 2939 (1954).