1-Methylindole from 1,1-Dimethylindolium Perchlorate.—To 2 ml. of methanol was added 108 mg. (0.44 mmole) of the perchlorate followed by 8 ml. of water and 10 ml. of 1 *M* aqueous sodium hydroxide. The solution was heated for a total of 17.5 hr. at 53–75° over a period of 2 days, until ultraviolet spectra showed no remaining indolium salt. At the end of this time the solution was cloudy and the odor of 1-methylindole was very strong. The mixture was extracted with ether and the ether extract dried over sodium sulfate and concentrated *in vacuo* to a volume of about 2 ml. To the residue was added a few milliliters of ethanol followed by about 5 ml. of a warm ethanolic solution containing 109 mg. of picric acid. The long red needles of picrate which formed after cooling were collected in two crops, giving a total yield of 85 mg. (54%). Two recrystallizations from ethanol did not change the melting point. A mixture melting point with an authentic sample of the picrate of 1-methylindole, m.p. 143–145° dec., lit.[18] m.p. 144–145° dec., was not depressed.

Anal. Calcd. for $C_9H_9N \cdot C_6H_3N_3O_7$: C, 50.00; H, 3.36; N, 15.55. Found: C, 50.05; H, 3.23; N, 15.52.

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[18] K. T. Potts and J. E. Saxton, *J. Chem. Soc.*, 2641 (1954).

New Thyroxine Analogs. Halogen Derivatives of 3-Carbethoxy-5-hydroxy-2-methylbenzofuran

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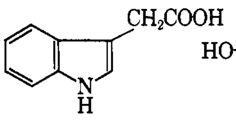
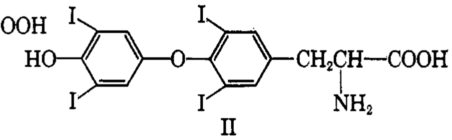
In an effort to combine the structural features of the plant growth hormone, indole-3-acetic acid, and the mammalian hormone, thyroxine, a number of mono and dihalo derivatives of the title compound (III) have been synthesized. Chlorination and bromination were achieved by use of the elemental halogens, whereas only a combination of iodine and morpholine, of a wide variety of reagents examined, was suitable for iodination. Bromination and iodination of III yielded the 6-monosubstituted derivatives, but chlorination afforded primarily the 4-monochloro derivative. Mercuration also occurred at the 4-position, affording a route to the 4-iodo derivative. Deiodination was readily effected by zinc and acetic acid without ring cleavage, but chlorine was not removed by this procedure. Iodine at the 4-position was especially labile toward base, and by the use of potassium cyanide in dimethyl sulfoxide a remarkably selective removal of a 4-iodo group was achieved while a 6-iodo was untouched. The 4,6-dihalo derivatives of III formed methanol- and water-insoluble salts with alkyl and alicyclic amines, as did many simple di-*o*-halophenols. Since mono-*o*-halophenols did not form such salts, the reaction is of value for identification and separation purposes. The 4- and 6-monoiodo derivatives of III showed thyromimetic activity.

Recent demonstrations in this laboratory of living systems in which the plant growth hormone indole-3-acetic acid ("auxin," I) and the mammalian hormone thyroxine (II) show similar types of behavior[1] suggested that interesting physiological activity might be found in a synthetic hormone having the structural features of both I and II. The 4,6-diiodo derivative IX of the title compound (III) approaches this hybrid form, the 2,3-double bond taking the place of the second benzene ring of II. This hydroxybenzofuran is also related to α-tocopherol (IV), one of the E vitamins. The known antioxidant character of IV[2] and the suggestion that antioxidant activity and hormonal behavior may be related in a general way[3,4] were additional reasons for choosing this system. Finally, these hydroxybenzofurans appeared to be readily accessible by condensation of *p*-benzoquinones with β-keto esters and β-diketones.[5–8]


I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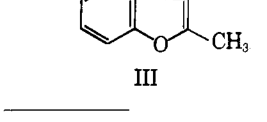
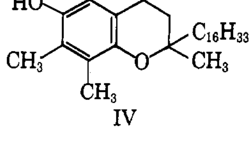

III


IV

There were few examples of the 2,3-disubstituted 5-hydroxybenzofurans in the literature prior to the recent work of Grinev, Terentyev, *et al.*,[5–7] and Bernatek, *et al.*[5,6,8] These authors have not discussed halogenation of this system, although the former group did describe the synthesis of two 6,7-dichloro derivatives by condensation of 2,3-dichlorobenzoquinone with the appropriate β-keto ester.[9] The earlier representatives of the series include 2-methyl-3-carbethoxy-, 2,3-dimethyl-, 2,3-diphenyl-, and 2,3-benzo-5-hydroxybenzofuran (2-hydroxydibenzofuran). Reactions of the last compound with bromine have been reported.[10] A compound, $C_{12}H_9Cl_3O_4$, obtained from the condensation of chloroanil with the sodium derivative of ethyl acetoacetate, is said[5b] to be the 4,6,7-trichloro derivative of III.

A description of the chlorination, bromination, and iodination of 3-carbethoxy-5-hydroxy-2-methylbenzo-

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[1] S. M. Siegel, F. Porto, and P. Frost, *Arch. Biochem. Biophys.*, **82**, 330 (1959); S. M. Siegel and P. Frost, *Proc. Natl. Acad. Sci. U. S.*, **45**, 1379 (1959).

[2] See, for example, "Handbook of Food and Agriculture," F. C. Blanck, Ed., Reinhold Publishing Co., New York, N. Y., 1955, pp. 243, 253, 286, 592; also "Autoxidation and Antioxidants," Vol. I, W. O. Lundberg, Ed., Interscience Publishers, Inc., New York, N. Y. 1962, pp. 1069–1084.

[3] S. M. Siegel, F. Porto, and P. Frost, *Physiol. Plantarum*, **12**, 727 (1959).

[4] S. M. Siegel and F. Porto, "Plant Growth Regulation," R. Klein, Ed., Iowa State University Press, Ames, Iowa, 1961, pp. 341–353.

[5] (a) H. von Pechmann, *Chem. Ber.*, **21**, 3005 (1888); (b) M. Ikuta, *J. prakt. Chem.*, [2]**45**, 65 (1892); (c) A. N. Grinev, P. B. Khvar, and A. P. Terentyev, *J. Gen. Chem. USSR*, **27**, 1172 (1957), and earlier papers; (d) E. Bernatek and T. Ledaal, *Acta Chem. Scand.*, **12**, 2053 (1958); (e) V. J. Grinšteins and V. A. Slavinskaya, *Latvijas Valsts. Univ. Kim. Fak. Zinatniskie Raksti*, **22**, 119 (1958); *Chem. Abstr.*, **53**, 7090*d* (1959).

[6] (a) E. Bernatek, *Acta Chem. Scand.*, **10**, 273 (1956); (b) A. N. Grinev, P. B. Khvar, and A. P. Terentyev, *J. Gen. Chem. USSR*, **27**, 897 (1957).

[7] A. N. Grinev, L. A. Bukhtenko, and A. P. Terentyev, *ibid.*, **29**, 927 (1959).

[8] E. Bernatek, *Acta Chem. Scand.*, **7**, 677 (1953).

[9] A. N. Grinev, N. K. Venevtseva, and A. P. Terentyev, *J. Gen. Chem. USSR*, **28**, 1900 (1958).

[10] H. Gilman and P. R. Van Ess, *J. Am. Chem. Soc.*, **61**, 1365 (1939).

TABLE I

N.M.R. SPECTRA OF 3-CARBETHOXY-5-HYDROXY-2-METHYLBENZOFURAN AND HALOGEN DERIVATIVES^a

					3-COOCH$_2$CH$_3$	
Compound	Aromatic region	5-OH	5-OCH$_3$	2-CH$_3$	-CH$_2$- quartet centered at	-CH$_3$- triplet centered at
III^b	Complex multiplet of not less than 9 peaks, between 2.42–3.27	3.73		7.27	5.57 (6.5)	8.57 (7)
III^{c,d}	Complex multiplet of not less than 7 peaks, between 2.66–3.35		6.20	7.32	5.65 (7)	8.58 (7)
V^{b,d}	First doublet, 2.82 (9) Second doublet, 3.19 (9)		6.14	7.42	5.64 (7)	8.60 (7)
VI^{b,d}	Singlet, 2.64		6.08	7.30	5.64 (7)	8.57 (7.5)
VIII^b	First doublet, 2.67 (8.5) Second doublet, 3.03 (8.5)	4.34		7.42	5.54 (6.5)	8.56 (7)
VII^b	Singlet, 2.62	4.03		7.38	5.60 (7)	8.60 (7)

^{a} Chemical shift in τ-units with tetramethylsilane as internal reference, J in c.p.s. given in parentheses. ^{b} CDCl$_3$. ^{c} CCl$_4$. ^{d} Methyl ether of designated compound.

furan (III) forms the principal part of this report.[11]

Reaction of compound III with 1 equiv. of chlorine in chloroform solution proceeded rapidly at −5°. Two monochlorinated derivatives of III were isolated in a combined yield of 92–100% (crude). The less soluble isomer (VI), obtained in about 8% yield, melted at 182–182.5°, whereas the principal isomer melted at 90–92°. Evidence for designating the chlorine substituents as *ortho* to the 5-hydroxyl was provided by the fact that both V and VI were readily chlorinated further to the same 4,6-dichlorohydroxybenzofuran (VII) that was obtained in 35% yield by condensation of 2,6-dichlorobenzoquinone with ethyl acetoacetate.[12]

Identification of the low-melting isomer as V, the 4-chloro derivative of III, was based on the proton magnetic resonance spectrum (Table I) of its methyl ether, which showed a pair of doublets centered at τ 2.82 and 3.19, each with a 9 c.p.s. splitting, indicating the presence of two protons situated *ortho* to each other on the aromatic ring.[13] Since the n.m.r. spectrum of the methyl ether of the high-melting isomer had a single sharp line in the aromatic region, it was identified as the 6-chloro derivative of III. This isomer was also obtained in low yield by reaction of chlorobenzoquinone and ethyl acetoacetate (Scheme I).

Compound III reacted with 2 equiv. of chlorine in chloroform solution at 0–5° to give high yields of the 4,6-dichloro derivative. At this temperature, an excess of chlorine did not have an adverse effect on the reaction, but, at 20° or higher, excess chlorine was absorbed exothermically, and an intensely orange oil was formed. Similar behavior was noted when excess chlorine reacted with the preformed 4,6-dichloro derivative. The nature of this and related products will be discussed elsewhere.

A number of other methods of chlorination were tried (see Experimental) but were of little preparative value.

Bromination was also carried out in chloroform, but in contrast to chlorination which effected substitution mainly at the 4-position, reaction of III with 1 equiv. of bromine gave high yields of the 6-bromo derivative (XII). From the reaction of a second equivalent of bromine a dibromo derivative was isolated in 50–77% yield. The mono and dibromo compounds are designated as 6- (XII), and 4,6- (XIII), respectively, owing to the close similarity of physical and spectral properties with the chloro and iodo analogs (Table II).

The 6-bromo compound (XII) was also the major product of the reaction of III with anhydrous cupric bromide and lithium bromide in hot dimethylformamide solution[14]; when applied to chlorination this method gave a mixture of the 4- and 6-chloro isomers. No satisfactory synthesis of the 4-bromo isomer was found.

Other methods were necessary to effect iodination of III, and a wide variety of procedures was examined (see Experimental) before it was found that iodine and morpholine[15] could be used effectively. Even substitution of other amines for morpholine gave unsatisfactory results. The reaction of III in methanol with elemental iodine and morpholine at 30–35° gave a monoiodo derivative of III in 53% yield, m.p. 194–194.5°. This product resembled the high-melting monochloro compound (VI) in the gross features of its ultraviolet spectrum, the positions of the peaks in the hydroxyl and carbonyl regions of the infrared (Table II), its solubilities in common organic solvents, and its ease of sublimation (~100° at 0.5 mm.). The methyl ether of this monoiodo compound showed a single sharp band in the aromatic region of its n.m.r. spectrum, and was therefore assumed to be the 6-iodo compound (X).

Proof of this assumption comes from the following chemical transformation, summarized in Scheme I. Compound X was treated with 1 equiv. of chlorine in chloroform solution at 5°; the resulting product analyzed for a monoiodo, monochloro derivative of III. From treatment of this dihalo compound with zinc dust

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[11] Fluorination with perchloryl fluoride [D. Taub, *Chem. Ind.* (London), 558 (1962)] in chloroform solution at 20 and 50° and in pyridine at 20° was attempted, but starting material was recovered quantitatively.

[12] The low-melting isomer, as well as the two monoiodo derivatives of III, were examined in the near infrared (Table II), where the hydroxyl absorption showed the splitting typical of *o*-halophenols [A. W. Baker, *J. Am. Chem. Soc.*, **80**, 3598 (1958)].

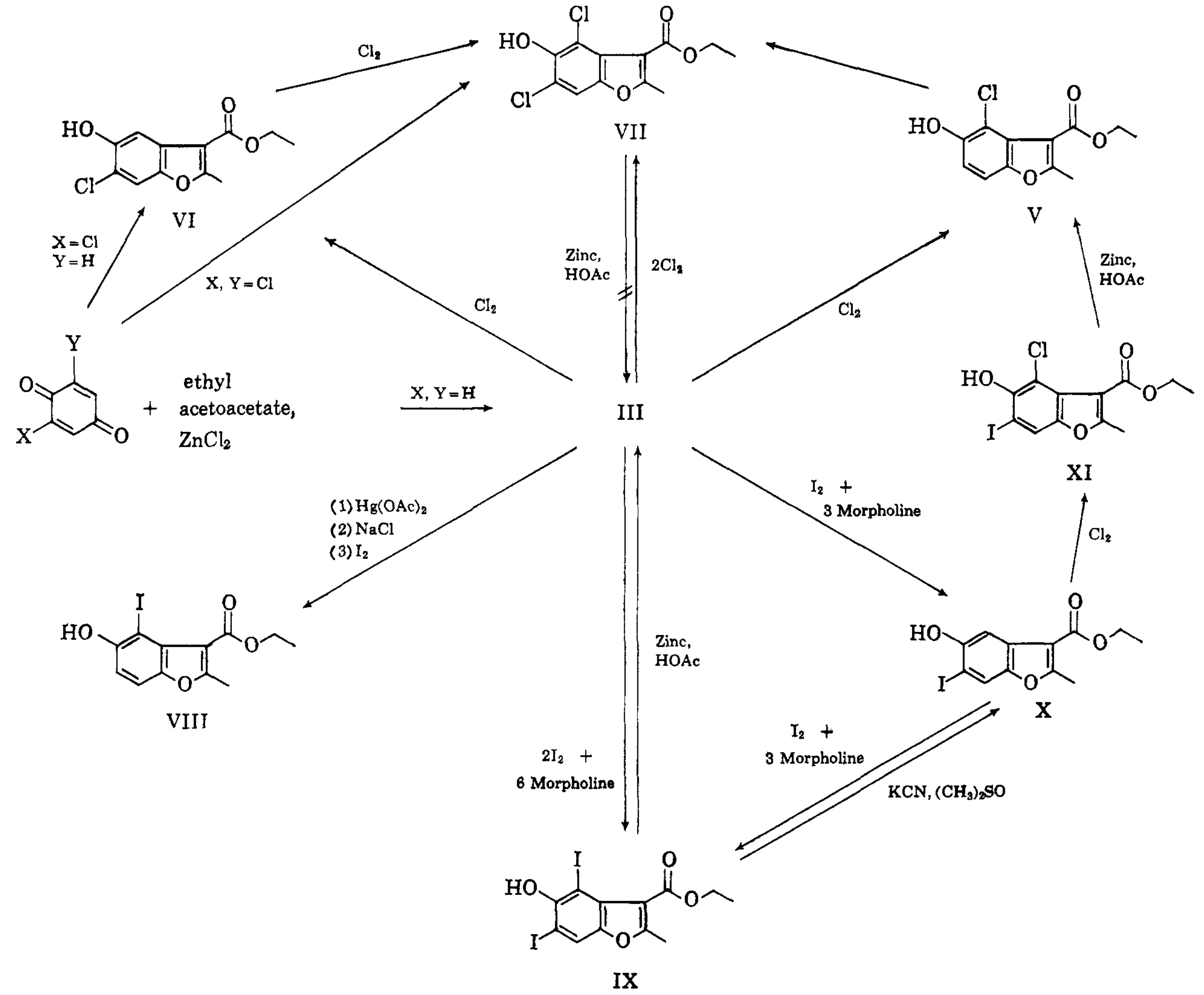
[13] J. A. Pople, W. G. Schneider, and H. J. Bernstein, "High Resolution Nuclear Magnetic Resonance," McGraw-Hill Book Co., Inc., New York, N. Y., 1959, p. 193. These authors quote a 5–8.5-c.p.s. range for *ortho*-proton splitting in benzene rings.

[14] E. M. Kosower, W. J. Cole, G. S. Wu, D. E. Cardy, and G. Meisters, *J. Org. Chem.*, **28**, 630 (1963).

[15] P. Chabrier, J. Seyden-Penne, and A. Fouace, *Compt. rend.*, **245**, 174 (1957); *Chem. Abstr.*, **53**, 21,726*c* (1959). These authors specify a 1:1:3 molar ratio of phenol, iodine, and morpholine, respectively (" . . . le rapport moleculaire morpholine/iode = 3 . . . "). The abstract incorrectly states " . . . and to the solution added 1 mole morpholine and 3 moles iodine."

SCHEME I

INTERRELATIONSHIPS AMONG THE HALOGEN DERIVATIVES OF 3-CARBETHOXY-5-HYDROXY-2-METHYLBENZOFURAN



in acetic acid, the only product isolated (>70% yield) was a monochloro derivative of III identical in every respect with the low-melting monochloro compound V. That only iodine was removed by the zinc dust treatment was established by quantitative recovery of the dichloro compound VII after treatment under similar conditions.[16]

A second monoiodo derivative of III was obtained *via* a mercuration sequence, from which a product presumed to be the 4-chloromercuri derivative was isolated. From treatment of the latter with a chloroform solution of elemental iodine a monoiodo derivative (VIII), m.p. 117–118°, was obtained in 44% yield. The infrared and n.m.r. spectra were all quite different from the high-melting iodo compound X, but were very similar to the spectra of the 4-chloro compound V.[12] The ultraviolet spectrum showed some resemblance to that of the 4-chloro derivative (V), but lacked the maximum in the 240-mμ region (Fig. 1). That VIII was the 4-iodo derivative of III was confirmed by its proton magnetic spectrum, which showed a pair of doublets centered at τ 2.67 and 3.03, with an 8.5 c.p.s. splitting of the aromatic hydrogens.[13]

A diiodo derivative (IX) was obtained in 53% yield by treatment of III with iodine and morpholine in 1:2:6 molar proportions. By analogy with the structure of the product formed by dichlorination of III, the diiodo derivative would be expected to have the halogens in the 4- and 6-positions. The physical properties and ultraviolet (see Fig. 2) and infrared spectra resemble those of the 4,6-dichloro compound (VII), 4,6-dibromo compound (XIII), and the 4-chloro-6-iodo derivative (XI). The diiodo compound formed a methanol- and water-insoluble morpholinium salt; all but one of the polyhalo phenols tested which had their *ortho* positions substituted by halogen also gave such salts, while those phenols with only one *ortho* halogen did not. This point is discussed in detail at the end of this paper.

An attempt was made to prepare an authentic sample of IX by reaction of 2,6-diiodobenzoquinone with ethyl acetoacetate, but only decomposition occurred in contrast to the success of the reaction with the chloroquinones. The failure may have been due to the sensitivity of the iodoquinone or of the product to the zinc

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(16) A number of attempts were made to prove the structure of the 6-iodo and 6-bromo derivatives of III by the metallation–carbonation sequence, and comparison of the product with the known compound, 3-carbethoxy-5-methoxy-2-methylbenzofuran-6-carboxylic acid. We were unable to effect reaction using either metallic lithium or *n*-butyllithium in ether, tetrahydrofuran, or diglyme, at several temperatures with either the halophenols or their methyl ethers, although this procedure has been used successfully in the dibenzofuran series [H. Gilman, J. Swislowsky, and G. E. Brown, *J. Am. Chem. Soc.*, **62**, 348 (1940)].

TABLE II

PHYSICAL AND SPECTRAL DATA ON 3-CARBETHOXY-5-HYDROXY-2-METHYLBENZOFURAN AND HALOGEN DERIVATIVES

Derivative of III	Designation	M.p., °C.	Infrared (KBr)		Ultraviolet (95% ethanol)[a]			
			OH	C=O				
	III	143.5–144	3.00	5.99	*b*	225	255	296
						11,350	8,025	4,730
6-Chloro-	VI	182–182.5	3.05	5.97	209	228	257	301
					39,000	12,850	8,870	6,660
5-Bromo-	XII	192.5–193	3.04	5.96	208	227	258	301
					40,000	13,800	9,150	7,220.
6-Iodo-	X	194–194.5	3.04[c]	5.97	210	232	260	305
					41,000	16,500	10,800	8,600
4-Chloro-	V	90–92	2.93[c]	5.85	211	238	256	298
					30,000	9,530	9,600	4,010
4-Iodo-	VIII	115–117.5	2.99[c]	5.86	215	244 (sh)	263	302 (309 sh)
					31,200	8,450	11,500	4,570 (4,050)
4,6-Dichloro-	VII	135–136	2.95	5.86	212		262	300
					35,000		10,180	5,170
4,6-Dibromo-	XIII	118–119	2.95	5.86	217		265	301 (309 sh)
					34,200		11,170	5,660 (5,450)
4,6-Diiodo-	IX	121.5–122.5	2.91	5.87	218	230	273	304 (312 sh)
					21,000	24,170	16,000	6,720 (6,930)
4-Chloro-6-Iodo-	XI	121.5–122.5	2.98	5.92	215		265	302 (309 sh)
					38,850		13,100	6,720 (6,250)

[a] Upper value is $\lambda_{\max}$ (mμ), lower is $\epsilon_{\max}$. [b] Minimum about 220 mμ, then only intense end absorption unlike halo derivatives. [c] Each of these compounds showed two peaks in the hydroxyl region of the near infrared (Beckman DK-2). The 4-iodo (0.02 *M* in CS$_2$) and 6-iodo (saturated solution in CS$_2$) derivatives had peaks at 3472 and 3571 cm.$^{-1}$, and at 3497 and 3546 cm.$^{-1}$, respectively, giving values of $\Delta\bar{\nu}$ of 99 and 68 cm.$^{-1}$, compared to a reported[12] value of 93 cm.$^{-1}$ for 0.07 *M* *o*-iodophenol in CCl$_4$. For the 4-chloro derivative (0.02 *M* in CS$_2$) peaks were at 3524 and 3571 cm.$^{-1}$, with $\Delta\bar{\nu} = 51$ cm.$^{-1}$, compared to 57 cm.$^{-1}$ found for *o*-chlorophenol and 58 cm.$^{-1}$ reported.[12] In the halo derivatives of III the peak at shorter frequency was about twice as intense as the other.

chloride, although facile deiodination of the diiodo derivative (IX) was effected by zinc and acetic acid from which the parent phenol (III) was isolated in 65% yield.

A difference in chemical reactivity of the two iodines in IX is shown by the remarkable preferential deiodination of IX to the 6-iodo derivative (X) when warmed with potassium cyanide in dimethyl sulfoxide solution. This reaction does not occur with dimethyl sulfoxide alone, nor have we been able to bring it about with simple *o*-diiodophenols such as 2,4,6-triiodophenol, 2,6-diiodo-4-nitrophenol, or 3,5-diiodotyrosine.

Methyl ethers of III and most of its halo derivatives were obtained easily by the use of dimethyl sulfate in basic solution. Exceptions were the 4-iodo derivative (VIII) and the 4,6-diiodo derivative (IX), from which ethers could not be obtained, probably due to the instability of these iodophenols under the basic reaction conditions. The instability of the 4-iodo derivatives to base is probably related to the facile deiodination by cyanide, mentioned above.

Halogenation of the methyl ether of III was also carried out. In contrast to the behavior of the parent phenol (III), the methyl ether gave the 6-chloro isomer in high yield when treated with 1 equiv. of chlorine in chloroform at 0°. Sodium hypobromite in acetic acid gave the 6-bromo ether in good yield, whereas hypochlorite gave a mixture of products which could not be identified.

The results of the halogenations of III indicate a seeming anomaly in that chlorination gives predominantly the 4-halo derivative, while bromination and iodination give only the 6-halo derivatives. One generally anticipates greater similarity in chlorination and bromination than in bromination and iodination, reflecting a difference in reactivity of the elements. Moreover, in our work the reaction conditions used in chlorination and bromination were very similar and different from those used in iodination.

This difference can be rationalized if it is assumed that electrophilic substitution of the 5-hydroxybenzofuran system is analogous to that of β-naphthol, and would occur at the 4-position but for steric crowding of that position by the 3-carbethoxy group, which tends to shift substitution to the 6-position as the bulk of the attacking species is increased. Crowding of the 4-position is clearly shown in models and this interpretation is supported by the observations that bromination of 2-hydroxydibenzofuran takes place at the 1-position[10] and, as noted above, chlorination of the methyl ether of III gave only the 6-chloro derivative.[17] Furthermore, crowding by the 3-carbethoxy group would be buttressed by the 2-methyl group, an interpretation advanced to explain results in a closely analogous system, the nitration of gramine. Both 4- and 6-nitro derivatives were obtained from gramine itself, but

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(17) Although β-naphthol is usually substituted at the 1-position, Friedel–Crafts reactions give 1- or 6-derivatives according to the conditions, and the 2-naphthyl ethers give only 6-acyl derivatives [E. H. Rodd and J. van Alphen, "Chemistry of Carbon Compounds," Vol. III, Elsevier, Amsterdam, 1956, p. 1309].

TABLE III

RATES OF PRECIPITATE FORMATION BY PHENOLS AND AMINES IN METHANOL

Phenol (with morpholine)[a]	Rate of formation of ppt. at 25°[b]	Amine (with 2,4,6-triiodophenol)[a]	Rate of formation of ppt. at 25°[b]
2,4,6-Cl_3–	R	Morpholine	R
2,4,6-Br_3–	R	Piperidine	R
2,4,6-I_3–	R	Piperazine	R
2,6-Cl_2–4–OH	R	Pyrrolidine	VS
2,6-Cl_2–4–NO_2–	S	Di-*n*-butylamine	R
2,6-Br_2–4–NO_2	R	Diethylamine	S
2,6-I_2–4–NO_2–	R	Dicyclohexylamine	X
2,6-Br_2–	S	Diethanolamine	X
4,6-Cl_2 III	S	N-Methylmorpholine	S
4,6-Br_2 III	R	N-Methylpiperazine	R
4,6-I_2 III	R	2-Methylpiperidine	R
2,4-Cl_2–	X	2-Methylpiperazine	S
2,4-Cl_2-1-Naphthol	X	2,6-Dimethylmorpholine	S
2,4-Br_2-1-Naphthol	X	2,6-Dimethylpiperidine	R
1,3,6-Br_3-2-Naphthol	X	Triethylamine	X
2,4-I_2-6-COOH–	X	N,N′-Dimethylcyclohexylamine	X[c]
3,5-I_2-L-tyrosine	X	*n*-Butylamine	S
2-I–	X	Ethylenediamine	X
2,4,6-(*t*-Bu)$_3$–	X	N-Methylaniline	X
2,6-(*t*-Bu)$_2$–	X	N,N-Dimethylaniline	X
3,5-(*t*-Bu)$_2$–	X	Pyridine	X
2,6-(MeO)$_2$–	X	Dimethylformamide	X
2,6-Me_2–	X	Di-*n*-butylformamide	X
2,3,6-Me_3–	X	Pyrrole	VS
4-NO_2–	X		

[a] About 2 g. of the phenol and 5 g. of the amine were dissolved in 10–20 ml. of methanol. [b] R = <1 min.; S = 30–120 min.; VS = ~15 hr.; X = no precipitate. [c] With chloranil hydroquinone.

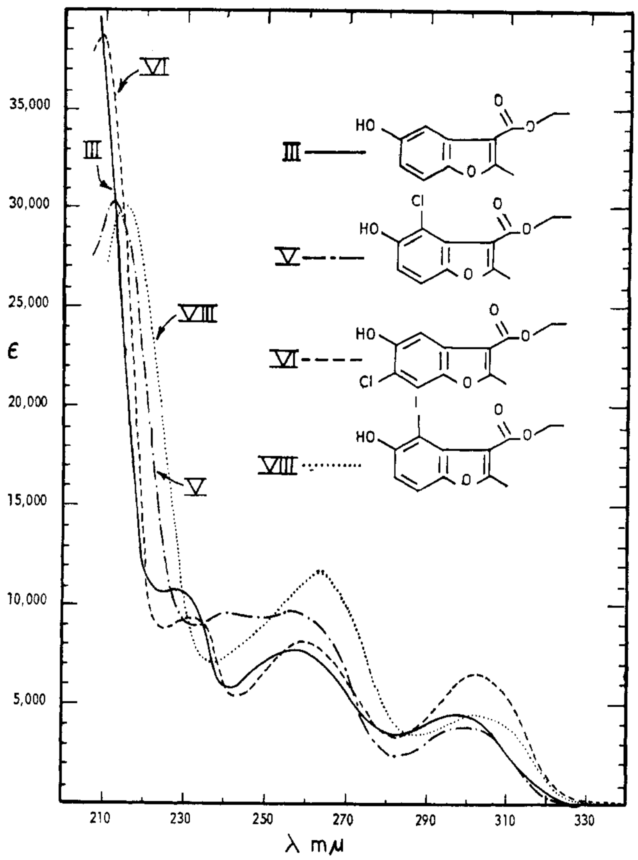

Fig. 1.—Ultraviolet absorption spectra of 3-carbethoxy-2-methyl-5-hydroxybenzofuran and monohalogen derivatives.

only the 6-nitro isomer was obtained from 2-methyl- and 1,2-dimethylgramine.[18]

Steric hindrance may also account for our observation that compound III gives a positive ferric chloride test under anhydrous conditions in a chloroform–pyridine mixture,[19] but, as reported previously,[5c] no coloration is observed in aqueous solution. It is known that this test with enolizable compounds is strongly dependent on steric factors in the enol,[20] and the solvation and hence the bulk of the ferric chloride would certainly differ in the two media.[21] Particularly pertinent are the reports that 5-hydroxy-2-methylbenzofuran readily gives a positive test with aqueous ferric chloride,[5c] but 7-hydroxy-1-naphthoic acid does not.[22]

That the effect of steric crowding on the balance between 4- and 6-substitution is a subtle one is shown by the fact that only the 4-nitro isomer was isolated (68% yield) from nitration of the methyl ether of III,[23] mercuration took place at the 4-position, and preliminary results on the sulfonation of III indicate that the 4-sulfonic acid is the chief product.[24]

Once substitution at the 4-position has been achieved, a marked effect of the halogen on the ester carbonyl absorption is observed in the infrared spectra (Table II). The position of the ester carbonyl in III is close to those of esters of anthranilic and salicylic acids (5.92–5.99 μ)[25] all of which have an ester carbonyl conjugated with an aromatic ring and an atom with unshared electron pairs. In all of the derivatives of III which bear at least one halogen at the 4-position, a shift of the ester carbonyl to shorter wave lengths is observed. This is the direction expected from decreased resonance interaction of the ester carbonyl with the remainder of the conjugated system, and is attributed to steric inhibition. The ultraviolet spectra of the isomeric monohalo derivatives also show differences (Fig. 1 and Table II) ascribable to these steric interactions. As would be expected on this basis, the monoiodo (Fig. 1) and diiodo (Fig. 2) derivatives show distinct differences from the derivatives bearing smaller halogens.

Morpholinium Salts.—In the course of studying iodination in the presence of morpholine, it was found that the diiodo derivative (IX) formed a stable mor-

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(18) G. Berti and A. Da Settimo, *Gazz. chim. ital.*, **90**, 525 (1960).

(19) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1956, p. 113.

(20) W. Hückel, "Theoretical Principles of Organic Chemistry," Elsevier, New York, N. Y., 1955, p. 312.

(21) Although the 5-hydroxyl group of III is acidic enough to form a sodium salt, in other ways it is not typically phenolic. In addition to its failure to give a positive ferric chloride test under aqueous conditions, no reaction was observed when III was treated with diazotized sulfanilic acid, nor when refluxed in toluene containing methyl iodide and aluminum chloride. Several attempts to replace the 5-hydroxyl group under Bücherer conditions were unsuccessful.

(22) M. Stümpf, *Ann.*, **188**, 6 (1877).

(23) A. N. Grinev and A. P. Terentyev, *J. Gen. Chem. USSR*, **28**, 80 (1958).

(24) Cases are known in which phenols react with electrophilic reagents such that one *ortho* position is favored more than the other (or even exclusively). With *m*-hydroxybenzaldehyde and *m*-nitrophenol chlorination and nitration occur at the 2-position, while bromination goes 6, closely paralleling our results. In 2-nitro-1,4-dimethoxybenzene nitration occurs at 3. An explanation of this behavior based on electronic factors has been advanced by P. B. D. De la Mare and J. H. Ridd, "Aromatic Substitution," Academic Press, New York, N. Y., 1959, p. 132.

(25) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1960, p. 179.

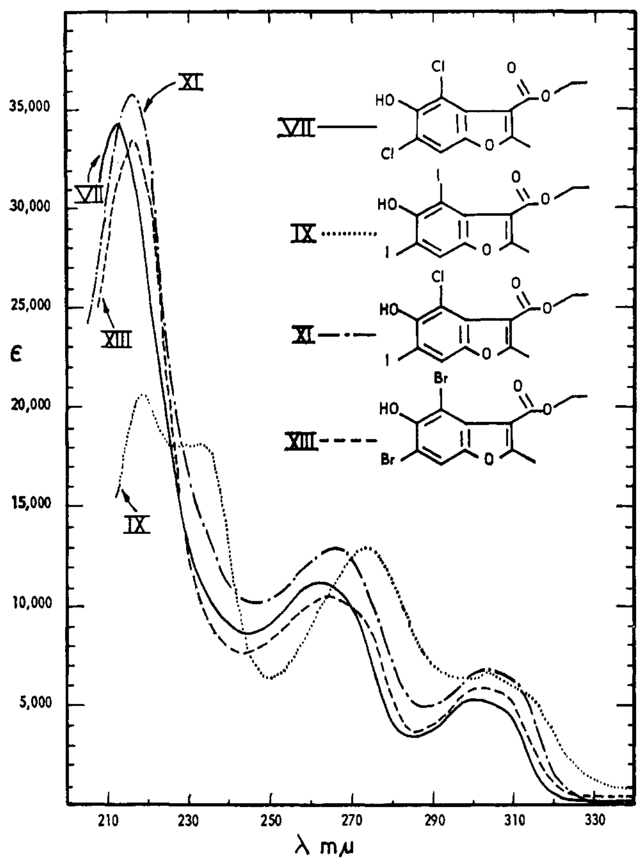

Fig. 2.—Ultraviolet absorption spectra of dihalo derivatives of 3-carbethoxy-2-methyl-5-hydroxybenzofuran.

pholinium salt insoluble in methanol. The dichloro- and dibromophenols (VII and XIII) also formed insoluble salts, but none of the monohalo derivatives gave precipitates under these conditions.

Several simpler phenols were tested for this property (Table III). Of ten di-*o*-halo phenols tested, only two failed to form insoluble salts, *viz.*, 1,3,6-tribromo-2-naphthol and 3,5-diiodotyrosine, the latter itself being virtually insoluble in methanol. If only one *ortho* halogen was present, even if a nonhalogen substituent occupied the other *ortho* position, and even if a second halogen was *para* to the hydroxyl, no salt precipitated. It is also apparent from Table III that while the amine must be secondary and quite basic, formation of a precipitate is highly dependent on subtle structural variations. Thus, morpholine, N-methylmorpholine, piperazine, and 1,4-diazabicyclooctane formed salts with 2,4,6-triiodophenol and chloranil hydroquinone, but N-phenylmorpholine, the anilines, the cyclohexylamines, diethylamine, propylamine, and pyrrolidine did not. The reaction is sensitive to small amounts of dihalo compound.

The property of certain bases to form insoluble salts with di-*o*-halo phenols but not with mono-*o*-halo phenols or similar phenols having other nonhalogen substituents can serve as a means of separation of such mixtures. One complication is the tendency of the moist salts to turn dark on standing in air; the dry salts are stable in this respect. The morpholinium salts of VII, IX, and XIII differ from the picrates of morpholine, piperidine, and piperazine in that they are much less soluble in methanol and other solvents. Furthermore, the melting points of the former group are generally higher than those of the picrates, and the $>$N$^+$–H salt bands in their infrared spectra are consistently more intense and spread over a broader range than are those of the picrates.

Physiological Properties.—The parent phenol (III) and several of its derivatives possess phytohormonal properties.[26] The monoiodo derivatives VIII and X possess substantial thyroactivity,[27] even though these molecules do not have the di-*o*-iodophenyl ether link generally assumed necessary.[28]

Experimental

All melting points are uncorrected. Infrared spectra were obtained on a Perkin-Elmer double beam recording spectrophotometer, Model 21; ultraviolet spectra on a Beckman DK-II recording spectrophotometer, with the 1-cm. quartz cells thermostatted at 25 ± 0.5°; proton magnetic resonance spectra on Varian Associates 60-Mc. n.m.r. instruments, Models A-60 and HR-60. Analyses were performed at the Schwarzkopf Microanalytical Laboratory, Woodside 77, N. Y.

3-Carbethoxy-5-hydroxy-2-methylbenzofuran (III).—This was prepared according to Grinev, *et al.*,[5c] but because of the great difficulty we (and others[5d]) have encountered, a detailed description of an improved procedure is given. About 140 g. (~1 mole) of commercial anhydrous zinc chloride was placed in a three-necked 1-l. round-bottomed flask, and kept molten under vacuum for 15 min. to remove moisture. Nitrogen was bled into the flask, which was fitted with a thermometer and continuous extraction apparatus. After 160 ml. of anhydrous ethanol (distilled from sodium ethoxide–diethyl phthalate) had been added, the contents were refluxed until the zinc chloride dissolved. The mixture was cooled to 25° and 260 ml. (~2 moles) of vacuum-redistilled ethyl acetoacetate was added, followed by 200 ml. of anhydrous ether from a newly opened container. The extractor thimble was charged with 103 g. (0.95 mole) of dry, steam-distilled *p*-benzoquinone, and a calcium chloride drying tube was affixed to the condenser. Nitrogen was flushed through the system for about 5 min. The reaction mixture was kept at an internal temperature of 78–82°, and quinone was extracted very slowly into the flask over a period of 66 hr.; heating was continued for one additional hour. On cooling to 25°, the reaction mixture solidified; the contents of the flask were transferred to a Büchner funnel and washed with 250 ml. of cold benzene. Of a wide variety of solvents tried, only glacial acetic acid was effective for crystallization of the crude product. This treatment followed by recrystallization from toluene gave product melting above 140° in about 70% yield. The highest melting point obtained from any run was 143.5–144°, and material of m.p. 143°, with correct analysis for $C_{12}H_{12}O_4$, was obtained routinely by the above procedure (lit.[5c] m.p. 137°, lit.[5d] 138°). The product from acetic acid crystallization was apparently a hemisolvate, since it still smelled of acetic acid after weeks of drying at room temperature, but further drying *in vacuo* over sodium hydroxide was accompanied by a loss in weight equal to 0.5 mole of acetic acid per mole of III.

Compound III did not give any observable color reaction with 1, 3, or 5% aqueous ferric chloride solution, but a stable blue-green color formed rapidly when a saturated solution of anhydrous ferric chloride in chloroform containing a few drops of pyridine was added. When a concentrated dioxane solution of III was treated with 30% aqueous sodium hydroxide solution, the sodium salt of III precipitated promptly. The moist salt turned brown in air, but the dry salt was stable. A deep purple color formed when III was warmed in concentrated sulfuric acid, a change said to be typical of compounds containing the benzofuran nucleus.[5b]

The methyl ether of III was prepared by adding to a dioxane solution of III an excess of dimethyl sulfate and 10% sodium hydroxide with vigorous shaking. To ensure complete reaction more dimethyl sulfate and base were added, followed by shaking.

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(26) C. A. Giza and S. M. Siegel, *Physiol. Plantarum*, **16**, 52 (1963).

(27) S. M. Siegel, C. A. Giza, G. Davis, and R. L. Hinman, *Proc. Natl. Acad. Sci. U. S.*, **49**, 107 (1963).

(28) C. D. Turner, "General Endocrinology," W. B. Saunders Co., Philadelphia, Pa., 1960, pp. 113–120.

After a third such addition, the methyl ether was isolated by pouring the reaction mixture onto crushed ice and filtering. The brown waxy solid was ultimately purified by molecular distillation of the melt, and then by recrystallization from a benzene–hexane mixture. It had m.p. 45–46°, lit.[5b] m.p. 47°, with correct analysis for $C_{13}H_{14}O_4$.

3-Carbethoxy-6-chloro-5-hydroxy-2-methylbenzofuran (VI). **Method A.**—Chlorobenzoquinone (7.1 g., 0.05 mole), from oxidation of chlorohydroquinone with aqueous potassium bromate was extracted continuously (see preparation of III) in 5.5 hr. into a solution of 7 g. of zinc chloride, 7 g. of anhydrous ethanol, and 10 g. (0.075 mole) of redistilled ethyl acetoacetate kept at 100°. The reaction mixture was cooled, and diluted with carbon tetrachloride, and the precipitated solid was filtered. Sublimation, followed by recrystallization from carbon tetrachloride, gave 2.2 g. (17%) of an off-white powder, m.p. 170–172°. This compound was identified as the 6-chloro derivative of III by comparison with an authentic sample (see following).

Method B.—In a three-necked, 500-ml. round-bottomed flask with stirrer, vented addition funnel, and thermometer, a suspension of 20.0 g. (0.091 mole) of III in 175 ml. of chloroform was prepared, and to it was added, in 1.5–2 hr. at −5 to 0°, 57.5 ml. (0.091 mole) of a chlorine solution made by diluting 28 g. of the trapped gas in chloroform until the total volume was 250 ml. The chlorine–chloroform solution in the dropping funnel was kept cold by surrounding the funnel with powdered carbon dioxide wrapped in a towel. After addition was complete, the solution was warmed to 10°, and the white solid (0.55 g., 2.3%) was isolated by filtration. Additional material was obtained from the filtrate, as described below. Recrystallization from 60 g. of carbon tetrachloride gave an analytical sample, m.p. 182–182.5°.

Anal. Calcd. for $C_{12}H_{11}ClO_4$: C, 56.59; H, 4.35; Cl, 13.92. Found: C, 56.61; H, 4.47; Cl, 13.38.

The **methyl ether** of VI was prepared by the method used for the ether of III. From 0.5 g. of VI was obtained, after recrystallization from methanol, 0.35 g. of ether. The analytical sample, recrystallized from *n*-hexane, melted at 125.5–126°. This same compound was obtained in nearly quantitative yield (crude) by chlorination of the methyl ether of III, using the procedure described above for VI itself (method B).

Anal. Calcd. for $C_{13}H_{13}ClO_4$: C, 58.11; H, 4.88; Cl, 13.20. Found: C, 58.25; H, 4.92; Cl, 13.00.

3-Carbethoxy-4-chloro-5-hydroxy-2-methylbenzofuran (V).—The filtrate from the reaction in method B above was evaporated to dryness. The residue weighed 23.4 g. [97.5%; total yield of isolated crude material (both isomers) was 23.95 g., or 100%]. On recrystallization from 125 g. of carbon tetrachloride, a precipitate of 16.6 g. was obtained and, on evaporation of the filtrate, a residue of 5.2 g. The filter cake was found (by infrared) to be a mixture of the 4- and 6-chloro compounds V and VI; the residue consisted essentially of the 4-isomer. By repeated recrystallization of the mixture an additional yield of 1.2 g. of the 6-chloro compound was obtained (total yield pure, 1.7 g., 7%). The total yield of the 4-chloro derivative (V) was 6.45 g., m.p. 82–85°. The analytical sample of V, m.p. 90–92°, was prepared by recrystallization from a methanol–water mixture.

Anal. Calcd. for $C_{12}H_{11}ClO_4$: C, 56.59; H, 4.35; Cl, 13.92. Found: C, 56.76; H, 4.40; Cl, 14.31.

The **methyl ether** was prepared as described under III, and purified by triturating the crude solid with hot hexane. On cooling to −5°, the hexane deposited large colorless cubes. The analytical sample, from hexane, melted at 47.5–48°.

Anal. Calcd. for $C_{13}H_{13}ClO_4$: C, 58.10; H, 4.88; Cl, 13.20. Found: C, 58.32; H, 4.87; Cl, 12.99.

3-Carbethoxy-4,6-dichloro-5-hydroxy-2-methylbenzofuran (VII). **Method A.**—The same general procedure was used as in the preparation of III, employing 14.5 g. (0.01 mole) of zinc chloride, 30 ml. of absolute ethanol, 20 ml. (0.15 mole) of redistilled ethyl acetoacetate, and 11.75 g. (0.065 mole) of 2,6-dichlorobenzoquinone. The quinone was extracted into the solution over a period of 13 hr. The dark red-brown solution was cooled to −5° and filtered. After washing with cold ethanol, 1.7 g. (9%) of an off-white microcrystalline solid was obtained, m.p. 130–133°. The filtrate was diluted with ether, washed with water, and dried; the solvents were removed by evaporation *in vacuo*. The oily black residue was distilled molecularly, and 7.8 g. of a yellowish solid was recovered. Recrystallization from carbon tetrachloride gave 5.1 g. (26%) of off-white solid, m.p. 131–133°. Total yield of solids melting over 130° was 6.8 g. (35%). The compound was identical with the dichloro compound obtained on chlorination of III (see method B following).

Method B.—Apparatus and procedure are the same as for VI, method B. Compound III (7.25 g. 0.033 mole) was suspended in 65 g. of chloroform and cooled to 10°. To this was added a chloroform solution containing not more than 4.9 g. (0.069 mole, 2.1 equiv.) of chlorine, at 10–14° within 30 min. After stirring for 0.5 hr. longer at 10°, the volume was reduced to one-half and the solid was filtered and washed with hexane, yielding 3.45 g., m.p. 134–135°. By repeated concentration of the filtrate a total yield of 8.4 g. (88%) of material melting over 131° was obtained. The analytical sample, m.p. 135–136°, was recrystallized from ethanol–water.

Anal. Calcd. for $C_{12}H_{10}Cl_2O_4$: C, 49.85; H, 3.48; Cl, 24.52. Found: C, 50.66; H, 3.53; Cl, 24.48.

Other methods of chlorination were tried, but were found to be of little preparative value. Compound III reacted readily with 2 equiv. of cupric chloride and lithium chloride in dimethylformamide solution,[14] forming a mixture of the 4- and 6-monochloro derivatives as chief products, with little unchanged III remaining. Although it was not possible to separate the isomers, their presence was established by means of their infrared spectra. Treating a cold acetic acid solution of III with dilute aqueous sodium hypochlorite did not give any of the three known chloro derivatives, but instead gave a bright yellow compound, melting about 104–106°, of as yet unproved structure. When III was refluxed in chloroform with sulfuryl chloride for several hours, III was recovered unchanged with only a trace of halogenated product. Reaction of III with N-chlorosuccinimide or chloramine T gave colored mixtures whose components were not separated or identified.

The **methyl ether** of VII was prepared as described under III; the reaction of 2.9 g. of VII with excess dimethyl sulfate gave 2.6 g. (86%) of crude product, m.p. 93–98°. After molecular distillation, 2.35 g. of a colorless solid was obtained with m.p. 96–98°. Recrystallized from methanol, the analytical sample melted at 99–100°.

Anal. Calcd. for $C_{13}H_{12}Cl_2O_4$: C, 51.51; H, 3.99. Found: C, 51.66; H, 3.94.

Compound VII (0.50 g.) was heated with excess zinc dust in glacial acetic acid at 100–110° for 16 hr., and was recovered (0.47 g.) unchanged (contrast with behavior of IX and XI, below).

3-Carbethoxy-5-hydroxy-6-iodo-2-methylbenzofuran (X).—To a solution of 18.5 g. (0.084 mole) of III in 65 ml. of anhydrous methanol in a glass-stoppered erlenmeyer flask was added 33.2 g. (0.14 mole, 1.6 equiv.) of elemental iodine, followed by 21.3 g. (0.25 mole, 2.9 equiv.) of morpholine. A purple solid separated immediately and the mixture was shaken under a cold water tap to dissipate the heat generated. The reaction mixture was then shaken mechanically for 90 hr. at 30–35°, filtered, and washed with cold (5°) methanol. The yellowish solid remaining was then continuously extracted with ether for 4 hr. The ether extract gave 8.0 g. of a white solid, m.p. 190–191.5°. When the original reaction filtrate was evaporated to dryness and then continuously extracted with ether, it gave 7.5 g. of solid, m.p. 190–191°. Total yield of material melting above 189° was 15.5 g. (53.5%). The combined solids were subjected to sublimation (from a 100–110° oil bath at 0.5 mm.), then recrystallized from ethyl acetate. The analytical sample, recrystallized from chloroform–hexane, was a microcrystalline white solid, m.p. 194–194.5°.

Anal. Calcd. for $C_{12}H_{11}IO_4$: C, 41.64; H, 3.20; I, 36.66. Found: C, 41.43; H, 3.44; I, 36.87.

The formation of the 6-iodo derivative from III is apparently slow, and complicated by a side reaction in which iodine is consumed without iodination of the phenolic substance. The side reaction is markedly favored by a rise in temperature. When III was treated with iodine and morpholine in anhydrous methanol for only 4.5 hr. at 70–75°, all the iodine disappeared, yet III was recovered quantitatively. However, when the same amounts of materials were allowed to react at 30–35° for 90 hr., a 53% yield of the 6-iodo compound X was obtained.

Attempts to use ethylamine, ethylenediamine, or diethanolamine in place of morpholine were largely unsuccessful. In the last case a high yield of the 6-iodo compound was obtained on a 1-g. scale but the yields were poor on a larger scale.

Other attempts to effect direct iodination of III were made, but these were by and large unsuccessful or of less preparative value. Formation of iodinated derivatives of III by the action of elemental iodine in chloroform or carbon tetrachloride at 20° and 75° was not observed; even adding metallic iron or ferric chloride catalyst, or prolonged reaction gave only traces of iodinated products, which were isolated as tars. Most of the starting material was recovered. The reaction of III with iodine monochloride in acetic acid at 50–60° gave a complex mixture from which approximately equal amounts (3–4% yield) of the 4- and 6-monoiodo derivatives, and the 4,6-diiodo compound, were separated along with much starting material. Reaction of iodine monochloride with III in chloroform solution did not appear to proceed until triethylamine was added, whereupon the color of the reagent disappeared rapidly and the 6-iodo compound was obtained pure in 20–30% yield. Reaction of III with sodium hypoiodite gave some 6-iodo product, but its purification was difficult. Also found of little utility were the reagents N-iodosuccinimide, iodine with mercuric oxide or dilute nitric acid, or sodium persulfate, all in mixed aqueous–organic solvents.

The **methyl ether** of X (same procedure as under III), recrystallized from acetone, was a white solid, m.p. 136.5–137.5°.

Anal. Calcd. for $C_{13}H_{13}IO_4$: C, 43.36; H, 3.64; I, 35.24. Found: C, 43.43; H, 3.73; I, 35.46.

3-Carbethoxy-4-chloro-5-hydroxy-6-iodo-2-methylbenzofuran (XI).—Following the chlorination procedure under VI, method B, 6.4 g. of partially purified (m.p. 187–188°) X was treated with 1 equiv. of chlorine–chloroform solution in 25–30 min. at 1–2°. The solution was allowed to stand 10 min., then nitrogen was passed through to remove acid fumes. On evaporation to dryness *in vacuo*, there remained 7.0 g. (100%) of an off-white solid, from which 6.6 g. of clustered needles, m.p. 121–122.5°, was obtained by recrystallization from 60 g. of carbon tetrachloride. The analytical sample, recrystallized from an acetone–water mixture, was a white solid, m.p. 121.5–122.5°.

Anal. Calcd. for $C_{12}H_{10}ClIO_4$: C, 37.87; H, 2.65. Found: C, 38.37; H, 2.67.

Deiodination of XI.—A solution of XI (0.42 g.) in glacial acetic acid was heated at 100–105° with excess zinc dust for 4 hr. It was filtered while hot onto 100 ml. of crushed ice. Filtration gave 0.18 g. (71%) of product, m.p. 81.5°, identified as V by comparison with an authentic specimen.

3-Carbethoxy-5-hydroxy-4-iodo-2-methylbenzofuran (VIII).—The clear solution obtained by warming 16 g. (0.073 mole) of III in glacial acetic acid was treated with 16 g. (0.074 mole) of yellow mercuric oxide, in 2-g. portions at 68–72°. The yellow oxide dissolved rapidly with loss of color, and a white solid began precipitating. After 3.25 hr. at 65–70°, the suspension was cooled and filtered. The dried solid (18.4 g.) was continuously extracted with acetone for 4 hr., leaving 15.8 g. of a gray powder, presumably the acetoxymercuri derivative of III, m.p. 262–263° dec. This solid, when refluxed with 6.5 g. of sodium chloride, 50 ml. of water, and 15 ml. of 95% ethanol (added to prevent foaming), was converted to a tan powder (14.9 g., 45% over-all yield from III), decomposing at 240–250°.

Fourteen grams (0.031 mole) of the latter solid was suspended in 50 ml. of chloroform, and treated with 7.8 g. (0.031 mole) of elemental iodine dissolved in 250 ml. of chloroform (iodine in aqueous potassium iodide could also be used), over a period of 1 hr. The first 50 ml. of iodine–chloroform solution was decolorized almost instantaneously, and a more pronounced brown color appeared in the suspension. Near the end of the reaction, the iodine color in 2 ml. of added solution was discharged in about 2 min. (In contrast, III did not decolorize iodine–chloroform solutions at all, even during several hours under these conditions.) A pale red amorphous solid was already forming toward the end of the addition. After standing overnight, the solid obtained by filtration weighed 10.4 g. (93%, assuming it was mercuric iodochloride). After evaporating the filtrate to dryness *in vacuo*, 10.7 g. of a red oily solid remained. Fractional crystallization from a carbon tetrachloride–hexane mixture gave 4.0 g. (37%) of an off-white solid, m.p. 114–118°. The analytical sample obtained by recrystallization from cyclohexane was a white solid, m.p. 115–117.5°.

Anal. Calcd. for $C_{12}H_{10}IO_4$: C, 41.64; H, 3.20; I, 36.66. Found: C, 41.45; H, 3.63; I, 36.56.

3-Carbethoxy-4,6-diiodo-5-hydroxy-2-methylbenzofuran (IX).—To 13.2 g. (0.06 mole) of III in 125 ml. of anhydrous methanol was added in one portion 30.4 g. (0.12 g.-atom, 2 equiv.) of elemental iodine. This suspension and a solution of 31.1 g. (0.36 mole, 6 equiv.) of morpholine in 20 g. of methanol were chilled in a refrigerator for 0.75 hr., then mixed. The heat of reaction was dissipated by swirling the flask under a cold water tap for several minutes, after which the reaction mixture was stirred magnetically for 92 hr. at 6°. Filtration, followed by two successive concentrations *in vacuo* and filtrations, yielded three crops of solid, weighing 24.5, 6.0, and 27.0 g., respectively. The first crop was recrystallized from about 600 ml. of ethyl acetate (the solution became dark in color as the temperature was raised) and gave 18 g. of a tan solid, which was identified as the morpholinium salt of the diiodo derivative (IX). By treatment of the salt with 10% sulfuric acid in the presence of ether, 15 g. (53%) of the diiodo compound (IX) was obtained. The analytical sample of the diiodo compound, recrystallized from methanol, was a pale yellow powder, m.p. 121.5–122.5°.

Anal. Calcd. for $C_{12}H_{10}I_2O_4$: C, 30.53; H, 2.14; I, 53.77. Found: C, 30.79; H, 2.19; I, 54.06.

The second crop was almost pure morpholine hydriodide, m.p. 207–211°, identical after recrystallization from a methanol–ether mixture with an authentic sample (m.p. 215–216°). The third crop, after continuous extraction with ether for 4 hr., weighed 24 g., m.p. 205–211°. After recrystallization from a methanol–ether mixture there remained 18.9 g. (m.p. 214–215°) of a white, water-soluble powder. The methanol–ether and ethyl acetate mother liquors (from the first crop) were combined and reduced to dryness. By sublimation and recrystallization 3.4 g. of the 6-iodo derivative (X) was obtained. The isolated iodinated derivatives accounted for 68% of the starting material.

Attempts to prepare a methyl ether of IX under the usual conditions with dimethyl sulfate and sodium hydroxide gave a tarry product. Sodium hydroxide solution alone had a similar effect on IX.

The isolated **morpholinium salt of the diiodo derivative (IX)** discussed above was found to be identical with a compound obtained by mixing a methanol solution of the purified diiodo compound with an excess of morpholine. The analytical sample was recrystallized from methanol. Though analytically pure it melted over a wide range (160–180°), the exact range depending on the rate of heating.

Anal. Calcd. for $C_{16}H_{19}I_2NO_5$: C, 34.37; H, 3.42; I, 45.39. Found: C, 34.69; H, 3.63; I, 45.76.

The morpholinium salt was more stable in ethanolic solution than the parent phenol. While solutions of IX in 95% ethanol quickly began turning yellow on standing under fluorescent laboratory lighting, the morpholinium salt of IX only acquired a very pale pink color and, after three months, the former solution was deep orange, the latter pale yellow. Under these conditions ethanolic solutions of III, V, VI, VII, X, XII, and XIII remained colorless, but that of XI turned yellow

Deiodination of IX (Complete).—After dissolving 0.5 g. of IX in 20 ml. of glacial acetic acid, an excess of zinc dust was added and the mixture was heated. A pale purple color formed and persisted for some 5 min., then disappeared. The reaction mixture was kept at 100–110° for 6 hr., left to cool overnight, then reheated, and filtered. The filtrate was poured onto 100 ml. of crushed ice. The white solid isolated by filtration and drying weighed 0.15 g. (65%), and melted at 142.5–143.5°. It was identical in melting point, mixture melting point, and infrared spectrum with an authentic sample of III. This complete deiodination is a marked contrast to the complete stability of the dichloro phenol (VII) under similar conditions.

Compound IX was tested for its stability under the conditions of the quinone–active methylene compound condensation. A quarter of a gram of IX was added to a solution of 0.25 g. of anhydrous zinc chloride in 2.5 g. of anhydrous ethanol. As no color change was noted within 10 min. at room temperature, the mixture was heated gently. As the temperature neared 65°, a dark red-brown violet color appeared suddenly. Heating was continued at 75–80° for 1.5 hr., and then the solution was poured onto 50 ml. of crushed ice. Ether extracts of the resulting dark-colored solution yielded only a small amount of an unidentified dark brown oil.

Deiodination of IX (Partial).—One-quarter gram (0.53 mmole) of IX was dissolved in acetone, and to this was added a solution of potassium cyanide (0.25 g. 3.85 mmoles) which had been dissolved in 1.0 g. of water and then diluted with 5.0 g. of acetone. A yellow color formed immediately, but did not intensify even on warming to 50° for several minutes. The solvent was removed *in vacuo* and replaced with dimethyl sulfoxide; a deep yellow color formed immediately. The reaction mixture was kept at 45–50° for 4–5 hr., then poured onto 50 ml. of crushed ice and diluted to 100 ml. The crude solid which precipitated was identified as the 6-iodo derivative (X) by melting point, mixture melting point, and infrared spectrum. The recrystallized solid weighed 0.10 g. (55%), m.p. 191.5–192.5°.

6-Bromo-3-carbethoxy-5-hydroxy-2-methylbenzofuran (XII).—The reaction apparatus used was that in method B for VI, except that nitrogen was bubbled through the reaction solution, and the exiting vapors were passed through a water-rinsed gas trap. Temperature was kept at 10–15° throughout the reaction. A solution of 22.0 g. (0.10 mole) of III in chloroform was treated with a solution of 16 g. (0.10 mole) of bromine in 100 ml. of chloroform over a period of 70–80 min. The bromine color of the first 75 ml. of this reagent solution was discharged rapidly, but the last 25 ml. were discharged more slowly. The mixture was stirred an additional 20 min., poured into 500 ml. of saturated sodium bicarbonate solution, and, after stirring 10 min. longer, was filtered. The filter crop was triturated with two 100-ml. portions of 5% aqueous sodium thiosulfate solution and with three 100-ml. portions of water. After drying, the solid weighed 24.5 g. (82%). It was dissolved in 600 g. of hot acetone, treated with charcoal, then filtered hot. When cooled, filtered, and air-dried for 4 hr., the microcrystalline white solid, m.p. 191–192°, was recovered from the acetone mother liquor. The total yield of XII melting over 191° was 24.1 g. (81%). The analytical sample was recrystallized from an ethanol–acetone mixture, m.p. 192.5–193°.

Anal. Calcd. for $C_{12}H_{11}BrO_4$: C, 48.18; H, 3.71; Br, 26.72. Found: C, 48.21; H, 3.89; Br, 26.85.

The **methyl ether** of XII was prepared as described under III. Treatment of 3.1 g. of XII gave 3.4 g. of the crude methyl ether; recrystallization from a benzene–pentane mixture (9 g., 20 g.) gave 1.6 g., m.p. 122.5–123.5°. Further recrystallization from carbon tetrachloride gave a granular white solid, m.p. 126.5–127.5°.

Anal. Calcd. for $C_{13}H_{13}BrO_4$: C, 49.86; H, 4.18; Br, 25.52. Found: C, 49.94; H, 4.25; Br, 25.78.

It is interesting that bromination proceeds smoothly in chloroform without added base or catalyst. In ether, or a 3:7 mixture of ether–chloroform, brominated derivatives of III were obtained only in trace quantities, III being recovered nearly quantitatively.

3-Carbethoxy-4,6-dibromo-5-hydroxy-2-methylbenzofuran (XIII).—The same procedure was used as for XII, except that 2 equiv. of bromine were used, and the temperature was kept at 22–26°. When 5.5 g. of III was allowed to react with bromine in this way for 3 hr., a crude product weighing 7.28 g. (77%) was obtained, m.p. 116–118°. Attempted recrystallization from ethanol was accompanied by formation of an orange-brown color. The recovered solid, 6.2 g., m.p. 115–118°, was somewhat orange in color. Further purification was by molecular distillation from a 120–125° oil bath at 0.5 mm. The analytical sample, from carbon tetrachloride, was a white solid, m.p. 118–119°.

Anal. Calcd. for $C_{12}H_{10}Br_2O_4$: C, 38.13; H, 2.66; Br, 42.28. Found: C, 38.07; H, 2.82; Br, 42.10.

The **methyl ether** of XIII was prepared as indicated under III, and recrystallized first from carbon tetrachloride, then from acetone–water (charcoal). The analytical sample was recrystallized from acetone–water (0.48 g. of methyl ether, 4.0 g. of acetone, 1.8 g. of water) to give long white needles (0.38 g.), m.p. 87.5–88.5°.

Anal. Calcd. for $C_{13}H_{12}Br_2O_4$: C, 39.83; H, 3.09; Br, 40.76. Found: C, 40.36; H, 3.44; Br, 40.35.

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Degradation and Synthesis of Desosamine

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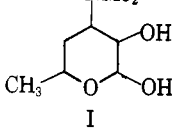
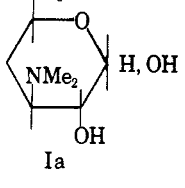
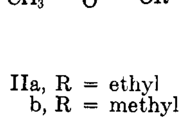
The degradation of desosamine (I) to 2-ethoxy-3,4-epoxy-6-methyl-tetrahydropyran (IVa) and the reconversion of the latter to desosamine are described. A synthesis of racemic IVa is also presented.

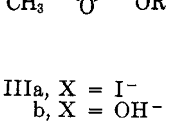
Desosamine (I), the amino sugar component of a considerable number of the macrolide antibiotics,[2,3] has recently evoked considerable interest. Foster, *et al.*, showed it to be a D-hexose.[4] Foster, *et al.*,[5] and Newman[6] presented chemical evidence which established a *trans* relationship between the C-2 hydroxyl and C-3 dimethylamino substituents, while n.m.r. studies by Hofheinz and Grisebach[7] and Woo, *et al.*,[8] established its configuration as D-*gluco* (Ia). Two nonstereospecific syntheses of I have been described,[6,9] as has its formation from 3-amino-3-deoxy-D-glucose by replacement of the C-4 and C-6 hydroxy substituents with hydrogen from suitably constituted intermediates.[10] In this paper we described, in detail, the degradation of desosamine hydrochloride (I + HCl) to 2-ethoxy-3,4-epoxy-6-methyltetrahydropyran (IVa), the synthesis of racemic IVa, and the reconversion of optically active IVa to desosamine hydrochloride (I + HCl).

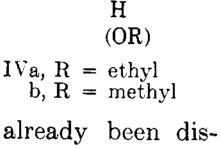

I


Ia

Ethyl desosaminide (IIa) was degraded to the epoxide IVa by pyrolysis of its quaternary hydroxide derivative IIIb which was, in turn, prepared from the corresponding methiodide IIIa. The stereochemical implication of this degradation has already been discussed.[6]


IIa, R = ethyl
b, R = methyl


IIIa, X = I^-
b, X = OH^-


IVa, R = ethyl
b, R = methyl

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