[CONTRIBUTION FROM THE COLLEGE OF PHARMACY, UNIVERSITY OF MICHIGAN]

The Action of Sulfuric Acid on Diarylphthalins. II. Mechanism of the Reaction[1]

BY F. F. BLICKE AND R. A. PATELSKI[2]

Interaction of a diarylphthalin and sulfuric acid may yield either a 9-arylanthrone-10, a 2,5-diaryl-3,4-benzofuran or a mixture of both types of compounds. Thus diphenyl-,[3] 4′,4″-dichlorodiphenylphthalin[4] and fluoranphthalin[5] are converted into anthrones while 4′,4″-dihydroxydiphenyl-,[6] 4′,4″-dimethoxydiphenyl-,[6] 2′,4″-dimethoxydiphenyl-,[7] 3′,3″,5′,5″-tetrabromo-4′,4″-dihydroxydiphenyl-,[8] 3′,3″,5′,5″-tetrabromo-4′,4″-diacetoxydiphenyl-,[9] and 4′,4″-bis-dimethylaminodiphenylphthalin[10] are transformed into benzofurans; 4′-hydroxydiphenyl-[11] and 4′-methoxydiphenylphthalin[12] yield a mixture of furan and anthrone.

The furans, when oxidized, yield 2-benzoylbenzophenones while the anthrones are converted into 9-hydroxyanthrones.

The transformation of a phthalin into a 9-arylanthrone-10, through loss of water, is readily understood but the formation of a furan is a more obscure process. In this paper we offer experimental evidence in favor of the following reaction scheme to account for the formation of a furan. According to this mechanism, illustrated in the case of 4′,4″-dimethoxydiphenylphthalin (I), the sulfuric acid converts the phthalin into the unstable 4′-methoxybenzhydrol-2-carboxylic acid (II) and anisole. Compound II changes, immediately, into 4′-methoxyphenylphthalide (III) which combines with anisole to yield either IV or V which is then converted into the furan VI through loss of water.

In support of the mechanism given we have found that a mixture of 4′-methoxyphenylphthalide (III) and anisole, when treated with sulfuric acid, yields 2,5-di-(*p*-methoxyphenyl)-3,4-benzofuran (VI) which was isolated in crystalline form; in three other instances it has been shown that a furan of type VI can be obtained from a suitable mono arylphthalide, phenol or anisole and sulfuric acid. The furans all possessed the characteristic yellow or greenish-yellow color and dissolved in organic solvents to produce highly fluorescent solutions but since many of the furans were exceedingly difficult to purify they were oxidized immediately to the corresponding 2-benzoylbenzophenones (type VII).

At present it is impossible to decide whether the intermediate, formed in the conversion of III into VI, should be represented by structure IV or V. A number of compounds, supposed to possess a structure analogous to IV, have been obtained by interaction of a mono arylphthalide and an arylmagnesium halide.[13] In many instances the initial reaction product could not be isolated since it was converted so rapidly into the furan. We attempted to synthesize V from 2-cyanobenzaldehyde and 4-anisylmagnesium iodide. The compounds reacted vigorously and a yellow-brown gum, presumably the imine of V, was obtained; this, upon hydrolysis, yielded the furan VI. From 2-cyanobenzaldehyde and phenylmagnesium bromide we obtained the crystalline imine of 2-benzoylbenzhydrol and this substance, when hydrolyzed, was converted into 2,5-diphenyl-3,4-benzofuran.

We are inclined to believe that under the conditions necessary for the hydrolysis of the imine of compound V and its phenyl analog there may be produced, successively, V, V′, IV and VI.

Two compounds analogous to IV and V are 2,2,5-triphenyl-5-hydroxy-2,5-dihydro-3,4-benzofuran (XI) and 2-benzoyltriphenylcarbinol (X). According to Barnett, Cook and Nixon[14] these compounds may represent "phases of an

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(1) This paper represents part of a dissertation to be submitted to the Graduate School by R. A. Patelski in partial fulfilment of the requirements for the degree of Doctor of Philosophy in the University of Michigan.

(2) The Upjohn Company Fellow.

(3) Baeyer, *Ann.*, **202**, 90 (1880).

(4) Blicke and Patelski, THIS JOURNAL, **58**, 274 (1936).

(5) "Beilstein," Vol. XVIII, 316 (1934); *ibid.*, Vol. XIX, 146 (1934).

(6) Blicke and Weinkauff, THIS JOURNAL, **54**, 1455 (1932).

(7) Ref. 4, p. 277.

(8) Ref. 4, p. 277.

(9) Ref. 4, p. 277.

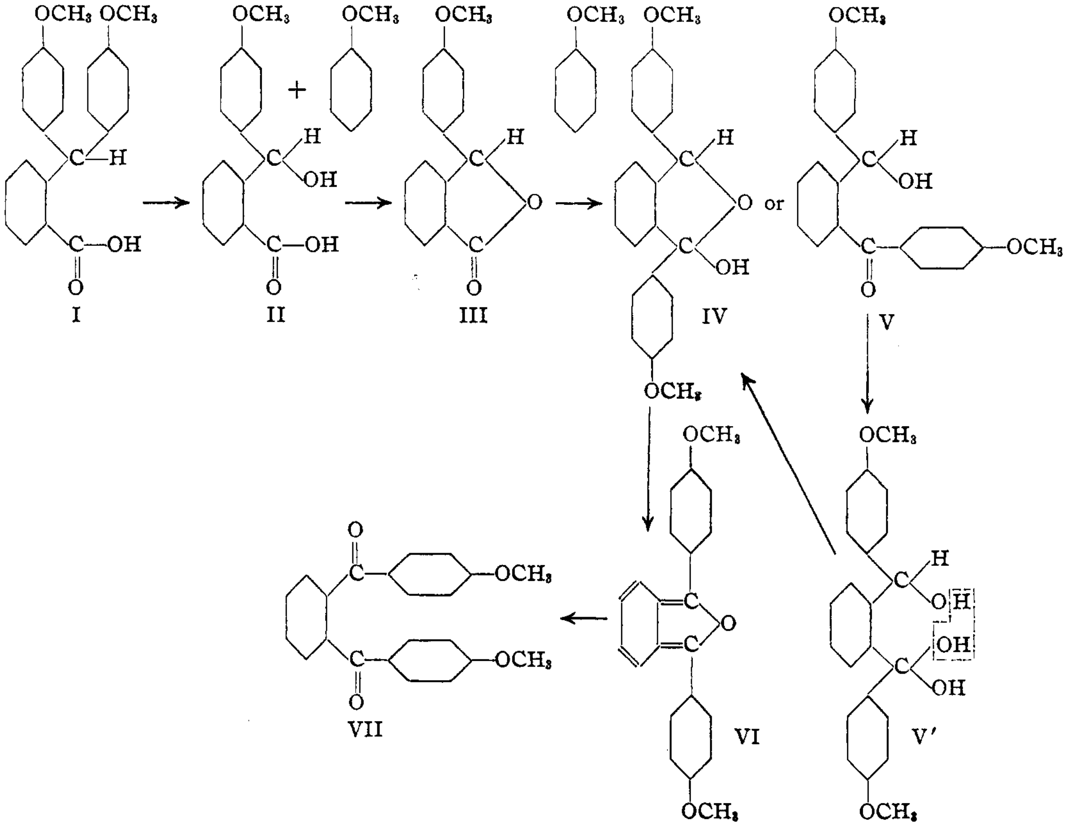
(10) Guyot and Haller, *Ann. chim. phys.*, [8] **19**, 320 (1910).

(11) From this substance von Pechmann [*Ber.*, **13**, 1616 (1880)] obtained two compounds, in a very impure state, which he claimed were 9-(4′-hydroxyphenyl)-anthrone-10 ("monoöxyphenylanthranol") and 9-hydroxy-9-(4′-hydroxyphenyl)-anthrone-10 ("monoöxyphenyloxanthranol"). We believe the first mentioned compound was a mixture of the anthrone and 2-phenyl-5-(4′-hydroxyphenyl)3,4-benzofuran and the second a mixture of the 9-hydroxyanthrone and 2-benzoyl-4′-hydroxybenzophenone.

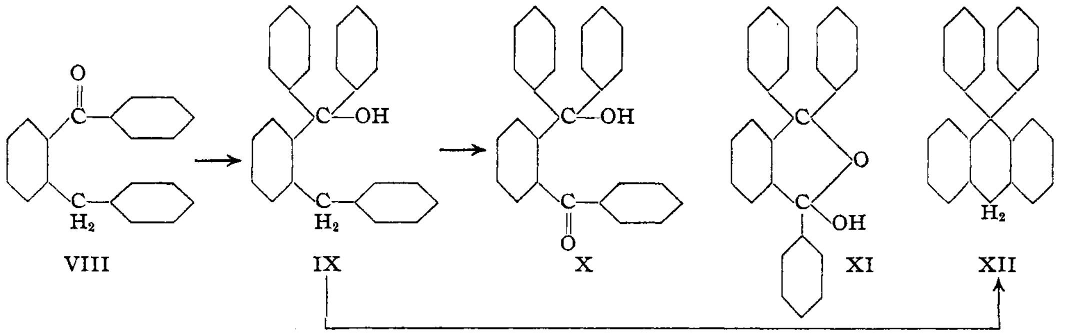
(12) Blicke and Swisher, THIS JOURNAL, **56**, 1407 (1934).

(13) Guyot and Catel, *Bull. soc. chim.*, [3] **35**, 1124 (1906); Guyot and Vallette, *Ann. chim. phys.*, [8] **23**, 369, 372, 395 (1911); Seer and Dischendorfer, *Monatsh.*, **34**, 1495 (1913); Seidel, *Ber.*, **61**, 2274 (1928); Blicke and Patelski, THIS JOURNAL, **58**, 275 (1936).

(14) Barnett, Cook and Nixon, *J. Chem. Soc.*, 506 (1927). See also "Beilstein," 4th ed., Vol. VIII, p. 223; *ibid.*, Vol. XVII, p. 149.



isodynamic change." Prepared by interaction of phenylmagnesium bromide with diphenylphthalide,[15] dimethyl phthalate,[16] diethyl phthalate,[17] methyl 2-benzoylbenzoate,[17] 2-benzoylbenzophenone, respectively,[17] or by oxidation of 2-(α-hydroxybenzyl)-triphenylcarbinol[17] the reaction product has been formulated in some cases as X, in others as XI.



We thought that compound X might be obtained by reaction of phenylmagnesium bromide with 2-benzylbenzophenone (VIII) and oxidation of the 2-benzyltriphenylcarbinol (IX) formed to the corresponding 2-benzoyl derivative (X) but 2-benzyltriphenylcarbinol,[18] obtained from 2-benzylbenzophenone and phenylmagnesium bromide, could not be oxidized to 2-benzoyltriphenylcarbinol due to the ease with which the carbinol is converted into 9,9-diphenyl-9,10-dihydroanthracene (XII); this transformation takes place when 2-benzyltriphenylcarbinol is heated for a few minutes in acetic acid solution or moistened

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(15) Guyot and Catel, *Bull. soc. chim.*, [3] **35**, 554, 562 (1906).

(16) Barnett, Cook and Nixon, *J. Chem. Soc.*, 510 (1927); see also Howell, This Journal, **42**, 2335 (1920).

(17) Vallette, Dissertation, Nancy, 1910; see Seidel, *Ber.*, **61**, 2268 (1928).

(18) An oily product, supposed to be 2-benzyltriphenylcarbinol, was obtained by Barnett, Cook and Nixon [*J. Chem. Soc.*, 504 (1927)] from esters of 2-benzylbenzoic acid; the material was converted readily into 9,9-diphenyl-9,10-dihydroanthracene.

with cold sulfuric acid; when the carbinol was boiled with dilute nitric acid 9,9-diphenylanthrone-10 was obtained.

Experimental Part

Interaction of a Mono Arylphthalide with Phenol or Anisole and Sulfuric Acid; General Procedure.—To 0.02 mole of the phthalide, dissolved in 10 cc. of concd. sulfuric acid at ordinary temperature, there was added 0.04 mole of phenol or anisole, whereupon the temperature of the mixture rose to 60–70°. The material was stirred for five minutes, the red-brown solution poured into 150 cc. of ice water and the green or yellow-green precipitated furan filtered. In the case of 2,5-di-(*p*-methoxyphenyl)-3,4-benzofuran the product can be purified easily by recrystallization from a mixture of alcohol and acetone; in all other instances the furan was oxidized to the corresponding 2-benzoylbenzophenone in the following manner: 5 g. of the crude furan, dissolved in 50 cc. of acetic acid, was treated with a mixture of 5 g. of sodium dichromate, 20 cc. of acetic acid and 1 cc. of sulfuric acid. The mixture was heated for fifteen minutes, diluted with 200 cc. of hot water, cooled and the precipitated benzophenone filtered. The crude benzophenones were digested with sodium carbonate solution and then recrystallized from alcohol.

From 4′-methoxyphenylphthalide and anisole there was obtained 2,5-di-(*p*-methoxyphenyl)-3,4-benzofuran (m. p. 125–126°[19]) in crystalline form; this was oxidized to 2-(4″-methoxybenzoyl)-4′-methoxybenzophenone, m. p. 157–159°.[20]

4′-Methoxyphenylphthalide and phenol, as well as 4′-hydroxyphenylphthalide and anisole, yielded 2-(*p*-hydroxyphenyl)-5-(*p*-methoxyphenyl)-3,4-benzofuran which was oxidized to the benzoylbenzophenone and the latter then methylated by heating 2.0 g. of the benzophenone, dissolved in 30 cc. of 10% sodium hydroxide solution, with 2.5 g. of dimethyl sulfate at 80°; the dimethyl ether melted at 157–159° after recrystallization from alcohol.

4′-Hydroxyphenylphthalide reacted with phenol to produce 2,5-di-(*p*-hydroxyphenyl)-3,4-benzofuran which was converted by oxidation into 2-(4″-hydroxybenzoyl)-4′-hydroxybenzophenone; m. p. 225–226°.[21]

The yields of the pure benzoylbenzophenones, based on the phthalide, varied from 20–35% of the calcd. amount.

Interaction of phenylphthalide with phenol or anisole yielded a green, gummy product which dissolved in organic solvents to produce the yellow-green fluorescence characteristic of benzofurans; however, the material consisted mainly of unchanged phenylphthalide with only a trace of the furan since oxidation of the product yielded 2-benzoylbenzoic acid.

The mono arylphthalides were prepared by reduction of the 2-benzoylbenzoic acids. Since many of the corresponding 2-benzylbenzoic acids possess melting points almost identical with those of the phthalides, care must be taken to prevent mistakes in identity.

2-Cyanobenzal Bromide.—Fifty-eight grams of *o*-tolunitrile[22] was heated, in a bath, to 180–200°, stirred mechanically and 60 cc. of bromine introduced below the surface of the liquid during the course of two hours. Dry air was then blown into the hot mixture for one-half hour. The crude, semi-solid product was digested with hot alcohol and the alcoholic solution boiled with charcoal. There was obtained 55 g. of pure product; m. p. 64–65°.[23]

2-Cyanobenzaldehyde.—To 34 g. of silver nitrate, dissolved in 150 cc. of 95% alcohol, there was added, portionwise, 27.5 g. of 2-cyanobenzal bromide, dissolved or 150 cc. of the same solvent. The mixture was heated for one-half hour on a steam-bath, the silver bromide removed and the alcoholic solution concentrated to a volume of 50 cc. After the addition of water the product soon separated from the mixture in the form of needles; the aldehyde melted at 108–109° after recrystallization from alcohol; yield 6.6 g. The material is very soluble in ether, benzene and acetic acid.

The *p*-bromophenylhydrazone was obtained in the following manner. A mixture of 7 g. of *p*-bromophenylhydrazine, 2 g. of the cyanoaldehyde and 20 cc. of alcohol was refluxed for three hours and the yellow crystalline precipitate separated from the hot solution, washed with alcohol and recrystallized from the same solvent; m. p. 194–195°.

Anal. Calcd. for $C_{14}H_{10}N_3Br$: Br, 26.66. Found: Br, 26.67.

2-Cyanobenzaldehyde and Phenylmagnesium Bromide.—Four grams of the aldehyde, suspended in 80 cc. of ether, was added to phenylmagnesium bromide, prepared from 10.5 g. of bromobenzene, 1.6 g. of magnesium and 40 cc. of ether. After the vigorous reaction had subsided the mixture was heated for ten hours on a steam-bath. The crystalline material which had formed was removed by filtration, washed with ether, treated with ice and ammonium chloride and recrystallized from alcohol; yield 7.5 g. This substance, the imine of 2-benzoylbenzhydrol, melted at 126–127° after recrystallization from alcohol.

Anal. Calcd. for $C_{20}H_{17}ON$: N, 4.87. Found: N, 4.83.

In order to hydrolyze the imine, a mixture of 5 g. of the material, 10 cc. of acetone and 3 cc. of hydrochloric acid was heated for ten minutes on a steam-bath and the yellow, crystalline precipitate recrystallized from alcohol. This substance possessed the characteristic properties of 2,5-diphenyl-3,4-benzofuran; mixed m. p. 125–126°[24]; yield of pure product 3.5 g. Upon oxidation of 3.5 g. of the furan with sodium dichromate 2.8 g. of 2-benzoylbenzophenone was obtained; mixed m. p. 147–148°.

2-Cyanobenzaldehyde and 4-Anisylmagnesium Iodide.—Three grams of the aldehyde, suspended in 50 cc. of ether, was added to the Grignard reagent obtained from 11.9 g. of 4-iodoanisole, 1.2 g. of magnesium, 80 cc. of ether and 10 cc. of dry benzene. The precipitate obtained, after the mixture had been heated for six hours, was filtered and decomposed with ice and ammonium chloride. The yellow-brown gummy imine produced possessed a yellow-green fluorescence when dissolved in organic solvents, which indicated the presence of the benzofuran. A mixture of 5.5 g. of the crude imine, 20 cc. of acetone

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[19] Ref. 6, reported 126–127°.

[20] The same melting point was found by Blicke and Weinkauff.

[21] Blicke and Weinkauff, Ref. 6, m. p. 225–226°.

[22] "Organic Syntheses," Vol. IV, p. 69, 1925.

[23] Fuson [This Journal, **48**, 1096 (1926)] reported 63–64°.

[24] Guyot and Catel [*Bull. soc. chim.*, [3] **35**, 1127 (1906)] reported 125°.

and 5 cc. of hydrochloric acid was heated for twenty-five minutes, diluted with an equal volume of water and the yellow, crystalline precipitate of 2,5-di-(*p*-methoxyphenyl)-3,4-benzofuran recrystallized from alcohol; mixed m. p. 126–127°.[25]

When oxidized the furan yielded 2-(4″-methoxyphenyl-4′-methoxybenzophenone; mixed m. p. 157–158°.

2-Benzyltriphenylcarbinol.—To phenylmagnesium bromide, prepared from 3.5 g. of bromobenzene, 0.5 g. of magnesium and 20 cc. of ether, there was added 3.0 g. of 2-benzylbenzophenone,[26] dissolved in 20 cc. of ether. The mixture was heated for three hours, the crystalline precipitate filtered, decomposed with ice and ammonium chloride and the crystalline 2-benzyltriphenylcarbinol recrystallized from alcohol; m. p. 133–134°.

Anal. Calcd. for $C_{26}H_{22}O$: C, 89.09; H, 6.33. Found: C, 88.70; H, 6.35.

The carbinol turns orange-red when moistened with concd. sulfuric acid and then rapidly becomes colorless due to the formation of 9,9-diphenyl-9,10-dihydroanthracene; mixed m. p. 195–196°.[27] The same transformation was effected when an acetic acid solution of the carbinol was boiled for three minutes. To identify the dihydroanthracene further, a portion was oxidized with sodium dichromate and sulfuric acid in acetic acid to 9,9-diphenylanthrone-10; mixed m. p. 191–192°.[28]

A mixture of 0.5 g. of 2-benzyltriphenylcarbinol, 10 cc. of water and 5 cc. of nitric acid was refluxed for three hours and the crystalline 9,9-diphenylanthrone-10 obtained recrystallized from acetic acid; mixed m. p. 191–192°; when reduced with zinc dust and acetic acid the anthrone was reduced to 9,9-diphenyl-9,10-dihydroanthracene; mixed m. p. 194–195°.

Summary

A reaction mechanism has been suggested to account for the formation of a 2,5-diaryl-3,4-benzofuran from the interaction of certain diarylphthalins and sulfuric acid.

In two instances it has been shown that a 2,5-diaryl-3,4-benzofuran can be obtained by reaction of an arylmagnesium halide with 2-cyanobenzaldehyde; 2-benzyltriphenylcarbinol can be converted very readily into 9,9-diphenyl-9,10-dihydroanthracene.

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(25) Blicke and Weinkauff [THIS JOURNAL, **54**, 1458 (1932)] reported the same melting point.

(26) Seidel, *Ber.*, **61**, 2275 (1928).

(27) Liebermann and Lindenbaum [*ibid.*, **38**, 1803 (1905)] reported 195–196°, Barnett, Cook and Nixon [*J. Chem. Soc.*, 508 (1927)] 200°. Although the melting points of 9,9-diphenyl-9,10-dihydroanthracene and 9,9-diphenylanthrone are nearly identical, we found that a mixture composed of equal parts of the two substances melted at 170–175°.

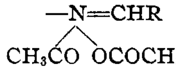
(28) Haller and Guyot [*Bull. soc. chim.*, [3] **17**, 878 (1897)] and Copisarow [*J. Chem. Soc.*, **111**, 17 (1917)] reported 192°.

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF COLORADO]

The Action of Acetic Anhydride upon Dibenzylidenehydrazine[1]

BY JOHN B. EKELEY AND J. WILLIAM LEFFORGE

The addition of acetic anhydride to the group —N═CHR (R = aryl) might occur in one of the following ways



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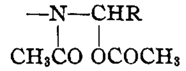
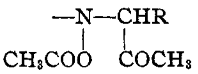


$$\begin{array}{ll} \text{—N—} & \text{CHR} \\ \quad | & \ \ | \\ \text{CH}_3\text{CO} & \text{OCOCH}_3 \end{array}$$

II



$$\begin{array}{ll} \text{—N—} & \text{CHR} \\ \quad | & \ \ | \\ \text{CH}_3\text{COO} & \text{COCH}_3 \end{array}$$

III

There is no evidence pointing to III.

Passerini and Macentcelli[2] assumed I in the addition of the anhydride to benzylideneaniline from the analogous addition of bromine as shown by James[3] and others. The above assumption was disputed by Ekeley, Swisher and Johnson,[4] who pointed out that the work of Ekeley and others[5] showed that in the case of benzylideneanthranilic acid the anhydride adds as in II.

The experimental observations herein recorded point definitely to II, since they show that from a reaction mixture of one mole of dibenzylidenehydrazine and three moles of acetic anhydride there can be isolated 14% 2,5-dimethyl-1-oxy-3,4-diazole, 19% of *sym*-diacetylhydrazine, and 40% of benzylideneacetylhydrazine based on one mole of dibenzylidenehydrazine.

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(1) Several years ago the senior author heated 20 g. dibenzylidenehydrazine intermittently with excess acetic anhydride. After each cooling of the solution the dibenzylidenehydrazine separated out unchanged. After some ten heatings, the boiling solution was forgotten on the hot plate. When later discovered all the acetic anhydride had been driven off and a colorless high boiling liquid was condensing and running down the sides of the flask, all of the dibenzylidenehydrazine having disappeared. On being cooled, the liquid solidified to a grayish white crystalline solid (high yield) which was easily separated into two colorless crystalline substances of different solubilities, melting points and composition, both containing nitrogen. After recrystallization many times, many checking analyses were obtained for each, which did not correspond to any possible compounds. After the products were used up, very many attempts to repeat the reaction failed, no reaction whatever being observed.

(2) Passerini and Macentcelli, *Gazz. chim. ital.*, **58**, 64 (1929).

(3) James, *Ber.*, **32**, 2277 (1899).

(4) Ekeley, Swisher and Johnson, *Gazz. chim. ital.*, **62**, 81 (1932).

(5) THIS JOURNAL, **34**, 161 (1912); **35**, 282 (1913); **36**, 603 (1914); **37**, 582 (1915); **44**, 1756 (1922).