ous solution was acidified with hydrochloric acid and the *o*-nitrobenzene sulfone anilide precipitate was recrystallized twice from alcohol. The yield was 64 g. (85%). The dimethylaniline was removed from the ether layer by washing it three times with dilute hydrochloric acid, neutralizing this solution with sodium hydroxide, and extracting the free amine with ether. The ether solution was dried and distilled. The yield of dimethylaniline was 21.4 g. (85%). The ether solution containing the *o*-nitrobenzene sulfone methyl anilide was concentrated and a dark, dirty red-brown product was obtained which was then treated with alcoholic sodium hydroxide to hydrolyze any disulfone derivative that might have been formed from the aniline. This solution was then diluted with water and extracted three times with ether, the ether evaporated and the resulting red-brown solid was recrystallized three times from alcohol. The yield of the pure *o*-nitrobenzene sulfone methyl anilide was 52 g. (74%).

The two purified yields of the above *o*-nitrobenzene sulfonanilide and methyl anilide were then subjected to the concentrated alkali hydrolysis procedure as described previously (80 g. of sodium hydroxide and 20 cc. of water). The distillates of aniline and methylaniline were extracted with ether, dried and distilled. The yield of aniline was 15.3 g. and of methylaniline 13.1 g. The percentage yield of aniline for this reaction was 71% and for methylaniline, 70%. The over-all yield of aniline was 61.2% while that of methylaniline was 52.4%.

Summary

Substituted benzenesulfonanilides containing nitro groups ortho or para to the sulfone group may be decomposed by concentrated alkali to the amine, nitrophenol and sodium sulfite. This cleavage between the carbon of the ring and the sulfur atom offers a different mode of decomposition from previous hydrolyses which attempted cleavage between the sulfur and nitrogen. It was found that an ortho-nitro group is more effective than a para-nitro group and that a meta-nitro group has little effect. The 2,4-dinitrobenzenesulfonanilides were very readily cleaved by alkali.

A mixture of primary, secondary and tertiary amines may be separated satisfactorily by means of *o*-nitrobenzenesulfonchloride and the amines recovered from the sulfonamides in good yields.

URBANA, ILL. RECEIVED JULY 10, 1933

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF KANSAS]

Iodo Derivatives of Diphenyl Ether. I. The Mono- and Certain Diiodo-Derivatives of Diphenyl Ether, and of 2- and 4-Carboxy Diphenyl Ethers[1]

BY R. Q. BREWSTER AND FRANKLIN STRAIN

The properties of the iodo derivatives of diphenyl ether, of which only a few have been prepared in connection with other researches, merit investigation not only from the standpoint of pure chemistry, but also from that of physiology, since Harington and Barger[2] have shown that the molecular structure of thyroxine is built upon a diphenyl ether nucleus containing four iodine atoms. Accordingly a systematic study of iodo derivatives of diphenyl ether, including those containing amino, hydroxyl and carboxyl groups, has been begun in this Laboratory. The present paper describes the three mono-iodo substitution products, five of the diiodo derivatives of diphenyl ether, and five of the iodo compounds of 2- and 4-carboxydiphenyl ethers, together with the intermediate nitro and amino compounds used in the syntheses.

Incidentally in the preparation of these substances the orienting influences of the carboxyl group and of the iodine atom, upon further substitution in the diphenyl ether nuclei, were found to conform to the general results obtained by other investigators[3] in their studies upon the orienting influences of other substituents in the diphenyl ether series.

The substances here reported, except possibly some of the iodo-carboxy compounds upon which tests are not yet complete, do not possess any marked physiological activity.

Experimental Part

The substances described here were for the most part prepared by well-known methods, any description of which is therefore omitted, and the process is recorded in the tabulated results only by letter, as follows: A, diazotization plus potassium iodide (Sandmeyer); B, same as A plus acetic acid as a solvent; C, iodination with iodine

---

[1] From the thesis of Franklin Strain, presented in partial fulfilment of the requirements for the degree of Doctor of Philosophy, June, 1933.

[2] Harington and Barger, *Biochem. J.*, **21**, 169 (1927).

[3] Lea and Robinson, *J. Chem. Soc.*, **129**, 376 and 411 (1926); Scarborough and collaborators, *ibid.*, **132**, 2361 (1929); **133**, 1202 (1930); **134**, 529 (1931); Henley and Turner, *ibid.*, **133**, 928 and 1115 (1930).

TABLE

IODO DERIVATIVES OF DIPHENYL

No	Ref.	Compound	Source
I	4	2-Iododiphenyl ether	2-Aminodiphenyl ether
II		3-Iododiphenyl ether	3-Aminodiphenyl ether
III	5	4-Iododiphenyl ether	ICl, 250 g.; diphenyl ether
IV	7	2-Iodo-4'-nitrodiphenyl ether	I
V	9	4-Iodo-4'-nitrodiphenyl ether	III
VI	10	2-Iodo-4'-aminodiphenyl ether	IV
VII		2-Iodo-4'-acetylaminodiphenyl ether	VI
VIII	11	2,4'-Diiododiphenyl ether	I
IX	12, 13	2-Nitro-4'-iododiphenyl ether	ICl, 25 g.; 2-nitrodiphenyl ether
X		3,4'-Dinitrodiphenyl ether	*p*-Nitrofluorobenzene, 28 g.; *m*-Nitrophenol-K
XI		3,4'-Diaminodiphenyl ether	X
		Diacetyl derivative of XI	XI
XII	14	3,4-Diiododiphenyl ether	XI
XIII		4-Phenoxyphenylurethan	4-Aminodiphenyl ether, $ClCOOC_2H_5$
XIV	15	4-(4-Iodophenoxy)-phenylurethan ($IC_6H_4OC_6H_4NHCOOC_2H_5$)	ICl, 12 g.; XIII
XV		4-(4-Iodophenoxy)-monophenyl urea ($IC_6H_4OC_6H_4NHCONH_2$)	4-Iodo-4'-aminodiphenyl ether and KNCO
XVI	5, 6	4,4'-Diiododiphenyl ether	ICl, 8.5 g.; III
XVII	16	2-Amino-4-nitrodiphenyl ether	2,4-Dinitrodiphenyl ether
XVIII		2-Iodo-4-nitrodiphenyl ether	XVII
XIX	17	2-Iodo-4-aminodiphenyl ether	XVIII
XX		2-Iodo-4-acetylaminodiphenyl ether	XIX
XXI		2,4-Diiododiphenyl ether	XIX
XXII	5, 19	3-Nitro-4-acetaminodiphenyl ether	4-Acetaminodiphenyl ether
XXIII	19	3-Amino-4-acetaminodiphenyl ether	XII
XXIV		3-Nitro-4-aminodiphenyl ether	XXII
XXV	20	3,4-Diaminodiphenyl ether	XXIV
		Diacetyl derivative of XXV	XXV or XXIII
XXVI		3-Nitro-4-iododiphenyl ether	XXIV
XXVII	21	3-Amino-4-iododiphenyl ether	XXVI
		Acetyl derivative of XXVII	XXVII
XXVIII	22	3,4-Diiododiphenyl ether	XXVII
XXIX		2-Phenoxybenzoic acid	Note 23
XXX		2-(4-Nitrophenoxy)-benzaldehyde	Note 24
XXXI	25	2-(4-Nitrophenoxy)-benzoic acid	XXX
XXXII		2-(4-Aminophenoxy)-benzoic acid	XXXI
		Acetyl derivative of XXXII	XXXII
XXXIII	26	2-(4-Iodophenoxy)-benzoic acid	ICl, 32.5 g.; XXIX
XXXIV		2-Iodoxanthone	XXXIII
XXXV		2-Phenoxy-5-nitrobenzoic acid	See note 29
XXXVI		2-Phenoxy-5-aminobenzoic acid	XXXV
	30	Acetyl derivative of XXXVI	XXXVI
XXXVII	31	2-Phenoxy-5-iodobenzoic acid	XXXVI
XXXVIII		2-(2-Nitrophenoxy)-benzaldehyde	See note 32
XXXIX		2-(2-Nitrophenoxy)-benzoic acid	XXXVIII
XL	33	4-Nitroxanthone	XXXIX
XLI		2-(2-Aminophenoxy)-benzoic acid	XXXIX
		Acetyl derivative of XLI	XLI
XLII		2-(2-Aminophenoxy)-benzoic acid lactam	XLI
XLIII		2-(2-Iodophenoxy)-benzoic acid	XLI
XLIV		4-(4-Iodophenoxy)-benzoic acid	4-(4-Aminophenoxy)-benzoic acid[35]
XLV		2-(4-Iodophenoxy)-5-nitrobenzoic acid	ICl, 9 g.; XXXV
XLVI		2-(4-Iodophenoxy)-5-aminobenzoic acid	XLV
XLVII		2-(4-Nitrophenoxy)-5-nitrobenzoic acid	XXXV
XLVIII		2-(4-Iodophenoxy)-5-iodobenzoic acid	XLVI

---

(4) Clarkson and Gomberg, THIS JOURNAL, **52**, 2885 (1930).

(5) Scarborough, *J. Chem. Soc.*, **132**, 2361 (1929).

(6) Fractionation gives 62 g. of unchanged diphenyl ether, 256 g. of II, b. p. 163° (3 mm.), and 80 g. of XVI, b. p. 210–215° (3 mm.).

(7) Also prepared from *p*-nitrofluorobenzene[8] and *o*-iodophenol, thus proving constitution.

(8) Rarick, Brewster and Dains, THIS JOURNAL, **55**, 1289 (1933).

I

ETHER AND THEIR INTERMEDIATES

G.	Procedure	Cryst. solvent	Yield, g.	M. p., °C.	Formula	Analyses, % Calcd.	Analyses, % Found	
37	A	Ligroin	35	56				
14	A		15.2	Oil	$C_{12}H_9OI$	I, 42.88	42.93	42.60
250	C	Ligroin	256^{6}	47				
23	D	95% EtOH	10	104	$C_{12}H_8O_3NI$	I, 37.22	37.24	
29.6	D	Ligroin	25.5	70	$C_{12}H_8O_3NI$	I, 37.22	37.32	
10	E	Ligroin	8.5	69	$C_{12}H_{10}ONI$	I, 40.81	40.90	
		EtOH		150	$C_{14}H_{12}O_2NI$	I, 35.95	35.92	
15	C	EtOH–Ether	15	48	$C_{12}H_8OI_2$	I, 60.18	60.32	
32	C	Ligroin	40	86				
30	F	Benzene	39	123	$C_{12}H_8O_5N_2$	N, 10.77	10.90	10.91
15	G	EtOH	9.8	72	$C_{12}H_{12}ON_2$	N, 14.00	13.92	13.75
		EtOH		192	$C_{16}H_{16}O_3N_2$	N, 9.86	9.89	9.84
4.5	A		4.7	Oil	$C_{12}H_8OI_2$	I, 60.18	60.25	60.10
	Usual			63	$C_{15}H_{15}O_3N$	N, 5.45	5.40	5.38
13.6	C	EtOH	14	126	$C_{16}H_{14}O_3NI$	I, 33.14	33.01	33.09
	Usual	EtOH		201	$C_{13}H_{11}O_2N_2I$	I, 35.85	36.07	
14.8		Ligroin	19.5	139	$C_{12}H_8OI_2$	I, 60.18	60.09	
104	E	EtOH	30	107				
11.5	B	EtOH	11.6	61	$C_{12}H_8O_3NI$	I, 37.22	37.30	
8	E		7.1	Oil	$C_{12}H_{10}ONI$	I, 40.81	40.79	
	Usual	Ligroin	Quant.	120	$C_{14}H_{12}O_2NI$	I, 35.95	36.12	
2.8	B		2.9	Oil	$C_{12}H_8OI_2$	I, 60.18	60.13	60.05
50	^{18}	EtOH	55	104				
24.2	H	EtOH	23.9	126	$C_{14}H_{14}O_2N_2$	N, 11.58	11.43	11.68
54.4	Hy.Ba(OH)$_2$	50% EtOH	43	82				
10	H	Ligroin	8.3	69	$C_{12}H_{12}ON_2$	N, 14.00	14.05	14.02
	Usual	EtOH		188	$C_{16}H_{16}O_3N_2$	N, 9.86	9.96	9.89
34.5	B		36	Oil	$C_{12}H_8O_3NI$	I, 37.22	37.24	
17.1	I		12	Oil	$C_{12}H_{10}ONI$	I, 40.81	40.91	
	Usual	EtOH		144	$C_{14}H_{12}O_2NI$	I, 35.95	35.71	
3	B		2.5	Oil	$C_{12}H_8OI_2$	I, 60.18	60.55	
		EtOH		112	$C_{13}H_9O_4N$	N, 5.76	5.83	5.96
20	J	Benzene	15	157	$C_{13}H_9O_5N$	N, 5.41	5.29	5.33
26	H		19	180	$C_{13}H_{11}O_3N$	N, 6.11	5.95	6.02
	Usual			185	$C_{15}H_{13}O_4N$	N, 5.17	5.14	5.23
42.8	C^{27}	50% EtOH	40	143	$C_{13}H_9O_3I$	I, 37.32	37.04	37.10
5	^{28}	EtOH	4	156	$C_{13}H_7O_2I$	I, 39.40	39.35	39.46
26	H	EtOH	22	164	$C_{13}H_{11}O_3N$	N, 6.11	6.09	6.21
	Usual	Abs. EtOH		165	$C_{15}H_{13}O_4N$	N, 5.17	5.28	5.11
10.8	B	Ligroin	10	148	$C_{13}H_9O_3I$	I, 37.32	37.58	37.20
		Ligroin	105	77	$C_{13}H_9O_4N$	N, 5.76	5.66	5.88
20	J	Benzene	16	153	$C_{13}H_9O_5N$	N, 5.41	5.31	5.25
5		HAc	4	190	$C_{13}H_7O_4N$	N, 5.80	5.67	5.65
18	H	EtOH	14.1	153	$C_{13}H_{11}O_3N$	N, 6.11	6.10	6.12
	Usual	EtOH		179	$C_{15}H_{13}O_4N$	N, 5.17	5.27	5.11
5	^{34}	50% EtOH	4.5	211	$C_{13}H_9O_2N$	N, 6.64	6.62	6.67
5	A	Ligroin	5	133	$C_{13}H_9O_3I$	I, 37.32	37.13	37.00
10	B	Benzene	12	217	$C_{13}H_9O_3I$	I, 37.32	37.07	37.18
11.4	C	50% EtOH	11	178	$C_{13}H_8O_5NI$	I, 32.97	33.15	33.26
5	^{36,37}	50% EtOH	4	185	$C_{13}H_{10}O_3NI$	I, 35.76	35.48	35.78
15	^{38,39}		10	Note 37	$C_{12}H_8O_7N_2$	N, 9.21	9.17	
5	B^{40}	Ligroin	4.5	176	$C_{13}H_8O_3I_2$	I, 54.50	54.52	54.28

---

(9) Also obtained in 81 g. yield from 64.5 g. of 4-nitrodiphenyl ether and 50 g. of ICl; procedure C; b. p. 214° (3 mm.).

(10) B. p. of VI, 198° (3 mm.); hydrochloride m. p. 216-217°.

(11) The position of the two iodine atoms in VIII was established by synthesis in 75% yield from VI; procedure C; b. p. of VIII, 235° (20 mm.).

(12) McCombie, Macmillan and Scarborough, *J. Chem. Soc.*, **134**, 529 (1931).

TABLE II

PHYSICAL PROPERTIES OF ABOVE COMPOUNDS WHICH ARE LIQUIDS

Compound	B. p., °C.	Density (25°)	Refractive index (n^{20})
II	155 (3 mm.) 194–196 (20 mm.)	1.616	1.643
XII	200 (3 mm.)	2.051	1.696
XIX	203 (3 mm.)	1.667	1.677
XXI	198 (3 mm.)	2.056	1.700
XXVI	195 (3 mm.)	1.722	1.657
XXVII	188 (3 mm.)	1.664	1.676
XXVIII	208 (3 mm.)	2.055	1.700

monochloride in glacial acetic acid solution; time of heating one or two hours; D, nitration of some of these iodine derivatives often eliminated iodine, but nitration with fuming nitric acid (sp. gr. 1.52) in a solution of equal parts of acetic acid and acetic anhydride was found to give the desired iodo-nitro compounds if the temperature was maintained at 40–50° (not higher) for twenty minutes; E, reduction with stannous chloride and hydrochloric acid. F, heating the dry potassium salt of a phenol with a slight excess of *p*-nitrofluorobenzene and copper powder at about 150° for fifteen minutes (5); G, reduction with tin and hydrochloric acid; H, reduction with hydrogen and a platinum catalyst; I, reduction in dry ether solution with anhydrous stannous chloride and gaseous hydrogen chloride; J, oxidation with sodium dichromate and sulfuric acid.

Summary

A number of iodo derivatives of diphenyl ether have been prepared and their properties studied. Further work in this series is in progress.

LAWRENCE, KANSAS RECEIVED JULY 13, 1933

---

(13) This compound has been prepared by others,[12] using this method, but the position of the iodine atom was not proved. We find that reduction of IX and deamination of the resulting 2-amino-4′-iododiphenyl ether by the diazo method gives 4-iododiphenyl ether (III), and also that the 2-amino-4′-iododiphenyl ether is readily converted into 2,4′-diiododiphenyl ether (VIII) by the Sandmeyer process, thus proving the constitution of IX.

(14) The same product was obtained in 70% yield by the iodination of II, method C.

(15) Also obtained from 4-iodo-4′-aminodiphenyl ether and ethyl chlorocarbonate.

(16) This product was evidently obtained by Bogert and Evans, *Ind. Eng. Chem.*, **18,** 299–302 (1926), who regarded it as 2-nitro-4-aminodiphenyl ether, but that it is actually the 2-amino-4-nitro compound was shown by the fact that deamination by us through the diazo process yielded 4-nitrodiphenyl ether, identical by mixed melting point with a known sample.

(17) Hydrochloride of XIX, m. p. 245°.

(18) Obtained in quantitative yield by nitration in acetic acid solution

(19) Oesterlin, *Monatsh.*, **57,** 31–44 (1931).

(20) Also obtained by simultaneous hydrolysis and reduction of XXII with zinc dust and potash in dilute ethyl alcohol solution, recorded m. p. 66°.[19]

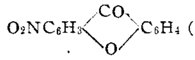
(21) In order to prevent loss of iodine an excess of stannous chloride must be avoided.

(22) Attempts to prepare this compound from XXV by the Sandmeyer method were unsuccessful.

(23) The following procedure allows this substance to be prepared in larger quantities than in five-gram lots as described in the literature [*Ber.*, **37,** 854 (1904)]. A mixture of 156 g. of *o*-chlorobenzoic acid, 90 g. of sodium hydroxide, 400 g. of phenol and 1 g. of copper powder contained in a copper flask fitted with an air reflux condenser, thermometer and efficient mechanical stirrer, was gradually heated to 190° where the temperature was maintained for fifteen minutes. After cooling and acidification with dilute sulfuric acid, the excess phenol was removed by distillation in steam and the crude 2-phenoxybenzoic acid recrystallized from ligroin; yield, 130–140 g.; m. p. 112–113°.

(24) To 120 g. of *p*-nitrochlorobenzene heated to 165–170°, was added in small portions with stirring 56 g. of the dry potassium salt of salicylic aldehyde and the temperature then raised to 190–200° where it was maintained for six hours. The excess *p*-nitrochlorobenzene was removed by steam distillation and the solid residue crystallized from 95% ethyl alcohol; yield, 55 g.

(25) This nitro acid was also obtained in 62% yield from XXIX (21.4 g.) by stirring for six to eight hours with 125 cc. of nitric acid (sp. gr. 1.42), keeping the initial temperature at 40–45°. The nitration product was proved to be 2-(4-nitrophenoxy)-benzoic acid by the fact that although different from the known 2-phenoxy-5-nitrobenzoic acid (XXXVI) both of these compounds gave quantitative yields of 2-nitroxanthone,



$O_2NC_6H_3\left<\begin{matrix}CO\\O\end{matrix}\right>C_6H_4$ (Ref. 28).

(26) Also obtained in 70% yield from XXXII, procedure A.

(27) Heated for ten hours.

(28) Heated with 25 cc. of concentrated sulfuric acid at 100° for ten minutes.

(29) The former method [*Ber.*, **30**, 738 (1897)] for the preparation of this acid may be improved by the following modification. Potassium hydroxide (40 g.) and 125 g. of phenol are heated to 160° to eliminate part of the water, cooled to 120° and 50 g. of 2-chloro-5-nitrobenzoic acid added with 0.2 g. of copper powder. The whole is then boiled gently with a reflux condenser for two hours and worked up as usual.

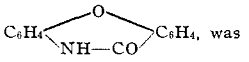
(30) This acetyl derivative crystallizes from hot water or dilute alcohol as a monohydrate, m. p. 111°. *Anal.* Calcd. for $C_{15}H_{13}O_4N{\cdot}H_2O$: N, 4.83. Found: N, 4.82, 4.73.

(31) This acid readily gives XXXIV when warmed with concentrated sulfuric acid

(32) 2-Nitrochlorobenzene (215 g.) and 100 g. of the dry potassium salt of salicylic aldehyde were used in same manner as Note 24.

(33) Recorded m. p. 127°, *J. Chem. Soc.*, **117,** 1057 (1920).

(34) This lactam,



$C_6H_4\left<\begin{matrix}O\\NH{-}CO\end{matrix}\right>C_6H_4$, was obtained by five minutes of heating of XLI to 215° or the acetyl derivative of XLI to 250°.

(35) Obtained in good yield from *p*-nitrofluorobenzene and *p*-hydroxybenzoic acid (Ref. 8) and reduction (Procedure H).

(36) Reduction of XLV to XLVI was accomplished in glacial acetic acid solution with iron powder.

(37) This same product was prepared by the action of 2 mols of iodine monochloride (Procedure C) on 2-phenoxy-5-acetylaminobenzoic acid hydrate (acetyl derivative of XXXVI). The acetyl group was removed during the reaction and the main product was XLVI.

(38) Nitration in the ordinary way with nitric acid (sp. gr. 1.42) and concentrated sulfuric acid. The acid XLVII was purified by precipitation from its barium salt. This acid XLVII was also obtained by nitration of XXXI, thus proving the location of both nitro groups.

(39) Acid XLVII could be obtained in two modifications. Crystallization from 50% acetic acid solution gave the α form, m. p. 158°, while precipitation of the acid from aqueous solutions of its sodium salt gave the β form, m. p. 170–171°. By maintaining the α form at a temperature just above its melting point it was soon converted into the β form. Recorded m. p. of this substance, 153°.

(40) Reduction of both nitro groups in XLVII and replacement of each by iodine (Sandmeyer) gives the diiodo acid (XLVIII), as also does iodination of XXXVII (Procedure C).