next placed in a bottle and sufficient toluene was added to prevent mold growth. The bottle, stoppered with cork, was kept at a temperature of 35–40° for ten days.

At the end of the hydrolysis period[12] (usually less than ten days) the calculated amount of dilute sulfuric acid was added to set free the galacturonic acid from its sodium salt. The hydrolyzate was clarified by filtration using infusorial earth as a filter aid and was concentrated to a thick sirup under vacuum. The sirup was purified by the addition of five volumes of 95% ethanol and three volumes of ethyl ether, which precipitated sodium sulfate, ethanol insoluble fractions of the enzyme preparation, and any unhydrolyzed polygalacturonic acid. After standing for twelve hours the ethanol–ether solution of galacturonic acid was decanted from the residue and evaporated to a thick sirup under vacuum. Crystallization,[13] which required approximately twenty-four hours for completion, was hastened by adding small amounts of 95% ethanol and seeding with a few crystals of galacturonic acid. The acid was triturated with cold 90% ethanol, filtered, and washed with ethanol. It was purified further by dissolving in 50% ethanol, treating with charcoal, filtering, and recrystallizing after the addition of sufficient ethanol to make the ethanol concentration 75%. The yield from 75 g. of polygalacturonic acid was 20 g. of the purified product. The m. p. was 113–115° (uncorr.).[14]

Acknowledgment.—The writers are indebted to the California Fruit Growers Exchange, Research Department, Ontario, California for citrus pectin, to General Foods Corporation, New York City, for apple pectin, and to Röhm and Haas Co., Bristol, Penna., for pectinase preparations. Acknowledgment is also made to Dr. I. A. Manville, University of Oregon School of Medicine, for helpful suggestions and criticisms.

Summary

A method has been developed for the quantity preparation of *d*-galacturonic acid by the action of a pectinase enzyme on polygalacturonic acid.

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[12] Indicated by treating a test portion with fresh enzyme for twenty-four hours and showing no increased reduction of Fehling's solution over previous samples.

[13] Direct crystallization of α-*d*-galacturonic acid from the purified hydrolyzate depends upon the use of starting materials which will not yield substances such as sugars interfering with crystallization.

[14] Link and Nedden, *J. Biol. Chem.*, **94**, 307 (1931).

PULLMAN, WASHINGTON RECEIVED APRIL 15, 1939

[CONTRIBUTION FROM THE BAILEY CHEMICAL LABORATORY OF THE UNIVERSITY OF KANSAS]

Iodo Derivatives of Phenyl Ether. II. Studies in Orientation

BY R. Q. BREWSTER AND H. S. CHOGUILL

Substances containing two or more benzene rings offer numerous problems in orientation. A given substituent may enter one of the nuclei at a certain position while another substituent may take an entirely different location. The experiments here reported were undertaken in order to obtain more information on these orientation effects in the phenyl ether series. Such knowledge was desirable in the continuation of a study of the iodinated derivatives of phenyl ether[1] which has been conducted in this Laboratory. Much work upon this subject has been done by several other investigators[2] using particularly those phenyl ether derivatives containing substituents of halogens, acetamino, nitro and to some extent methoxy groups. The present work is concerned primarily with the derivatives of 2-methoxy- and 4-methoxyphenyl ether. Since the methoxy radical is one of the more strongly directing groups, it would be expected that 4-methoxyphenyl ether would undergo substitution at position 3 and so it does upon nitration, 3-nitro-4-methoxyphenyl ether being the sole product.[2c] We find that halogenation however introduces the halogen atom at position 4′. If that position should be occupied, the halogen attaches itself to the carbon atom at 3 unless the substituent at 4′ is a group such as hydroxy or amino which exceeds the methoxy group in orienting power. Likewise the methoxy group is the controlling factor in the nitration of 2-methoxyphenyl ether as the product obtained is 5-nitro-2-methoxyphenyl ether, yet halogens substitute at position 4′ and take position 5 only if 4′ is occupied. In the halogenation of 4-nitrophenyl ether or 2-nitrophenyl ether, McCombie, Macmillan and Scarborough[2b] showed that a halogen enters at 4′, *i. e.*, para to the ether oxygen and always in the non-nitrated nucleus. The strong preference of a halogen for a position para to the ether oxygen is shown in the iodination of 4-methoxy-2′-nitrophenyl ether where the iodine takes position 4′ (Compound XIII) in spite of the presence of a nitro group in the same ring. However, in the iodination of 2-methoxy-4-nitro-

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[1] Brewster and Strain, THIS JOURNAL, **56**, 117 (1934).

[2] (a) Scarborough and colleagues, *J. Chem. Soc.*, 2361 (1929); (b) *ibid.*, 529 (1931); (c) Lea and Robinson, *ibid.*, 411 (1926); (d) Oesterlin, *Monatsh.*, **57**, 31 (1931); (e) Raiford, Thiessen and Wernert, THIS JOURNAL, **52**, 1205 (1930).

TABLE I

No.	Ref.	Phenyl ether	Source	Procedure	M. p., °C.	Analyses, % Calcd.	Found
I	5	4-Methoxy-4′-iodo		C	115	I, 38.95	38.62
II	6	Benzoyl der. of 4-hydroxy			97	C, 78.61	78.30
						H, 4.83	4.75
III		Benzoyl der. of 4-hydroxy-4′-iodo	II	C	122	I, 30.53	30.40
IV	7	4-Hydroxy-4′-iodo	III		116	I, 40.70	40.82
V	8	4-Methoxy-3-amino		F	70	N, 6.51	6.42
		Acetyl der. of V			148	N, 5.45	5.39
VI	9	4-Methoxy-3-iodo	V	H	76	I, 38.95	38.70
VII	10	4-Methoxy-3-bromo	V	H	55	Br, 28.67	28.79
VIII	11	4-Methoxy-3-bromo-4′-iodo	I, VII	D, C	88	Br, 19.75	19.85
						I, 31.36	31.50
IX	12	4-Methoxy-3,4′-diiodo	I, VI, XI	C, H	101	I, 56.20	55.80
X	13	4-Methoxy-3-nitro-4′-iodo	I	E	92	I, 34.23	33.95
XI	14	4-Methoxy-3-amino-4′-iodo	X	G	85	I, 37.24	36.95
XII	15	4-Methoxy-2′-nitro		A	77	N, 5.71	5.87
XIII		4-Methoxy-2′-nitro-4′-iodo	XII	C	70	I, 34.23	34.28
XIV	16	4-Methoxy-2′-amino-4′-iodo	XIII	G	102	I, 37.24	37.15
XV	17	4-Methoxy-2′-,-3-dinitro	XII	E	132	N, 9.66	9.45
XVI	17	4-Methoxy-2′,4′-dinitro		A	110	N, 9.66	9.55
XVII	18	2 Methoxy-4′-iodo		H	B. p. 228 (28 mm.)	I, 38.95	38.80
XVIII	18	2-Methoxy-5-nitro-4′-iodo	XVII, XX	E, C	115	I, 34.24	33.90
XIX	19	2-Methoxy-5-iodo-4′-nitro		C	109	I, 34.24	33.97
XX	20	2-Methoxy-5-nitro		E	72	N, 5.71	5.64

phenyl ether the iodine atom is directed to position 5 even though position 4 is unoccupied, *i. e.*, the methoxy group exceeds the 4-nitrophenoxy radical in power of orientation.

Experimental

The laboratory procedures used in these experiments are of standard types and are referred to in the table by letters as follows: A, preparation of phenyl ethers by the Ullmann reaction[3]; B, the modified Ullmann reaction using nitrofluorobenzene[4] in place of nitrochlorobenzene; C, iodination by heating on the steam-bath with iodine monochloride in acetic acid solution for one or two hours; D, bromination in acetic acid solution; E, nitration with nitric acid (d. 1.42) in acetic acid solution; F, reduction of nitro compounds free from halogen substituents with hydrogen and the Adams platinum catalyst; G, reduction of nitro compounds containing halogen with iron powder in

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(3) *Org. Syntheses*, **14**, 66 (1934).

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

(5) Potassium phenate and 4-bromoanisole according to the procedure of Oesterlin[2d] gave a 70% yield of 4-methoxyphenyl ether while bromobenzene and hydroquinone monomethyl ether gave only a 20% yield. Iodination of 4-methoxyphenyl ether gave I which was also obtained from 4-methoxy-4′-aminophenyl ether by the Sandmeyer reaction. The samples made by both methods were identical by a mixed melting point test.

(6) 4-Methoxyphenyl ether (100 g.) was heated with anhydrous aluminum chloride (65 g.) for one hour in an oil-bath at 130°. Fifteen grams of additional aluminum chloride was then added and the temperature raised to 140–150° for another hour after which the mass was cooled and poured into water; yield of 4-hydroxyphenyl ether, 75 g., m. p. 84°. It forms the benzoyl derivative readily upon shaking with benzoyl chloride and alkali.

(7) Thirty grams of III was hydrolyzed to IV by boiling with 100 cc. of ethyl alcohol and 50 cc. of 20% sodium hydroxide solution for one hour; yield 20 g.

(8) Nitration of 4-methoxyphenol ether in acetic acid solution[2e] gave a 70% yield of 4-methoxy-3-nitrophenyl ether which gave practically a quantitative yield of V upon reduction.

(9) For diazotization 22.5 g. (0.1 mole) of V was dissolved in 300 cc. of water and 50 cc. of concentrated sulfuric acid and cooled in ice. Crystals of the sulfate separated but redissolved readily upon diazotization with 7.5 g. of sodium nitrite which was added all at once. After ten minutes 5 g. of urea was added, the solution filtered and poured into 25 g. of potassium iodide in 100 cc. of water.

(10) Distils at 182–187°, ten mm.

(11) Compound VIII was obtained both by the bromination of I and the iodination of VII. The two samples were purified from ethyl alcohol and from ligroin and showed no lowering of the melting point on mixing.

(12) Produced by iodination of either I or VI and through the diazo reaction from XI.

(13) No. X was also obtained by iodination of 4-methoxy-3-nitrophenyl ether. Both specimens were shown to be identical by a mixed melting point.

(14) The Sandmeyer reaction with XI gave IX.

(15) Obtained in 70% yield from *o*-nitrochlorobenzene and hydroquinone monomethyl ether.

(16) Deamination of XIV gave I showing that the iodination of XII occurred at 4′.

(17) Compound XV, produced by the nitration of XII, most probably has the composition here assigned as it was not identical with XVI made from 2,4-dinitrochlorobenzene and hydroquinone monomethyl ether.

(18) For conversion to a solid derivative, XVII was nitrated in acetic acid solution giving XVIII. The location of the iodine atom at position 4′ in XVII was established by its synthesis from 2-methoxy-4′-aminophenyl ether through the Sandmeyer reaction. This sample also gave XVIII upon nitration. The fact that the nitro group in XVIII was at position 5 was shown by the preparation of an identical sample by iodination of XX.

(19) In the iodination of 2-methoxy-4′-nitrophenyl ether the iodine enters at 5, producing compound XIX, identical by mixed melting point with a sample prepared from 4-nitrofluorobenzene and the potassium salt of 2-methoxy-5-iodophenol (4-iodoguaiacol).

(20) Lea and Robinson[2c] obtained compound XX by the nitration of 2-methoxyphenyl ether but considered that the nitro group most probably took position 6. We proved that its location was at 5 by synthesis of 2-methoxy-5-nitrophenyl ether, identical with XX by a mixed melting point, from potassium phenate and 2-methoxy-5-nitrobromobenzene.

acetic acid solution; and H, replacement of an amino group by halogen through the Sandmeyer reaction. Other explanatory comments are given in the footnotes.

Summary

The study of the orienting effect of the methoxy group in phenyl ether derivatives has been extended. In determining this orientation a group of new compounds has been prepared and the structure of each proved.

LAWRENCE, KANSAS RECEIVED AUGUST 4, 1939

[CONTRIBUTION FROM THE ORGANIC LABORATORIES OF THE UNIVERSITY OF FLORIDA]

Derivatives of Piperazine. XVIII. Synthesis of Substituted Piperazines and the Hydrolysis of Amines

BY J. P. BAIN[1] AND C. B. POLLARD

It has been shown that N-phenylpiperazine[2] may be prepared readily by heating a mixture of aniline and diethanolamine hydrochlorides. We have found that this method cannot be extended conveniently to the preparation of C-substituted piperazines from arylamines and diisopropanolamine. We have shown that piperazines may be prepared from amino alcohols[3] using the catalytic alkylation methods of Paden and Adkins[4] and Hill and Adkins.[5] This paper reports an extension of the synthesis of piperazines by this method and the formation of alcohols by hydrolysis of amines under catalytic alkylation conditions. This interesting side reaction does not appear to have been reported by other investigators.

Experimental

N-Cyclohexylamines were prepared by passing ethylene oxide into a methanol solution of cyclohexylamine. After removal of the solvent at atmospheric pressure the amino alcohols were distilled at 10 mm. pressure. N-Cyclohexylethanolamine distilled at 118° and N-cyclohexyldiethanolamine at 175°. The neutral equivalents of these compounds were determined using methyl red as the indicator: N-cyclohexylethanolamine, neut. equiv. calcd. 143.2, found 143.0; $n^{25}\mathrm{D}$ 1.4842; N-cyclohexyldiethanolamine, neut. equiv. calcd. 187.3, found 187.2; $n^{25}\mathrm{D}$ 1.4927.

N-Phenyldiisopropanolamine was prepared by heating one mole of aniline with two moles of propylene oxide in 300 cc. of dioxane to 170° in a bomb for several hours. The product was a viscous straw-colored liquid boiling at 184–185° at 10 mm.; N calcd. 6.69, found 6.60.

N-*p*-Tolyldiisopropanolamine was prepared similarly. After removal of solvent the product solidified and was recrystallized several times from hexane and from diisopropyl ether as slightly pink needles, m. p. 112°; N calcd. 6.27, found 6.20.

1,4-Dicyclohexylpiperazine was prepared by two methods. (a) Six hundred ml. of dioxane containing 1 mole each of cyclohexylamine and N-cyclohexyldiethanolamine was heated to 250–270° and shaken for three to four hours in hydrogen at a pressure of 34 atmospheres with 25 g. of copper–chromium oxide catalyst. After filtration from the catalyst and removal of the dioxane, the reaction mixture was distilled at 10 mm. pressure. The first fraction of 20 g., boiling at 60–61°, was identified as cyclohexanol by conversion to the phenylurethan, m. p. 82.5°. The second fraction, 19 g., boiling at 109–110°, was not identified. The third fraction, distilling between 170° at 10 mm. and 200° at 5 mm. partly solidified on cooling. Recrystallized first from pentane and then from aqueous methanol it yielded the piperazine in 20% yield, m. p. 118°. For analysis it was converted to the sparingly soluble dihydrobromide: Br calcd. 38.77, found (gravimetric) 38.76, neut. equiv. calcd. 206, found (by titration with phenolphthalein in the presence of benzene to remove the free amine as formed). (b) Cyclohexylethanolamine treated under the same conditions gave the piperazine in the same yield as well as the two low boiling fractions.

1-Cyclohexyl-2,6-dimethyl-4-phenylpiperazine, b. p. 205–210° at 2 mm., was prepared in 20% yield from cyclohexylamine and N-phenyldiisopropanolamine. The dihydrobromide was used for analysis: N calcd. 6.45, found 6.41; Br calcd. 36.81, found 36.83.

1-Cyclohexyl-2,6-dimethyl-4-*p*-tolylpiperazine, prepared from cyclohexylamine and N-*p*-tolyldiisopropanolamine, boiling at 175–230° at 5 mm., 15% yield, was converted to the hydrobromide and recrystallized from water; for the monohydrobromide, Br calcd. 21.72, found 21.67.

Cyclohexanol from Cyclohexylamine.—Sixty grams of cyclohexylamine, 300 ml. of dioxane, 20 ml. of water and 20 g. of copper–chromium oxide catalyst were placed in a bomb under 500 lb./sq. in. (34 atm.) hydrogen pressure and heated at 260–270° for four hours with shaking. After removal of low boiling material the product was fractionated at 10 mm. The fraction boiling at 55–65° was acidified and the neutral material extracted with ether. The neutral material distilled at 60–61° at 10 mm. and was identified as cyclohexanol by conversion to the phenylurethan, m. p. 82.5°. The yield of the pure alcohol was 20%.

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(1) This paper is abstracted from a portion of a dissertation submitted by J. P. Bain to the Graduate Council of the University of Florida in partial fulfilment of the requirements for the degree of Doctor of Philosophy, May, 1939.

(2) Pollard and MacDowell, THIS JOURNAL, **56**, 2199 (1934).

(3) Bain and Pollard, *ibid.*, **61**, 532 (1939).

(4) Paden and Adkins, *ibid.*, **58**, 2487 (1936).

(5) Hill and Adkins, *ibid.*, **60**, 1033 (1938).