238° after recrystallization from methanol and then from water.

Anal. Calcd. for $C_{12}H_{13}O_2N_5$ (259): C, 55.6; H, 5.1; N, 27.0. Found: C, 55.5; H, 4.9; N, 26.9.

Enzyme Studies.—The data given in Table I are self-explanatory though it should be noted that in some cases the values given for % hydrolysis were interpolated from a smooth curve drawn through the experimentally determined points when such points did not coincide with the time interval given in Table I. The extent of hydrolysis was determined by a modified formal titration based upon coincident use of primary or secondary amine buffers. The advantages of this new analytical method will be described in a subsequent communication.

TABLE I

HYDROLYSIS OF ACYLATED α-AMINO ACID AMIDES BY CHYMOTRYPSIN[a]

Acylated α-amino acid amide used as substrate	s_0[b]	E_0[c]	Hydrolysis, % 15 min.	30 min.	60 min.
Acetyl-DL-phenyl-	10	0.15		5	9
alanin-	5	.15		6	12
Benzoyl-DL-phenyl-	1.25	.15	52	80	96
alanin-[d]	1.25	.075	34	56	80
Nicotinyl-DL-phenyl-	5	.15	20	36	58
alanin-	5	.075	10	18	34
	1.25	.15	32	56	80
	1.25	.075	16	34	56
Nicotinyl-L-phenyl-	10	.15	21	40	63
alanin-	10	.075	11	18	34
	5	.15	22	44	68
	5	.075	14	26	44
Nicotinyl-L-tyrosin-	5	.075	34	58	92
	10	.075	26	50	78
	20	.075	20	38	66
Nicotinyl-*p*-chloro-	1.25	.15	44	72	92
DL-phenylalanin-	1.25	.075	20	38	64
Nicotinyl-L-trypto-	10	.15	41	69	91
phan-	10	.075	20	38	61
	5	.15	60	84	98
	5	.075	34	60	86
Nicotinyl-DL-	10	.15	26% in 24 hours		
methionin-					
Nicotinyl-L-histidin-	10	.15	none in 24 hours		

[a] At 25° and *p*H 7.8 (0.02 formal ethylenediamine–hydrochloric acid buffer). [b] Initial substrate concentration of the L-isomer in micromoles per ml. reaction mixture. [c] Initial enzyme concentration in mg. protein nitrogen per ml. reaction mixture. [d] Previously reported not to be hydrolyzed by chymotrypsin.[23]

Summary

The nicotinyl-L-phenylalanin-, L-tyrosin and L-tryptophanamides have been found to be useful and practical substrates for the evaluation of chymotrypsin activity.

(23) M. Bergmann and J. S. Fruton, *J. Biol. Chem.*, **124**, 321 (1938).

PASADENA 4, CALIFORNIA RECEIVED SEPTEMBER 2, 1949

[A COMMUNICATION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

Synthesis of Alkylcyclohexanols from Phenols

BY HOMER ADKINS,[1] ALVAN DONNAN AND ROBERT H. LEVIN

A number of mono- and di-alkylcyclohexanols have been prepared from certain phenols through the sequence of reactions: phenol → aryl ester → isomeric acylphenols (separated) → alkylphenols → alkylcyclohexanols.

This sequence of reactions has been applied to the acetates, propionates and *n*-butyrates of phenol, *o*-, *m*- and *p*-cresols and *o*-ethylphenol. The aryl esters preferably were prepared from the phenols and the appropriate acyl chloride; the Fries rearrangements of these esters and separations of the resulting acylphenols were carried out essentially as described by Miller and Hartung.[2]

The acylphenols were hydrogenated to the alkylphenols in good yields over both Raney nickel and copper–chromium oxide. The hydrogenation over W-2 Raney nickel proceeded at a lower temperature (90–130°) than over the copper–chromium oxide catalyst,[3] which requires temperatures of 150–175°. These hydrogenations usually were complete within ten to thirty minutes, but with the less pure samples of the acylphenols a longer time (one to two hours) usually was required for their completion. As Raney nickel is more active toward the benzenoid ring than is copper–chromium oxide, the latter is the preferred catalyst for the preparation of the alkylphenols; also the nickel catalyst is more susceptible to poisoning by impurities in the acylphenols.

The hydrogenation of the various alkylated phenols to the corresponding cyclohexanols usually was complete in about two hours at 175° over Raney nickel. The simpler phenols were hydrogenated more rapidly and at a lower temperature while the more substituted phenols required a slightly longer time and temperatures as high as 200°. However, the purity of the sample appears to be a more important factor in determining the rate of hydrogenation than the precise structure of the phenol. With a more active Raney nickel such as W-6, these hydrogenations doubtless could be accomplished under milder conditions.[4]

The yields, properties, analyses and certain

(1) Deceased August 10, 1949.

(2) Miller and Hartung, "Org. Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, 1943, p. 543; *cf.* also Blatt, "Organic Reactions," John Wiley and Sons, Inc., New York, 1942, Vol. I, p. 342.

(3) Connor, Folkers and Adkins, THIS JOURNAL, **54**, 1138 (1932).

(4) Adkins and Billica, *ibid.*, **70**, 695 (1948).

TABLE I

ALKYLPHENOLS AND ALKYLCYCLOHEXANOLS

Compound	Yield, %	B. p., °C.	Mm.	$n^{25}D$	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Phenylurethan	Phenylurethan M. p., °C.	Nitrogen, % Calcd.	Nitrogen, % Found
2-Ethyl-4-*n*-propylphenol	75	123–125	10	1.5178	$C_{11}H_{16}O$	80.4	80.0	9.8	9.8	$C_{18}H_{21}O_2N$	132–134	4.95	4.89
2-Ethyl-4-*n*-butylphenol	80	137–139	10	1.5103	$C_{12}H_{18}O$	81.2	81.2	9.1	8.9	$C_{19}H_{23}O_2N$	121–123	4.71	4.75
2-Methyl-4-ethylcyclohexanol	86	80–83 199–200	7 750	1.4612	$C_9H_{18}O$	76.0	76.1	12.8	12.8	$C_{16}H_{22}O_2N$	122–123	5.36	5.27
2-Methyl-4-*n*-propylcyclohexanol	80	113–114 215.5	215 740	1.4610	$C_{10}H_{20}O$	76.8	76.8	12.9	12.9	$C_{17}H_{24}O_2N$	121–122.5	5.09	5.14
2-Methyl-4-*n*-butylcyclohexanol	84	119–120 234	15 740	1.4620	$C_{11}H_{22}O$	77.6	77.6	13.0	13.1	$C_{18}H_{26}O_2N$	112–113	4.84	4.86
2-Methyl-6-*n*-butylcyclohexanol	81	113 228	155 740	1.4631	$C_{11}H_{22}O$	77.6	77.4	13.0	13.0	.....	.....	..	..
3-Methyl-4-ethylcyclohexanol	84	109.5–110.5 209	21 740	1.4650	$C_9H_{18}O$	76.0	75.9	12.8	12.8	.....	.....	..	..
3-Methyl-6-*n*-butylcyclohexanol	78	70 233.5	1 740	1.4603	$C_{11}H_{22}O$	77.6	77.5	13.0	13.0	.....	.....	..	..
4-Methyl-2-ethylcyclohexanol	75	101–102.5 197.5	23 740	1.4599	$C_9H_{18}O$	76.0	75.9	12.8	12.8	$C_{16}H_{19}O_6N_3$[a]	82–83	8.36	8.42
4-Methyl-2-*n*-butylcyclohexanol	85	90–91 231	3 740	1.4601	$C_{11}H_{22}O$	77.6	77.5	13.0	13.0	.....	.....	..	..
2,4-Diethylcyclohexanol	92	97.5–99.5	9	1.4622	$C_{10}H_{20}O$	76.8	76.5	12.9	12.9	$C_{17}H_{25}O_2N$	110–114	5.14	5.34
2-Ethyl-4-*n*-butylcyclohexanol	96[b]	158–162 (semi-solid)	10	1.4667	$C_{12}H_{24}O$	78.2	78.3	13.1	13.3	.....	.....	..	..

[a] 3,5-Dinitrobenzoate. [b] This is a total yield, including a lower boiling (126–127° (11 mm.)) liquid fraction which is probably a different isomer, but was not completely characterized.

derivatives of those alkylphenols and alkylcyclohexanols not previously reported in the literature are listed in Table I. The yields of the alkylphenols and alkylcyclohexanols which were prepared in the course of this work and have been described previously in the literature, were comparable to those listed in Table I.

Summary

A number of aryl esters have been converted to acylphenols, alkylphenols and alkylcyclohexanols in good yields, through the application of the Fries rearrangement and catalytic hydrogenations.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

Reactions of Polyacylglycosyl Halides with Grignard Reagents

BY CHARLES D. HURD AND ROMAN P. HOLYSZ[1]

The present work is an extension using other carbohydrates and other organomagnesium compounds, of the findings of Hurd and Bonner[2] dealing with the formation of glycosylated hydrocarbons by interaction of polyacylglycosyl halides and Grignard reagents.

Maltose.—Heptaacetyl-α-maltosyl chloride reacted readily with phenylmagnesium bromide to give methyldiphenylcarbinol and a mixture of maltosylbenzenes. About four-fifths of the latter was acetylated and characterized as crystalline heptaacetyl-β-maltosylbenzene. On the basis of analytical and optical rotation data, the remaining glassy product was probably the anomeric heptaacetyl-α-maltosylbenzene.

Gentiobiose.—Heptaacetyl-β-gentiobiosylbenzene and its α-anomer have been obtained (40 and 25% yields, respectively) from the acetylated reaction products of heptaacetyl-α-gentiobiosyl bromide with phenylmagnesium bromide. Deacetylation of these acetates gave the α- and β-gentiobiosylbenzenes as sirups.

Mannose.—The product of reaction of phenylmagnesium bromide and tetraacetyl-α-D-mannopyranosyl bromide gave on acetylation a sirup (which was not investigated) and two crystalline products, one of which was designated as tetraacetyl-α-D-mannopyranosylbenzene because of its high rotation, $[\alpha]_D$ 53.6°. The yield was 41%. Deacetylation gave α-D-mannopyranosylbenzene, $[\alpha]_D$ 65.2°, whose consumption of two equivalents of periodate and liberation of one equivalent of formic acid indicate a six-membered ring, and which gives benzoic acid on oxidation with alkaline permanganate. The second crystalline acetate, $[\alpha]_D$ −25.6°, obtained in 24% yield, was deacetylated to β-D-mannopyranosylbenzene, $[\alpha]_D$ 60.0°, which gave benzoic acid on permanganate oxidation, leading to designation of the second acetate as tetraacetyl-β-D-mannopyranosylbenzene. Oxidation with periodate also supported the pyranose structure.

This is the first instance wherein two crystalline

(1) Corn Products Refining Company Fellow, 1945–1947; present address: Commercial Solvents Corporation, Terre Haute, Ind.

(2) Hurd and Bonner, THIS JOURNAL, **67**, 1972 (1945).