Experimental

Benzene, alkylbenzenes, benzyl chloride and nitromethane used were commercial products of highest available purity. They were further purified by fractionation on an Aldershaw column rated at 50 theoretical plates. Monoalkyldiphenylmethane isomers were prepared in this Laboratory from the corresponding alkylbenzyl chlorides. The purity of the reference materials was checked by gas–liquid chromatography and infrared spectra.

$AlCl_3$ was resublimed Fisher certified reagent.

General Procedure for Competitive Benzylation.—Benzene (0.25 mole) and 0.25 mole of alkylbenzene were dissolved in 30 g. of nitromethane and 0.05 mole of $AlCl_3$ dissolved in 20 g. of nitromethane was added into this solution. The reaction flask was placed into a constant temperature bath (25°) and 0.05 mole of benzyl chloride dissolved in 20 g. of nitromethane was added dropwise into the vigorously stirred solution. The reaction time was generally 15 minutes. After the addition of the benzyl chloride the mixture was stirred for another 5 minutes, then it was washed with 100 ml. of 5% HCl–water solution, then twice with 50 ml. of water, dried over $CaCl_2$ and a small amount of K_2CO_3 and analyzed by gas–liquid chromatography.

Analytical Procedure.—The analyses were carried out by gas–liquid chromatography using a Perkin–Elmer model 154-C vapor Fractometer. Separations of methyl- and ethyldiphenylmethanes were done on a Perkin–Elmer model 154-D vapor Fractometer employing a Golay column (polypropylene glycol coating) and hydrogen flame ionization detector.

In the model 154-C vapor fractometer a 4-meter by 0.25 inch stainless steel packed column of polypropylene glycol (Ucon LB550-X) on diatomaceous earth (30% w./w.) was used with a thermistor thermal conductivity cell detector. The column temperature was 196° for all determinations. Hydrogen flowing at 60 ml. per minute was used as carrier gas. Sample sizes of 100 μml. were generally injected. Peak areas were determined with a Perkin–Elmer model 194 electron printing integrator. Relative response data were determined by running solutions of the respective alkyl-diphenylmethane isomers with diphenylmethane in benzene in approximately a 1/1/10 ratio. The retention times observed are tabulated.

The isomeric methyldiphenylmethanes and ethyldiphenylmethanes were not separable on the packed column. For the determination of these isomers a 150′ Golay capillary column (Perkin–Elmer "R-polypropylene glycol") with a hydrogen flame ionization detector was used. For the methyldiphenylmethane isomer separation, a column temperature of 100° and a helium carrier gas pressure of 30 p.s.i.g. were employed; for the ethyldiphenylmethanes, 125° and 25 p.s.i.

RETENTION TIMES OF ALKYLDIPHENYLMETHANES AT 195° ON PACKED COLUMN

Diphenylmethane	Retention time, min.	Diphenylmethane	Retention time, min.
Unsubstd.	35	3-*n*-Butyl-	103
2-Methyl-	51	4-*n*-Butyl-	125
4-Methyl-	54	3,4-Dimethyl-	66
2-Ethyl	58	2,6-Dimethyl-	53
4-Ethyl-	67	2,4-Dimethyl-	60
2-*n*-Propyl-	63	2,5-Dimethyl-	52
3-*n*-Propyl-	69	2,4,6-Trimethyl-	100
4-*n*-Propyl	80		
2-*n*-Butyl-	90		

RETENTION TIMES OF ISOMERIC METHYLDIPHENYLMETHANES AND ETHYLDIPHENYLMETHANES ON GOLAY COLUMN

Alkyldiphenylmethane	Retention time, min.
2-Methyl-	60
3-Methyl-	62
4-Methyl-	65
2-Ethyl-	23
3-Ethyl-	24
4-Ethyl-	27

Determination of Kinetic Isotope Effect.—A mixture of 0.1 mole of benzene and 0.1 mole of benzene-d_6 was benzylated in nitromethane solution at 25° in the same manner as were the other competitive benzylations carried out. The resulting mixture was washed, dried and analyzed by mass spectroscopy.

Competitive benzylation of toluene (0.1 mole) and benzene-d_6 (0.1 mole) in nitromethane solution at 25° was carried out similarly, but products were analyzed by gas–liquid chromatography.

Acknowledgment.—The authors are indebted to R. S. Gohlke (Chemical Physics Research Laboratory, The Dow Chemical Co., Midland, Mich.) for the mass spectroscopic analyses.

[CONTRIBUTION NO. 55 FROM THE EXPLORATORY RESEARCH LABORATORY, DOW CHEMICAL OF CANADA, LTD., SARNIA, ONTARIO, CAN.]

Aromatic Substitution. XI.[1] The $AlCl_3CH_3NO_2$-Catalyzed Benzylation of Halobenzenes with Benzyl Chloride in Nitromethane Solution

BY GEORGE A. OLAH, STEPHEN J. KUHN AND SYLVIA H. FLOOD

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Competitive $AlCl_3 \cdot CH_3NO_2$-catalyzed benzylation of benzene and halobenzene with benzyl chloride in homogeneous nitromethane solution was investigated. Relative rates and isomer distributions were determined by a gas–liquid chromatographic analytical method using a Golay type capillary column and a hydrogen flame ionization detector. The observed relative rates, the reactions being first order in aromatics show good correlation with relative π-complex stabilities of the halobenzenes. The mechanism of the reactions is discussed based on the obtained experimental data.

Introduction

In the previous paper of this series[1] the $AlCl_3 \cdot CH_3NO_2$-catalyzed benzylation of alkylbenzenes with benzyl chloride in nitromethane solution was investigated. This work has now been extended to a similar investigation of the benzylation of halobenzenes.

Results

Competitive benzylations of benzene and halobenzenes were carried out under identical conditions as described previously in the case of alkylbenzenes. All benzylations were carried out in nitromethane solutions at +25°. Under the employed experimental conditions only monobenzylation takes place. No di- or higher benzylated products were detectable in the reaction mixtures either by gas–liquid chromatographic or spectroscopic methods. The reaction mixtures were analyzed by a gas–liquid chromatographic method, using a Golay-type capillary column and a hydrogen flame ionization detector. From the areas of individual peaks (obtained by the use of an electronic printing

(1) Part X, *J. Am. Chem. Soc.*, **84**, 1688 (1962).

integrator) mole % figures were calculated for each product after first determining the individual response data.

The observed reactivities of the halobenzenes relative to that of benzene, together with the isomer distributions of the monobenzylated products, are summarized in Table I. (All data reported represents the average of at least three parallel experiments.)

TABLE I

COMPETITIVE $AlCl_3 \cdot CH_3NO_2$-CATALYZED BENZYLATION OF HALOBENZENES AND BENZENE WITH BENZYL CHLORIDE IN NITROMETHANE SOLUTION AT 25°

Benzene	Relative rate	Isomer distribution, % ortho	meta	para
Unsubstd.	1.00			
Fluoro-	0.46	14.7	0.2	85.1
Chloro-	.24	33.0	.6	66.4
Bromo-	.18	32.5	.7	66.8
Iodo-	.28	30.6	.7	68.7

The accuracy of the gas–liquid chromatographic method was found to be better than 3 relative per cent., based on analyses of mixtures of known composition. For all the investigated halobenzenes, the benzylations were found to have taken place under non-isomerizing conditions. Pure isomeric halodiphenylmethanes were recovered unchanged when excess benzene was benzylated in their presence under the generally used conditions.

The method of competitive reaction rate determination can be applied only if the observed relative rates are indeed dependent on the aromatic substrates. Changing the concentration of either of the aromatic components in the competitive benzylation of fluorobenzene and benzene from the 1:1 ratio to 4:1 and 1:4 showed that the relative rate ratio remains almost unchanged if a first-order dependence on the aromatic substrates is accepted (Table II).

TABLE II

FIRST-ORDER DEPENDENCE IN AROMATICS OF THE $C_6H_5CH_2Cl + AlCl_3 \cdot CH_3NO_2$ BENZYLATION OF HALOBENZENES

Fluorobenzene:benzene ratio	Obsd. relative rate	Relative rate according to first-order dependence in aromatics
4:1	1.72	0.43
2:1	0.90	.45
1:1	.46	.46
1:2	.27	.54
1:4	.14	.57
	Average	0.49

Discussion of Results

The observed relative reactivities of halobenzenes and benzene show good agreement with relative stabilities of complexes of halobenzenes with π-acids such as Ag^+, Br_2, I_2, HCl and tetracyanoethylene. Table III shows a comparison of the relative rates of the $AlCl_3 \cdot CH_3NO_2$-catalyzed benzylations with benzyl chloride in nitromethane solution with the relative stabilities of complexes of halobenzenes. The previously established[2] relative nitration rates with $NO_2^+BF_4^-$ are also included for sake of comparison in the table. The question of steric hindrance in influencing relative complex stabilities and rates was pointed out previously, in connection with nitration of the halobenzenes.[2] At the same time the question of relative basicity of the halobenzenes was also discussed to some degree. Therefore in connection with present data we feel it only necessary to point out the remarkable resemblance of present benzylation data with the previously obtained nitration data. In both cases a good agreement with relative π-complex stabilities seems to exist. Low substrate selectivity with only a very minor amount of *meta* isomers formed, was observed.

TABLE III

COMPARISON OF RELATIVE STABILITIES OF COMPLEXES OF HALOBENZENES WITH BENZYLATION RATES

Benzene	Ag^+[a]	Br_2[b]	I_2[c]	HCl[d]	$C_2(CN)_4$[e]	$NO_2^+BF_4^-$[f] nitration rates	$C_6H_5CH_2Cl + AlCl_3 \cdot CH_3NO_2$ benzylation rates
Unsubstd.	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Fluoro-	0.18			0.74		0.45	0.46
Chloro-	.29	0.86	0.50	.50	0.39	.14	.24
Bromo-	.40	1.13	0.86	.41	.31	.12	.18
Iodo-	2.08	1.53	1.5	.40	.62	.28	.28

[a] L. J. Andrews and R. M. Keefer, *J. Am. Chem. Soc.*, **72**, 3113 (1950). [b] R. M. Keefer and L. J. Andrews, *ibid.*, **72**, 4677 (1950). [c] L. J. Andrews and R. M. Keefer, *ibid.*, **74**, 4500 (1952). [d] H. C. Brown and J. D. Brady, *ibid.*, **72**, 3573 (1949). [e] R. E. Merrifield and W. D. Phillips, *ibid.*, **80**, 2779 (1958). [f] G. A. Olah, S. J. Kuhn and S. H. Flood, *ibid.*, **83**, 4581 (1961).

Experimental

Benzene, halobenzenes, benzyl chloride and nitromethane were commercial materials of highest available purity. They were further purified by fractionation on an Oldershaw column rated at 50 theoretical plates. The isomeric halodiphenyls used as standards in the analytical determinations were prepared from the corresponding halobenzyl chlorides. Their purity was observed by gas–liquid chromatography and infrared spectra. The Al_2Cl_6 used was Fisher reagent grade.

General Procedure for Competitive Benzylations.—Benzene (0.25 mole), 0.25 mole of halobenzene and 0.05 mole of $AlCl_3$ were dissolved in 50 g. of nitromethane. The reaction

TABLE IV

RETENTION TIMES OF HALODIPHENYLMETHANES ON PERKIN–ELMER CAPILLARY COLUMN "R-POLYPROPYLENE GLYCOL" 150'

Diphenylmethane	Temp., °C.	He press. (carrier gas), p.s.i.g.	Retention time, min.
o-Fluoro-	125	25	15.4
m-Fluoro-	125	25	15.6
p-Fluoro-	125	25	16.5
o-Chloro-	125	25	32
m-Chloro-	125	25	36.5
p-Chloro-	125	25	39
o-Bromo-	150	20	23
m-Bromo-	150	20	26
p-Bromo-	150	20	28
o-Iodo-	150	25	28
m-Iodo-	150	25	32
p-Iodo-	150	25	35
Unsubstd.	125	25	15
	150	20	9

(2) G. A. Olah, S. J. Kuhn and S. H. Flood, *J. Am. Chem. Soc.*, **83**, 4581 (1961).

flask was placed in a constant temperature bath and 0.05 mole of benzyl chloride dissolved in 20 g. of nitromethane was added dropwise into the vigorously stirred aromatic, $AlCl_3$, nitromethane solution. The usual reaction time was 15 minutes. After the addition of the benzyl chloride the mixture was stirred for another 5 minutes, then washed with 100 ml. of 5% HCl water solution, followed by washing twice with 50 ml. of water. The organic layer was dried over $CaCl_2$ and a small amount of K_2CO_3 and analyzed by gas–liquid chromatography.

Analytical Procedure.—The analyses were carried out on a Perkin–Elmer model 154-D vapor fractometer equipped with a 150′ Golay capillary column and a hydrogen flame ionization detector. Peak areas were obtained with a Perkin–Elmer model 194 electronic printing integrator.

The capillary column used was obtained from Perkin–Elmer Corp. designated "R-polypropylene glycol" and was 150′ in length. The operating parameters differed for the various halodiphenylmethanes and are listed with the retention times in Table IV.

Response data were determined by running solutions of the respective pure halodiphenylmethane isomers and diphenylmethane in benzene in the approximate ratios in which they occurred in the reaction mixtures.

[CONTRIBUTION FROM THE NATIONAL INSTITUTE OF ARTHRITIS AND METABOLIC DISEASES, NATIONAL INSTITUTES OF HEALTH, BETHESDA 14, MD.]

Preparation, Resolution and Optical Stability of 3,4-Dehydroproline and 3,4-Dehydroprolinamide

BY ALEXANDER V. ROBERTSON[1] AND BERNHARD WITKOP

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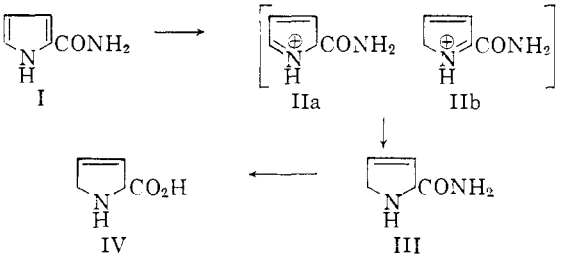
The reduction of pyrrole-2-carboxamide with phosphonium iodide in fuming hydriodic acid under special conditions leads to 70% of 3,4-dehydro-DL-prolinamide (III) and 10% of 3,4-dehydro-DL-proline (IV) which were isolated and purified by ion exchange technique. The structure of III and IV was proved by catalytic hydrogenation to proline and prolinamide, by nuclear magnetic resonance spectroscopy and by resolution. Chemical resolution yielded the optically labile 3,4-dehydro-D-prolinamide, $[\alpha]^{30}D > +320°$, $t_{1/2} \sim 48$ hours. Combination of enzymatic hydrolysis of III with its asymmetric transformation yielded 75% of 3,4-dehydroproline containing at least 90% of the L-configuration. 3,4-Dehydro-L-proline in aqueous solution is comparatively stable at room temperature, but has a half-life time of six days at 90°. The implication of the principle of 100% conversion of a racemate into one natural optical isomer is discussed with regard to the origin of asymmetry in nature.

The 3,4-dehydroproline system is of interest because the double bond in the allylic position to the asymmetric center will make the antipodes optically labile and, in addition, the class will lend itself to the preparation of novel functional derivatives of proline and hydroxyproline which are needed in current metabolic studies. This communication reports on the aspects of optical lability.[2]

Extensive efforts to convert hydroxyproline to 3,4-dehydroproline were of little success[3a]; a better approach is the method of Fischer and Gerlach[3b] who reduced pyrrole-2-carboxamide (I) with phosphonium iodide in fuming hydriodic acid and obtained a 25% yield of a compound which was presumed but not proved to be 3,4-dehydroproline. Modification of the reaction conditions together with application of modern isolation techniques afford ready access to the 3,4-dehydroproline oxidation level in high yield. The product of reduction is 3,4-dehydroprolinamide (III) which then slowly hydrolyzes to the amino acid IV in the strongly acidic reaction mixture. The concentration of fuming hydriodic acid is critical. The reduction is complete in 2 hours with acid saturated at −20°, but takes 8 hours with acid saturated at 0° and the yields are lower. No reduction occurs with phosphonium iodide and constant boiling acid. Much iodine was liberated when pyrrole-2-carboxamide was treated with fuming hydriodic acid alone, and starting material was the only homogeneous compound isolable. These facts can best be accommodated by assuming that the reaction proceeds *via* the pyrroleninium ions (IIa, IIb) which are stabilized in the very strong acid. Reduction of the immonium double bond leads to III in which the Δ^3-double bond is isolated and resistant to further reduction. Phosphonium iodide removes free iodine as it is formed, thus avoiding electrophilic attack on unreacted starting material.



The combined yield of III and IV is 70–80%, and the ratio of the compounds depends on the speed and temperature of isolation from the strongly acidic reaction mixture. Under optimum conditions 70% of the amide and 10% of the amino acid were obtained. Differences in their solubilities and in their adsorption on ion exchange resin made their separation and purification easy.

Dehydroprolinamide gave positive tests for olefin and amide functions. The formation of 3,4-dehydroproline on acid hydrolysis showed that the double bond position in III and IV was identical. The amide absorbed one mole of hydrogen over platinum, yielding DL-prolinamide.

Dehydroproline gave positive tests for unsaturation, and a yellow ninhydrin color. It was quantitatively reduced by platinum and one mole of

(1) Visiting Scientist of the USPHS, 1959–1961.

(2) *Cf.* A. V. Robertson and B. Witkop, *J. Am. Chem. Soc.*, **82**, 5008 (1960).

(3) (a) J. E. Francis and B. Witkop, unpublished; (b) E. Fischer and F. Gerlach, *Ber.*, **45**, 2453 (1912).