TABLE I

BENZYL ESTER HYDROCHLORIDES

Amino acid	Formula	M.p., °C.	Nitrogen, % Calcd.	Found	$[\alpha]^{25}D$ (0.1 N HCl)[a]	C[b]
L-Alanine	$C_{10}H_{14}O_2NCl$	140[c]	6.5	6.5	−14.3[d]	2.11
L-Leucine	$C_{13}H_{20}O_2NCl$	128[e]	5.4	5.4	− 6.6[f]	2.06
L-Phenylalanine	$C_{16}H_{18}O_2NCl$	203	4.8	4.7	−22.5[g]	1.01
L-Tyrosine	$C_{16}H_{18}O_3NCl$	205	4.5	4.6	−23.3	0.97
L-Cysteine	$C_{10}H_{14}O_2NSCl$	106	5.7	5.5	−26.6	1.01
L-Cystine	$C_{20}H_{26}O_4N_2S_2Cl_2$	166 dec.	5.7	5.5	+32.8	0.68
DL-Phenylalanine	$C_{16}H_{18}O_2NCl$	196	4.8	4.9		

[a] All rotations are calculated as the free ester. [b] Concentration in g./100 ml. for optical rotation measurement. [c] Erlanger and Brand (ref. 5) report 140°. [d] The value reported by Erlanger and Brand (ref. 5) is not calculated as free ester. If calculated as free ester, $[\alpha]^{25}D$ becomes −13.2°. [e] Miller and Waelsch (ref. 6) report 128°. [f] Miller and Waelsch (ref. 6) report $[\alpha]^{30}D$ −8° (2% in 0.1 N HCl). [g] In 0.25 N HCl.

data are presented in Table I. The benzyl ester hydrochlorides of L-phenylalanine, L-tyrosine, L-cysteine and L-cystine have not heretofore been described. The benzyl esters of L-leucine, L-phenylalanine and L-tyrosine were reduced to their respective amino acids which were found to be unracemized. The oxidation of cysteine benzyl ester to cystine benzyl ester was performed with iodine in ethyl alcohol. The yield was not very satisfactory and this cannot be considered the synthetic method of choice. Iodine in acetic acid[12] was just as unsatisfactory.

The presence of a free phenolic group in L-tyrosine benzyl ester hydrochloride was confirmed by a positive Millon test. The presence of a free SH group in the L-cysteine benzyl ester hydrochloride was confirmed by a positive nitroprusside test.

Experimental[13]

Starting Materials.—The specific rotations of the amino acids used are as follows: L-alanine + 14.2 (6 N HCl), L-cysteine +4.3 (N HCl), L-leucine +15.2 (6 N HCl), L-phenylalanine −35.1 (H_2O), L-tyrosine −13.0 (3 N NaOH, T = 18°).

DL-Phenylalanine Benzyl Ester Hydrochloride.—Two grams (0.012 mole) of DL-phenylalanine was added to a large test-tube containing a homogenous solution of 25 ml. of benzyl alcohol and 5 g. of polyphosphoric acid. The mixture was stirred in an oil-bath at 90–95° for four hours. (The DL-phenylalanine dissolves within a few minutes.) The solution was then poured into 200 ml. of water containing about 10 ml. of concentrated HCl. Ether was added and the water layer collected. The ether layer was then washed three times with 2% HCl. All aqueous fractions were collected, brought to a pH of about 10 with solid Na_2CO_3 and shaken with three 100-ml. portions of ether. The ether layer was dried over magnesium sulfate and nearly saturated with HCl gas. The DL-phenylalanine benzyl ester hydrochloride, which precipitated, weighed 2.3 g. (65%). The crude product, m.p. 195–196°, was recrystallized from ethyl acetate–petroleum ether.

All the other benzyl ester hydrochlorides were prepared in the same way and in similar yield as DL-phenylalanine benzyl ester hydrochloride with certain exceptions which will be mentioned below.

L-Alanine benzyl ester hydrochloride: recrystallized from methanol–ether.

L-Leucine Benzyl Ester Hydrochloride.—After the dried ether solution had been saturated with HCl gas, the ether was removed *in vacuo*. The residue was crystallized by dissolving in warm ethyl acetate and carefully adding ligroin. It was recrystallized from chloroform–cyclohexane. Upon hydrogenolysis in the presence of palladium black, the recovered amino acid had $[\alpha]^{25}D$ +14.5° (c 2, in 6 N HCl).

L-Phenylalanine Benzyl Ester Hydrochloride.—Hydrogenolysis yielded free amino acid with $[\alpha]^{24}D$ −33.6° (c 1.20, H_2O).

L-Tyrosine Benzyl Ester Hydrochloride.—Hydrogenolysis yielded free amino acid with $[\alpha]^{26}D$ −12.6° (c 1.35 in 3 N NaOH). The Millon test was positive.

L-Cysteine Benzyl Ester Hydrochloride.—The temperature of the bath during the reaction was 105°. At the end of four hours, about 200 ml. of ether was added to incipient turbidity. The solution was saturated with HCl gas, the walls of the container were scratched and the solution kept in the ice-box for 48 hours. The benzyl ester, which crystallized, weighed 1.35 g. (45% of theory); m.p. 91–97°. It was recrystallized from ethyl acetate. The nitroprusside test for sulfhydryl groups was positive.

L-Cystine Benzyl Ester Hydrochloride.—Two hundred and forty-eight mg. (0.001 mole) of L-cysteine benzyl ester hydrochloride was dissolved in 5 ml. of 60% ethanol. To this solution was added dropwise a N solution of iodine in 95% ethanol until a yellow color persisted (1.95 ml. was necessary). The solvent was removed *in vacuo*, 5 ml. of water was added and the pH brought to about 9.5 with K_2CO_3. It was then shaken twice with 20-ml. portions of ether. The ether solution was dried over magnesium sulfate and then HCl gas passed in. The cystine benzyl ester hydrochloride, which precipitated, weighed 60 mg. (25% yield). It was recrystallized as needles from methanol–water.

NOTE ADDED IN PROOF.—We have succeeded in preparing ε-carbobenzoxy L-lysine benzyl ester hydrochloride.[9] Also, L-phenylalanine benzyl ester hydrochloride may be isolated by adding three volumes of ether to the reaction mixture and saturating with hydrogen chloride gas. (See cysteine benzyl ester hydrochloride.)

DEPARTMENT OF MICROBIOLOGY
COLLEGE OF PHYSICIANS AND SURGEONS
COLUMBIA UNIVERSITY
NEW YORK 32, NEW YORK

(12) *Cf.* T. W. Rall and A. L. Lehninger, *J. Biol. Chem.*, **194**, 120 (1952); also, R. Kuhn, L. Birkofer and F. W. Quackenbush, *Ber.*, **72**, 407 (1939).

(13) All melting points are corrected.

Nucleophilic Displacement of Groups in Substituted Duryl Phenyl Ketones by the Action of Phenylmagnesium Bromide

BY REYNOLD C. FUSON AND WILLIAM S. FRIEDLANDER[1]

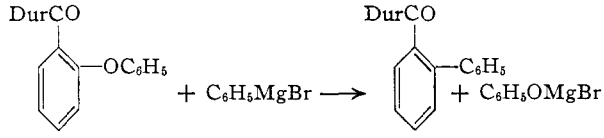
RECEIVED JUNE 29, 1954

In previous papers of this series nucleophilic displacement by the action of Grignard reagents on hindered diaryl ketones has been accomplished with halogen, methoxyl, acyloxyl and cyano groups.[2] The present paper reports the result of a study of certain duryl phenyl ketones that have substituents in the *ortho* position of the phenyl radical. Phenylmagnesium bromide has been employed in all the experiments since previous studies had shown that the ease of displacement of groups

(1) Procter and Gamble Company Fellow, 1953–1954.

(2) R. C. Fuson and W. S. Friedlander, THIS JOURNAL, **75**, 5410 (1953).

from an *ortho* position in such ketones is not influenced greatly by the nature of the Grignard reagent. The displacement of the phenoxyl group is illustrative.



Interest in the displacement of the phenoxyl group refers primarily to its low donor capacity, which might be expected to render less likely the intervention of a coördination compound involving both oxygen atoms. On the other hand, the high order of stability of the phenoxide ion would lead to the prediction that displacement would be facilitated. Experiment showed that displacement is practically quantitative.

Since the phenoxyl group is displaced more readily than the methoxyl, it seemed probable that, in the sulfur series, phenylmercapto might be displaced more easily than methylmercapto. Experiment bore out this prediction; displacement of phenylmercapto occurred in 61% yield while with the methylmercapto group the yield was only 37%.

This ratio reversed itself in the corresponding sulfones, the phenyl and methylsulfonyl groups being displaced in yields of 68 and 94%, respectively. Since the sulfones, as well as the ethers and thioethers, are capable of forming cyclic coördination complexes it is not clear to what extent, if at all, the displacement depends on this factor.

The behavior of the methyl sulfone is of special interest since it should be able to form a Grignard reagent[3] which in turn might undergo ring closure or bring about displacement. The high yield of the phenylated product makes the occurrence of such reactions seem improbable.

Experimental[4]

The various displacement reactions were all carried out under similar conditions; a description of the general procedure follows. A solution of phenylmagnesium bromide was prepared in ether and then filtered through glass wool into boiling ether. The substituted duryl phenyl ketone, dissolved in benzene, was then added. During this addition and the early stages of the reflux period very intense color changes usually were noted. After several hours of refluxing the mixtures were poured into dilute hydrochloric acid; the organic layers were separated, washed with a saturated sodium chloride solution and finally dried over sodium sulfate. Evaporation of the solvents left clear viscous oils from which the product, *o*-duroylbiphenyl, could be induced to crystallize by the addition of methanol. The *o*-duroylbiphenyl melted at 130.5–131.5° when crystallized from ethanol or isopropyl alcohol, and after sublimation melted at 136.5–137.5°.

Anal. Calcd. for $C_{23}H_{22}O$: C, 87.86; H, 7.05. Found: C, 87.83; H, 6.78.

A mixed melting point of this compound with a sample of *o*-duroylbiphenyl prepared by the addition of phenyllithium to duryl phenyl ketone[5] was not depressed.

Experimental details are shown in Table I.

TABLE I

DISPLACEMENT OF A IN *o*-AC_6H_4CODur[a]

Ketone A = (mole)	Phenylmagnesium bromide, mole	Ether, ml.	Benzene, ml.	Time, hr.	Yield of *o*-duroylbiphenyl, %
OC_6H_5 (0.0091)	0.027	115	50	4	99
SC_6H_5 (0.0145)	.03	110	50	10.5	61
SCH_3 (0.007)	.015	50	40	14	37
$SO_2C_6H_5$ (0.004)	.01	60	50	4	68
SO_2CH_3	.02	80	60	17.5	94

[a] For the methods of preparation of the ketones see R. C. Fuson and W. S. Friedlander, THIS JOURNAL, **76**, 4989 (1954).

(3) L. Field and J. W. McFarland, THIS JOURNAL, **75**, 5582 (1953).

(4) All melting points are corrected.

(5) R. C. Fuson, G. P. Speranza and R. Gaertner, *J. Org. Chem.*, **15**, 1155 (1950).

NOYES CHEMICAL LABORATORY
UNIVERSITY OF ILLINOIS
URBANA, ILLINOIS

Some 1,2-, 2,3- and 3,4-Disubstituted Dibenzofurans

BY HENRY GILMAN, THOMAS H. COOK, JOHN A. HOGG JACK SWISS AND ROBERT G. JOHNSON

RECEIVED MAY 15, 1954

A number of *ortho* disubstituted dibenzofurans has been described in the literature.[1-3] The methods of synthesis employed for the preparation of these compounds were, in general, those which have been used for the synthesis of *ortho* derivatives of monosubstituted benzenes.

An earlier paper[1a] from this Laboratory has discussed at some length the homonuclear substitution of dibenzofuran. Available evidence indicated that the strong *ortho–para* directing functions orient an incoming group to the same nucleus, there being two positions available for the introduction of the second substituent.

In the course of further studies concerned with orientation in the dibenzofuran series, we have prepared a variety of 1,2-, 2,3- and 3,4-disubstituted dibenzofurans. The results of our work confirm the previous observations in regard to the orientation tendencies shown by monosubstituted dibenzofurans.

Although 2-diacetamidodibenzofuran is brominated in the 3-position,[1a] reaction of the free amine with bromine yields the 2-amino-1-bromo compound.[4] The structure of the latter compound was proven by its deamination to the known 1-bromodibenzofuran.[1c]

A by-product of the bromination reaction was a dibromo derivative. It was identical with both the bromination product of 2-amino-3-bromodibenzofuran and that of 1-bromo-2-aminodibenzofuran; hence, the dibromo compound must be 1,3-dibromo-2-aminodibenzofuran.

(1) (a) H. Gilman, G. E. Brown, W. G. Bywater and W. H. Kirkpatrick, THIS JOURNAL, **56**, 2473 (1934); (b) H. Gilman, A. L. Jacoby and J. Swislowsky, *ibid.*, **61**, 954 (1939); (c) H. Gilman and P. R. Van Ess, *ibid.*, **61**, 1365 (1939); (d) H. Gilman, P. T. Parker, J. C. Bailie and G. E. Brown, *ibid.*, **61**, 2836 (1939); (e) H. Gilman and M. W. Van Ess, *ibid.*, **61**, 3146 (1939).

(2) R. J. Moualim and K. Venkataraman, *J. Sci. Ind. Research*, **3**, 447 (1945) [*C. A.*, **39**, 4605 (1945)].

(3) K. Schimmelschmidt, *Ann.*, **566**, 184 (1950).

(4) Because the ring-activating amino group (protected by acetylation) in an aminodibenzofuran always has been found to direct an incoming group to the same ring, the structure which we have assigned here to the bromoamine seems more probable than that of the heterosubstituted amine, *i.e.*, 1-bromo-8-aminodibenzofuran.