I is readily monobrominated, but has resisted all efforts to produce a dibromo derivative. α-Bromo-*sym*-tetraphenylacetone (II) reacts readily with methanol, ethanol and aqueous sodium carbonate to yield the corresponding methoxy (III), ethoxy[8] (IV) and hydroxy (V) derivative

$$Ph_2CBrCOCHPh_2 + ROH \longrightarrow Ph_2C(OR)COCHPh_2$$

II; III, R = Me; IV, R = Et; V, R = H

The infrared spectrogram of III and of V reveals a strong absorption at 5.85 μ (carbonyl). The infrared spectrogram of V also shows a strong absorption at 2.92 μ (hydroxyl). An active hydrogen determination of V shows the presence of 2 active hydrogens.[9]

The active hydrogen determination of II gave results indicating 100% enolization and 100% addition. However, only I was formed in this reaction and it was isolated quantitatively. While the gas evolved was not analyzed, these results suggest[10]

$$Ph_2CBrCOCHPh_2 + 2MeMgI \longrightarrow (Ph_2CCOCHPh_2)MgI + C_2H_6 + MgBrI$$

Experimental[11]

Attempted Preparation of Carbonyl Derivatives of I.—Using vigorous and prolonged conditions I was recovered unchanged on treatment with hydrazine, phenylhydrazine, 2,4-dinitrophenylhydrazine, semicarbazide, hydroxylamine (a sealed tube reaction was not tried), and thioglycolic acid.[12] An active hydrogen determination showed 91% enolization and no addition.

Reduction of I by Lithium Aluminum Hydride.—The reaction was run in the regular manner.[13] From 9 g. of I, 8.3 g., 92%, of tetraphenylisopropyl alcohol, m.p. 107–108°, was produced. *Anal.* Calcd. for $C_{27}H_{24}O$: C, 88.97; H, 6.64. Found: C, 88.75; H, 6.76.

Attempted Huang-Minlon Reduction of I.—Following the procedure in the literature,[5] 6.93 g., 73%, of diphenylmethane, m.p. and mixture m.p. 26–27°, was isolated from the reaction of 10 g. of I. In a qualitative test 0.5 g. of I was refluxed for 15 hours with ethanolic potassium hydroxide. A small amount of diphenylacetic acid was isolated. While diphenylmethane was not isolated, its unmistakably characteristic odor pervaded the apparatus. This test shows that hydrazine is not necessary for the cleavage of I.

Autooxidation of I.[7]—A solution of 0.04 mole (14.5 g.) of I and 0.08 mole of potassium *t*-butoxide in 400 ml. of anhydrous *t*-butyl alcohol was heated at 60–65° for five hours while passing in a stream of oxygen. After removal of 200 ml. of solvent by distillation, 100 ml. of water was added and an additional 100 ml. of solvent distilled. The residue was steam distilled, yielding 2.6 g. (0.014 mole) of benzophenone, m.p. 50°, which separated from the distillate. Extraction of the distillate with ether and reaction with excess semicarbazide hydrochloride gave 4.9 g. (0.021 mole) of benzophenone semicarbazone, m.p. 164–165°. This represents a total of 0.035 mole or 87.5% of benzophenone. The alkaline residue from the steam distillation was filtered and the white crystalline material (1.22 g.) was recrystallized from ethanol, yielding 0.55 g., 3.8%, of V, m.p. and mixture m.p. 117–118°. The alkaline solution remaining was boiled with Norite, filtered and acidified, giving 7.0 g. (0.033 mole), 82.5%, of diphenylacetic acid, m.p. 144–145°. When the experiment was repeated, using nitrogen instead of oxygen, I was recovered quantitatively.

Preparation of II.—A solution of 54 g. of I and 50 ml. of bromine in 900 ml. of carbon tetrachloride was heated at 50–60° under reflux for 72 hr. The reaction mixture was irradiated with three ordinary 200 watt light bulbs. After cooling the solution was poured into 800 ml. of cold 10% sodium hydroxide solution. The organic layer was separated, washed with two 300-ml. portions of water and dried over anhydrous sodium sulfate. After filtering, the solvent was removed at the water-pump and the residue was recrystallized from acetone and petroleum ether. The yield of II was 53 g., 82%, m.p. 108–109°. *Anal.* Calcd. for $C_{27}H_{21}OBr$: Br, 18.1; mol. wt., 441. Found: Br, 18.5; mol. wt., 442 (cryoscopic in benzene).

Many unsuccessful attempts to prepare the α,α′-dibromo derivative have been made, starting with both I and II.[14,15] An active hydrogen determination of II showed 103% enolization and 106% addition. On working up the reaction, however, a 93.5% yield of I was the only product which could be found.

Preparation of III, IV and V.—Either III or IV may be prepared in essentially quantitative yield by dissolving II in the appropriate alcohol, refluxing for 5–6 hours, removing excess solvent at the water-pump, cooling and filtering. III is a white crystalline compound, m.p. 73–74°. *Anal.* Calcd. for $C_{28}H_{24}O_2$: C, 85.71; H, 6.38. Found: C, 85.43; H, 6.20. The infrared spectrogram of III shows a strong absorption at 5.85 μ, characteristic of a carbonyl compound. IV is a white crystalline compound, m.p. 78–79°. *Anal.* Calcd. for $C_{29}H_{26}O_2$: C, 85.71; H, 6.40. Found: C, 85.79; H, 6.33. Heating II with isobutyl alcohol or *n*-amyl alcohol resulted in a quantitative recovery of II.[15]

A solution of 23.75 g. of II dissolved in 300 ml. of acetone was added to a solution of 15 g. of sodium carbonate in 200 ml. of water. The mixture was heated under reflux for 12 hr. The acetone was removed by distillation. After solidification the residue was filtered and recrystallized from ethanol, giving 18.2 g., 90%, of V, m.p. 118–119°. *Anal.* Calcd. for $C_{27}H_{22}O_2$: C, 85.66; H, 5.82. Found: C, 85.79; H, 5.88. The infrared spectrogram of V showed strong absorption at 2.92 μ (hydroxyl) and at 5.85 μ (carbonyl). Heating 1 g. of V with aqueous 50% hydrogen iodide converted it quantitatively into I, m.p. and mixture m.p. 133–134°. An active hydrogen determination showed 1.93 active hydrogens per molecule of V. A solution of 3.5 g. of V in 50 ml. of acetic anhydride was heated under reflux for 25 hours. After removal of 25 ml. of solvent at the water-pump, the residue was poured onto ice and filtered. The resulting solid was crystallized from ethanol, yielding 2.74 g., 70%, of α-acetoxy-*sym*-tetraphenylacetone, m.p. 165–167°. *Anal.* Calcd. for $C_{29}H_{24}O_3$: C, 82.86; H, 5.71. Found: C, 82.68; H, 5.73.

(8) The ease of formation of IV from II led Vorlander, ref. 4, to report the m.p. of II, recrystallized from ethanol, as 78°. This is in fact the m.p. of IV.

(9) This evidence precludes the possibility of structures of the type, $Ph_2C(O)(OR)CCHPh_2$, sometimes formed by the solvolysis of α-haloketones; *cf.* C. L. Stevens, W. Malik and R. Platt, THIS JOURNAL, **72**, 4758 (1950). While the spectrogram of IV was not prepared, there is no reason to suppose that ethanol would react any differently from methanol.

(10) A. Löwenbein and L. Schuster, *Ann.*, **481**, 106 (1930), have reported a similar reaction: $Ph_2CBrCOPh + 2PhMgBr \rightarrow (Ph_2CCOPh)MgBr + PhPh + MgBr_2$.

(11) All m.p.'s are uncorrected. Active hydrogens were determined in the usual manner, using methylmagnesium iodide in dibutyl ether. Microanalyses for carbon and hydrogen were performed by Drs. G. Weiler and F. B. Strauss, Oxford, England. The infrared spectrograms were prepared on Nujol mulls by Samuel P. Sadtler and Sons, Inc., Philadelphia, Pa.

(12) J. J. Ritter and M. J. Lover, THIS JOURNAL, **74**, 5576 (1952).

(13) R. F. Nystrom and W. G. Brown, *ibid.*, 2548 (1947).

(14) R. A. Day, M.S. Thesis, Emory University, 1937.

(15) M. R. Bush, M.S. Thesis, Emory University, 1938.

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Nucleophilic Displacement Reactions of Duryl Halophenyl Ketones

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

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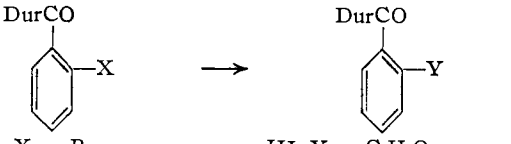
The method developed earlier for making methoxy derivatives[2] of hindered diaryl ketones has now

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

(2) R. C. Fuson and W. C. Hammann, THIS JOURNAL, **73**, 1851 (1951).

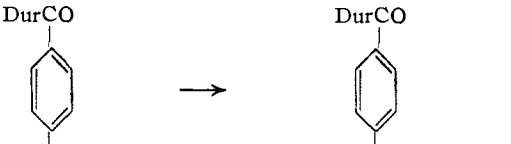
been used successfully for a number of related compounds. *o*-Bromophenyl duryl ketone (I) reacted with sodium phenoxide to give duryl *o*-phenoxyphenyl ketone (III) in a yield of 96%. With *o*-bromophenoxide the yield of duryl *o*-(2-bromophenoxy)-phenyl ketone (IV) was only 31%, as might have been expected on steric grounds.



I, X = Br
II, X = F

III, Y = C_6H_5O–
IV, Y = *o*-BrC_6H_4O–
V, Y = CH_3S–
VI, Y = C_6H_5S–
VII, Y = *p*-$NO_2C_6H_4O$–

The sodium salts of methyl and phenyl mercaptans gave the *o*-methylmercapto V and *o*-phenylmercapto VI derivatives in yields of 97 and 79%, respectively. From the *o*-fluoro ketone II the corresponding phenoxy III and *p*-nitrophenoxy VII derivatives were prepared in yields of 97 and 25%, respectively. The low yield of the nitro derivative may be related to the decrease in basicity which the nitro group exerts on the phenoxide ion. The *p*-phenoxy derivative X was obtained from the *p*-fluoro compound (VIII) in a yield of 98% and in a lower yield from the *p*-bromo ketone IX.



VIII, X = F
IX, X = Br

X

The authors wish to thank Dr. G. C. Finger of the Illinois Geological Survey for generous supplies of *o*- and *p*-fluorobenzoic acids.

Experimental[3]

Duryl *o*-Fluorophenyl Ketone (II).—*o*-Fluorobenzoyl chloride was prepared by treating the corresponding acid with thionyl chloride. To a mixture of 7.88 g. of the acid chloride, 8.05 g. of durene and 90 ml. of carbon disulfide was slowly added 8.0 g. of aluminum chloride. After the mixture had been stirred for 2 hours at room temperature, it was poured into dilute hydrochloric acid. The duryl *o*-fluorophenyl ketone, isolated by conventional procedures, was recrystallized from ethanol; yield 80%. The analytical sample melted at 103–104°.

Anal.[4] Calcd. for $C_{17}H_{17}OF$: C, 79.66; H, 6.69. Found: C, 79.43; H, 7.25.

Duryl *p*-Fluorophenyl Ketone (VIII).—The procedure was similar to that described for the *ortho* isomer; yield 96%. After recrystallization from ethanol and sublimation, the ketone melted at 116–116.5°.

Anal. Calcd. for $C_{17}H_{17}OF$: C, 79.66; H, 6.69. Found: C, 79.73; H, 6.96.

The Procedure for the Displacement Reactions.—The displacement of halogen was accomplished in each case by prolonged heating at rather elevated temperatures of a mixture of the haloketone with the sodium salt of the phenol or mercaptan. The sodium salts of the nitrophenols were prepared by treatment of the molten phenols with solid sodium hydroxide.

(3) All melting points are corrected.

(4) Microanalyses by Mrs. Lucy Chang, Mrs. Esther Fett and Mr. Joseph Nemeth.

The sodium salts of the other phenols were prepared by adding metallic sodium cautiously at 110°. A vigorous reaction occurred, the temperature being controlled with a cold water-bath. It was found possible to use boiling *n*-butyl alcohol as solvent in the reactions involving the mercaptides.

Sodium methyl mercaptide was formed by treatment of the cold mercaptan with a cold 40% aqueous solution of sodium hydroxide.

In the reactions which were carried out without a solvent the products were isolated by pouring the hot reaction mixture into water followed by extraction of the resulting mixture, after cooling, with ether. The ether solutions were washed with dilute sodium hydroxide solution, and with water, and dried over sodium sulfate. The products, obtained by evaporation of the ether, were recrystallized from ethanol. In the reactions of the mercaptides, for which *n*-butyl alcohol was employed as solvent, the products were obtained in crystalline form by filtering the hot reaction mixture and allowing it to cool.

The reactants and the reaction conditions are shown in Table I. The products, their melting points and analytical data are shown in Table II.

TABLE I

REACTIONS OF DURYL HALOPHENYL KETONES

Expt.	Ketone, moles	Phenol or mercaptan, moles	Base, equiv.	Time, hours	Temp., °C.
1	*o*-Br (0.0316)	C_6H_5ONa (0.32)	Na (0.1)	90	160[a]
2	*o*-Br (0.0316)	*o*-BrC_6H_4ONa (0.31)	Na (0.06)	19	145
3	*o*-Br (0.0095)	C_6H_5SNa (0.23)	Na (0.015)	15	Reflux[b,c,d]
4	*o*-Br (0.0095)	CH_3SNa (0.21)	NaOH[e] (0.1)	20	Reflux
5	*o*-F (0.00585)	C_6H_5ONa (0.27)	Na (0.02)	21	150
6	*o*-F (0.00585)	*p*-$NO_2C_6H_4ONa$ (0.18)	NaOH (0.02)	18	160
7	*p*-F (0.0195)	C_6H_5ONa (1.06)	Na[b] (0.08)	20	150
8	*p*-Br[f] (0.0316)	C_6H_5ONa (0.53)	Na (0.1)	41	175

[a] When the reaction was carried out in boiling toluene, only starting material could be isolated. [b] This reaction was carried out under nitrogen. [c] When this reaction was conducted in boiling ethanol, only starting material was isolated. [d] In an alternative procedure a mixture of 0.23 mole of thiophenol, 0.15 mole of sodium hydroxide, 15 ml. of water and 100 ml. of *n*-butyl alcohol was heated under reflux for 18 hours; the yield of the thioether was satisfactory. [e] The sodium hydroxide was dissolved in 10 ml. of water and the solution added to the mercaptan at 0°; *n*-butyl alcohol was then added. [f] For the preparation of this compound see R. C. Fuson, W. S. Friedlander and G. W. Parshall, THIS JOURNAL, **76**, in press (1954). The product of this reaction was a mixture, indicating that the bromo compound undergoes displacement less readily than the fluoro compound or that the reaction takes a different course.

***o*-Duroylphenyl Phenyl Sulfone.**—A solution of 2.4 g. of potassium permanganate in 72 ml. of water was added to a solution of 3.30 g. of duryl *o*-phenylmercaptophenyl ketone in the minimum amount of glacial acetic acid. After the mixture had been allowed to stand for 20 minutes, sulfurous acid was added until the color was discharged. The sulfone, precipitated by pouring the mixture on ice, was recrystallized from a mixture of isopropyl and *sec*-butyl alcohols; yield 2.65 g. The analytical sample melted at 170.5–172°.

Anal. Calcd. for $C_{23}H_{22}O_3S$: C, 72.99; H, 5.86; S, 8.47. Found: C, 72.80; H, 5.85; S, 8.58.

Methyl *o*-Duroylphenyl Sulfone.—By the procedure just described 10 g. of duryl *o*-methylmercaptophenyl ketone was

TABLE II

REACTION PRODUCTS

Expt.[a]	DurCOC$_6$H$_4$X (in which X =)	M.p., °C.	Mol. formula	Analyses, % Calcd. C	Calcd. H	Calcd. S	Found C	Found H	Found S
1	*o*-OC$_6$H$_5$	124.5–125.5	C$_{23}$H$_{22}$O$_2$	83.60	6.71	....	83.51	6.83	...
2	*o*-O-C$_6$H$_4$-Br	210.5–211.5	C$_{23}$H$_{21}$O$_2$Br	67.49	5.17	....	67.90	5.31	...
3	*o*-SC$_6$H$_5$	155.5–156.5	C$_{23}$H$_{22}$OS	79.73	6.40	9.25	79.83	6.44	9.19
4	*o*-SCH$_3$	191.5–192.5	C$_{18}$H$_{20}$OS	75.99	7.09	11.27	76.12	7.07	11.49
5	*o*-OC$_6$H$_5$	124.5–125.5							
6	*o*-O-C$_6$H$_4$-NO$_2$	156–157	C$_{23}$H$_{21}$NO$_4$	73.58	5.64	3.73[b]	73.86	5.64	3.66[b]
7	*p*-OC$_6$H$_5$	146–147.5	C$_{23}$H$_{22}$O$_2$	83.60	6.71	....	83.63	6.90	....

[a] These numbers correspond to the experiments enumerated in Table I. [b] These values are for nitrogen.

treated with 7.5 g. of potassium permanganate in 240 ml. of water; the yield of sulfone was 82%. After recrystallization from methanol, it melted at 195.3–196.3°.

Anal. Calcd. for C$_{18}$H$_{20}$O$_3$S: C, 68.30; H, 6.37; S, 10.13. Found: C, 68.32; H, 6.51; S, 10.23.

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Unsymmetrically-Substituted Piperazines. VII.

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RECEIVED MARCH 11, 1954

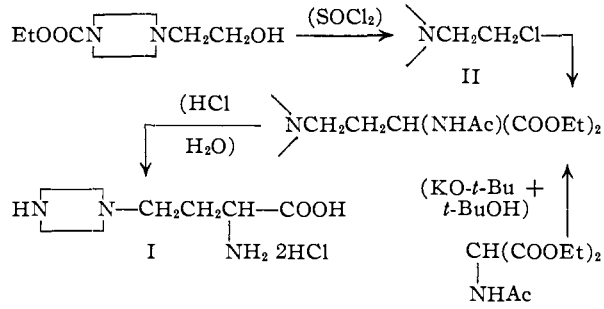
Some unsymmetrically-substituted piperazines prepared in connection with a continuing program[1] for the synthesis and pharmacological evaluation of such compounds were found to possess a moderate order of anthelmintic activity against *Syphacia obvelata*, a mouse pinworm.[2] The preparation and properties of some of the piperazines prepared, most of which have polar substituents, are reported here.

The synthetic routes used, in general, involved the alkylation of N-carbethoxypiperazine[3] by the appropriate halide in a suitable solvent, using an additional equivalent of the amine and filtering at the end of the alkylation to remove amine hydrohalide, or using potassium carbonate or sodium ethoxide to bind the acid which was produced. This procedure served to eliminate the tedious separations and low yields which frequently accompany the direct mono-alkylation of piperazine. 1-Nonyl-4-carbethoxypiperazine was prepared by treating 1-nonylpiperazine[1] with ethyl chlorocarbonate, and converting the hydrochloride so produced to the base with the theoretical amount of sodium ethoxide in ethanol.

Hydrolytic removal of the carbethoxyl group was accomplished by heating with constant-boiling aqueous hydrochloric acid under reflux, the preferred procedure[3] for the extremely water-soluble lower piperazine homologs, and subsequent conversion of the resulting hydrochlorides to the bases with sodium ethoxide in anhydrous ethanol. The carbethoxyl group was removed from 1-octyl-4-carbethoxypiperazine at a reasonable rate by heating it under reflux with aqueous ethanolic sodium hydroxide, provided that vigorous stirring was used. The resulting 1-octylpiperazine was converted by a Schotten–Baumann reaction to its *p*-nitrobenzoyl derivative, whose water-insoluble hydrochloride was reduced by hydrogen and Adams catalyst to 1-octyl-4-p-aminobenzoylpiperazine, the piperazine analog of a piperidine reported[4] to have antitubercular and amoebastatic activity.

For the preparation of the very water-soluble amino acid α-piperazinopropionic acid (Table, line 13), ethyl α-(4-carbethoxypiperazino)-propionate (Table, line 12) was hydrolyzed with boiling aqueous barium hydroxide under reflux. Treatment with carbon dioxide, and subsequent boiling of the solution, allowed the barium to be removed as carbonate. The success of this procedure indicates that the amino acid exists as a zwitterion, as would be expected.

The amino acid I, modelled as a possible antimetabolite to histidine, was prepared in excellent yield as outlined in the partial formulas.



Potassium *t*-butoxide in *t*-butyl alcohol[5] was used as the condensing agent, to ensure the absence of side reactions. The initial condensation product could not be crystallized readily, and so was converted without purification to the amino acid.

The details of the procedure used to recover 2-(4-benzylpiperazino)-propanol from the lithium aluminum hydride reduction of the corresponding propionic acid are given in the Experimental section, since they illustrate some minor modifications of the

(1) For the previous paper of this series, see R. Baltzly, THIS JOURNAL, **76**, 1164 (1954).

(2) H. W. Brown, K. F. Chan and K. L. Hussey, *Am. J. Trop. Med. Hyg*, **3**, 504 (1954).

(3) T. S. Moore, M. Boyle and V. M. Thorne, *J. Chem. Soc.*, 39 (1929).

(4) P. Truitt, G. Sammons and D. Zachry, THIS JOURNAL, **74**, 5961 (1952).

(5) The *t*-butyl alcohol was dried by storing it over calcium hydride at a temperature over its m.p., venting the hydrogen produced. The dry *t*-butyl alcohol produced in this way requires no distillation for synthetic purposes, but is simply decanted from the hydride as needed. It is neutral to test paper.