Experimental

2,2,7-Trimethyl-1-oxo-1,2,3,4-tetrahydronaphthalene.—This compound was prepared by the method of Sengupta,[5] who reported only a boiling point of 121° (5 mm.). Our material, b.p. 141–142° (11 mm.), melted at 38–39°.

2,2,7-Trimethyl-1-oxo-1,2-dihydronaphthalene.—This unsaturated ketone was prepared by bromination and dehydrobromination of 2,2,7-trimethyl-1-oxo-1,2,3,4-tetrahydronaphthalene according to the directions used by Marvell and Geiszler[3] to prepare a similar ketone. The product was obtained in 45% yield, b.p. 122–124° (10 mm.), $n^{20}D$ 1.5682, d^{20}_{20} 1.083.

Anal. Calcd. for $C_{13}H_{14}O$: C, 83.8; H, 7.58. Found: C, 83.3; H, 7.63.

3,4,6-Trimethyl-1-naphthyl Acetate.—A solution of 2.0 g. (0.11 mole) of the above ketone in 25 ml. of acetic anhydride containing 15 drops of sulfuric acid was allowed to stand for six hours. At the end of that time the solution was stirred with ice-water for one-half hour and the product isolated on a büchner funnel, 2.17 g. (95%), m.p. 59–66°. Recrystallization from an ethanol–water mixture raised the melting point to 87–88°.

Anal. Calcd. for $C_{15}H_{16}O_2$: C, 78.8; H, 7.07. Found: C, 78.5; H, 7.16.

3,4,6-Trimethyl-1-naphthol.—One gram (0.0044 mole) of the acetate was treated for ten minutes with 20 ml. of boiling 5% methanolic potassium hydroxide. This solution was poured over a mixture of ice and sufficient dilute hydrochloric acid to neutralize the base. The solid product, 0.77 g. (96%), was isolated by suction filtration. After recrystallization from methanol–water mixture the naphthol melted at 99–101°. A melting point of 99–100° has been reported[6] for this naphthol.

3,4,6-Trimethyl-1-methoxynaphthalene.—A solution containing 0.4 g. (0.0021 mole) of the above naphthol in 2 ml. of dry methanol was mixed with 7.0 ml. of an ethereal solution of diazomethane. The mixture was allowed to stand 24 hours at room temperature, after which time the solvents were removed by evaporation. The yellow solid residue was dissolved in ether, washed with dilute sodium hydroxide and the ether removed by evaporation. The residue was recrystallized from ethanol giving a solid melting at 89.5–90° (lit.[6,7] m.p. 88, 89–90°).

The trinitrobenzene adduct of the above ether crystallized from methanol as long orange needles, m.p. 191–193°. This adduct is reported[6] to melt at 193–194°.

CORVALLIS, OREGON

[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

Displacement of Nuclear Halogen Atoms in Hindered Aryl Ketones by the Action of Grignard Reagents

BY REYNOLD C. FUSON, WILLIAM S. FRIEDLANDER[1] AND GEORGE W. PARSHALL[2]

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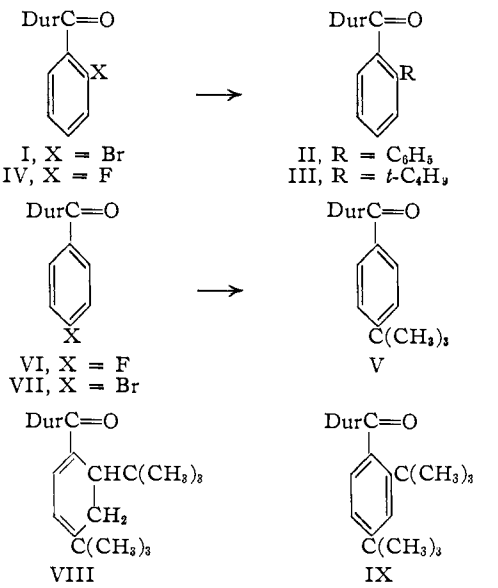
Duryl *p*-fluorophenyl ketone reacts with *t*-butylmagnesium chloride to give *p*-*t*-butylphenylduryl ketone in high yield. The analogous bromo ketone gives the same product accompanied by 2,4-di-*t*-butyl-2,3-dihydrophenyl duryl ketone. *o*-Bromophenyl duryl ketone undergoes replacement with phenylmagnesium bromide to give *o*-duroylbiphenyl. With the *t*-butyl reagent loss of bromine is also observed but the *t*-butyl radical enters the *para* position. Duryl *o*-fluorophenyl ketone also undergoes *p*-*t*-butylation with the *t*-butyl reagent, the fluorine atom being retained.

In the preceding papers of this series[3] it has been shown that Grignard reagents effect nucleophilic displacement of methoxyl, acyloxyl and cyano groups from the *ortho* and *para* positions of hindered aryl ketones. The present paper deals with the displacement of halogen atoms from such ketones. A displacement of this type was reported earlier for *o*-bromophenyl mesityl ketone, which reacted with phenylmagnesium bromide to give 2,6-diphenylphenyl mesityl ketone in a low yield.[4] Also, an attempted displacement of bromine from *p*-bromophenyl mesityl ketone by the phenyl and α-naphthyl reagents produced compounds which, while not identified, are known to contain bromine.[5]

In the present work, which deals with halogen derivatives of duryl phenyl ketone, it has been found that, although displacement at the *ortho* position occurs, the products are obtained only in low yields. *o*-Bromophenyl duryl ketone (I) reacts with phenylmagnesium bromide, for example, to give *o*-duroylbiphenyl (II) in a yield of only 6.7%. With *t*-butylmagnesium chloride and *o*-bromophenyl duryl ketone (I) the product, obtained in a yield of 15%, is *p*-*t*-butylphenyl duryl ketone (V) rather than the expected *ortho* isomer III. It is presumed that the dihydroaromatic compound, produced by addition, is aromatized by loss of the elements of hydrogen bromide. Under similar conditions, however, duryl *o*-fluorophenyl ketone (IV) gave duryl 2-fluoro-4-*t*-butylphenyl ketone, the halogen atom being retained; the yield was 35%.



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

(2) National Science Foundation Fellow, 1952–1953; Allied Chemical and Dye Corporation Fellow, 1953–1954.

(3) For the preceding communication see R. C. Fuson and W. S. Friedlander, THIS JOURNAL, **75**, 5410 (1953).

(4) R. C. Fuson and S. B. Speck, *ibid.*, **64**, 2446 (1942).

(5) R. C. Fuson, M. D. Armstrong and S. B. Speck, *J. Org. Chem.*, **7**, 297 (1942).

Displacement of halogen atoms from the *para* position, however, proceeded much more satisfactorily. The *p*-*t*-butyl phenyl ketone V was obtained from the *p*-fluoro ketone VI in a yield of 84% and from the *p*-bromo ketone VII in a yield of 50%. In the latter case 2,4-di-*t*-butyl-2,3-dihydrophenyl duryl ketone (VIII) was obtained also, the yield being 42%. Dehydrogenation of the dihydro compound over a palladium–charcoal catalyst at 250° gave the fully aromatized di-*t*-butylphenyl duryl ketone (IX). That the second *t*-butyl group is in the position *ortho* to the ketone function seems certain since steric requirements at the *meta* position of the phenyl ring or at the *para* position of the duryl ring seem prohibitive.[6]

The reaction of *t*-butylmagnesium chloride with *p*-*t*-butylphenyl duryl ketone under conditions similar to those used in the displacement of bromine also gave 2,4-di-*t*-butyl-2,3-dihydrophenyl duryl ketone. This reaction serves to establish the structure of the latter product since it has been shown that *p*-*t*-butylphenyl duryl ketone is alkylated in the *ortho* position by the methyl Grignard reagent.[7] Furthermore, a similar arrangement of the double bonds has been shown to exist in the *ortho* alkylation product obtained from duryl phenyl ketone and methylmagnesium iodide.[8]

Experimental[9]

p-Bromophenyl Duryl Ketone (VII).—A mixture of 50 g. of *p*-bromobenzoic acid and 50 ml. of thionyl chloride was boiled under reflux for 6 hours and the excess thionyl chloride was distilled. The *p*-bromobenzoyl chloride distilled at 123–125° (20 mm.), yield 47.5 g. (87%). A solution of the *p*-bromobenzoyl chloride and 29 g. of durene in 200 ml. of carbon disulfide was stirred vigorously while 31 g. of anhydrous aluminum chloride was added. The reaction mixture was stirred at room temperature for 90 minutes after the completion of the addition. It was poured into cold water, and the product which precipitated was collected by filtration. The organic layer of the filtrate was removed, dried over magnesium sulfate and freed of solvent by distillation. The residual *p*-bromophenyl duryl ketone was combined with that collected by filtration, washed with cold ether and recrystallized from benzene. It separated as colorless cubical crystals, m.p. 182–184°, yield 60 g. (86%).

Anal.[10] Calcd. for $C_{17}H_{17}BrO$: C, 64.36; H, 5.40; Br, 25.19. Found: C, 64.76; H, 5.27; Br, 25.05.

Action of *t*-Butylmagnesium Chloride on *p*-Bromophenyl Duryl Ketone.—The Grignard reagent was prepared by treating 2.4 g. of magnesium with 13.0 ml. of *t*-butyl chloride in 75 ml. of ether. A solution of 6.4 g. of *p*-bromophenyl duryl ketone in 75 ml. of hot benzene was added and the mixture was heated, with stirring, for one hour and decomposed with cold dilute hydrochloric acid. The organic layer was separated, dried over magnesium sulfate and freed of solvent by evaporation. The residue was dissolved in methanol and water was added until a light yellow solid precipitated. The latter was fractionally sublimed. The fraction which sublimed at 95–105° (0.04 mm.) consisted primarily of *p*-*t*-butylphenyl duryl ketone (V). It crystallized from methanol as white flakes which melted at 124.5–126°, yield 3.0 g. (50%). A mixed melting point with an authentic sample showed no depression. The fraction which sublimed at 130–140° (0.04 mm.) crystallized from methanol as fine colorless needles which melted at 130–131°. The yield of 2,4-di-*t*-butyl-2,3-dihydrophenyl duryl ketone (VIII) was 3.0 g. (42%).

Anal. Calcd. for $C_{25}H_{36}O$: C, 85.17; H, 10.29. Found: C, 85.31; H, 10.49.

The infrared spectrum[11] contains bands at 1645 and 1574 cm.$^{-1}$ assignable to a hindered conjugated carbonyl group and a system of conjugated ethylenic double bonds, respectively.

2,4-Di-*t*-butylphenyl Duryl Ketone (IX).—A mixture of 0.65 g. of 2,4-di-*t*-butyl-2,3-dihydrophenyl duryl ketone and 0.14 g. of 10% palladium-on-charcoal was heated at 250–260° for 12 minutes in a nitrogen-swept flask. After being cooled, the residue was extracted with methanol. Addition of water to the methanol solution induced the precipitation of a white solid, which was dried and sublimed at 130° (0.05 mm.). The 2,4-di-*t*-butylphenyl duryl ketone crystallized from methanol as white needles which melted at 155.5–156.5°.

Anal. Calcd. for $C_{25}H_{34}O$: C, 85.66; H, 9.78. Found: C, 85.82; H, 9.83.

The infrared spectrum contains bands assignable to a hindered and conjugated carbonyl group (1672 cm.$^{-1}$) and to a 1,2,4-trisubstituted benzene ring.

Action of *t*-Butylmagnesium Chloride and *p*-*t*-Butylphenyl Duryl Ketone.—By a procedure similar to that outlined for *p*-bromophenyl duryl ketone, 3 g. of *p*-*t*-butylphenyl duryl ketone was treated with the *t*-butyl reagent. After the usual work-up procedure, the crude product was fractionally sublimed. The fraction subliming at 95–105° (0.04 mm.) consisted of 1.5 g. of unchanged *p*-*t*-butylphenyl duryl ketone. From the fraction subliming at 130–140° (0.04 mm.), 1 g. of 2,4-di-*t*-butyl-2,3-dihydrophenyl duryl ketone (VIII) was obtained, m.p. 129.5–130.5°. A mixed melting point determination with the product obtained from *p*-bromophenyl duryl ketone was not depressed.

Action of *t*-Butylmagnesium Chloride on *o*-Bromophenyl Duryl Ketone.—The usual procedure was applied to 6.4 g. of the ketone. The product was dissolved in methanol and fractionally precipitated by addition of water. The first fraction was an intractable yellow oil, but the succeeding fractions were yellow solids. The crude solids were sublimed at 100–105° (0.03 mm.). After recrystallization from methanol, 0.9 g. (15%) of *p*-*t*-butylphenyl duryl ketone (V) was obtained, m.p. 124.5–126°. A mixed melting point with an authentic sample was not depressed.

Action of Phenylmagnesium Bromide on *o*-Bromophenyl Duryl Ketone.—To a filtered, boiling solution of phenylmagnesium bromide made from 0.72 g. (0.03 gram atom) of magnesium and 4.8 g. (0.03 mole) of bromobenzene in 70 ml. of absolute ether was added, during 15 minutes, a solution of 3 g. (0.0095 mole) of *o*-bromophenyl duryl ketone in 50 ml. of dry benzene. After the mixture had been heated under reflux for 15 hours, it was poured into dilute hydrochloric acid; the ether layer was removed and dried over sodium sulfate. Evaporation of the solvent left a brown oil, which was dissolved in hot ethanol. The solution was treated with Darco, filtered and cooled; 0.2 g. of crude *o*-duroylbiphenyl crystallized, m.p. 125–128° (3.7% yield). After recrystallization from ethanol it melted at 130–131°; a mixture melting point with an authentic sample was not depressed.

Action of *t*-Butylmagnesium Chloride on Duryl *o*-Fluorophenyl Ketone.—A solution of the Grignard reagent, made from 0.96 g. of magnesium, 3.68 g. of *t*-butyl chloride and 30 ml. of absolute ether, was filtered into 20 ml. of boiling ether. To this solution was added, during 5 minutes, a solution of 2.0 g. of duryl *o*-fluorophenyl ketone[12] in 40 ml. of ether. A blue color developed and persisted during the reflux period of 15 hours. The mixture was then poured into dilute hydrochloric acid and the crude product isolated as described above. By crystallization of the product from absolute ethanol and sublimation of the mother liquor residue, 0.5 g. (35% yield) of material was obtained, m.p. 84–88°. Several recrystallizations from methanol and a sublimation gave pure duryl 2-fluoro-4-*t*-butylphenyl ketone, m.p. 88–88.5°.

Anal. Calcd. for $C_{21}H_{25}OF$: C, 80.73; H, 8.06. Found: C, 80.56; H, 8.03.

(6) H. C. Brown, G. K. Barbaras, H. L. Berneis, W. H. Bonner, R. B. Johannesen, M. Grayson and K. L. Nelson, THIS JOURNAL, **75**, 1 (1953); H. C. Brown and K. L. Nelson, *ibid.*, **75**, 24 (1953).

(7) R. C. Fuson and R. Tull, *ibid.*, **71**, 2543 (1949).

(8) R. C. Fuson, B. C. McKusick and J. Mills, *J. Org. Chem.*, **11**, 60 (1946).

(9) All melting points are corrected.

(10) Microanalyses by Mrs. Esther Fett and Mr. Joseph Nemeth.

(11) The infrared spectra were recorded and interpreted by Miss Helen Miklas.

(12) R. C. Fuson and W. S. Friedlander, THIS JOURNAL, **76**, 1089 (1954).

The infrared spectrum has absorption maxima that are attributable to hindered carbonyl, 1,2,4-trisubstituted phenyl and *t*-butyl groups and to the fluorine atom.

Action of *t*-Butylmagnesium Chloride on Duryl *p*-Fluorophenyl Ketone.[12]—The procedure was similar to that just described. The crude product weighed 2.45 g. (84% yield) and, after crystallization from ethanol, melted at 126–127°. A mixed melting point with an authentic sample of *p*-*t*-butylphenyl duryl ketone (V) was not depressed.

URBANA, ILLINOIS

[CONTRIBUTION FROM THE STERLING-WINTHROP RESEARCH INSTITUTE]

Derivatives of 4-Amino-2-hydroxybenzoic Acid. III. Thiol Esters

BY R. O. CLINTON, U. J. SALVADOR AND S. C. LASKOWSKI

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Dialkylaminoalkyl ester derivatives of 4-amino- and 4-alkylamino-2-alkoxythiolbenzoic acids have been prepared for testing as local anesthetics. Among these thiol esters have been found compounds far surpassing in activity any local anesthetics hitherto known.

In previous communications[1,2] from these laboratories there have been described several series of dialkylaminoalkyl-4-amino- and 4-alkylamino-2-hydroxybenzoates and the corresponding 2-alkoxy- and 2-benzyloxybenzoates, prepared in a search for more active local anesthetics.

Prior investigations[3] have shown that basic esters derived from thiolbenzoic acids are frequently more active as local anesthetics than the corresponding oxygen analogs (*e.g.*, 2-diethylaminoethyl 4-aminothiolbenzoate (Thiocaine) *vs.* 2-diethylaminoethyl 4-aminobenzoate (procaine)[4]), although this increase in activity is usually accompanied by a proportionate increase in toxicity and a *more* than proportionate increase in irritancy.[5] However, when we extended previous series[1,2] to include the corresponding thiol esters, a surprisingly large increase in local anesthetic activity was noted and, further, this increase in activity was not accompanied by a proportionate increase in irritancy.[6]

A single position isomer of the compounds presently described has appeared in the literature. Harris and Braker[7] have prepared 2-diethylaminoethyl 3-amino-4-butoxythiolbenzoate, but no pharmacological data on this compound have been published.

The dialkylaminoalkyl 2-alkoxy-4-nitrothiolbenzoates were readily synthesized from the parent 2-alkoxy-4-nitrobenzoic acids[2] and dialkylaminoalkylthiols[8] by a modification of the procedure used for the preparation of the corresponding oxygen analogs.[2] Reduction to the 4-amino derivatives and subsequent reductive alkylation to the 4-alkylamino derivatives offered no difficulties. The alternative path used for the preparation of the latter compounds, *i.e.*, through condensation of a dialkylaminoalkanethiol with a 4-alkylamino-2-alkoxybenzoyl chloride hydrochloride, gave poor yields, and purification of the products was very difficult.

The thiol ester derivatives of 4-amino-2-hydroxybenzoic acid are listed in Tables I–III.

In order to determine whether the unexpectedly high local anesthetic activity found with the dialkylaminoalkyl 2-alkoxy-4-aminothiolbenzoates was anomalous, or could be ascribed to other alkoxy aminothiolbenzoates, we also prepared several position isomers of this type. In these isomers the alkoxy group occupied the 2-, 3- or 4-position and the amino group occupied the 3-, 4- or 5-position; included was the example given by Harris and Braker.[7] All of these compounds proved to be much less active and much more irritating than the corresponding 2-alkoxy-4-amino analogs. The properties of these compounds are listed in Table IV.

Experimental[9]

Dialkylaminoalkyl 2-Alkoxy-4-nitrothiolbenzoates.—All of the nitrothiolbenzoates were prepared by a standard procedure, involving a definite ratio of components. An example follows.

To a stirred mixture of 26.7 g. (0.10 mole) of 2-hexyloxy-4-nitrobenzoic acid, 9.5 g. (0.12 mole) of pure, dry pyridine and 300 ml. of dry benzene was added, dropwise, a solution of 9.5 g. (0.08 mole) of pure thionyl chloride in 50 ml. of dry benzene during a period of ten minutes. The heterogeneous mixture was stirred and refluxed for ten minutes, cooled to 40°, and there was added slowly with stirring a solution of 8.0 g. (0.06 mole) of 2-diethylaminoethanethiol in 50 ml. of dry benzene. After stirring for ten minutes at 50°, the mixture was cooled, water was added and the aqueous layer was made strongly alkaline by the addition of solid potassium carbonate. The benzene layer was separated and washed with water, dilute sodium bicarbonate solution, and again with water. After drying over Drierite the benzene solution was decolorized by means of Darco G-60 and concentrated to dryness *in vacuo*. The residual oil was diluted with toluene and again concentrated *in vacuo* to remove traces of pyridine. There was thus obtained crude 2-diethylaminoethyl 2-hexyloxy-4-nitrothiolbenzoate as a pale yellow oil. The yields varied from 80–90%. The derivatives were prepared by the usual methods.

Dialkylaminoalkyl 2-Alkoxy-4-aminothiolbenzoates.—These compounds were prepared by the iron–hydrochloric acid reduction of the nitrothiol esters by the general method

(1) R. O. Clinton, S. C. Laskowski, U. J. Salvador and Mary Wilson, THIS JOURNAL, **73**, 3674 (1951).

(2) R. O. Clinton, S. C. Laskowski, U. J. Salvador and Mary Wilson, *ibid.*, **74**, 592 (1952).

(3) R. O. Clinton, U. J. Salvador and S. C. Laskowski, *ibid.*, **71**, 3366 (1949); N. F. Albertson and R. O. Clinton, *ibid.*, **67**, 1222 (1945).

(4) L. S. Fosdick and H. L. Hansen, *J. Pharmacol.*, **50**, 323 (1934); Y. K. Nolle, *Farm. i. Farmacol. (U.S.S.R.)*, No. 2, 1 (1937) [*C. A.* **34**, 3820 (1940)].

(5) *Inter al.*, Thiocaine is more than seven times as irritating as procaine by the Standard Trypan Blue test (unpublished observations of Dr. F. P. Luduena).

(6) Preliminary pharmacological results: F. P. Luduena, R. O. Clinton and S. C. Laskowski, *Science*, **118**, 138 (1953).

(7) S. E. Harris and W. Braker, U. S. Patent 2,342,142 (1944).

(8) *Cf.* ref. 3 and references cited therein.

(9) All melting points are corrected. They were determined in a modified Hershberg apparatus, using total-immersion N.B.S. calibrated thermometers. The sample was immersed 15° below the melting point, 3° rise per minute. The analyses were done by Mr. M. E. Auerbach, Mr. K. D. Fleischer, and their staffs.