Conversion of 2 to *o*-Bromobenzoic Acid. A solution of **2** was prepared as described in A and prior to quenching was added to bromine (excess in carbon tetrachloride). The acid **1** was isolated by conventional means and obtained in nearly quantitative yield.

***m*-Benzoylbenzoic acid** was prepared from *m*-bromobenzoic acid (0.0125 mol) by a procedure essentially identical with that described in B; the mixture was maintained at −20 to −10° (5 hr) prior to quenching with water. There was obtained (1) benzoic acid (mp 118–120°, 9.2%), (2) *m*-benzoylbenzoic acid [**8**, 69%, mp 155–158°; 63% from chloroform–petroleum ether,[6] mp and mmp 161–162° (lit.[8] mp 161–162°)]. The neutral fraction contained only trace quantities of products other than valerophenone (9%).

***p*-Benzoylbenzoic acid** was prepared from *p*-bromobenzoic acid as described for **8**. The acid fraction on chromatography [silica gel, petroleum ether[6]–diethyl ether (70:30) as eluent] gave *p*-benzoylbenzoic acid [40%, mp 199–201° (lit.[9] mp 197–200°)] and benzoic acid (30%).

When the amount of tetrahydrofuran was increased twofold, only benzoic acid was obtained.

When the procedure was carried out as described for **8** but with a mixture of tetrahydrofuran–hexane (60:40) the yield of *p*-benzoylbenzoic acid was 55–60% (multiple runs).

Acknowledgment. The authors would like to express their appreciation to the U. S. Army Research Office through Grant DAHCO4 74 GD128 for partial support of this work.

Registry No.—**1**, 88-65-3; **2**, 51310-60-2; **4**, 51310-61-3; **6**, 85-52-9; **8**, 579-18-0; **10**, 611-95-0; *n*-butyllithium, 109-72-8; benzoic acid, 65-85-0; *m*-bromobenzoic acid, 585-76-2; *p*-bromobenzoic acid, 586-76-5.

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(2) G. Kobrich and P. Buck, *Chem. Ber.*, **103**, 1412 (1970).
(3) The possibility that **6** was formed by a sequence involving reaction of **2** with *n*-butyl bromide to form an ester with subsequent condensation of the derived ester with **2** was not supported by the observation that the lithium salt of benzoic acid does not react with *n*-butyl bromide at −20°.
(4) (a) A. H. Gleason and G. Dougherty, *J. Amer. Chem. Soc.*, **51**, 310 (1929); (b) L. F. Fieser, "Experiments in Organic Chemistry," 3rd ed, D. C. Heath, Boston, Mass., 1957, p 159.
(5) *Cf.* E. Barnett, "Anthracene and Anthraquinones," Baillière, Tindall and Cox, London, 1921.
(6) Boiling point 30–60°.
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Synthesis of Isomeric Methyl Benzoylbenzoates and Substituted *o*-, *m*-, and *p*-Benzoylbenzoic Acids

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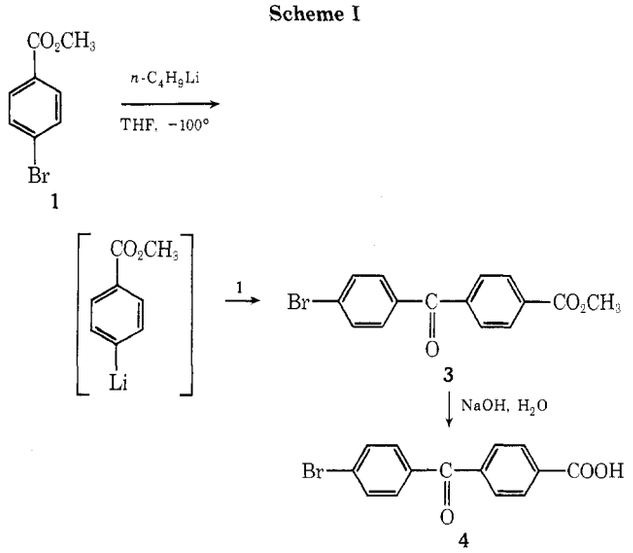
n-Butyllithium reacts selectively at −100° with isomeric methyl bromobenzoates by halogen–metal exchange. The corresponding anions derived from the meta and para isomers react readily with methyl ester functions at −100°; however, the anion derived from the ortho isomer reacts only slowly at this temperature, which permits complete metal–halogen interchange. The self-condensation of isomeric methyl bromobenzoates, and the reactions of dianions derived from the isomeric bromobenzoic acids with substituted methyl benzoates, provide ready access to a wide variety of *o*-, *m*-, and *p*-benzoylbenzoic acids.

In a previous communication[1] we reported a convenient procedure for a one-step conversion of bromobenzoic acids to *o*-, *m*-, and *p*-benzoylbenzoic acids. While it is apparent that this concept can be extended to a variety of substituted halobenzene derivatives, we were particularly interested in examining comparable reactions of the isomeric methyl bromobenzoates with *n*-butyllithium; it was anticipated that an understanding of competitive halogen–metal exchange *vs.* carbonyl addition reactions in such systems would permit a more versatile procedure for the preparation of a variety of isomeric aroylbenzoic acids.

A. Self-Condensation of Methyl Bromobenzoates. Methyl esters are considerably more reactive to anion addition reactions than carboxylate ions previously studied;[1] nevertheless, reaction of methyl *p*-bromobenzoate with *n*-butyllithium in tetrahydrofuran at −100° is selective in that the primary reaction involves halogen–metal interchange rather than addition of alkyllithium to the carbonyl ester function. The derived anion **2** did, however, react as formed at the ester function of unreacted **1**, as shown in Scheme I.

Scheme I



The principal product, methyl 4-(*p*-bromobenzoyl)benzoate (**3**), obtained pure in 63% yield when 0.75 molar equiv of *n*-butyllithium was employed, was unknown, and was further characterized by hydrolysis (~100% yield) to the corresponding acid **4**. The yield of **3** was optimum with approximately 0.75 molar equiv of *n*-butyllithium. The yield of **3** dropped to 49% when 0.6 molar equiv of *n*-butyllithium was employed, and in this case 9% of **1** was recovered unchanged; when 1 molar equiv of *n*-butyllithium was employed the yield of **3** was 57%.

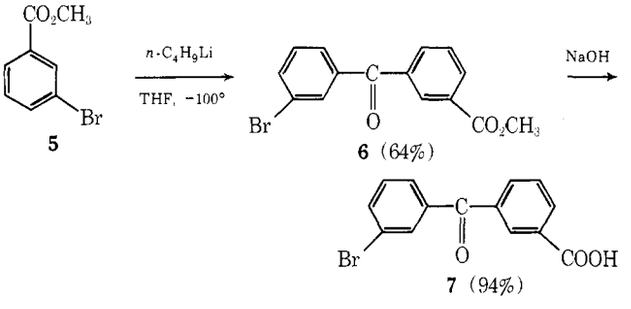
The temperature of the above reaction was found to be critical if high yields of bromo ester **3** are to be obtained.

When 1 was treated with *n*-butyllithium at −75° the yield of 3 was only 10–15%. The principal product in this case was a neutral oil which contained OH, n-C_4H_9, and CO_2CH_3 functions (by ir and nmr), establishing competitive reactions of *n*-butyllithium with ester or carbonyl functions; however, this material gave an oily acid on hydrolysis and was not examined further.

The above sequence provides a remarkably easy route to methyl 4-(*p*-bromobenzoyl)benzoate (3) and it is assumed that the method can be extended to related compounds containing substituents less reactive to anion addition than the ester function.

The sequence is by no means limited to the synthesis of benzoic acids substituted in the para position. Thus, when methyl *m*-bromobenzoate was treated similarly with 0.75 molar equiv of *n*-butyllithium at −100°, no unchanged bromo ester 5 was detected and methyl 3-(*m*-bromobenzoyl)benzoate (6) (Scheme II) was obtained directly in 64% yield (pure). The ester 6 was unknown and was further characterized by conversion to the new acid 7.

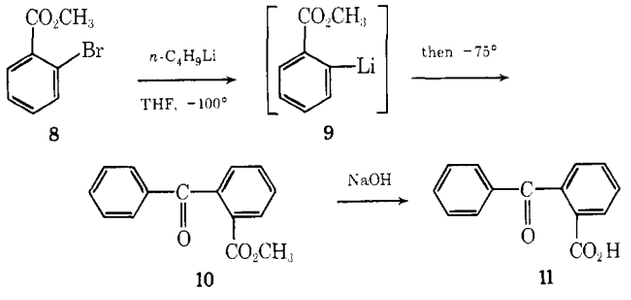
Scheme II



5 6 (64%) 7 (94%)

The reaction of methyl *O*-bromobenzoate (8) with *n*-butyllithium followed a different course than that observed for the meta and para isomer, although, as for reactions of 1 and 5, metal–halogen interchange occurred rather than direct addition of alkyllithium to the ester function (Scheme III). Reaction of the intermediate anion 9 with unchanged bromo ester 8 was slow at −100°, as anticipated from steric considerations, which permitted complete metalation of 8 to 9. When the mixture was warmed to −75° the anion 9 self condensed and, subsequent to addition of water, there was obtained an 88% yield of methyl *o*-benzoylbenzoate (10). Although we could not induce this low-melting ester to crystallize, it was pure by nmr, and was hydrolyzed in essentially quantitative yield to *o*-benzoylbenzoic acid (11).

Scheme III

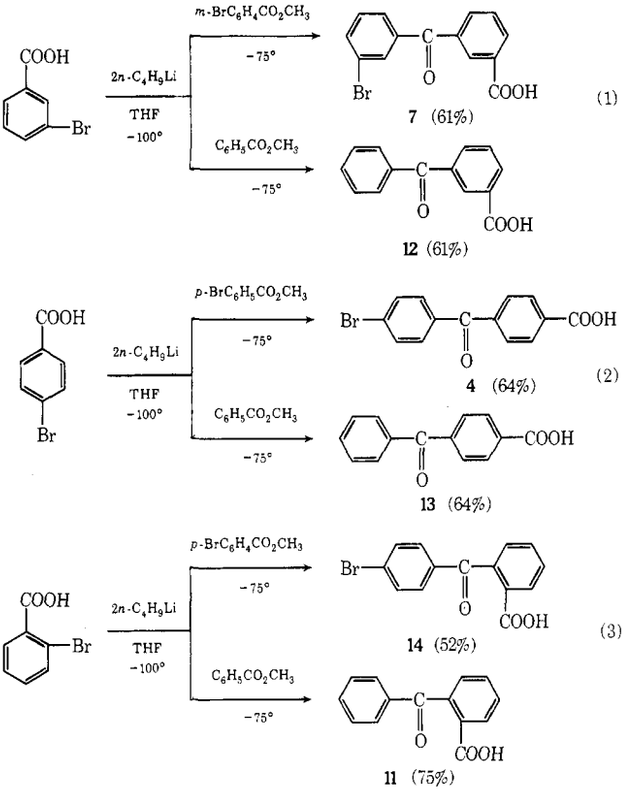


8 9 10 11

In the above experiment it was found expedient to use 1 molar equiv of *n*-butyllithium; use of 0.75 molar equiv of *n*-butyllithium gave 10 in 49% yield and appreciable starting ester 8 (31%).

B. Crossover Experiments. In view of the stability of the dianions prepared from the isomeric bromobenzoic acids[1] at −100° and the reactivity of the methyl ester group toward aryl anions observed at −100 to −75°, it became apparent that a seemingly broad spectrum of substituted benzoic acids could be prepared by crossover experiments. While we have not yet defined the scope of this method, we have demonstrated its utility by the examples outlined in Scheme IV.

Scheme IV

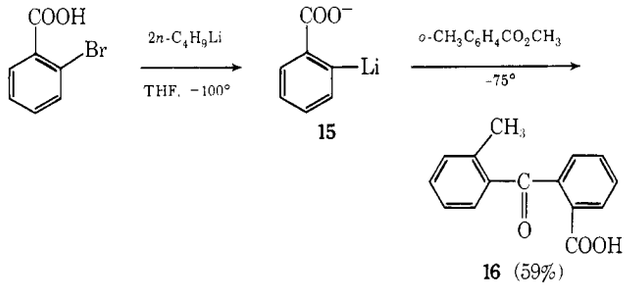


Since the only obvious limitation to this synthesis of isomeric aroylbenzoic acids is that the ester moiety contain functional groups less reactive toward nucleophilic addition than the ester function itself, it is apparent that this scheme constitutes a useful method, based on Gilman's pioneering work, for the synthesis of aromatic compounds. In view of the limited scope of the only other practical synthesis of anthraquinones (from *o*-benzoylbenzoic acids prepared by the Friedel–Crafts phthalic anhydride synthesis[2]) this procedure should prove of value for the preparation of precursors to anthraquinones and polynuclear aromatic systems not easily available by other routes.

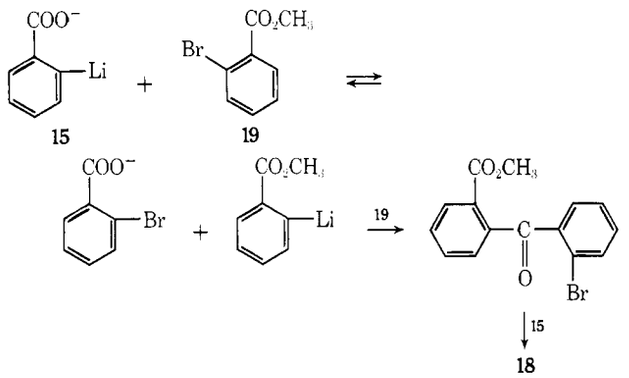
The procedure is also applicable for the preparation of the more hindered ortho,ortho-substituted cases summarized in Scheme V. Thus, reaction of 15 with methyl *o*-toluate gave 16 (59%, pure). Reaction of 15 with methyl *o*-bromobenzoate was of interest since in addition to the expected acid 17 (45%), there was also obtained an appreciable quantity (29%) of trimer acid 18. While 18 could theoretically form by addition of 15 to the salt of 17, this seems unlikely, since in no other case have we observed such addition to carboxylate functions at −75°. It seems more likely that 18 is formed by competitive lithium exchange reactions as, for example, shown in Scheme VI; however, this possibility has not been examined.

It would appear that the condensation of dianions of type 15 with acid halides is not as efficient for the preparation of *o*-benzoylbenzoic acids as is condensation with the corresponding ester. Formation of considerable amounts of 23 (19%) along with 16 (41%) by addition of 20

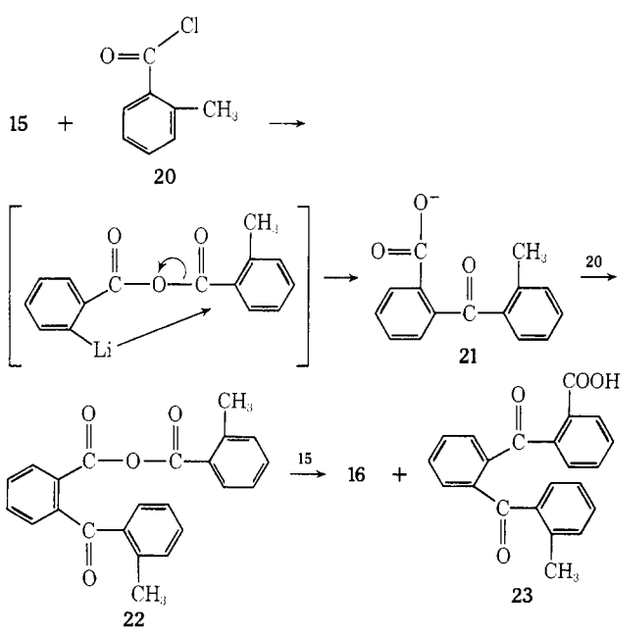
Scheme V



Scheme VI



Scheme VII



to **15** at −75° is consistent with the conclusion that anhydride formation is faster (or competitive) with carbanion addition as summarized in Scheme VII. Similarily, addition of *o*-bromobenzoyl chloride to **15** at −75° gave a mixture of **17** (31%) and **18** (29%).

Experimental Section

Self-Condensation of Methyl Bromobenzoates. Reaction of Methyl *p*-Bromobenzoate (1) with *n*-Butyllithium. *n*-Butyllithium (9.4 ml of ~2 *M* solution in hexane, ~0.0185 mol) was slowly added (1 hr) to a solution of **1** (5.4 g, 0.025 mol, predried) in tetrahydrofuran (50 ml, distilled from $LiAlH_4$). The mixture was under nitrogen and the temperature was not allowed to rise above −95° (liquid N_2, diethyl ether). The mixture was allowed to warm to −75° and after 3 hr was poured into 5% aqueous hydrochloric acid (50 ml). The resulting mixture was extracted with ether and the extracts were dried ($MgSO_4$). The white solid (5.2 g, mp 110–130°) obtained by removal of ether was recrystallized from chloroform–methanol to give 2.5 g of methyl 4-(*p*-bromobenzoyl)benzoate (**3**, 63% yield, mp 177–178°).

Anal. Calcd for $C_{15}H_{11}BrO_3$: C, 56.45; H, 3.47; Br, 25.04. Found: C, 56.66; H, 3.63; Br, 24.95.

When 0.6 molar equiv of *n*-butyllithium was used, the yield of **3** was 49%; 9% of **1** was recovered; with 1 molar equiv of *n*-butyllithium the yield of **3** was 57%.

4-(*p*-Bromobenzoyl)benzoic acid (**4**, 96% yield, mp 274° from chloroform–methanol) was obtained from **3** by alkaline hydrolysis.

Anal. Calcd for $C_{14}H_9BrO_3$: C, 55.10; H, 2.97; Br, 26.19. Found: C, 54.77; H, 3.28; Br, 26.29.

Methyl 3-(*m*-bromobenzoyl)benzoate (**6**, 64% yield, mp 98–99° from methanol) was obtained from methyl *m*-bromobenzoate (**5**) as described above for **3**.

Anal. Calcd for $C_{15}H_{11}BrO_3$: C, 56.45; H, 3.47; Br, 25.04. Found: C, 56.22; H, 3.67; Br, 25.21.

3-(*m*-Bromobenzoyl)benzoic acid (**7**, 94% yield, mp 231–232° from chloroform–methanol) was obtained from **6** by alkaline hydrolysis.

Anal. Calcd for $C_{14}H_{19}BrO_3$: C, 55.10; H, 2.97; Br, 26.19. Found: C, 54.93; H, 3.07; Br, 26.34.

Methyl *o*-Benzoylbenzoate (10). Reaction of methyl *o*-bromobenzoate with *n*-butyllithium (0.75–1.0 molar equiv) was carried out as described above for **3** to give a yellow oil which showed one major and two minor components by tlc [silica gel, petroleum ether[3]–diethyl ether (80:20)]. The product was chromatographed on silica gel to give 0.264 g (88% yield) of **10** as a light yellow oil (lit.[4] mp 52°) which showed no impurities by nmr. Hydrolysis of the ester with aqueous sodium hydroxide gave quantitative conversion to *o*-benzoylbenzoic acid (mp and mmp[5] 128–129°).

Crossover Experiments. 3-(*m*-Bromobenzoyl)benzoic Acid (7). In a typical experiment *m*-bromobenzoic acid (2.5 g, 0.0125 mol) was converted to the corresponding dianion with *n*-butyllithium (0.25 mol) as previously described.[1] The temperature was allowed to warm to −75° for 2 hr and a solution of methyl *m*-bromobenzoate (2.7 g, 0.0125 mol) in dry tetrahydrofuran (10 ml) was added sufficiently slowly to maintain the mixture at −75 to −70°. The resulting mixture was stirred for 2 hr at −75° then allowed to warm to −20° and poured into 5% aqueous hydrochloric acid (100 ml); the resulting mixture was extracted with ether (400 ml total) which was in turn washed with water (50 ml). Acidic products were removed from the ether extract by extraction with 10% aqueous sodium hydroxide (50 ml) and the acids were regenerated (dilute hydrochloric acid) and collected by filtration. The crude acids (3.5 g, mp 205–220°) was recrystallized from chloroform–methanol to give 3-(*m*-bromobenzoyl)benzoic acid (61% yield, mp and mmp 232°).

***m*-Benzoylbenzoic acid** [**12**, 61% pure, mp and mmp 161–162° by chromatography (preparative tlc, silica gel using petroleum ether[3] as eluent, lit.[6] mp 161–162°)] was obtained from *m*-bromobenzoic acid and methyl benzoate.

4-(*p*-Bromobenzoyl)benzoic acid (**4**, 64% yield, mp and mmp of product obtained from methyl *p*-bromobenzoate was 274°) was obtained from *p*-bromobenzoic acid and methyl *p*-bromobenzoate.

***p*-Benzoylbenzoic acid** [**13**, 64% yield, mp 198–201°, by chromatography on silica gel, petroleum ether[3]–diethyl ether (80:20) as eluent, lit.[7] mp 197–200°] was prepared from *p*-bromobenzoic acid and methyl benzoate.

2-(*p*-Bromobenzoyl)benzoic acid (**14**, 52% yield, mp 170–172° from chloroform–petroleum ether,[3] lit.[8] mp 172–173°) was prepared from *o*-bromobenzoic acid and methyl *p*-bromobenzoate.

o-**Benzoylbenzoic acid** (75% yield, mp 127–129° from benzene–petroleum ether,[3] lit.[5] mp 128–129°) was prepared from *o*-bromobenzoic acid and methyl benzoate.

2-(*o*-Methylbenzoyl)benzoic Acid (16) and the Acid 23. A. The acidic product obtained as described for **7** by reaction of methyl *o*-toluate with the dianion prepared from *o*-bromobenzoic acid was chromatographed on silica gel [preparative tlc, petroleum ether[3]–diethyl ether (70:30) as eluent] to give 2-(*o*-methylbenzoyl)benzoic acid (**16**), 59% yield, mp 107–109°[9] from benzene–petroleum ether.[3] No appreciable amount of **23** was isolated.

Anal. Calcd for $C_{15}H_{12}O_3$: C, 74.99; H, 5.03; neut equiv, 240.02. Found: C, 75.03; H, 5.25; neut equiv, 238.

B. When *o*-toluoyl chloride was used instead of methyl *o*-toluate and the acidic product was chromatographed as in A the yield of **16** was 41% and the acid **23** was obtained in 19% yield, mp 240–242° from ethanol–water.

Anal. Calcd for $C_{22}H_{16}O_4$: C, 76.73; H, 4.68; neut equiv, 344.3. Found: C, 76.58; H, 4.89; neut equiv, 345.

2-(*o*-Bromobenzoyl)benzoic Acid (17) and the Acid 18. A. The acidic product obtained as described for **7** by reaction of methyl *o*-bromobenzoate (2.77 g, 0.125 mol) with the dianion prepared from *o*-bromobenzoic acid was recrystallized from methanol–chloroform to give **18** as a white solid, 29% yield, mp 284–286°.

Anal. Calcd for $C_{21}H_{13}BrO_4$: C, 61.63; H, 13.20; Br, 19.45; neut equiv, 409.2. Found: C, 61.43; H, 3.67; Br, 19.16; neut equiv 408.

The mother liquor obtained above was chromatographed on silica gel [preparative tlc, petroleum ether[3]–diethyl ether (60:40) as eluent] to give 2-(*o*-bromobenzoyl)benzoic acid (**17**), 45%, mp 134° from chloroform–petroleum ether.[3]

Anal. Calcd for $C_{14}H_9BrO_3$: C, 55.10; H, 2.97; Br, 26.19; neut equiv, 305.1. Found C, 54.89; H, 2.91; Br, 26.00; neut equiv, 304.

B. When *o*-bromobenzoyl chloride was used instead of methyl *o*-bromobenzoate, the yield of **18** was 27–30% and the yield of **17** was 40–44% (multiple runs including addition of the dianion at −75° to the acid chloride solution in hexane at room temperature, *i.e.*, reversed addition).

Acknowledgment. The authors would like to express their appreciation to the U. S. Army Research Office through Grant DAHCO4 74 GD128 for partial support of this work.

Registry No.—**1**, 619-42-1; **3**, 51310-29-3; **4**, 51310-30-6; **5**, 618-89-3; **6**, 51310-31-7; **7**, 51310-32-8; **10**, 606-28-0; **16**, 5469-51-2; **17**, 51310-33-9; **18**, 5130-34-0; **23**, 51310-35-1; *n*-butyllithium, 109-72-8; methyl *o*-bromobenzoate, 610-94-6; *m*-bromobenzoic acid, 585-76-2; methyl benzoate, 93-58-3; *p*-bromobenzoic acid, 586-76-5; *o*-bromobenzoic acid, 88-65-3; methyl *o*-toluate, 118-90-1; *o*-toluoyl chloride, 933-88-0; *o*-bromobenzoyl chloride, 7154-66-7.

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(9) M. S. Newman and C. D. McCleary, *J. Amer. Chem. Soc.*, **63**, 1537 (1941), reported a melting point of 130–132° after standing for several months; however, the initial melting point of the acid was 113.8–115°.

Stereochemistry of Amino Carbonyl Compounds. IX.[1] Lithium Aluminum Hydride and Lithium Trialkoxyaluminum Hydride Reduction of α-Asymmetric β-Aminopropiophenones

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The stereochemical course of the reduction by lithium aluminum hydride ($LiAlH_4$), lithium trimethoxyaluminum hydride (TMH), and lithium tri-*tert*-butoxyaluminum hydride (TBH) of some α-asymmetric β-amino ketones has been investigated by varying hydride concentration, solvent, and reaction temperature. The stereoselectivity was found to be strongly dependent on the nature of the substrate and, to a lesser extent, on the other factors. Some considerations concerning the transition states are given.

Several papers concerning asymmetric induction of the reaction between acyclic asymmetric ketones bearing a heteroatom in the β position and nucleophilic reagents (organometallics and hydrides) have been published.[2] The discussion of the mechanism of such reactions is complicated, with respect to the corresponding substrates not containing heteroatoms, by the possibility of additional complexing and solvating effects which may affect the nature of the species involved.[3] In particular, an important question which arises whenever a rationalization of the stereochemical course of the reaction is attempted is concerned with the situation of the reducing species in the transition state.

In this connection we have investigated the role played by such factors as nature of the hydride, concentration of the reducing agent, solvent, and reaction temperature.

Results and Discussion

The reduction of the amino ketones **1–3** (Scheme I) was performed with hydride concentrations of about 0.01, 0.1, and 0.5 *M*, at 0° and at reflux in THF, and at 0° in Et_2O. The results are collected in Table I and graphically depicted in Figure 1.

The relative amounts of the obtained diastereomeric 1-phenyl-3-dialkylaminopropan-1-ols **4–6** were determined on the crude reaction mixture[4] by integration of the nmr signal due to the proton bonded to C-1, as described in a previous paper.[2h]

Most of the reaction yields were quantitative (nmr) in amino alcohols, except when the reduction was carried out with the alkoxy hydrides, particularly at low concentrations and at 0° (Table I). In such cases longer reaction times as well as higher temperatures (room temperature) were required in order to obtain appreciable amounts of product. The diastereomeric ratios, however, were not affected by the reaction time, thus confirming that no equilibration occurred under the adopted conditions.

The experimental results show a general predominance of the erythro amino alcohols **4–6** and, in addition, allow the following observations to be made.