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Registry No.—1, 624-48-6; 2, 624-49-7; *cis*-9, 18305-60-7; *trans*-9, 7633-38-7; *cis*-10, 55556-65-5; *trans*-10, 55556-66-6; butenedioic acid, dimethyl ester radical ion, 55569-40-9; butenedioic acid, di-*tert*-butyl ester radical ion, 55569-41-0; butenedioic acid, methyl, *tert*-butyl ester radical ion, 55569-42-1.

References and Notes

(1) S. F. Nelsen, *Tetrahedron Lett.*, 3795 (1967).
(2) S. F. Nelsen, *J. Org. Chem.*, **38**, 2693 (1973).
(3) A. V. Il'yasov, Yu. M. Kargin, N. N. Sotnikova, V. Z. Kondranina, B. V. Mel'nikov, and A. A. Vafina, *Bull. Russ. Acad. Sci., Chem. Ser.*, 855 (1971).
(4) A. V. Il'yasov, Yu. M. Kargin, and Y. Z. Kondranina, *ibid.*, 850 (1971).
(5) (a) V. J. Puglisi and A. J. Bard, *J. Electrochem. Soc.*, **120**, 748 (1973); (b) I. B. Goldberg, D. Boyd, R. Hirasawa, and A. J. Bard, *J. Phys. Chem.*, **78**, 295 (1974); (c) A. J. Bard, V. J. Puglisi, J. V. Kenkel, and A. Lomax, *Faraday Discuss. Chem. Soc.*, **56**, 353 (1973).
(6) I. H. Elson, T. J. Kemp, D. Greatorex, and H. D. B. Jenkins, *J. Chem. Soc., Faraday Trans. 2*, **69**, 1402 (1973).
(7) W. J. Vanden Hoek, W. G. B. Hyusmans, and M. J. C. van Geinert, *J. Magn. Reson.*, **3**, 137 (1970).
(8) (a) E. Forrest and C. P. Smyth, *J. Am. Chem. Soc.*, **86**, 3474 (1964); (b) S. K. Gard and C. P. Smyth, *J. Chem. Phys.*, **46**, 373 (1967).
(9) G. W. Anderson and F. W. Callahan, *J. Am. Chem. Soc.*, **82**, 3359 (1960).
(10) A. L. McCloskey, G. S. Fonlin, R. N. Kluiber, and W. S. Johnson, "Organic Syntheses", Collect. Vol. IV, Wiley, New York, N.Y., 1963, p 261.

Selective Lithiation of Bromoarylalkanoic Acids and Amides at Low Temperature. Preparation of Substituted Arylalkanoic Acids and Indanones[1]

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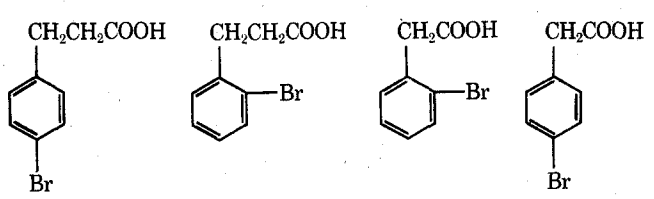
Studies of *p*-bromophenylpropanoic acid suggest that *p*-, and presumably *m*-, bromoarylalkanoic acids can be conveniently elaborated by selective halogen–metal exchange with *n*-butyllithium at −100° followed by reaction with E^+. Metal–halogen exchange is also selective for ortho-substituted acids; however, *o*-bromoarylpropanoic acids lead directly to indanones in high yield. Amide anions have been shown to be less reactive toward organolithium derivatives than carboxylate; consequently, by masking the carboxylic acid group by conversion to the amide anion, indanone formation can be obviated and elaboration of *o*-bromophenylpropanoic acid can be achieved. *o*-Bromophenylacetic acid (**3**) reacts with *n*-butyllithium at −100 or at −78° to give the dilithio derivative **21** and the trilithio derivative **23**. The trilithio derivative undergoes anion decay, with time, by reaction with solvent, to give **21**; consequently, by control of conditions, products can be obtained selectively from either **21** or **23**. Similar results were obtained with *p*-bromophenylacetic acid (**4**); however, in contrast to the results obtained with **3**, alkylation of intermediate anions with *n*-butyl bromide, formed during metal interchange, occurs which detracts from synthetic applications in the latter case.

Although Grignard (or lithium) reagents of aryl halides are useful intermediates for formation of aryl–carbon bonds, utilization of such derivatives has been of limited value for aromatic nuclei containing sensitive electron-withdrawing groups. Meyers and Temple[2] have obviated problems associated with aromatic carboxylic acids by disguising the carboxylic function as the corresponding oxazoline derivative. Recently we have shown[3a,b] that the lithium salt of aryl carboxylic acid function provides adequate protection of the carboxylic acid group at −100° to lithium reagents, and that high yields of elaborated arylcarboxylic acids can be obtained directly from *o*-, *m*-, and *p*-bromobenzoic acids.

We have now examined the reaction of acids **1–4** with *n*-butyllithium at −100° as part of a program designed to test

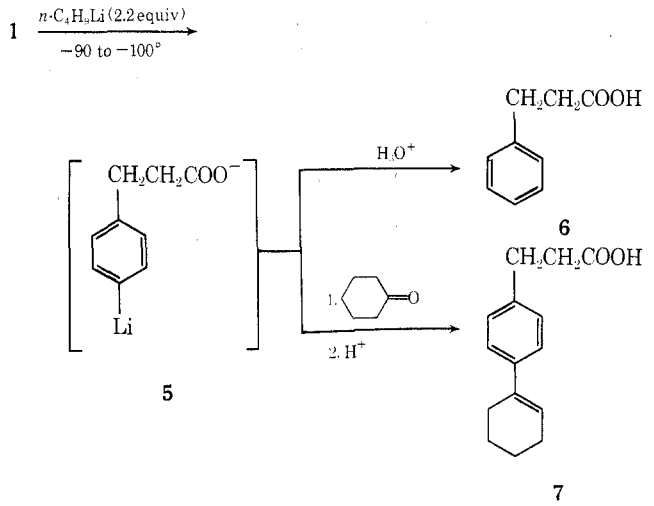


1 **2** **3** **4**

the generality of the above method for the elaboration of alkanoic acids. Acid **1** was selected as a model for the behavior expected for a broad series of para- and meta-substituted bromoarylalkanoic acids. Limitations for utilization of bromoarylalkanoic acids were anticipated where favorable entropy relationships might result in intramolecular reaction of derived aryllithium reagents with carboxylate functions (as in **2**), and in phenylacetic acids (**3** and **4**) where the methylene group α to the carboxylate function is more acidic. In all cases, progress of metal–halogen exchange was followed by quenching aliquots[4] with dilute acid and determining the ratio (by NMR) of recovered bromo acid to acid derived by replacing bromine with hydrogen.

A. β-(*p*-Bromophenyl)propanoic Acid (1). Two equivalents of *n*-butyllithium was added rapidly to a solution of **1** in THF–hexane at −100° at such a rate that the temperature did not exceed −90°. Examination of an aliquot showed that halogen–lithium exchange was ~80% after 30 min and the ratio did not change appreciably after an additional 90 min at −100°. Additional *n*-butyllithium (up to 0.4 to 1 equiv) increased the degree of exchange only slightly (ratio of **1**:**6** was ~85%); however, with excess *n*-butyllithium and time, small quantities of butylated products were detected (NMR) in the neutral component of the aliquots. In subsequent experiments 2.2 equiv of *n*-butyllithium was employed and the mixture was stirred at −100° for 45 min prior to quenching. In one experiment (see Scheme I) the mixture was quenched with water; the yield

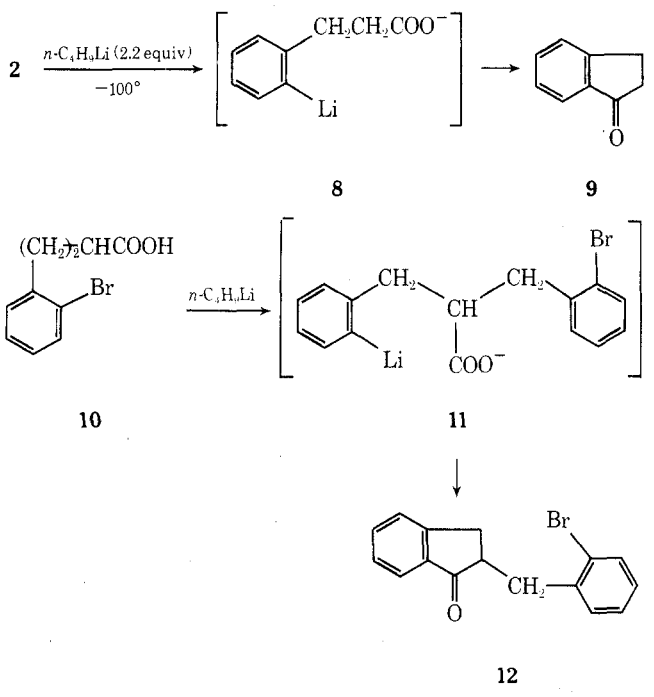
Scheme I



of **6**, isolated pure by distillation, was 86%. The residual acidic product was a mixture of **1**, **6**, and a trace of butylated acid.[5] In another experiment **5** was quenched with cyclohexanone;[6] the yield of nearly pure **7** was 67% (59% pure). In no case was there any evidence that **5** self-condensed at −100°. It was concluded, therefore, that, except for the limitations described in B and C (below), the procedure described should prove to be a useful one for the elaboration of *m*- and *p*-arylalkanoic acids.

B. β-(*o*-Bromophenyl)propanoic Acid (2). This acid was chosen for study since it was anticipated that favorable entropy considerations may lead to self-condensation of **8**, leading to indanone (**9**).

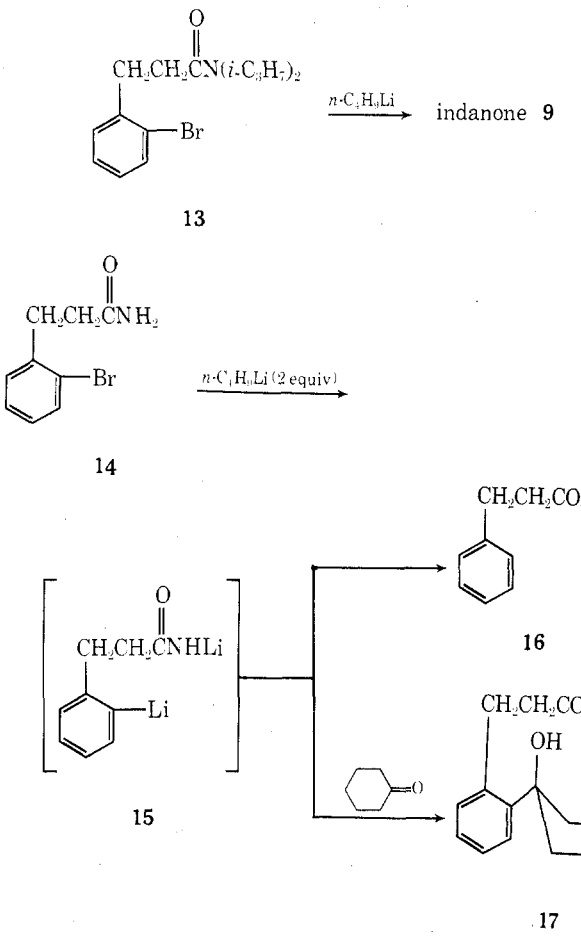
Scheme II



Reaction of **2** with *n*-butyllithium was indeed selective at −100° in that halogen–metal exchange occurred without proton abstraction from the methylene group or without addition of *n*-butyllithium to carboxylate; however, as anticipated, cyclization occurred at −100° to give indanone. Studies of aliquots[4] showed that cyclization was appreciable after 60 min at −100°. The mixture was stirred at −100° for 3 hr; the yield of indanone,[6] isolated pure by distillation, was 76%. While this observation defines a limitation to the general elaboration of bromoarylalkanoic acids suggested in A (above), this new synthesis should be of value for the preparation of indanones not easily available by more conventional routes.[7] In a similar experiment, reaction of **10** (Scheme II) with 2 equiv of *n*-butyllithium afforded a good yield of **12** (66%). Significantly, reaction of **10** with 3 equiv of *n*-butyllithium leads to 2-benzylindanone (72% yield).[8]

Amide ions were found to be less reactive than carboxylate ions toward organolithium reagents; consequently, cyclization of *o*-bromoarylpropanoic acids to indanones can be obviated by utilizing certain amides derived from the acid (Scheme III). Reaction of the dialkylamide **13** with 1

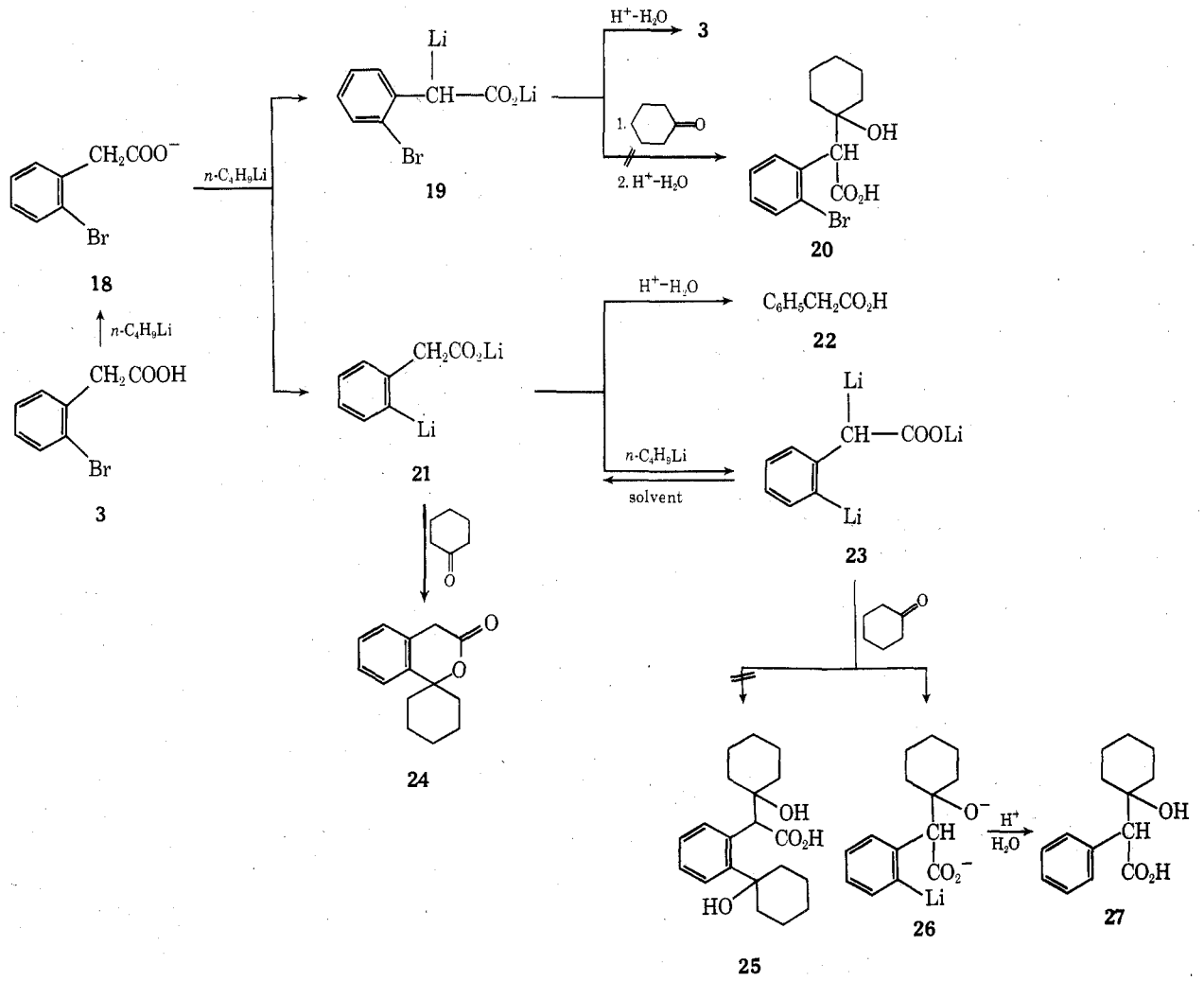
Scheme III



equiv of *n*-butyllithium at −100° leads directly to indanone (61% yield by isolation). By contrast, reaction of the unsubstituted amide **14** with 2 equiv of *n*-butyllithium leads to the dilithio derivative **15**, which does not cyclize at −100°. Reaction with acid gave **16** in 81% yield (isolated); amide **17** was isolated pure in 40% yield when **15** was quenched with cyclohexanone. Use of such amides appears attractive as masking agents of carboxyl functions in such reactions.

C. *o*-Bromophenylacetic Acid (3). Halogen–metal interchange in *o*-bromophenylacetic acid is more complex owing to trianion formation (**23**) and incomplete halogen–metal exchange; however, by utilizing "anion decay" (see below), reasonable yields of elaborated products (**24**) can be obtained. Results of these studies, which are summarized in Scheme IV, have led us to the following conclusions and comments.

Scheme IV



1. Metalation of the rapidly formed salt **18** with the second equivalent of *n*-butyllithium was slow at −100°[4e] and leads to the dilithio derivative **21** and presumably to the trilithio derivative **23**. Whether **19** is formed at all, or whether it was unreactive owing to solubility or steric reasons, was not determined; however, no products derived from **19**, other than recovered **3**, were obtained in subsequent reactions. Examination of aliquots which were quenched with dilute acid showed no change in degree of metalation (ratio of *o*-bromophenylacetic acid to phenylacetic acid 36:64) after 4 hr.[4b]

2. The salt **19**, if formed, does not undergo appreciable further metalation. Addition of a third equivalent of *n*-butyllithium changed the above ratio to 30:70; however, further addition of *n*-butyllithium (up to 6 equiv) caused no appreciable further change in this ratio, and in the amount of *o*-bromophenylacetic acid recovered.

3. The dilithio derivative **21** does react with *n*-butyllithium to give the trilithio derivative **23**; however, **23** is unstable at −100° and reacts with solvent to regenerate **21**. Thus, addition of additional *n*-butyllithium has little effect on the ultimate composition of the mixture; **23** is formed from **21**, which decays back to **21**, and this process is repeated by addition of additional *n*-butyllithium.

4. The dilithio derivative **21** reacts with cyclohexanone by addition to give, subsequent to acidification, lactone **24**, and undoubtedly some phenylacetic acid by enolate formation with the ketone. Maximum yield of lactone **24** (42%, 60% based on converted **3**) was obtained when a mixture of *o*-bromophenylacetic and 3 equiv of *n*-butyllithium was stirred at −100° for 5 hr, to permit decay of **23** to **21**, prior to addition of excess cyclohexanone. The only other acids formed in this reaction were *o*-bromophenylacetic acid and phenylacetic acid (ratio 40:60).

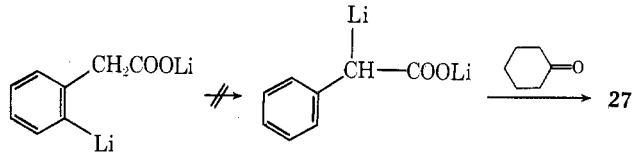
5. The trilithio derivative **23** reacts with cyclohexanone to give hydroxy acid **27**; in no case was hydroxy acid **25** detected. The anion **23** rapidly decays to **21** and after 4–5 hr at −75 to −100° is completely converted to **21**. Thus, if cyclohexanone is added only 1 hr after addition of the third equivalent of *n*-butyllithium to the reaction mixture obtained from **3** and 2 equiv of *n*-butyllithium (7 hr, −100°), **23** is present. Under these conditions hydroxy acid **27** is formed which was isolated in 39% yield; lactone **24** was isolated in 24% yield. If this solution is aged prior to addition of cyclohexanone (see 4, above), no hydroxy acid **27** is produced. The lifetime of **23** was examined (in separate experiments) by adding cyclohexanone after different time intervals following the addition of the third equivalent of *n*-butyllithium. The maximum yield of **27** (54%, 77% based on converted **3**) was obtained by adding excess cyclohexanone to an aged mixture (14 hr) prepared from **3** and 3 equiv of *n*-butyllithium 15 min after addition of a fourth equivalent of *n*-butyllithium; 10% yield of lactone **24** was also isolated in this case. Failure to isolate the disubstituted product **25** from the trilithio derivative is interpreted to mean that either (1) reaction with ketone occurred preferentially at the anion adjacent to carboxylate, and that the derived aryllithium intermediate **26** does not react further with cyclo-

hexanone for steric reasons, or (2) that the aryllithium in **26** is lost and converted to the salt of **27** by reaction with solvent. It is of interest to note that the corresponding trilithio derivative **30** derived from the para isomer reacts with cyclohexanone at both carbon anionic centers.

6. Loss of trilithio derivative **23** is a function of concentration and temperature. Reaction of **3** under identical conditions described in 5 (above), but at one-fourth the molar concentration (i.e., more concentrated in solvent tetrahydrofuran), led to greater loss of **23.** The yield of **27** decreased from 39% to 26% while the yield of lactone derived from **24** increased from 24% to 30% (by isolation). Furthermore, addition of cyclohexanone to a mixture prepared from **3** (2 equiv of *n*-butyllithium) 3 hr after adding the third molar equivalent of *n*-butyllithium at −100° led to a 13% yield of **27,** but to no **27** when the extra 3 hr of aging was at −75°.

7. An alternate pathway for the formation of **27** as shown in Scheme V is rejected. If this process was of signif-

Scheme V



icance, then aging prior to addition of cyclohexanone should result in an increase in yield of **27,** which is in complete contradiction to the results observed.

Studies of metalation of *p*-bromophenylacetic acid (**4**) gave similar results and provided more conclusive evidence for formation of products derived from the trilithio derivative **30** (Scheme VI); however, the reaction products were more complex than those obtained from **3.** The following observations were made.

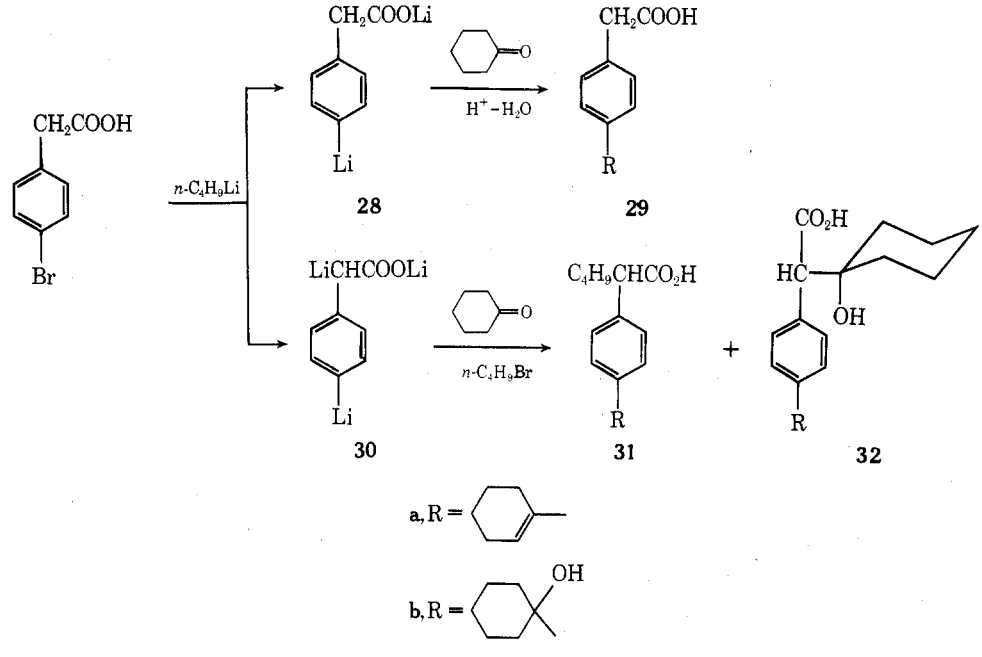
1. The degree of halogen–lithium interchange was 40% with 2 equiv of *n*-butyllithium after 2 hr and this value was unchanged after an additional 4 hr.[4c] The degree of halogen–lithium interchange decreased in more concentrated solutions. Thus, under similar conditions but at four times the molar concentration of **4** in solvent, the degree of halogen–lithium interchange was only 20%. This decrease is attributed to insolubility of the carboxylate salt of **4.** The maximum degree of halogen–lithium interchange (60%) was achieved by addition of 3 equiv of *n*-butyllithium to **4** and stirring the resulting mixture (~17 hr). The solution was a mixture containing **28** and **30.** The degree of halogen–lithium interchange was unchanged by addition of a fourth equivalent of *n*-butyllithium.

2. The trilithio derivative **30,** like the analogous salt **23,** decays to dilithio derivative **28** with time by reaction with solvent. Thus, addition of a fourth equivalent of *n*-butyllithium to a mixture prepared from **4** and 3 equiv of *n*-butyllithium gave a mixture rich in **30** relative to **28.** When excess cyclohexanone was added 15 min after addition of the fourth equivalent of *n*-butyllithium, the product mixture contained little **29**[9] which would be derived from the dilithium derivative **28.** The acidic products were separated by preparative plate chromatography. The principal products were (a) an oil (~25% crude yield), the NMR spectrum of which was consistent with **31a** (this product could not be induced to crystallize and was not characterized by composition analysis),[10] and (b) alcohol **32a** (~25% crude yield) which was obtained pure.

In contrast, when the above solution was aged for 12 hr at −75°, there was considerable loss of trilithio derivative **30** to dilithio derivative **28.** In this case, addition of excess cyclohexanone led to a significant quantity (~33% crude yield) of **29b.** Chromatography of the mixed acids gave, in addition to **29b,** products derived from the trilithio derivative **30** but in reduced yields: (a) diol **31b** (~16% yield) which was obtained pure, and (b) a mixture (by NMR spectral analysis) of **32a** and **32b** (~16% total yield) which was not resolved.

3. Alkylations of lithium derivatives derived from **4** by *n*-butyl bromide formed during halogen–lithium exchange, to give products of type **31,** detract from the synthetic utility of such syntheses with *p*-bromophenylacetic acid, an observation in sharp contrast to that observed with *o*-bromo-

Scheme VI



phenylacetic acid. We currently believe, but have not established, that alkylation at −100° occurs only with the very reactive trianion **30**, a process which is sterically inhibited with the ortho isomer **23**; consequently, we believe that significant amounts of alkylation at −100° will be encountered only in the phenylacetic acid series (meta or para).

While some exceptions have been defined, notably *p*-bromophenylacetic acid, the procedures described in A–C (above) offer useful routes for the elaboration of a seemingly broad variety of types of bromoalkanoic acids.

Experimental Section

A. Conversion of β-(*p*-Bromophenyl)propanoic Acid (1) to Phenylacetic Acid. β-(*p*-Bromophenyl)propanoic acid[11a] (2.29 g, 0.01 mol), mp 137–138° (lit.[11b] mp 136°), tetrahydrofuran (~125 ml, freshly distilled over lithium aluminum hydride), and dry hexane[13] (25 ml) were introduced, under nitrogen, into a three-neck flask equipped with a low-temperature thermometer, addition funnel, and nitrogen inlet tube. The reaction mixture was cooled to −100° (liquid nitrogen–diethyl ether bath) and *n*-butyllithium (9.2 ml, 0.022 mol, 2.4 *M* solution) was added rapidly (the rate of addition was adjusted such that the temperature did not exceed −90°). The reaction mixture was stirred at −100° for 45 min and poured into dilute aqueous hydrochloric acid (~50 ml). The organic layer was separated and the aqueous layer was extracted with four 100-ml portions of ether. The ether extracts were combined and extracted with two 50-ml portions of 10% aqueous sodium hydroxide. The aqueous basic extracts were combined, cooled, and added to cold dilute aqueous hydrochloric acid; the resulting mixture was extracted with four 100-ml portions of ether. The ether extracts were combined, dried ($MgSO_4$), and concentrated (rotary evaporation) to afford 1.55 g of light yellow semisolid. This material was distilled to give 1.29 g (86% yield, mp[12] and mmp 45–46°) of pure phenylacetic acid (**6**). The residue (0.26 g) was shown (NMR) to be a mixture of **1**, **6**, and a small amount of butylated acid (position of butyl group undetermined).

B. Preparation of β-(*p*-1-Cyclohexenylphenyl)propanoic Acid (7). Reaction of **1** (0.02 mol) in a mixture of THF (250 ml)–hexane[13] (50 ml) with *n*-butyllithium (0.044 mol) was carried out as in A. Cyclohexanone (0.10 mol) in dry hexane[13] (10 ml) was added; the mixture was warmed to 25° and poured into dilute hydrochloric acid (250 ml). The organic layer was extracted (four 150-ml portions) with ether. The acid, obtained by extraction of the ether extract with alkali, weighed 3.9 g (white solid, mp 105–112°). This material was sublimed [80° (0.01 Torr), 24 hr] to remove unchanged **1** (0.49 g, mp[11] and mmp 133–135°); the residue (3.1 g, 67% yield, mp 114–117°) was nearly pure **7**. Pure **7** (2.7 g, 59% yield from petroleum ether[14a]–chloroform) had mp 117–118°; NMR ($CDCl_3$) δ 1.72 (m, 4, aliphalic CH_2), 2.28 (m, 4, allylic CH_2), 2.72 (m, 2, CH_2Ar), 3.00 (m, 2, CH_2COOH), 6.23 (m, 1, vinyl H), 7.40 (m, 4, aromatic H), ~11.0 (broad s, 1, OH).

Anal. Calcd for $C_{15}H_{18}O_2$: C, 78.23; H, 7.88. Found: C, 78.32; H, 7.80.

The residue (0.55 g) from the recrystallization of **7** was a mixture of phenylpropanoic acid (0.4 g, 13%) and unchanged **1**.

C. Indanones. 1. From β-(*o*-Bromophenyl)propanoic acid[15] (2). Reaction of **2** [0.01 mol, mp 99–101° (lit[17] mp 98°)] in THF (125 ml)–hexane[13] (25 ml) with *n*-butyllithium (0.02 mol) was carried out as in A; the reaction mixture was stirred for 3 hr at −100°. From the neutral component of the reaction product there was obtained 1.0 g [76% yield; bp 60–65° (0.2–0.15 Torr); mp and mmp[16a] 42°; mp of 2,4-dinitrophenylhydrazone 256–257° (lit.[16b] mp 258°)] of pure indanone (**9**).

The reaction was repeated at −78°; examination of aliquots showed that the reaction was faster and complete after only 30 min. The yield of isolated indanone was 77%.

2. From 3-*o*-Bromodiisopropylamide (13). Amide **13** [0.01 mol, bp 130–140° (0.02–0.01 Torr); 96% yield from 3-*o*-bromophenylpropanoyl chloride[17] and diisopropylamine in ether] in THF (125 ml)–hexane[13] (25 ml) was allowed to react with *n*-butyllithium (0.01 mol) as in A. Examination of aliquots[4] by NMR showed that after 1 hr at −100° the reaction product was indanone contaminated with a small amount of butylated material. The mixture was quenched with water and the dried material obtained from the ether extract was distilled to give 0.8 g (61% yield) of pure indanone.

3. 2-(*o*-Bromobenzyl)-1-indanone (12). The starting acid **10** (mp 152–153°) was prepared in high yield from crude diethyl di(*o*-bromophenyl)malonate (by hydrolysis and decarboxylation of the derived malonic acid) obtained as a by-product in the synthesis of **2** from *o*-bromobenzyl bromide and diethyl malonate.

Anal. Calcd for $C_{16}H_{14}Br_2O_2$: C, 48.27; H, 3.54; Br, 40.15; neut equiv, 398. Found: C, 48.03; H, 3.67; Br, 39.94; neut equiv, 396.

Reaction of **10** (0.02 mol) with *n*-butyllithium (2 equiv) in THF (300 ml) and hexane[13] (50 ml) was carried out as in C-1 and gave 4.1 g (66% yield) of pure 2-(*o*-bromobenzyl)-1-indanone (**12**), bp 165–170° (0.05–0.04 Torr).

Anal. Calcd for $C_{16}H_{13}BrO$: C, 63.80; H, 4.35; Br, 26.54. Found: C, 63.96; H, 4.28, Br, 26.61.

4. 2-Benzyl-1-indanone. Reaction of **10** with *n*-butyllithium (3 equiv) was carried out as described in C-3 above. Distillation of the crude product gave 3.2 g (72% yield) of pure 2-benzyl-1-indanone, bp 135–140° (0.03 Torr).

Anal. Calcd for $C_{16}H_{14}O$: C, 86.45; H, 6.35. Found: C, 87.70; H, 6.35.

D. Reactions of β-(*o*-Bromophenyl)propionamide (14). 1. Conversion to Phenylpropionamide. Amide **14**[18] (0.01 mol) was treated with *n*-butyllithium (0.02 mol) in THF (125 ml)–hexane[13] (25 ml) as described in A. An aliquot (25 ml) taken after 30 min at −100° was quenched with water; NMR analysis showed only 3-phenylpropionamide.[4d] The mixture was quenched with water, and the crude product obtained by extraction with ether was recrystallized from water to give 1.22 g (81% yield) of pure 3-phenylpropionamide (mp and mmp[19] 104–105°).

2. Conversion to *o*-(1-Hydroxycyclohexyl)-3-phenylpropionamide (17). The reaction was carried out as in D-1 above, and quenched after 30 min with cyclohexanone (0.04 mol) in dry hexane[13] (20 ml) at −100°. The crude product (5.5 g) obtained after addition of water and extraction with ether and containing cyclohexanone was recrystallized from petroleum ether[14a] to give 2.1 g of white solid which was a mixture of **16** and **17**. This material was chromatographed on silica gel (200 g). Elution of the column with petroleum ether[14a]–ether (70:30) gave 0.88 g (59% yield) of 3-phenylpropionamide; elution with petroleum ether[14a]–ether (50:50) gave 1.1 g of white solid which was recrystallized from chloroform–petroleum ether to give 0.97 g (40% yield) of pure **17** (mp 148–150°).

Anal. Calcd for $C_{15}H_{21}NO_2$: C, 72.84; H, 8.56; N, 5.66. Found: C, 73.00; H, 8.42; N, 5.49.

E. Metalation of *o*-Bromophenylacetic Acid (3) with *n*-Butyllithium. 1. Degree of Metal–Halogen Exchange. Reaction of **3**[20] (0.025 mol) with *n*-butyllithium (0.05 mol) in THF (150 ml) and hexane[13] (30 ml) was carried out as in B. Examination of an aliquot[4c] (10 ml) taken after 30 min at −100° showed that the degree of halogen–metal exchange [ratio of *o*-bromophenylacetic acid (**3**) to phenylacetic acid (**22**)] was 50:50. The ratio of **3** to **22** was 40:60 after an additional 1 hr; after an additional 2.5 hr the ratio was 36:64 and this ratio did not change after an additional 2 hr at −100°.

A third molar equivalent of *n*-butyllithium was added to the reaction mixture at −100°; and the mixture was stirred for an additional 1 hr at −100°. Examination of an aliquot (10 ml) showed that the ratio of **3** to **22** was 30:70. Additional reaction time (at −100°) and/or further addition of *n*-butyllithium (up to a total of 6 molar equiv) caused no appreciable change in the above ratio (30:70).

Examination of aliquots from a similar reaction but at −78° (instead of −100°) showed no appreciable change in the progress and/or degree of metalation.

Synthesis of Spirolactone 24. Metalation of *o*-bromophenylacetic acid[21] (5.4 g, 0.025 mol) was effected with *n*-butyllithium (0.075 mol) as described above. The mixture was aged for 5 hr at −95 to −100° (ratio of *o*-bromophenylacetic acid to phenylacetic acid 30:70 by NMR spectral analysis)[4c] and cyclohexanone (9.8 g, 0.1 mol) in hexane (20 ml) was added to the mixture maintained at −100°. The resulting mixture was allowed to warm to room temperature and was added to a mixture of ether (200 ml) and aqueous sodium hydroxide (200 ml, 5%). The two layers were separated and the aqueous layer was extracted with ether (four 100-ml portions). The basic layer containing the salt of **24** was acidified (hydrochloric acid), brought to boil, cooled, and extracted with ether (400 ml). The ether extract was cooled (0–5°) and extracted with cold (0–5°) aqueous sodium hydroxide (100 ml, 3%). The ether layer was washed with cold water (50 ml), dried ($MgSO_4$), and concentrated to give nearly pure **24** (2.3 g, 42% yield, mp 95–105°; 2.1 g, 39% yield, mp 105–106° from petroleum ether[14b]).

Anal. Calcd for $C_{14}H_{16}O_2$: C, 77.75; H, 7.46. Found: C, 77.96; H, 7.40.

The NMR spectrum of the acid material (2.2 g) obtained from the alkaline extract showed it to be a mixture of *o*-bromophenylacetic acid (**3**) and phenylacetic acid (**22**) in the ratio 40:60 (20 and 33% yield, respectively).

Preparation of Hydroxy Acid 27. The reaction was conducted as described for **25** with the following modifications. The mixture was stirred for 7 hr after addition of 2 equiv of *n*-butyllithium, but only 15 min after addition of the third equivalent of *n*-butyllithium prior to addition of cyclohexanone. The yield of lactone **24** (mp and mmp 105–106°) was 10%.

Concentration of the dried ether extract obtained from the acidified alkaline extract gave a mixture of **27**, *o*-bromophenylacetic acid (**3**), and phenylacetic acid (**22**). Fractional crystallization of the product from chloroform–petroleum ether[14c] gave 2.92 g of pure **27** (54% yield, mp 114–146°).

Anal. Calcd for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 71.95; H, 8.00.

F. Reactions of *p*-Bromophenylacetic Acid (4). 1. Reaction of *p*-bromophenylacetic acid (5.4 g, 0.025 mol) was carried out exactly as described for **3** except the temperature was −78°[4b] (Dry Ice–acetone bath). Progress of metalation was followed as for **3**.[4c]

The ratio of recovered *p*-bromophenylacetic acid to phenylacetic acid was 60:40 after 2 hr and the ratio did not change after an additional 2–4 hr. An additional molar equivalent of *n*-butyllithium was added and the mixture was stirred at −78° for 17 hr. An aliquot showed the above ratio of acids to be 40:60. A fourth equivalent of *n*-butyllithium was added, and after 15 min at −78° an excess of cyclohexanone (5 equiv) dissolved in hexane (35 ml) was added rapidly. The mixture was allowed to warm to room temperature and was then partitioned between aqueous sodium hydroxide (100 ml, 10%) and ether (100 ml). Acidification of the alkaline layer (hydrochloric acid) gave 6.22 g of acidic product as a semisolid which was collected by ether extraction. Elution of the mixed acids (600 mg) from a preparative silica gel plate (fluorescent indicator) with a mixture of petroleum ether[14a] and ether (80:20) gave two major fractions. (1) 160 mg (~25%, higher R_f) of an oil. The NMR spectrum ($CDCl_3$) of this product was consonant with slightly impure **31a**: δ 0.9 (t, 3, CH_3), 1.25–2.3 (m, 1, aliphatic H), 3.55 (broad t, 1, benzylic methine), 6.2 (m, 1, vinyl H), 7.4 (broad, 4, aromatic H). This material could not be induced to crystallize and was not purified.[10] (2) 300 mg (lower R_f) of an oil. This product was rechromatographed as above, to give one major fraction (180 mg, ~25% yield) of an oil, the NMR spectrum ($CDCl_3$–DMSO-d_6) of which suggested that it was **32a** [δ 0.9–2.0 (m, 16, aliphatic H), 2.15–2.58 (m, 2, allylic H)]. The material crystallized from chloroform and melted at 193–200° dec.

Anal. Calcd for $C_{20}H_{26}O_3$: C, 76.40; H, 8.34. Found: C, 76.17; H, 8.49.

2. The reaction was carried out as above except that the mixture was aged for 12 hr prior to addition of excess cyclohexanone. Analysis of an aliquot, as discussed in the text, showed that the ratio of acids remained constant at 40:60. A portion (580 mg) of the mixed acids (5.8 g, yellow semisolid) was purified by preparative plate chromatography (as in F-1) to give three major bands. (1) 180 mg (~33% yield) of an oil (higher R_f), the NMR spectrum of which was consistent with alcohol **29b**: NMR ($CDCl_3$) δ 1.4 (broad m, 10, aliphatic H), 3.6 (broad s, 2, benzylic methylene), 7.4 (broad m, H, aromatic H). The material crystallized from chloroform, mp 134–136°.

Anal. Calcd for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 72.00; H, 8.00.

(2) 120 mg (~16% yield) of an oil (medium R_f) whose NMR spectrum was consistent with **31b**: NMR ($CDCl_3$) δ 1.0 (t, 3, $-CH_3$), 1.6 (m, 16, aliphatic H), 3.7 (t, 1, benzylic methine), 6.8 (broad s, 1, –OH), 7.6 (m, 4, aromatic H). This material crystallized from chloroform, mp 110–114°.

Anal. Calcd for $C_{18}H_{26}O_3$: C, 74.44; H, 9.03. Found: C, 74.66; H, 8.86.

(3) 130 mg (~16% yield) of an oil (lower R_f) which was not resolved; however, the NMR spectrum was consistent with **32b** contaminated with **32a**. Compound **32a** was characterized in the preceding experiment.

Registry No.—**1**, 1643-30-7; **2**, 15115-58-9; **3**, 18698-97-0; **4**, 1878-68-8; **7**, 55223-22-8; **9**, 83-33-0; **10**, 55223-23-9; **12**, 55223-24-0; **13**, 55223-25-1; **14**, 55223-26-2; **17**, 55223-27-3; **24**, 55223-28-4; **27**, 5449-68-3; **29b**, 55223-29-5; **31a**, 55223-30-8; **31b**, 55223-31-9; **32a**, 55223-32-0; **32b**, 55223-33-1; diethyl di-(*o*-bromophenyl)malonate, 55223-34-2; 2-benzyl-1-indanone, 16307-30-5.

References and Notes

(1) Supported by the U.S. Army Research Office through Grant DAHCO4 74 GD128.
(2) A. J. Meyers and D. L. Temple, Jr., *J. Am. Chem. Soc.*, **92**, 6646 (1970).
(3) (a) W. E. Parham and Y. A. Sayed, *J. Org. Chem.*, **39**, 2051 (1974); (b) *Ibid.*, **39**, 2053 (1974).
(4) In general, 0.02 mol of acid in ~300 ml of solvent was employed; aliquots of 10 ml were quenched with water and the organic material was extracted with ether. The extract was concentrated to give sample for NMR analysis. In many cases, neutral components were separated from acids by conventional extraction procedures and analyzed separately by NMR. (a) *p*-Bromophenylpropanoic acid (A, A′, B, B′ aromatic pattern) could easily be differentiated from phenylpropanoic acid (simple singlet for aromatic protons); however, the absorptions overlapped so that only estimates of composition were possible. (b) *o*-Bromophenylacetic acid and phenylacetic acid show benzylic methylenes at δ 3.8 and 3.60 (60 MHz), respectively. The ratio of these two acids is based on integrations of these two absorptions. (c) *p*-Bromophenylacetic acid shows benzylic methylene at δ 3.56, sufficiently resolved from phenylacetic acid (δ 3.60) to permit accurate analysis. (d) 3-(*o*-Bromophenyl)propionamide shows a complex pattern for the aromatic protons (δ 6.9–7.7) while 3-phenylpropionamide shows only a single peak at δ 7.1. (e) Similar results were obtained at −78°. (f) Similar results were obtained at −100°.
(5) The position of the butyl group was not determined.
(6) Part of the aryllithium reagent is reduced by proton abstraction to give the enolate of cyclohexanone; cyclohexanone was chosen for elaboration of **5** since we felt that the yields of products would provide a more realistic evaluation of the synthetic utility of the process than would use of nonenolizable carbonyl functions.
(7) (a) Possible application of this reaction for the syntheses of tetralones and related materials is being investigated. (b) Indanones are usually prepared by cyclization of arylpropanoic acids. The method described in this report obviates isomers encountered by direct cyclization of unsymmetrically substituted arylpropanoic acids; furthermore, Friedel–Crafts type cyclization cannot be employed when the aryl group is substituted with meta-directing groups.
(8) This observation supports the conclusion that both bromine atoms in **10** undergo metal exchange prior to cyclization when 3 equiv of *n*-butyllithium is employed. The product (**12** with bromine replaced by lithium) reacts with itself by enolization of carbonyl rather than addition to carbonyl, probably because of unfavorable entropy considerations for addition.
(9) (a) Compounds **29a,b** were not detected upon preparative plate chromatography; however, conversion of an aliquot of the products to the methyl esters (with diazomethane) with subsequent GLC and NMR analysis showed that **29a** and/or **29b** (detected as **29a**) was present in very low yield.
(10) In a subsequent experiment the hydroxy acid **31b** was obtained pure and was characterized by compositional analysis (see Experimental Section).
(11) (a) This acid was prepared from *p*-bromobenzyl chloride by a malonic ester synthesis similar to that reported for the preparation of α-bromo-β-phenylpropionic acid: C. Marvel, "Organic Syntheses", Collect. Vol. III, Wiley, New York, N.Y., 1955, p 705. (b) S. Gabriel and J. Zimmerman, *Chem. Ber.*, **13**, 1683 (1880).
(12) E. Schwenk and D. Papa, *J. Org. Chem.*, **11**, 798 (1946).
(13) Practical grade stored over molecular sieves.
(14) (a) bp 30–60°; (b) bp 90–110°; (c) bp 60–90°.
(15) Prepared from *o*-bromobenzyl bromide by malonic ester synthesis (see ref 11a).
(16) (a) R. Pacaud and C. Allen, *Org. Synth.*, **18**, 47 (1938); (b) N. Levin, B. Grahm, and H. Kolloff, *J. Org. Chem.*, **9**, 380 (1944).
(17) F. Mayer, H. Phillips, F. Ruppert, and A. Schmitt, *Chem. Ber.*, **61**, 1966 (1928).
(18) A. Gonzalez, *An. Fis. Quim.*, **40**, 1182 (1944).
(19) C. Davis and M. Cormack, *J. Org. Chem.*, **12**, 76 (1947).
(20) P. Bedson, *J. Chem. Soc.*, **37**, 96 (1880).
(21) C. L. Jackson and W. Lowery, *Am. Chem. J.*, **3**, 247 (1881).