inertness of this difluoramino structure toward base.[7] Both primary and secondary alkyldifluoramines are readily dehydrofluorinated in basic media.[3]

Several attempts were made to add tetrafluorohydrazine to the 1-butene **7** under various conditions without success. Most of the reactions were done at elevated temperatures and resulted in the decomposition of **7**. Reaction of 1-butyne **9** with difluoramine in concentrated sulfuric acid did not give the tetrakis(difluoramino) derivative nor was it possible to effect the hydration of **9** to the ketone **4** using mercuric salts. Acetylene hydration has been established as an intermediate step in the formation of *gem*-bis(difluoramino)alkanes from dialkylacetylenes and difluoramine in sulfuric acid.[4b]

Experimental Section

Caution! Difluoramine and tetrafluoramine are explosive and should be handled with extreme care; see ref 3 and 8 for precautions.

Infrared spectra were obtained with a Perkin-Elmer Model 137B Infracord. The nmr spectra were obtained in tetramethylsilane–Freon 11 (CCl_3F) solution (used as references) using Varian Associates Model A-60 and HR-60 spectrometers. Both 4-chloro-2-butanone[9] and 3,4-dibromo-2-butanone[10] were prepared as described in the literature. 3-Trifluoroacetoxy-2-butanone [$n^{22}D$ 1.3568, bp 87–90° (131 mm)] was prepared from 3-bromo-2-butanone and silver trifluoroacetate. 2,2-Bis(difluoramino)-3-trifluoroacetoxybutane was prepared from the corresponding ketone and difluoramine. Alcohol exchange of the former with methanol gave 3,3-bis(difluoramino)-2-butanol. The three compounds in this reaction sequence as well as the analogous cyclohexyl derivatives (prepared similarly) were isolated, purified, and fully characterized.

3,3-Bis(difluoramino)-2-butanone (**4**).—A solution of 0.099 g (0.09 mmol) of chromium trioxide in 1 ml of glacial acetic acid was degassed using a liquid nitrogen cooling bath and then charged with 0.173 g (0.9 mmol) of 3,3-bis(difluoramino)-2-butanol *via* a vacuum bulb-to-bulb transfer. The reaction mixture was stirred under a static vacuum at room temperature for 3 hr. The entire liquid contents of the reactor were separated from chromium salts by a vacuum bulb-to-bulb transfer. The colorless liquid was then treated with small portions of solid sodium carbonate until the evolution of carbon dioxide ceased. A final distillation of the residual liquid from the sodium acetate gave the volatile liquid ketone (**4**): 0.087 g (50%); ν_{gas} 1723 (C=O), 970 and 925 cm^{-1} (NF); H^1 nmr τ 8.22 (quintet, $CH_3C(NF_2)_2$), 7.6 (s, CH_3-C=O); ^{19}F nmr Φ −31.7 ($C(NF_2)_2$).

Anal. Calcd for $C_4H_6F_4N_2O$: C, 27.58; N, 16.09; F, 43.66. Found: C, 27.3; N, 14.7; F, 42.6.

2,2-Bis(difluoramino)cyclohexanone (**5**).—The oxidation of 2,2-bis(difluoramino)cyclohexanol with chromium trioxide in glacial acetic acid was done in a manner similar to that described above for the preparation of **4**. The cyclohexanone **5** was obtained in 39% yield as a colorless liquid: ν_{neat} 1723 (C=O),1010, 980, 910, and 900 cm^{-1} (NF); ^{19}F nmr Φ −27.6 ($C(NF_2)_2$).

Anal. Calcd for $C_6H_8F_4N_2O$: C, 36.0; N, 14.0; F, 37.97. Found: C, 36.6; N, 13.4; F, 38.3.

3,3-Bis(difluoramino)-1-chlorobutane (**6**).—Sulfuric acid (2 ml, 100%) in a 20-ml glass pressure reactor[11] was degassed using a liquid nitrogen cooling bath, and 0.8 g (0.0075 mol) of 4-chloro-2-butanone was added to the frozen acid by vacuum transfer. The mixture was then charged with 2.5 g (0.047 mol) of difluoramine at −128° (Freon 21–liquid nitrogen bath). The reaction mixture was allowed to warm to 25° and stirred at ambient temperature for 2 hr. Removal of the excess difluoramine and vacuum transfer gave product **6**: 1.07 g (74%); ν_{neat} 1000, 900, 910, and 885 cm^{-1} (NF), 740 (CCl); ^1H nmr τ 7.46 and 6.31 (2 doublets, J_{HH} = 8.0 Hz), 8.34 (quintet, J_{HF} = 2.0 Hz); ^{19}F nmr Φ −27.5 ($C(NF_2)_2$).

Anal. Calcd for $C_4H_7ClF_4N_2$: C, 24.69; N, 14.39. Found: C, 24.89; N, 15.54.

3,3-Bis(difluoramino)-1-butene (**7**).—A solution of 0.618 g (0.0032 mol) of **6** in 2 ml of a potassium hydroxide–triethylene glycol solution[13] was stirred for 2.5 hr at 25° under static vacuum. Vacuum bulb-to-bulb transfer gave the volatile liquid product **7**: 0.45 g (90%); ν_{neat} 3110 (C=CH_2), 990, 980, 955, 900, and 880 cm^{-1} (NF). The ^1H nmr spectrum consisted of a quintet at τ 8.29 (J_{HF} = 2.0 Hz) and an ABC pattern for the vinyl protons centered at τ 3.80, 4.25, and 4.32 (J_{AB} = 8.0 Hz, J_{BC} = 20 Hz, J_{AC} = 19 Hz). The ^{19}F nmr spectrum had one signal at Φ −28.9 ($C(NF_2)_2$).

Anal. Calcd for $C_4H_6F_4N_2$: C, 30.38; N, 17.72; F, 48.07. Found: C, 30.34; N, 17.55; F, 47.0.

3,3-Bis(difluoramino)-1,2-dibromobutane (**8**).—This compound was prepared in 91% yield from 3,4-dibromo-2-butanone and difluoramine in 100% sulfuric acid using a procedure similar to that described for compound **6**. The infrared spectrum of **8** showed the characteristic –NF frequencies at 1000, 980, 910, and 895 cm^{-1}. The ^1H nmr of **8** exhibited signals at τ 8.22 (CH_3), 6.48 (–CHBr), and 5.61 (CH_2Br) and the ^{19}F nmr spectrum had one signal at Φ −29.2 ($C(NF_2)_2$).

Anal. Calcd for $C_4H_6Br_2F_4N_2$: C, 15.11; H, 1.88; N, 8.80. Found: C, 15.32; H, 1.67; N, 8.61.

3,3-Bis(difluoramino)-1-butyne (**9**).—A solution of 1.01 g (0.0032 mol) of **8** in 3 ml of a potassium hydroxide–triethylene glycol solution[13] was stirred for 5 hr at 25° under static vacuum. Vacuum bulb-to-bulb transfer provided 0.50 g of a liquid condensate at −128°. However, upon warming to 25°, the liquid vaporized to a gas. This gaseous product was established as a 6:1 mixture of the 1-butyne (**9**) and 3,3-bis(difluoramino)-2-bromo-1-butene,[14] respectively, by vpc analysis on a 2-m 30% DC-200 on a Chromosorb column. The assignment of the 1-butyne structure **9** to the major component of this mixture was based upon the following data: ν_{gas} 3320 and 2120 (C≡CH), 990, 910, and 895 cm^{-1} (NF); ^1H nmr τ 8.13 (C≡CH); ^{19}F nmr Φ −32.1 and −37.3 (AB system, Δ_{FF} = 5.2 ppm and J_{FF} = 615 Hz).

Registry No.—**4**, 27723-17-7; **5**, 27723-18-8; **6**, 24426-01-5; **7**, 27723-20-2; **8**, 27723-21-3; **9**, 27723-22-4.

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(13) This solution was prepared by stirring a mixture of 2.8 g of potassium hydroxide in 10 ml of triethylene glycol at room temperature for 1 hr and decanting the supernatant liquid for use in the reaction.

(14) This compound was isolated by preparative vpc and its structure established by nmr analysis.

The Synthesis of β-Hydroxy Acids Using α-Lithiated Carboxylic Acid Salts

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The recent publications by Creger[2] have reported the α lithiation of aliphatic carboxylic acids using lithium diisopropylamide in tetrahydrofuran. The α-lithiated acid salts thus formed have been shown to react with alkyl halides and with epoxides.

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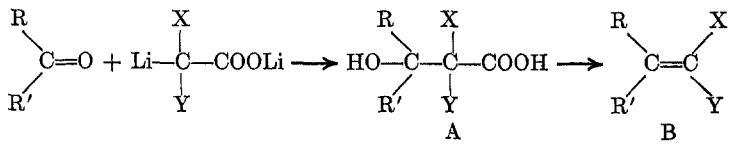
TABLE I
REACTANTS AND YIELDS OF PRODUCTS



			Registry no.	% yield[a]	Mp, °C	Formula[h]
1	Benzophenone	Isobutyric acid	27925-29-7 (A)	31[b]	175–176	$C_{17}H_{18}O_3$
			27925-30-0 (A amine salt)	4.5[b] 74	170–177 175–177	$C_{23}H_{33}O_3N$ $C_{17}H_{18}O_3$
2	Benzophenone	2-Ethylbutyric acid	27925-31-1 (A)	17	129–131	$C_{19}H_{22}O_3$
3	Benzophenone	3,3-Dimethylbutyric acid	27925-32-2 (A)	92	225–226 dec	$C_{19}H_{22}O_3$
4	Benzophenone	Phenylacetic acid	4347-27-7 (A)	32	232–233[c]	$C_{21}H_{18}O_3$
5	Benzophenone	Cyclohexaneacetic acid	27925-34-4 (A)	75	226–227 dec	$C_{21}H_{24}O_3$
6	Benzophenone	Cycloheptanecarboxylic acid	27925-35-5 (A)	38	147–148	$C_{21}H_{24}O_3$
7	Benzophenone	α-Ethylcyclohexaneacetic acid		0		
8	Benzophenone	2-Phenylbutyric acid		0[d]		
9	Benzophenone	Diphenylacetic acid		0		
10	4,4′-Dichlorobenzophenone	Isobutyric acid	27925-36-6 (A)	82	172–173	$C_{17}H_{16}Cl_2O_3$
11	4-Hydroxybenzophenone[e]	Isobutyric acid	27925-37-7 (A)	39	146–148 dec	$C_{17}H_{18}O_4$
12	Dicyclohexyl ketone	Isobutyric acid		0		
13	Dicyclopropyl ketone	Isobutyric acid	27925-38-8 (A)	71	62–64	$C_{11}H_{18}O_3$
14	3-Pentanone	Isobutyric acid	27925-39-9 (A)	77	bp 119–120 (32 mm)	$C_9H_{18}O_3$
15	Cyclohexanone	Isobutyric acid	27925-40-2 (A)	60	90–92	$C_{10}H_{18}O_3$
16	Adamantanone	Isobutyric acid	27925-41-3 (A)	75	200–201 dec	$C_{14}H_{22}O_3$
17	Camphor	Isobutyric acid		0		
18	4-Methoxyacetophenone	Isobutyric acid	27925-42-4 (A)	64	119–122	$C_{13}H_{18}O_4$
19	Progesterone	Isobutyric acid	27925-43-5 (A)	15[f]	180–190	$C_{25}H_{36}O_3$
			27925-44-6 (B)	9 (B)	178–180	$C_{24}H_{36}O$
20	Diphenylacetaldehyde	Isobutyric acid	27925-45-7 (A)	50	182–183	$C_{18}H_{20}O_3$
21	4,4′-Dichlorobenzophenone	2-Ethylbutyric acid	27925-46-8 (A)	31	134–135	$C_{19}H_{20}Cl_2O_3$
22	4-Hydroxy-4′-methylbenzophenone[e]	2-Ethylbutyric acid	27925-47-9 (B)	33 (B)	90–91	$C_{19}H_{22}O$
23	Dicyclohexyl ketone	2-Ethylbutyric acid		0		
24	Camphor	2-Ethylbutyric acid		0		
25	Benzaldehyde	2-Ethylbutyric acid	27925-48-0 (A)	98[g]	80–81	$C_{13}H_{18}O_3$

[a] The product is the hydroxy acid (A) or the olefin (B) except where otherwise indicated. [b] In this run, 31% of the 3-hydroxy-2,2-dimethyl-3,3-diphenylpropionic acid was obtained with a 4.5% yield of the ether soluble diisopropylamine salt of this acid. The amine salt appeared as crystals from the ether–heptane layer from procedure A. A more thorough extraction of the layer with water removes the amine salt to the aqueous solution where acidification liberates the acid. [c] Lit.[8] mp 205–206°, 206–207°. The melting point is very sensitive to the rate of heating. Thus on a Mettler apparatus the melting points were 181.0 and 181.4° at 0.2°/min; 189.7 and 189.8° at 1°/min; 200.3 and 200.5° at 3°/min; 213.2 and 213.4° at 10°/min. The melting points in Table I were determined on a Fisher-Johns block apparatus. [d] The only product is 2-hydroxy-2-phenylbutyric acid, mp 133.2–133.5°. [e] The hydroxyl function was protected by formation of the trimethylsilyl ether. [f] The products obtained in this reaction are (A) α,α-dimethyl-20-oxopregna-3,5-diene-3-acetic acid in 15% yield, and (B) 3-isopropylidenepregn-4-en-20-one in 9% yield. [g] The product was isolated as the β-keto acid following Jones oxidation of the crude product. The yield given is that of the crude acid, from which the β-keto acid was obtained in 73% yield. [h] All the products in this table gave satisfactory C and H analyses (±0.4). In addition, the product, $C_{23}H_{33}O_3N$, of reaction 1 gave satisfactory N analysis and the products of reactions 10 and 21 gave satisfactory Cl analyses. All of the analyses were made available to the editors and to the referees.

The reaction of these α-lithiated acid salts with carbonyl compounds appeared to offer an improved route to the β-hydroxy acids usually obtained by hydrolysis of the β-hydroxy ester products of Reformatsky reactions.[3] The procedure would have the advantage of using readily available acids as starting materials rather than esters[3c] or α-halo esters[3a,b] and thus eliminate the ester hydrolysis step.

We have attempted the reaction of a group of ketones and aldehydes with mono- and disubstituted acetic acids. The results (Table I) show the suitability of the reaction for the synthesis of a range of β-hydroxy acids. However, a number of acids failed to react, as did a number of the ketones tried. Failure of the reaction appears from the data to attend increasing steric hindrance. Since only a few of the reactions were examined in repeated attempts, neither the yields reported nor the reaction failures should necessarily be regarded as limiting. It may be noted that larger substituent groups on the α-bromoacetic esters used in the Reformatsky reaction also resulted in lower yields which could be improved by various techniques. Thus, the use of ethyl α-bromodiethylacetate in reaction with cyclohexanone was reported to give a 6% yield which

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was increased to 19% by use of Mg instead of Zn,[4] and to a yield of 65% by use of methylal as solvent.[5]

In the absence of α hydrogens, *i.e.*, when α,α-disubstituted acids are used, the product β-hydroxy acids on heating or on heating with acids will undergo reversal of the condensation[6] or an elimination–decarboxylation to the olefin. In some cases, olefins were obtained from the reaction procedure. Such behavior parallels that found in the β-hydroxyimine products of the directed aldol condensation.[7]

Hamrick and Hauser[8] have effected the condensation of disodio- and dilithiophenylacetate with benzophenone and with cyclohexanone using Na and Li amides in liquid ammonia. The present work offers an extension to other acids and the use of the more convenient butyllithium and tetrahydrofuran.

Experimental Section

Melting points and boiling points are uncorrected. Infrared spectra were recorded by Mr. E. Schoeb on a Beckman IR-9 spectrophotometer. Nmr spectra were taken by Mr. R. B. Scott on a Varian A-60 spectrometer using tetramethylsilane as internal standard. Microanalyses were carried out by Mr. C. E. Childs and his staff.

General Procedure for the Preparation of α-Lithiated Carboxylic Acid Lithium Salts.—Redistilled diisopropylamine (2 molar equiv) and tetrahydrofuran (dried over CaH_2 and run through Woelm basic alumina just prior to use) were introduced into the N_2-swept flask and cooled to 0–5° by an external ice bath. *n*-Butyllithium in heptane solution (Foote Mineral Co.) (2.1 molar equiv) was introduced in a fine steam by means of a syringe and needle through a rubber septum. The mixture was then stirred for 0.25–0.5 hr while still being cooled. A solution of 1 molar equiv of the carboxylic acid in dry tetrahydrofuran was dropped in by means of a second syringe (the surface of the septum should be wiped clean of any lithium hydroxide to prevent possible plugging of the syringe needle). The reaction was kept cold during the acid addition and stirred throughout. Stirring was continued for 0.5 hr with cooling and then at 40–50° (warm water bath) for 1–1.5 hr.

General Procedure for the Reaction of Carbonyl Compound with α-Lithiated Acid Salts.—The solution of the α-lithiated acid salt was cooled in ice and 1 molar equiv or slightly less of the carbonyl compound in tetrahydrofuran solution was dropped in from an addition funnel. The reaction was protected from moisture, kept under N_2, and stirred throughout. After addition was complete, the reaction was stirred for 1 hr and then overnight to room temperature.

Two procedures were used to work up the reaction mixtures.

A. The reaction was cooled in an ice bath and decomposed by the addition of water slowly with stirring. Excess (*ca.* 1 vol) water was added and the heptane layer separated. This was then extracted with water and the combined aqueous solutions were extracted with ether. The aqueous solution and wash were cooled and acidified with 3 *N* hydrochloric acid. The precipitated acid was separated by filtration or by extraction.

B. The reaction was cooled in an ice bath and decomposed by the addition of 1 *N* hydrochloric acid (*ca.* 1 vol) slowly with stirring. The heptane layer was separated and the aqueous layer extracted with ether. The ether–heptane solution was then extracted with 0.1 *N* NaOH solution which was then cooled and acidified with 3 *N* hydrochloric acid. The acid product was then separated by filtration or by extraction into ether.

Where olefins were produced, they were found in the heptane–ether layer (procedure A) or in the ether solution after NaOH extraction (procedure B). In procedure A, the β-hydroxy acid product occasionally appeared in the heptane–ether solution as a salt with diisopropylamine. Procedure B avoided this complication.

The β-hydroxy acids were generally recrystallized from acetonitrile.

Acknowledgment.—The authors are indebted to Dr. P. L. Creger for sharing his experience in the lithiation of carboxylic acids.

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Lithium–Ammonia Reduction of α,β-Unsaturated Acids and β-Keto Acid Methoxymethyl Enol Ethers

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Although reductions of α,β-unsaturated ketones with alkali metals in liquid ammonia have been studied extensively, there are few reported examples of similar reductions of α,β-unsaturated acids to saturated acids[2-4] and no reported reductions of β-keto acid enol ethers. Except for *trans*-cinnamic acid,[4] the unsaturated acids which have been previously reduced are complicated steroid molecules for which steric hindrance could have affected the results of the reduction. We now wish to report that reduction of simple α,β-unsaturated acids with excess lithium in liquid ammonia proceeds cleanly to give high yields of saturated acids as shown in Table I. The yields are highest for those

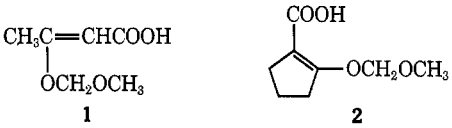
TABLE I
REDUCTION OF VARIOUS α,β-UNSATURATED ACIDS TO SATURATED ACIDS

α,β-Unsaturated acid	% yield of corresponding saturated acid[a]
1-Cyclohexenecarboxylic acid	94
1-Cyclopentenecarboxylic acid	82
Cyclohexylideneacetic acid	93
trans-Cinnamic acid[b]	65
α-Methylcinnamic acid	95
Crotonic acid	73
3-Methylcrotonic acid	92
2-Dodecenoic acid	70

[a] Isolated yield, product recrystallized or distilled. [b] For a previous reduction, see ref 4.

unsaturated acids with more highly substituted double bonds. In the cases of *trans*-cinnamic acid and crotonic acid, some dimeric or polymeric materials appeared to be present in the crude reduction products and are probably due to coupling of anion radical intermediates.

The lithium–ammonia reduction of two other α,β-unsaturated acids, acetoacetic acid methoxymethyl enol ether (**1**) and 2-cyclopentanonecarboxylic acid



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