Table I
Half-Lives for Solvolyses[a] of the Seven Isomeric Chlorooctanoic Acids in 84, 90, and 96% H_2SO_4 at 25°

Registry no.	Position of Cl	Half-life (hr) at 84% H_2SO_4	90% H_2SO_4	96% H_2SO_4
53431-81-5	2	$>10^3$	$>10^3$	$>10^3$
53431-82-6	3	$>10^3$	$>10^3$	$>10^3$
53431-83-7	4		2×10^2	4×10
53466-52-7	5	2×10^2	11	1.5
53431-84-8	6	70	5.2	1.0
53431-85-9	7	50	5.5	0.9
1795-62-6	8	$>10^3$	$>10^3$	$>10^3$

[a] The inertness of the 2-Cl and 8-Cl acids was demonstrated by nmr monitoring. Using these as standards, disappearance rates were determined by periodic dilution of aliquots with ice, ether extraction of the acids, esterification with diazomethane, and gc of the methyl esters as described in ref 6 and 13.

H_2SO_4,[5-8] ethers[6-8] in 85–96% H_2SO_4, alcohols in 20–70% H_2SO_4,[6-9] and alkanes in 84% H_2SO_4.[10]

A potential hazard in these chlorinations is that the chloro substitutent will selectively solvolyze and the product ratios be altered. This paper describes some experiments on the solvolysis of chlorooctanoic acids which show that the solvolysis of chloro substituents is highly sensitive to the H_2SO_4 concentration and to the position of the secondary chloro substituent relative to the carboxyl function.

The rates of solvolysis increase from 84 to 96% H_2SO_4 (Table I). This acid catalysis can be rationalized in terms of acidic species (H_3O^+, H_2SO_4) pulling off chloride ion. The value of $-\mathrm{d} \log k/\mathrm{d}H_R'$ is ~1.4 for the 5-, 6-, and 7-chlorooctanoic acids.[11]

The solvolysis rates also increase with an increase in distance between chloro substituent and carboxyl group up to the 6-chloro (rates for 6-Cl and 7-Cl are equal). This is a result of the positive charge that develops on the carbon undergoing substitution. The carboxyl group inhibits the formation of this positive charge and protonation of the carboxyl[12] intensifies this effect.

We regret to state that these results invalidate the conclusion that chlorination of octanoic acid by Cl_2 in 96% H_2SO_4 gives selectivity for 4-Cl and 8-Cl products.[13] The apparent selectivity was in fact the result of selective destruction of the 5–7 chloro products.

This same problem affects (to a lesser extent) other chlorination studies. Most of Minisci's chlorinations were conducted in 96% H_2SO_4. Selective solvolysis must have been significant in products derived from reactants such as methyl hexanoate and heptanoate so that the selectivity for $\omega - 1$ chlorination is greater than the 70–80% reported. In our own work, octanoic acid was reported to give 80% 7-chlorooctanoic acid in 84% H_2SO_4.[6] At 84% H_2SO_4, the ratio of $RCOOH_2^+$ to RCOOH is about 4 so that higher selectivity for $\omega - 1$ chlorination would be expected in 96% H_2SO_4 where protonation of octanoic acid is more complete. However, this was not found and the selectivity for $\omega - 1$ seemed to be much less. It is now clear that the selectivity was probably greater, but that this was obscured by selective solvolysis. The results of Kollonitsch were on such short chains[1-3] that selective solvolysis would be unlikely. However, extrapolation of Kollonitsch's conclusions and methods to longer chains would excounter selective solvolysis problems.

Registry No.—H_2SO_4, 7664-93-9.

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Improved Procedures for Ethynylcarbinol Hydration and Oxime Reduction to Amino Alcohols[1]

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Because of a need for 3-amino-2-methyl-2-butanol (**1**) and 1-(1-aminoethyl)cyclohexanol (**2**) in other research, we considered several routes for their synthesis. Early syntheses of **1** involved catalytic reduction of the oxime of 3-hydroxy-3-methyl-2-butanone[3] and of 2-methyl-3-nitro-2-butanol[4] over Raney nickel, whereas **2** has been prepared in several steps starting from cyclohexanone cyanohydrin.[5-7] As either the yields or the procedures involved in the earlier syntheses left much to be desired, we have developed improved procedures for **1** and **2**. The chemistry used should be readily adaptable to the preparation of other amino alcohols.

The starting materials were the readily available ethynylcarbinols, $R_2C(OH)C{\equiv}CH$, **3a** and **3b**, prepared by reaction of acetone and of cyclohexanone, respectively, with acetylene.[8] Although reference to the hydration of acetylenes to ketones is frequently made,[9] the best yield for the preparation of 1-acetylcyclohexanol by this method that we have located in the literature is 69% in a two-step reaction of ethynylcyclohexanol with mercuric oxide and sulfuric acid.[10] We have obtained a 90% yield by a simplified one-step process. Similarly, 3-hydroxy-3-methyl-2-butanone was obtained from **3a** in 80% yield.

The ketones were then converted into the corresponding oximes which were hydrogenated over 5% rhodium-on-alumina[11] to yield the desired **1** and **2** in excellent overall yield. This facile high-yield reduction of hydroxy oximes over a rhodium catalyst is notable in view of our unsuccessful attempts to reduce the same oximes catalytically over platinum or palladium catalysts. In addition, reduction procedures involving sodium in liquid ammonia or $LiAlH_4$ in ether failed to yield the desired amino alcohols in more than small yield.

Monoacylation of **1** and **2** on nitrogen was effected in over 90% yields by carrying out the acylation with 1 equiv

of acetic anhydride in absolute ethanol. The effectiveness of this method of monoacetylation[12] should be noted.

Experimental Section

3-Hydroxy-3-methyl-2-butanone. To a warm vigorously stirred solution of 65 g of yellow mercuric oxide in 500 ml of water and 90 ml of concentrated sulfuric acid was added dropwise 420.5 g (5.0 mol) of 2-methyl-3-butyn-2-ol[8] during 1.5 hr. The mixture was then heated to 70° for 30 min, cooled, and filtered through a Celite layer. The organic product was extracted into ether and the ether layer washed with water and $NaHCO_3$ solution. After pouring through a layer of $MgSO_4$ the solvent was removed and the residue distilled to yield 409.5 (80%) of 3-hydroxy-3-methyl-2-butanone, bp 137.8–139.0° (750 mm).

1-Acetylcyclohexanol. In a similar way 620 g of 1-ethynylcyclohexanol[8] was converted into 640 g (90%) of 1-acetylcyclohexanol, bp 100–101° (25 mm).

3-Hydroxy-3-methyl-2-butanone Oxime. To a well-stirred solution of 102.1 g (1.0 mol) of 3-hydroxy-3-methyl-2-butanone, 112 g of hydroxylamine hydrochloride, 400 ml of ethanol, and 50 ml of water was added portionwise 80 g of NaOH pellets. After heating to reflux for 10 min after the NaOH had all dissolved the reaction mixture was cooled and diluted with 500 ml of water, and the product isolated by ether extraction. On distillation 90 g (84%) of the oxime, mp 86–87°, was obtained.

1-Acetylcyclohexanol Oxime. In a manner similar to the above 142 g of 1-acetylcyclohexanol was converted into the oxime which was isolated by crystallization from benzene instead of distillation. The product, mp 104–105°, was obtained in 90% yield.

3-Amino-2-methyl-2-butanol (1). A solution of 23.4 g (0.2 mol) of 3-hydroxy-3-methyl-2-butanone oxime in 125 ml of freshly distilled absolute ethanol was shaken with 1.25 g of 5% rhodium-on-alumina[12] at about 40 psi for 9.5 hr. After removal of the catalyst by filtration through Celite, there was obtained 19.0 g (94%) of **1**, bp 59–61° (2 mm), as a colorless oil. The vacuum should be broken through a KOH tower in order to prevent access of CO_2 which produces a colorless solid immediately on contact with **1**. For acetylation 10.3 g (0.1 mol) of the freshly distilled amine was dissolved in 75 ml of ethanol and treated dropwise with 10.2 g (0.1 mol) of acetic anhydride. After refluxing the mixture for 30 min the alcohol was removed under reduced pressure. Vacuum distillation afforded a white solid which was recrystallized from benzene–hexane to yield 13.3 g (92%) of 3-acetylamino-2-methyl-2-butanol, mp 83.5–84.5°. This compound proved identical with that prepared previously by Liang[13] by the hydrolysis of 4,5,5-trimethyloxazolidone to **1** followed by acetylation essentially as above.

Anal.[14] Calcd for $C_7H_{15}NO_2$: C, 57.9; H, 10.4. Found: C, 58.1; H, 10.3.

1-(1-Aminoethyl)cyclohexanol (2). A solution of 31.4 g (0.19 mol) of 1-acetylcyclohexanol oxime in 150 ml of freshly distilled ethanol was reduced for 48 hr at 60–65° over 5% rhodium-on-alumina at 40–50 psi. The reaction mixture was worked up as for **1** to yield 25.7 g (90%) of **2**, bp 150–153° (40 mm), sensitive to CO_2. For acetylation 21.5 g (0.14 mol) of **2** in 100 ml of ethanol was treated with 15.4 g (0.15 mol) of acetic anhydride as in the case of **1**. After isolation as above there was obtained the acetylamino compound which distilled at 138–140° (4.5 mm). The solid distillate was recrystallized from acetone–benzene to yield 24.6 g (90%) of 1-(1-acetylaminoethyl)cyclohexanol: mp 107–108°; nmr ($CDCl_3$) δ 1.14 (d, 3 H, $CHCH_3$), 1.50 (m, 10 H, cyclohexyl protons), 1.99 (s, 3 H, $COCH_3$), 3.27 (s, 1 H, OH), 4.00 (m, 1 H, $CHCH_3$), and 6.70 (m, 1 H, NH); ir (KBr) 3.00 (NH and OH) and 6.10 μ (>C=O).

Anal.[14] Calcd for $C_{10}H_{19}NO_2$: C, 65.0; H, 10.2; N, 7.6. Found: C, 64.9; H, 10.4; N, 7.5.

Registry No.—**1**, 6291-17-4; **2**, 3183-55-9; **3a**, 115-19-5; **3b**, 78-27-3; 3-hydroxy-3-methyl-2-butanone, 115-22-0; 1-acetylcyclohexanol, 1123-27-9; 3-hydroxy-3-methyl-2-butanone oxime, 7431-25-6; hydroxylamine hydrochloride, 5470-11-1; 1-acetylcyclohexanol oxime, 53336-53-1; 3-acetylamino-2-methyl-2-butanol, 53336-55-3; 1-(1-acetylaminoethyl)cyclohexanol, 53336-54-2.

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Lithium Aluminum Hydride Reduction of 9b-(4-Chlorophenyl)-1,2,3,9b-tetrahydro-5*H*-imidazo[2,1-*a*]isoindol-5-one in Tetrahydrofuran

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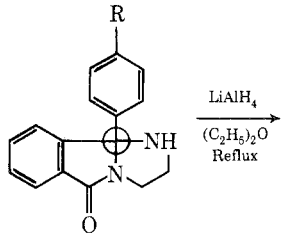
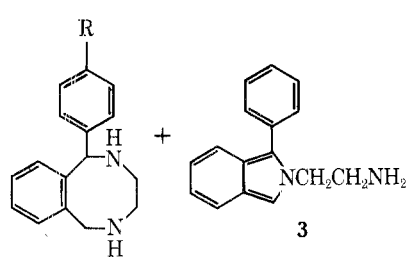
The lithium aluminum hydride ($LiAlH_4$) reduction of the 9b-aryl-1,2,3,9b-tetrahydro-5*H*-imidazo[2,1-*a*]isoindol-5-ones (**1a** and **1b**) in refluxing diethyl ether has been reported to give the 1-aryl-1,2,3,4,5,6-hexahydro-2,5-benzodiazocines (**2a** and **2b**)[1-4] and 2-(2-aminoethyl)-1-phenylisoindole (**3**)[3].



1a, R = H
b, R = Cl



3

2a, R = H
b, R = Cl

We have carried out the $LiAlH_4$ reduction of **1** in tetrahydrofuran (THF) at 20–25° and found that the reaction leads to different products. In the present report, our findings with 9-(*p*-chlorophenyl)-1,2,3,9b-tetrahydro-5*H*-imidazo[2,1-*a*]isoindol-5-one (**1b**) are given.[5]

Compound **1b** was treated with $LiAlH_4$ in THF at 20–25° and then hydrolyzed with aqueous sodium hydroxide. After standing for about 4 hr at room temperature, the mixture was dried with anhydrous Na_2SO_4 to give a compound with ir and nmr spectrum in agreement with the phthalimidine (**4**). The same phthalimidine was obtained when **1b** was hydrogenated in the presence of platinum.

When the reduction was carried out as above and treated immediately after hydrolysis with anhydrous Na_2SO_4, a labile solid compound A, isomeric with **4**, was isolated in 95% yield.