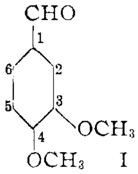
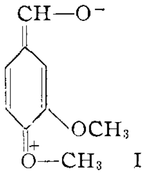
When the reagent is nucleophilic, the favored points of attack in 3-nitrotoluene are predicted to be 2, 4 and 6, so that the *ortho–para* directing nitro group predominates over the *meta*-directing methyl group. This prediction, which is not very sensitive to the values chosen for the parameters, is verified by experiment.[4,5] As with 3-nitrophenol, no data regarding radical attack are available; the predicted orientation must surely be correct, however, since both substituents are *ortho–para* directing.

A superficial consideration of veratraldehyde (I) leads to the conclusion that, since the two methoxy groups oppose each other, the orientation should be determined by the formyl group. On

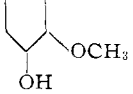


I

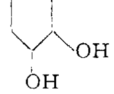


II

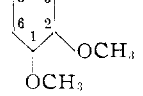
this basis, then, attack by an electrophilic reagent should occur at position 5. Experimentally,[4] however, nitration gives 6-nitroveratraldehyde, and bromination gives the analogous 6-bromoveratraldehyde. For these somewhat unexpected observations, Rây and Robinson[6] proposed an explanation which, when re-expressed in more modern terms, takes the following form. In veratraldehyde, there must be resonance not only between the two Kekulé structures that are implied by the symbol I, but also with the quinoid structure II. As a result of this resonance, only the methoxy group in position 3 is free to exert its full normal orienting effect; consequently, the entering substituent is directed largely by this one group. Although this explanation seems rather reasonable, it cannot be complete since, by centering attention upon only the normal unreacting molecule, it ignores all those respects in which the reactions at positions 5 and 6 differ from each other; it is therefore incapable of accounting for the relative rates of these competing reactions. Only by explicitly comparing the stabilities of the respective activated complexes, in fact, can we avoid this difficulty. The required comparison is shown in the table, from which it is evident that the more detailed calculations are in agreement with the earlier suggestion of Rây and Robinson. No satisfactory explanation for all the pertinent data can, however, be obtained either in this way or in any other way that is immediately apparent since the orientation observed with veratraldehyde is not always encountered with other substances of closely similar structure.[4] In both the nitration and the bromination of vanillin (III), for example, the substitution takes place at position 5, and in the bromination of protocatechualdehyde (IV), the substitution again takes place at position 5. Moreover, 4-nitroveratrole (V) is brominated at position 6 but nitrated at position 5. Clearly, no satisfactory explanation can now be offered for such conflicting data.



III



IV



V

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[5] F. W. Bergstrom, I. M. Granara and V. Erickson, *J. Org. Chem.*, **7** 98 (1942).

[6] J. N. Rây and R. Robinson, *J. Chem. Soc.*, **127**, 1618 (1925).

Higher Amino Alcohols *via* the Mannich Reaction

By Joseph Matt[1] and Ellen P. Gunther

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In connection with studies of the reactions of higher aliphatic ketones, amino ketones have been prepared by means of the Mannich reaction. The amino ketones have been reduced to the corresponding amino alcohols and these in turn have been converted to amine and quaternary ammonium salts.

Amino ketones $RCH(COR')CH_2NMe_2$ prepared by the reaction of higher aliphatic ketones with formaldehyde and dimethylamine hydrochloride were unstable and could not be distilled. However, prompt reduction of the partially purified bases by means of lithium aluminum hydride or sodium borohydride afforded the corresponding amino alcohols which distilled without decomposition.

Exhaustive hydrogenation of the amino ketones with Raney nickel catalyst at 200° and 2000 pounds pressure gave saturated alcohols. In an experiment involving the dimethylamino ketone derived from 2-tridecanone, the alcohol obtained was not 3-tetradecanol, but was 3-methyl-2-tridecanol, indicating that aminomethylation had occurred[2] on the methylene group of the long chain adjacent to the carbonyl.

The amino alcohols were treated with hydrogen chloride, methyl chloride and benzyl chloride to give the corresponding salts.

Table I lists the conversions, properties and analyses of the bases and salts. Conversions given for the bases represent fractions of reasonable purity; the physical constants apply to center cuts.

Experimental

A typical preparation is that of 3-dimethylaminomethyl-2-heptadecanol, $C_{14}H_{29}CH(CH_2NMe_2)CHOHMe$. Methyl pentadecyl ketone (240 g., 0.95 mole), 35% formaldehyde solution (170 g., 2.0 moles) and dimethylamine hydrochloride (89.1 g., 1.1 moles) were refluxed in one liter of ethanol containing 10 ml. of concd. hydrochloric acid for five days. After removal of much of the solvent *in vacuo*, the solution was made alkaline and extracted with ether, and the extract was washed free of dimethylamine. After removal of ether, reduction of the crude amino ketone was effected at room temperature in methanol solution (250 ml.) by dropwise addition, with stirring, of sodium borohydride (16.1 g., 0.425 mole) dissolved in a mixture of methanol (100 ml.) and 5% sodium hydroxide solution (50 ml.), followed by refluxing for one hour. After dilution with 500

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[1] Virginia Carolina Chemical Corp., Richmond, Va. Address communications regarding this work to H. J. Harwood, Research Division, Armour and Co., Chicago, Ill.

[2] F. F. Blicke, "Organic Reactions," Vol. I, John Wiley and Sons, Inc., New York, N. Y., p. 303.

TABLE I

ALCOHOLS $RCH(CHOHR')CH_2NMe_2$ AND SALTS $[RCH(CHOHR')CH_2NMe_2R'']Cl$ FROM KETONES $RCHCOR'$

R	R′	R″	Conversion of ketone to alcohol, %		B.p. of base,		$n^{25}D$ of base	Conversion of alcohol to salt, %	Empirical formula	Neut. equiv.		Nitrogen, %		Chlorine, %	
			NaBH4	LiAlH4	°C.	Mm.				Calcd.	Found	Calcd.	Found	Calcd.	Found
Hexyl	Methyl			45	112	2			$C_{12}H_{27}NO$	201	206				
		Hydrogen						93	$C_{12}H_{28}NOCl$			5.89	5.65	14.92	15.60
		Methyl						35	$C_{13}H_{30}NOCl$			5.56	5.38	14.09	13.95
		Benzyl[a]						86	$C_{19}H_{34}NOCl$			4.27	4.15	10.82	10.50
Octyl	Methyl		36	45	120	0.7	1.4457		$C_{14}H_{31}NO$	229	236				
		Hydrogen						77	$C_{14}H_{32}NOCl$			5.27	5.10	13.34	13.20
		Methyl						55	$C_{15}H_{34}NOCl$			5.00	4.59	12.67	12.32
		Benzyl						54	$C_{21}H_{38}NOCl$			3.93	3.92	9.97	10.25
Decyl	Methyl			51	147	.9	1.4510		$C_{16}H_{35}NO$	257	255				
		Hydrogen						71	$C_{16}H_{36}NOCl$			4.77	4.70	12.07	12.20
		Methyl						78	$C_{17}H_{38}NOCl$			4.55	4.30	11.52	11.95
		Benzyl						63	$C_{23}H_{42}NOCl$			3.65	3.66	9.24	9.25
Tetradecyl	Methyl		45	41	165	.4	1.4532		$C_{20}H_{43}NO$	313	315				
		Hydrogen						67	$C_{20}H_{44}NOCl$			4.00	3.96	10.13	10.08
		Methyl						47	$C_{21}H_{46}NOCl$			3.85	3.88	9.74	9.95
		Benzyl						81	$C_{27}H_{50}NOCl$			3.18	3.02	8.06	7.72
Hexyl	Heptyl			68[c]	130	.3	1.4502		$C_{18}H_{39}NO$	286	295				
		Hydrogen						69	$C_{18}H_{40}NOCl$			4.35	4.00	11.04	11.58
		Benzyl						90	$C_{25}H_{47}NOCl$			3.40	3.60	8.61	8.72
Octyl	Nonyl		34		160	.2	1.4542		$C_{22}H_{47}NO$	341	360				
		Hydrogen						91	$C_{22}H_{48}NOCl$			3.71	3.48	9.38	9.82
		Benzyl[b]						86	$C_{29}H_{54}NOCl$			2.93	2.94	7.58	7.48
Decyl	Undecyl		46[c]		190–195	.2	1.4564		$C_{26}H_{55}NO$	398	485				
		Benzyl						58	$C_{33}H_{62}NOCl$			2.68	2.68	6.78	6.54

[a] M.p. 135–138°. [b] M.p. 117–120°. [c] Crude.

ml. of water and careful hydrolysis with 200 ml. of concentrated hydrochloric acid, the mixture was clarified by addition of ethanol, and extracted with Skellysolve F to remove non-basic material. After removal of ethanol, the residue was made alkaline and extracted with Skellysolve F. The extract was washed, dried, and fractionally distilled to give the crude base in 45% conversion. Pure material was obtained by a second fractionation, b.p. 165–170° at 4 mm. Infrared examination of the forerun revealed the presence of small amounts of unsaturated alcohol, probably the reduction product of the unsaturated ketone arising by deamination of the Mannich base.

A portion of the base obtained from methyl undecyl ketone was reduced at 200° and 2000 pounds pressure with Raney nickel catalyst. The product, which was shown by infrared examination to contain about 5% ketone, was reduced further with sodium in ethanol. Distillation gave a liquid, b.p. 100° at 0.2 mm., $n^{25}D$ 1.4446. Infrared examination showed this to be a secondary alcohol, differing from 3-tetradecanol ($n^{25}D$ 1.4428) in its much stronger methyl band at 7.3 μ.

Anal. (Galbraith Laboratories, Knoxville, Tenn.). Calcd. for $C_{14}H_{30}O$: C, 78.50; H, 14.02. Found: C, 78.57; H, 14.05.

Salts of the amino alcohols were made by three methods depending upon the halide used: (a) the base was mixed with an equivalent of benzyl chloride, and warmed for several days in an ethyl acetate–methanol mixture; (b) the base was heated for several hours at 125° in a bomb with excess methyl chloride in methanol; (c) hydrogen chloride was passed into a solution of the base in Skellysolve F. The products, or alcoholic solutions thereof, were freed of starting materials by several washings with Skellysolve F, affording analytically pure products. In general, these were hygroscopic solids, possessing no definite decomposition or melting points.

The salts of bases derived from symmetrical ketones were soluble in Skellysolve F, especially in the presence of even small amounts of polar solvents. Purification was achieved by trituration of the dry solid with Skellysolve F.

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The Synthesis of Certain Ketones and Carbinols Containing Perfluoroalkyl Groups[1]

BY THOMAS F. MCGRATH[2] AND ROBERT LEVINE

RECEIVED FEBRUARY 24, 1955

In an earlier paper[3] we reported that the addition of one equivalent of trifluoroacetic acid to two or more equivalents of phenyllithium in refluxing ether gave none of the expected trifluoroacetophenone. Instead some or all of the following cleavage products were obtained: benzoic acid, benzophenone, triphenylmethane and tetraphenylethylene.

It has now been found (Table I) that a mixture of trifluoroacetophenone and benzoic acid is obtained when one equivalent of trifluoroacetic acid is added to two equivalents of phenyllithium (Standard Addition Technique) at 0°. When the reaction temperature is decreased to −40 or −65°, the yield of ketone is increased at the expense of the cleavage product, benzoic acid. Similar reactions were effected using perfluoropropionic and perfluoro-*n*-butyric acids.

Since the use of the standard addition technique in the reaction between perfluoro-*n*-butyric acid

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(2) Monsanto Chemical Co., Fellow, 1953–1954.

(3) T. F. McGrath and R. Levine, THIS JOURNAL, **77**, 3634 (1955).