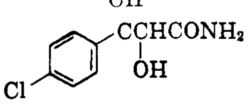
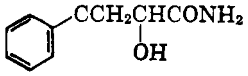
TABLE I

α-HYDROXY ACID AMIDES

Amide	M.p., °C.	Lit. m.p., °C.	Method[a]	% yield
$CH_3\underset{OH}{C}HCONH_2$	74–75	74[b]	B	59
$CH_3CH_2\underset{OH}{C}HCONH_2$	104–105	105[c]	A	55
$(CH_3)_2\underset{OH}{C}CONH_2$	97–99	96–98[d]	B	80
$(CH_3)_2CH\underset{OH}{C}HCONH_2$	102–104	104[e]	B	78
$CH_3CH_2\overset{CH_3}{\underset{OH}{C}}CONH_2$	68–69	160[f]	B	56
$(CH_3)_2CHCH_2\underset{OH}{C}HCONH_2$	81–82	51–52[g]	A	79
$CH_3CH_2\overset{CH_3}{C}H\underset{OH}{C}HCONH_2$	49–56[h]		B	70
$CH_3(CH_2)_5\underset{OH}{C}HCONH_2$	151–152	150[i]	B	44[l]
	124–125	122–123[j]	A	45
	110–112	111–112[k]	A	71

[a] Method A: inert solvent with equivalent quantities of alcohol. Method B: alcohol used as a solvent. [b] J. Wislicenus, *Ann.*, **133**, 257 (1865). [c] H. Bredereck, R. Gompper, and G. Theilig, *Ber.*, **87**, 537 (1954). [d] G. Ciamician and P. Silber, *ibid.*, **38**, 1671 (1905). [e] A. Lipp, *Ann.*, **205**, 1 (1880). [f] G. Ciamician and P. Silber, *Ber.*, **47**, 1806 (1914). *Anal.* Calcd. for $C_5H_{11}NO_2$: C, 51.26; H, 9.46; N, 11.96. Found: C, 51.27; H, 9.73; N, 11.94. [g] P. Nicolle, *Bull. soc. chim. France*, [4] **39**, 55 (1926). *Anal.* Calcd. for $C_6H_{13}NO_2$: C, 54.94; H, 9.99; N, 10.68. Found: C, 55.13; H, 9.68; N, 10.75. [h] An obvious mixture of isomers. *Anal.* Calcd. for $C_6H_{13}NO_2$: C, 54.94; H, 9.99; N, 10.68. Found: C, 55.16; H, 10.03; N, 10.63. [i] E. Erlenmeyer and O. Sigel, *Ann.*, **177**, 102 (1875). [j] H. G. Rule, *J. Chem. Soc.*, **113**, 3 (1918). [k] A. McKenzie, G. Martin, and H. G. Rule, *ibid.*, **105**, 1583 (1914). [l] Recrystallized yield.

Some ammonium chloride (up to 15%) was always formed during the reaction sequence and limited attempts were made to overcome its formation. Since this salt formation is most likely the result of alcoholysis of the imido ester, a brief study of the effect of various alcohols on the formation of ammonium chloride was conducted. Contrary to the striking effects of "subtle" changes in alcohol structure observed in the related synthesis of α-amino acid amides[2], little difference in the course of the reaction was noted when 2-propanol, 2-butanol, and 3-pentanol were employed as solvents.

Those α-hydroxy acid amides analogous to the essential α-amino acids valine, leucine, and phenylalanine were evaluated for their ability to replace them nutritionally in a mouse diet. As expected, complete replacement was observed.

Experimental[4]

2-Hydroxy-3-phenylpropionamide. Procedure A.—A mixture of 649 g. (4.41 moles) of phenylacetaldehyde cyanohydrin, 210 g. (4.57 moles) of ethanol, and 2.6 l. of dry benzene (dry xylene was used in all other cases) was saturated with anhydrous hydrogen chloride (358 g.) at 25°. The mixture was stirred for 20 hr. at 25° and then heated under reflux for 6 hr. During this time the product precipitated and was collected after cooling the mixture to 10°. A total of 586 g. of light yellow crystalline product was obtained, m.p. 107–112° and was found to contain 6% ammonium chloride as calculated from a chloride analysis. The product was crystallized from 3 l. of benzene containing 450 ml. of ethanol to give 450 g. (62%) of colorless crystals, m.p. 110–112°.

2-Hydroxy-3-methylbutyramide. Procedure B.—A solution of 500 g. (5.06 moles) of isobutyraldehyde cyanohydrin in 3 l. of isopropyl alcohol was saturated with anhydrous hydrogen chloride at 25–30°. The mixture was stirred at 25° for 20 hr. and then excess alcohol and hydrogen chloride were removed by evaporation under reduced pressure. The remaining residue was heated slowly to 170° under 20–50-mm. pressure and then cooled to room temperature. Two liters of ethanol was added and the ammonium chloride present was removed by a filtration (11 g.). Evaporation of the ethanol followed by distillation of the residue gave 461 g. (78%) of colorless distillate, b.p. 145–150° (2 mm.) m.p. 93–98°. Crystallization from an isopropyl ether–ethanol mixture raised the melting point to 102–104°.

Acknowledgment.—The authors wish to thank C. R. McClure for able assistance and Q. Quick and his associates for microanalyses and spectral data.

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(4) Melting points are corrected.

The Brominating Properties of Tetramethylammonium Tribromide[1a]

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Organic ammonium perbromides are considered mild brominating agents. Pyridinium bromide perbromide was introduced by Djerassi and Scholz for the bromination of keto steroids and has since been used widely in place of bromine, which occasionally causes undesired substitution or oxidation reactions.[2] Unlike N-bromosuccinimide (NBS), it lacks the ability to perform allylic bromination. Marquet and coworkers preferred phenyltrimethylammonium perbromide (PTAP) to pyridinium bromide perbromide because of the greater stability of the former.[3] With this reagent they were able to brominate ketones and 1,3-dioxolanes, without affecting isolated ethylenic double bonds, present in the same molecule. Its mild brominating characteristic and specificity were shown in the reaction with 2-acetyl-6-methoxynaphthalene. In tetrahydrofuran 2-bromoacetyl-6-methoxynaphthalene was obtained, while in acetic acid a 1:1 mixture of this bromoacetyl compound and the nuclear substituted derivative, 2-acetyl-5-bromo-6-methoxynaphthalene was formed. Although NBS is considered a specific reagent for allylic bromination,[4] it can bro-

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(1) (a) Taken in part from the M.S. thesis of J. Weiss, Bar Ilan University, 1963; (b) Weizmann Institute of Science, Rehovoth, Israel.

(2) C. Djerassi and C. R. Scholz, *J. Am. Chem. Soc.*, **70**, 417 (1948); P. C. Merker and J. A. Vona, *J. Chem. Educ.*, **26**, 613 (1949); J. A. Vona and P. C. Merker, *J. Org. Chem.*, **14**, 1048 (1949); N. B. Lorette, T. B. Gage, and S. H. Wender, *ibid.*, **16**, 930 (1951).

(3) A. Marquet, M. Dvolaitzky, H. B. Kagan, L. Mamlock, C. Onannes, and J. Jacques, *Bull. soc. chim. France*, 1822 (1961); A. Marquet and J. Jacques, *ibid.*, 90 (1962).

(4) C. Djerassi, *Chem. Rev.*, **43**, 271 (1948).

TABLE I

BROMINATION BY MEANS OF TETRAMETHYLAMMONIUM TRIBROMIDE

	Method A				Method B			
Starting material	Product	Time, hr.	M.p. or b.p. (mm.), °C.	Yield, %	Product	Time, min.	M.p. or b.p. (mm.), °C.	Yield, %
Toluene	Benzyl bromide[a]		194–198[b] (760)	59	*p*-Bromotoluene[a,c]		184–186[d] (760)	72
Fluorene	9-Bromofluorene	5	104[e]	70	2-Bromofluorene	30	112–113[f]	82
1-Methylnaphthalene	1-Bromomethylnaphthalene	24[g]	55–56[h]	57	2-Bromo-1-methylnaphthalene	20	35–37[i]	65
2-Methylnaphthalene	2-Bromomethylnaphthalene	8	54–55[j]	62	1-Bromo-2-methylnaphthalene	20	112–115[k] (2)	72
2-Acetyl-6-methoxynaphthalene	2-Bromoacetyl-6-methoxynaphthalene	3	110–110.5[l]	70	2-Acetyl-5-bromo-6-methoxynaphthalene	10	126–127[m]	50
Cyclohexene	1,2-Dibromocyclohexane[n]		134–136[o] (40)	86	1,2-Dibromocyclohexane[n]	10	134–136[o] (40)	78

[a] This reaction is described separately in the Experimental section. [b] Lit.[15] b.p. 198°. [c] When the reaction was performed as described in method B in the presence of catalytic amounts of ferric chloride, benzyl bromide was obtained in 50% yield. [d] Lit.[16] b.p. 184°. [e] Lit. m.p. 104° [Elsevier's "Encyclopaedia of Organic Chemistry," Vol. 13, Elsevier Publishing Co., Inc., New York, 1948, p 41]. [f] Lit. m.p. 113° [*ibid.*, p. 92]. [g] The orange tribromide did not disappear completely. [h] Lit. m.p. 56° [ref. 15, p. 343]. [i] Lit.[9] m.p. 35°; picrate m.p. 104–106°, lit.[9] m.p. 105–106°. [j] Lit. m.p. 56°. Hexamine complex m.p. 159°, lit. m.p. 160° [F. Mayer and A. Sieglitz, *Ber.*, **55**, 1835 (1922)]. [k] n^{20}D 1.6493, picrate m.p. 113–114°. Lit. b.p. 117–118° (2 mm.), n^{20}D 1.6484, picrate m.p. 114.7–115.1° [M. S. Newman and A. I. Kosak, *J. Org. Chem.*, **14**, 375 (1949)]. [l] Lit. m.p. 110–111°, pyridinium salt m.p. 240–241°, lit. m.p. 241° [A. Marquet and J. Jacques, *Tetrahedron Letters*, **9**, 24 (1959)]. [m] Lit. m.p. 126–127° [H. A. Weidlich and M. Meyer-Delius, *Ber.*, **72**, 1941 (1939)]. [n] The reaction was started by adding slowly a solution of cyclohexene in the corresponding solvent to the solution or the suspension of the tribromide and was performed at room temperature. [o] Lit. b.p. 145–146° (100 mm.) [ref. 15, Vol. II, p. 79]; n^{20}D 1.5507, lit.[11] n^{20}D 1.5516.

minate, in the presence of equimolar amounts of certain metal chlorides, the nucleus of benzene and of toluene.[5]

Previous to the work of Marquet, one of the present authors suggested that a mixture of tetramethylammonium perbromides (Me_4NBr_x; $x = 5.1–6.2$) could be used for the convenient preparation of dibromopropanol from allyl alcohol.[6] In the present investigation we have studied the brominating properties of tetramethylammonium tribromide[7] (TMAT, Me_4NBr_3), preferring this solid compound to the previously mentioned liquid mixture of the polybromides. The stable and easily prepared tribromide is an orange solid, melting at 118–118.5°, containing 50.9% of active bromine and like phenyltrimethylammonium perbromide (PTAP), is also a mild brominating agent. While each of these tribromides gives only 2-bromoacetyl-6-methoxynaphthalene, when used in nonpolar solvents, only TMAT gives the nuclear brominated derivative (2-acetyl-5-bromo-6-methoxynaphthalene) as the sole product in acetic acid.

Subsequently we investigated the effect of this reagent on several aromatic hydrocarbons which could undergo either nuclear or benzylic bromination. The direction of the substitution could be controlled by varying the nature of the reaction medium. These results are summarized in Table I. In benzene solution containing benzoyl peroxide, toluene, fluorene, and 1- and 2-methylnaphthalenes undergo benzylic bromination. In acetic acid solution, even in the absence of a catalyst, regular aromatic substitution takes place. It is interesting to note the unusual orientation of the bromine in the product obtained from the reaction of this reagent with 1-methylnaphthalene in acetic acid. In contrast with bromine, which gives 1-methyl-4-bromonaphthalene,[8] we obtained the 2-bromo derivative.[9] The bromination of toluene with this reagent in acetic acid is anomalous; in the absence of a catalyst, benzyl bromide is formed, while in the presence of an equimolar amount of ferric chloride *p*-bromotoluene is obtained. Cyclohexene was used as a model compound for comparing the brominating properties of TMAT with those of NBS. The latter affords 3-bromocyclohexene in 80–90% yield[10]; in the presence of alkylammonium halides the yield of this product is markedly reduced and an appreciable amount of the addition product, 1,2-dibromocyclohexane, is isolated.[11] In contrast TMAT, in benzene in the absence of a catalyst, afforded only the addition product in 80% yield. Varying the solvent did not affect the nature of the product, even in the presence of benzoyl peroxide.

The results of this investigation would indicate that this brominating agent is highly dissociated in polar solvents like acetic acid.[12] The liberated bromine molecule undergoes the usual heterolytic fission in ionic reactions, like the aromatic substitution observed in this investigation. In nonpolar solvents (for example, benzene) and in the presence of free-radical initiators, the complex presumably undergoes homolytic fission to perform free-radical reactions, like benzylic substitution. This convenient, versatile reagent resembles bromine in its ability to perform ionic addition and substitution reactions, as well as NBS in performing free-radical substitution under mild conditions.

Experimental[13]

The starting materials were obtained from regular commercial sources and were purified by recrystallization or distillation when necessary. TMAT was prepared from tetramethylammonium bromide and bromine in acetic acid in an 87% yield, as described by Chattaway and Hoyle.[7] 2-Acetyl-6-methoxynaphthalene was prepared by acetylation of 2-methoxynaphthal-

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[5] H. Schmid, *Helv. Chim. Acta*, **29**, 1144 (1946).

[6] L. Farkas and O. Schächter, *J. Am. Chem. Soc.*, **71**, 2252 (1949).

[7] F. D. Chattaway and G. Hoyle, *J. Chem. Soc.*, **123**, 654 (1923).

[8] F. Mayer and A. Sieglitz, *Ber.*, **55**, 1835 (1922).

[9] This compound is usually prepared from the diazotized 2-amino-1-methylnaphthalene [V. Veselý, F. Štursa, H. Olejniček, and E. Rein, *Chem. Abstr.*, **24**, 3008 (1930)].

[10] K. Ziegler, A. Späth, E. Schaaf, W. Schumann, and E. Winkelmann, *Ann.*, **551**, 80 (1942).

[11] E. A. Braude and E. S. Waight, *J. Chem. Soc.*, 1116 (1952).

[12] The brown color of the solution of TMAT in acetic acid is reminiscent of that of a solution of bromine in acetic acid. To repress this dissociation, the presence of an excess of bromine is required when the reagent is prepared in acetic acid.

[13] The boiling and melting points are uncorrected.

ene according to the procedure described by Robinson and Rydlon.[14]

The identities of the reaction products were confirmed by their inability to depress the melting points of authentic samples. The yields in Table I refer to compounds whose boiling points or melting points are given in the same table.

Method A.—To a solution of 0.01 mole of starting material in 20 ml. of benzene containing a catalytic amount of benzoyl peroxide, was added 0.01 mole of TMAT. The mixture was stirred at room temperature for the specified reaction period, which was determined by the disappearance of the tribromide and the cessation of hydrogen bromide evolution. The colorless tetramethylammonium bromide was dissolved by adding water. The organic layer was separated, washed with water and aqueous sodium carbonate in succession, dried over sodium sulfate, and the solvent removed. The reaction product was isolated by recrystallization, distillation, or by both procedures.

Method B.—A solution of 0.01 mole of the starting material and 0.01 mole of TMAT in 30 ml. of acetic acid was refluxed for the specified reaction time until the bromide color disappeared and no more hydrogen bromide was evolved. The cold reaction mixture was poured into water to dissolve the precipitated tetramethylammonium bromide, and the aqueous solution was then extracted with ether. The organic layer was treated, and the product isolated, as described in method A.

Benzyl Bromide.—A mixture of 0.921 g. (0.01 mole) of toluene, 6.27 g. (0.02 mole) of TMAT, and a trace of benzoyl peroxide was heated under reflux for 15 min. The cold reaction mixture was treated as described in method B to yield 1.00 g. (59%), b.p. 194–198° (lit.[15] b.p. 198°).

Benzoic acid was obtained on oxidation of the reaction product with potassium permanganate in aqueous sodium carbonate solution at reflux temperature.

***p*-Bromotoluene.**—A mixture of toluene (35 ml.), anhydrous ferric chloride (13.85 g.), and TMAT (21.55 g.) was stirred at 60° for 6 hr. The mixture was poured into water and extracted with ether. The organic layer was washed with dilute hydrochloric acid, followed by sodium carbonate solution. After removing the solvent, the residue was fractionated to afford 7.12 g. (72% yield), b.p. 184–186° (lit.[16] b.p 184°).

Oxidation of the reaction product with dilute nitric acid gave *p*-bromobenzoic acid.

Acknowledgment.—The authors are indebted to Prof. I. A. Kaye from Brooklyn College, Brooklyn, New York, for helpful discussions in the preparation of the manuscript.

[14] R. Robinson and H. N. Rydlon, *J. Chem. Soc.*, 1394 (1939).

[15] I. Heilbron, "Dictionary of Organic Compounds," Vol. I, Eyre and Spottiswoode, London, 1953, p. 271.

[16] Ref. 15, p. 374.

The Reaction of Secondary Amines with Formaldehyde

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The reaction of secondary amines with formaldehyde can lead to two products: aminomethylols (I) and methylenebisamines (II).[1] Although many examples of II

$$R_2NH + HCHO \longrightarrow \underset{\text{I}}{R_2NCH_2OH} \xrightarrow{R_2NH} \underset{\text{II}}{R_2NCH_2NR_2} + H_2O$$

have been reported, only a few examples of I have been isolated. Usually the methylols are unstable and form none of the derivatives of alcohols or amines.[2]

Since aminomethylols have never been isolated in these reactions, and only weak evidence has been presented for their existence,[3] we wished to learn if they indeed exist in any significant amount in this reaction. Our evidence suggests that in the cases studied the methylenebisamine is the predominant product.

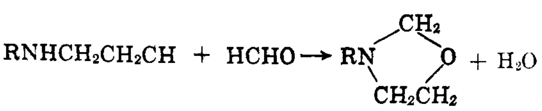
We used the following approach. One mole of formaldehyde was added to two moles of amine and the temperature rise ΔT_1 measured in a simple Nernst type calorimeter.[4] A second mole of formaldehyde was then added to this mixture and ΔT_2 measured. The data presented in Table I are corrected for heats of dilution of amine in water. Since alleged preparations of aminomethylols were reported at 0–5°,[2,3,5,6] we made determinations at that temperature and at room temperature. The ΔT_1 and ΔT_2 values are readily explained by considering the equilibria involved.

$$R_2NH + HCHO \rightleftharpoons R_2NCH_2OH \overset{R_2NH}{\rightleftharpoons} R_2NCH_2NR_2 + H_2O$$

On addition of the first equivalent of formaldehyde, equilibrium is established. If the equilibrium greatly favors the aminomethylol, then there is still one equivalent of amine left to react with the second equivalent of formaldehyde. The addition of this second portion of formaldehyde, then, results in a ΔT_2 which is nearly equal to ΔT_1. If, however, the equilibrium greatly favors the methylenebisamine, then there is no unchanged amine left to react with the second portion of formaldehyde and $\Delta T_1 > \Delta T_2$. If there is no aminomethylol at equilibrium after addition of the first portion of formaldehyde, ΔT_2 is zero except for heat of dilution of formaldehyde, which in these experiments can only account for temperature rises of less than 0.05.[7]

The data of Table I indicate that in most cases equilibrium favors the methylenebisamine at both temperatures. Moreover, in nearly all the cases studied the ratio $\Delta T_1/\Delta T_2$ (Table I) was greater at 30° than at 5°. This is explained by the greater stability of methylene bisamines over aminomethylols.

Two of the compounds which exhibited low ratios of $\Delta T_1/\Delta T_2$ are N-ethylethanolamine and diethanolamine-which form the oxazolidine on reaction with formaldehyde.



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[1] E. C. Wagner, *J. Org. Chem.*, **19**, 1862 (1954).

[2] K. Bodendorf and G. Koralewski, *Arch. Pharm.*, **271**, 101 (1933).

[3] E. R. Alexander and E. J. Underhill *J. Am. Chem. Soc.*, **71**, 4014 (1949). The only evidence heretofore that aminomethylols are present at equilibrium was offered by these authors who stated that the dimethylaminomethylol which they prepared had only a weak infrared band in the OH region. We have examined the infrared spectrum of dimethylaminoethanol which has a strong OH band. This compound, because of a greater possibility of intramolecular hydrogen bonding, should have a weaker absorption in this region. This leads us to believe that the concentration of dimethylaminomethylol was probably small in the reference cited.

[4] J. M. Sturdevant, "Calorimetry, Technique of Organic Chemistry," Vol. I (1), 3rd Ed., A. Weissberger, Ed., Interscience Publishers, Inc., New York, N. Y., 1959, p. 572.

[5] M. Zief and J. P. Mason, *J. Org. Chem.*, **8**, 1 (1943).

[6] H. G. Johnson, *J. Am. Chem. Soc.*, **68**, 12 (1946).

[7] J. F. Walker, "Formaldehyde," Reinhold Publishing Corp., New York, N. Y., 1953, p. 90.