Reactions of 2-Picoline 1-Oxide with Reactive Halides[1]

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Received January 3, 1962

Acetyl or benzoyl chloride reacts with 2-picoline 1-oxide in nonaqueous solvents at the reflux temperature to yield primarily the ester (IV) of 2-pyridylmethanol and a small amount of 2-pyridylmethyl chloride (V). At temperatures below 20°, acetyl, benzoyl, and thionyl chlorides form the monomeric hydrochloride (VIII) of the amine oxide (I). At higher temperatures, thionyl chloride reduces the amine oxide to 2-picoline (VII). Phosphorus trichloride brings about this reduction at all temperatures and does not yield VIII. Benzenesulfonyl chloride yields 2-pyridylmethyl chloride (V) and no IV or VIII under any condition. Aqueous hydrochloric and hydrobromic acids and ethanolic hydrogen chloride form the monomeric hydrohalides (VIII) of the amine oxide. Benzene solutions of hydrogen chloride, hydrogen bromide, and hydrogen iodide or aqueous hydriodic acid yield the dimeric hydrohalides (IX). The monomeric hydrochloride and hydrobromide are converted to the dimeric hydriodide (IX) by treatment with sodium iodide. Reaction of the amine oxide with sodium iodide yields the sodium derivative (X) of the dimeric hydriodide. Methyl iodide yields the ether (XI), which is readily split by picric acid. A mechanism for the formation of the esters (IV) and chloride (V) as well as an explanation for the formation of two types of hydrohalides has been presented.

The reaction between 2-picoline-1-oxide (I) and acetic anhydride yields 2-pyridylmethyl acetate.[2] Also, quinaldine oxide has been shown to form 2-quinolylmethyl benzoate when treated with benzoyl chloride in aqueous alkali.[3] However, the reaction between I and *p*-tolylsulfonyl chloride has been reported to yield 2-pyridylmethyl chloride (V).[4] We found that benzenesulfonyl chloride in nonaqueous solvents at room temperature or under reflux conditions also yields only the chloride (V) and does not react with I in aqueous alkali.

Thus, it seemed desirable to investigate the reactions of I with a series of reactive halides under various conditions. It was found that I reacts with acetyl or benzoyl chloride in nonaqueous solvents, yielding under reflux conditions the 2-pyridylmethyl esters (IV) primarily and a small amount of the chloride (V). These products were identified by their infrared spectra and by their picrates. Saponification of the esters and hydrolysis of the chloride yielded 2-pyridylmethanol. At temperatures below 20°, the reaction between I and benzoyl chloride in benzene yields only 18% of the ester (IV), and no ester is formed with acetyl chloride. The main product of this reaction with both of these halides is the hydrochloride (VIII). This compound is discussed in detail later. Benzenesulfonyl chloride under these conditions yields the chloride (V) and no VIII.

The reaction between thionyl chloride and I in benzene at temperatures below 20° gives smaller yields of VIII than benzoyl or acetyl chloride, but at higher temperatures it reduces I to 2-picoline (VII). Phosphorus trichloride[5] also brings about this reduction even at the lower temperatures and does not yield any of product VIII. The deoxygenation of pyridine oxides has been recently reported in some detail.[6]

These reactions suggest the possibility of the formation of intermediate compounds as shown in Chart I, paralleling in part the sequence proposed by Traynelis and Martello.[7] It seems that the primary factor, which determines the course of the reaction, is the relative stability of structure II, as it is influenced by temperature and by the nature of group Y. Thus, with thionyl chloride and to a greater extent with phosphorus trichloride, above room temperature the degree of instability in II leads to the formation of 2-picoline (VII) through the loss of sulfuryl chloride and phosphorus oxychloride, which were identified by hydrolysis to sulfuric and phosphoric acids. At temperatures below 20°, with benzoyl chloride, acetyl chloride, and to a lesser extent with thionyl chloride, structure II is sufficiently stable to undergo the change to structure III through the abstraction of a proton from its 2-methyl group by another molecule of I, resulting in the formation of the hydrochloride (VIII), the main product of this reaction. This was shown experimentally by obtaining approximately twice as much of the hydrochloride (VIII) by doubling the molar ratio of I to acyl halide in this reaction. The existence of structure III was not confirmed directly, since the liquid material, which was recovered from the filtrates, yielded a gummy mass, which could not be purified, when treated with picric acid. Distillation of this same liquid led to the recovery of a small amount (18%) of 2-pyridylmethyl benzoate and the formation of a resinous material, indicating, perhaps, that polymerization of III had occurred. No 2-pyridylmethyl acetate was recovered from the filtrate obtained from the reaction with acetyl chloride. At the reflux temperature, structures II and III that are formed in the reactions with acetyl or benzoyl

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[1] Supported in part by the Research Committee of the Graduate School from special funds voted by the State Legislature.

[2] V. Boekelheide and W. J. Linn, *J. Am. Chem. Soc.*, **76**, 1286 (1954).

[3] I. J. Pachter, *ibid.*, **75**, 3026 (1953).

[4] E. Matsumura, *J. Chem. Soc. Japan*, **74**, 363 (1953); *Chem. Abstr.*, **46**, 6648 (1952).

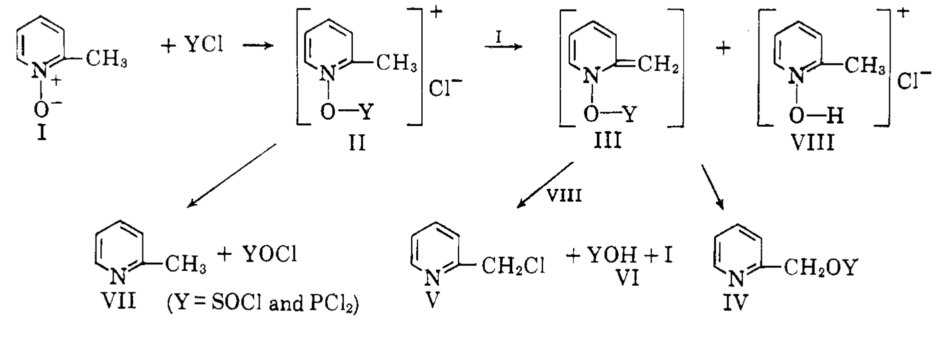
[5] E. Ochiai, M. Ikehara, T. Kato, and N. Ikehara, *J. Pharm. Soc. Japan*, **71**, 1385 (1951).

[6] D. I. Relyea, P. O. Tawney, and A. R. Williams, *J. Org. Chem.*, **27**, 477 (1962).

[7] V. J. Traynelis and R. F. Martello, *J. Am. Chem. Soc.*, **80**, 6590 (1958).

Chart I

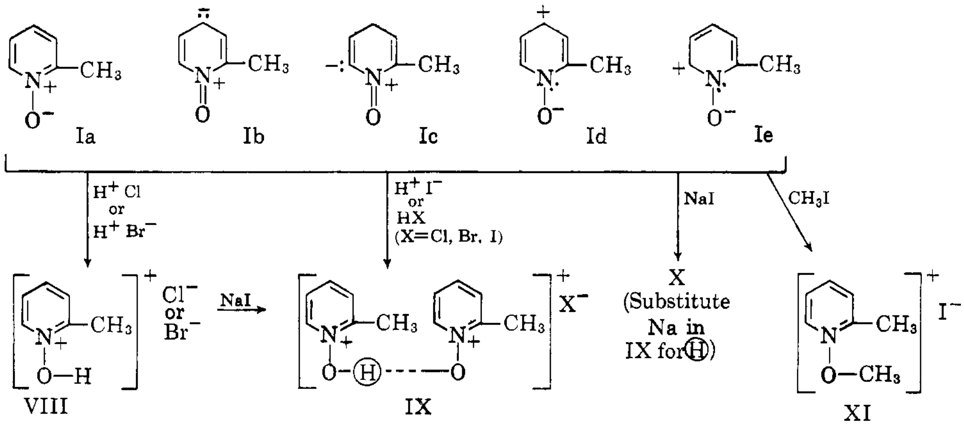
Y = C_6H_5CO, CH_3CO, $SOCl$, $C_6H_5SO_2$, PCl_2



chloride are much less stable, leading primarily to the formation of the esters (IV) through the intramolecular rearrangement of III.

Benzenesulfonyl chloride yields the chloride V but no ester IV or hydrochloride VIII at all temperatures. This suggests that nucleophilic attack by the chloride ion on the exocyclic methylene carbon of III causes expulsion of the benzenesulfonyl group quite readily in comparison to the acetyl and benzoyl groups, which yield only small amounts of V. The corresponding acids (VI) were identified in the reaction mixtures. The results of these experiments have been summarized in Table I.

Chart II



Reaction between I and the hydrogen halides or hydrohalic acids yields two types of products, the monomeric salts (VIII) and the dimeric compounds (IX) in Chart II. In each case, these structures represent one of the forms contributing to the resonance hybrids of these molecules. Of particular interest is the fact that hydrogen iodide or hydriodic acid forms only the dimeric hydriodide (IX). This is indicated by elemental analyses and by n.m.r. and infrared spectra, which showed no free or associated hydroxyl groups. Instead, the broad band at 2970 cm.$^{-1}$ (not affected by dilution) and the sharp band at 1615 cm.$^{-1}$ suggest an intermolecular chelate type of bond between two amine oxide units. It is also significant that the band at 1266 cm.$^{-1}$, which is attributed to the nitrogen–oxygen linkage in the amine oxide,[8] is absent. This dimerization bears a degree of similarity to the dimerization to attain stability through intermolecular chelation of the sterically hindered 5,5-dimethyl-1,3-cyclohexanedione,[9] which shows a broad band at 2632 cm.$^{-1}$ and a sharp band at 1605 cm.$^{-1}$. Rationalization of this kind of intermolecular chelation in the case of the amine oxide (I) is aided by considering the resonance structures indicated in Chart II by formulas Ia–Ie, which are similar to those proposed for pyridine oxide for which the highest electron density was calculated to be on the oxygen atom.[10] Also, infrared studies indicate that the nitrogen-oxygen bond in I has a certain degree of double bond character.[8] Thus, it seems possible that the addition of a proton to the oxygen of a molecule of I could yield a structure resembling the enol form of a ketone, which under certain conditions (discussed later) could lead to dimerization to attain stability.

The n.m.r. spectrum of IX which was taken in a 30.0% solution in deuterated chloroform at 60 Mc., using tetramethylsilane as an internal standard,

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[8] R. H. Wiley and S. C. Slaymaker, *J. Am. Chem. Soc.*, **79**, 2233 (1957).

[9] R. S. Rasmussen, D. D. Tunnicliff, and R. R. Brattain, *ibid.*, **71**, 1068 (1949).

[10] H. H. Jaffe, *ibid.*, **76**, 3527 (1955).

shows an unsplit band at 885 c.p.s., corresponding to τ — 4.75, which indicates an enolic hydrogen, the one that is involved in the intermolecular chelation. Integral analysis of the high-resolution spectrum of this compound further shows a doublet at 532 and 529 c.p.s. and another doublet at 525 and 523 c.p.s., both agreeing well with the expected line positions for the two α-pyridine ring protons. Six other pyridine ring hydrogens are indicated by the area under a complex band consisting of peaks at 479, 476, 472, and 467 c.p.s. These line positions are reasonable for the β- and γ-pyridine ring protons. A single band, representing about 15.0–20.0% of one proton, appears at 446 c.p.s. Further reference to this band will be made later. Finally, two upfield peaks, one at 177 c.p.s. and the other at 166 c.p.s., indicate the siz protons of the two methyl groups. Further evidence for this intermolecular chelation was obtained from product X, which is formed from I by treating with sodium iodide in acetone. In this compound the sodium ion replaces the proton in structure IX. This is indicated by elemental analyses and by the characteristic metallic chelate bands in its infrared spectrum at 2950, 1562, 1400, and 1387 cm.$^{-1}$. Again, the band at 1266 cm.$^{-1}$, characteristic of the free nitrogen–oxygen linkage, is missing.

The dimeric hydriodide is very stable; but the dimeric hydrobromide is less stable, and the dimeric hydrochloride is very unstable. The latter decomposes readily to the monomeric hydrochloride (VIII) on standing, on being heated, or on crystallizing from a polar solvent such as ethanol. The dimeric hydrochloride and hydrobromide will not form in aqueous solution. Benzene solutions of these hydrogen halides give the best yields, although the dimeric hydrobromide can be prepared less satisfactorily with hydrogen bromide in *n*-amyl alcohol. On the other hand, both benzene solutions of hydrogen iodide and aqueous hydriodic acid give good yields of the stable dimeric hydriodide.

The variation in the stability of the intermolecular chelate bond in these dimeric hydrohalides suggests that there must be a significant difference in the electron density on the oxygen atoms of these compounds. This can be explained in terms of the electron donating power of the halide ion, which is either formed by the interaction of the hydrogen halide molecule with I in non-ionizing solvents or is already present in the aqueous hydriodic acid reaction mixture. The ability to donate electrons decreases, of course, in the order: iodide ion, bromide ion, chloride ion. Thus, only the iodide ion seems capable of creating a sufficiently high electron density on the oxygen atom of the amine oxide to result in the formation of an intermolecular chelate bond that is stable in water or ethanol.

Both the monomeric hydrochloride and hydrobromide (VIII) are obtained in good yield from aqueous solutions of the hydrohalic acids, while the former forms in ethanolic hydrogen chloride, too. Their infrared spectra are quite similar, and neither shows a free or associated hydroxyl group. In this region of the spectrum, the strong bands appear at 2450 cm.$^{-1}$ for the hydrobromide and at 2100 cm.$^{-1}$ in a broader form for the hydrochloride with a much weaker one at 2420 cm.$^{-1}$. Also, at 1620 cm.$^{-1}$ the hydrobromide shows a stronger band than the hydrochloride.

Integral analysis of the high-resolution n.m.r. spectrum of the monomeric hydrochloride, which was taken in a 30.0% solution in deuterated chloroform at 60 Mc., using tetramethylsilane as an internal standard, shows an unsplit sharp band at 881 c.p.s. (τ — 4.68), indicating the $>\!N^{+}\text{—}O\text{—}H$ linkage. One α-pyridine ring proton is indicated by the split band at 548 and 554 c.p.s. The other three ring protons appear in a complex band consisting of six peaks at 508, 499, 493, 483, 477, and 470 c.p.s. The three methyl group protons are indicated in the unsplit band at 177 c.p.s. An unsplit band at 451 c.p.s., representing about 15.0–20.0% of one proton, is also present in the spectrum of this compound. The n.m.r. spectrum of the monomeric hydrobromide, which was taken in a 30.0% solution in deuterium oxide at 60 Mc. with water as the external standard (because of the limited solubility of this compound in chloroform), proved to be very similar to that of the monomeric hydrochloride except that it does not show a band at 881 c.p.s. nor one at 451 c.p.s. This indicates that the $>\!N^{+}\text{—}O\text{—}H$ linkage is not stable in deuterium oxide, while the absence of the band at 451 c.p.s. indicates, perhaps, that in nonpolar solvents another form of the salts may exist in small amounts.

The influence of the halide ion on the formation and stability of the intermolecular chelate bond was further demonstrated by the quantitative conversion of the monomeric hydrochloride and hydrobromide to the dimeric hydriodide by treating them with sodium iodide, as shown in Chart II.

The reaction between I and methyl iodide in forming the nitrogen–methoxide type of linkage as shown in XI, yielded additional information concerning the nature of the nitrogen–oxygen bond. The infrared spectrum of this ether shows a very strong band at 1215 cm.$^{-1}$, which is in the range characteristic of aryl and unsaturated ethers and another band at 1050 cm.$^{-1}$, typical of aralkyl ethers. Complete absence of the band at 1266 cm.$^{-1}$ is further evidence of the involvement of the oxygen in this linkage. However, the fact that treatment of XI with an ethanolic solution of picric acid at room temperature yielded the picrate of I

TABLE I

PRODUCTS OF THE REACTIONS BETWEEN 2-PICOLINE 1-OXIDE AND REACTIVE HALIDES

Halide	Product formed, %	M.p., °C.	B.p., °C.	Pressure, mm.	Reaction solvent	Reaction temp., °C.	M.p., °C., picrate formed
C_6H_5COCl	IV, 56.2		124–125	1.2	Dioxane	Reflux	160–161
	V, 15.6		107–110	14.0	Dioxane	Reflux	141–142^{a}
	VIII, 39.6^{b}	105–106			Benzene	15–20	125–126^{c}
	IV, 17.8^{b}				Benzene	15–20	
	VIII, 74.2^{d}				Benzene	15–20	
	IV, 18.6^{d}				Benzene	15–20	
CH_3COCl	IV, 53.7		106–108	2.0	HOAc	Reflux	161–162^{e}
	V, 7.0				HOAc	Reflux	
	VIII, 37.0^{b}	105–106			Benzene	15–20	125–126^{c}
	VIII, 72.7^{d}				Benzene	15–20	
$SOCl_2$	VIII, 34.2	105–106			Benzene	15–20	125–126^{c}
	VII, 92.0				Benzene	50–reflux	168–169^{f}
$C_6H_5SO_2Cl$	V, 47.6				Benzene	25	
	V, 71.8				Benzene	Reflux	
PCl_3	VII, 94.0		128–129	755.0	Benzene	15–reflux	167–168
HCl gas	VIII, 78.8	105–106			Ethanol	15–20	125–126^{c}
Concd. HCl	VIII, 84.5	105–106			Water	25	125–126^{c}
HCl gas	IX, 55.0	48–49			Benzene	15–20	125–126^{c}
HBr gas	IX, 58.3	142–143			Benzene	15–20	125–126^{c}
Concd. HBr	VIII, 92.8	144–145			Water	25	125–126^{c}
HI gas	IX, 60.2	145–146			Benzene	15–20	125–126^{c}
Concd. HI	IX, 89.2	145–146			Water	25	125–126^{c}
NaI	X, 94.1	183–184			Acetone	25	125–126^{c}
CH_3I	XI, 72.3	74–75			Excess CH_3I	25	125–126^{c}

[a] Lit.,[11] 142–143°. [b] 1:1 molar ratio of halide to I. [c] Picrate of I. [d] 1:2 molar ratio of halide to I. [e] Lit.,[12] 162–165°. [f] Lit.,[13] 169–171°.

TABLE II

ANALYSES OF PRODUCTS LISTED IN TABLE I

Product	Recrystallizing solvent	Empirical formula	Carbon, %		Hydrogen, %		Halide, %	
			Calcd.	Found	Calcd.	Found	Calcd.	Found
VIII	CH_3COCH_3	C_6H_8ClNO	49.31	49.12	5.48	5.31	24.36	24.31
VIII	n-$C_5H_{11}OH$	C_6H_8BrNO	37.89	37.61	4.21	3.98	42.33	42.12
IX	$CHCl_3$-CCl_4	$C_{12}H_{15}ClN_2O_2$	56.47	56.28	5.88	5.59	13.95	13.55
IX	n-$C_5H_{11}OH$	$C_{12}H_{15}BrN_2O_2$	48.16	47.92	5.02	4.92	26.75	26.62
IX	CH_3COCH_3	$C_{12}H_{15}IN_2O_2$	41.63	41.64	4.36	4.14	36.71	36.51
X	CH_3COCH_3	$C_{12}H_{14}IN_2O_2Na$	39.13	39.01	3.81	3.60	34.54	34.38
XI	CH_3COCH_3-ether	$C_7H_{10}INO$	33.47	33.21	3.98	3.68	50.59	50.32

indicates that this linkage is much weaker than the usual ether linkage. The results of these experiments and the analyses and properties of the products that have been presented have been summarized in Tables I and II.

Experimental

All reactions were carried out under nitrogen in flasks fitted with a gas inlet tube, dropping funnel with a pressure equilizer, and a condenser. The 2-picoline 1-oxide was redistilled, b.p. 85–86° (0.5 mm.); m.p. 46–47° (sealed tube); picrate, m.p. 125–126°. A typical procedure for each type of reaction has been presented.

Reaction of 2-Picoline 1-Oxide with Benzoyl Chloride. Method A.—To a solution of 12.0 g. (0.11 mole) of 2-picoline 1-oxide (I) in 30.0 ml. of dioxane, 18.0 g. (0.13 mole) of benzoyl chloride was added slowly while the mixture refluxed gently. Heating was continued for 2 hr. The cold reaction mixture was then treated with 100.0 ml. of 5.0% hydrochloric acid and extracted with 100.0 ml. of benzene. The cold aqueous layer was then made strongly basic with cold 10.0% sodium hydroxide and extracted with 250.0 ml. of chloroform. After washing the chloroform solution with 50.0 ml. of water, it was dried over anhydrous sodium sulfate and distilled, yielding 2.0 g. of V (Table I). Hydrolysis of V in 10.0% potassium hydroxide gave 2-pyridylmethanol; picrate, m.p. 161–162° (lit.,[14] m.p. 159–161°)—no depression of melting point in a mixture with an authentic sample. The hydrolysate gave a positive chloride test.

Continuation of the distillation yielded 12.0 g. of 2-pyridylmethyl benzoate (IV), b.p. 124–125° (1.2 mm.); n^{25}_{D} 1.5652; d^{20}_{4} 1.1569; infrared spectrum in chloroform: 1725, 1320 cm.$^{-1}$. Saponification of this ester yielded 2-pyridylmethanol and benzoic acid.

To determine whether benzoic acid was formed in this reaction, the original reaction mixture was treated with 5.0 ml. of aniline and then with an ether solution of hydrogen chloride. From the dioxane–ether solution, which was obtained after separating the insoluble hydrochlorides, 0.4 g. of benzanilide and 1.2 g. (0.01 mole) of benzoic acid were recovered.

Note: When acetyl chloride was used in this reaction, a solution of 25.0 ml. (0.35 mole) of this halide in 4.0 ml. of acetic acid was added to 0.11 mole of I and the mixture was heated for 10 hr. in an oil bath at 120°.

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[11] E. Matsumura, *J. Chem. Soc. Japan*, **74**, 363 (1953).

[12] G. Kobayashi and S. Furukawa, *Pharm. Bull.*, **1**, 347 (1953).

[13] I. Heilbron, "Dictionary of Organic Compounds," Oxford University Press, New York, N.Y., 1953, p. 202.

[14] O. H. Bullitt and J. T. Maynard, *J. Am. Chem. Soc.*, **76**, 1370 (1954).

Method B.—To a cold solution of 11.0 g. (0.1 mole) of I in 25.0 ml. of benzene, 14.1 g. (0.1 mole) of benzoyl chloride in 20.0 ml. of benzene was added slowly with cooling to maintain the temperature between 15° and 20°. The reaction mixture was allowed to stand at this temperature for 2 hr. and then filtered, yielding 5.8 g. of product VIII. From the filtrate, 3.8 g. of 2-pyridylmethyl benzoate was obtained by distillation (Table I).

Reaction of 2-Picoline 1-Oxide with Hydrogen Halides. Method A.—To a cold solution of 10.9 g. (0.1 mole) of 2-picoline 1-oxide (I) in 15.0 ml. of dry benzene was added 0.12 mole of hydrogen chloride in benzene. After adding 15 ml. of dry ether and cooling for 1 hr. in an ice bath, product IX was filtered (Table I). Recrystallization of this dimeric hydrochloride from ethanol yielded successively smaller amounts of material, showing progressively higher melting points, so that after three crystallizations, the product melted at 105–106° and was identical to VIII. It underwent a similar change on standing several days in a desiccator or on heating it to its melting point.

The dimeric hydrobromide, which is produced by a similar procedure with a benzene solution of hydrogen bromide, could be stored and dried at 80° without decomposing. Treatment of an ethanolic solution of all three dimeric hydrohalides with picric acid yielded the picrate of I, m.p. 125–126°.

Method B.—From a solution of 10.9 g. (0.10 mole) of 2-picoline 1-oxide (I) in 15.0 ml. of concentrated hydrochloric acid, which was taken to dryness at diminished pressure over a steam bath, the monohydrochloride (VIII) was obtained in 84.5% yield after recrystallization from acetone (Table I).

Concentrated hydrobromic acid yielded the monomeric hydrobromide (VIII) (Table I) by the same procedure.

Concentrated hydriodic acid yielded the dimeric hydriodide (IX) by this procedure (Table I). Treatment of an ethanolic solution of these hydrohalides with picric acid gave the picrate of I.

Reaction of 2-Picoline 1-Oxide with Sodium Iodide.—To (0.03 mole) of 2-picoline 1-oxide (I) in 10.0 ml. of acetone was added 4.5 g. (0.03 mole) of sodium iodide in 25.0 ml. of acetone, yielding product X (Table I). This product burned with a bright yellow flame and left a residue.

Conversion of the Monomeric Hydrochloride and Hydrobromide (VIII) to the Dimeric Hydriodide (IX).—To a solution of 0.02 mole of the monohydrohalides (VIII) in 10.0 ml. of acetone was added 0.03 mole of sodium iodide in 20.0 ml. of acetone. The solid product which separated immediately was filtered and washed with ethanol. This amounted to 1.08 g. of sodium chloride and 1.91 g. of sodium bromide. From the filtrate was obtained 3.2 g. (92.5%) of product, m.p. 145–146°, which was shown to be identical to the dimeric hydriodide (IX)—same analysis and infrared spectrum and no depression of its melting point in a mixture.

The Addition of Methyl Grignard to 4-*t*-Butylcyclohexanone

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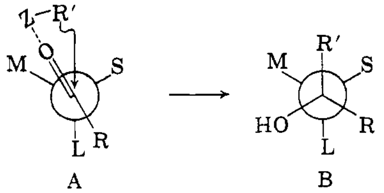
Received July 27, 1962

The addition of methyl Grignard to 4-*t*-butylcyclohexanone has been studied under a variety of experimental conditions. It has been found that the *cis:trans* ratio of the resultant 1-methyl-4-*t*-butylcyclohexanol is affected by the methyl halide used to form the Grignard reagent, the solvent, and the addition of magnesium halide. The magnesium source, presence of air, or cuprous halide had negligible effect on the reaction. For the reactions carried out in diethyl ether, the *cis:trans* ratios are methylmagnesium iodide—1.02, methylmagnesium bromide—1.36, dimethylmagnesium—1.40, methylmagnesium chloride—1.44, methylmagnesium bromide di(magnesium bromide)—1.84. The reaction of methylmagnesium bromide in various solvents gave anisole—1.11, diethyl ether—1.36, tetrahydrofuran—2.26. Methyllithium in diethyl ether gave a ratio of 1.86.

The addition of methyl Grignards[2] to ketones has found extensive application in the synthesis of tertiary alcohols.[3] For noncyclic ketones complexing only at the carbonyl oxygen, Cram[4] and co-workers have been able to correlate the stereochemistry of the new asymmetric center resulting from organometallic addition by use of the "open-chain" model A. Application of A has led to the



A B

prediction that the most probable mode of addition of the organometallic R′Z would be where R′ enters by the least hindered approach to give B.[5] Extension of this model to a conformationally simple cyclohexanone such as C which contains only 1,2-and 1,3-nonbonded hydrogen interactions would lead to the *a priori* prediction that the major

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[1] Presented at the 140th National Meeting of the American Chemical Society, Chicago, Ill., September, 1961, p. 180.

[2] The representation of the Grignard reagent as RMgX apparently is not correct, as indicated by the recent work of Dessy and Hamelin. In this paper the formula RMgX is used only for convenience or when referring to prior work where it has been applied to interpret a reaction. For recent work on the constitution of the Grignard reagent see (a) R. E. Dessy, *J. Org. Chem.*, **25**, 2260 (1960), J. H. Wotiz, R. E. Dessy, and C. A. Hollinsworth, *J. Am. Chem. Soc.*; **79**, 358 (1957); (b) A. Kirrmann and R. Hamelin, *Compt. rend.*, 2990 (1960); R. Hamelin, *Bull. soc. chim.* (France), 684, 698 (1961); and R. Hamelin and S. Hayes, *ibid.*, 692 (1961); (c) N. M. Bikales and E. I, Becker, *Chem. Ind.*, 1831 (1961); (d) M. Antenius, *J. Org. Chem.*, **26**, 4214 (1961); **27**, 596 (1962); and (e) D. O. Cowan and H. S. Mosher, *ibid.*, **27**, 1 (1962).

[3] For numerous examples see (a) "Grignard Reactions of Nonmetallic Substances," by M. S. Kharasch and O. Reinmuth, Prentice-Hall, Inc., New York, N. Y., 1954, and (b) "Handbook of Magnesium-Organic Compounds," by S. T. Yoffee and A. N. Nesmeyanov, Pergamon Press, London, 1957.

[4] For leading references see D. J. Cram and K. P. Kopecky, *J. Am. Chem. Soc.*, **81**, 2748 (1960).

[5] For some constructive discussion on the use of this model refer to J. H. Stocker, R. Sidisunthorn, B. M. Benjamin, and C. J. Collins, *ibid.*, **82**, 3913 (1960).