[A CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY AND PHYSICS OF THE PENNSYLVANIA STATE COLLEGE]

Pseudo Bases. V. Reactions of Certain N-Methyldihydropyrazinium Salts and their Derivatives

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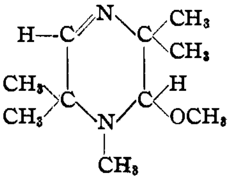
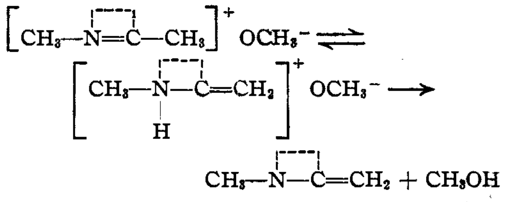
When 1,2,2,3,5,5,6 - heptamethyldihydropyrazinium iodide is treated with sodium hydroxide, 1,2,2,3,5,5-hexamethyl-6-methylenetetrahydropyrazine results instead of the pseudo base.[1] The present paper deals with the action of sodium methylate and the Grignard reagent upon this salt and other compounds related to it.

When 1,2,2,3,5,5,6 - heptamethyldihydropyrazinium iodide is treated with sodium methylate in methyl alcohol, again the 6-methylene compound results instead of 1,2,2,3,5,5,6-heptamethyl-6 - methoxytetrahydropyrazine, whereas 1,2,2,5,5-pentamethyldihydropyrazinium iodide yields the expected methyl ether, I.



I

It is worth noticing that the methyl ether, I, is also produced when the corresponding pseudo base, 1,2,2,5,5 - pentamethyl - 6 - hydroxytetrahydropyrazine, is refluxed for fifteen minutes with absolute methyl alcohol and the solution distilled. The ethyl ether can be made using ethyl alcohol in the same manner.[2] The mechanism A explains this peculiar behavior of the 1,2,2,3,5,5,6-heptamethyldihydropyrazinium iodide with sodium methylate and exactly parallels that already given for the reaction with sodium hydroxide.

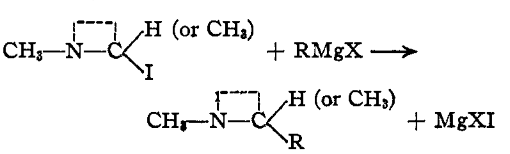


$$[CH_3-N=C-CH_3]^+ OCH_3^- \rightleftharpoons [CH_3-\underset{H}{N}-C=CH_2]^+ OCH_3^- \longrightarrow CH_3-N-C=CH_2 + CH_3OH \quad (A)$$

In these formulas and those following, the dotted line represents the rest of the pyrazine ring and its substituents.

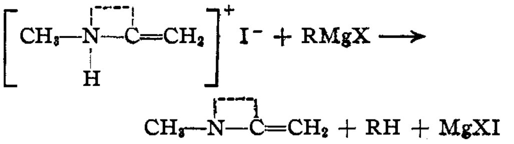
The possibility of loss of methyl alcohol from the ether must not be overlooked. However, from the behavior of the salt with sodium hydroxide, it appears that the formation of the ether would occur much more slowly than any step in reaction A.[1,3]

With various Grignard reagents 1,2,2,5,5-pentamethyldihydropyrazinium iodide behaves normally as the salt of a pseudo-basic system.[4]



(B)

While 1,2,2,3,5,5,6 - heptamethyldihydropyrazinium iodide undergoes a similar reaction for the most part, it also undergoes a side reaction as indicated by the production of more than one mole of methane during the action of methylmagnesium iodide in the Zerewitinoff apparatus. This side reaction is apparently



$$[CH_3-\underset{H}{N}-C=CH_2]^+ I^- + RMgX \longrightarrow CH_3-N-C=CH_2 + RH + MgXI \quad (C)$$

About 70% of the salt reacts according to B and the rest according to C, while an active hydrogen, presumably on the 3 methyl group, reacts completely to yield methane.

Reaction B indicates a rearranged (or "pseudo") un-ionized form of the salt as taking part in the reaction. It is believed that the salt acts in this form because such a form would be expected to be more soluble in the solvent ether than the ionized form of the salt. Moreover, in the case of the heptamethyl derivative only the ionized form of the salt could undergo a prototropic change such as that in reaction A. If the un-ionized (pseudo) form of the salt is much more soluble than the ionized form, smooth replacement of the halogen by reaction B would be ex-

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(1) Aston, THIS JOURNAL, 52, 5254 (1930).

(2) 40% formaldehyde and diethylamine with ethyl alcohol yield the ethyl ether of α-hydroxymethyldiethylamine upon saturating the mixture with potassium carbonate [Robinson and Robinson, *J. Chem. Soc.*, 119, 1472 (1921)].

(3) Professor T. D. Stewart has suggested the possibility that the equilibrium might even favor a slow addition of methyl alcohol to the methylene compound to yield the ether.

(4) Freund and Bode, *Ber.*, 42, 1746 (1909).

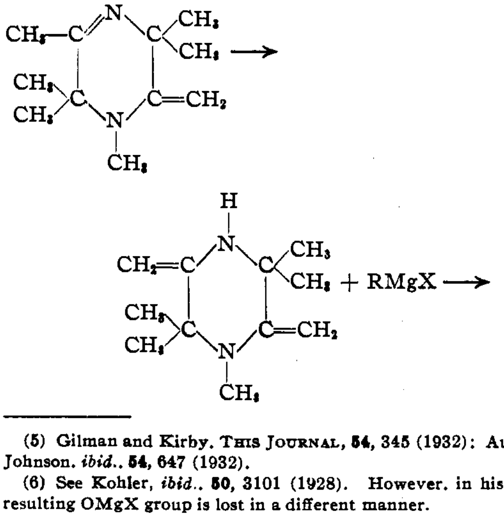
pected rather than reaction with the labile hydrogen of the tautomeric form of the positive ion (reaction C), provided that the *specific* reaction rates are about the same.

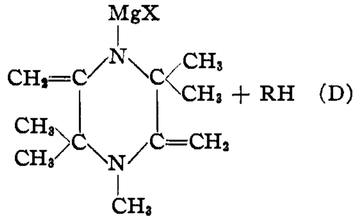
When benzyl Grignard reagent acts on the salts, there seems to be no rearrangement of the benzyl group,[5] as was shown by oxidation of the products to benzoic acid.

When 1,2,2,5,5-pentamethyl-6-hydroxytetrahydropyrazine is treated with a second mole of the Grignard reagent, smooth replacement of the 6-hydroxy group by the hydrocarbon radical of the Grignard reagent occurs. The first mole of the Grignard reagent is changed to hydrocarbon.[6]

Because the results in the previous paper[1] did not exclude entirely the rapid addition of water to the double bond of 1,2,2,3,5,5-hexamethyl-6-methylenetetrahydropyrazine as an explanation of the fact that the 6-methylene compound in water immediately yielded a base of the same properties as that formed from a solution of 1,2,2,3,5,5,6-heptamethyldihydropyrazinium iodide and dilute sodium hydroxide, it was decided to investigate this question further.

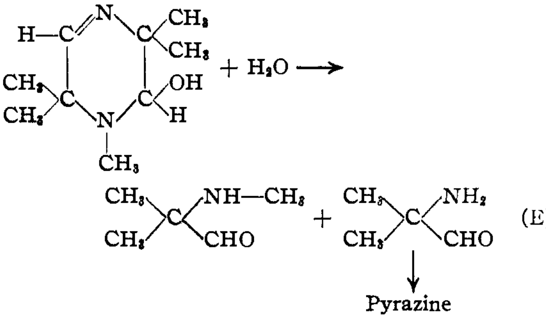
An olefinic linkage which would add water with such a rapidity might be expected to resemble the carbonyl group and therefore add the Grignard reagent. The reaction of the Grignard reagent with the 6-methylene compound has been investigated but no addition of this type seems to occur.[7] The only reaction which does occur involves an active hydrogen presumably on the 3-methyl group.





The prototropic change in D is quite similar to that in A.

When 1,2,2,5,5-pentamethyl-6-hydroxytetrahydropyrazine was boiled with concentrated sodium hydroxide, the only cleavage product isolated was 2,2,5,5-tetramethyldihydropyrazine in nearly theoretical yield, which was probably formed by the reaction



We had hoped to isolate as well N-methyl-α-aminoisobutyraldehyde or its Cannizzaro products but no such products could be found.

Experimental

1,2,2,5,5 - Pentamethyl - 6 - methoxytetrahydropyrazine.—(1) Forty grams of 1,2,2,5,5-pentamethyldihydropyrazinium iodide (0.143 mole) was added to a solution of 4 g. (0.17 mole) of sodium in 150 cc. of anhydrous methanol. The mixture was refluxed for twelve hours and distilled directly from the sodium iodide. The product boiling at 110–120° (35 mm.) weighed 14.5 g. (55% of the theoretical). It was a clear colorless light oil, and on redistilling boiled at 111.5–113° (27 mm.), n^{20}_{D} 1.4620.

Anal. Calcd. for $C_{10}H_{20}N_2O$: C, 65.16; H, 10.94; N, 15.21; OCH_3, 16.84. Found: C, 64.62; H, 11.07; N (Dumas), 15.23; OCH_3, 17.19, 17.04. *Mol. wt.* by freezing point lowering in benzene: calcd., 184.2; found, 176. 175.

(2) 4.0 g. (0.023 mole) of 1,2,2,5,5-pentamethyl-6-hydroxytetrahydropyrazine was dissolved in 25 cc. of anhydrous methanol. The solution was boiled for fifteen minutes and the excess methanol was slowly distilled off. The residue was distilled *in vacuo* and boiled at 124–126° (42 mm.); yield, 3.3 g. (74% of the theoretical), n^{20}_{D} 1.4630.

Anal. Calcd. for $C_{10}H_{20}N_2O$: OCH_3, 16.84. Found: OCH_3, 17.11.

1,2,2,5,5 - Pentamethyl - 6 - ethoxytetrahydropyrazine.—Four grams (0.023 mole) of 1,2,2,5,5-pentamethyl-6-hydroxytetrahydropyrazine was dissolved in 10 cc. of absolute alcohol. The solution was handled as in the

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(5) Gilman and Kirby, This Journal, **54**, 345 (1932): Austin and Johnson, *ibid.*, **54**, 647 (1932).

(6) See Kohler, *ibid.*, **50**, 3101 (1928). However, in his case the resulting OMgX group is lost in a different manner.

(7) *Cf.* Kohler's anhydro bases, which contain the linkage —N=CH_2, and hence are quite reactive with Grignard reagents, *loc. cit.*, 3099.

case of the methoxy compound and gave 3.2 g. (68% of the theoretical yield) of clear liquid boiling at 118–122° (30 mm.), n_{D}^{20} 1.4589.

Anal. Calcd. for $C_{11}H_{22}N_2O$: C, 66.60; H, 11.19; OC_2H_5, 22.73. Found: C, 66.40; H, 11.15; OC_2H_5, 22.22.

Reaction of the Heptamethyl Salt with Sodium Methylate.—When 1,2,2,3,5,5,6-heptamethyldihydropyrazinium iodide was treated with sodium methylate as above, it gave a 75% yield of 1,2,2,3,5,5-hexamethyl-6-methylenetetrahydropyrazine, which was identified by boiling point and molecular weight in benzene. A Zeisel determination showed no methoxyl group.

1,2,2,5,5 - Pentamethyl - 6 - benzyltetrahydropyrazine.—(1) Forty grams (0.143 mole) of 1,2,2,5,5-pentamethyldihydropyrazinium iodide was added in the course of forty-five minutes to an ethereal solution of benzylmagnesium chloride containing 8 g. (0.33 mole) of magnesium in 200 g. of ether. As the salt struck the surface of the solution a rapid reaction took place with the evolution of a small amount of heat. Finally, the mixture was refluxed and stirred for six hours. Only a small amount of solid material then remained undissolved. Hydrolysis was effected by pouring into a mixture of ice and hydrochloric acid. The ether layer yielded 5.9 g. of toluene and a small amount of dibenzyl.

The water layer was made alkaline with potassium hydroxide. The dark colored oil which separated was dissolved in ether. The solution was then continuously extracted with ether. The ether extracts yielded 20.3 g. of oil, boiling at 188–205° (30 mm.) (58% of the theoretical yield). On standing, this material froze to a yellow solid, m. p. 63–64°. Attempts to recrystallize this solid were unsuccessful. It is soluble in ether, alcohol, benzene and ligroin; insoluble in water. On redistilling, the bulk of the material boiled at 192–194° (30 mm.). The melting point was unchanged.

Anal. Calcd. for $C_{16}H_{24}N_2$: C, 78.62; H, 9.90; N, 11.48. Found: C, 78.35; H, 9.77; N (Dumas), 11.59. *Mol. wt.* by freezing point lowering in benzene: calcd., 244.2; found, 246, 245. *Neutral equivalent.* Equiv. wt. calcd. as a monoacidic base, 244.2; found, 228.

Oxidation.—2.60 g. (0.011 mole) of $C_{16}H_{24}N_2$ was mixed with a solution of 45 g. of sodium dichromate in 125 cc. of water; 30 cc. of concentrated sulfuric acid was dropped onto the mixture through a reflux condenser. The flask was shaken intermittently and the addition of acid required twenty minutes. The mixture was boiled gently for ten minutes, then cooled in an ice-bath. The benzoic acid which separated was dissolved in ether and the solution was twice extracted using 20-cc. portions of ether. From the ether solutions sodium carbonate extracted 0.09 g. of benzoic acid, m. p. 120°, mixed m. p. with known sample 121°. Considerable charring had taken place during the addition of the sulfuric acid.

(2) 1,2,2,5,5-Pentamethyl-6-benzyltetrahydropyrazine was also prepared in 56% yield from 15 g. (0.088 mole) of 1,2,2,5,5-pentamethyl-6-hydroxytetrahydropyrazine and a solution of benzylmagnesium chloride containing 5 g. (0.206 mole) of magnesium in 200 g. of ether, adding the solid base to the solution. Its identity was established by the method of mixed melting points and by its identical boiling range. Six grams of toluene was recovered from the acid extraction in this experiment.

1,2,2,5,5,6 - Hexamethyltetrahydropyrazine.—A solution of methylmagnesium iodide containing 7 g. (0.288 mole) of magnesium in 50 cc. of ether was added gradually to a solution of 14.5 g. (0.085 mole) of 1,2,2,5,5-pentamethyl-6-hydroxytetrahydropyrazine in 150 cc. of ether. The mixture was refluxed for twenty-four hours and then hydrolyzed with dilute hydrochloric acid. During the hydrolysis 0.035 mole of methane was given off. The aqueous layer was made alkaline and steam distilled. The steam distillate was made acid and concentrated to 30 cc. By the addition of 10 g. of solid potassium hydroxide and ether extracting there was obtained 6 g. (0.036 mole) (42.5% of the theoretical) of an oil, the main fraction of which boiled at 72–74° (13 mm.).

Anal. Calcd. for $C_{10}H_{20}N_2$: C, 71.33; H, 11.99. Found: C, 70.6, 70.6; H, 11.41, 11.45. *Mol. wt.* by freezing point lowering in benzene: calcd., 168.2; found, 165.5, 173.8.

1,2,2,5,5 - Pentamethyl - 6 - phenyltetrahydropyrazine.—To an ethereal solution of phenylmagnesium bromide containing 11.6 g. (0.48 mole) of magnesium and 75 g. of ether was added a solution of 34 g. (0.20 mole) of 1,2,2,5,5-pentamethyl-6-hydroxytetrahydropyrazine in 450 cc. of ether. The mixture, containing some precipitate which formed during the addition, was refluxed for twenty-four hours. The ethereal extract from the acid hydrolysis yielded benzene, biphenyl and phenol.

The aqueous solution after acid hydrolysis was made alkaline and steam distilled as long as the distillate came over alkaline. The distillate on extraction with ether yielded 10 g. (21% of the theoretical) of oil boiling 146.5–154° (10 mm.). A fraction, b. p. 151.5–153.5° (10 mm.), was analyzed.

Anal. Calcd. for $C_{15}H_{22}N_2$: C, 78.26; H, 9.50; N, 12.17. Found: C, 78.79, 78.00; H, 9.39, 9.55; N (Dumas), 11.82, 11.90. *Mol. wt.* by freezing point lowering in benzene: calcd., 230; found, 223, 222.

This compound is soluble in acetic acid, ether, acetone, and benzene; insoluble in water.

1,2,2,3,5,5,6 - Heptamethyl - 6 - benzyltetrahydropyrazine.—Forty grams (0.130 mole) of 1,2,2,3,5,5,6-heptamethyldihydropyrazinium iodide was added, as in (1) above for the preparation of the pentamethyl-6-benzyl compound, to an ethereal solution of benzylmagnesium chloride containing 10 g. (0.41 mole) of magnesium in 200 g. of ether. Similarity of reaction was evident, and the method of handling was the same throughout. The ethereal solution resulting from hydrolysis with acid contained 12.5 g. of toluene and some dibenzyl.

After addition of potassium hydroxide to the aqueous portion and continuous extraction with ether, 21.0 g. of a light yellow oil boiling 205–215° (28 mm.) (59% of the theoretical) was obtained from the ether layer. This material showed no tendency to solidify. On redistilling, the bulk of it boiled between 210–213° (28 mm.).

Anal. Calcd. for $C_{18}H_{28}N_2$: C, 79.34; H, 10.34; N, 10.29. Found: C, 78.80, 78.71; H, 10.24, 10.41; N (Dumas), 10.32. *Mol. wt.* by freezing point lowering in benzene; calcd., 272.2; found, 253, 256. *Neutral equivalent.* Equiv. wt. calcd. as a monoacidic base: 272.2; found, 267.

Oxidation.—4.5 g. (0.016 mole) of $C_{18}H_{28}N_2$ was mixed with a solution of 7 g. of potassium permanganate in 300 cc. of water and boiled for fifteen minutes with intermittent shaking. The warm solution was acidified with dilute sulfuric acid, chilled in an ice-bath and extracted with three 10-cc. portions of ether. Sodium carbonate extracted 0.3 g. of benzoic acid from the ether solutions, m. p. 121°, mixed m. p. with known sample of benzoic acid, 121°.

An attempt to prepare 1,2,2,3,5,5,6-heptamethyl-6-benzyltetrahydropyrazine from benzyl Grignard reagent and the anhydro base resulted in failure to isolate any reaction product.

Reactions with Methylmagnesium Iodide.—The apparatus and method used were as described by Kohler, Stone and Fuson, modified by Kohler and Richtmyer.[8] The results are collected for convenience in Table I.

TABLE I

Compound	Time of heating, min.	Temp., °C.	Reagent consumed per mole of cpd.	Gas per mole	Addn. per mole
1,2,2,5,5-Pentamethyldihydropyrazinium iodide	20	100	1.19	0.15	1.04
	20	100	1.25	.16	1.09
1,2,2,3,5,5,6-Heptamethyldihydropyrazinium iodide	20	100	2.15	1.51	0.64
	40	100	2.39	1.60	.79
1,2,2,3,5,5-Hexamethyl-6-methylenetetrahydropyrazine	50	100	1.19	1.15	.04
	45	100	1.30	1.15	.15
	40	100	1.47	1.29	.18
	35	100	1.44	1.30	.14
	60	120	1.45	1.45	.00
	30	140	2.04	1.74	.30
	45	145	1.87	1.63	.24

The somewhat erratic results in the case of 1,2,2,3,5,5-hexamethyl-6-methylenetetrahydropyrazine are difficult to explain, particularly the increase of gas above one mole at higher temperatures. It would be difficult to be sure all traces of water were absent and possibly the high results are due to this cause. The amount of addition shown in the last column, at least at reaction temperatures below 120°, seems to be practically zero within experimental error.

Behavior of Pentamethyl-6-hydroxytetrahydropyrazine on Refluxing with Alkali.—Ten grams (0.059 mole) of pentamethyl-6-hydroxytetrahydropyrazine was refluxed with 60 cc. of 1 *N* sodium hydroxide solution for fifty hours. At the end of this time, most of the base had gone into solution. The solution was extracted continuously with ether. The extract contained 4 g. (0.029 mole) of 2,2,5,5-tetramethyldihydropyrazine and less than a gram of high-boiling material.

The aqueous layer was then mixed with an equal volume of concentrated hydrochloric acid and saturated with hydrogen chloride gas. The remainder of the procedure was adapted from Gabriel's method of preparation of α-methylaminoisobutyric acid.[9]

In one run a small amount of white crystals was obtained, but an attempt to make the phenyl cyanate described by Friedmann was inconclusive.[10]

Further attempts to isolate the α-methylaminoisobutyric acid were likewise fruitless.

Summary

1. 1,2,2,5,5 - Pentamethyl - 6 - methoxytetrahydropyrazine has been prepared for the first time by the action of sodium methylate on pentamethyldihydropyrazinium iodide. This compound as well as the ethyl ether can be prepared by the direct action of the appropriate alcohol on the pseudo base.

2. With sodium methylate 1,2,2,3,5,5,6 - heptamethyldihydropyrazinium iodide yields only 1,2,2,3,5,5-hexamethyl - 6 - methylenetetrahydropyrazine.

3. The 1,2,2,5,5 - pentamethyl - 6 - benzyl - (6-methyl, and -6-phenyl)-tetrahydropyrazines have been prepared for the first time by the reaction of the appropriate Grignard reagents with 1,2,2,5,5-pentamethyl - 6 - hydroxytetrahydropyrazine. Pentamethyl-6-benzyltetrahydropyrazine has also been prepared by the reaction of benzyl Grignard with pentamethyldihydropyrazinium iodide.

4. 1,2,2,3,5,5,6 - Heptamethyl - 6 - benzyltetrahydropyrazine has been prepared for the first time by the reaction of benzyl Grignard reagent with heptamethyldihydropyrazinium iodide.

5. 1,2,2,3,5,5 - hexamethyl - 6 - methylenetetrahydropyrazine has been shown to yield no addition with methyl or benzyl Grignard reagents.

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[8] (a) Kohler, Stone and Fuson, THIS JOURNAL, **49**, 3181 (1927); (b) Kohler and Richtmyer, *ibid.*, **52**, 3738 (1930).

[9] Gabriel, *Ber.*, **46**, 1355 (1913).

[10] Friedmann, *Chem. Zentr.*, I, 970 (1908).