

Anal. Calcd. for $C_{12}H_{12}N_2O$: C, 73.56; H, 5.70. Found: C, 74.09; H, 6.08.

This ketone formed a 2,4-dinitrophenylhydrazone, m.p. 153–154.4° (from ethanol).

Anal. Calcd. for $C_{12}H_{12}N_2O_4$: C, 58.15; H, 4.11. Found: C, 58.15; H, 4.23.

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[CONTRIBUTION NO. 1115 FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF PITTSBURGH]

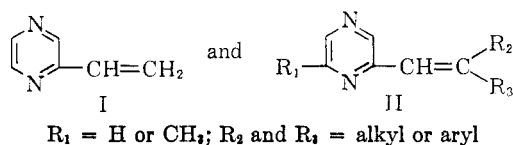
The Chemistry of Pyrazine and Its Derivatives. VII. The Synthesis of Vinylpyrazine and Substituted Vinylpyrazines¹

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Vinylpyrazine has been synthesized by a Hofmann exhaustive methylation reaction on the Mannich product obtained from the reaction of methylpyrazine with formaldehyde and dimethylamine hydrochloride. Substituted vinylpyrazines were also synthesized by the iodine-catalyzed dehydration of pyrazylmethylcarbinols.

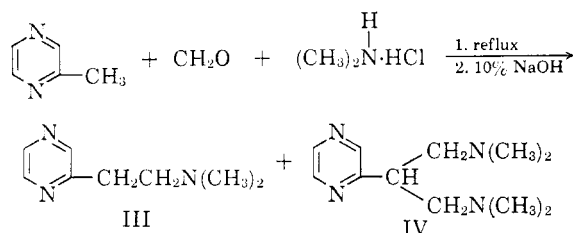
As a part of the investigation in these laboratories on the chemistry of pyrazine derivatives, it was desirable to synthesize vinylpyrazine, I, and substituted vinylpyrazines, II. Such compounds will have an ethylenic double bond which is



conjugated with the pyrazine ring and thus may undergo nucleophilic addition reaction—*i.e.*, Michael condensations. There are many examples in the literature³ which show the reactivity of 2- and 4-vinylpyridine in such condensations.

Although the synthesis of vinylpyrazine has been reported previously by Kitchen and Hanson,⁴ a different synthesis was undertaken in the present study, which appears to be simpler and gives higher yields of vinylpyrazine. Kitchen and Hanson condensed formaldehyde with methylpyrazine in an autoclave (mole ratio, 1:4.5) and obtained a maximum yield of 38% of pyrazylethanol. This carbinol was dehydrated with molten potassium hydroxide to give an 80% yield of vinylpyrazine (30.4% based on methylpyrazine).

In the present synthesis, a Hofmann exhaustive methylation procedure is employed. The Mannich product, III, was obtained from the reaction of methylpyrazine (0.6 mole), formaldehyde (1.05 moles), and dimethylamine hydrochloride (0.63 mole). In addition some bis-Mannich product, IV, was obtained. The free amines were obtained by



the reaction of the hydrochlorides with 10% aqueous sodium hydroxide.

When a larger excess of formaldehyde (1.2 moles) was employed, the yield of the bis product rose from 20.0% to 24.7%. The formation of bis-Mannich products from the reaction of 2,5-dimethylpyrazine, formaldehyde, and secondary amine hydrochloride has been previously observed by Linder and Spoerri.⁵ Wiley⁶ attempted the condensation of methylpyrazine, formaldehyde, and diethylamine hydrochloride, but he was unable to isolate the free Mannich base.

The compound, III, was quaternized by reaction with methyl iodide to give β -pyrazylethyltrimethylammonium iodide, V. The quaternary compound, V, was then converted to vinylpyrazine by two methods. The first involves the exchange of the iodide ion by a hydroxide ion by the reaction of V with silver hydroxide (from silver oxide and water), to give the quaternary ammonium hydroxide compound, VI. When VI was refluxed in aqueous sodium hydroxide solution, vinylpyrazine was obtained (63.3% yield). The second method involves the direct conversion of the quaternary compound, V, to vinylpyrazine (60.5%) by treatment with aqueous sodium hydroxide.

The trimethylamine formed in these degradations was identified as its picrate by bubbling the gases formed during the reflux into a saturated alcoholic solution of picric acid.

(1) This work was supported in part by a grant from Wyandotte Chemical Corp.

(2) This paper is based on part of a thesis presented by M. R. Kamal to the University of Pittsburgh in partial fulfillment of the requirements of the Ph.D. degree.

(3) E. Bergmann, D. Ginsburg, and R. Pappo, *Org. Reactions*, **10**, 179 (1959).

(4) L. J. Kitchen and E. S. Hanson, *J. Am. Chem. Soc.*, **73**, 1838 (1951).

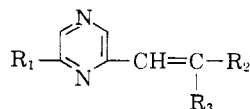
(5) S. Linder and P. Spoerri, *J. Am. Chem. Soc.*, **74**, 1517 (1952).

(6) P. F. Wiley, *J. Am. Chem. Soc.*, **76**, 4924 (1954).

TABLE I

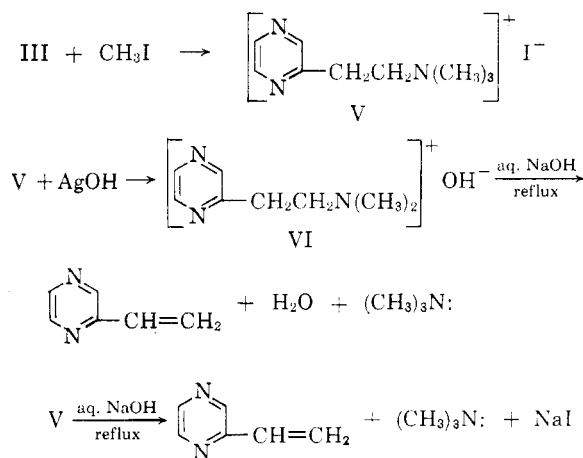
THE IODINE-EFFECTED DEHYDRATION OF PYRAZYMETHYLCARBINOLS OF THE TYPE^a R_1 --CH₂-C(OH)(R₂)-R₃ TO GIVE

ALKENES OF THE TYPE



Compound	Carbinol		Effective ^d Solvent	Yield, %	B.P.	Mm.	M.P.	n_D^{25}	Formula	Carbon, %		Hydrogen, %	
	R ₂	R ₃								Calcd.	Found	Calcd.	Found
(1)	CH ₃	CH ₃	Toluene	68.4	109-111	19.5		1.5424	C ₉ H ₁₂ N ₂	72.93	72.75	8.16	8.56
(2)	CH ₃	C ₂ H ₅	Benzene	89.7	112-113	13		1.5252	C ₁₀ H ₁₄ N ₂	74.03	74.19	8.70	8.77
(3)	CH ₃	<i>i</i> -C ₃ H ₇	Benzene	74.5	86-89	2		1.5245	C ₁₁ H ₁₆ N ₂	74.95	74.92	9.15	9.17
(4)	C ₂ H ₅	C ₂ H ₅	None	48.9	69-72	0.7		1.5220	C ₁₁ H ₁₆ N ₂	74.95	75.15	9.15	9.24
(5)		-C ₆ H ₁₀ ^b	None	40.9	103-104	1.5		1.5408	C ₁₂ H ₁₆ N ₂	76.55	76.49	8.57	8.60
(6)	C ₆ H ₅	H	Toluene	51.4	135-138	1.0		1.6380	C ₁₃ H ₁₂ N ₂	79.56	79.20	6.16	6.42
(7)	C ₆ H ₅	CH ₃	Toluene	65.1	134-136	1.6		1.6300	C ₁₄ H ₁₄ N ₂	79.96	79.75	6.71	7.04
(8)	C ₆ H ₅	C ₂ H ₅	Toluene	44.6	134-136	0.8		1.6012	C ₁₆ H ₁₆ N ₂	80.32	80.42	7.19	7.54
(9)	C ₆ H ₅	C ₆ H ₅	Benzene	90.0	183-184	1.0	54.6-56.0 ^f		C ₁₈ H ₁₆ N ₂	83.79	84.19	5.92	6.16
(10)	C ₆ H ₇	H	Benzene	50.5	198-200 ^e	2.5	100.4- 101.2 ^g		C ₁₆ H ₁₆ N ₂	74.97	74.74	6.71	6.56
(11)	CH ₃	CH ₃	Toluene	66.8	104-107	25		1.5514	C ₈ H ₁₀ N ₂	71.60	72.05	7.51	7.91
(12)	C ₆ H ₅	C ₆ H ₅	Benzene	65.2	177-180 ^e	17	58.2- 59.2 ^h		C ₁₈ H ₁₄ N ₂	83.69	83.86	5.46	5.69

^a R₁ = CH₃ in all the carbinols dehydrated, except in compounds (11) and (12), where R₁ = H. ^b The ketone was cyclohexanone. ^c C₆H₇ = the 1-styryl radical. ^d Generally benzene was attempted first. ^e These compounds solidified upon standing. ^f Recrystallized from pentane. ^g Recrystallized from an ether-pentane mixture. ^h Recrystallized from petroleum ether (b.p. 30-60°).



In addition to the synthesis of vinylpyrazine by Kitchen and Hanson,⁴ the only other type of vinylpyrazine which is reported in the literature is that which was prepared by Franke,⁷ by the condensation of aromatic aldehydes with 2,5-dimethylpyrazine using zinc chloride as the catalyst. He obtained mono- and disubstituted olefinic products, which resulted from the dehydration of the originally formed carbinols.

We have previously reported that methylpyrazine⁸ and 2,6-dimethylpyrazine⁹ undergo aldol-type condensations with aliphatic and aromatic aldehydes and ketones using sodium amide in liquid

ammonia as a condensing agent to give good yields of the corresponding pyrazylmethylcarbinols and 2-methyl-6-pyrazylmethylcarbinols, respectively. Therefore, the study of the possible dehydration of these carbinols as a route to the synthesis of substituted vinylpyrazines was undertaken.

The dehydration of 1,1-diphenyl-2-(2-methyl-6-pyrazyl)ethanol (VII. R₁ = CH₃, R₂ = R₃ = C₆H₅) was attempted using phosphorus pentoxide as the dehydrating agent. After five hours of refluxing in a benzene solution, 92.4% of the starting material was obtained. When zinc chloride and hydrochloric acid were allowed to react with a benzene solution of 1-(2-methyl-6-pyrazyl-2-phenylpropanol-2, (VII. R₁ = CH₃, R₂ = C₆H₅, R₃ = CH₃), no alkene was isolated. Instead, 2,6-dimethylpyrazine and acetophenone were obtained.⁹ These results indicate that a reverse aldol-type reaction has taken place.

Catalytic quantities of iodine have been shown to bring about the dehydration of alcohols. Hibbert¹⁰ used catalytic quantities of iodine for the dehydration of diacetone alcohol to yield mesityl oxide. He showed that this type of dehydration is of general application and that the ease of dehydra-

(7) R. Franke, *Ber.*, **38**, 3724 (1905).

(8) J. D. Behun and R. Levine, *J. Am. Chem. Soc.*, **81**, 5666 (1959).

(9) M. R. Kamal and R. Levine, *J. Org. Chem.*, **27**, 1360 (1962).

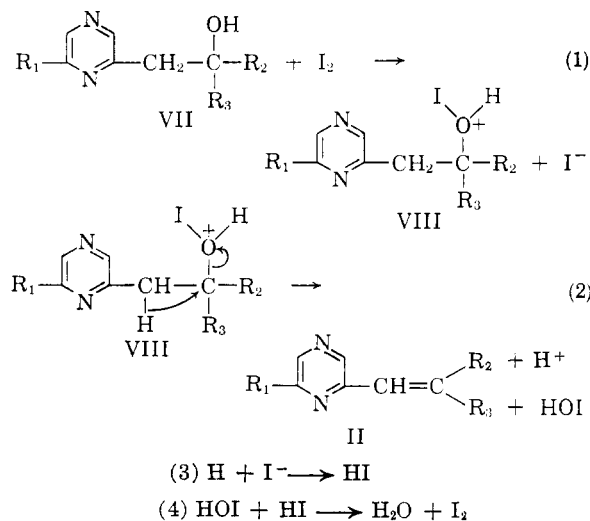
(10) H. Hibbert, *J. Am. Chem. Soc.*, **37**, 1748 (1915).

tion varies in a marked measure with the nature of the alcohol employed. Other examples are available in the literature showing^{11,12} the applicability of this method for dehydration.

No generalized procedure for the iodine-effected dehydration of the pyrazylmethylcarbinols and the 2-methyl-6-pyrazylmethylcarbinols could be applied, although most of the examples studied were tertiary alcohols. Dehydration was effected by either azeotropic distillation of the water with benzene or toluene for sixteen hours or by heating the carbinol-iodine mixture at about 185° for one hour. The results of the dehydrations are summarized in Table I.

All the alkenes showed C=C stretching frequencies in the infrared between 1595–1635 cm.⁻¹, indicating conjugation.

Although iodine has been used widely as a dehydrating agent, there does not seem to be any generally accepted mechanistic interpretation for the catalytic action of iodine. Hibbert¹⁰ suggested that iodine reacts with two moles of the tertiary alcohol to yield a tertiary alkyl halide, a tertiary alkyl hypoiodite, and water. The iodide and the hypoiodite then decompose to give the alkene, hydrogen iodide, and hypoiodous acid. Then hydrogen iodide and hypoiodous acid combine to regenerate iodine and form water. Houben¹³ suggests that the dehydration is brought about by the hydroiodic acid which is formed from the decomposition of the tertiary alkyl iodide. We would like to suggest another probable mechanism which does not require the formation of an alkyl halide and which can also explain the catalytic action of iodine. It can be represented by the following scheme.



(11) M. S. Newman and S. Otsaka, *J. Org. Chem.*, **23**, 707 (1958).

(12) A. J. Cartro, *J. Am. Chem. Soc.*, **72**, 5311 (1950).

(13) J. Houben, "Die Methoden der Organischen Chemie," Vol. II, Third Ed., Georg Thieme, Leipzig, 1925, p. 561.

The iodine which is found in the fourth step can then react further with some carbinol and then act as a catalyst. The water which is formed is removed by forming an azeotrope when an aromatic solvent is used or is distilled out as steam when no solvent is employed.

EXPERIMENTAL¹⁴

1. *Synthesis of Vinylpyrazine. a. β -Dimethylaminoethylpyrazine.* In a 3 neck, round bottom flask having ground glass joints and equipped with a mechanical stirrer, a reflux condenser, and an addition funnel were placed methylpyrazine (0.6 mole, 56.4 g.) and dimethylamine hydrochloride (0.63 mole, 52.2 g.). The mixture was heated until it began refluxing and formaldehyde (1.05 moles, 78.8 g. of 40% aqueous solution) was added over a 2-hr. period. The resulting brown viscous mass was refluxed for an additional 2½ hr. The mixture was cooled to room temperature. It was diluted with 150 ml. of water, made basic with 10% sodium hydroxide solution and extracted with chloroform. After removing the chloroform by distillation at atmospheric pressure, the residue was distilled to give 58.3 g. (64.2%) of β -dimethylaminoethylpyrazine, b.p. 114–122° at 20 mm.

Anal. Calcd. for C₈H₁₂N₂: C, 63.54; H, 8.66. Found: C, 63.55; H, 9.11.

There was also obtained 12.0 g. (20.0%) of the bis-Mannich product [1,3-bis(dimethylamino)-2-propyl]pyrazine, b.p. 138–144° at 20 mm.

b. β -(Pyrazylethyl)trimethylammonium iodide. To β -dimethylaminoethylpyrazine (0.02 mole, 3.02 g.), dissolved in 20 ml. of anhydrous ether, was added methyl iodide (0.022 mole, 3.0 g.). The mixture was allowed to stand overnight at room temperature and the white solid which had formed was filtered to give 5.7 g. (97.2%) of the quaternary compound. This compound was very hygroscopic. An analysis was not obtained and the compound was used directly in the next step of the synthesis.

c. Vinylpyrazine. The quaternary compound formed from the reaction of 0.1 mole (15.1 g.) of β -dimethylaminoethylpyrazine and 0.106 mole (15.0 g.) of methyl iodide was extracted with 100 ml. of water. The aqueous solution was placed in a 3 neck, round bottom flask equipped with a mechanical stirrer, a condenser, and a thermometer. The solution was cooled to 0° by the use of a salt-ice bath, and silver oxide (0.2 mole, 46.0 g.) was added. The mixture was stirred for 2½ hr. The solid which formed was then removed by filtration. The aqueous phase was transferred to a 200-ml. round bottom flask equipped with a reflux condenser. Then 4.0 g. (0.1 mole) of sodium hydroxide pellets was added and the mixture was refluxed for 1 hr. During that time the gaseous trimethylamine which was formed in this reaction left the reaction mixture through the condenser and was identified by bubbling it through a saturated alcoholic solution of picric acid. The picrate melted at 115–117° (lit. value for m.p. of trimethylamine picrate is 117°).¹⁵ The mixture was then cooled to room temperature and was extracted with several portions of methylene chloride. The combined extracts were dried over anhydrous sodium sulfate. After removing the methylene chloride by heating over a steam bath, the residue was distilled to give 6.7 g. (63.3%, based on the β -dimethylaminoethylpyrazine) of vinylpyrazine, b.p. 63–64° at 21 mm., n_D^{25} 1.5533 (lit. values for vinylpyrazine, b.p. 61° at 21 mm., and n_D^{25} 1.5565).⁴

(14) The methylpyrazine and 2,5-dimethylpyrazine used in this study were supplied through the courtesy of Wyandotte Chemicals Corporation.

(15) R. L. Shriner and R. C. Fuson, "The Systematic Identification of Organic Compounds," Wiley, New York, 1948, p. 234.

The vinylpyrazine forms a picrate, m.p. 99–100° after recrystallization from methanol, (lit. value 99.2–100.2°).⁴

The reaction was repeated except that no silver oxide was used.

The quaternary ammonium iodide compound formed from the reaction of β -dimethylaminoethylpyrazine (0.1 mole, 15.1 g.) and 0.106 mole (15.0 g.) of methyl iodide was dissolved in 100 ml. of water. Then 4.0 g. (0.1 mole) of sodium hydroxide pellets was added and the mixture was refluxed for 1 hr. After working up the reaction by the method which was described above, there was obtained 6.4 g. (60.5%) of vinylpyrazine, b.p. 61–62° at 19 mm.

2. *Attempted dehydration of 1,1-diphenyl-2-(2-methyl-6-pyrazyl)ethanol using phosphorus pentoxide.* A mixture of the carbinol (0.03 mole, 8.7 g.), dissolved in 100 ml. of dry benzene, and 5 g. of phosphorus pentoxide were refluxed for 5 hr. There seemed to be no water forming, as the phosphorus pentoxide appeared to be unchanged. The reaction mixture was allowed to cool to room temperature and then it was poured over ice. The benzene layer was separated and the remaining aqueous phase was extracted with several portions of benzene. After evaporation of the benzene, there was obtained 7.8 g. (92.4%) of the recovered starting material, m.p. 143.4–144.4° alone and when mixed with an authentic sample.

3. *Dehydration of 1,1-diphenyl-2-(2-methyl-6-pyrazyl)ethanol using iodine as a catalyst.* Using the dehydration of 1,1-diphenyl-2-(2-methyl-6-pyrazyl)ethanol as an example for the iodine-effected dehydration of the carbinols where a solvent was employed, the procedure used follows.

The alcohol (0.0516 mole, 15.0 g.) was dissolved in 50

ml. of dry benzene and was placed in a 100 ml. round bottom flask equipped with a Barrett trap and a condenser. To the solution 1 g. of iodine was added and the mixture was allowed to reflux for 16 hr. During the reflux there was some water formed which settled at the bottom of the Barrett trap indicating that dehydration has presumably taken place. The mixture was cooled to room temperature and was then washed with several portions of 10% aqueous solution of sodium thiosulfate to remove the residual iodine. The benzene portion was then dried over anhydrous sodium sulfate. After removing the solvent by distillation, there was obtained 12.6 g. (90%) of 1,1-diphenyl-2-(2-methyl-6-pyrazyl)ethylene, b.p. 183–184° at 1.0 mm. This olefin solidified upon standing and melted at 54.6–56.0° after recrystallization from pentane.

4. *Dehydration of 3-(2-methyl-6-pyrazylmethyl)pentanol-3 using iodine as a catalyst and no solvent.* Using the dehydration of this carbinol as an example for the iodine-effected dehydration without employing a solvent, the procedure used follows.

The carbinol, 3-(2-methyl-6-pyrazylmethyl)pentanol-3, (0.051 mole, 10.0 g.) was mixed with 1 g. of iodine in a 50-ml. round bottom flask equipped with an air-cooled condenser. The mixture was heated in a Woods metal bath at 185° for 1 hr. After cooling the reaction mixture to room temperature, 50 ml. of benzene were added to it. The benzene solution was then worked in the manner as described in the previous experiment to give 4.4 g. (48.9%) of 1-(2-methyl-6-pyrazyl)-2-ethylbutene-1, b.p. 69–72° at 0.7 mm.

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[CONTRIBUTION FROM THE ORGANIC CHEMICAL RESEARCH SECTION, LEDERLE LABORATORIES DIVISION, AMERICAN CYANAMID COMPANY]

Pteridine Chemistry. VIII. The Cyanoethylation of Some Hydroxypteridines

WILLIAM V. CURRAN AND ROBERT B. ANGIER

Received October 9, 1961

The reaction of acrylonitrile with 2-hydroxy-4-amino-6-methylpteridine (I) and some 2,4-dihydroxypteridines (VI) and the reaction of ethyl acrylate with 2-methylthio-4-hydroxy-6,7-dimethylpteridine (XIV) have been shown to give normal adducts. Some reactions dealing with the structure elucidation of these compounds are also discussed.

Previously we have described the addition of acrylonitrile to 2-amino-4-hydroxypteridines to give 8,9-dihydro-11*H*-pyrimido[2,1-*b*]pteridine-7,11-diones¹ and to 4-hydroxy-7-methylpteridine to give 3-cyanoethyl-7-methyl-4(3*H*)pteridinone.² As a continuation of this work we are now describing similar reactions carried out with several other hydroxypteridines.

2-Hydroxy-4-amino-6-methylpteridine (I). Compound I was prepared in good yield by condensing 2-hydroxy-4,5,6-triaminopyrimidine sulfate³ with methylglyoxal in an aqueous solution containing sodium sulfite and sodium bisulfite.⁴ Attempted acid

hydrolysis to the known 2,4-dihydroxy-6-methylpteridine^{5a} by the usual procedure of refluxing in 6 *N* hydrochloric acid^{5b} gave instead a dark red solid. Paper chromatography of the reaction mixture indicated the presence of the desired compound but none was isolated. The nature of the red solid was not investigated but in all probability it was similar to the dipteridylmethines which have been reported by Karrer.⁶ Compound I was readily converted to 2,4-dihydroxy-6-methylpteridine^{5a} by refluxing for six hours in 1 *N* sodium hydroxide.

When compound I was treated with acrylonitrile in refluxing aqueous pyridine for eight to ten hours, one product was formed as shown by paper

(1) R. B. Angier and W. V. Curran, *J. Am. Chem. Soc.*, **81**, 5650 (1959).

(2) W. V. Curran and R. B. Angier, *J. Org. Chem.*, **26**, 2364 (1961).

(3) A. Bendich, J. F. Tinker, and G. B. Brown, *J. Am. Chem. Soc.*, **70**, 3112 (1948).

(4) We wish to thank Drs. J. H. Boothe and A. Green for the details of this preparation.

(5) (a) R. B. Angier *et al.*, *J. Am. Chem. Soc.*, **74**, 408 (1952). (b) E. C. Taylor and C. K. Cain, *J. Am. Chem. Soc.*, **71**, 2538 (1949).

(6) P. Karrer and R. Schwyzer, *Helv. Chim. Acta*, **33**, 39 (1950), and previous papers.