were calculated from the slopes of plots log $([v_i - v_\infty]/[v_t - v_\infty])$ *vs.* time, where v is the volume of standard potassium thiocyanate solution used in the Volhard analysis of rate samples and the subscripts, i, t, and ∞, apply, respectively, to samples taken at the outset of reaction, at time t and at infinite reaction time. These plots generally were linear to at least 80% of completion of the reactions, and the analysis for chloride ion at infinite reaction time checked well with the analysis for tertiary chloride at the outset of reaction (see preceding).

Two sets of check experiments were conducted to establish the validity of rate constants obtained in runs with unpurified samples of the carbomethoxycumyl chlorides (obtained by the photochlorination procedure) as comparative measures of the relative reactivities of the tertiary halides. In the first case a pure sample of cumyl chloride was prepared from phenyldimethylcarbinol and hydrogen chloride[4] and its solvolysis rate in 90% aqueous acetone at 25° was compared with that of a crude sample prepared by photochlorination of cumene in an over-all procedure similar to that described for the runs on the carbomethoxycumyl chlorides. The k_s values for these two samples were respectively 14.5×10^{-5} sec.$^{-1}$ and 15.1×10^{-5} sec.$^{-1}$.

The second check experiment was designed to determine the possible influence of unphotochlorinated cumenes and of traces of carbon tetrachloride solvent on solvolysis rate constants evaluated in rate runs using crude samples of the cumyl chlorides (prepared by the photochlorination procedure described earlier). A sample of cumyl chloride, prepared from phenyldimethylcarbinol and hydrogen chloride, was used in making a rate run (25°) in which the initial concentrations of materials in 90% aqueous acetone solution were 0.113 M cumyl chloride, 0.590 M carbon tetrachloride, and 0.31 M cumene. The k_s value for this run was 14.4×10^{-5} sec.$^{-1}$

Acknowledgment.—The authors are indebted to the National Science Foundation for a grant in support of this research.

Nucleophilic Substitution at the Pyridazine Ring Carbons. II. Synthesis of Pyridazinonyl- and Bispyridazinonylpyridazines[1,2]

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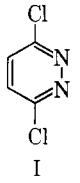
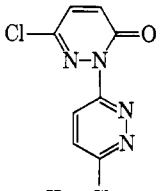
While preparing 3,6-dichloropyridazine (I), Druey and co-workers[3] isolated a small amount of another compound which on the basis of analytical, molecular weight, and infrared data was assigned the structure 3-(3′-chloro-6′(1′*H*)-pyridazinonyl)-6-chloropyridazine (II).



I

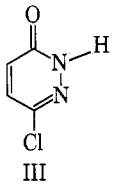


II

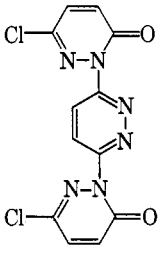
Feuer and Rubenstein[4] published experimental details for obtaining this product in small yield (less than 11%) by means of a long and tedious process.

Since compound II would be a starting material with interesting possibilities for synthetic work, possessing two halogens with strikingly different activities toward substitution, a search was undertaken in this laboratory for a synthetic route for preparation of this compound from readily obtainable materials.

The approach to this goal was to accomplish a nucleophilic displacement of one of the halogens of compound I using 6-chloro-3-(2*H*)-pyridazinone (III) as the nucleophile. It is of interest to note the difference of activity toward nucleophilic substitution of the chloro atom in compound III and the chloro atoms in compound I. Actually, compound III is prepared by boiling compound I in 3 N sodium hydroxide[5] or in 10% hydrochloric acid.[6] Once the pyridazinone is formed, the remaining chloro atom is stable toward nucleophilic attack by these reagents. Since attempts to synthesize II in an aqueous media failed,[3,4] different solvents were tested, such as xylene, tetrahydronaphthalene, and dichloropyridazine, the latter being the most successful. With a molar ratio of dichloropyridazine to 6-chloro-3(2*H*)-pyridazinone of 2:1, yields averaging 66% of compound II were obtained. In addition, a small amount (about 11%) of a higher melting compound was obtained which differed markedly in physical properties and solubility from compound II. Elemental and spectral analysis suggest the formation of a bispyridazinonylpyridazine, compound IV.



III



IV

By changing the molar ratio of 3,6-dichloropyridazine to 6-chloro-3(2*H*)-pyridazinone from 2:1 to the reverse ratio, 1:2, a 75% yield of compound IV was obtained. Compound IV was also prepared by heating compound II with excess compound III. It is of interest to note that compound III is stable at temperatures well over 200° and does not react with itself. Thus, the nucleophilic attack on compound II clearly occurs at the pyridazine ring carbon to give compound IV.

This method was used successfully to prepare 3-(6′(1′*H*)-pyridazinonyl)-6-chloropyridazine (V) and 3,6-bis(6′(1′*H*)-pyridazinonyl)pyridazine (VI). 3,6-Dichloropyridazine (I) was condensed with 3(2*H*)pyridazinone (VII) in the preceding manner. Compound VII forms an extremely stable hydrate.[7] Anhydrous VII was prepared previously by decarboxylation[8,9] of carboxy-3(2*H*)-pyridazinone or by hydrogenation of 4,5-dichloro-3(2*H*)-pyridazinone[12] with isolation according to special techniques described by Eichenberger

(1) Presented before the Pacific Southwest Regional Meeting of the American Chemical Society, December 1, 1962.

(2) For paper I, see P. Coad, R. A. Coad, S. Clough, J. Hyepock, R. Salisbury, and C. Wilkins, *J. Org. Chem.*, **28**, 218 (1963).

(3) J. Druey, K. Meier, and K. Eichenberger, *Helv. Chim. Acta*, **37**, 121 (1954).

(4) H. Feuer and H. Rubenstein, *J. Org. Chem.*, **24**, 811 (1959).

(5) S. Du Breuil, *ibid.*, **26**, 3382 (1961).

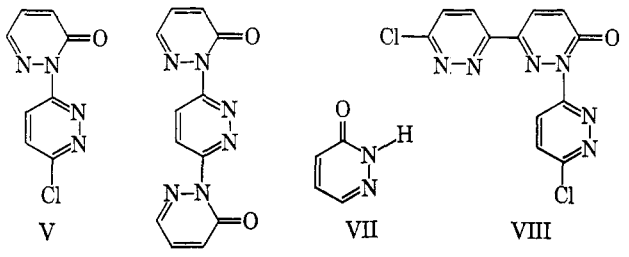
(6) H. Feuer and H. Rubenstein, *J. Am. Chem. Soc.*, **80**, 5873 (1958).

(7) C. Grundmann, *Ber.*, **81**, 6 (1948).

(8) F. McMillan and J. A. King, *J. Am. Chem. Soc.*, **77**, 3376 (1955).

(9) S. Gabriel, *Ber.*, **42**, 657 (1909).

and co-workers[10] and by Igeta.[11] The method of Mowry[12] was employed. However, significant improvements in the synthesis of 4,5-dichloro-3(2*H*)-pyridazinone and in the isolation of anhydrous VII have been made.



V VI VII VIII

From the reaction of I with anhydrous VII, 3-(6'-(1'*H*)-pyridazinonyl)-6-chloropyridazine (V) was obtained in yields of approximately 33%. Only traces of compound VI (5% or less) could ever be obtained in this reaction regardless of variation of ratio of reactants, solvents, temperature, reaction time, or pH. Traces (approximately 5%) of a new compound were isolated, and on the basis of elemental and spectral analysis and chemical solubility it has been assigned the tentative structure, VIII. The major product in each run was black polymeric material. A small part of this polymeric material was soluble in acid; a second small part was soluble in base; and the major portion was not soluble in acid, base, or common organic solvents.

The polymeric material was formed due to the activity of the hydrogens α to the ring nitrogen in compounds V, VI, and VII. It should be noted that α hydrogens are lacking in compounds II, III, and IV, and polymerization does not occur in these cases. Thus, the bifunctional nature of compound VII as an attacking nucleophile with centers at ring atoms 2 and 6 becomes monofunctional in compound III with the lone center at ring atom 2 due to the replacement of the hydrogen at ring atom 6 with the more electronegative chlorine atom.

Experimental

3,6-Dichloropyridazine (I) was prepared by the method of Coad, Coad, *et al.*,[2] from maleic hydrazide and phosphorus oxychloride with one modification. After the maleic hydrazide had dissolved in the phosphorus oxychloride, an equivalent amount of granular sodium chloride was added with a resulting evolution of hydrogen chloride. The mixture was heated an additional hour and was cooled, triturated, and extracted as previously described. Dichloropyridazine was obtained in a yield of 54%, m.p. 67–68° (lit.[2] 39%, m.p. 67–68°).

3-(3'-Chloro-6'(1'*H*)-pyridazinonyl)-6-chloropyridazine (II).—A finely ground mixture of 5.96 g. (0.04 mole) of 3,6-dichloropyridazine and 5.35 g. (0.041 mole) of 6-chloro-3(2*H*)-pyridazinone[5] was placed in a three-necked flask equipped with a thermometer, a nitrogen inlet, and an exit tube. The exit tube was connected to a trap cooled with an ice–salt bath. The exit gases were titrated with standardized sodium hydroxide to follow the course of the reaction. The flask was heated in an oil bath maintained at 134°. The internal temperature of the contents of the flask was 120°. Gas was evolved continuously from the surface of the solution. At the end of 20 min. a second phase appeared. The reaction was stopped at the end of 30 min. by sudden cooling of the flask in an ice bath. Sweeping with nitrogen was continued until all of the hydrogen chloride gas was removed. There was titrated 0.037 equivalent of acid. The solid was removed from the flask, powdered, and thoroughly ground in 50 ml. of cold 1 *N* sodium hydroxide, and separated by filtration. The solid was added to 50 ml. of cold water. The supernatant liquid was neutralized with cold hydrochloric acid. The mixture was filtered. The residue was extracted with three 100-ml. portions of boiling water. The extracts were combined and cooled. Slightly beige crystals of II were formed giving 3.0 g., m.p. 149–151°. An additional amount, 3.5 g., m.p. 149–151°, of II was obtained by concentrating the filtrate to 50 ml. and cooling, yielding a total of 6.5 g. (67%) of II. Recrystallization from cyclohexane gave white needles, m.p. 151–152°. This material has an infrared spectrum identical with authentic II as prepared by the method of Feuer and Rubenstein.[4] From the residue which was not dissolved during the hot water extractions, 1.5 g., m.p. 263–264°, of pure compound IV was isolated.

3,6-Bis(3'-chloro-6'(1'*H*)-pyridazinonyl)pyridazine (IV).—An intimately ground mixture of 5.96 g. (0.04 mole) of I and 10.44 g. (0.08 mole) of III was placed in a flask equipped as before. The bath was warmed to 160°, and hydrogen chloride was rapidly evolved. After 45 min. 0.064 mole of hydrogen chloride (80% of the stoichiometric amount) was evolved and the reaction rate markedly decreased. The mixture was poured into a mortar and ground with 100 ml. of cold 1 *N* sodium hydroxide solution and separated by filtration. The solid was treated with 150 ml. of water and the supernatant liquid was neutralized with hydrochloric acid. The mixture was boiled for 15 min. and filtered hot. This was repeated with an additional 500 ml. of boiling water. There remained a light gray powder, 10.1 g. (75% yield), m.p. 263–264°, infrared carbonyl band at 5.93 μ. White crystals could be obtained from dioxane by continuous extraction of the light gray solid for 48 hr. However, only the color was altered. Melting point, analysis, and spectrum did not change.

Anal. Calcd. for $C_{12}H_6Cl_2N_6O_2$: C, 42.73; H, 1.77; N, 24.92; Cl, 21.02. Found: C, 42.68; H, 1.86; N, 24.14; Cl, 20.1.

4,5-Dichloro-3(2*H*)-pyridazinone.—The method of Mowry[12] was modified. To a solution of 34 g. of hydrazine (95%) and 500 ml. of water was added 110 ml. of concentrated hydrochloric acid. The solution was placed in a flask equipped for stirring and was heated to boiling. A boiling solution of 169 g. (1 mole) of mucochloric acid and 200 ml. of water was added slowly with stirring. The reaction was exothermic and heat was discontinued during the course of the addition. The mixture was stirred for 15 min. and filtered warm. The precipitate was a beige solid, 157 g. (95.2%), m.p. 200–202° (lit. m.p. 201–202°).[10]

3(2*H*)-Pyridazinone (VII). **A. From 6-Chloro-3(2*H*)-pyridazinone** (III). **B. From 4,5-Dichloro-3(2*H*)-pyridazinone.**—The Parr hydrogenation apparatus was used in the hydrogenolysis of 0.4 mole of the respective halopyridazine using Shellacol,[13] a slight excess of concd. ammonium hydroxide, and 5.0 g. of activated 10% palladium on carbon. The solution was cooled and filtered. The residue was washed with 50 ml. of Shellacol. The solution and wash were combined and flash distilled using a bath temperature of at least 120° to prevent foaming and bumping. When the total volume was reduced to about 70 ml., 150 ml. of dry xylene was added and distillation was continued with a bath temperature of about 160°. When the distillation temperature reached 139°, an additional 150 ml. of hot dry xylene was added. The mixture was filtered hot, stoppered, and allowed to cool. Long pale yellow needles formed at room temperature to give 32 g. (85%), m.p. 102–103° (lit.[9] m.p. 103–104°).

3-(6'(1'*H*)-Pyridazinonyl)-6-chloropyridazine (V). **A. Tetralin as Solvent. Type I.**—In a flask equipped with a thermometer, a nitrogen inlet, a dropping funnel, and a reflux condenser with exit tube, was placed 29.8 g. (0.2 mole) of I and 50 ml. of tetralin. The flask was heated with an oil bath at 205°; the internal temperature varied from 180–195° during the course of the reaction. Over a period of 1 hr. a hot solution of 9.6 g. (0.1 mole) of VII in 50 ml. of tetralin was added through the dropping funnel. The reaction was continued for 2 hr. with smooth evolution of hydrogen chloride, at which time 0.09 equivalent of hydrogen chloride had been evolved. The mixture was filtered hot to remove a black solid. The bulk of this solid was insoluble in acid, base, and the usual organic solvents. The hot tetralin filtrate was cooled overnight. Beige crystals, 8.2 g., were formed which were fractionally recrystallized from Shellacol and

(10) K. Eichenberger, R. Rometsch, and J. Druey, *Helv. Chim. Acta*, **39**, 1755 (1956).

(11) H. Igeta, *Chem. Pharm. Bull.*, **8**, 559 (1960).

(12) T. Mowry, *J. Am. Chem. Soc.*, **75**, 1909 (1953).

(13) Commercial Solvents Corp. anhydrous denatured ethanol.

decolorized. The less soluble material, VIII, was isolated as white crystals, 1.5 g., m. p. 239–240°. The more soluble material was V. It was isolated as white crystals and recrystallized from butanol to give 6.6 g. (33%), m.p. 173–174°, carbonyl band at 5.92 μ.

Anal. Calcd. for $C_8H_5ClN_4O$: N, 26.87; Cl, 16.94. Found: N, 26.17; Cl, 16.6.

Type II.—Using a molar ratio of 1:1 of compounds I and VII with the conditions described earlier, the yield of V dropped to 5.0 g. (25%). No compound VIII was found.

B. Compound I as Solvent.—Into an erlenmeyer flask equipped with a magnetic stirrer and thermometer was placed 30.0 g. of I. The flask was warmed to 130°. Over a period of 45 min. 9.6 g. of VII was added. The yellow solution turned black and copious amounts of hydrogen chloride were evolved. The black melt was poured directly into a mortar, allowed to solidify, and ground to a fine powder. The powder (39.0 g.) was extracted for 4 hr. in a Soxhlet extractor. There remained after extraction 17.5 g. of the powder. This black powder was boiled in 500 ml. of Shellacol and filtered hot. The precipitate, 5.0 g., was a black solid, the bulk of which was not soluble in base, acid, nor the usual organic solvents. The hot Shellacol solution was treated with Norit and cooled. A black solid, 6.7 g., was separated. When recrystallized from butanol, using Norit as a decolorizing agent, there were produced white needles, 5.0 g. (25%), m.p. 173–174°.

C. Compound VII as Solvent.—In a three-necked flask equipped as described previously, was placed a finely ground mixture of 19.6 g. (0.2 mole) of VII and 14.9 g. (0.1 mole) of I. Once the internal temperature reached 118° the reaction became violent and exothermic. It was completed in 10 min. The black solid was removed from the flask, ground to a powder, and triturated consecutively with 3 *N* ammonium hydroxide, 300 ml. of Shellacol, and 300 ml. of ether. The black solid, 12.0 g., was extracted using a Soxhlet extractor for 48 hr. with dioxane. From the dioxane was isolated 1.3 g. of VI, m.p. 244–245°. None of compound V was isolated from the Shellacol fraction.

Acknowledgment.—The authors express their gratitude to Miss June Hyepock for preparation of several of the starting materials. The authors are indebted to the Analytical Staff of Riker Laboratories, Inc., Northridge, California, for providing analytical data.

The Pyrolysis of Pyrazineethanol and 2-Pyridineethanol

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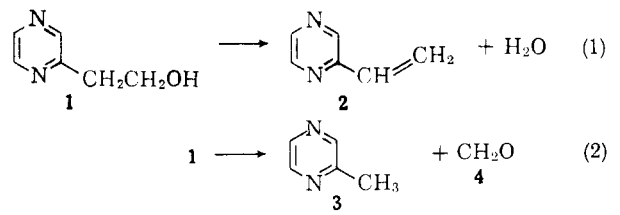
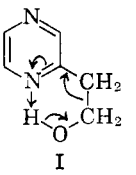
Received February 4, 1963

Gas chromatographic examination of a sample of pyrazineethanol (**1**) revealed the presence of small amounts of three lower boiling substances with retention-times corresponding to vinylpyrazine (**2**), methylpyrazine (**3**), and formaldehyde (**4**). On the assumption that these minor peaks did not represent impurities in **1** but were artefacts formed in the preheater ($T\sim$ 240°) of the chromatography column according to equations 1 and 2, samples of **1** were chromatographed at progressively higher preheater temperatures giving correspondingly larger amounts of the more volatile substances. At a preheater temperature of 370° only about 20% of the injected sample emerged unchanged.

If the dehydration (equation 1) were the result of a base-catalyzed bimolecular elimination and the fragmentation (equation 2) that of a unimolecular reaction, a change in the preheater assembly should affect the ratios of the products formed. The glass wool in the preheater, serving as a site for bimolecular elimination, was removed leaving the preheater as a hot tube with greatly diminished surface area. Samples of **1** were then chromatographed giving only traces of decomposition at 225° and about 85% decomposition at 380°. From ratios of peak areas it was estimated that the decomposition proceeded almost exclusively (~99%) *via* equation 2, whereas with a packed preheater about 10% of the decomposition proceeded *via* equation 1. That the decomposition products were in fact **2**, **3**, and **4** was established by comparison of derivatives, retention times, and physical measurements of collected samples.

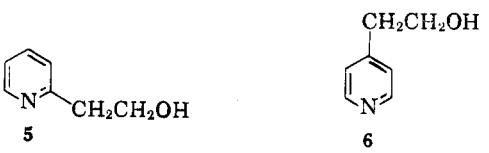


Based on the foregoing observations the following mechanism involving a cyclic transition state was considered for the formation of **3** and **4** from **1**.

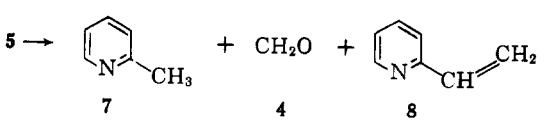


I

As a test of this hypothesis samples of 2-pyridineethanol (**5**) and 4-pyridineethanol (**6**) were chromatographed over a range of preheater temperatures. Compounds **1** and **5** are structurally analogous and should undergo an analogous pyrolytic breakdown, while **6**, though electrically similar,[2] does not embody the structural features required for facile fragmentation.



Samples of **5** were chromatographed at preheater temperatures of 195° to 390° giving the anticipated products (equation 3). As in the pyrolysis of **1**, only traces of decomposition occurred at 195° with progressively more up to about 90% at 390°. In analogy to



(3)

the pyrolysis of **1** about a per cent of **8** was formed. An additional small broad peak which emerged from the column prior to unchanged **5** was observed in the lower temperature runs and was shown to be **8**, probably

(1) (a) Research Associate, 1958–1960; (b) Medical Research Laboratories, Chas. Pfizer and Co. Inc., Groton, Conn.

(2) For discussions of similarity between the pyridine 2- and 4-positions see (a) W. E. Doering and R. A. N. Weil, *J. Am. Chem. Soc.*, **69**, 2461 (1947) and (b) H. S. Mosher, "The Chemistry of the Pyridines" in Elderfield, "Heterocyclic Compounds," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1950, p. 397.