product with alloxan monohydrate and boric acid was found to give a better yield when stirred at room temperature for three days. After recrystallization from 18% hydrochloric acid, a 75% yield of orange product was obtained, which melted at 238–240°. The reported value[3] is 237–243°.

Metal Chelates of Riboflavin.—To a mixture of 2 g. (0.005 mole) of riboflavin (U.S.P.) and 50 ml. of water was added sufficient 5% sodium hydroxide solution to dissolve the riboflavin. An aqueous solution (10 ml.) of metal salt (0.005 mole), either ferrous sulfate, cobaltous chloride, nickel nitrate, zinc chloride, cupric chloride or manganese chloride of analytical grades, was added slowly (ten minutes) to the stirred solution along with sufficient 5% sodium hydroxide solution to maintain a *p*H of 9. After 30 minutes further of stirring and adjusting the *p*H, the mixture was filtered. The filtrate was acidified with 5% hydrochloric acid, and the unreacted riboflavin was collected and dried for further use. The residue was washed with several portions of water, extracted with acetone in a Soxhlet extractor for four hours, and dried *in vacuo*. Quantitative yields of brown product were obtained, which had characteristic softening points, as shown in Table I, but did not melt below 300°.

The formation of a mercury salt with mercuric chloride was carried out in the same manner, except that no additional alkali was needed to maintain a *p*H of 9.

Metal Chelates of 6,7-Dichloro-9-(1′-D-sorbityl)-isoalloxazine.—Metal chelates of this compound were prepared in an identical manner to that for the riboflavin chelates, using cobaltous chloride and nickel nitrate. A 94% yield of green-brown cobaltous chelate was obtained, which softened at 160–165°.

Anal. Calcd. for $C_{16}H_{12}O_7N_4Cl_2Co_2 \cdot 5H_2O$: Co, 18.11. Found: Co, 18.48.

The orange nickel chelate was obtained in 93% yield, and softened at 135–140°.

Anal. Calcd. for $C_{16}H_{12}O_7N_4Cl_2Ni_2 \cdot 5H_2O$: Ni, 17.09. Found: Ni, 18.14.

MADISON, WISCONSIN

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, THE POLYTECHNIC INSTITUTE OF BROOKLYN]

Synthesis in the Pyridazine Series. II. The Preparation of Pyridazines from Substituted Maleic Anhydrides. Some Properties of 4-Methylpyridazine[1]

BY R. H. MIZZONI[2] AND PAUL E. SPOERRI

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The preparation of pyridazine from hydrazine salts and maleic anhydride, previously described (ref. 3), has been extended to the synthesis of various substituted pyridazines. 4-Methylpyridazine has been obtained from citraconic anhydride and hydrazine dihydrochloride in high over-all yield; some properties of this potentially interesting substance are discussed.

The preparation of pyridazine and 3,6-dichloropyridazine from maleic anhydride was described in a recent paper.[3] In a test of the generality of this method, a number of substituted maleic anhydrides were condensed with hydrazine dihydrochloride in aqueous medium. followed by chlorination with phosphorus oxychloride and catalytic hydrogenolysis under mild conditions. This process found ready application in the case of citraconic anhydride; 4-methylpyridazine, previously unknown, was obtained in high yield. The transformation of chloromaleic anhydride into 4-chloro-3,6-pyridazinediol and 3,4,6-trichloropyridazine proceeded easily and in good yield. *cis*-Aconitic anhydride in turn was converted to 4-(3,6-dihydroxypyridazyl)-acetic acid.

These results lend further testimony to the marked effect of reaction medium on condensations of maleic anhydrides and hydrazine. The formation of substances such as N-aminomaleimides which are produced in alcoholic solution is substantially repressed in an aqueous medium of high acidity.[4] No reaction between succinic anhydride and hydrazine salts under similar conditions has been found to occur. There is apparently a driving force of some magnitude operating in the formation of the pyridazine ring.

It seemed of interest to determine whether the methyl group of 4-methylpyridazine was reactive in the sense previously demonstrated for the 3-isomer.[5] Thus, 4-methylpyridazine undergoes typical aldol-like condensations with anisaldehyde and with chloral, through the agency of a resonance-stabilized carbanion intermediate (Fig. 1).

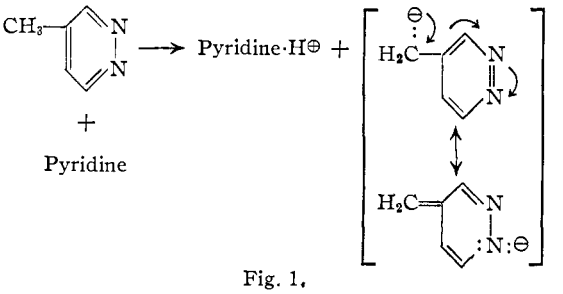

Fig. 1.

The quaternization of 4-methylpyridazine with methyl iodide was found to occur with great facility; in the absence of solvent the reaction proceeded with almost explosive violence. The product of this reaction was homogeneous and represented one of two possible isomers. The N-1 nitrogen atom seemed the more basic center in the molecule by virtue of hyperconjugation and hence the more likely site for reaction; the quaternary salt formed would then be 1,4-dimethylpyridazinium iodide, as shown in Fig. 2. In support of this proposed structure, the quaternary salt was converted to the carbocyanine iodide by the method of Hamer,[6] a process which could not occur with the other isomer.

Acknowledgments.—We are indebted to Ciba Pharmaceutical Products, Inc., for the use of its

(1) Abstracted from the Ph.D. thesis of R. H. Mizzoni, June, 1952.

(2) Ciba Pharmaceutical Products, Inc., Summit, N. J.

(3) R. H. Mizzoni and Paul E. Spoerri, THIS JOURNAL, **73**, 1873 (1951).

(4) L. H. Flett and W. H. Gardner, "Maleic Anhydride Derivatives," John Wiley and Son, Inc., New York, N. Y., p. 130.

(5) O. Poppenberg, *Ber.*, **34**, 3257 (1901).

(6) F. M. Hamer, *J. Chem. Soc.*, 2796 (1927).

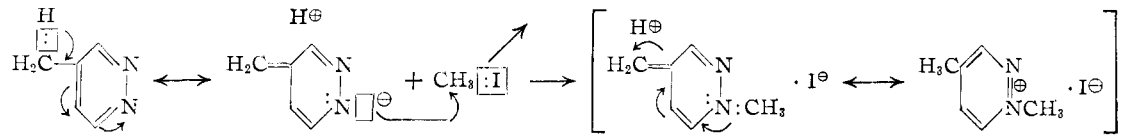

Fig. 2.

laboratory facilities, and to Mr. Louis Dorfman and his staff for their kindness in supplying the microanalytical results.

Experimental

Melting points are uncorrected.

4-Methyl-3,6-pyridazinediol.—Citraconic anhydride (336 g., 3 moles) was added during one minute to a boiling solution of 315 g. (3 moles) of hydrazine dihydrochloride in 700 cc. of water. Boiling was continued for five minutes followed by heating on a steam-bath for five hours. The large quantity of crystals which separated on cooling was filtered and washed freely with water. A large second crop was obtained on dilution of the filtrate with water and was combined with the first lot; this material was dried at 75° *in vacuo*, m.p. 286.5–287° (355 g., 94%).[7]

Anal. Calcd. for $C_5H_6N_2O_2$: C, 47.61; H, 4.80; N, 22.22. Found: C, 47.70; H, 4.34; N, 22.73.

4-Methyl-3,6-dichloropyridazine.—A solution of 355 g. of 4-methyl-3,6-pyridazinediol in three liters of phosphorus oxychloride was heated under reflux for five hours. Excess phosphorus oxychloride was removed *in vacuo*, and the cooled residue was poured onto a large quantity of ice. The precipitate was filtered, washed thoroughly with water, and vacuum-dried at 40° (361 g., m.p. 86.5–87°). The combined filtrate and washings were made alkaline with ammonium hydroxide (28%), cooled, and extracted twice with chloroform. The extract was dried over anhydrous magnesium sulfate, then decolorized with Norite and filtered. The solvent was removed under reduced pressure and the residue dried *in vacuo* (69 g., m.p. 83.5–84°). The combined yield was 430 g. (94%). The melting point was not improved by vacuum sublimation.

Anal. Calcd. for $C_5H_4Cl_2N_2$: Cl, 43.50; N, 17.19. Found: Cl, 43.42; N, 17.37.

4-Methylpyridazine.—A mixture composed of 32.6 g. of 4-methyl-3,6-dichloropyridazine, 1.6 g. of palladium–charcoal (5%), 40 cc. of ammonium hydroxide (28%), and 70 cc. of alcohol was hydrogenated at three atmospheres pressure. The theoretical uptake of hydrogen was noted after two hours. Four such runs were combined; following removal of the catalyst, the filtrate was concentrated to about one-half the original volume. Sufficient caustic soda solution (1:1) was added to effect separation of the oily base. The solution was extracted with four portions of ethylene dichloride. The extract was dried over anhydrous magnesium sulfate, filtered, and the solvent removed under reduced pressure. The crude base was distilled, b.p. 103–105° (13 mm.), $n^{24}D$ 1.5188 (67.8 g., 91.4%).

Anal. Calcd. for $C_5H_6N_2$: C, 63.60; H, 6.43; N, 29.77. Found: C, 63.68; H, 6.42; N, 29.27, 29.39.

Picrate (from ethanol), m.p. 126–126.5°.

Anal. Calcd. for $C_{11}H_9N_5O_7$: N, 21.67. Found: N, 21.70.

4-Chloro-3,6-pyridazinediol.—Chloromalcic anhydride (66 g.) was added during 15 minutes to a boiling solution of hydrazine dihydrochloride (52.6 g.) in 250 cc. of water. Heating was continued for 30 minutes. The hot solution was filtered. The product was combined with a second crop and digested with boiling water. This material was filtered and vacuum-dried, m.p. 265–268° dec. (59 g., 80.5%).

Anal. Calcd. for $C_4H_3ClN_2O_2$: Cl, 24.20; N, 19.12. Found: Cl, 23.63; N, 19.42.

3,4,6-Trichloropyridazine.—A solution of 30 g. of 4-chloro-3,6-pyridazinediol in 300 cc. of phosphorus oxychloride was refluxed for three hours. Excess phosphorus oxychloride was removed *in vacuo*, and the cooled residue was poured onto ice. The tan solid which separated was filtered. An additional crop was obtained by addition of ammonium hydroxide (28%) to the filtrate and extraction with chloroform. The combined dried material (29.6 g.) was purified by vacuum sublimation, m.p. 57–57.5° (26.6 g., 70.6%).

Anal. Calcd. for $C_4HCl_3N_2$: Cl, 57.99; N, 15.28. Found: Cl, 57.77; N, 15.39.

4-(3,6-Dihydroxypyridazyl)-acetic Acid.—*cis*-Aconitic anhydride (15.4 g.)[8] was added to a boiling solution of hydrazine dihydrochloride (16.8 g.) in 75 cc. of water. Boiling was continued for 15 minutes. The material was filtered after chilling overnight and washed freely with cold water. The substance was dried at 50° *in vacuo*, m.p. 278–281° dec. No improvement in melting point resulted on recrystallization from hot water.

Anal. Calcd. for $C_6H_6N_2O_4$: C, 42.36; H, 3.56; N, 16.47. Found: C, 41.85; H, 3.61; N, 16.37.

1,4-Dimethylpyridazinium Iodide.—A solution of 1.9 g. (0.02 mole) of 4-methylpyridazine in 10 cc. of anhydrous ethanol was treated with 6.25 g. of methyl iodide and heated for 15 minutes on a steam-bath. Upon cooling and addition of ether an oil separated which crystallized on scratching. The substance was filtered, washed with ether and vacuum dried, m.p. 64.5–66° (4.2 g., 88%).

Anal. Calcd. for $C_6H_9IN_2$: I, 53.76; N, 11.87. Found: I, 53.77; N, 11.68.

1,1-Dimethylpyridazyl-4,4′-carbocyanine Iodide.—A solution of 4.7 g. of 1,4-dimethylpyridazinium iodide, 6.0 g. of ethyl orthoformate and 25 cc. of pyridine (anhydrous) was refluxed for three hours. The oily residue crystallized on cooling; dark green crystals resulted on recrystallization from ethanol, m.p. 244–245° (0.8 g.).

Anal. Calcd. for $C_{13}H_{15}IN_4 \cdot 1H_2O$: I, 34.10; N, 15.05. Found: I, 34.37; N, 15.68.

4-[1-(3,3,3-Trichloro-2-hydroxy)-propyl]-pyridazine.[9]—A solution of 4.7 g. of 4-methylpyridazine and 10 g. of chloral (stabilized with hydroquinone) in 20 cc. of dry pyridine was heated on a steam-bath for 16 hours. About five cc. of pyridine was removed *in vacuo*. The residue was shaken continuously for one hour with 85 cc. of 2 *N* hydrochloric acid. The solution was filtered and the residue was washed with 40 cc. of acid. The combined filtrate was treated with Norite, filtered, and made basic with ammonium hydroxide (28%). The solution was then distilled to dryness under reduced pressure. The residue was extracted with four portions of boiling benzene. The extract was chilled, yielding 2.8 g. of substance m.p. 117–118°. Additional material was obtained upon addition of petroleum ether to the mother liquor, m.p. 111–113° (1.4 g.). The material was recrystallized from benzene, m.p. 117–118°.

Anal. Calcd. for $C_7H_7Cl_3N_2O$: Cl, 44.04; N, 11.60. Found: Cl, 43.75; N, 11.73.

β-(4-Pyridazyl)-acrylic Acid.—A solution of 2.56 g. of the chloral condensation product of 4-methylpyridazine and 4.0 cc. of 12.5 *N* sodium hydroxide in 15 cc. of ethanol was warmed on a steam-bath until a vigorous reaction set in. After five minutes the ethanol was removed under reduced pressure and the residue was treated with 1.6 cc. of concentrated hydrochloric acid (to *p*H 2). The brown solid was filtered after an hour, washed with cold water and dried, m.p. 224–225° (1.1 g.). No change in melting point resulted upon recrystallization from hot water.

Anal. Calcd. for $C_7H_6N_2O_2$: N, 18.66. Found: N, 18.88.

4-(*p*-Methoxystyryl)-pyridazine.—A mixture of 5.0 g. of 4-methylpyridazine and 8.0 g. of anisaldehyde was heated at 150° for 17 hours. The product was removed from the pressure tube with the aid of chloroform and then steam

(7) M. Freri, *Gazz. chim. ital.*, **66**, 23 (1936); C. A., **30**, 6388 (1936).

(8) R. Malachowski, M. Gredroyć and Z. Jerzmanowska, *Ber.*, **61**, 2525 (1928).

(9) Adapted from the method of R. G. Jones, *et al.*, THIS JOURNAL, **72**, 3541 (1950).

distilled. The gummy residue was digested with *ca.* 5 *N* hydrochloric acid, and then treated with Norite and filtered. The red crystals which formed on chilling were filtered and recrystallized from ethanol, m.p. 226–228° (2.3 g.).

Anal. Calcd. for $C_{13}H_{18}ClN_2O$: Cl, 14.20; N, 11.22. Found: Cl, 13.98; N, 11.09.

BROOKLYN, N. Y.

[CONTRIBUTION FROM THE COLLEGE OF PHARMACY, UNIVERSITY OF MICHIGAN]

The Preparation of Several Analogs of Amidone and Isoamidone[1]

BY F. F. BLICKE AND EU-PHANG TSAO[2,3]

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One analog of Amidone and three analogs of isoamidone which contain hexa- or heptamethylenimino radicals as the basic substituents were synthesized. Reaction of diphenylacetonitrile and the necessary basic alkyl chlorides yielded the required nitriles which were converted into the final products by treatment with ethylmagnesium bromide. The structures of the nitriles were established by exhaustive methylation.

The object of this investigation was the preparation of several analogs of Amidone and isoamidone which contained hexamethylenimino and heptamethylenimino radicals as the basic portions of the molecule. The products obtained were 4,4-diphenyl-6-(1-hexamethylenimino)-3-heptanone (IV), 4,4-diphenyl-5-methyl-6-(1-hexamethylenimino)-3-hexanone (IX), 4,4-diphenyl-5-methyl-6-(1-heptamethylenimino)-3-hexanone (XVI) and a cyclic analog 1,1-hexamethylene-2,5-dimethyl-4,4-diphenyl-3-ketopiperidinium bromide (XI).

Compounds IV and IX were prepared in the following manner. Diphenylacetonitrile was condensed with β-(1-hexamethylenimino)-propyl chloride and sodamide to form a mixture of 2,2-diphenyl-4-(1-hexamethylenimino)-valeronitrile (I) and 2,2-diphenyl-3-methyl-4-(1-hexamethylenimino)-butyronitrile (VI). Advantage was taken of the greater solubility of the hydrochloride of I in isopropyl alcohol to separate the mixture into its components. Compounds I and VI reacted with ethylmagnesium bromide to form the desired ketones IV and IX.

In order to prove the structure of nitrile I, the nitrile was converted by methyl iodide into the quaternary iodide (II). The latter substance was heated with a mixture of silver oxide and water whereby 1,1-diphenyl-1-cyano-2-butene (III) and 1-methylhexamethylenimine were formed. Compound III was converted by lithium aluminum hydride into 1-amino-2,2-diphenyl-3-pentene and the latter substance was hydrogenated to 1-amino-2,2-diphenylpentane.

The structure of nitrile VI was established by conversion of the nitrile into the quaternary compound VII; when the latter substance was treated with silver oxide and water, 1,1-diphenyl-1-cyano-2-methyl-2-propene (VIII) and 1-methylhexamethylenimine were obtained. Reduction of VIII with lithium aluminum hydride yielded 1-amino-2,2-diphenyl-3-methyl-3-butene which was hydrogenated to form 1-amino-2,2-diphenyl-3-methylbutane.

Compound IX was converted into the hydrobromide (IX·HBr) which after bromination yielded X. After treatment of X with ammonia water, a product was obtained which we believe is 1,1-hexamethylene-2,5-dimethyl-4,4-diphenyl-3-ketopiperidinium bromide (XI). Compound IV was submitted to the same series of reactions. In this instance interaction of V with ammonia water yielded a crystalline substance but the analytical data did not correspond to that calculated for a piperidone analogous to XI.

When diphenylacetonitrile was condensed with β-(1-heptamethylenimino)-propyl chloride and sodamide, a mixture of the basic nitriles, XII and XIII, was obtained. The mixture was treated with hydrochloric acid, and the two hydrochlorides were then separated by the use of isopropyl alcohol.

The structures of nitriles XII and XIII were also established by exhaustive methylation. Compound XII yielded butene III and 1-methylheptamethylenimine, while compound XIII was decomposed to propene VIII and 1-methylheptamethylenimine.

The ketone XVI, as well as the cleavage product XVII, was obtained in the usual manner from nitrile XIII.

Tested in the Parke, Davis and Company laboratories, it was found that compounds IX and XVI were less active than Amidone; in the case of XVII, there was uncertainty regarding the analgesic quality of action; analgesic activity, if present, in IV and XI was confounded with side effects.

Experimental Part

2,2-Diphenyl-3-methyl-4-(1-hexamethylenimino)-butyronitrile (VI) and 2,2-Diphenyl-4-(1-hexamethylenimino)-valeronitrile (I).—Diphenylacetonitrile (58 g., 0.3 mole), dissolved in 230 cc. of benzene, was added dropwise to a stirred suspension of 15 g. of pulverized sodamide in 150 cc. of benzene. The mixture was stirred at 40° for 1 hour, 53 g. (0.3 mole) of β-(1-hexamethylenimino)-propyl chloride[4] added dropwise and the mixture was stirred and heated at 50° for 10 hours. Water was added, the organic layer was separated and the aqueous layer was extracted with benzene. The solvent was removed from the combined extract and the organic layer and the residue distilled; b.p. 168–170° (0.01 mm.), yield 92.6 g. (93%).

A mixture of the hydrochlorides of VI and I precipitated when an ethereal solution of the base was treated with hydrogen chloride. The mixture was dissolved in the smallest possible amount of hot isopropyl alcohol. The hydrochloride of VI, which precipitated from the cold solution (A), melted at 234–235° after recrystallization from isopropyl alcohol. Analytical data indicated that the hydro-

(1) Abstracts of Papers, 123rd Meeting of the American Chemical Society, Los Angeles, Calif., March 15–19, p. 14L.

(2) This paper represents part of a dissertation submitted by Eu-Phang Tsao in partial fulfillment of the requirements for the Ph.D. degree in the University of Michigan, 1952.

(3) Parke, Davis and Company Fellow.

(4) N. J. Doorenbos, Dissertation, University of Michigan, 1953.