Anal.[7] Calcd. for $C_5H_7O_2N_3 \cdot {}^1/_2H_2O$: C, 40.00; H, 5.37. Found after drying at 60°: C, 40.07; H, 5.55. Calcd. for $C_5H_7O_2N_3$: C, 42.55; H, 5.00; N, 29.78. Found after drying at 100° over P_2O_5 *in vacuo* for 50 hours: C, 42.61; H, 5.14; N, 29.72.

Ultraviolet absorption maximum on the anhydrous sample in water, 270 mμ (E_m 5970); in 0.1 *N* HCl, 279.5–280 mμ (E_m 9620); in 0.1 *N* NaOH, 283.5–284 mμ (E_m 7660).[8]

Infrared curves obtained on mineral oil mulls of the anhydrous material and a sample of Wyatt and Cohen's anhydrous material were identical.[9]

When diethyl Carbitol was used as the solvent in this procedure the ether extraction of the water extract was unnecessary and similar results were obtained.

(B).—A solution of 1.0 g. (0.005 mole) of 2-ethylthio-4-amino-5-hydroxymethylpyrimidine in 20 ml. of *N* hydrochloric acid was refluxed for 4 hours. After cooling, the solution was made alkaline with sodium hydroxide solution and chilled. Any precipitate at this point was removed and discarded. The solution was neutralized with hydrochloric acid, concentrated to a small volume under reduced pressure and chilled. The resulting crystals were filtered, and washed with acetone by suspension. After one recrystallization from water the yield was about 60%.

Anal. Found[7] after repeated recrystallization from water and drying at 100° for 60 hours *in vacuo* over P_2O_5: C, 42.56; H, 4.96; N, 29.75.

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[8] We are indebted to W. R. McGaughran for the ultraviolet measurements.

[9] We are indebted to E. H. Unger for the infrared measurements.

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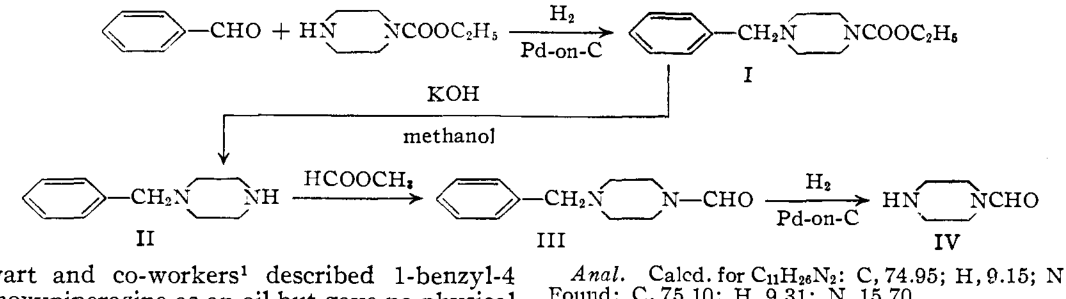
1-Formylpiperazine and Related Compounds

BY BRUCE W. HORROM, MORRIS FREIFELDER AND GEORGE R. STONE

RECEIVED AUGUST 26, 1954

In general, reaction of piperazine with many reagents produces bis-substitution products or mixtures from which the mono-product is not readily separated. However, in this Laboratory we were able to obtain 1-formylpiperazine in 58–60% yield by heating equimolecular quantities of piperazine and methyl formate. In order to show how readily the 1,4-bis-formyl derivative was formed we mixed piperazine with two equivalents of methyl formate and distilled the reaction mixture after less than five minutes standing. A 74% yield of 1,4-bis-formylpiperazine was obtained.

1-Formylpiperazine also was prepared in good over-all yield by the procedure



Stewart and co-workers[1] described 1-benzyl-4-carbethoxypiperazine as an oil but gave no physical constants. 1-Benzylpiperazine (II) has been prepared by another method.[2] The excellent formylation procedure of Human and Mills[3] was used to obtain compound III.

The carbamyl, acetyl and benzenesulfonyl derivatives of 1-formylpiperazine were made by standard procedures for purposes of identification.

Experimental

1-Formylpiperazine (IV).—Thirty grams (0.5 mole) of methyl formate was added in one portion to 43 g. (0.5 mole) of anhydrous piperazine in a flask equipped with a reflux condenser. The temperature rose to 85° in one to two minutes. The mixture was then heated at 85° for five hours after which time it was distilled. The product boiled at 94–97° (0.5 mm.), $n^{25}D$ 1.5074, yield 33 g. (58%).

Anal. Calcd. for $C_5H_{10}N_2O$: C, 52.62; H, 8.83; N, 24.54. Found: C, 52.62; H, 8.74; N, 24.78.

Formylpiperazine is water soluble and forms a carbonate readily on exposure to air.

When the same quantities were heated in a stainless steel bomb for two hours at 100° a yield of 34.2 g. (60%) was obtained, b.p. 87–95° (0.3–0.4 mm.). Under the same autoclave conditions another experiment was carried out using a 1:3 ratio of methyl formate and piperazine. An 81% yield of IV was obtained, but the product was contaminated with piperazine.

1,4-Bis-formylpiperazine.—Sixty grams (1.0 mole) of methyl formate was added in one portion to 43 g. (0.5 mole) of anhydrous piperazine. The vigorous reaction which took place subsided in a few minutes. The material was distilled immediately. The product boiled at 151–159° (0.2–0.3 mm.) and solidified on standing, yield 52.5 g. (74%). After recrystallization from benzene it melted at 126–127°.

Anal. Calcd. for $C_6H_{10}N_2O_2$: N, 19.71. Found: N, 19.91.

1-Benzyl-4-carbethoxypiperazine (I).—Excess benzaldehyde (47.7 g., 0.45 mole) was mixed with 47.4 g. (0.3 mole) of carbethoxypiperazine. The mixture became warm and was allowed to stand 20 minutes when 100 cc. of absolute alcohol was added. Seven grams of 5% palladium-on-charcoal was added cautiously and the mixture hydrogenated under a pressure of 45 p.s.i. at 55–60° for one hour. After filtration and removal of solvent, distillation yielded 64 g. (86%) of a thick oil, b.p. 130–135° (0.15 mm.), $n^{26}D$ 1.5238.

Anal. Calcd. for $C_{14}H_{20}N_2O_2$: C, 67.71; H, 8.11; N, 11.28. Found: C, 67.81; H, 7.84; N, 11.32.

1-Benzylpiperazine (II).—A mixture of 63 g. (0.254 mole) of 1-benzyl-4-carbethoxypiperazine (I), 28.5 g. (0.508 mole) of potassium hydroxide and 170 cc. of methanol was heated to reflux and the methanol then distilled off slowly during a two-hour period. Heating was continued until the temperature of the residue was 130–135°. It was then cooled and treated with 75 cc. of benzene and 100 cc. of water. The aqueous portion was extracted with two 100-cc. portions of benzene. The benzene extract, after drying over anhydrous magnesium sulfate and removal of solvent, was distilled and 35.8 g. (80%) of 1-benzylpiperazine obtained, b.p. 89–96° (0.2 mm.), $n^{28}D$ 1.5430.

Anal. Calcd. for $C_{11}H_{26}N_2$: C, 74.95; H, 9.15; N, 15.90. Found: C, 75.10; H, 9.31; N, 15.70.

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[1] H. W. Stewart, R. J. Turner and J. J. Denton: S. Kushner, L. M. Brancone, W. L. McEwen, R. I. Hewitt and Y. SubbaRow, *J. Org. Chem.*, **13**, 141 (1948).

[2] (a) R. Baltzly, J. S. Buck, E. Lorz and W. Schön, THIS JOURNAL, **66**, 263 (1944); (b) J. S. Buck and R. Baltzly, U. S. Patents 2,415,785, 2,415,786 and 2,415,787.

[3] J. P. E. Human and J. A. Mills, *J. Chem. Soc.*, 1457 (1948).

1-Benzyl-4-formylpiperazine (III).—A mixture of 357 g. (2.03 moles) of 1-benzylpiperazine and 1218 g. (20.3 moles) of methyl formate was heated in a 3-liter rocker type bomb for 1.5 hours at 100–110°. After cooling the solution was fractionated and 393.3 g. (95%) of a thick oil obtained which solidified on standing, b.p. 166–169° (0.5 mm.), $n^{27}\text{D}$ 1.5533, m.p. 61–62°.

Anal. Calcd. for $C_{13}H_{16}N_2O$: C, 70.85; H, 7.90; N, 13.72. Found: C, 70.48; H, 7.92; N, 13.79.

In a similar manner 1-formyl-4-(4-methoxybenzyl)-piperazine was prepared in 92% yield, b.p. 183–189° (1.5 mm.), $n^{26}\text{D}$ 1.5559. This product also solidified on standing, m.p. 54–56°.

Anal. Calcd. for $C_{13}H_{18}N_2O_2$: N, 11.96. Found: N, 11.96.

1-Formylpiperazine (IV).—A solution of 70 g. (0.35 mole) of 1-benzyl-4-formylpiperazine in 150 cc. of absolute ethanol was hydrogenated in the presence of 14 g. of 5% palladium-on-charcoal under a pressure of 40 p.s.i. at 55–60°. The calculated drop in pressure was reached in about four hours. A second run was carried out under the same conditions, and the two were combined and worked up as one. After removal of the catalyst and distillation to remove the solvent, the residue was distilled, b.p. 94–97° (0.5 mm.), $n^{25}\text{D}$ 1.5084. The product weighed 66.8 g. (84%).

Anal. Calcd. for $C_5H_{10}N_2O$: C, 52.62; H, 8.83; N, 24.54. Found: C, 52.53; H, 8.82; N, 24.64.

1-Carbamyl-4-formylpiperazine.—A solution of 9.5 g. (0.083 mole) of 1-formylpiperazine in 30 cc. of water was acidified (*ca. p*H 6) with dilute hydrochloric acid and treated with 9.3 g. (0.115 mole) of potassium cyanate. The reaction mixture was warmed on the steam-bath for 20 minutes and evaporated to dryness. The solid residue was extracted three times with boiling ethanol and the alcoholic extracts concentrated to dryness. The oily solid (10.6 g.) was recrystallized from 75 cc. of absolute alcohol and after prolonged cooling yielded 7 g. of colorless needles, m.p. 180–182°. A sample, recrystallized for analysis, melted at 185–186°.

Anal. Calcd. for $C_6H_{11}N_2O_2$: C, 45.84; H, 7.05; N, 26.73. Found: C, 45.80; H, 6.79; N, 26.71.

1-Benzenesulfonyl-4-formylpiperazine.—To 15 g. (0.085 mole) of benzenesulfonyl chloride in 100 cc. of dry benzene was added with stirring 19.4 g. (0.17 mole) of 1-formylpiperazine in 100 cc. of dry benzene. The reaction was carried out at room temperature. The mixture was filtered from amine hydrochloride and taken to dryness after which 20.6 g. of a water-insoluble solid was obtained, m.p. 140–143°. The product was recrystallized from absolute alcohol as colorless needles, m.p. 141–143°. A sample, recrystallized a second time for analysis, melted 141–142°.

Anal. Calcd. for $C_{11}H_{14}N_2O_3S$: C, 51.95; H, 5.54; N, 11.01. Found: C, 51.97; H, 5.64; N, 11.06.

1-Acetyl-4-formylpiperazine.—Ketene was passed into a mixture of 22.8 g. (0.2 mole) of 1-formylpiperazine in 200 cc. of dry benzene for one half-hour. The solvent was removed from the yellow reaction mixture and the resultant solid residue was distilled. The product boiled at 145–149° (0.5 mm.) and weighed 16.5 g.[4]

Anal. Calcd. for $C_7H_{12}N_2O_2$: C, 53.83; H, 7.61; N, 17.93; O, 20.63. Found: C, 53.91; H, 7.41; N, 17.79; O, 21.12.

Acknowledgment.—The authors are deeply grateful to Mr. E. F. Shelberg, Chief Microanalyst, and his staff for the analyses herein.

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[4] After standing the thick oil solidified and melted over a range 72–77°. It is very soluble in water.

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n-Acrylylmorpholine

BY JOHN W. LYNN

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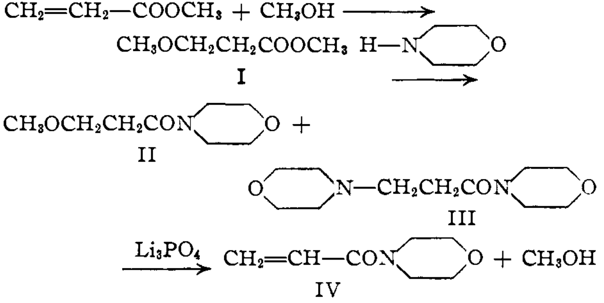
This new monomer may be obtained in substantial yield by the vapor phase dealcoholation of N-(3-methoxypropionyl)-morpholine. A recently issued patent[1] describes the syntheses of N-acrylylmorpholine by the reaction of acrylyl chloride with morpholine, but does not report any yields or physical properties.

Methyl acrylate was treated with methanol using sodium hydroxide catalyst to give methyl 3-methoxypropionate (I), which on heating with morpholine gave N-(3-methoxypropionyl)-morpholine (II) in good yield. A small amount of by-product, N-[3-(N-morpholino)-propionyl]-morpholine (III), also was obtained. Pyrolysis of the foregoing mixture in the vapor phase over lithium phosphate gave N-acrylylmorpholine (II) in about 47% yield and 65% efficiency.



Experimental[2]

Methyl 3-Methoxypropionate (I).—The procedure originally described by Purdie[3] was modified by the use of sodium hydroxide in place of sodium as catalyst. Excellent yields and efficiencies were obtained.

N-(3-Methoxypropionyl)-morpholine (II).—A mixture of 118 g. (1 mole) of methyl 3-methoxypropionate, 147 g. (2 moles) of morpholine and 18 g. (1 mole) of water was heated for 6 hours at 125° while removing 28 g. (0.87 mole) of methanol by distillation. Fractional distillation gave 144 g., an 81% yield, of N-(3-methoxypropionyl)-morpholine boiling at 127–131° (3.5 mm.) and melting at 37.5°.

Anal. Calcd. for $C_8H_{15}NO_3$: C, 55.5; H, 8.67; N, 8.09. Found: C, 55.75; H, 8.68; N, 8.33.

N-[3-(N-Morpholino)-propionyl]-morpholine (III).—A small amount of higher-melting solid was filtered from the cuts boiling higher than the products of the preceding distillation. This material proved to be the expected by-product III, melting at 91–92° of 98.8% purity by acid titration.

Anal. Calcd. for $C_{11}H_{20}N_2O_3$: C, 57.58; H, 8.78; N, 12.29. Found: C, 58.1; H, 8.82; N, 12.44.

N-Acrylylmorpholine (IV).—The method previously described by Phillips and Starcher[4] was employed for the pyrolysis step. A mixture of 342 g. (1.97 moles) of N-(3-methoxypropionyl)-morpholine, 171 g. of methanol and 2.5 g. of Agerite Powder was passed over 225 cc. of granular lithium phosphate in a 1-inch nickel tube at 390° during a 5-hour period. A slow stream of nitrogen was fed concurrently. The crude product was distilled in the presence of hydroquinone through a light-protected column. N-Acrylylmorpholine (b.p. 114–116° (8 mm.), $n^{30}\text{D}$ 1.5060, d^{20}_{20} 1.1070) was obtained in 47% yield and 65.5% efficiency.

Anal. Calcd. for $C_7H_{11}NO_2$: C, 59.6; H, 7.8; N, 9.94. Found: C, 59.95; H, 8.02; N, 9.83.

Acknowledgment.—The author is grateful to Messrs. John Smith, Jr., and Harvey C. Shue for technical assistance and to Mr. Quentin Quick for microanalyses.

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(1) G. E. Ham, U. S. Patent 2,683,703.

(2) All boiling points and melting points are uncorrected.

(3) T. Purdie and W. Marshall, *J. Chem. Soc.*, **59**, 474 (1891).

(4) B. Phillips and P. S. Starcher, U. S. Patent 2,587,209.