Ethyl α-Acetamino-α-carbethoxy-β-(3-indazole)-propionate (VI).—In a three-necked flask equipped with an air-tight, ground-glass jointed stirrer, a Graham coil condenser surmounted by a calcium chloride tube, and a nitrogen inlet, were placed 50 ml. of absolute ethanol and 0.46 g. (0.02 gram atom) of sodium. To this solution was added 4.34 g. (0.02 mole) of acetaminomalonic ester in 15 ml. of absolute ethanol, and, after a few minutes of stirring, 6.34 g. (0.02 mole) of V dissolved in 30 ml. of warm absolute ethanol. The stirred solution was heated under reflux and a gentle stream of dry nitrogen was passed through the system. The reaction was allowed to continue, usually about 20 hours, until moist pink litmus paper held at the condenser mouth was no longer turned blue by escaping trimethylamine. The alcohol was removed by distillation under reduced pressure. The residual yellow oil was taken up in a 1:1 mixture of chloroform and ether, and the precipitated sodium iodide was removed by filtration. The organic layer was washed with water, dried over magnesium sulfate, and finally concentrated under reduced pressure, leaving a yellow paste. This was dissolved in 95% ethanol, treated with Darco, and water was added to incipient crystallization. After standing for 2 hours at 5° white needles of VI which had been deposited were removed by filtration. A second crop of VI was obtained by adding more water to the filtrate. The combined crops were recrystallized again from ethanol–water. There was obtained 5.1 g. (74%) of VI, as short white needles, m.p. 84–87°.

Anal. Calcd. for $C_{16}H_{21}N_3O_5$: C, 58.77; H, 6.09; N, 12.10. Found: C, 58.53; H, 6.39; N, 12.18.

By the same procedure, from 6.34 g. (0.02 mole) of V and 4.06 g. (0.02 mole) of formylaminomalonic ester there was obtained 4.5 g. (67.5%) of ethyl α-formylamino-α-carbethoxy-β-(3-indazole)-propionate as white needles, m.p. 140–140.5°.

Anal. Calcd. for $C_{17}H_{19}N_3O_5$: C, 57.66; H, 5.75; N, 12.61. Found: C, 57.55; H, 5.75; N, 12.75.

α-Acetamino-α-carboxy-β-(3-indazole)-propionic Acid (VII).—A mixture of 4.0 g. (0.012 mole) of VI and 2.4 g. (0.06 mole) of sodium hydroxide in 25 ml. of water was heated under reflux for four hours. The solution was then cooled in an ice-bath and 9 ml. of concentrated hydrochloric acid was added slowly so that the temperature did not exceed 25°. The solution was held at 5° overnight, white crystals of VII precipitating during this time. The product was washed with water and recrystallized from ethanol. The white granular solid shrinks at 131–135°, and melts at 222–223° (dec.).

Since a mixture of VII and VIII melts at 222–223° (dec.), which is the melting point of VIII alone, it is apparent that decarboxylation occurs in the range in which shrinkage of VII is observed.

Anal. Calcd. for $C_{13}H_{13}N_3O_5 \cdot H_2O$: C, 50.45; H, 4.89; N, 13.59. Found: C, 50.49; H, 5.15; N, 13.63.

α-Amino-β-(3-indazole)-propionic Acid (IX).—In a Wood's metal bath heated to 150–170° was placed a 50-ml. erlenmeyer flask containing 2.6 g. of the dry malonic acid VII. A gentle stream of dry nitrogen was passed into the flask and the heating was continued for one hour. The yellowish powdery product was dissolved in ethanol and treated with Darco. The alcohol solution was concentrated to one-third its initial volume, mixed with an equal volume of water, and allowed to stand overnight at 5°. The large yellow crystals which were deposited were mixed with 5.5 g. of barium hydroxide octahydrate in 20 ml. of water and boiled under reflux for 24 hours in an atmosphere free of carbon dioxide. At the end of this period 100 ml. of boiling water was added to the reaction mixture and while the solution was maintained at the boiling point, 1 *M* sulfuric acid was added until the *p*H, as indicated by Nitrazine paper,[18] was 4.5–5.0. The precipitate of barium sulfate was removed by filtration. The filtrate was concentrated under reduced pressure to *ca.* 15 ml., whereupon a white solid separated. This was removed by filtration, treated with Darco and recrystallized thrice from water, yielding 1.4 g. of white needles of IX (yield 74% from VII). The pure amino acid darkens at 239° and melts at 249–250° (dec.). The compound gives a positive ninhydrin test.

Anal. Calcd. for $C_{10}H_{11}N_3O_2$: C, 58.51; H, 5.40; N, 20.58; α-amino-nitrogen,[19] 6.8. Found: C, 58.77; H, 5.52; N, 20.75; α-amino-nitrogen, 6.7, 6.8.

The malonic acid also decarboxylated when dissolved in water and heated at the reflux temperature for four hours. During this period the less soluble VIII precipitated. In one such experiment VIII was isolated and recrystallized twice from 20% ethanol, giving fine white needles, m.p. 222–223°.

Anal. Calcd. for $C_{12}H_{13}N_3O_3$: C, 58.29; H, 5.30; N, 17.00. Found: C, 58.20; H, 5.50; N, 16.89.

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[18] Nitrazine Paper, sold by E. R. Squibb and Sons, New York, indicates hydrogen ion concentration in the range *p*H 4 to 8.

[19] The authors are indebted to Mrs. June Hearn for carrying out the ninhydrin analysis for α-amino-nitrogen.

URBANA, ILLINOIS RECEIVED NOVEMBER 3, 1951

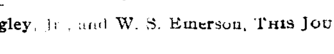
[CONTRIBUTION FROM THE CENTRAL RESEARCH DEPARTMENT, MONSANTO CHEMICAL COMPANY]

Some Reactions of 2-Alkoxy-3,4-dihydro-2H-pyrans

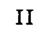
BY RAYMOND I. LONGLEY, JR., WILLIAM S. EMERSON AND THEODORE C. SHAFER

2-Alkoxy-3,4-dihydro-2H-pyrans have been hydrogenated to 2-alkoxytetrahydropyrans and hydrogenolyzed to 5-alkoxypentanols. The dihydropyrans have been converted to 1,5-pentanediols by hydrolysis and hydrogenation in both two- and one-step operations. The diols have been dehydrogenated to δ-lactones by both liquid and vapor phase procedures. The δ-lactones also have been prepared by treating the corresponding dialdehydes with aqueous alkali. Treatment of the δ-lactones with ammonia has yielded piperidones, which in turn have been alkylated and vinylated.

The selective hydrogenation of the now readily available 2-alkoxy-3,4-dihydro-2H-pyrans[1] offers a variety of synthetic possibilities. At 125° in the presence of Raney nickel, hydrogenation of 2-ethoxy-3,4-dihydro-2H-pyran and of 2-methoxy-3,4-dihydro-2H-pyran yielded 77 and 92%, respectively, of the corresponding 2-alkoxytetrahydropyrans. At 250–255° in the presence of copper chromite some hydrogenolysis occurred. Thus 2-ethoxy-3,4-dihydro-2H-pyran yielded, besides 39% of 2-ethoxytetrahydropyran, 13% of 5-ethoxypentanol. 2-*n*-Butoxy-3,4-dihydro-2H-pyran yielded tetrahydropyran (I), 22% of 2-*n*-butoxytetrahydropyran (II) and 19% of 5-*n*-butoxypentanol (III). This type of hydrogenolysis has been




I



II

$CH_3(CH_2)_3O(CH_2)_5OH$

III

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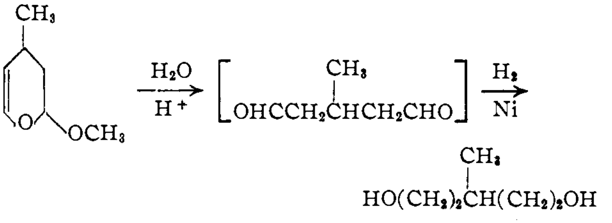
[1] R. I. Longley, Jr., and W. S. Emerson, THIS JOURNAL, **72**, 3079 (1950).

observed previously in the case of other acetals.[2]

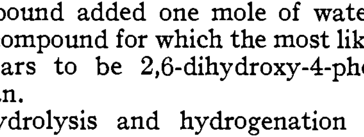
Hydrolysis of the 2-alkoxy-3,4-dihydro-2H-pyrans with dilute aqueous acid followed by neutralization with sodium bicarbonate and hydrogenation in the presence of Raney nickel gave good yields of the corresponding pentanediols. In the case of 3-methyl-1,5-pentanediol the yield was 91% and in the case of 3-furyl-1,5-pentanediol, 58%.



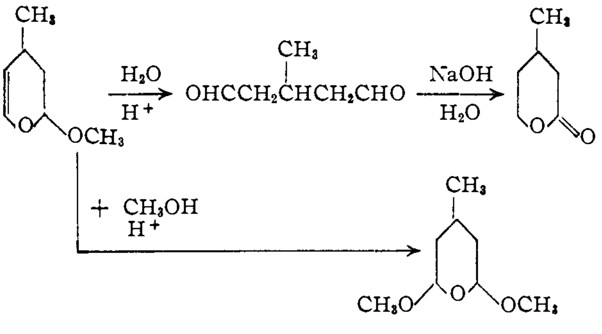
Hydrolysis of 2-ethoxy-4-phenyl-3,4-dihydro-2H-pyran yielded 41% of 3-phenylglutaraldehyde. This compound added one mole of water to give 66% of a compound for which the most likely structure appears to be 2,6-dihydroxy-4-phenyltetrahydropyran.

This hydrolysis and hydrogenation could be effected in one step by conducting the reaction in the presence of water and copper chromite at 180–260°. In this way 2-methoxy-4-methyl-3,4-dihydro-2H-pyran, 2-methoxy-3,4-dihydro-2H-pyran and 2-methoxy-3-ethyl-3,4-dihydro-2H-pyran yielded 75–90% of the corresponding diols. In the presence of nickel on kieselguhr the yield of 3-methyl-1,5-pentanediol fell to 70%. 1,5-Pentanediol has been prepared from dihydropyran by a similar procedure[3] and recently from 2-methoxy-3,4-dihydro-2H-pyran using Raney nickel.[4]

From one hydrogenation of 2-methoxy-4-methyl-3,4-dihydro-2H-pyran some β-methyl-δ-valerolactone was isolated as a by-product. The yield of lactone was raised to 52% by omitting the hydrogen. This lactone was prepared in 90% yield by passing 3-methyl-1,5-pentanediol vapors over a copper-on-pumice catalyst and in 95% yield by heating the glycol in the liquid phase with copper chromite.[5] β-Methyl-δ-valerolactone, δ-valerolactone and β-phenyl-δ-valerolactone were obtained in 47–54% yields by treating the corresponding dialdehydes with aqueous alkali.[6] A small amount of what probably was the corresponding dialkoxytetrahydropyran always appeared as a by-product of the hydrolysis step.



Treatment of δ-valerolactone and β-methyl-δ-valerolactone with ammonia gave 50% conversion (79% yield) to 2-piperidone and 69% conversion (91% yield) to 4-methyl-2-piperidone, respectively.



β-Methyl-δ-valerolactone reacted with 4-(2-aminoethyl)-morpholine to give 60% of 1-[2-(morpholino)-ethyl]-4-methyl-2-piperidone.

Treatment of 2-methyl-2-piperidone with sodium hydride in xylene followed by methallyl bromide yielded 30% of 1-methallyl-4-methyl-2-piperidone. Both 2-piperidone and 4-methyl-2-piperidone were vinylated[7] by treatment with acetylene in the presence of potassium. 1-Vinyl-2-piperidone was obtained in 43% conversion and 67% yield and 4-methyl-1-vinyl-2-piperidone in 33% conversion and 43% yield.

The authors are grateful to Dr. Gail H. Birum for assistance in one or two of the preparations.

Experimental

2-Ethoxytetrahydropyran.—A rocking autoclave was charged with 150 g. of 2-ethoxy-3,4-dihydro-2H-pyran and 13 g. of Raney nickel. The bomb was heated to 70°, filled with hydrogen to 1200 lb./sq. in. and shaken at 125° for one hour. After the catalyst had been filtered from the mixture, the product was distilled. It was collected in two fractions: I, 99 g., b.p. 138–143° (146°),[8] $n^{25}\mathrm{D}$ 1.4220–1.4230 ($n^{25}\mathrm{D}$ 1.4248)[8] and II, 18 g., b.p. 40–41° (14 mm.), $n^{25}\mathrm{D}$ 1.4230. The total yield was 117 g. (77%). An analytical sample boiled at 136°, $n^{25}\mathrm{D}$ 1.4238.

Anal.[9] Calcd. for $C_7H_{14}O_2$: C, 64.6; H, 10.8. Found: C, 64.7; H, 10.9.

2-Methoxytetrahydropyran was prepared similarly by the hydrogenation of 797 g. of 2-methoxy-3,4-dihydro-2H-pyran in the presence of 13 g. of Raney nickel. The total yield was 748 g. (92%), b.p. 123–126° (125°),[8] $n^{25}\mathrm{D}$ 1.4223–1.4227 (1.4260).[8]

Anal. Calcd. for $C_6H_{12}O_2$: C, 62.0; H, 10.4. Found: C, 62.2; H, 10.6.

5-Ethoxypentanol.—A rocking autoclave containing 160 g. of 2-ethoxy-3,4-dihydro-2H-pyran and 11 g. of copper chromite was charged with hydrogen to a pressure of 1000 lb./sq. in. and heated rapidly to 200°. The temperature was raised slowly to 250° at 1600 lb./sq. in. and held there for four hours. Distillation of the filtered reaction mixture yielded 33 g. of ethanol and tetrahydropyran, b.p. 74–77°; 63 g. (39%) of crude 2-ethoxytetrahydropyran, b.p. 77° (760 mm.)-50° (20 mm.), $n^{25}\mathrm{D}$ 1.4212; 4 g. of intermediate; and 21 g. (13%) of 5-ethoxypentanol, b.p. 94–97° (14 mm.) (88–91° (9 mm.)),[10] $n^{25}\mathrm{D}$ 1.4277 ($n^{20}\mathrm{D}$ 1.4291).[10]

An analytical sample boiled at 98° (14–15 mm.), $n^{25}\mathrm{D}$ 1.4288.

Anal. Calcd. for $C_7H_{16}O_2$: C, 63.6; H, 12.2. Found: C, 63.5; H, 12.1.

5-*n*-Butoxypentanol was prepared similarly by the hydrogenation of 140 g. of 2-*n*-butoxy-3,4-dihydro-2H-pyran in

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[2] L. W. Covert, R. Connor and H. Adkins, *ibid.*, **54**, 1651 (1932); M. Cabanac, *Compt. rend.*, **188**, 1257 (1929).

[3] J. G. M. Bremner, F. Starkey and Imperial Chemical Industries Ltd., U. S. Patent 2,440,929; *C. A.*, **42**, 5466 (1948).

[4] C. W. Smith, U. S. Patent 2,546,019.

[5] L. P. Kyrides and F. B. Zienty, THIS JOURNAL, **68**, 1385 (1946).

[6] H. Meerwein, *Ber.*, **53**, 1829 (1920).

[7] J. W. Copenhaver and M. H. Bigelow, "Acetylene and Carbon Monoxide Chemistry," Reinhold Publishing Corp., New York, N. Y., 1949, p. 66.

[8] G. F. Woods and D. N. Kramer, THIS JOURNAL, **69**, 2246 (1947).

[9] Analyses by Mr. P. J. Adams, Mr. Donald Soltz and Mrs. Helen LeMay of this Laboratory and the Micro-Tech Laboratories, 8000 Lincoln Ave., Skokie, Illinois.

[10] M. H. Palomaa and R. Jansson, *Ber.*, **64**, 1606 (1931).

the presence of 6 g. of copper chromite. The mixture was heated rapidly to 255° at 1700 lb./sq. in. and held there for three hours. The product comprised 19 g. of crude tetrahydropyran, b.p. 80–100°; 22 g. of crude butanol, b.p. 100° (760 mm.)–35° (12 mm.); 19 g. of intermediate; 31 g. (22%) of 2-*n*-butoxytetrahydropyran, b.p. 70–72° (12 mm.), $n^{26}\mathrm{D}$ 1.4294; 6 g. of intermediate; and 27 g. (19%) of 5-*n*-butoxypentanol, b.p. 115–118° (12 mm.) (90–94° (2 mm.)),[11] $n^{25}\mathrm{D}$ 1.4334 ($n^{25}\mathrm{D}$ 1.4334).[11] An analytical sample boiled at 108° (9–10 mm.), $n^{25}\mathrm{D}$ 1.4342.

Anal. Calcd. for $C_9H_{20}O_2$: C, 67.5; H, 12.6. Found: C, 67.3; H, 12.5.

3-Methyl-1,5-pentanediol.—A mixture of 425 g. of 2-methoxy-4-methyl-3,4-dihydro-2H-pyran, 800 cc. of water and 30 cc. of concentrated hydrochloric acid was stirred at 24–42° for two hours, when it became homogeneous. After the addition of enough sodium bicarbonate to neutralize the acid, the mixture weighed 1275 g. A 1004-g. portion was charged to a rocking autoclave with 39 g. of Raney nickel and shaken with hydrogen (1625 lb./sq. in. initial pressure) at 125° for four hours. The mixture was filtered and distilled to yield 281 g. (91%) of 3-methyl-1,5-pentanediol, b.p. 139–146° (17 mm.) (134–137° (6 mm.)),[12] $n^{25}\mathrm{D}$ 1.4518–1.4512 ($n^{25}\mathrm{D}$ 1.4512).[12]

3-Furyl-1,5-pentanediol was prepared in the same way as 3-methyl-1,5-pentanediol. The hydrolysis of 100 g. of 2-ethoxy-4-furyl-3,4-dihydro-2H-pyran was effected at 50° in the presence of 200 cc. of methanol, 50 cc. of water and 5 cc. of concentrated hydrochloric acid. After neutralization with 6 g. of sodium bicarbonate, the mixture was hydrogenated at 140–160° and 600–1700 lb./sq. in. for 2.5 hours in the presence of 24 g. of Raney nickel. The product (53 g., 58%) distilled at 167° (5 mm.)–147° (1 mm.), $n^{25}\mathrm{D}$ 1.4842–1.4847. A middle cut of pure 3-furyl-1,5-pentanediol, b.p. 173° (5 mm.), $n^{25}\mathrm{D}$ 1.4843, d^{25}_{25} 1.088 was analyzed.

Anal. Calcd for $C_9H_{14}O_3$: C, 62.1; H, 10.3. Found: C, 61.8; H, 10.4.

3-Phenylglutaraldehyde.—A mixture of 102 g. of 2-ethoxy-4-phenyl-3,4-dihydro-2H-pyran, 300 cc. of dioxane, 45 cc. of water and 10 cc. of concentrated hydrochloric acid was heated to 60° when it became homogeneous. After standing one hour at 60–45°, 11 g. of sodium bicarbonate was added and the lower layer was separated. Distillation of the upper layer yielded 31 g. (41%) of 3-phenylglutaraldehyde, b.p. 140–143° (0.6 mm.), $n^{25}\mathrm{D}$ 1.5484–1.5481. An analytical sample boiled at 140–142° (0.6 mm.), $n^{25}\mathrm{D}$ 1.5484.

Anal. Calcd. for $C_{11}H_{12}O_2$: C, 75.0; H, 6.8. Found: C, 74.8; H, 6.9.

2,6-Dihydroxy-4-phenyltetrahydropyran.—A mixture of 9 g. of 3-phenylglutaraldehyde and 1 g. of water was allowed to stand for several days. The resulting white solid was washed with ether and dried *in vacuo* to give 6.5 g. (66%) of 2,6-dihydroxy-4-phenyltetrahydropyran, m.p. 96.0–98.5°. An analytical sample was crystallized from benzene, m.p. 102–104°.

Anal. Calcd. for $C_{11}H_{14}O_3$: C, 68.1; H, 7.2. Found: C, 68.1; H, 7.3.

3-Methyl-1,5-pentanediol.—A mixture of 325 g. of 2-methoxy-4-methyl-3,4-dihydro-2H-pyran, 100 cc. of water and 40 g. of copper chromite was shaken in a rocking autoclave at 180° and 2800 lb./sq. in. for 7 hours. The mixture was filtered and the filtrate distilled to give 268 g. (90%) of 3-methyl-1,5-pentanediol, b.p. 103° (5 mm.) –106° (1.5 mm.), $n^{25}\mathrm{D}$ 1.4515.

The above experiment was repeated at 1500 to 2250 lb./sq. in. with four hours' heating at 180° and 45 minutes at 210°. Distillation yielded after a 10-g. forerun, 29 g. (10%) of β-methyl-δ-valerolactone, b.p. 72° (2 mm.), $n^{25}\mathrm{D}$ 1.4496 (*Anal.* Calcd. for $C_6H_{10}O_2$: C, 63.1; H, 8.8. Found: C, 63.1; H, 8.4) 10 g. of intermediate; and then 113 g. (38%) of 3-methyl-1,5-pentanediol, b.p. 106° (2 mm.).

The hydrogenation of 350 g. of 2-methoxy-4-methyl-3,4-dihydro-2H-pyran was repeated in the presence of 100 cc. of water and 40 g. of nickel on kieselguhr catalyst. Heating was for six hours at 160–235° and 1200–2000 lb./sq. in. After a 17-g. forerun there was obtained 229 g. (70%) of 3-methyl-1,5-pentanediol, b.p. 109.5° (3 mm.), $n^{25}\mathrm{D}$ 1.4525.

3-Methyl-1,5-pentanediol Dibenzoate.—A mixture of 130 g. of benzoic acid, 59 g. of 3-methyl-1,5-pentanediol and 45 cc. of benzene was boiled under reflux (pot temperature 230°) for 17 hours, while the evolved water was collected as formed in a Dean and Stark trap. After the mixture had cooled, it was diluted with hexane and washed with a solution of 10 g. of sodium hydroxide in 60 cc. of water. Distillation of the organic portion yielded 137 g. (84%) of 3-methyl-1,5-pentanediol dibenzoate, b.p. 174° (0.1 mm.), $n^{25}\mathrm{D}$ 1.5371, d^{25}_{25} 1.110.

Anal. Calcd. for $C_{20}H_{22}O_4$: C, 73.6; H, 6.7. Found: C, 73.9; H, 6.7.

1,5-Pentanediol was prepared in the same way as 3-methyl-1,5-pentanediol by the hydrogenation of 325 g. of 2-methoxy-3,4-dihydro-2H-pyran in the presence of 100 cc. of water and 40 g. of copper chromite for 7.5 hours at 165–180° and 1400–2250 lb./sq. in. Distillation yielded 257 g. (87%), b.p. 141° (19 mm.)–144° (20 mm.) (145–147° (17 mm.)),[13] $n^{25}\mathrm{D}$ 1.4462–1.4482 ($n^{20}\mathrm{D}$ 1.4499).[14]

2-Methoxy-3-ethyl-3,4-dihydro-2H-pyran[1] was prepared by heating 60 g. of acrolein and 100 g. of 1-butenyl methyl ether at 160° for 16 hours. The yield was 105 g. (74%), b.p. 50–51° (13 mm.), $n^{25}\mathrm{D}$ 1.4424–1.4419. A middle cut was analyzed, b.p. 51° (13 mm.), $n^{25}\mathrm{D}$ 1.4420, d^{25}_{25} 0.962.

Anal. Calcd. for $C_8H_{14}O_2$: C, 67.6; H, 9.9. Found: C, 67.5; H, 9.8.

2-Ethyl-1,5-pentanediol was prepared similarly by hydrogenating 102 g. of 2-methoxy-3-ethyl-3,4-dihydro-2H-pyran in the presence of 12 g. of copper chromite and 25 cc. of water for two hours at 240–260° and 2600–4000 lb./sq. in. After the catalyst had been separated by filtration, the filtrate was distilled to yield 71 g. (75%) of 2-ethyl-1,5-pentanediol, b.p. 143–146° (11 mm.) (140–142° (11 mm.)),[15] $n^{25}\mathrm{D}$ 1.4567, d^{25}_{25} 0.967.

Anal. Calcd. for $C_7H_{16}O_2$: C, 63.7; H, 12.1. Found: C, 63.7; H, 11.8.

β-Methyl-δ-valerolactone from 2-Methoxy-4-methyl-3,4-dihydro-2H-pyran.—A mixture of 353 g. of 2-methoxy-4-methyl-3,4-dihydro-2H-pyran, 100 cc. of water and 30 g. of copper chromite was shaken in a rocking autoclave at 200° for five hours. The mixture was filtered and the filtrate distilled to give after a 35.5-g. forerun, 163.5 g. (52%) of β-methyl-δ-valerolactone, b.p. 107° (14 mm.), $n^{25}\mathrm{D}$ 1.4493–1.4496.

From 3-Methyl-1,5-pentanediol in the Vapor Phase.—A Pyrex tube was packed with pumice impregnated with basic copper carbonate.[16] While the tube was held at 100°, a slow stream of nitrogen was passed through it for 12 hours. The temperature was raised to 200° and hydrogen was passed through for 24 hours. While the hydrogen stream was continued at 240°, 150 g. of 3-methyl-1,5-pentanediol was dropped in over a three-hour period. Distillation of the material in the receiver yielded 130 g. (90%) of β-methyl-δ-valerolactone, b.p. 107° (14 mm.), $n^{25}\mathrm{D}$ 1.4495–1.4498, d^{25}_{25} 1.044.

From 3-Methyl-1,5-pentanediol in the Liquid Phase.—A mixture of 197 g. of 3-methyl-1,5-pentanediol and 10 g. of copper chromite was stirred at 190–205° for 90 minutes at which time the evolution of hydrogen had ceased. The mixture was distilled directly to yield 180 g. (95%) of β-methyl-δ-valerolactone, b.p. 110–111° (15 mm.), $n^{25}\mathrm{D}$ 1.4495.

From 3-Methylglutaraldehyde.—A mixture of 493 g. of 2-methoxy-4-methyl-3,4-dihydro-2H-pyran, 900 cc. of water and 30 cc. of concentrated hydrochloric acid was stirred for 70 minutes. After the aldehyde solution had cooled for one hour, a solution of 200 g. of sodium hydroxide in 800 cc. of water was added over a five-hour period at a temperature below 45°. Stirring was continued for another 1.5 hours. After standing overnight the mixture was extracted with three 150-cc. portions of ether. Distillation of the combined extracts yielded 42 g. (7%) of an oil which probably is 2,6-dimethoxy-4-methyltetrahydropyran, b.p. 76–78° (20 mm.), $n^{25}\mathrm{D}$ 1.4252, d^{25}_{25} 0.983.

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[11] W. S. Emerson, G. F. Deebel and R. I. Longley, Jr., *J. Org. Chem.*, **14**, 696 (1949).

[12] B. Wojcik and H. Adkins, THIS JOURNAL, **55**, 4939 (1933).

[13] A. Franke, F. Lieben and S. Glaubach, *Monatsh.*, **43**, 225 (1922).

[14] W. E. Kaufmann and R. Adams, THIS JOURNAL, **45**, 3029 (1923).

[15] J. v. Braun, L. Mannes and M. Reuter, *Ber.*, **66**, 1499 (1933).

[16] J. W. Copenhaver and M. H. Bigelow, "Acetylene and Carbon Monoxide Chemistry," Reinhold Publishing Corp., New York, 1949, p. 152.

Anal. Calcd. for $C_8H_{16}O_3$: C, 60.0; H, 10.0. Found: C, 59.9; H, 9.7.

The aqueous portion of the reaction mixture was acidified with 420 cc. of concentrated hydrochloric acid, saturated with sodium chloride and extracted with three 200-cc. portions of ether. Distillation yielded 232 g. (47%) of β-methyl-δ-valerolactone, b.p. 116–117° (20 mm.).

δ-Valerolactone.—A mixture of 400 g. of 2-methoxy-3,4-dihydro-2H-pyran, 600 cc. of water and 20 cc. of concentrated hydrochloric acid was stirred for one hour. The clear solution was added with stirring over a two-hour period to a solution of 187 g. of sodium hydroxide in 1500 cc. of water held at 25–35°. Stirring at this temperature was continued for 16 hours. Then the mixture was saturated with sodium chloride and extracted with ten 250-cc. portions of ether. Distillation of the combined extracts yielded 22 g. (4%) of an oil which probably is 2,6-dimethoxytetrahydropyran, b.p. 65–67° (21 mm.), n^{25}_{D} 1.4262, d^{25}_{25} 1.013.

Anal. Calcd. for $C_7H_{14}O_3$: C, 57.6; H, 9.6. Found: C, 57.6; H, 9.7.

A mixture of 1.5 g. of the 2,6-dimethoxytetrahydropyran and 3 cc. of 4% aqueous hydrochloric acid was heated to boiling, cooled, and saturated with sodium bicarbonate. While 3 g. of hydroxylamine hydrochloride was added gradually with stirring, the mixture was kept alkaline with sodium bicarbonate and then diluted with 5 cc. of water. The glutaraldoxime was separated by filtration and crystallized from water, m.p. 165–167° (171°).[17]

The aqueous layer from the original reaction was filtered free of excess salt and resin and then acidified with 400 cc. of concentrated hydrochloric acid. The mixture was extracted continuously with ether for 56 hours. Distillation of the extract yielded 190 g. (54%) of δ-valerolactone, b.p. 112–116° (22 mm.) (215–220°).[18] n^{25}_{D} 1.4546–1.4573 (n^{20}_{D} 1.4600).[18]

When the alkali was added to the glutaraldehyde solution, the product was largely polymeric.

β-Phenyl-δ-valerolactone.—While a solution of 13 g. of sodium hydroxide in 150 cc. of water was stirred at 25–35°, a solution of 57 g. of crude 3-phenylglutaraldehyde in 80 cc. of ether was added over a ten-minute period. The precipitate which first formed dissolved on further stirring. After one hour stirring the mixture was allowed to stand overnight. The aqueous layer was separated and acidified with 30 cc. of concentrated hydrochloric acid. The organic layer was separated and the aqueous portion extracted with 100 cc. of benzene. The extract and organic portion were combined and distilled to give, after a small forerun, 29 g. (51%) of β-phenyl-δ-valerolactone, b.p. 135° (0.4 mm.), n^{25}_{D} 1.5475, d^{25}_{25} 1.150.

Anal. Calcd. for $C_{11}H_{12}O_2$: C, 75.0; H, 6.8. Found: C, 74.7; H, 7.0.

Distillation of the ether layer from the original reaction mixture yielded 15 g. of an oil which probably is 2,6-diethoxy-4-phenyltetrahydropyran, b.p. 143–146° (1.0 mm.), n^{25}_{D} 1.4980, d^{25}_{25} 1.035. This product apparently was a contaminant of the 3-phenylglutaraldehyde with which it distilled.

Anal. Calcd. for $C_{15}H_{22}O_3$: C, 72.0; H, 8.8. Found: C, 72.2; H, 8.8.

2-Piperidone.—A 1300-cc. stainless-steel rocking autoclave was charged with 430 g. of δ-valerolactone and about 100 g. of liquid ammonia was added under hydrogen pressure from a 300-cc. autoclave. The mixture was heated and rocked at 230° for 15 hours, then cooled. Excess ammonia was vented and the product was poured into a distilling flask. The autoclave was rinsed with three 100-cc. portions of benzene. The combined solutions were distilled through a 2 × 120-cm. Vigreux column to obtain 106 g. (25%) of crude recovered lactone; 254 g. (59% conversion, 79% yield) of crude 2-piperidone, b.p. 147–150° (dec.) (23 mm.) (137° (14 mm.))[19]; about 15 g. of liquid, b.p. about 80° (10 mm.) and 47 g. of black, fluid residue.

4-Methyl-2-piperidone.—A 1300-cc. rocking autoclave was charged with 644 g. of β-methyl-δ-valerolactone and sealed. A 300-cc. autoclave was cooled in Dry Ice–acetone, charged with 130 g. of liquid ammonia, sealed and charged with hydrogen to 1200 lb./sq. in. pressure. The ammonia was then run into the larger autoclave. After rocking for 13 hours at 230° it was cooled and opened. The solid product melted on heating to 70° and ammonia was driven off. It was cooled to 45° and the product was poured out. On distillation with stirring through a 2 × 120-cm. Vigreux column there was obtained 5 g. of forerun; 153 g. (24%) of recovered crude lactone, b.p. 105–142° (13 mm.); 445 g. (69% conversion, 91% yield) of 4-methyl-2-piperidone, b.p. 143–145° (13 mm.) (rapid take-off) and 25 g. of residue. The melting point of the last part of the piperidone cut appeared to be lower. A sample recrystallized twice from hexane melted at 88–91°.

Anal. Calcd. for $C_6H_{11}NO$: C, 63.7; H, 9.7. Found: C, 63.8; H, 9.4.

1-[2-(4-Morpholino)-ethyl]-4-methyl-2-piperidone.—A mixture of 65 g. of 4-(2-aminoethyl)-morpholine, 60 g. of β-methyl-δ-valerolactone and 40 cc. of benzene was heated under reflux for 22 hours at 240° while 6.5 cc. of evolved water was collected in a Dean and Stark trap. The residue was distilled through a 2.5 × 40-cm. Vigreux column to separate 10 g. of forerun, b.p. 102–135° (12 mm.), n^{25}_{D} 1.4552; 71 g. (60%) of crude 1-[2-(4-morpholino)-ethyl]-4-methyl-2-piperidone, b.p. 144° (1 mm.)–120° (dec.) (0.25 mm.), and 23 g. of residue. A middle cut, b.p. 150–151° (1 mm.), n^{25}_{D} 1.4953, was analyzed.

Anal. Calcd. for $C_{12}H_{22}O_2N_2$: N, 12.4. Found: N, 12.4.

1-Methallyl-4-methyl-2-piperidone.—In a 1-l. flask swept with nitrogen, 26 g. of sodium hydride was stirred under 200 g. of dry xylene. A warm solution of 113 g. of 4-methyl-2-piperidone in 100 g. of xylene was added slowly at < 70°. After addition was complete the stirring was continued 30 minutes more at 60–70° to form a gel. The mixture was warmed to 90° and 135 g. of methallyl bromide was added slowly at 90–100°. The stirring was continued one hour at 90–100°, then the mixture was filtered by suction while warm, with evaporation of considerable xylene. On distillation through a 2.5 × 40-cm. Vigreux column there was obtained 20 g. of crude product, b.p. to 71° (0.2 mm.), n^{25}_{D} 1.4797 and 50 g. of pure 1-methallyl-4-methyl-2-piperidone, b.p. 80° (0.5 mm.), n^{25}_{D} 1.4834. The total yield was 70 g. (30%).

Anal. Calcd. for $C_{10}H_{17}ON$: N, 8.4. Found: N, 8.5.

1-Vinyl-2-piperidone.[7]—About 1 g. of potassium was dissolved in molten 2-piperidone in a nitrogen atmosphere and the solution was charged to an autoclave. After purging with nitrogen and with acetylene, more acetylene was added to 250 lb./sq. in. at 140° with shaking. Heat of reaction raised the temperature to 159°. Reaction was continued 2 hours at 255 lb./sq. in. and at 155°. A flash distillation left a residue of 20 g. of tar. The distillate was redistilled through a 2 × 120-cm. Vigreux column to separate 10 g. of forerun, b.p. 110–114° (15 mm.); 63 g. (43% conversion, 67% yield) of crude 1-vinyl-2-piperidone, b.p. 114–135° (15 mm.) and about 38 g. (33%) of recovered 2-piperidone. A sample was redistilled for analysis, b.p. 125–126° (25 mm.), m.p. 42–48° after one crystallization from hexane.

Anal. Calcd. for $C_7H_{11}ON$: N, 11.2. Found: N, 11.2.

4-Methyl-1-vinyl-2-piperidone.—In a nitrogen atmosphere about 1 g. of potassium was dissolved in 150 g. of molten 4-methyl-2-piperidone and the resulting solution was charged to a 300-cc. autoclave. After purging twice with hydrogen and three times with acetylene, more acetylene was added to 230 lb./sq.in. while rocking and heating to 150°. After 2 hours the reaction was stopped. At 30° the product was semi-solid. It was flash-distilled to separate much tar. The distillate was redistilled through a 2 × 120-cm. Vigreux column to obtain 4 g. of forerun; 59 g. (33% conversion, 43% yield) of brown product, b.p. 123° (18 mm.) to 135° (12 mm.); 64 g. (43%) of 4-methyl-2-piperidone and a small residue. On standing the brown color of the product faded. By redistillation there was isolated 49 g. of 4-methyl-1-vinyl-2-piperidone, b.p. 113–114° (12 mm.), n^{25}_{D} 1.5040, d^{24}_{25} 1.006.

Anal. Calcd. for $C_8H_{13}ON$: N, 10.1. Found: N, 10.0.

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[17] C. Harries, *Ber.*, **43**, 1194 (1910).

[18] C. S. Marvel and E. R. Birkhimer, THIS JOURNAL, **51**, 260 (1929).

[19] O. Wallach, *Ann.*, **312**, 171 (1900).