The filtrate upon concentration *in vacuo* yielded 0.46 g. of VI, m.p. >300°, silver nitrate test negative; $\lambda_{\max(\mu)}^{\text{Nujol}}$ 3.12, 3.25 (NH), 5.72, 5.44 (C═O of uracil), 9.00, 9.10 (C—O—C of ether).

Anal. Calcd. for $C_8H_{12}N_2O_4$: C, 48.0; H, 6.05; N, 14.0. Found: C, 47.7; H, 6.00; N, 14.0.

Reduction of 5-(chloromethyl)uracil (IV) *to thymine* (III). A suspension of 5.00 g. (0.03 mol.) of 5-(chloromethyl)uracil (IV), prepared by chloromethylation of uracil, in 150 ml. of concentrated hydrochloric acid was heated to 60°. The reaction mixture was kept at 60° and 35.0 g. of tin was added over a period of 20 min. with stirring. After being stirred and heated for 3 hr., the reaction mixture was decanted to remove the excess tin. The solution was evaporated to one third its volume under reduced pressure on a water bath at 60°. The solution was diluted with 750 ml. of hot, distilled water and filtered. The filtrate was treated with hydrogen sulfide for 15 min., then heated for 30 min. at 80°, the mixture cooled to room temperature, and the tin sulfide removed by filtration. The filtrate yielded 3.49 g. of white crystals when concentrated *in vacuo*. This crude thymine was recrystallized from dilute aqueous ethanol to give 3.2 g. (82%) of thymine; $\lambda_{\max(\mu)}^{\text{Nujol}}$ 3.15 (NH), 5.68, 5.94 (C═O of uracil), 6.65, 7.00 (ring). The spectrum was identical with that of an authentic sample of thymine.

The compound had the following R_f values as compared with thymine: in benzene-methanol-water (2:1:6) on Schleicher and Schuell No. 2043B acetylated paper, R_f 0.64 (thymine, 0.64); in 1-butanol-water on Whatman No. 1 paper, R_f 0.45 (thymine, 0.45); in isopropanol-ammonium hydroxide-water (70:5:25), R_f 0.79 (thymine, 0.79); in isopropanol-2*N* hydrochloric acid (65:35), R_f 0.85 (thymine, 0.83).

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New Di- and Tetrahydropyran Derivatives

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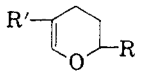
In connection with another study, certain di- and tetrahydropyran dibasic acids and amino acids were desired whose preparation is described below.

The dibasic acids were obtained through the addition of phosgene to the requisite 2,3-dihydro-4*H*-pyran derivative, followed by the elimination of the elements of hydrogen chloride, saponification of the acid chloride and, if desired, by hydrogenation. Alternatively, the acid chlorides were converted into amides which, on dehydration, yielded nitriles. An amino acid derivative was also prepared through the addition of *N*-substituted 2-aminoethanol to 5-carbethoxy-2,3-dihydro-4*H*-pyran.

It is known that when a mixture of 2,3-dihydro-4*H*-pyran and phosgene is allowed to react and the resulting addition product is subsequently heated under reduced pressure, hydrogen chloride is eliminated and 2,3-dihydro-4*H*-pyran-5-carbonyl chloride is formed.[2] By adapting this method, Ia was obtained in 42% yield. Attempts to add phosgene to 2-formyl-2,3-dihydro-4*H*-pyran failed to produce an acid chloride, the phosgene reacting instead with the formyl group. However, acid chloride Ig was obtained from compound Ii in which the aldehyde function was masked through formation of the acetal derivative. In the absence of interfering substituents, the addition of phosgene may be a general method for the introduction of a carbonyl chloride group into the dihydropyran nucleus.

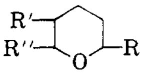
With Raney nickel catalyst, dihydropyran derivatives show a wide variation of susceptibility to hydrogenation, ranging from ready reactions at room temperature[3] to slow hydrogenations at elevated temperatures and pressures.[4,5] 2,5-Dicarbethoxy-2,3-dihydro-4*H*-pyran (Id) was difficult to reduce over Raney nickel at 150° and at 300 atm. pressure. However, over rhodium or palladium catalysts in glacial acetic acid, hydrogenation of Id could be effected with ease at room temperature and ordinary pressure.

Substituted 2,3-Dihydro-4*H*-pyran



Ia. R = $COOC_2H_5$, R′ = COCl; Ib. R = $COOC_2H_5$, R′ = COOH; Ic. R = R′ = COOH; Id. R = R′ = $COOC_2H_5$; Ie. R = $COOC_2H_5$, R′ = $CONH_2$; If. R = R′ = $CONH_2$; Ig. R = $CH(OC_2H_5)_2$, R′ = COCl; Ih. R = $CH(OC_2H_5)_2$, R′ = $COOC_2H_5$; Ii. R = $CH(OC_2H_5)_2$, R′ = H; Ik. R = $CONH_2$, R′ = H; Il. R = CN, R′ = H; Im. R = R′ = CN; In. R = $COOC_2H_5$, R′ = CN.

Substituted Tetrahydropyrans



IIa. R = R″ = H, R′ = $COOC_2H_5$; IIb. R = R″ = H, R′ = COOH; IIc. R = R′ = $COOC_2H_5$, R″ = H; IId. R = CHO, R′ = H, R″ = OC_2H_5; IIe. R = $OCH_2CH_2NHCOCH_3$, R′ = R″ = H; IIf. R = $OCH_2CH_2NHCOCH_3$, R′ = H, R″ = $COOC_2H_5$; IIg. R = $OCH_2CH_2NHCOC_6H_4NO_2$, R′ = R″ = H.

The replacement of the carbethoxy by a carboxamide group occurred easily when dihydropyran derivative Ia was treated with ammonium hydroxide at 0°. The carboxamides were converted to the nitriles by *p*-toluenesulfonyl chloride and

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(2) P. A. Hawkins and N. Bennett, British Patent **570,974.**

(3) M. Delépine and A. Horeau, *Bull. soc. chim. France*, (5) **5**, 339 (1938).

(4) J. G. M. Bremner and D. G. Jones, British Patent **612,314.**

(5) R. R. Whetstone and S. A. Ballard, *J. Am. Chem. Soc.*, **73**, 5280 (1951).

pyridine at 60 to 130°.[6] Several other methods[7] resulted either in the recovery of the starting material or in complete destruction of the molecule.

Owing to its basicity, 2-aminoethanol, not unexpectedly, failed to add to the double bond of dihydropyran under conditions similar to those usually employed for the addition of alcohols.[8] The *N*-acetyl and *N*-nitrobenzoyl derivatives of 2-aminoethanol underwent the desired addition reaction in the presence of catalytic amounts of hydrochloric acid, resulting in compounds IIe, IIf, and IIg, respectively.

EXPERIMENTAL[9]

2-Carbethoxy-2,3-dihydro-4H-pyran-5-carbonyl chloride (Ia). A mixture of 24 g. (0.154 mol.) of 2-carbethoxy-2,3-dihydro-4*H*-pyran[5] and 34 g. (0.342 mol.) of phosgene was maintained for 7 days at 40° in a sealed glass tube. Vacuum distillation of the mixture yielded 9.4 g. (39%) of the initial ester, contaminated with hydrogen chloride, followed by 14.1 g. (42% yield) of compound Ia, b.p. 155–156° (8 mm.). When the reaction was conducted at 15° most of the starting material was recovered unchanged. In the presence of BF_3 the only product obtained was a clear resin.

2-Carbethoxy-5-carboxy-2,3-dihydro-4H-pyran (Ib). Acid chloride Ia was hydrolyzed with water at 5° to give Ib, (m.p. 127–128° from water). Saponification with 10% NaOH under reflux for 1 hr. gave the dicarboxylic acid Ic, (m.p. 237° from water).

Anal. Calcd. for $C_9H_{12}O_5$ (Ib): C, 54.2; H, 6.0; OC_2H_5, 22.5. Found: C, 53.8; 54.3; H, 6.2, 6.3; OC_2H_5, 22.2, 22.2.

2,5-Dicarbethoxy-2,3-dihydro-4H-pyran (Id). Acid chloride Ia, (28 g., 0.128 mol.), was added at 5° with stirring to 50 ml. of ethanol. After 1 hr., 130 ml. of water was added and the diester was extracted with ether (82%, b.p. 161–163° [11 mm.]).

Anal. Calcd. for $C_{11}H_{16}O_5$: C, 58.1; H, 7.1; OC_2H_5, 39.4. Found: C, 58.0; H, 7.3; OC_2H_5, 38.8.

2-Carbethoxy-5-carboxamide-2,3-dihydro-4H-pyran (Ie). Acid chloride Ia, (22 g., 0.1 mol.), was slowly added with stirring at −20° to a mixture of 12 ml. (0.2 mol.) of conc. ammonium hydroxide and 110 ml. of benzene (65%, m.p. 150–151.5° [from water]).

Anal. Calcd. for $C_9H_{13}NO_4$: C, 54.8; H, 6.6; N, 7.1; OC_2H_5, 22.5. Found: C, 54.8; H, 6.7; N, 7.1; OC_2H_5, 22.1.

2,5-Dicarboxamide-2,3-dihydro-4H-pyran (If). Acid chloride Ia, (8 g., 0.037 mol.), was slowly added with stirring at ordinary temperature to a mixture of 12 ml. (0.2 mol.) of conc. ammonium hydroxide and 40 ml. of benzene (48%, m.p. 256–257° dec.).

Anal. Calcd. for $C_7H_{10}N_2O_3$: C, 49.3; H, 5.9; N, 16.4; OC_2H_5, 0.0. Found: C, 49.6, 49.1; H, 6.4, 6.1; N, 16.3, 16.4; OC_2H_5, 0.0, 0.0.

2-Diethoxymethylene-2,3-dihydro-4H-pyran (Ii). Using the method of Fischer and Baer,[10] 44.8 g. (0.4 mol.) of 2-formyl-2,3-dihydro-4*H*-pyran[11] was treated with 72 g. (0.48 mol.) of ethyl orthoformate, 15 ml. of ethanol and 1.5 g. of NH_4NO_3. The yield was 50%, b.p. 94° (12 mm.).

Anal. Calcd. for $C_{10}H_{18}O_3$: C, 64.8; H, 9.7; OC_2H_5, 48.3. Found: C, 64.2, 63.7; H, 10.3, 9.9; OC_2H_5, 49.1, 47.5.

Only 2-formyl-5-ethoxy-tetrahydropyran (IId) was obtained when a few drops of alcoholic HCl were added at −5° to a mixture of 2-formyl-2,3-dihydro-4*H*-pyran and ethanol. The yield was 40%, b.p. 85° (12.5 mm.).

Anal. Calcd. for $C_8H_{14}O_3$: C, 60.8; H, 8.9; OC_2H_5, 28.5. Found: C, 60.4; H, 9.1; OC_2H_5, 28.6.

2-Diethoxymethylene-2,3-dihydro-4H-pyran-5-carbonyl chloride (Ig). Phosgene, 10 g. (0.101 mol.), was condensed into 17 g. (0.092 mol.) of Ii and the mixture kept at ordinary temperature in a closed Erlenmeyer flask for 4 days. Vacuum distillation yielded 4 g. (22%) of unchanged acetal, 6 g. (24%) of acid chloride Ig, b.p. 164° (16 mm.), and 4 g. of resinous residue. When the reaction was run with 2-formyl-2,3-dihydro-4*H*-pyran, the only product was a clear resin.

2-Diethoxymethylene-5-carbethoxy-2,3-dihydro-4H-pyran (Ih). Acid chloride Ig, (3.9 g., 0.0157 mol.), was added with stirring to 7.5 ml. of ethanol. After 1 hr. water was added and the acetal-ester extracted with ether. Vacuum distillation of the ether extract gave Ih (88%, b.p. 162–165° [12 mm.]).

Anal. Calcd. for $C_{13}H_{21}O_5$: C, 60.5; H, 8.5; OC_2H_5, 52.3. Found: C, 60.4; H, 8.9; OC_2H_5, 53.3.

3-Carbethoxytetrahydropyran (IIa). (a) 2,3-Dihydro-4*H*-pyran-5-carboxylic acid,[2] (32 g., 0.250 mol.), in 100 ml. of ethanol was hydrogenated over 5 g. of Raney nickel for 10 hr. at 150° and 200 atm. IIa (18 g., b.p. 89–91° [13 mm.]) and saturated acid IIb (b.p. 142–145° [12 mm.], *p*-bromophenacyl ester, m.p. 98–99° [lit.[4] m.p. 96°]) were obtained.

Anal. Calcd. for $C_8H_{14}O_3$: C, 60.7; H, 8.9. Found: C, 60.8; H, 8.9. Calcd. for $C_6H_{10}O_3$: C, 55.3; H, 7.7. Found: C, 55.7; H, 7.9.

(b) Ester IIa was obtained in 25% yield when 32 g. of 5-carbethoxy-2,3-dihydro-4*H*-pyran[2] was hydrogenated over 4 g. of Raney nickel for 4 hr. at 110° and 150 atm.

2,5-Dicarbethoxytetrahydropyran (IIc). (a) Id, (20 g., 0.088 mol.), in 30 ml. of ethanol was hydrogenated over 3 g. of Raney nickel for 3 hr. at 150° and 300 atm. (82%, b.p. 158–158.5° [12 mm.]).

Anal. Calcd. for $C_{11}H_{18}O_5$: C, 57.4; H, 7.9; OC_2H_5, 39.1. Found: C, 56.4; H, 8.1; OC_2H_5, 38.3.

(b) Id, (5 g., 0.022 mol.) in 25 ml. of glacial acetic acid was hydrogenated at ordinary temperature and pressure over rhodium and palladium catalyst. With 3 g. of Rh catalyst (5% Rh on charcoal), the theoretical amount of hydrogen was taken up after 1 hr.; with 0.5 g. of Pd catalyst (10% Pd on asbestos), 48 hr. were required for complete hydrogen uptake. In both cases hydrogenation was considerably slowed in an ethanol medium. The saturated diester was saponified with 10% aqueous NaOH. The free acid, very water soluble, was isolated as the silver salt and as the *p*-bromophenacyl ester, m.p. 163–165°.

Anal. Calcd. for $C_{15}H_{15}BrO_6$ (monoester): C, 48.5; H, 4.1; Br, 21.53. Calcd. for $C_{23}H_{20}Br_2O_7$ (diester): C, 48.6; H, 3.5; Br, 28.2. Found: C, 48.5; 49.1; H, 3.9, 4.0; Br, 26.9.

2-Carboxamide-2,3-dihydro-4H-pyran (Ik). 2-Carbethoxy-2,3-dihydro-4*H*-pyran (76 g., 0.487 mol.), and 50 ml. of liquid ammonia were heated in an autoclave for 8 hr. at 150° under 50 atm. hydrogen (76%, m.p. 117° [from water and benzene]).

Anal. Calcd. for $C_6H_9NO_2$: C, 56.8; H, 7.1; N, 11.0. Found: C, 57.4; H, 7.4; N, 11.4.

2-Carbonitrile-2,3-dihydro-4H-pyran (Il). Amide Ik, (12.7 g., 0.1 mol.), pyridine, (18 ml., 0.22 mol.) and *p*-toluenesulfonyl chloride (19.1 g., 0.1 mol.) were heated to 60°. The homogeneous solution which formed solidified on cooling. The solid was pulverized and extracted with ether. Vacuum distillation of the ether extract gave the nitrile (40%, b.p. 99–101° [14 mm.]).

Anal. Calcd. for C_6H_7NO: C, 66.0; H, 6.4; N, 12.9. Found: C, 65.4; H, 6.6; N, 12.9.

2,5-Dicarbonitrile-2,3-dihydro-4H-pyran (Im). Diamide If, (3.2 g., 0.019 mol.), pyridine (10 ml., 0.124 mol.) and *p*-toluenesulfonyl chloride (10 g., 0.053 mol.) were heated to

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(7) D. T. Mowry, *Chem. Revs.*, **42,** 257 (1948).

(8) R. C. Elderfield, *Heterocyclic Compounds*, John Wiley and Sons, Inc., New York, 1950, Vol. 1, p. 344.

(9) All melting points are uncorrected.

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(11) K. Alder and E. Rüden, *Ber.*, **74,** 920 (1941).

130°. After cooling, the solid residue was crushed and extracted with ether, m.p. 46–48°.

Anal. Calcd. for $C_7H_6N_2O$: C, 62.7; H, 4.5; N, 20.9. Found: C, 62.1; H, 4.9; N, 20.6.

2-Carbethoxy-5-carbonitrile-2,3-dihydro-4H-pyran (In). Amide-ester Ie (5 g., 0.025 mol.), pyridine (6.3 ml., 0.078 mol.), and *p*-toluenesulfonyl chloride (4.71 g., 0.025 mol.) were heated to 80°, and treated further as under Im. On concentration of the ethereal extract 3 ml. of an oil was obtained.

Anal. Calcd. for $C_9H_{11}NO_3$: C, 60.0; H, 6.1; N, 7.8; OC_2H_5, 24.8. Found: C, 59.5; H, 6.1; N, 8.0; OC_2H_5, 24.7.

2-(2-Acetaminoethoxy)tetrahydropyran (IIe). Equimolecular quantities of 2-acetamino-ethanol[12] and 2,3-dihydro-4*H*-pyran[13] were heated with stirring in the presence of 3 drops of conc. HCl. When the mixture became homogeneous, the solution was cooled, neutralized with aqueous Na_2CO_3, extracted with ether and distilled, (b.p. 180–182° [12 mm.]).

Anal. Calcd. for $C_9H_{17}NO_3$: C, 57.8; H, 9.1; N, 7.5. Found: C, 57.8; H, 9.4; N, 7.4.

2-(2-Acetaminoethoxy)tetrahydro-6-carbethoxypyran (IIf). A mixture of 10.3 g. (0.1 mol.) of 2-acetaminoethanol,[12] 15.6 g. (0.1 mol.) of 2-carbethoxy-2,3-dihydro-4*H*-pyran,[5] and 3 drops of conc. HCl was heated with stirring until a homogeneous solution was formed. It was purified as above (31%), b.p. 150–170° (0.3 mm.).

Anal. Calcd. for $C_{12}H_{21}NO_5$: C, 55.6; H, 8.1; N, 5.4; OC_2H_5, 17.3. Found: C, 54.4; H, 8.0; N, 5.9; OC_2H_5, 18.0.

2-(2-p-Nitrobenzaminoethoxy)tetrahydropyran (IIg). A mixture of 4.5 ml. (0.05 mol.) of 2,3-dihydro-4*H*-pyran,[13] 10 g. (0.05 mol.) of 2-(*p*-nitrobenzamino)-ethanol,[14] 2 drops of conc. HCl and 50 ml. of xylene was heated on a water bath. After cooling, the crystals which formed were filtered, dried, and recrystallized from benzene and ethanol, m.p. 103–106°.

Anal. Calcd. for $C_{14}H_{18}N_2O_5$: C, 57.2; H, 6.1; N, 9.5. Found: C, 56.5; H, 6.4; N, 9.9.

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[12] G. F. D'Alelio and E. E. Reid, *J. Am. Chem. Soc.*, **59,** 111 (1937).

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