Reductive Ring Openings of Glutarimides and Barbiturates with Sodium Borohydride

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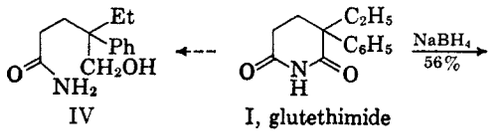
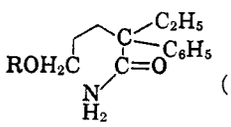
Facile hydrogenolytic ring opening of cyclic imides with sodium borohydride in aqueous solution at room temperature was observed with the central nervous system (CNS) depressant glutethimide (I), the barbiturate antagonist bemegride (V), and the teratogenic thalidomide (XIII). Glutethimide (I) gave the reduction product expected from hydrogenolysis at the nonhindered amide carbonyl, *via* ω-hydroxy-α-ethyl-α-phenylvaleramide (II). Bemegride (V) underwent slower hydrogenolysis to yield 40% of ω-hydroxy-β-methyl-β-ethylvaleramide (VI), 40% of β-methyl-β-ethyl-δ-valerolactone (VIII), and 20% of β-methyl-β-ethyl-1,5-amylene glycol (IX). Thalidomide (XIII) was hydrogenolyzed rapidly to 30% of a product formulated as ω-hydroxy-α-dihydrophthalimidovaleramide (XIV) and phthalide XVI (3%). While analogous reductive ring openings were observed with N-cyclohexyl- and N-ethylphthalimide, N-chloromethylphthalimide (XVII) yielded 3-hydroxyisoindolinones with N-CH_2OR substituents. Succinimide hydrogenolyzed somewhat more slowly to give δ-hydroxybutyramide. In the barbiturate group, barbital, which was hydrogenolyzed much less readily than the nonsymmetric N-methylated hexobarbital and prominal, yielded urea and 2,2-diethyl-1,3-propylene glycol. While hydantoin opened up to β-ureidoethanol, 5,5-diphenylhydantoin (dilantin) and the quinazoline-2,4-dione (XXXVI) were stable to reduction by $NaBH_4$. The conversion of cyclic imides into four types of compounds, carbinolamides, amido alcohols, γ- and δ-lactones, and glycols, is potentially useful for their diagnosis and selective modifications.

The facile reductive ring opening of 5,6-dihydro-2,4-dioxopyrimidines, *e.g.*, of dihydrouracil,[2] dihydrothymine,[3] dihydrothymidine,[3] and the photo dimer of thymine,[4] by sodium borohydride in aqueous solution prompted an investigation of the stability of other heterocyclic imides toward this reagent. While as a rule, amides are resistant to reduction by borohydride, which may occur only under special conditions, *e.g.*, in pyridine under reflux,[5] this paper describes reductive modifications and hydrogenolytic ring openings of a number of cyclic imides which were singled out because of their medicinal importance and because of pharmacological interest in their reduction products.

The CNS depressant α-ethyl-α-phenylglutarimide (glutethimide, I)[6] reacted with sodium borohydride in 50% aqueous methanol at room temperature to yield the neutral reduction product II which was characterized as the *p*-nitrobenzoate (III) (eq 1). The triplet



IV I, glutethimide



(1)

II, R = H (108°)
III, R = *p*-$NO_2C_6H_4CO$ (177°)

signals in the nmr spectra of II and III clearly indicate the partial structure $-CH_2-CH_2-OH$. The alternative structure IV would show the δ protons as singlet. Reductive ring cleavage, therefore, takes place almost exclusively at the less hindered amide carbonyl.[7] The nmr spectrum of the acetylation mixture from the crude reduction products suggests the presence of a small amount of the isomeric acetate IV by a characteristic singlet at 4.30 ppm. The isomeric amides II and IV did not separate by chromatography on silica gel.

When the barbiturate antagonist bemegride, β-methyl-β-ethylglutarimide (V), was treated with sodium borohydride under the same mild conditions as glutethimide (I), starting material was recovered quantitatively. Prolongation of the reaction time for 2 days decreased the recovery of starting material to 40%. After acetylation and column chromatography on silica gel three major products were obtained (eq 2). One product was ω-acetoxy-β-methyl-β-ethylvaleramide (VII). The nmr spectrum contains two methylenes coupled to each other as a pair of triplets (J = 7.5 cps) at 4.19 and at 1.74 ppm. The two triplets belong to the primary alcoho land its adjacent methylene: $HO-CH_2-CH_2C<$. The methylene between the amide carbonyl and the quaternary carbon shows up as a singlet at 2.15 ppm.

The second reduction product, a colorless oil which contained neither nitrogen nor acetyl, was identified as β-methyl-β-ethyl-δ-valerolactone VIII. This structure is supported by the mass spectrum fragmentation pattern. The formation of lactone VIII is due to hydrolysis of amide VII and is the result of a neighboring-group effect, as has been observed in related systems.[8] The δ-lactone fraction is contaminated by a trace amount of a Dragendorf-positive amine, presumably XII, which separates on thin layer chromatography.

The diacetate of the third major reduction product,

(1) Associate in the Visiting Program of the U. S. Public Health Service, 1966–1967; on leave of absence from Tohoku University, Sendai, Japan.

(2) P. Cerutti, Y. Kondo, and B. Witkop, *J. Am. Chem. Soc.*, in press.

(3) G. Ballé, P. Cerutti, and B. Witkop, *ibid.*, **88**, 3946 (1966); Y. Kondo and B. Witkop, *ibid.*, in press.

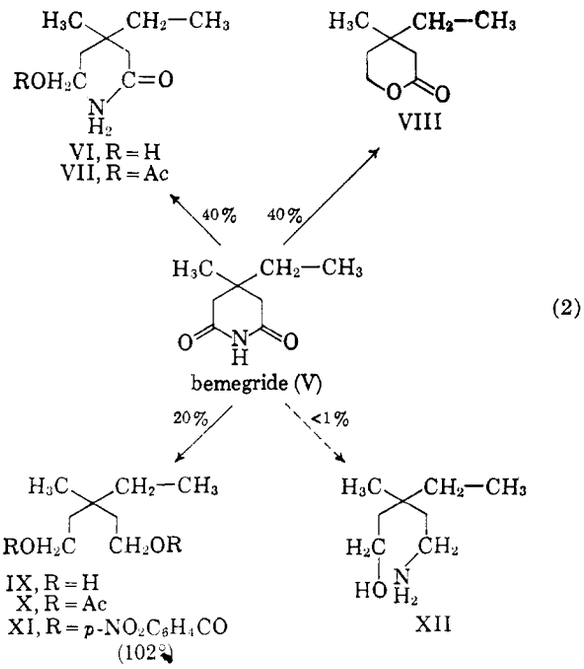
(4) T. Kunieda and B. Witkop, *ibid.*, **89**, 4232 (1967).

(5) S. Yamada, Y. Kikukawa, and S. Ikegami, *Chem. Pharm. Bull.* (Tokyo), **13**, 394 (1965); *cf.* E. Schenker, *Angew. Chem.*, **73**, 81 (1961).

(6) E. Tagmann, E. Sury, and K. Hoffmann, *Helv. Chim. Acta*, **35**, 1541 (1952). In addition, glutethimide and related compounds induce the synthesis of the enzyme δ-aminolevulinic acid synthetase [S. Granick, *J. Biol. Chem.*, **241**, 1359 (1965)], may cause porphyria [D. P. Tschudy, *J. Am. Med. Assoc.*, **191**, 718 (1965)], and inhibit bacterial growth [H. M. Raven and M. Stern, *Arzneimittel-Forsch.*, **16**, 96 (1966)]. The metabolism of ^{14}C-marked glutethimide in rats and dogs involves *oxidative dealkylation rather than hydrolytic or reductive ring opening* of the glutarimide ring: H. Keberle, K. Hoffmann, and K. Bernhard, *Experientia*, **18**, 105 (1962).

(7) *Cf.* H. C. Brown, E. J. Mead, and B. C. Subba Rao, *J. Am. Chem. Soc.*, **77**, 6209 (1955); K. Bowden and M. Hardy, *Tetrahedron*, **22**, 1169 (1966).

(8) (a) J. Brown, S. C. K. Su, and J. A. Shafor, *J. Am. Chem. Soc.*, **88**, 4468 (1966); (b) J. W. Faigle, H. Keberle, W. Riess, and K. Schmid, *Experientia*, **18**, 389 (1962).

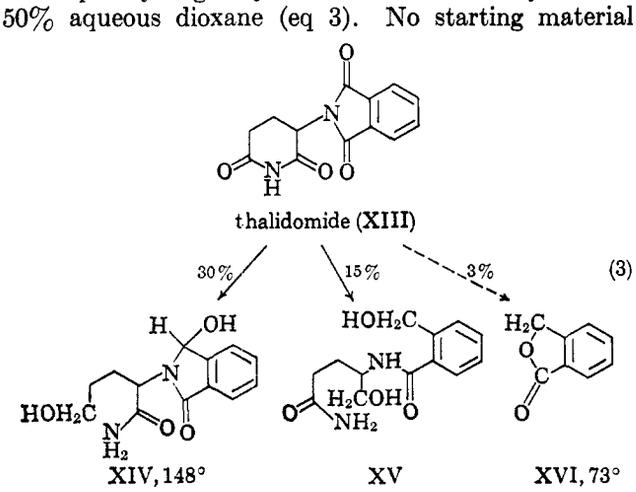


(2)

a colorless oil, was also nitrogen free. The structure of the symmetric O,O-diacetate X is supported by the nmr spectrum which showed a pair of triplets at 1.60 and 4.17 ppm (J = 7.5 cps) totaling eight protons in the characteristic arrangement $-O-CH_2-CH_2-$. The symmetric diacetate of 3-methyl-3-ethyl-1,5-amylene glycol (X), on saponification with alcoholic potash, gave the diol IX, which was converted into the crystalline bis-*p*-nitrobenzoate (XI). The nmr spectrum of XI showed that the $-O-CH_2-$ protons had shifted downfield owing to the paramagnetic shielding effect of the *p*-nitrobenzoyl groups.

The nmr signals of the ethyl groups of compounds V, VII, VIII, X, and XI, in all cases, had characteristic assignable peaks corresponding to the A_2B_3 system.[9]

The teratogenic and mutagenic drug thalidomide, *i.e.*, α-phthalimidoglutarimide (XIII), is of special interest in that it contains two doubly acylated nitrogens, one in a five-membered "aromatic" ring, the other in an aliphatic six-membered ring system. α-Phthalimidoglutarimide (XIII) underwent complete and rapid hydrogenolysis with sodium borohydride in 50% aqueous dioxane (eq 3). No starting material



(3)

was left after 2 hr. Column chromatography on silica gel furnished three reduction products. The substance to be eluted first formed colorless crystals, mp 73° (3% yield), and was identified as phthalide (XVI). The ultraviolet and nmr spectra agree with the published data.[10,11]

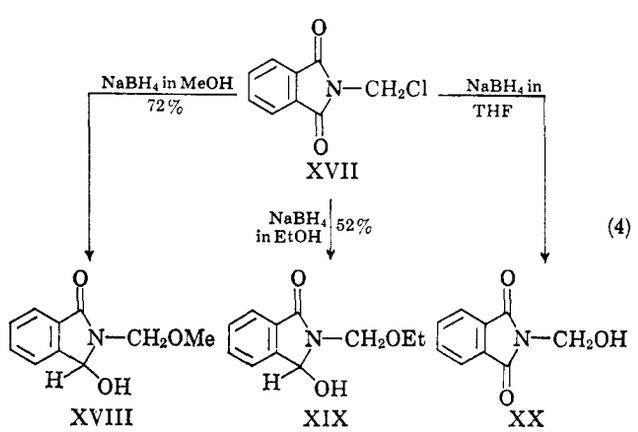
The second reduction product, whose nmr spectrum contained a two-proton triplet at 3.19 and at 5.60 ppm for the C_3 proton of 3-hydroxy-1-isoindolinone, is tentatively formulated as XIV.

The third reduction product was a viscous unstable oil whose nmr spectrum indicated the partial structure $HO-CH_2-CH<$. Two benzylic protons show up as a doublet at 3.65 (J = 5 cps) and at 4.70 ppm, respectively. The structure of δ-hydroxy-γ-(2-hydroxymethylbenzamido)valeramide (XV) is tentatively assigned to this reduction product.

The instability of this polyfunctional product is probably due to the possibility of multiple interaction which permits various kinds of ring-chain tautomerism.[12]

The major urinary metabolites of thalidomide are hydrolysis and not hydrogenolysis products, *viz.*, N-(*o*-carboxybenzoyl)glutamic acid imide, N-phthalylglutamine, and N-phthalylglutamic acid.[8b]

The reductive ring opening of N-substituted phthalimides,[13] in the same way, leads to 3-hydroxy-1-isoindolinones, *o*-hydroxymethyl-N-alkylamides, and to phthalide. On reexamination of the reduction of phthalimide we even noticed the formation of phthalyl alcohol, mp 64°, albeit in a yield of less than 1.0%. Reductive ring opening of phthalimides may depend on the nature of the N-substituent: N-chloromethylphthalimide (XVII) gave N-methoxymethyl- (XVIII) or N-ethoxymethyl-3-hydroxy-1-isoindolones (XIX) on reduction with $NaBH_4$ in methanol and ethanol, respectively, while in anhydrous tetrahydrofuran only N-hydroxymethylphthalimide (XX) was formed[14] (eq 4). N-Cyclohexyl- and N-ethylphthalimides, two



(4)

examples so far not reported in the literature, gave the expected reduction products (eq 5 and 6).

(9) B. R. McGarvey and G. Slomp, Jr., *J. Chem. Phys.*, **30**, 1536 (1959).

(10) High Resolution NMR Spectra Catalog, Vol. 2, Varian Associates, Palo Alto, Calif., Spectrum No. 496.

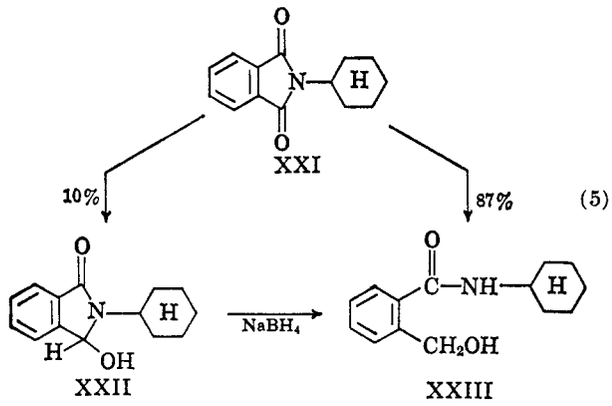
(11) W. A. Schroeder, P. E. Wilcox, K. N. Trueblood, and A. O. Dekker, *Anal. Chem.*, **23**, 1740 (1951).

(12) *Cf.* α-hydroxyphenylbutazone [E. Girod, A. Delley, and F. Häfliger, *Helv. Chim. Acta*, **40**, 408 (1957)] and 1-oxo-3-hydroxyisoindolines [W. Graf, E. Girod, E. Schmid, and W. G. Stoll, *ibid.*, **42**, 1085 (1959)].

(13) Z. Horii, C. Iwata, and Y. Tamura, *J. Org. Chem.*, **26**, 2273 (1961); F. C. Uhle, *ibid.*, **26**, 2998 (1961).

(14) It is noteworthy that borohydride in aqueous or alcoholic systems at room temperature, or even under ice cooling, is a more effective reducing agent than in refluxing anhydrous solvents.[15]

(15) H. Seki, K. Koga, H. Matsuo, S. Ohki, I. Matsuo, and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **13**, 995 (1965)].



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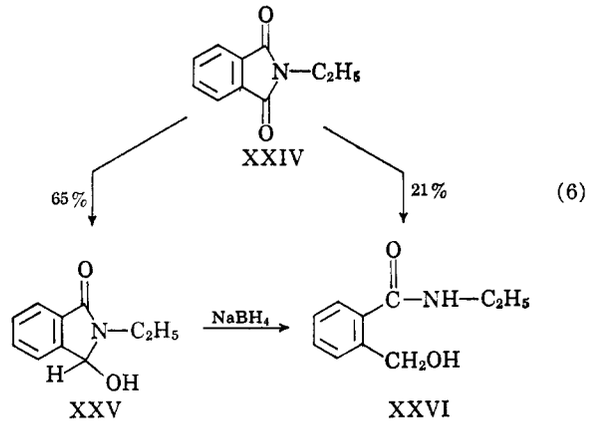
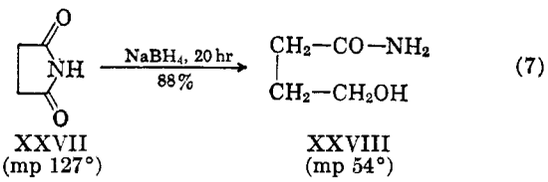


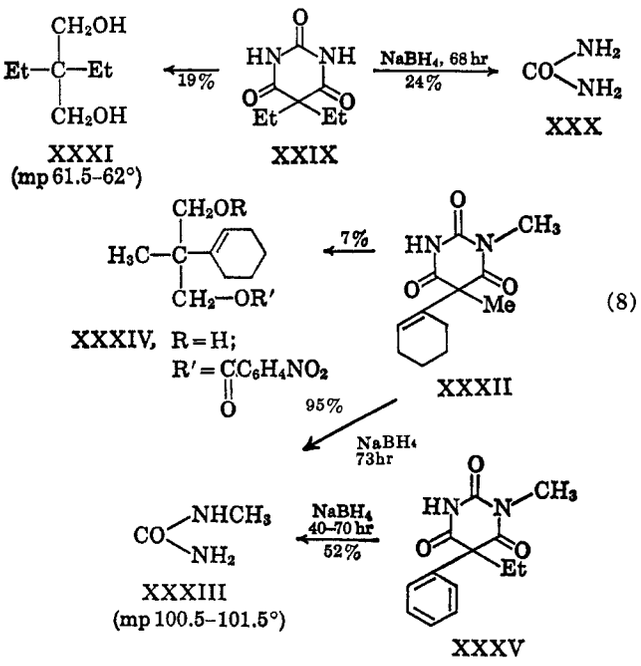
(6)

In the same way as in thalidomide, succinimide itself was opened with sodium borohydride in the course of 20 hr to yield 87.6% of γ-hydroxybutyramide (eq 7).



(7)

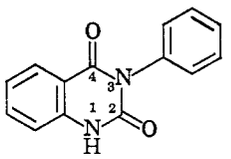
The symmetric molecule of barbital (XXIX) was more resistant to hydrogenolysis than two other N-substituted barbiturates, hexobarbital (XXXII) and



(8)

prominal (XXXV). The novel feature of the reduction of barbiturates is the production of urea (XXX) or N-methylurea (XXXIII) rather than of open amides or ureides (eq 8). The malonyl part of the barbiturates is reduced to the corresponding glycols.

While hydantoin opened up to β-ureidoethanol, 5,5-diphenylhydantoin (dilantin) and the quinazolone XXXVI were resistant to hydrogenolysis by $NaBH_4$.



XXXVI

Experimental Section

General Procedures.—Melting points are uncorrected. Thin layer chromatography was carried out on silica gel G (DRSCo) in the solvent systems: (A) chloroform–methanol (9:1), (B) chloroform–methanol (7:3), (C) chloroform, and (D) ethyl acetate. Spots were made visible either by spraying with sulfuric acid and baking in the oven or by exposure to iodine vapor. Nuclear magnetic resonance spectra were taken on a Varian A-60 spectrometer. The chemical shifts (measured in parts per million) were calculated on the basis of tetramethylsilane as an internal standard. Mass spectra were determined on an AEI-MS 9 mass spectrometer. A Cary Model 11 spectrophotometer was used to record ultraviolet spectra.

Reductive Ring Opening to α-Ethyl-α-phenylglutarimide (Glutethimide, I) with Sodium Borohydride.—To a solution of 1.0 g of I in 100 ml of 50% aqueous methanol was added 0.09 g of sodium borohydride under stirring. After 30 min another 0.09 g of $NaBH_4$ was added and the solution stirred for 30 min. The resulting solution was passed through a column (20 × 90 mm) of IRC-50 (H^+ form). The methanol was removed from the eluate by a stream of nitrogen. The aqueous solution was lyophilized. The lyophilizate was evaporated three times with excess methanol in order to remove boric acid. The residue, a colorless, viscous oil, showed one major and four minor spots on thin layer chromatography in solvent A.

Procedure A.—The oily reduction product (0.5 g) was dissolved in chloroform and put on a column of silica gel (20 × 250 mm, particle size ϕ 0.05–0.20 mm). Elution with 350 ml of chloroform removed *ca.* 25% of unchanged starting material. The column was then eluted with chloroform–methanol (9:1), and fractions of 5 ml each were collected and pooled as follows: fractions 5–8, oil (trace); fractions 11–16, mixture of four compounds not separable by column chromatography; fractions 18–22, crystalline compound II (R_f 0.44); fractions 23–24, oil (trace).

ω-Hydroxy-α-ethyl-α-phenylvaleramide (II).—Fractions 18–22 were homogeneous (R_f 0.44), when chromatographed by the thin layer technique in solvent system A. The residue obtained after the removal of the solvent was redissolved in ether and kept at 0° until colorless crystals (yield 56.6%) appeared. Recrystallization from ether gave colorless plates, mp 107.5–108°, freely soluble in methanol and ethanol, soluble in colorform and methylene chloride, slightly soluble in ether or benzene, and very sparingly soluble in water.

Anal. Calcd for $C_{13}H_{19}NO_2$: C, 70.55; H, 8.65; N, 6.33. Found: C, 70.70; H, 8.61; N, 6.45.

The nmr spectrum ($CDCl_3$) gave peaks at 0.77 (t, J = 7.4 cps) (CH_3–CH_2–), 1.1–2.0 (m) (–CH_2CH_2–), 2.02 (q, J = 7.4 cps) (CH_3–$CH_2C<$), 2.48 (s) (OH), 3.59 (t, J = 6.1 cps) (HO–CH_2–CH_2–), 5.63 and 5.74 (b) (–NH_2), and 7.37 ppm (s) (phenyl). The infrared spectrum (Nujol) gave signals at 3460 and 3247 (NH_2 and OH), 1664 (amide I), 1610 (amide II), 1575 (phenyl), 1049 (ν_{CO}), 694 cm^{-1} (phenyl).

ω-p-Nitrobenzoyloxy-α-ethyl-α-phenylvaleramide (III).—To a chilled solution of 0.15 g of the amide II in dry pyridine (1.5 ml) was added with stirring 0.145 g of *p*-nitrobenzoyl chloride. The reaction mixture was allowed to stand overnight at room temperature and then poured into ice water. The precipitate was collected, washed with water, and recrystallized from ethanol to

yield the *p*-nitrobenzoate III as slightly yellow needles, mp 176.5–177°.

Anal. Calcd for $C_{20}H_{22}N_2O_5$: C, 64.85; H, 5.99; N, 7.57. Found: C, 64.59; H, 5.96; N, 7.60.

The nmr spectrum ($CDCl_3$) gave peaks at 0.90 (t, J = 7.5 cps) (CH_3–CH_2–), 1.3–2.4 (m) [(–CH_2–)$_2$], 4.41 (t, J = 6.5 cps) (–O–CH_2–), 5.4 (b) (NH_2), 7.52 (phenyl), 8.36, 8.46 ppm (dd, J = 9.5 cps) (O_2N–C_6H_4–CO). The infrared spectrum (Nujol) gave signals at 3534, 3226 (–NH_2), 1712 (*p*-nitrobenzoyl), 1672 (amide I), 1595 (amide II), 1515, 1346 (nitro group), 719, 697 cm^{-1} (aromatic).

Procedure B.—To a solution of 0.5 g of the crude reduction product in 6 ml of dry pyridine was added 3 ml of acetic anhydride. After standing overnight the reagents were evaporated under reduced pressure to give an oily residue. The crude acetates which were chromatographed in chloroform on a silica gel column (10 × 100 mm) consisted of a mixture of the acetates of II (86.8%) and IV (13.2%) according to nuclear magnetic resonance analysis. In order to hydrolyze the O-acetates the mixture was chromatographed on neutral alumina (50 g, aluminum oxide, active, Merck). The column was eluted with benzene (1000 ml), benzene–methanol (9:1, 30 ml), and benzene–methanol (1:1, 50 ml). The eluates with benzene–methanol (9:1), which were homogeneous (R_f = 0.46) according to thin layer chromatography in solvent A, were pooled and evaporated under reduced pressure. Recrystallization of the residue from ether afforded colorless plates of II, mp 107.5–108°.

Anal. Calcd for $C_{13}H_{19}NO_2$: C, 70.55; H, 8.65; N, 6.33. Found: C, 70.43; H, 8.54; N, 6.21.

This material was undepressed on admixrure with ω-hydroxy-α-ethyl-α-phenylvaleramide (II) obtained by procedure A. Their infrared spectra and R_f values on thin layer chromatography in solvent system A were identical.

Reductive Ring Opening of β-Ethyl-β-methylglutarimide (Bemegride, V) with Sodium Borohydride.—A stirred solution of 3.88 g of V in 250 ml of 40% methanol was treated with 1.5 g of sodium borohydride. After stirring for 49 hr at room temperature, excess sodium borohydride was destroyed by the addition of acetone. The resulting solution was passed through a column (20 × 300 mm) of IRC-50 (H^+ form). The organic solvent was removed under reduced pressure and the aqueous solution lyophilized. The residue was codistilled three times with methanol *in vacuo*. The resulting product on trituration with benzene gave 1.55 g (40%) of crystalline starting material. The benzene-soluble fraction, which showed four spots on thin layer chromatography in solvent system A, was evaporated under reduced pressure, and 1.0 g of the residue acetylated by the usual procedure. The mixture of acetates was chromatographed on a column of silica gel (20 × 400 mm) and the column eluted with ethyl acetate in 5-ml fractions. Each fraction was evaporated under reduced pressure and the residual oil rechromatographed by preparative tlc in solvent D: fraction 5, oil, bp 105° (0.25 mm); fractions 6–8, crystals (starting material) and oil, bp 95° (0.67 mm); fractions 9–12, oil, bp 100–105° (0.5 mm); fractions 13–32, oil, bp 170–175° (0.25 mm); fraction 36–46, oil (trace).

3-Methyl-3-ethyl-1,5-amylene Glycol O,O-Diacetate (X).—Fraction 5 was distilled to give a colorless oil, bp 105° (bath temperature, 0.25 mm).

Anal. Calcd for $C_{12}H_{22}O_4$: C, 62.58; H, 9.63. Found: C, 62.52; H, 9.92.

The nmr spectrum ($CDCl_3$) gave peaks at 0.86 (CH_3–CH_2–), 0.92 (CH_3–), *ca.* 1.3 (CH_3–CH_2–), 1.60 (t, J = 7.5 cps) (–CH_2–C<), 2.05 ($2CH_3CO$–), 4.17 ppm (t, J = 7.5 cps) (O–CH_2–). The infrared spectrum (liquid film) gave signals at 1745 (acetyl), 1236 (acetyl), 1042 cm^{-1} (ν_{CO}).

β-Methyl-β-ethyl-δ-valerolactone (VIII). Procedure A.—The combined Dragendorf-positive fractions 6–8 were washed with ether to separate the oil from the crystals which had mp 125–126° and were identical with starting material. The combined mother liquors on evaporation left a viscous oil which showed two spots (R_f 0.41 and 0.04 in solvent system C; R_f 0.93 and 0.10 in solvent system A). The slower moving spot gave a positive Dragendorf test. The oil was dissolved in chloroform, washed with 5% HCl, and purified on a silica gel column (10 × 100 mm) by elution with chloroform. There was obtained on distillation a colorless oil, bp 95° (bath temperature, 0.67 mm).

Anal. Calcd for $C_8H_{14}O_2$: C, 67.57; H, 9.93; mol wt, 142.12. Found: C, 67.44; H, 9.96; mol wt, 142 (mass spectrum).

The nmr spectrum ($CDCl_3$) gave peaks at 0.90 (CH_3–CH_2), 1.05 (CH_3–), 1.37 (CH_3–CH_2–), 1.70 (>CH_2–CH_2–O–), 2.32 (s) (>C–CH_2–C=O), 4.36 ppm (t, J = 6.0 cps) (–CH_2–O–). The infrared spectrum (liquid film) showed signals at 1736 (δ-lactone) 1250, 1233 cm^{-1} (ν_{CO}).

The analogous work-up of fractions 9–12 yielded a colorless oil, bp 100–105° (bath temperature, 0.5 mm), identical, with regard to infrared spectrum and thin layer chromatography, with the lactone VIII obtained from fractions 6–8.

Procedure B.—The crude reduction product was extracted with petroleum ether (bp 40–41°). The residue, obtained after the removal of the solvent, was worked up as described above and distilled *in vacuo* to afford a colorless oil, bp 100–105° (bath temperature, 0.5 mm). This material was identical with β-methyl-β-ethyl-δ-valerolactone (VIII) obtained above with regard to infrared and nuclear magnetic resonance spectra and thin layer chromatography.

ω-Acetoxy-β-methyl-β-ethylvaleramide (VII).—Fractions 13–32 were pooled and the solvent was removed by a stream of nitrogen. The residual oil, which showed a single spot when chromatographed by tlc in solvent D, was distilled to give a colorless oil, bp 170–175° (bath temperature, 0.25 mm).

Anal. Calcd for $C_{10}H_{19}NO_3$: C, 59.67; H, 9.52; N, 6.96. Found: C, 59.67; H, 9.40; N, 7.03.

The nmr spectrum ($CDCl_3$) gave signals at 0.88 (CH_3–CH_2–), 1.03 (CH_3–), 1.38 (CH_3–CH_2–), 1.74 (t, J = 7.5 cps) (>C–CH_2–CH_2–), 2.05 (CH_3CO), 2.15 (s) (>C–CH_2–CO), 4.19 (t, J = 7.5 cps) (–CH_2–O–CO–CH_3), 6.11 ppm (b) (–NH_2). The infrared spectrum (liquid film) gave signals at 3571, 3436, 3257 (NH_2), 1739 (CH_3CO–), 1672, 1664 (amide), 1236 (acetyl), 1033 cm^{-1} (ν_{CO}).

3-Methyl-3-ethyl-1,5-amylene Glycol Bis-*p*-nitrobenzoate (XI).—A solution of 0.2 g of diacetate X, in 5 ml of ethanol, was warmed with 5 ml of 1.0 *N* ethanolic potassium hydroxide on a steam bath for 30 min and allowed to cool. After the addition of 10 ml of water, the reaction mixture was passed over a column (10 × 100 mm) of Amberlite IRC-50 (H^+-form). Solvents were removed under reduced pressure to yield the free 3-methyl-3-ethyl-1,5-amylene glycol (IX) as a colorless oil. This bis-*p*-nitrobenzoate was prepared in analogy to the above procedure. Recrystallization from methanol gave slightly yellow rosettes or needles, mp 100–102°, very soluble in cold methanol.

Anal. Calcd for $C_{22}H_{24}N_2O_8$: C, 59.18; H, 5.87; N, 6.28. Found: C, 59.19; H, 5.61; N, 6.16.

The nmr spectrum ($CDCl_3$) gave signals at 0.95 (CH_3–CH_2–), 1.08 (CH_3–), 1.41 (CH_3–CH_2–), 1.84 (4 H) (t, J = 7.1 cps) (>C–CH_2–CH_2–), 4.51 (4 H) (t, J = 7.1 cps) (–CH_2–O–), 2.28 ppm (8 H) (s) (*p*-nitrobenzoyl).

The infrared spectrum (Nujol) gave signals at 1712 (*p*-nitrobenzoyl carbonyl), 1605 (aromatic), 1520 and 1342 (–NO_2), 1277 (*p*-nitrobenzoyl), 1119 and 1100 (ν_{CO}), 715 cm^{-1} (aromatic).

Reduction of α-Phthalimidoglutarimide (XIII) with Sodium Borohydride.—To a solution of 1.0 g of XIII in 120 ml of 50% dioxane was added 0.31 g of sodium borohydride. After stirring for 2 hr at room temperature the deposit was removed by filtration. Excess sodium borohydride was decomposed and the reaction mixture was passed through an IRC-50 (H^+-form) column (20 × 100 mm) and worked up as usual. The colorless viscous oil (1.01 g) which was obtained showed two major and one minor spot on thin layer chromatography in solvent B. It was dissolved in chloroform–methanol (7:3) and poured on a column of silica gel (20 × 270 mm). The column was eluted with the same solvent mixture. Fractions of 5 ml each were taken: fraction 9, crystals, mp 73° (phthalide); fractions 11–14, crystals + oil (ω-hydroxy-α-dihydrophthalimidovaleramide XIV); fractions 15–22, oil (δ-hydroxy-γ-(2-hydroxymethylbenzamido)valeramide, XV).

Benzo[*c*]furan-2-one (Phthalide XVI).—Fraction 9, on evaporation, left a crystalline residue. The ether-insoluble part was removed by filtration. The ether-soluble fraction was recrystallized from petroleum ether (bp 41–45°) to afford colorless plates, mp 73° (yield 3%), very soluble in methanol, ethanol, ether, chloroform, and ethyl acetate.

Anal. Calcd for $C_8H_6O_2$: C, 71.63; H, 4.51. Found: C, 71.59; H, 4.52.

The ultraviolet spectrum (CH_3OH) showed λ_{max} 277 mμ (log ε 4.00), 273 mμ (log ε 3.24), 280 mμ (log ε 3.22). The infrared spectrum (Nujol) gave signals at 1742 (conjugated carbonyl), 1587 (aromatic), 1049 (ν_{CO}), 739 cm^{-1} (aromatic). The nmr spectrum ($CDCl_3$) gave peaks at 5.33 (C_6H_5–CH_2–O–), 7.6 (m), 7.92 ppm (aromatic protons).

ω-Hydroxy-α-dihydrophthalimidovaleramide (XIV).—Fractions 11–14 were dissolved in a small volume of methanol and ethyl acetate was added until the solution stayed turbid. The crystals which deposited on standing were collected and recrystallized from methanol–ethyl acetate (2:8) to yield colorless needles, mp 148°, which showed a single spot (R_f 0.66) when chromatographed in solvent B. It was soluble in methanol and ethanol and slightly soluble in chloroform, acetone, and ether.

Anal. Calcd for $C_{13}H_{16}N_2O \cdot 0.25H_2O$: C, 58.09; H, 6.14; N, 10.42. Found: C, 58.31; H, 6.33; N, 10.72.

The ultraviolet spectrum gave $\lambda_{max}^{CH_3OH}$ 210 mμ (log ε 4.2), 221 (shoulder) (4.05), 267 (3.05); $\lambda_{max}^{0.1\ N\ HCl}$ 210 mμ (log ε 4.00), 220 (shoulder) (3.92), 265 (2.93); $\lambda_{max}^{0.1\ N\ NaOH}$ 221 mμ (log ε 4.03), 267 (3.96). The infrared spectrum (Nujol) gave 3378 and 3215 (–NH_2 and –OH), 1692, 1669, 1639, 1595 and 1587 (aromatic), 1054 cm^{-1} (ν_{CO}). The nmr spectrum (CD_3COCD_3) showed peaks at 1.5–2.0 (m) (–CH_2–CH_2–), 3.19 (t, J = 6 cps) (–O–CH_2–), 3.5 (*CH*–CO–NH_2), 5.60 (d, J = 6 cps) (>*CH*–OH), and 7.0–17.35 ppm (aromatic ring protons).

Fractions 15–22 were pooled and evaporated to give a viscous unstable oil (0.308 g) which showed a single spot (R_f 0.53) in solvent system B. The infrared spectrum (liquid film) gave signals at 3448 (–NH_2 and –OH), 1667 (amide and imide carbonyl), 1054 cm^{-1} (ν_{CO}). The nmr spectrum (CD_3COCD_3) showed peaks at 1.6–2.5 (–CH_2–CH_2–), 3.65 (d, J = 5 cps) (O–*CH*$_2$–CH(NH)–), 4.70 (benzylic protons), and 7.47 ppm (aromatic protons). This unstable fraction has properties expected from a hydrogenolysis product such as δ-hydroxy-γ-(2-hydroxymethylbenzamido)valeramide (XV).

Reduction of Phthalimide with Sodium Borohydride.[13]—To a solution of 5.0 g of XVII in 250 ml of ethanol was added 200 ml of a 1.25% aqueous solution of sodium borohydride. After stirring for 16 hr at room temperature the deposit, mainly inorganic salt, was removed by filtration. The reaction mixture was passed through an IRC-50 (H^+ form) column (24 × 200 mm). Most of the organic solvent was removed under reduced pressure. The remaining aqueous solution was lyophilized to leave a crystalline residue which showed three spots in solvent system A. The mixture was chromatographed on a silica gel column (24 × 300 mm), the column was eluted with a mixture of chloroform–methanol (9:1) and fractionated into 5-ml portions: fractions 21–27, crystals (R_f 0.91) of phthalide; fraction 29, crystals (R_f 0.42) of phthalyl alcohol; fractions 31–44, crystals (R_f 0.18) of 2-hydroxymethylbenzamide.

Phthalyl Alcohol.—Fraction 29 was evaporated to leave a residue which gave a single spot (R_f 0.42) in solvent system A. Recrystallization from a mixture of ether and petroleum ether (8:2) gave 30 mg (0.6%) of colorless plates, mp 63° (lit.[16] mp 64°).

Anal. Calcd for $C_8H_{10}O_2$: C, 69.54; H, 7.30. Found: C, 69.33; H, 7.42.

The infrared spectrum (Nujol) gave signals at 3279 (–OH), 1597 (aromatic), 1032 (ν_{CO}), and 760 cm^{-1} (aromatic).

Diacetate.—The diacetate was prepared according to the published procedure. Crystallization from a mixture of ether and petroleum ether gave colorless needles, mp 34–36° (lit.[17] mp 35–37°).

Reduction of N-Chloromethylphthalimide XVII with Sodium Borohydride. A. In Methanol.—To a solution of 5.87 g (3 × 10^{-2} mole) of XVII in 300 ml of methanol was added 2.268 g (6 × 10^{-2} mole) of sodium borohydride under cooling and stirring. After stirring for 4 hr at room temperature, the reaction mixture was passed through a column (24 × 200 mm) of Amberlite IRC-50 (H^+ form). After the organic solvent was removed under reduced pressure, the residue was extracted with methylene chloride, the extract evaporated, the residue taken up in ether and allowed to stand to deposit colorless crystals of XVIII. Recrystallization from ether gave colorless prisms, mp 103.5–104.5°, yield 4.10 g (70.7%). The Beilstein test was negative.

Anal. Calcd for $C_{10}H_{11}NO_3$: C, 62.16; H, 5.74; N, 7.25. Found: C, 62.38; H, 5.69; N, 6.95.

The infrared spectrum (Nujol) gave 3356 (hydroxy), 1672 (carbonyl), 1612 (aromatic), 1021 and 1011 (ν_{CO}), 746 cm^{-1} (aromatic). The nmr spectrum ($CDCl_3$) gave signals at 3.25 (–O*CH*$_3$), 4.24 (d, J = 10.1 cps) (>CH–O*H*), 4.81 (q, J_1 = 10.2 cps, J_2 = 2 cps, AB-type) (>N–*CH*$_2$–O–), 5.92 (d, J = 10.1 cps) (>C*H*–OH), and 7.60 ppm (m) (aromatic ring protons). In $CDCl_3$ + 1 drop of D_2O nmr signals appeared at 3.25 (–O*CH*$_3$), 4.81 (q, J_1 = 10.2 cps, J_2 = 2 cps) (>N–CH_2–O–), 5.91 (S) (>C*H*–OD), 7.60 ppm (m) (aromatic ring protons).

B. In Ethanol.—The procedure described above was employed using 0.978 g (5 × 10^{-3} mole) of N-chloromethylphthalimide and 0.378 g (10^{-2} mole) of sodium borohydride in 80 ml of ethanol. Crystallization from a mixture of ether–petroleum ether gave colorless prisms of XIX, mp 92–93°, yield 0.551 g (52.7%).

Anal. Calcd for $C_{11}H_{13}NO_3$: C, 63.75; H, 6.32; N, 6.76. Found: C, 63.77; H, 6.39; N, 6.54.

The infrared spectrum (Nujol) gave signals at 3378 (hydroxy), 1681 (carbonyl), 1613 (aromatic), 1019 and 1010 (ν_{CO}), 749 cm^{-1} (aromatic). The nmr spectra ($CDCl_3$) gave signals at 1.13 (t, J = 7.1 cps) (–CH_2–*CH*$_3$), 3.49 (q, J = 7.1 cps) (–*CH*$_2$–CH_3), 4.25 (d, J = 10.2 cps) (>CH–O*H*), 4.85 (q, J_1 = 10.5 cps, J_2 = 7.8 cps, AB-type) (>N–*CH*$_2$–O–), 5.96 (d, J = 10.2 cps) (>C*H*–OH), 7.60 ppm (m) (aromatic ring protons). In $CDCl_3$ + 1 drop of D_2O nmr signals appeared at 1.13 (t, J = 7.1 cps) (–CH_2–*CH*$_3$), 3.49 (q, J = 7.1 cps) (*CH*$_2$–CH_3), 4.85 (q, J_1 = 10.5 cps, J_2 = 7.8 cps) (>N–CH_2–O–), 5.96 (s) (>C*H*–OD), 7.60 ppm (m) (aromatic ring protons).

C. In Tetrahydrofuran.—To a solution of N-chloromethylphthalimide in tetrahydrofuran there was added under magnetic stirring sodium borohydride. After stirring for 24 hr, the reaction mixture was worked up in the usual manner to give colorless plates of XX from benzene, mp 147–149°, undepressed on admixture with an authentic specimen of N-hydroxymethylphthalimide.

Anal. Calcd for $C_9H_7NO_3$: C, 61.01; H, 3.98; N, 7.91. Found: C, 60.44; H, 3.91; N, 7.74.

The infrared spectrum (Nujol) gave signals at 3521 (hydroxy), 1773 and 1698 (carbonyl), 1603 (aromatic), 1054 (ν_{CO}), 733 cm^{-1} (aromatic).

Hydrogenolysis of N-Cyclohexylphthalimide (XXI) with Sodium Borohydride.—A solution of 0.5 g of XXI in 50 ml of methanol was reduced with 0.15 g of sodium borohydride in the course of 2 hr. The reaction mixture was worked up in the same manner as described above to yield 0.404 g of crude crystalline product.

N-Cyclohexyl-3-hydroxy-1-isoindolinone (XXII).—Fractional recrystallization of the above fractions from ether gave a first crop of colorless prisms, mp 125–126°.

Anal. Calcd for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.50; H, 7.42; N, 6.00.

The infrared spectrum (Nujol) gave signals at 3436 and 3333 (–OH), 1667 (imide carbonyl), 1653 (shoulder), 1616 (aromatic), 1040 (ν_{CO}), 745 cm^{-1} (aromatic). The nmr spectrum ($CDCl_3$) gave signals at 1.02–2.4 (m) (cyclohexanyl protons), 3.84 (br) (–OH), 5.88 (bf) (<C*K*–OH), and 7.27-7.67 ppm (m) (benzene ring protons). On admixture with 1 drop of D_2O nmr signals appeared at 1.0–2.4 (m) (cyclohexyl protons), 5.87 (sharp singlets) (<C*K*–OD), 7.27–7.67 (m) (aromatic protons).

2-Hydroxymethyl-N-cyclohexylbenzamide (XXIII).—The mother liquor of XXII left a residue which was recrystallized from a mixture of ether and petroleum ether to yield colorless needles, mp 129–129.5°.

Anal. Calcd for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; N, 6.00. Found: C, 72.17; H, 8.31; N, 6.01.

The infrared spectrum (Nujol) gave signals at 3344 (>NH and –OH), 1623 (imide carbonyl), 1590 and 1570 (aromatic), 1031 (ν_{CO}), and 745 cm^{-1} (aromatic).

Hydrogenolysis of N-Cyclohexyl-3-hydroxy-1-isoindolinone (XXII) to 2-Hydroxymethyl-N-cyclohexylbenzamide (XXIII).—A solution of 0.229 g of XXII in 20 ml of methanol was reduced with 0.07 g of sodium borohydride in the course of 10 hr. The reaction mixture was worked up as described above. Chromatography of the residue on a silica gel column (10 × 200 mm) and elution with a mixture of methylene chloride–methanol (9:1) gave 2-hydroxymethyl-N-cyclohexylbenzamide which, after recrystallization from ether, showed mp 129–129.5°, yield 0.201 g (87.0%).

2-Hydroxymethyl-N-cyclohexylbenzamide *p*-Nitrobenzoate.—The *p*-nitrobenzoate was prepared in the usual fashion. Crystallization from a mixture of ether and petroleum ether gave colorless needles, mp 174–176° dec.

Anal. Calcd for $C_{21}H_{22}N_2O_5$: C, 65.95; H, 5.80; N, 7.33. Found: C, 65.81; H, 5.92; N, 7.28.

The infrared spectrum (Nujol) gave signals at 3367 (–NH), 1724 (*p*-nitrobenzoyl carbonyl), 1629 (imide carbonyl), 1595 and 1582 (aromatic), 1527 and 1350 (–NO_2), 1264 and 1096 (ν_{CO}), 743 and 717 cm^{-1} (aromatic).

(16) R. F. Nystrom and W. G. Brown, *J. Am. Chem. Soc.*, **69**, 1198 (1947).
(17) J. Hessert, *Ber.*, **12**, 646 (1879).

Hydrogenolysis of N-Ethylphthalimide XXIV with Sodium Borohydride.—A solution of XXIV (5.2557 g, 0.03 mole) in 400 ml of methanol was admixed with a solution of 2.268 g (0.06 mole) sodium borohydride in 100 ml of water and kept stirring for 2 hr. The reaction mixture was then worked up as described above and the crude crystalline fraction chromatographed over silica gel (24 × 350 mm) and eluted with chloroform–methanol (9:1) to yield colorless needles, which, in spite of a single spot (R_f 0.69) on thin layer chromatography in solvent system A, were a mixture.

N-Ethyl-3-hydroxy-1-isoindolinone (XXV).—The crystalline mixture was fractionally recrystallized from ether to yield colorless prisms as a first crop: mp 108–109°; yield 3.780 g (65.2%); R_f 0.62 (solvent A).

Anal. Calcd for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.26; N, 7.91. Found: C, 67.78; H, 6.26; N, 7.68.

The infrared spectrum (Nujol) gave signals at 33.56 (–OH), 1664 (imide carbonyl), 1613 and 1595 (aromatic), 1032 (ν_{CO}), 1747 cm^{-1} (aromatic). Nmr signals ($CDCl_3$) appeared at 1.18 (t, J = 7.5 cps) (CH_3–CH_2–), 3.43 (m) (CH_3–CH_2–), 4.68 (br) (–OH), 5.77 (br s) (>C*H*–OH), 7.55 (m) ppm (aromatic protons).

2-Hydroxymethyl-N-ethylbenzamide (XXVI).—The mother liquor of XXV was concentrated until crystallization commenced. Four recrystallizations from a mixture of ether and petroleum ether gave colorless needles, mp 87–87.5°, yield 1.130 g (21.0%), R_f 0.60 (solvent A).

Anal. Calcd for $C_{10}H_{13}NO_2$: C, 67.02; H, 7.31; N, 7.82. Found: C, 67.08; H, 7.23; N, 7.82.

The infrared spectrum (Nujol) gave signals at 3344 (>NH and –OH), 1637 (imide carbonyl), 1595 and 1580 (aromatic), 1026 (ν_{CO}), 723 cm^{-1} (aromatic). Nmr signals ($CDCl_3$) appeared at 1.24 (t, J = 7 cps) (CH_3–CH_2–), 3.48 (m) (CH_3–CH_2–), 4.61 (s) (–CH_2OH), 5.78 (br) (–CO–NH–), 7.3–7.7 ppm (m) (aromatic protons).

The mother liquors showed a spot corresponding to benzo[*c*]-furan-2-one on thin layer chromatography, but pure crystalline material was not isolated.

***p*-Nitrobenzoate.**—The *p*-nitrobenzoate of XXVI was prepared as described. Crystallization from a mixture of methylene chloride and ether gave needles, mp 135–135.5°.

Anal. Calcd for $C_{17}H_{16}N_2O_5$: C, 62.19; H, 4.91; N, 8.53. Found: C, 62.32; H, 5.00; N, 8.31.

The infrared spectrum (Nujol) gave signals at 3333 (>NH), 1715 (*p*-nitrobenzoyl carbonyl), 1637 (imide carbonyl), 1597 (aromatic), 1538 and 1368 (–NO_2), 1116 and 1099 (ν_{CO}), 715 cm^{-1} (aromatic). Nmr signals appeared at ($CDCl_3$) 1.23(t, J = 7 cps) (CH_3–CH_2–), 3.51 (m) (CH_3–CH_2), 5.73 (s) (–CH_2–O), 6.34 (br) (–CO–*NH*–), 7.59 (m) (aromatic protons), 8.40 ppm (s) (*p*-nitrophenyl protons).

Hydrogenolysis of Succinimide to γ-Hydroxybutyramide.—A solution of 5.0 g of succinimide in 400 ml of water was reduced with 3.5 g of sodium borohydride. After stirring for 20 hr at room temperature the resulting solution was deionized by filtration over a column (20 × 210 mm) of IRC-50 (H^+ form). The lyophilized solution left an oil which showed a single spot (R_f 0.40) in solvent system B. Purification by chromatography over a silica gel column (30 × 400 mm) and crystallization from ether gave colorless plates, 4.558 g (87.6% yield), mp 53–54°.

Anal. Calcd for $C_4H_9NO_2$: C, 46.59; H, 8.80; N, 13.58. Found: C, 46.60; H, 8.86; N, 13.51.

The infrared spectrum (film) gave signals at 3435 and 3145 (–OH and –NH_2), 1664 (amide), 1610 (amide), 1060 cm^{-1} (ν_{CO}).

***p*-Nitrobenzoate.**—The *p*-nitrobenzoate of ω-hydroxybutyramide was prepared by the usual procedure. Crystallization from a mixture of methylene chloride and ether yielded needles, mp 143° dec.

Anal. Calcd for $C_{11}H_{12}N_2O_5$: C, 52.38; H, 4.80; N, 11.10. Found: C, 52.12; H, 4.75; N, 10.70.

The infrared spectrum (Nujol) gave signals at 3448 and 3236 (–NH_2), 1718 (*p*-nitrobenzoyl carbonyl), 1642 (amide), 1605 (aromatic), 1538 and 1348 (–NO_2), 1258, 1120, and 1101 (ν_{CO}), 718 cm^{-1} (aromatic).

Reduction of Barbital (XXIX) with Sodium Borohydride.—To a stirred solution of 5.52 g (3×10^{-2} mole) of barbital in 500 ml of 50% aqueous ethanol was added 4 equiv of sodium borohydride. The resulting mixture was stirred for 68 hr at room temperature. The deposited inorganic salt was removed by filtration and the solution was passed through a column of IRC-50 (H^+ form) cation-exchange resin. The effluent was concentrated under reduced pressure. The residue was dissolved in methanol and the solution was evaporated *in vacuo*. This procedure was repeated three times. The reduced product was purified by silica gel column chromatography. In this way 4.04 g (73.1%) of starting material was separated from the oil reduction product which showed three spots on tlc, two of which were positive toward modified Ehrlich reagent and one negative. The oil was dissolved in chloroform and allowed to stand at 0°. The crystalline deposit was collected and recrystallized from methanol–chloroform to yield colorless tetragonal prisms, mp 132–133°, yield 0.43 g (23.8%), R_f 0.35 (solvent B), positive toward modified Ehrlich reagent. This crystalline fraction was identified with an authentic sample of **urea** by infrared spectrum and its R_f value on tlc. The nitrate, prepared in the usual manner, gave colorless prisms, mp 153°, undepressed on admixture with authentic **urea nitrate.**

β,β′-Diethylpropylene Glycol (XXXI).—The urea mother liquor was evaporated and the residue was dissolved in chloroform–methanol (9:1) and chromatographed on silica gel (column 24 × 300 mm) followed by elution with the same solvent system. Each fraction had a volume of 5 ml: fractions 14–18, R_f 0.86, negative toward modified Ehrlich reagent (β,β′-diethylpropylene glycol); fractions 21–23, R_f 0.73, positive toward modified Ehrlich reagent.

Fractions 14–18 were pooled and evaporated *in vacuo* and the residual oil was dissolved in a small amount of ether. Petroleum ether (bp 40–45°) was added until the solution became turbid. The solution was allowed to stand until no more crystals deposited. Recrystallization from ether–petroleum ether gave colorless needles: mp 61.5–62°; R_f 0.86 (solvent B); yield 0.755 g (19.0%).

Anal. Calcd for $C_7H_{16}O_2$: C, 63.59; H, 12.20. Found: C, 63.61; H, 12.02.

The infrared spectrum (Nujol) gave signals at 3413 (–OH), 1019 cm^{-1} (ν_{CO}). Nmr signals ($CDCl_3$) appeared at 0.81 (CH_3–CH_2–), 1.22 (CH_3–CH_2–), 3.49 ppm (HO–CH_2–C≤).

β,β′-Diethylpropylene Glycol Di-*p*-nitrobenzoate.—To a stirred solution of 132 mg of the above glycol in 5 ml of dry pyridine was added 349 mg of solid *p*-nitrobenzoyl chloride. The reaction mixture was kept at 50° overnight and poured into ice water, and the deposit was separated, washed several times with water, and recrystallized from methanol to yield colorless needles, mp 143–144°.

Anal. Calcd for $C_{21}H_{22}N_2O_8 \cdot 0.5H_2O$: C, 57.39; H, 5.27; N, 6.37. Found: C, 57.06; H, 5.20; N, 5.76.

The infrared spectrum (Nujol) gave signals at 1721 (*p*-nitrobenzoyl carbonyl), 1608 (aromatic), 1517 and 1339 (–NO_2), 1269, 1122 and 1100 (ν_{CO}), 717 cm^{-1} (aromatic).

Fractions 21–23 on evaporation yielded a crystalline residue which was recrystallized from ether to afford colorless plates, mp 140–142° dec, yield 70 mg. The infrared spectrum is consistent with a product resulting from hydrogenolysis of one acylureido bond. However, the analytical results (C, 54.31; H, 8.60; N, 15.50) do not fit the structure of α,α′-diethyl-β-hydroxypropionylurea.

Hydrogenolysis of Hexobarbital (XXXII).—A solution of 2.0 g of the sodium salt of hexobarbital was reduced with 1.17 g (4 equiv) of sodium borohydride in 200 ml of water for 75 hr. The resulting mixture was worked up as described for barbital. The colorless viscous oil showed three spots, one of them positive toward modified Ehrlich reagent, on a thin layer plate in solvent system B. The oily product was extracted with chloroform. The insoluble part was removed by filtration and the chloroform layer chromatographed on silica gel (column: 24 × 270 mm). The column was eluted (5-ml fractions) with 200 ml of chloroform–methanol (9:1), 175 ml of chloroform–methanol (7:3), and 1175 ml of chloroform–methanol (1:1): fraction 26, colorless oil; fractions 58–110, crystalline, positive toward modified Ehrlich reagent (methylurea).

β-Methyl-β′-cyclohexenylpropylene Glycol (XXXIV).—Fraction 26 was evaporated to leave a viscous oil which was contaminated with a trace of starting material (tlc). After removal of the starting material as sodium salt, the glycol was obtained as a colorless oil, yield 91 mg (6.9%).

β-Methyl-β′-cyclohexenylpropylene Glycol Di-*p*-nitrobenzoate.—The *p*-nitrobenzoate was prepared in the same way as that of β,β′-diethylpropylene glycol. Crystallization from methanol gave colorless needles, mp 120–122°.

Anal. Calcd for $C_{24}H_{24}N_2O_8$: C, 61.53; H, 5.16; N, 5.98. Found: C, 61.33; H, 5.20; N, 6.14.

The infrared signals (Nujol) appeared at 1715 (*p*-nitrobenzoyl carbonyl), 1600 (aromatic), 1517 and 1335 ($-NO_2$), 1263, 1112 and 1099 (ν_{CO}), and 717 cm^{-1} (aromatic).

Methylurea.—The chloroform-insoluble crystalline material and the combined fractions 58–110 were pooled and recrystallized from methanol–methylene chloride mixture to afford colorless needles which showed a homogeneous spot (R_f 0.53) by thin layer chromatography in solvent system B, were positive toward modified Ehrlich reagent, and had mp 100.5–101.5° and a yield of 0.55 g (93.3–95.9%).

Anal. Calcd for $C_2H_6N_2O$: C, 32.42; H, 8.16; N, 37.82. Found: C, 32.33; H, 8.07; N, 37.51.

The infrared spectrum (Nujol) gave signals at 3509, 3390 and 3268 ($-NH_2$ and >NH), 1684 (shoulder), 1639 and 1567 cm^{-1} ($-NHCONH_2$). The product was identical with an authentic specimen of methylurea with regard to infrared spectrum and R_f value (tlc).

Methylurea Nitrate.—The above methylurea was dissolved in 10% nitric acid and the solution was evaporated under reduced pressure. The crystalline residue was recrystallized from methanol to afford colorless rods, mp 129.5–131° dec.

Hydrogenolysis of Prominal (XXXV).—To a solution of 2.0 g of prominal in 200 ml of 50% aqueous methanol was added 1.228 g (4 equiv) of sodium borohydride. After 43 hr at room temperature the reaction mixture was worked up according to the general procedure. The reduced product was chromatographed on silica gel (column: 24 × 270 mm) and the column eluted with chloroform–methanol (9:1). The fractions (5 ml each) gave the following distribution: fractions 28–29, mp 179–179.5° (117 mg), recovered starting material (5.9%); fractions 30–33, crystalline (mp 189–190°) (unidentified); fractions 65–75, crystalline (mp 183–184°), positive toward modified Ehrlich reagent (unidentified); fractions 78–135, crystalline, positive toward modified Ehrlich reagent (methylurea).

Fractions 30–33 on evaporation yielded a crystalline residue. Recrystallization from ether gave colorless prisms: mp 189–190° dec; yield 35 mg; negative toward modified Ehrlich test; infrared signals (Nujol) at 3509, 3226, 3106, 1686 cm^{-1}. Fractions 65–75 which showed a positive color test in the modified Ehrlich reagent were pooled and evaporated, and the crystalline residue was recrystallized from acetone to afford colorless needles: mp 183–184°; yield 20 mg; infrared signals (Nujol) at 3448, 2336 (shoulder), 1626 cm^{-1}.

Methylurea from Prominal.—Methylurea was eluted into fractions 78–135. After evaporation the residue was recrystallized from methanol–methylene chloride to yield colorless needles, mp 100.5–101.5°, with a yield of 315 mg (51.8%).

Anal. Calcd for $C_2H_6N_2O$: C, 32.42; H, 8.16; N, 37.82. Found: C, 32.26; H, 7.93; N, 37.56.

Hydrogenolysis of Hydantoin.—A solution of 5.004 g of hydantoin in 500 ml of ethanol was reduced with 7.56 g (4 equiv) of sodium borohydride. After 60 hr at room temperature the reaction mixture was worked up as described above. There was 4.209 g (84.1%) of starting material recovered. The mother liquor was chromatographed on a silica gel column (20 × 270 mm). The column was eluted with chloroform–methanol (7:3). The fractions, 5 ml each, showed the following distribution: fractions 11–12, yellowish crystals (trace); fractions 21–22, mixture of two components (0.19 g); fractions 24–27, oil, positive toward modified Ehrlich reagent.

β-Ureidoethanol.—Fractions 24–27 were collected and evaporated to leave an oily residue which was homogeneous (tlc, solvent system B), yield 0.391 g (7.5%). The modified Ehrlich reagent gave a positive test. The infrared spectrum (liquid film) gave signals at 3425 (–OH, $-NH_2$, and >NH), 1653, 1605 and 1558 ($-NHCONH_2$), 1063 cm^{-1} (ν_{CO}). Nmr signals (D_2O) appeared at 3.24 (t, J = 5 cps) (DO–CH_2–CH_2–ND), 3.63 ppm (t, J = 5 cps) (DO–CH_2–CH_2–ND–). Chemical shifts are based on 3-(triethylsilyl)-1-propanesulfonic acid as reference.

β-Ureidoethanol O,N-Bis-*p*-nitrobenzoate.—A solution of 122 mg of β-ureidoethanol was allowed to react with *p*-nitrobenzoyl chloride (0.434 g) in dry pyridine at 50° for 30 hr. The O,N-bis-*p*-nitrobenzoate was isolated and recrystallized from ethanol to give yellow needles, mp 244–246° dec.

Anal. Calcd for $C_{17}H_{14}N_4O_8$: C, 50.75; H, 3.51; N, 13.93. Found: C, 50.96; H, 3.69; N, 13.66.

The infrared spectrum (Nujol) gave signals at 3322 (shoulder), 3257 and 3135 (>NH), 1727 and 1706 (*p*-nitrobenzoyl carbonyl), 1675 (ureido carbonyl), 1597 (aromatic), 1511 and 1348 ($-NO_2$), 1269 and 1098 (ν_{CO}), and 718 cm^{-1} (aromatic).

Registry No.—Sodium borohydride, 1303-74-8; II, 15025-14-6; III, 15025-15-7; VII, 15025-16-8; VIII, 15025-17-9; X, 15025-18-0; XI, 15077-29-9; XIV, 15083-68-8; XV, 15025-19-1; XVI, 87-41-2; phthalyl alcohol, 612-14-6; XVIII, 15025-21-5; XIX, 15025-22-6; XX, 118-29-6; XXII, 15025-23-7; XXIII, 15026-23-0; *p*-nitrobenzoate of XXIII, 15026-24-1; XXV, 15025-24-8; XXVI, 15025-25-9; *p*-nitrobenzoate of XXVI, 15025-26-0; XXVIII, 927-60-6; *p*-nitrobenzoate of XXVIII, 15025-27-1; XXXI, 115-76-4; β,β-diethylpropylene glycol di-*p*-nitrobenzoate, 15025-29-3; XXXIII, 598-50-5; XXXIV (R = $COC_6H_4NO_2$), 15077-28-8; methylurea nitrate, 598-11-8; β-ureidoethanol, 2078-71-9; β-ureidoethanol O,N-bis-*p*-nitrobenzoate, 15025-32-8.

The Formation of N-Substituted Pyrazoles from the Pyrolysis of Certain α,β-Unsaturated Azines[1]

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Cinnamaldehyde azine and derivatives of this azine were pyrolyzed at temperatures near 200° to give homogeneous isomeric products in high yield. Chemical degradation and spectroscopic analysis show that these products are N-propenylated pyrazoles. For example, cinnamaldehyde azine was converted pyrolytically in 90% yield to 1-(*cis*-3-phenylpropenyl)-5-phenylpyrazole. This pyrolytic synthesis allows the preparation of a previously unreported class of pyrazoles in high yield.

The thermochemical instability of azines was first observed by Curtius, who reported that benzaldehyde azine, on pyrolysis, yielded stilbene.[2] This reaction was subsequently shown to be fairly typical of azines (excluding aryl ketazines), but these studies were limited to structurally uncomplicated substrates.[3] However, the mechanism of the reaction reported by Curtius[2] remained obscure until recently, when Zimmerman and Somasekhara demonstrated an ionic chain process, in which the chain-transfer agent is an aryldiazomethane.[4] This mechanism was established by demon-

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(4) H. E. Zimmerman and S. Somasekhara, *ibid.*, **82**, 5865 (1960).