221–223° when crystallized from a mixture of ether and hexane.

Anal. Calcd. for $C_{24}H_{37}NO_6$: C, 66.17; H, 8.10. Found: C, 66.00; H, 8.32.

3β-Acetoxy-17α-(2-carboxyethyl)-17β-amino-5β-androstane Lactam (IVb).—A solution of 7.5 g. of the nitro derivative (IIIb) in 100 ml. of ethanol was treated with hydrogen at 1000 p.s.i. and 100° in the presence of 1.0 g. of W-5 Raney nickel catalyst[7] for 5 hr. After removal of catalyst and stripping of solvent the residue was crystallized from a mixture of ethanol and water, yielding 5.2 g. of the lactam, m.p. 230–233°, λ_{max}^{KBr} 3.01, 3.2, 5.74, 5.84, and 8.0 μ.

The 5α-isomer (IVa) similarly obtained melted at 308–312° and exhibited congruent infrared spectrum.

Anal. Calcd. for $C_{24}H_{37}NO_3$: C, 74.32; H, 9.64. Found: C, 74.17; H, 9.42.

3β-Hydroxy-17α-(2-carboxyethyl)-17β-amino-5β-androstane Lactam (Vb).—A solution of 1.5 g. of the acetate (IVb) and 2.0 g. of potassium carbonate in 80 ml. of methanol and 20 ml. of water was stirred at room temperature for 24 hr. Addition of 200 ml. of water and collection of the solid precipitate on a funnel gave 1.3 g. of Vb melting at 224–230°, λ_{max}^{KBr} 2.9–3.1, 3.2, 5.83 with a shoulder at 5.9 μ.

Anal. Calcd. for $C_{22}H_{35}NO_2$: C, 76.47; H, 10.21. Found: C, 76.36; H, 10.25.

The 5α-isomer (Va) possessed an infrared spectrum essentially identical with the above and melted at 330–335°.

17α-(2-Carboxyethyl)-17β-amino-5β-androstan-3-one (VIb).—A rapidly stirred solution of 2.0 g. of the alcohol (Vb) in 50 ml. of acetic acid was treated during a 2-min. period with 1.6 ml. of 8 *M* chromic acid in aqueous sulfuric acid. After an additional 2 min., 5 ml. of isopropyl alcohol was added and then the acetic acid was distilled in vacuum. A suspension of the residue in 120 ml. of 10% sodium hydroxide was extracted with chloroform and the extract was washed with water. Removal of the solvent and crystallization of the residue from a mixture of chloroform and hexane afforded 1.8 g. of the ketone (VIb), m.p. 259–261°, λ_{max}^{KBr} 3.15, 3.25, 5.85, and 5.90 μ.

(7) Subsequent experiments have shown this reduction to be equally successful when conducted at room temperature and atmospheric pressure using T-1 Raney nickel as the catalyst.

Anal. Calcd. for $C_{22}H_{33}NO_2$: C, 76.92; H, 9.68. Found: C, 76.74; H, 9.44.

The 5α-isomer (VIa) melted at 310–320° and exhibited infrared spectrum similar to that of the 5β-derivative.

Anal. Calcd. for $C_{22}H_{33}NO_2$: C, 76.92; H, 9.68. Found: C, 76.72; H, 9.69.

17α-(2-Carboxyethyl)-17β-aminoandrost-4-en-3-one Lactam (VII).—A stirred solution of 1.75 g. of the ketone (VIb) in 40 ml. of acetic acid was treated with 5 ml. of 1 *N* hydrobromic acid in acetic acid. Water (5 ml.) was added to dissolve the precipitate which formed. Bromine (1.8 g.) in 18 ml. of acetic acid was added dropwise during a 10-min. period. Dilution with 150 ml. of water gave a solid which was collected and crystallized from a mixture of methanol and water. The 4-bromo ketone weighed 1.1 g. and melted at 202–204°, λ_{max}^{KBr} 3.0, 5.75–5.95 μ (doublet).

A mixture of 500 mg. of the 4-bromo ketone and 500 mg. of lithium bromide in 15 ml. of dimethylformamide was heated at 100° for 2 hr. Water was added slowly to the point of crystallization and the solid was collected. Recrystallization from a mixture of chloroform and ethyl acetate yielded 240 mg. of the conjugated ketone (VII) melting at 286–290°, λ_{max}^{KBr} 3.1, 3.22, 5.8, 5.92, 6.17 μ, $\lambda_{max}^{CH_3OH}$ 241 mμ, 15,500.

Anal. Calcd. for $C_{22}H_{31}NO_2$: C, 77.37; H, 9.15. Found: C, 77.23; H, 9.20.

3β-Hydroxy-5α-androstan-17-spiro-2′-pyrrolidine-(17β-N) Hydrochloride (VIII).—A solution of 2.5 g. of the lactam (IVa) in 50 ml. of tetrahydrofuran (THF) was added dropwise to a refluxing suspension of 4.0 g. of lithium aluminum hydride in 200 ml. of THF. After a 5-hr. reflux period, 4 ml. of water, 3 ml. of 20% sodium hydroxide, and finally 14 ml. of water were added successively. The precipitate was suspended in 200 ml. of a 1:1 solution of THF in ether and the insoluble material was removed by filtration. The dried amine weighed 2.0 g. Crude amine (1 g.) dissolved in the minimum volume of methanol was treated with one equivalent of methanolic hydrogen chloride. The warm solution was diluted with ether until crystallization began. The crystalline hydrochloride (VIII) was washed well with ether and dried in vacuum. It weighed 0.75 g. and melted above 300°, λ_{max}^{KBr} 2.94, 3.6–4.1, 6.28 μ.

Anal. Calcd. for $C_{22}H_{38}ClNO$: C, 71.80; H, 10.41. Found: C, 72.20; H, 10.45.

Cyclizations Leading to 3-Anilinohydantoin[1]

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3-Anilinohydantoin is formed in the base-catalyzed cyclization of S-benzylthiocarboxyglycine phenylhydrazide, carboethoxyglycine phenylhydrazide, and N-carboxyphenylhydrazidoglycine ethyl ester. Carboethoxyglycine phenylhydrazidd reacts with alcoholic potassium hydroxide to give the potassium salt of N-carboxyphenylhydrazidoglycine. The evidence indicates that this rearrangement proceeds though an 3-anilinohydantoin intermediate.

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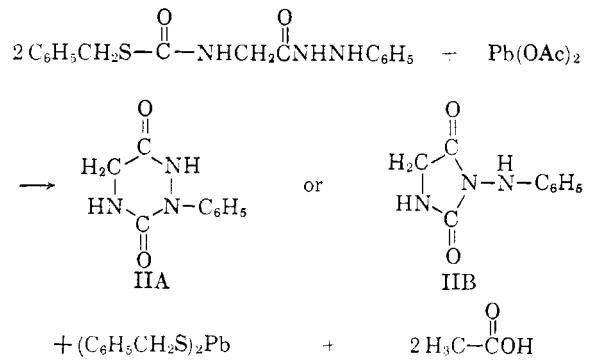
We recently reported a reaction in which S-benzylthiocarboxyglycine phenylhydrazide[3] (I) was

(1) This investigation was supported in part by a research grant (R.G. 5259) from the U. S. Public Health Service. Presented in part at the 140th Meeting of the American Chemical Society, Chicago, Illinois, September, 1961.

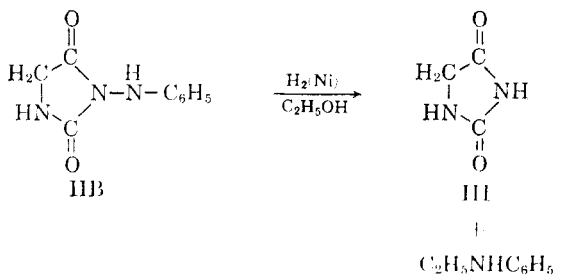
(2) Portion of a thesis presented by Duane W. Fish in partial fulfillment of the requirements for the degree of Doctor of Philosophy, Washington State University.

(3) H. B. Milne, S. L. Razniak, R. P. Bayer, and D. W. Fish, *J. Am. Chem. Soc.*, **82**, 4582 (1960).

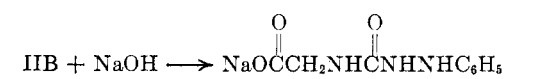
treated with lead acetate in ethanol yielding a compound (II), $C_9H_9N_3O_2$. By analogy to the reaction of phenylthiocarboxyglycine carbobenzoxyhydrazide with lead acetate, which Hofmann[4] had reported as yielding 2-carbobenzoxy-3,6-dioxohexahydro-1,2,4-triazine, compound II was reported as 2-phenyl-3,6-dioxohexahydro-1,2,4-triazine (IIA). However, because of the high carbonyl frequencies in the infrared spectrum of II and the report by Schlögl, *et al.*,[5] that, when carbobenzoxyamino acid methyl esters were refluxed with hydrazine in alcohol, 3-aminohydantoins rather than 3,6-dioxohexahydro-1,2,4-triazines were formed, it was felt that compound II could be either 2-phenyl-3,6-dioxohexahydro-1,2,4-triazine (IIA) or 3-anilinohydantoin (IIB) and that the structure should be investigated further.



On the basis of the evidence presented below, it now appears that compound II is 3-anilinohydantoin (IIB): (a) It was cleaved by Raney nickel to give hydantoin (III) and ethylaniline[6] rather than 5-phenylhydantoin acid amide.

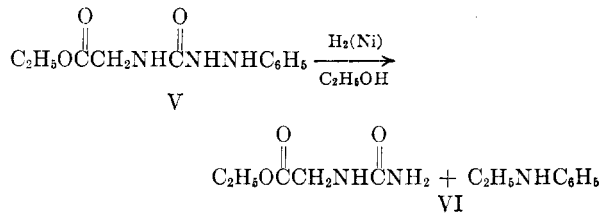


(b) It was hydrolyzed by dilute sodium hydroxide to give N-carboxyphenylhydrazidoglycine (IV).

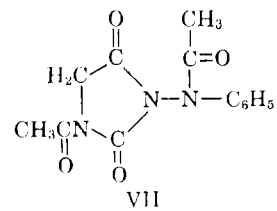


(c) The infrared spectrum of compound II showed carbonyl stretching frequencies at 1779 and 1724 cm.$^{-1}$, corresponding to the frequencies reported for known hydantoins[5] and 3-aminohydantoins[5] rather than to the frequencies observed for 1,2-succinyl-1-phenylhydrazine.[7] (d) The ultraviolet spectrum of II shows maxima at 2300 and 2800 Å., characteristic of 2-acyl-1-phenylhydrazines rather than 1-acyl-1-phenylhydrazines.[8]

The structure of N-carboxyphenylhydrazidoglycine (IV) is based on the following evidence: (1) Its infrared spectrum shows a single peak at 3247 cm.$^{-1}$ and an amide II absorption at 1553 cm.$^{-1}$, characteristic of secondary amides.[9] (2) Its ultraviolet spectrum has maxima at 2330 and 2820 Å., characteristic of 2-acyl-1-phenylhydrazines.[8] (3) Its ethyl ester was cleaved by Raney nickel to give hydantoic acid ethyl ester (VI).



3-Anilinohydantoin formed several derivatives. It reacted with acetic anhydride to form a diacetate[3] (VII), $C_{15}H_{13}N_3O_4$. The infrared spectrum showed carbonyl stretching frequencies at 1802, 1754, and 1704 cm.$^{-1}$. The ultraviolet spectrum showed no absorption maximum in the 3200 to 2200 Å. region, but instead showed an increasing absorption from 2900 to 2200 Å. These observations and the report of Harries and Weiss[10] that hydantoin reacts with acetic anhydride and forms 1-acetylhydantoin under similar conditions indicates that the diacetate has the following structure.



3-Anilinohydantoin reacted with bromine in acetic acid to give a dibromide (VIII), $C_9H_7Br_2N_3O_2$. Because the carbonyl stretching frequencies in the infrared spectrum were essentially the same as in 3-anilinohydantoin and the maxima in the ultraviolet spectrum showed a shift to longer wave lengths, the dibromide is assigned the following structure.

(4) A. Lindenmann, N. H. Kahn, and K. Hofmann, *J. Am. Chem. Soc.*, **74**, 476 (1952).

(5) K. Schlögl, J. Derkosch, and E. Wawersich, *Monatsh.*, **85**, 607 (1954).

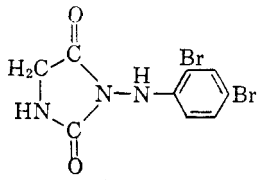
(6) C. Ainsworth, *J. Am. Chem. Soc.*, **78**, 1635 (1956), reported that N-ethylaniline is formed when aniline and Raney nickel are refluxed in ethyl alcohol.

(7) R. Gompper, *Chem. Ber.*, **93**, 200 (1960).

(8) N. A. Valyashko and I. T. Depeshko, *Zh. Obschei. Khim.* (*J. Gen. Chem.*), **20**, 1667 (1950).

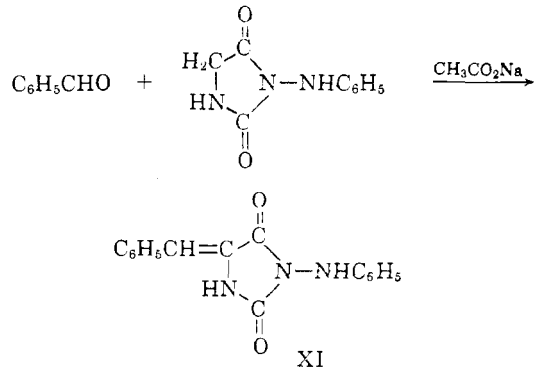
(9) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd ed., John Wiley and Sons, Inc., New York, 1958, pp. 206–209.

(10) C. Harries and M. Weiss, *Ann.*, 327, 355 (1903).



VIII

3-Anilinohydantoin also gave a reaction characteristic of hydantoin, namely, it reacted with benzaldehyde to give 5-benzal-3-anilinohydantoin (XI). The infrared spectrum of this compound



XI

showed carbonyl stretching frequencies at 1764 and 1715 cm.$^{-1}$ and a strong band at 1656 cm.$^{-1}$; this was attributed to aliphatic C=C absorption. The ultraviolet spectrum showed one maximum at 2300 Å. and another strong maximum at 3180 Å.; the latter is characteristic of benzalhydantoins.[11] 5-Benzal-3-anilinohydantoin was reduced to 5-benzyl-3-anilinohydantoin with phosphorus and hydriodic acid and with Raney nickel.

The cyclizations leading to 3-anilinohydantoin were base-catalyzed. When S-benzylthiocarboxyglycine phenylhydrazide (I) was refluxed with triethylamine in absolute ethanol, a 62% yield of 3-anilinohydantoin (II) was obtained. When chloroform was used as a solvent, the rate of 3-anilinohydantoin formation was slower, but the yield was 67%. 3-Anilinohydantoin (II) was formed also in 59% yield when S-benzylthiocarboxyglycine ethyl ester (IX) was refluxed with phenylhydrazine and triethylamine in absolute ethanol. This latter reaction is further evidence for 3-anilinohydantoin as the structure of II because, if triazines were formed in these reactions, 1-phenyl-3,6-dioxohexahydro-1,2,4-triazine rather than 2-phenyl-3,6-dioxohexahydro-1,2,4-triazine (IIA) would have been produced.

N-Carboxyphenylhydrazidoglycine ethyl ester (V) [an expected intermediate in the reaction of S-benzylthiocarboxyglycine ethyl ester (IX) with phenylhydrazine and triethylamine] was easily cyclized under similar conditions. A 74.4% yield of 3-anilinohydantoin (II) was obtained when a solution of N-carboxyphenylhydrazidoglycine ethyl ester (V) and triethylamine in absolute ethanol was refluxed for four hours.

It was of interest to compare the cyclization of N-carboxyphenylhydrazidoglycine ethyl ester (V) with that of the isomeric carboethoxyglycine phenylhydrazide (X). Under conditions such that N-carboxyphenylhydrazidoglycine ethyl ester (V) rapidly forms 3-anilinohydantoin, carboethoxyglycine phenylhydrazide (X) was recovered unchanged after nine hours of refluxing in an ethanolic solution of triethylamine. Carboethoxyglycine phenylhydrazide (X) did react, however, when a stronger base was used; when it was refluxed with one equivalent of potassium hydroxide in absolute ethanol, a 71% yield of the potassium salt of N-carboxyphenylhydrazidoglycine (IV) was isolated. This rearrangement can be explained if 3-anilinohydantoin (II) is an intermediate in the reaction. This reaction is a convenient method of preparing N-carboxyphenylhydrazido derivatives of D,L-amino acids starting with carboethoxy, carbobenzoxy, or carboallyloxy derivatives of the amino acids. However, a limitation has been observed when working with optically active compounds; when L-carboallyloxyleucine phenylhydrazide was refluxed with potassium hydroxide in absolute ethanol, the resulting N-carboxyphenylhydrazidoleucine showed no optical activity.

The products isolated from a reaction in which carboethoxyglycine phenylhydrazide (X) was refluxed with an equivalent of sodium ethoxide in absolute ethanol were 3-anilinohydantoin (II) (22%), carboethoxyglycine phenylhydrazide (11.8%), the sodium salt of N-carboxyphenylhydrazidoglycine (IV) (5.9%), and an unidentified acid (8%).

These cyclizations are summarized in Chart I.

The several cyclizations above involve the formation of an imide from compounds which are amides and esters (or thio ester). Such changes are not without precedent. de Mouilpied and Rule[12] obtained succinimide by treating methyl succinimate with alkali. Sondheimer and Holley[13] found that treatment of glutamine and asparagine esters with alkali resulted in imide formation. The formation of products with an N-amino imide structure has been noted with other hydrazide esters; for example, Curtius[14] obtained N-aminosuccinimide when diethyl succinate was heated with hydrazine hydrate.

The cyclizations leading to 3-anilinohydantoin are consistant with the mechanism proposed by Sondheimer and Holley[13] to explain imide formation when carbobenzoxy-L-asparagine methyl ester was stirred with sodium hydroxide. In this mechanism, the base removes a proton from the amide

(11) M. J. McLean and D. R. Seeger, *J. Am. Chem. Soc.*, **62**, 1416 (1940).

(12) A. T. de Mouilpied and A. Rule, *J. Chem. Soc.*, **91**, 176 (1907).

(13) E. Sondheimer and R. W. Holley, *J. Am. Chem. Soc.*, **76**, 2467 (1954).

(14) T. Curtius, *J. prakt. Chem.*, **92**, 74 (1915).

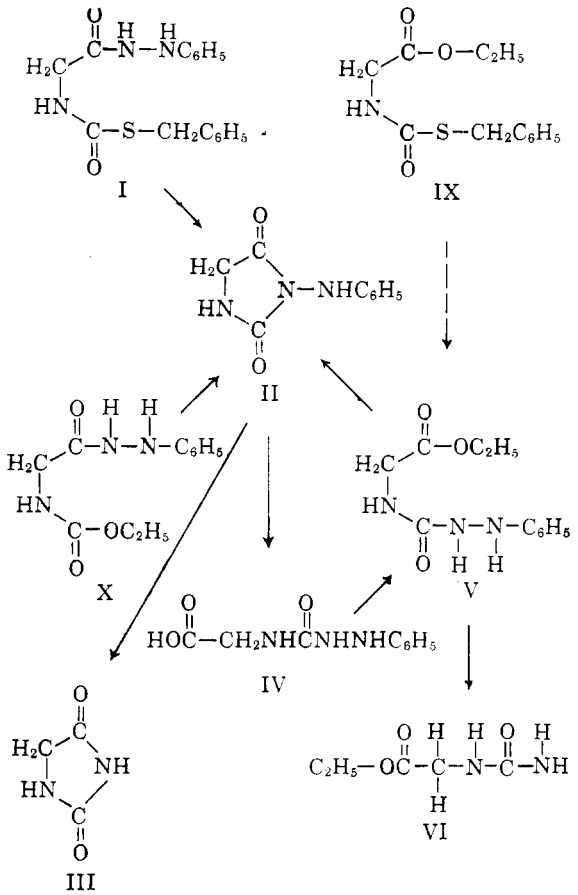


Chart I

N—H giving a resonance-stabilized amide ion which then attacks the ester carbonyl to give a cyclic ion; this ion in turn loses alcohol to give the cyclic product.

Experimental[15]

S-Benzylthiocarboxyglycine Phenylhydrazide (I).—The preparation and properties of S-benzylthiocarboxyglycine phenylhydrazide are described in a previous paper.[3]

3-Anilinohydantoin (II). Method A.—A suspension containing 4.0 g. (12.7 mmoles) of S-benzylthiocarboxylgycine phenylhydrazide in 5 ml. (36.4 mmoles) of triethylamine and 100 ml. of absolute ethanol was refluxed for 30 min. The suspended material was removed by filtration, and the solvent was evaporated under reduced pressure (aspirator, steam bath). The residue was washed with a small amount of dry ether; yield, 1.5 g. (61.9%); m.p. 161–166°. A sample of this material recrystallized from water melted at 165–166°.

Infrared spectrum of solid film deposited from ethyl acetate: N—H stretch, 3236 cm.$^{-1}$; C=O stretch, 1779, 1724 cm.$^{-1}$; C—H out-of-plane deformation, 751, 693 cm.$^{-1}$.

Ultraviolet spectrum in 95% ethanol: λ_{max} 2300 Å., ϵ 10,300; λ_{max} 2800 Å., ϵ 1160.

Method B.—A suspension of 1 g. of S-benzylthiocarboxyglycine phenylhydrazide and 4 ml. of triethylamine in 30 ml. chloroform was refluxed for 2 hr. The clear solution was cooled overnight in a refrigerator. The resulting crystals were filtered and recrystallized from water; yield, 0.40 g. (67%), of 3-anilinohydantoin, m.p. 165–166°.

Method C.—S-Benzylthiocarboxyglycine (6.0 g., 27 mmoles) was dissolved in 100 ml. of absolute ethanol saturated with hydrogen chloride. The solution was allowed to stand overnight at 5°. The solution was then evaporated to an oil under reduced pressure. The oil was dissolved in 50 ml. of absolute ethanol and 3 ml. of phenylhydrazine and 3 ml. of triethylamine were added. The solution was refluxed for 24 hr. The solution was then cooled and allowed to stand overnight. The crystalline precipitate was filtered and recrystallized from water. The total yield of 3-anilinohydantoin was 3.0 g. (59%), m.p. 165–166°.

When an excess of phenylhydrazine (6 ml.) was used in the above reaction, 3.0 g. of a compound (m.p. 204–205°) was isolated with the correct analysis for *N-carboxyphenylhydrazidoglycine phenylhydrazide.*

Anal. Calcd. for $C_{15}H_{17}N_5O_2$: C, 60.20; H, 5.67; N, 23.41. Found: C, 60.29; H, 5.87; N, 23.58.

Samples of 3-anilinohydantoin (II) prepared by methods A, B, and C were shown to be identical by mixed melting point determinations and by comparison of their infrared and ultraviolet spectra; they were shown to be identical with the compound previously reported as 2-phenyl-3,6-dioxohexahydro-1,2,4-triazine prepared by the reaction of S-benzylthiocarboxyglycine phenylhydrazide with lead acetate.[3]

Reductive Cleavage of 3-Anilinohydantoin.—The procedure developed by Hinman[16] was employed for this reaction. A mixture of 1.5 g. (7.85 mmoles) of 3-anilinohydantoin and approximately 15.0 g. of W-2 Raney nickel[17] in 75 ml. of absolute ethanol was vigorously stirred while refluxing for 20 hr. At the end of the reaction period, the liquid layer was separated by decantation. The catalyst was washed with 50 ml. of absolute ethanol. The combined ethanol solutions were evaporated to an oil (aspirator, steam bath). On standing, crystallization of hydantoin took place. The crystalline mass was washed with petroleum ether. The remaining solid, on recrystallization from 95% ethanol, gave 0.16 g. (20.3% yield) of hydantoin (III). Identification was made by a mixed melting point determination (m.p. 219–220°) and by comparison of the infrared spectrum with an authentic sample of hydantoin.

The petroleum ether washings were evaporated to an oil. The oil was distilled and collected on a cold finger and was identified as ethylaniline by comparison of the infrared spectrum with that of an authentic sample of ethylaniline.

N-Carboxyphenylhydrazidoglycine (IV). A. From 3-Anilinohydantoin (II) and Sodium Hydroxide.—To a solution of 1.0 g. of sodium hydroxide in 50 ml. of water was added 2.5 g. (13.0 mmoles) of 3-anilinohydantoin. After standing for 1.5 hr. at room temperature, the 3-anilinohydantoin had dissolved. The clear solution was acidified with concentrated hydrochloric acid (pH 2, pH paper). The solid that precipitated was removed by filtration and washed with 30 ml. of dry ether. Recrystallization from acetone yielded 2.15 g. (78.5%) of N-carboxyphenylhydrazidoglycine (IV), m.p. 195–197° dec.

Anal. Calcd. for $C_9H_{11}N_3O_3$: C, 51.67; H, 5.30; N, 20.09. Found: C, 51.94; H, 4.98; N, 19.85.

Infrared spectrum of solid film deposited from dioxane: N—H stretch, 3247 cm.$^{-1}$; acid C=O stretch, 1724 cm.$^{-1}$; amide I, 1669 cm.$^{-1}$ (broad); amide II, 1553 cm.$^{-1}$ (broad).

(15) All melting points are uncorrected. The microanalytical work was performed by the Galbraith Laboratories, Knoxville, Tennessee, and by Dr. G. Weiler and Dr. F. B. Strauss, Microanalytical Laboratories, 164 Banbury Road, Oxford, England. The infrared spectra were determined on a Beckman IR-5 spectrophotometer. The spectra were obtained from samples in potassium bromide pellets (0.8 mg. per 350 mg. potassium bromide) and from films deposited on rock salt plates from the solvents listed. The ultraviolet spectra were determined by a Cary Model 14 recording spectrophotometer using 1-cm. quartz cells with 95% ethanol as solvent.

(16) R. L. Hinman, *J. Org. Chem.*, **22**, 148 (1957).

(17) The W-2 Raney nickel used in this investigation was prepared by the method of Mozingo, "Organic Syntheses," Col. Vol. III, John Wiley and Sons, Inc., New York, 1959, p. 181.

Ultraviolet spectrum in 95% ethanol: λ_{max} 2330 Å., ϵ 12,400; λ_{max} 2820 Å., ϵ 1600.

B. From Carboethoxyglycine Phenylhydrazide (X).—To a solution of 1.12 g. of potassium hydroxide in 75 ml. of absolute ethanol in a nitrogen atmosphere was added 5.4 g. (22.8 mmoles) of carboethoxyglycine phenylhydrazide. The solution was refluxed for 4 hr. (After 10–15 min. of heating, a solid suspension formed.) The reaction mixture was cooled, and the suspended solid collected by filtration and washed with dry ether; yield, 4.0 g. (71.2%), of potassium N-carboxyphenylhydrazidoglycinate. The potassium salt was converted to the free acid (IV), m.p. 196–197°, with hydrochloric acid.

C. From Carbobenzoxyglycine Phenylhydrazide.—A solution of 5 g. (16.7 mmoles) of carbobenzoxyglycine phenyl hydrazide and 1.05 g. (18.6 mmoles) of potassium hydroxide in 80 ml. of absolute ethanol was refluxed for 4 hr. The reaction mixture was treated as described in (B) to give 2.53 g. (73%) of N-carboxyphenylhydrazidoglycine (IV), m.p. 196–197°.

The products isolated in A, B, and C were shown to be identical by mixed melting point determinations (196–197°) and by comparison of their infrared spectra.

***N*-Carboxyphenylhydrazido-D,L-leucine.**—Carboallyloxy-L-leucinephenylhydrazide[18] (5.3 g.), m.p. 112–113°, $[\alpha]^{25}D$ −68.0°, was refluxed with 1 g. of potassium hydroxide in 100 ml. of absolute ethanol for 9 hr. The reaction mixture was treated as described in B to give 3 g. (65.0%) of N-carboxyphenylhydrazido-D,L-leucine, m.p. 171–172°, $[\alpha]^{25}D$ 0.

Anal. Calcd. for $C_{18}H_{19}N_3O_3$: C, 58.87; H, 7.18; N, 15.85. Found: C, 58.69; H, 7.30; N, 15.95.

N-Carboxyphenylhydrazidoglycine Ethyl Ester (V).—A solution of 1.0 g. (4.78 mmoles) of N-carboxyphenylhydrazidoglycine in 75 ml. of absolute ethanol was cooled in an ice bath and saturated with dry hydrogen chloride. The solution was allowed to stand at room temperature for 5 hr. and then evaporated under reduced pressure (aspirator, steam bath) to an oil. The addition of 20 ml. of water caused the precipitation of a white solid. This solid was recrystallized from benzene yielding 0.75 g. (65.0%) of crude ester, m.p. 119–125°. Recrystallization from water gave a product with a melting point of 128–130°.

Anal. Calcd. for $C_{11}H_{15}N_3O_3$: C, 55.69; H, 6.37; N, 17.71. Found: C, 55.69; H, 6.32; N, 17.60.

Infrared spectrum of solid film deposited from methanol: N—H stretch, 3268 cm.$^{-1}$; ester C=O stretch, 1727 cm.$^{-1}$; amide I, 1658 cm.$^{-1}$; amide II, 1555 cm.$^{-1}$ (broad).

Ultraviolet spectrum in 95% ethanol: λ_{max} 2340 Å., ϵ 11,400; λ_{max} 2820 Å., ϵ 1570.

Reductive Cleavage of N-Carboxyphenylhydrazidoglycine Ethyl Ester (V).—A suspension of approximately 15.0 g. of W-2 Raney nickel in a solution of 1.0 g. of N-carboxyphenylhydrazidoglycine ethyl ester in 100 ml. of absolute ethanol was stirred vigorously and refluxed for 20 hr. The Raney nickel was removed by filtration and washed with 100 ml. of hot 95% ethanol. The combined filtrates were evaporated under reduced pressure (aspirator, steam bath). The residue was washed with petroleum ether, and the solid portion was recrystallized from water; 0.30 g. (48.6% yield) of hydantoic acid ethyl ester (VI), m.p. 136–137°. The infrared spectrum of this material was indentical to that of a sample of hydantoic acid ethyl ester (VI), m.p. 136–138°.[19]

Acetylation of 3-Anilinohydantoin. Method A.—A solution of 0.5 g. (2.6 mmoles) of 3-anilinohydantoin in 20.0 g. of acetyl chloride was evaporated to a brown oil on a steam bath. The oil was dissolved in a benzene–petroleum ether solution, and from it crystals were obtained; yield, 0.22 g. (30.6%); m.p. 157–158°.

Anal. Calcd. for $C_{13}H_{13}N_3O_4$: C, 56.72; H, 4.76; N, 15.26. Found: C, 56.64; H, 4.82; N, 15.30.

Method B.—A solution of 1.92 g. (0.01 mmole) of 3-anilinohydantoin, 3 drops of concentrated sulfuric acid, and 25.0 g. of acetic anhydride was allowed to stand for 1 hr. at room temperature. The volatile portion was evaporated under reduced pressure (aspirator, steam bath). The viscous residue was dissolved in 50 ml. of 50% ethanol. On standing, crystallization took place yielding 2.35 g. (85.5%) of a white solid melting at 151–156°. Recrystallization from 95% ethanol increased the melting point to 157–158°. A mixed melting point determination (m.p. 157–158°) and a comparison of their infrared spectra showed that the products obtained by both methods were identical.

Infrared spectrum of solid film deposited from dioxane: N—H stretch, absent; C=O stretch, 1802, 1754, and 1704 cm.$^{-1}$.

Ultraviolet spectrum in 95% ethanol: no maxima in the 3200 to 2200-Å. region; increasing absorption from 2900 to 2200 Å.

Reaction of 3-Anilinohydantoin with Bromine in Acetic Acid.—A solution of 3.0 g. (18.8 mmoles) of bromine in 15 ml. of glacial acetic acid was added dropwise to a rapidly stirred solution of 1.0 g. (5.22 mmoles) of 3-anilinohydantoin and 1.6 g. of sodium acetate in 25 ml. of glacial acetic acid and 5 ml. of water. The mixture was allowed to stand at room temperature for 12 hr. The solid that separated was filtered and washed with water; yield, 1.35 g. (74.2%) of product. Recrystallization from 95% ethanol gave a compound with a melting point of 250–252°.

Anal. Calcd. for $C_9H_7Br_2N_3O_2$: C, 30.97; H, 2.02; N, 12.04; Br, 45.80. Found: C, 31.12; H, 2.25; N, 12.24; Br, 45.55.

Infrared spectrum of solid film deposited from acetic acid: N—H stretch, 3247 cm.$^{-1}$; C=O stretch, 1786, 1727 cm.$^{-1}$; C—H out-of-plane deformation, 877 cm.$^{-1}$ (one free hydrogen atom), and 854 cm.$^{-1}$ (two free adjacent hydrogen atoms).

Ultraviolet spectrum in 95% ethanol: λ_{max} 2440 Å., ϵ 10,100; λ_{max} 3030 Å., ϵ 1390.

5-Benzal-3-anilinohydantoin (XI).—This reaction was carried out according to the method described by Wheeler and Hoffman.[20] A mixture of 2.0 g. (10.4 mmoles) of 3-anilinohydantoin, 1.58 g. (14.8 mmoles) of benzaldehyde, 2.0 g. of sodium acetate, 1 ml. of acetic anhydride, and 5 ml. of glacial acetic acid was heated under reflux for 2 hr. The excess benzaldehyde, acetic anhydride, and acetic acid were removed under reduced pressure (aspirator, steam bath). The solid residue was washed with 50 ml. of ice water. Recrystallization from toluene gave a product with a m.p of 220–221.5°. Two more recrystallizations from ethyl acetate yielded 1.8 g. (62.0%) of white crystals melting at 222–224°.

Anal. Calcd. for $C_{16}H_{13}N_3O_2$: C, 68.80; H, 4.67; N, 15.05. Found: C, 68.73; H, 4.59; N, 14.89.

Infrared spectrum of potassium bromide pellet: N—H stretch, 3390 cm.$^{-1}$, C=O stretch, 1764, 1715 cm.$^{-1}$; C=C stretch, 1656 cm.$^{-1}$.

Ultraviolet spectrum in 95% ethanol: λ_{max} 2300 Å., ϵ 20,100; λ_{max} 2350 Å. (shoulder), ϵ 17,400; λ_{max} 3180 Å., ϵ 27,800.

5-Benzyl-3-anilinohydantoin. Method A.—The procedure of Wheeler and Hoffman[20] was employed for the preparation of this derivative. A mixture of 1.0 g. (3.58 mmoles) of 5-benzal-3-anilinohydantoin, 0.3 g. of red phosphorus, and 5 ml. of hydriodic acid (50%) was boiled for 45 min. The mixture was evaporated on a steam bath to near dryness. The residue was washed with water and then warmed with 95% ethanol. The insoluble red phosphorus was removed by filtration. The volume of the ethanol was reduced, and the solution was placed in a refrigerator. The crystals that deposited were removed by filtration, washed with water, and dried; yield, 0.4 g. (30.8%), of a product melting

(18) H. B. Milne and C. M. Stevens, *J. Am. Chem. Soc.*, **72**, 1742 (1950).

(19) This sample was prepared by the method of C. Harries and M. Weiss, *Ber.*, **33**, 3418 (1900).

(20) H. L. Wheeler and C. Hoffman, *Am. Chem. J.*, **45**, 368 (1911).

at 204–206°. A second recrystallization from 95% ethanol did not raise the melting point.

Anal. Calcd. for $C_{16}H_{15}N_3O_2$: C, 68.31; H, 5.37; N, 14.94. Found: C, 68.15; H, 5.48; N, 14.78.

Method B.—To a solution of 1.0 g. (3.58 mmoles) of 5-benzal-3-anilinohydantoin in 50 ml. of absolute ethanol was added 12.0 g. of moist W-2 Raney nickel. The pressure of hydrogen in the reaction flask was adjusted to 1.5 atm., and the flask was shaken for 20 hr. The Raney nickel was removed by filtration and washed with 50 ml. of hot 95% ethanol. The combined filtrates were distilled under reduced pressure (aspirator, steam bath), and the volume was reduced to about 50 ml. The crystals that formed on cooling the residue were removed by filtration; yield, 0.7 g. (69.5%) of 5-benzyl-3-anilinohydantoin melting at 204–206°. Identification was made by a mixed melting point determination (m.p. 204–206°) and by comparison of the infrared spectrum of this product with that of the product obtained by method A.

That the >C=C< bond of the starting material had been reduced was indicated by the absence of an absorption band at 1656 $cm.^{-1}$ in the infrared spectrum (potassium bromide pellet).

Cyclization of N-Carboxyphenylhydrazidoglycine Ethyl Ester (V).—A solution of 1.0 g. (4.22 mmoles) of N-carboxyphenylhydrazidoglycine ether ester (V) and 2.0 ml. of triethylamine in 25.0 ml. of absolute ethanol was refluxed for 4 hr. The solution turned pink when heating was started, and this gradually changed to a light yellow color. The solvent was removed under reduced pressure (aspirator, steam bath). The solid residue was recrystallized from 10% ethanol and washed with dry ether; yield, 0.6 g. (74.4%), of crude 3-anilinohydantoin melting at 157–160°. Recrystallization from water gave white needles melting at 165–166°. The infrared spectrum of the product was identical with the spectrum of an authentic sample of 3-anilinohydantoin.

Carboethoxyglycine Phenylhydrazide (X).—A solution of 31.5 g. (0.226 mole) of glycine ethyl ester hydrochloride and 65 ml. of triethylamine in 250 ml. of chloroform was cooled in an ice bath. The solution was rapidly stirred while 24.5 g. (0.0226 mole) of ethyl chloroformate was added dropwise. After the addition of ethyl chloroformate was completed, the ice bath was removed, and the solution was stirred for an additional hour. Triethylamine hydrochloride was precipitated by the addition of 500 ml. of dry ether and removed by filtration. The solvent was distilled under reduced pressure (aspirator, steam bath), and the colorless oil (36.0 g., 0.205 mole) was not purified further. A mixture of this oil, 22.2 g. (0.205 mole) of phenylhydrazine, and 1.0 g. of sodium methoxide was heated on a steam bath for 12 hr. At the end of the reaction period, the volatile portion was removed under reduced pressure (aspirator, steam bath). Trituration of the viscous residue with dry ether resulted in the solidification of the residue. This solid was washed repeatedly with ether until the filtrate was colorless; yield, 23.1 g. (43% based on glycine ethyl ester hydrochloride), of a product melting at 118–120°. Recrystallization from either chloroform or 10% ethanol gave a compound melting at 125°.[21]

(21) C. Niemann and P. L. Nichols, Jr., *J. Biol. Chem.*, **143**, 191 (1942), prepared this compound by a papain-catalyzed reaction and reported m.p. 123°.

Infrared spectrum of solid film deposited from benzene: N—H stretch, 3236 $cm.^{-1}$; carbonate C=O stretch, 1692 $cm.^{-1}$; amide I, 1678 $cm.^{-1}$.

Ultraviolet spectrum in 95% ethanol: λ_{max} 2340 Å., ϵ 10,000; λ_{max} 2830 Å., ϵ 1380.

Attempted Cyclization of Carboethoxyglycine Phenylhydrazide (X) with Triethylamine and with Pyridine.—A solution of 2.5 g. of carboethoxyglycine phenylhydrazide and 4 ml. of triethylamine in 50 ml. of chloroform was refluxed for 9 hr. The volatile portion was removed under reduced pressure (aspirator, steam bath), and the residue was recrystallized from dilute ethanol; yield, 1.26 g. (50.4%), of solid melting at 122–125°; mixed melting point determination with carboethoxyglycine phenylhydrazide, m.p. 123–125°.

A solution of 2.53 g. of carboethoxyglycine phenylhydrazide in 50 ml. of pyridine was refluxed for 45 hr. A small amount of the reaction mixture was evaporated on a rock salt plate; the infrared spectrum obtained was identical to the spectrum of the starting material. A 70.5% (1.78 g.) recovery of starting material (m.p. 123–125°) was obtained.

Reaction of Carboethoxyglycine Phenylhydrazide (X) with an Equal Molar Quantity of Sodium Ethoxide.—A solution of sodium ethoxide was prepared by adding 2.3 g. (0.1 g.-atom) of sodium to 75 ml. of absolute ethanol. After the sodium had dissolved, a slurry of 23.7 g. (0.1 mole) of carboethoxyglycine phenylhydrazide in 25 ml. of absolute ethanol was added. The resulting solution was refluxed for 5 hr. in a nitrogen atmosphere. The solution was allowed to cool to room temperature, and the resulting suspended sodium N-carboxyphenylhydrazidoglycinate was removed by filtration. This salt (1.36 g., 5.9% yield) was dissolved in 10 ml. of water; acidification with concentrated hydrochloric acid precipitated the free acid. Recrystallization from ethyl acetate yielded 1.16 g. (5.5%) of N-carboxyphenylhydrazidoglycine (IV), m.p. 195° dec.

The alcoholic filtrate obtained from the sodium N-carboxyphenylhydrazidoglycinate suspension was acidified by the addition of 17 ml. of 6 *M* hydrochloric acid, the sodium chloride formed was removed by filtration, and the filtrate was neutralized with saturated sodium bicarbonate solution. The filtrate was evaporated to an oil, and the oil was extracted with hot ethyl acetate. The insoluble residue was dissolved in saturated sodium bicarbonate solution. The free acid was precipitated by acidification with concentrated hydrochloric acid. A total of 3.1 g. of an acid with a melting point of 255–256° was obtained.[22]

The combined ethyl acetate extracts were evaporated to an oil, and the oil was dissolved in chloroform. The addition of dry ether caused the precipitation of 3-anilinohydantoin. A total of 4.2 g. (22.0% yield) of 3-anilinohydantoin (II) and 2.8 g. (11.8% recovery) of starting material was obtained by the repeated additions of dry ether, filtration of the solid that formed, and reduction of the volume of the filtrate.

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(22) *Anal.* Found: C, 55.64, 55.65; H, 4.68, 4.82; N, 21.77 21.54; neut. equiv., 370.