aluminum hydride in 200 ml. of anhydrous tetrahydrofuran was added, dropwise, a solution of 5.5 g. of VI in 50 ml. of anhydrous tetrahydrofuran. When the addition was completed, the reaction mixture was stirred at room temperature for 2 hr. and then was heated under reflux for 1 hr. The reaction mixture was cooled in ice, and 50% aqueous tetrahydrofuran (30 ml.) was added cautiously, followed by 25 ml. of 10% sodium hydroxide solution. The reaction mixture was filtered and the filtrate was taken to dryness on a rotary evaporator. The oily residue which was deposited was triturated with 15 ml. of ethyl acetate resulting in a crystalline product (1.8 g.), m.p. 159–166°. Recrystallization from ethyl acetate afforded VII, m.p. 170–173°; λ_{max} 6.10 μ (C=O).

Anal. Calcd. for $C_{15}H_{13}ClN_2O$: C, 66.05; H, 4.80; Cl, 13.00; N, 10.27. Found: C, 65.88; H, 4.67; Cl, 12.55; N, 10.36.

7-Chloro-2,3,4,5-tetrahydro-2-phenyl-1*H*-1,4-benzodiazepine (VIII).—The reduction of 10.8 g. of VI with 4.6 g. of lithium aluminum hydride in 250 ml. of tetrahydrofuran was carried out as described in the previous example, except that the reaction mixture was heated under reflux for 3.5 hr. before work-up. Recrystallization from methanol resulted in a hygroscopic product (2.5 g.), m.p. 60–68°.

Anal. Calcd. for $C_{15}H_{15}ClN_2$: C, 69.63; H, 5.84; N, 10.83. Found: C, 69.33; H, 6.13; N, 10.43.

Acknowledgment.—The authors are indebted to Ronald D. Stewart and Murray D. Rosenberg for their technical assistance, to Dr. Gordon Ellis and staff for the microanalyses, to Mr. Bruce Hofmann for helpful discussions of the spectra, and to Dr. B. R. Baker for his suggestions during the course of this work.

Ethyl Hydantoin-5-carboxylates[1-3]

WILLIAM GARNER[4] AND HOWARD TIECKELMANN

The Chemistry Department and the School of Pharmacy, State University of New York at Buffalo, Buffalo, New York

Received April 23, 1963

Ethyl hydantoin-5-carboxylates have been prepared from ureidomalonates in the presence of sodium ethoxide.

Hydantoins and structurally related compounds, natural and synthetic, are legion in the chemical literature. There are, however, few specific references to derivatives of hydantoin-5-carboxylic acid. This acid, as would be predicted because of its structural relationship to malonic and acetoacetic acids, possesses a reactive substituted methylene group and is difficult to isolate owing to ready decarboxylation. Amides of substituted hydantoin-5-carboxylic acid were isolated by both Fischer[5] and Biltz[6,7] as degradation products of methylated purines. In most cases, attempts to isolate acids from these amides were thwarted by decarboxylation. Biltz,[7] however, isolated 3-methylhydantoin-5-carboxylic acid which was decarboxylated when heated to 130°.

Johnson and Nicolet[8] prepared hydantoin-5-carboxamide (VI) by the ring closure of N-carbethoxyaminomalonamide. The compound was not investigated further except to fuse it with urea in an attempt to prepare uric acid. Johnson and Nicolet also attempted to prepare the intermediate, pseudouric acid, by the reaction of ethyl ureidomalonate (I) and urea in the presence of sodium ethoxide. An alcohol-insoluble precipitate formed which was described as "the sodium salt of ethyl ureidomalonate."

The potential of this latter reaction led us to repeat Johnson's experiment with a variety of ureidomalonates which were readily prepared by the addition of ethyl aminomalonate to the appropriate isocyanate.

When treated with sodium ethoxide, the ureidomalonates cyclize. Under these conditions, ethyl ureidomalonate gave the stable sodium salt of ethyl hydantoin-5-carboxylate (II). The isolation of the parent ester was technically difficult. Initially, ring closure of ethyl ureidomalonate was demonstrated by (1) failure to regenerate ethyl ureidomalonate from the sodium salt on acidification, (2) conversion of the salt to hydantoin (IV) by digestion with concentrated hydrochloric acid, and (3) conversion of the salt to the amide (VI) by cold concentrated ammonium hydroxide.

In alcohol–water solutions, an irreversible change can be observed in the ultraviolet spectrum of I in the region 210–230 mμ on treatment with base followed by acidification. Since no change occurs in the spectrum of I on direct treatment with acid, it was assumed that cyclization occurred on treatment with base. Cyclization occurred so rapidly in basic solution that it was not possible to record the spectrum of the ethyl ureidomalonate anion. Elemental analysis of the sodium salt and successful isolation of the ester III by neutralization with acid-form Dowex-50 resin confirmed ring closure.

The ultraviolet spectra of ethyl hydantoin-5-carboxylates have a strong maximum in the region 290–310 mμ in basic alcohol–water solutions (Table I). The maximum fades rapidly and in this respect these substances have spectral properties similar to those of diethyl malonate and ethyl acetoacetate. Ionization on the 5-position is indicated. The rapid fading of the maximum is due to the saponification of the ester to the corresponding hydantoin-5-carboxylate anion.

Although in sodium ethoxide the cyclization of I occurred at room temperature, reflux was employed to obtain a more easily filtered product. The cyclization of ethyl N′-phenylureidomalonate, however, was a slower reaction and reflux in ethanol was necessary to obtain a good yield of ethyl 3-phenylhydantoin-5-carboxylate (VIII).

Ethyl N′-tetra-O-acetylglucosylureidomalonate formed an insoluble salt when treated with alcoholic

---

(1) This work was supported in part by a grant from the Rho Pi Phi International Leukemia Foundation.

(2) Presented in part at the 139th National Meeting of the American Chemical Society, St. Louis, Mo., March, 1961.

(3) Abstracted from the dissertation of William Garner which was submitted to the Faculty of the Graduate School of Arts and Sciences of the University of Buffalo in partial fulfillment of the requirement for the degree of Doctor of Philosophy, June, 1959.

(4) To whom inquiries should be addressed at Department of Civil Engineering, New Mexico State University, University Park, New Mexico.

(5) E. Fischer, *Ann.*, **215**, 253 (1882).

(6) H. Biltz, *Ber.*, **43**, 1600 (1910).

(7) H. Biltz, *ibid.*, **46**, 3407 (1913).

(8) T. B. Johnson and B. H. Nicolet, *J. Am. Chem. Soc.*, **36**, 345, 355 (1914).

Table I

Ultraviolet Spectra of Sodium Salts of Esters of Hydantoin-5-carboxylic Acids and of Ethyl Acetoacetate in Water

Compound	λ_{max}, mμ	ϵ_{max} (approximate)
Ethyl hydantoin-5-carboxylate	292	5.5×10^3
Ethyl 3-phenylhydantoin-5-carboxylate	293	1.5×10^4
Ethyl 3-phenyl-2-thiohydantoin-5-carboxylate	305	1.8×10^4
N′-Tetra-O-acetylglucosylureidomalonate (XI) treated with base	291	1.6×10^4
N′-Tetra-O-acetylglucosylthioureidomalonate (XII) treated with base	307	1.8×10^4
Ethyl acetoacetate	272	2.2×10^4

sodium ethoxide. Neutralization of the salt with acid-form Dowex 50 gave a glass which could not be crystallized. The ultraviolet spectrum of the salt, however, gave a characteristic pattern for a hydantoin-5-carboxylate with an absorption maximum at 291 mμ and it is assumed that ring closure was effected.

The simple digestion in boiling water, as well as the treatment with ammonia or sodium ethoxide, was found to convert ethyl N′-phenylthioureidomalonate to ethyl 3-phenyl-2-thiohydantoin-5-carboxylate.

Ethyl N′-tetra-O-acetylglucosylthioureidomalonate when treated with sodium ethoxide and neutralized with acid-form Dowex-50 gave a water-insoluble oil which could not be crystallized. The ultraviolet spectrum of the product indicated that ring closure occurred (Table I).

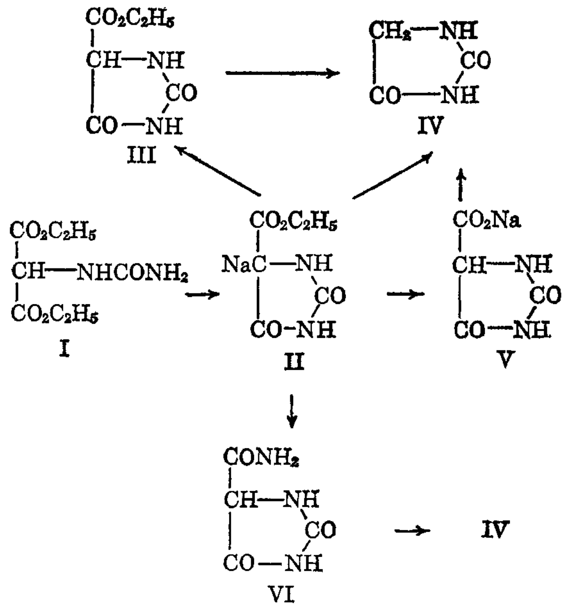
Compound II reduces a variety of mild oxidizing agents including Benedict's solution, Tollens reagent, and potassium triiodide. In experiments where the isolation of III from II was attempted by neutralization with dilute acid followed by multiple extraction with ether, two compounds were isolated in small quantities. These compounds were obtained only when ether was employed and when the reaction mixture was allowed to stand in this solvent. Their elemental analyses corresponded to oxidation products. However, they were not characterized. A reaction employing ether in the isolation procedure which was intended to give ethyl 3-phenylhydantoin-5-carboxylate (VIII) produced in good yield a compound with elemental analyses corresponding to ethyl 5-hydroxy-3-phenylhydantoin-5-carboxylate. This latter compound was degraded with ammonium hydroxide to phenylurea and mesoxalic acid in a manner similar to the "alloxan cleavage" reported by Biltz[6] for the glycol of tetramethyluric acid. No comparable products could be isolated from reactions involving the intentional oxidation of the hydantoin-5-carboxylates with mild permanganate, peroxide, Benedict's solution, or potassium triiodide. In the oxidation products of hydantoin-5-carboxylates, the characteristic ultraviolet absorption at 290 mμ was absent.

Experimental[9]

Ultraviolet Spectra.—Absorption maxima of the anions of the ethyl hydantoin-5-carboxylates faded rapidly owing to hydrolysis. Estimation of the extinction coefficients was accomplished by determining the position of the maxima with an aliquot of alkaline sample. A fresh aliquot of the sample, in which saponification was "quenched" by dilute hydrochloric acid or 1% of ammonium chloride, was placed in the cell. The wave length was set at the maximum and base was added to the cell while absorbance was recorded. The absorbance increased rapidly owing to formation of the anion and then faded rapidly at ambient temperatures as the anion of the ester was hydrolyzed to the hydantoin-5-carboxylate ion. The maximum movement of the pen was used to estimate the extinction coefficient.

Scheme I

Summary of Reactions of Ethyl Hydantoin-5-carboxylate



Ethyl Sodiohydantoin-5-carboxylate (II).—Sodium ethoxide solution (0.23 mole), prepared from 5.3 g. of sodium in 300 ml. of absolute alcohol, was added over a period of 2.5 hr. to a stirred refluxing solution of 50 g. (0.23 mole) of ethyl ureidomalonate[11] in 700 ml. of absolute alcohol under nitrogen. After cooling, the solids were collected in a sintered-glass funnel and washed twice with 200-ml. portions of absolute alcohol and once with 200 ml. of absolute ether to give 43.6 g. (98%) of II.

Anal. Calcd. for $C_6H_7N_2O_4Na$: N, 14.4. Found: N, 14.1.

"Autosaponification" and Decarboxylation of II.—A solution of 8.7 g. of II in 500 ml. of water was allowed to stand at room temperature for 48 hr. At the end of this time, the characteristic 292-mμ absorption maximum was absent from the solution. The solution was shaken with 100 ml. of acid-form Dowex-50 and a gas was evolved. The supernatant from this mixture was then passed through a column which contained more of the resin. This effluent plus the column washings was evaporated under reduced pressure to 15 ml. There was deposited 3.6 g. of crystalline hydantoin which without further purification melted at 221–223° (72%).

Ethyl Hydantoin-5-carboxylate (III).—Twenty-five grams of II was dissolved in 200 ml. of ice-cold water. One gram of decolorizing carbon was added; the mixture was shaken for 1 min. The charcoal was removed by filtration and the filtrate was passed rapidly through acid-form Dowex-50 resin in a 25 × 300 mm. column. The total effluent plus washings was evaporated under reduced pressure to a clear sirup. The sirup was dried azeotropically with absolute alcohol and covered with 250 ml. of absolute ether. When this sirup failed to change in appearance after 24 hr., 10 ml. of absolute alcohol was added to the ether. The sirup crystallized after standing an additional 48 hr., m.p. 82°, 13.5 g. (60%). It was very soluble in water, methanol, ethanol, and acetone, and slightly soluble in boiling benzene. The analytical sample was recrystallized from benzene in poor yield, m.p. 87.5–88.5°.

Anal. Calcd. for $C_6H_8N_2O_4$: C, 41.8; H, 4.7; N, 16.3. Found: C, 42.0; H, 4.9; N, 16.3.

---

[9] All melting points were determined by the liquid-bath capillary method with a thermometer which had been calibrated with U.S.P. Melting Point Reference Standards. Hydantoin, after recrystallization from water, melted, then decomposed at 222–223° (lit.[10] m.p. 220°).

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

[11] (a) V. Cerchez, *Bull. soc. chim. France*, [4]**47**, 1287 (1930); (b) J. C. Sheehan and H. K. Bose, *J. Am. Chem. Soc.*, **73**, 1761 (1951).

One gram of III was digested with 10 ml. of concentrated hydrochloric acid and the mixture was evaporated to dryness. The yield of hydantoin on recrystallization from 95% ethanol was 0.35 g. (60%), m.p. 221–222°.

Ethyl 3-Phenylhydantoin-5-carboxylate (**VIII**).—Sodium ethoxide solution (10 mmoles) was added over a period of 15 min. to a stirred, refluxing solution of 3.0 g. (10 mmoles) of dry ethyl N′-phenylureidomalonate[12] in 25 ml. of absolute alcohol. Reflux was maintained for an additional 15 min. After cooling to room temperature, the solution was diluted with 50 ml. of water and immediately passed through a column containing acid-form Dowex-50. The effluents were then evaporated under reduced pressure. The residual sirup was dissolved in 50 ml. of absolute alcohol and this solution was allowed to evaporate spontaneously. After 3 days, the sirup showed evidence of crystallizing. The mass was covered with 2 ml. of 50% alcohol and triturated. After standing for 24 hr., the entire mass became crystalline. The crystals were collected by filtration, washed with 15 ml. of water, and air dried to give 1.2 g. (47%), m.p. 110°.

Anal. Calcd. for $C_{12}H_{12}N_2O_4$: C, 58.1; H, 4.9; N, 11.3. Found: C, 58.3; H, 5.0; N, 11.6.

A sample of VIII was digested with 6 *N* hydrochloric acid and the mixture was evaporated to dryness. The residue when recrystallized from a small volume of water proved to be 3-phenylhydantoin, m.p. 151–152°, lit.[12,13] m.p. 154–154.5°. A mixture melting point with an authentic sample gave no depression.

In one experiment the reaction mixture of sodium ethoxide and ethyl N′-phenylureidomalonate (20 g.) was acidified with 6 *N* hydrochloric acid in alcohol in lieu of the Dowex-50 column. After cooling, the sodium chloride was removed by filtration. An equal volume of ether was added to the filtrate and on standing a second, much smaller, amount of sodium chloride was obtained. The ether–alcohol filtrate was evaporated under reduced pressure to yield a clear sirup. The sirup was extracted with hot benzene to yield 11.5 g. of crystalline material, the analysis of which corresponded to ethyl 5-hydroxy-3-phenylhydantoin-5-carboxylate, m.p. 116–118° (64%). A mixture melting point with ethyl N′-phenylureidomalonate (m.p. 118–121°) was 95–98°.

Anal. Calcd. for $C_{12}H_{12}N_2O_5$: C, 54.5; H, 4.6; N, 10.6. Found: C, 54.6; H, 4.5; N, 10.4.

When this substance was treated with ammonium hydroxide, phenylurea was obtained. A second product of this reaction decomposed at 120°. This is the reported decomposition temperature for mesoxalic acid.[14] The reaction mixture also responded to the test of Parrod[15] for mesoxalic acid.

Ethyl N′-Phenylthioureidomalonate (**IX**).—Phenyl isothiocyanate 18.5 g. (0.137 mole) was added dropwise to 18.5 g. (0.105 mole) of ethyl aminomalonate. The mixture was heated for 10 min. on a steam bath and then cooled in an ice bath. The crystalline mass was then washed by decantation with two 50-ml. portions of ligroin (b.p. 60–90°) and crystallized from absolute alcohol–ligroin to give 24.6 g. (75%), m.p. 98–99°.

Anal. Calcd. for $C_{14}H_{18}N_2O_4S$: C, 54.2; H, 5.8; N, 9.03; S, 10.3. Found: C, 53.9; H, 5.9; N, 9.06 (Dumas)[16]; S, 10.3.

When IX was recrystallized from boiling water, cyclization occurred to give X.

Ethyl 3-Phenyl-2-thiohydantoin-5-carboxylate (**X**).—An equivalent amount of sodium ethoxide in 100 ml. of absolute alcohol was added dropwise over a period of 0.5 hr. to a stirred, refluxing solution of 15.5 g. of IX in 200 ml. of absolute alcohol. Reflux was maintained for an additional hour. After cooling and neutralization with dilute hydrochloric acid, the mixture was evaporated to dryness under reduced pressure. The boiling absolute alcohol extract of this residue gave on cooling 7.3 g. (55.3%), m.p. 156–157°.

Anal. Calcd. for $C_{12}H_{12}N_2O_3S$: C, 54.5; H, 4.6; N, 10.6, S, 12.1. Found: C, 53.9; H, 4.4; N, 10.7; S, 12.5.

A sample of the above material was digested with concentrated hydrochloric acid and the mixture was evaporated to dryness. The residue when recrystallized from boiling water proved to be 3-phenyl-2-thiohydantoin.

Ethyl N′-Tetra-O-acetylglucosylureidomalonate (**XI**).—Ten grams of ethyl aminomalonate was distilled into a chilled receiver which contained 15.7 g. of tetra-O-acetylglucosyl isocyanate.[17] The vessel was kept at ice temperature for an hour. Ten milliliters of chloroform was then added to ensure homogeneity. The mixture was allowed to warm to room temperature and stand for an additional hour. The chloroform was then removed under reduced pressure, and the crude product was recrystallized from equal volumes of absolute alcohol and ligroin to give 14.5 g. (63%), m.p. 157–159°.

Anal. Calcd. for $C_{22}H_{32}N_2O_{14}$: C, 48.2; H, 5.8; N, 5.11. Found: C, 48.0; H, 5.9; N, 5.08.

Ring Closure of XI.—Two milliliters of 1.18 *N* sodium ethoxide solution diluted with 13 ml. of absolute alcohol was added over a period of 15 min. to a stirred, refluxing solution of 1.30 g. (2.36 mmoles) of XI in 35 ml. of absolute alcohol. A precipitate appeared toward the end of the addition. Reflux was maintained for an additional 0.5 hr. After cooling, 20 ml. of water was added to the suspension to give a solution. This solution was passed immediately through a column containing Dowex-50-H^+ and washed with 250 ml. of water. An ultraviolet spectrum of the basicified effluent showed a maximum of 293 mμ. Evaporation under reduced pressure gave a clear glass which did not crystallize.

Ethyl N′-Tetra-O-acetylglucosylthioureidomalonate (**XII**).—Seven and one-half grams (0.0428 mole) of ethyl aminomalonate was distilled into a chilled receiver which contained 14 g. (0.0361 mole) of tetra-O-acetylglucosyl isothiocyanate.[18] The reaction mixture was allowed to warm to room temperature and the mixture was dissolved in dry benzene to ensure homogeneity. The benzene was removed at reduced pressure and the residue was recrystallized from a mixture of equal volumes of absolute alcohol and ligroin to give 18.0 g. (89%), m.p. 135–137°.

Anal. Calcd. for $C_{22}H_{32}N_2O_{13}S$: C, 46.8; H, 5.7; N, 5.0; S, 5.7. Found: C, 47.1; H, 5.2; N, 4.9; S, 5.6.

Ring Closure of XII.—Two milliliters of 1.18 *N* sodium ethoxide was diluted with 3 ml. of absolute alcohol and added dropwise over a period of 15 min. to a stirred, refluxing solution of 1.33 g. (2.36 mmoles) of XII in 35 ml. of absolute alcohol. Reflux was maintained for an additional 15 min. The solution was allowed to cool to room temperature, and was passed through a column containing Dowex-50-H^+. The column was washed with 200 ml. of 95% alcohol. Evaporation of the effluent at reduced pressure gave a clear, slightly yellow glass which did not crystallize. The ultraviolet spectra of the reaction mixture and the column effluent showed an absorption maximum at 307 mμ.

Hydantoin-5-carboxamide (**VI**).—Thirty milliliters of frozen concentrated ammonium hydroxide was allowed to warm to a slush and poured on 4 g. of II. After 40 hr. in the refrigerator, the clear solution was evaporated to dryness under reduced pressure. The gummy residue was redissolved in 100 ml. of water and neutralized to a methyl orange end point with dilute hydrochloric acid. After evaporation to dryness under reduced pressure and extraction with cold absolute alcohol, the residue crystallized. It decomposed at 320–325° (1.2 g., 41%).

Anal. Calcd. for $C_4H_5N_3O_3$: N, 29.4. Found: N, 29.4.

Compound VI, prepared by the condensation of carbethoxyaminomalonamide with alcoholic potassium hydroxide, decomposed at 320–325°, and gave an ultraviolet spectrum identical with that of the product of ammonolysis.

---

[12] E. S. Gatewood, *J. Am. Chem. Soc.*, **47**, 2175 (1925).

[13] J. Guareschi, *Ber.*, **25R**, 327 (1892).

[14] W. Denis, *Am. Chem. J.*, **38**, 561 (1907).

[15] J. Parrod, *Compt. rend.*, **206**, 355 (1938).

[16] This compound, in contrast to several structurally related compounds, was not amenable to Kjeldahl analysis. Several determinations by this method gave a value of 8.00 ± 0.1% nitrogen content.

[17] T. B. Johnson and W. Bergmann, *J. Am. Chem. Soc.*, **54**, 3360 (1932).

[18] K. M. Haring and T. B. Johnson, *ibid.*, **55**, 395 (1933).