Substitution in the Hydantoin Ring. VII. N-3-Propionic Acid and Its Ethyl Ester and N-3-(2-Cyanoethyl) Derivatives

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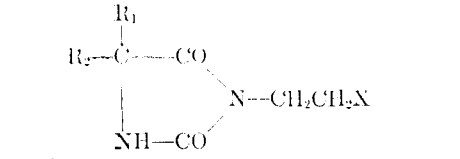
The preparation of N-3-propionic acid and its ethyl ester and N-3-(2-cyanoethyl) derivatives of 5,5-diphenylhydantoin, 5-methyl-5-phenylhydantoin, 5-methyl-5-(2-thienyl)hydantoin, and 5,5-pentamethylenehydantoin by the following three methods is described: (1) alkylation of the hydantoin with ethyl 3-chloropropanoate and saponification of the resulting ethyl ester; (2) condensation of the hydantoin with ethyl acrylate and subsequent saponification; and (3) condensation of the hydantoin with acrylonitrile followed by acid-catalyzed ethanolysis and hydrolysis of the resulting N-3-(2-cyanoethyl) derivative. The preparation of 5,5-diphenylhydantoin-3-propionamide and 5,5-pentamethylenehydantoin-3-propionamide and -anilide is reported. The pharmacology of 5-methyl-5-phenylhydantoin-N-3-propionic acid, 5-methyl-5-(2-thienyl)hydantoin-N-3-propionic acid, and N-3-(2-cyanoethyl)-5,5-diphenylhydantoin is described. These compounds did not afford protection against chemically or electrically induced seizures in mice, nor did they possess analgetic properties. However, spontaneous motor activity was depressed.

A previous report described the preparation of hydantoin-N-3-acetic acid derivatives by the alkylation of hydantoins with ethyl chloroacetate and saponification of the resulting ester.[4] In the present study the preparation of N-3-propionic acid derivatives of four hydantoins by three methods is described. The first method consists of alkylating the hydantoins with ethyl 3-chloropropanoate, then hydrolyzing the resulting esters (Ia–IVa) to the corresponding acids (Ib–IVb). In this method the best procedure for obtaining the ester was that of conducting the reaction in absolute ethanol with potassium hydroxide as the base. The results of using other solvents and bases is illustrated in the preparation of IVa as described in the Experimental Section. Small quantities of the propionic acid derivative and unreacted hydantoin were isolated and identified in this alkylation reaction.



Ia–d, $R_1 = R_2 = C_6H_5$
IIa–c, $R_1 = CH_3$; $R_2 = C_6H_5$
IIIa–c, $R_1 = CH_3$; $R_2 = CH{=}CHCH{=}C{-}S{-}$
IVa–d, R_1 and $R_2 = (CH_2)_5$
X = $COOC_2H_5$ (a), COOH (b), CN (c), $CONH_2$ (d), $CONHC_6H_5$ (e)

In the second synthetic method the Michael condensation of the four hydantoins with ethyl acrylate was used to prepare the esters Ia–IVa.[5] Subsequent saponification of these esters resulted in the corresponding acids (Ib–IVb), and both the esters and acids were shown to be identical with the products formed by the alkylation with ethyl 3-chloropropanoate.

In the alkylation of hydantoins with ethyl acrylate the best procedure was generally that of conducting the reaction in an autoclave, using solvents such as acetone and absolute ethanol, and catalyzing the reaction with potassium hydroxide. The reaction of 5,5-diphenylhydantoin and ethyl acrylate under varying experimental conditions has been studied extensively, and the results are given in Table I. The condensation of hydantoins with several α,β-unsaturated esters has been investigated by Sato.[6]

TABLE I
ALKYLATION OF 5,5-DIPHENYLHYDANTOIN WITH ETHYL ACRYLATE[a]

Solvent, ml	Ethyl acrylate, mole	KOH, equiv	Time, hr	—Yield, %— Ester Ia	Acid Ib
Abs EtOH, 450	0.12	1×10^{-2}	12[b]	34	0
DMF, 90	0.11	2×10^{-2}	8[b]	47	2
2-CH_3OEtOH, 50	0.15	1×10^{-2}	10[b]	84	0
EtOH, 200	0.11	5×10^{-2}	24[c]	0	58
Abs EtOH, 350	0.10	1×10^{-2}	8[c]	42	14
$(Me)_2CO$, 100	0.10	6×10^{-2}	10[c]	35	43
$(Me)_2CO$, 50	0.10	6×10^{-2}	20[c]	62	2
$(Me)_2CO$, 50	0.11	1×10^{-2}	48[d,e]	52	42
$(Me)_2CO$, 50	0.10	1×10^{-2}	48[e,f]	20	61

[a] All reagent quantities are per 0.1 mole of 5,5-diphenylhydantoin. [b] The reaction mixture was refluxed at atmospheric pressure with stirring. [c] The reaction was conducted in an autoclave at 110°. [d] The reaction was conducted in an autoclave at 115°. [e] The KOH was dissolved in 1.7 ml of H_2O prior to being added to the autoclave. [f] The reaction was conducted in an autoclave at 120°.

The third synthetic method employed involved the condensation of the hydantoins with acrylonitrile as the α,β-unsaturated addend. This resulted in the formation of the N-3-(2-cyanoethyl) derivatives (Ic–IVc) which underwent acid-catalyzed ethanolysis and hydrolysis, respectively, to form the corresponding ethyl esters and acid derivatives identical with those prepared by the two previous methods. Recent reports of hydantoins undergoing the Michael condensation with acrylonitrile to produce mono- and dicyanoethylated products are recorded.[7,8]

Ammonolysis of the acid chloride of Ib produced Id, and IVd was prepared by conservative acid hydrolysis

(1) Taken in part from the M.S. Thesis of J. W. S., Bucknell University, 1966.
(2) Undergraduate research participant, Bucknell University, summer 1965.
(3) National Science Foundation Undergraduate Research Participant, Bucknell University, summer 1965.
(4) M. B. Winstead and C. R. Hamel, *J. Med. Chem.*, **8**, 120 (1965).
(5) E. D. Bergmann, D. Ginsburg, and R. Pappo, *Org. Reactions*, **10**, 184 (1959).
(6) M. Sato, *Nippon Kagaku Zasshi*, **83**, 620 (1962).
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of IVc. The anilide IVe was prepared from IVb by the method described by Klosa.[9]

Pharmacology.—Pharmacological evaluation of 5-methyl-5-phenylhydantoin-N-3-propionic acid (IIb), 5-methyl-5-(2-thienyl)hydantoin-N-3-propionic acid (IIIb), and N-3-(2-cyanoethyl)-5,5-diphenylhydantoin (Ic) was conducted by Hazleton Laboratories, Inc., Falls Church, Va. The tests utilized were (1) gross pharmacotoxic characterization, (2) spontaneous motor activity, (3) forced locomotor activity (rotarod), (4) pentylenetetrazole seizure, (5) maximum electroshock seizure, (6) minimum electroshock seizure, (7) hot plate reaction time, (8) hexobarbital potentiation, and (9) phenylquinone writhing.

Male Swiss-Webster ICR mice were used in all tests. The test compounds were prepared fresh daily as suspensions in 0.5% carboxymethylcellulose and administered in a constant volume of 10 ml/kg. The oral route of administration was utilized for tests 8 and 9; the intraperitoneal route was used for all other tests. Each compound was evaluated at a dose of 100 mg/kg unless stated otherwise. The compounds were tested as a block of three utilizing a common control group which received a dose of 10 ml/kg of carboxymethylcellulose.

The gross pharmacotoxic characterization test was the initial test performed and served as an indication of the onset of action, type of pharmacologic activity, and toxicity of each compound. Doses of 56.2, 100, 178, 316, 562, and 1000 mg/kg of each compound were administered to six groups of five mice each for observation of gross pharmacotoxic signs. Observations were made at 0.25, 0.5, 1, 2, 4, 24, and 48 hr after dosing and were recorded on a standard laboratory protocol. The intensity of gross pharmacotoxic signs and the reaction ratio (number of animals which showed a symptom over the number of animals tested) were noted. For characterization as a major pharmacotoxic sign, the degree of effect observed was required either to be graded ++ (moderate) or +++ (marked) at peak effect in more than one animal in the group or to be graded + (slight) in a majority of animals in the group.

Three Woodard Research Corp. photocell activity chambers were used in the spontaneous motor activity test. Groups of six mice were treated with test compound or carboxymethylcellulose. Activity counts were recorded on a squad of three mice at a time using a block design of eight squads. Fifteen minutes after treatment, the mice were placed in the activity chambers and cumulative counts were recorded for 20 min. The number of counts accumulated during the last half of the 20-min period was used for comparison with controls.

The method of Dunham and Miya[10] was used to assess neurologic deficit in mice undergoing the forced locomotor activity test. In the pentylenetetrazole and electroshock seizure tests groups of ten mice were treated with compound or vehicle prior to subcutaneous injection of pentylenetetrazole or shock treatment. Analysis of analgetic activity was performed according to the Woolfe and MacDonald technique[11] as modified by Eddy.[12] In the hexobarbital potentiation test groups of ten mice were given compound or vehicle orally following an overnight fast. Thirty minutes later they were injected intraperitoneally with 100 mg/kg of hexobarbital. In the phenylquinone writhing test, a modification of the method of Siegmund was used.[13]

Each of the three hydantoin derivatives tested appeared to be relatively nontoxic when administered by the intraperitoneal route. At the doses studied, LD_{50}'s could not be calculated from the data obtained, but are probably greater than 562 mg/kg for IIIb and greater than 1000 mg/kg for IIb and Ic. Few pharmacologic signs were observed following administration of IIb. A short period of writhing occurred immediately after dosing at all levels. Limb spasticity was also noted at all levels. Other major pharmacological signs observed at levels of 100 mg/kg and higher were ataxia, ptosis, and decreased activity. Limb weakness was noted only at the highest level. Few pharmacologic signs were observed following administration of IIIb at doses below 562 mg/kg. Limb spasticity was seen at all levels tested and a short period of writhing followed treatment with doses of 100 mg/kg and higher. Additional signs observed at the highest levels (562 and 1000 mg/kg) included ataxia, decreased activity, lacrimation, ptosis, and decreased muscle tone. At doses up to 1000 mg/kg, Ic induced few pharmacological signs. Decreased activity was noted at all dosages used, and decreased muscle tone occurred after doses of 316 and 562 mg/kg. A short period of writhing was noted following most doses. Although limb spasticity was seen in mice in most levels, the degree of prevalence was not great enough to warrant including this effect as a major sign. Compound Ic appeared to induce less neurological deficit as assessed by incidence of ataxia.

In the spontaneous motor activity test, as measured in actophotometers, Ic and IIb decreased the mean cumulative activity count from 66 (control) to 32, thereby registering a 52% decrease in activity; IIIb did not appear to have a net marked effect on spontaneous motor activity. None of the test compounds impaired performance of the mice undergoing forced locomotion.

At doses of 100 and 400 mg/kg, none of the test compounds afforded protection against chemically (pentylenetetrazole) or electrically induced seizures (maximum and minimum electroshock) for a 2-hr period following drug treatment. For comparison purposes, phenobarbital and diphenylhydantoin, each at 50 mg/kg ip, protected ten of ten mice and seven of ten mice, respectively, against maximum seizures when the mice were shocked 60 min postdrug. The compounds did not possess analgetic properties as determined by the hot plate reaction time and phenylquinone writhing tests. The results obtained in the former test with samples IIIb and Ic indicated an increased perceptiveness or sensitivity, determined as a function of time, to the heat stimulus. Narcosis induced by hexobarbital was significantly prolonged following 100 mg/kg of IIb administered orally. Similar observations were made with IIIb. Although the duration of anesthesia

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(12) N. B. Eddy, *ibid.*, **98**, 121 (1950).

(13) E. Siegmund, *J. Pharmacol., Exptl. Therap.*, **119**, 184 (1957).

induced by hexobarbital was slightly increased following treatment with Ic, the difference was not significant. Data obtained from the hexobarbital potentiation test correlated with the finding of decreased activity by gross observation and measurement in actophotometers.

Experimental Section

Melting points were determined with a Mel-Temp apparatus and are corrected. C and H analyses were determined by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y., N analyses in this laboratory by the semimicro Kjeldahl method.[14] Uv spectrograms were obtained with a Cary Model 15 spectrophotometer. Ir spectrograms (in Nujol and KBr) were obtained with Perkin-Elmer Models 137 and 521 spectrophotometers and a Beckman Model IR-4 spectrophotometer. Nmr spectrograms were determined by means of a Varian Model A-60A spectrophotometer (TMS).

5,5-Diphenylhydantoin was commercially available and was purified by dissolving at pH 11 in aqueous NaOH, decolorizing and clarifying with Norit and Celite, respectively, then precipitating with HCl. The resulting slurry was buffered with $NaHCO_3$, filtered, and recrystallized from 80% aqueous EtOH; mp 294–294.5°, lit.[15] mp 295–298°. 5-Methyl-5-phenylhydantoin and 5,5-pentamethylenehydantoin were prepared from acetophenone and cyclohexanone, respectively, $(NH_4)_2CO_3$, KCN, and aqueous EtOH;[16] 5-methyl-5-phenylhydantoin (recrystallized from aqueous EtOH), mp 198–198.5°, lit.[17] mp 198.5°; 5,5-pentamethylenehydantoin (recrystallized from EtOH), mp 217°, lit.[17] mp 217–217.5°. Similarly 5-methyl-5-(2-thienyl)hydantoin was prepared from methyl 2-thienyl ketone;[18] recrystallized from H_2O, mp 138.5–140.5°, lit. mp 138.5–140°,[18] 136.5–138°.[16] Ethyl 3-chloropropanoate, ethyl acrylate, and acrylonitrile were commercially available and were used without further purification.

Method I. Alkylation with Ethyl 3-Chloropropanoate. A. Ethyl 3-(2,5-Dioxo-4,4-diphenyl-1-imidazolidinyl)propanoate (Ia).—A mixture of 12.6 g (0.05 mole) of 5,5-diphenylhydantoin, 4.2 g of KOH, and 200 ml of absolute EtOH was heated to reflux and a solution containing 8.2 g (0.06 mole) of ethyl 3-chloropropanoate and 20 ml of absolute EtOH was added dropwise during 30 min. After refluxing 24 hr, 200 ml of EtOH was removed by distillation. The concentrated reaction mixture was cooled to room temperature and poured into 700 ml of iced H_2O with rapid stirring, while maintaining the pH at 11 with dilute NaOH. Upon standing in the aqueous solution the material slowly solidified to yield 15 g (86%) of Ia: recrystallized from EtOH, yield 12 g (70%), mp 93–93.5°; λ_{max}^{MeOH} 263.5 mμ (ε 476), 257.5 mμ (ε 719); no change in MeOH–HCl or MeOH–KOH; nmr ($CDCl_3$), δ 1.13 (t, 3), 2.62 (t, 2, CH_2CO), 3.95 (m, 4), 7.35 (s, 10), 7.70 ppm (s, 1, NHCO). *Anal.* ($C_{20}H_{20}N_2O_4$) C, H, N. The alkaline filtrate was neutralized with HCl and buffered with 5 g of $NaHCO_3$ to yield 1 g (8%) of unreacted 5,5-diphenylhydantoin as shown by mixture melting point and ir spectra. The filtrate was acidified to pH 1 with HCl to yield 0.5 g (3%) of Ib.

B. Ethyl 3-(2,5-Dioxo-4,4-pentamethylene-1-imidazolidinyl)propanoate (IVa). Procedure B-1.—A mixture of 16.8 g (0.1 mole) of 5,5-pentamethylenehydantoin, 16.4 g (0.12 mole) of ethyl 3-chloropropanoate, 27.6 g (0.2 mole) of anhydrous K_2CO_3, and 150 ml of DMF was refluxed with stirring for 23 hr. The hot solution was filtered and the residue was washed with hot DMF. After dissolving this residue in H_2O and filtering, the resulting solution was acidified with dilute H_2SO_4 to yield 6.4 g (27%) of bicarbonate-soluble acid IVb: recrystallized (aqueous EtOH), mp 215–216°; nmp (with the hydantoin, mp 217°) 180–190°; nmr (CF_3CO_2H), δ 1.80 (m, 10, $(CH_2)_5$), 2.89 (t, 2, CH_2CO), 4.00 (t, 2, $CH_2N(CO)_2$), 7.76 ppm (s, 1, NHCO). *Anal.* ($C_{11}H_{16}N_2O_4$) C, H, N. Evaporation of the DMF *in vacuo*, then adding the concentrated filtrate to iced H_2O, produced a negligible quantity of the ester IVa.

Procedure B-2.—A mixture of 34.5 g (0.25 mole) of anhydrous K_2CO_3, 16.8 g (0.1 mole) of 5,5-pentamethylenehydantoin dissolved in 100 ml of hot DMSO, and 16.4 g (0.12 mole) of ethyl 3-chloropropanoate was stirred and heated at 135–145° for 10 hr, cooled, and filtered to remove the insoluble salts. In contrast to procedure B-1 the salts contained no organic material. The filtrate was concentrated, then poured into iced H_2O to yield 9 g (34% based on IVa) of a mixture of IVa and IVb. This material was extracted with 5% NaOH to yield 4.2 g (16%) of alkali-insoluble ester IVa: recrystallized from aqueous EtOH, mp 109–110°; nmr ($CDCl_3$), δ 1.23 (t, 3), 1.68 (m, 10, $(CH_2)_5$), 2.63 (t, 2, CH_2CO), 3.77 (t, 2, $CH_2N(CO)_2$), 4.10 (q, 2), 7.78 ppm (s, 1, NHCO). *Anal.* ($C_{13}H_{20}N_2O_4$) C, H, N. Acidification of the alkaline filtrate yielded 3 g (12.5%) of acid IVb which, after extraction with aqueous $NaHCO_3$, filtering, acidifying with diluted H_2SO_4, and recrystallization from aqueous EtOH, yielded the acid IVb, mp 214.5–215.5°, identical with the acid produced in procedure B-1 as shown by mixture melting point and ir.

Procedure B-2 was repeated and the reaction mixture was stirred and heated at 160–165° for 20 hr, filtered, then concentrated *in vacuo* to one-half its volume. Addition of the filtrate to iced H_2O produced no precipitate of IVa as previously obtained. Acidification of the aqueous solution with diluted H_2SO_4 and subsequent evaporation in the hood for several days produced 32.5 g (68%) of bicarbonate-soluble acid IVb, recrystallized from aqueous EtOH, yield 29 g (60%), mp 212.5–214°, identical with the acid from procedure B-1 as shown by mixture melting point and ir. The reaction of 0.2 mole of 5,5-pentamethylenehydantoin, 0.25 mole of ethyl 3-chloropropanoate, 0.2 equiv of KOH, and 250 ml of absolute EtOH at 115° for 21 hr in an autoclave resulted in the recovery of 60% of unreacted hydantoin, 6% of ester IVa, and 20% of acid IVb.

Method II. Condensation with Ethyl Acrylate. A. Ethyl 3-(2,5-Dioxo-4,4-diphenyl-1-imidazolidinyl)propanoate (Ia).—Into a 1-l. stainless steel autoclave were placed 25.2 g (0.1 mole) of 5,5-diphenylhydantoin, 10 g (0.1 mole) of ethyl acrylate, 0.05 g of KOH, and 100 ml of Me_2CO. The mixture was heated at 110° for 20 hr and, after cooling, was evaporated to dryness. The resulting solid was ground and stirred for 30 min in 500 ml of H_2O held at pH 11 by the addition NaOH. The alkali-insoluble material was filtered, washed, and dried to yield 27 g (77%) of Ia, mp 93–94°, identical with an authentic sample of Ia as prepared in method I as shown by ir and mixture melting point. The alkaline filtrate was adjusted to pH 7 with HCl and buffered with 5 g of $NaHCO_3$ to yield 3.4 g (13.5%) of unreacted 5,5-diphenylhydantoin. The bicarbonate filtrate was acidified to pH 1 with HCl to yield 2.6 g (8%) of Ib, recrystallized from EtOH, mp 169–170°. Mixture melting point with Ib prepared by the saponification of Ia and the acid hydrolysis of Ic gave no depression, and ir spectrograms were identical. The results of additional condensation reactions of 5,5-diphenylhydantoin with ethyl acrylate under varying experimental conditions are given in Table I.

B. Ethyl 3-(2,5-Dioxo-4-methyl-4-phenyl-1-imidazolidinyl)propanoate (IIa).—A mixture of 19 g (0.1 mole) of 5-methyl-5-phenylhydantoin, 10 g (0.1 mole) of ethyl acrylate, 0.06 g of KOH, and 100 ml of EtOH was heated at 110° in a autoclave for 40 hr. Upon cooling, the yellow reaction mixture was evaporated, and the resulting oil was extracted with two portions of Et_2O. The Et_2O extract was extracted twice with 1% NaOH, then dried over anhydrous Na_2SO_4. Acidification of the alkaline solution produced several grams of bicarbonate-insoluble unreacted hydantoin. Partial evaporation of the Et_2O extract, then addition of hexane, produced a clear oil which solidified slowly. Recrystallization from aqueous EtOH at 55° produced 18 g (62%) of IIa: mp 66–67°; nmr ($CDCl_3$), δ 1.15 (t, 3), 1.80 (s, 3), 2.58 (t, 2, CH_2CO), 3.75 (t, 2, $CH_2N(CO)_2$), 4.05 (q, 2), 7.25–7.62 (m, 5), 7.77 ppm (s, 1, NHCO). *Anal.* ($C_{15}H_{18}N_2O_4$) C, H, N.

C. Ethyl 3-(2,5-Dioxo-4-methyl-4-(2-thienyl)-1-imidazolidinyl)propanoate (IIIa).—A mixture of 19.6 g (0.1 mole) of 5-methyl-5-(2-thienyl)hydantoin, 13 g (0.13 mole) of ethyl acrylate, and 0.84 g of KOH (dissolved in a minimum of H_2O) was dissolved in 75 ml of absolute EtOH, placed in a 1-l. autoclave, and heated for 24 hr at 110°. After cooling and filtering, the filtrate was evaporated to one-half its volume, and the concentrated solution was added to iced H_2O. An oil formed which crystallized slowly to give 21.5 g (72%) of product melting at 61–64°.

(14) Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values.

(15) H. Biltz, *Ber.*, **41**, 1391 (1908).

(16) L. H. Goodson, I. L. Honigberg, J. J. Lehman, and W. H. Burton, *J. Org. Chem.*, **25**, 1920 (1960).

(17) H. R. Henze and R. J. Speer, ADI Document 1603; supplement to *J. Am. Chem. Soc.*, **64**, 522 (1942).

(18) J. J. Spurlock, *ibid.*, **75**, 1115 (1953).

After dissolving these crystals in a large volume of ether, the resulting solution was extracted twice with 5% NaOH. Partial evaporation and cooling of the ether layer produced 17 g (57%) of IIIa: recrystallized from C_6H_6–petroleum ether (60–110°), yield 15 g (50%), mp 60.5–61.5°; λ_{max}^{MeOH} 233.5 mμ (ε 8016); no change in MeOH–HCl; $\lambda_{max}^{MeOH-KOH}$ 230 mμ (ε 8535); nmr ($CDCl_3$), δ 1.19 (t, 3), 1.83 (s, 3), 2.61 (t, 2, CH_2CO), 3.80 (t, 2, $CH_2N(CO)_2$), 4.10 (q, 2), 6.90-7.40 ppm (m, 4, $NHCO$ and thiophene ring protons). *Anal.* ($C_{13}H_{16}N_2O_4S$) C, H, N. Acidification of the alkaline solution gave crystals which, after dissolving in aqueous $NaHCO_3$, filtering, and acidifying, produced 4.3 g (16%) of IIIb, recrystallized from H_2O, mp 120–121.5°.

D. Ethyl 3-(2,5-Dioxo-4,4-pentamethylene-1-imidazolidinyl)-propanoate (IVa). Procedure D-1.—Into a 1-l. autoclave were placed 33.6 g (0.2 mole) of 5,5-pentamethylenehydantoin, 21 g (0.21 mole) of ethyl acrylate, 1.7 g of KOH dissolved in 5 ml of H_2O, and 200 ml of Me_2CO. This mixture was heated at 115° for 29 hr, cooled, and filtered to remove a small amount of charred residue. The Me_2CO was evaporated, and the resulting residue was extracted with NaOH and filtered to yield 28.6 g (55%) of IVa, mp 107.5–108.5°; identical with the ester IVa produced in method I-B, procedure B-2, as shown by ir and mixture melting point. Acidification of the alkaline filtrate yielded 11.7 g (24%) of product, which, after extraction with aqueous $NaHCO_3$, filtering, and acidifying yielded 10 g (21%) of acid IVb, mp 214–215°, recrystallized from aqueous EtOH, identical with an authentic sample of IVb (method I-B, procedure B-1) as shown by mixture melting point and ir.

Procedure D-2.—A mixture of 0.15 mole of 5,5-pentamethylenehydantoin, 0.15 mole of ethyl acrylate, and 0.015 equiv of KOH in 150 ml of absolute EtOH was heated in the autoclave at 115° for 23 hr. After cooling, the mixture was added to iced H_2O producing 22 g of product, which, upon extraction with 5% NaOH, resulted in 20% of ester IVa, recrystallized from aqueous EtOH, mp 110–111°; mixture melting point with authentic ester gave no depression. Acidification of the alkaline solution produced 10% of bicarbonate-soluble acid IVb, recrystallized from EtOH, mp 212–213.5°, identical with an authentic sample of IVb as shown by mixture melting point and ir.

Procedure D-3.—A mixture of 0.2 mole of 5,5-pentamethylenehydantoin, 0.21 mole of ethyl acrylate, and 0.03 equiv of KOH in 200 ml of absolute EtOH was heated in the autoclave at 115° for 29 hr. Working up in the manner as described in procedure D-2 above produced 26 g (49%) of alkali-insoluble ester IVa, recrystallized from EtOH, yield 24 g (45%), mp 109–110°. No mixture melting point depression with an authentic sample of IVa was observed. However, in contrast to the previous procedure, acidification of the alkaline solution produced 13 g (39%) of unreacted 5,5-pentamethylenehydantoin, as shown by mixture melting point and ir. Only 0.5 g of bicarbonate-soluble acid IVb was produced in this procedure.

Method III. Condensation with Acrylonitrile. A. N-3-(2-Cyanoethyl)-5,5-diphenylhydantoin (Ic).—A mixture of 37.8 g (0.15 mole) of 5,5-diphenylhydantoin, 50 ml of DMF, and 0.056 g of KOH was heated to reflux temperature and a solution of 8.1 g (0.15 mole) of acrylonitrile and 30 ml of DMF was added dropwise during 30 min. Reflux was continued for 1 hr, then 60 ml of DMF was removed by distillation. The concentrated reaction mixture was cooled to room temperature and poured with stirring into 1 l. of iced H_2O held at pH 11 with NaOH. An oily precipitate of Ic formed which solidified upon continued stirring to yield 39.3 g (86%) of Ic: recrystallized from C_6H_6, yield 35. 7 g (78%), mp 193.5–194.5°; nmr (CF_3CO_2H), δ 3.04 (t, 2, CH_2CN), 4.15 (t, 2, $CH_2N(CO)_2$), 7.42 (s, 10), 7.87 ppm (s, 1, $NHCO$). *Anal.* ($C_{18}H_{15}N_3O_2$) C, H, N. Acidification of the alkaline filtrate to pH 7 with HCl gave 2.8 g (7%) of unreacted 5,5-diphenylhydantoin.

B. N-3-(2-Cyanoethyl)-5-methyl-5-phenylhydantoin (IIc).—Over a period of 15 min a solution of 3 g (56.5 mmoles) of acrylonitrile in 10 ml of 4-butyrolactone was added dropwise to a solution of 10 g (53 mmole) of 5-methyl-5-phenylhydantoin and 20 ml of 10% Me_4NOH in 20 ml of 4-butyrolactone. After heating at 95° for 2 hr, the mixture was poured over ice. The resulting oil crystallized after being magnetically stirred for several hours, and yielded 10 g (78%) of IIc: recrystallized from aqueous EtOH, mp 96–97°; nmr ($CDCl_3$), δ 1.88 (s, 3), 2.72 (t, 2, CH_2CN), 3.81 (t, 2, $CH_2N(CO_2)_2$), 7.05 (s, 1, $NHCO$), 7.45 ppm (m, 5). *Anal.* ($C_{13}H_{13}N_3O_2$) C, H, N.

C. N-3-(2-Cyanoethyl)-5-methyl-5-(2-thienyl)hydantoin (IIIc) was prepared in a manner analogous to that described for IIc above. Crystallization of IIIc required a minimum of 1 week; recrystallized from aqueous EtOH, yield 14 g (75%), mp 89.5–90.5°; nmr ($CDCl_3$), δ 1.85 (s, 3), 2.69 (t, 2, CH_2CN), 3.78 (t, 2, $CH_2N(CO)_2$), 6.9–7.4 ppm (m, 4, $NHCO$ and thiophene ring protons). *Anal.* ($C_{11}H_{11}N_3O_2S$) C, H, N.

D. N-3-(2-Cyanoethyl)-5,5-pentamethylenehydantoin (IVc).—To a refluxing mixture of 16.8 g (0.1 mole) of 5,5-pentamethylenehydantoin and 0.056 g of KOH in 60 ml of DMF was added 5.4 g (0.1 mole) of acrylonitrile in 20 ml of DMF over a period of 30 min. The mixture was refluxed an additional 3.5 hr to yield, after the usual work-up as described in method III-A for Ic, 13.8 g (63%) of IVc: recrystallized from EtOH, yield 12.7 g (58%), mp 156.5–157°; no uv maxima were observable; nmr (CF_3CO_2H), δ 1.84 (m, 10, $(CH_2)_5$), 2.97 (t, 2, CH_2CN), 4.00 (t, 2, $CH_2N(CO)_2$), 7.80 ppm (s, 1, $NHCO$). *Anal.* ($C_{11}H_{15}N_3O_2$) C, H, N. Upon standing overnight the alkaline filtrate deposited 1.1 g (4%) of crystals melting at 109–110°, which, based upon ir analysis (no N–H stretching frequency at 3.1 μ) and a prior report,[8] were taken to be N-1,N-3-bis(2-cyanoethyl)-5,5-pentamethylenehydantoin.

3-(2,5-Dioxo-4,4-diphenyl-1-imidazolidinyl)propanoic Acid (Ib). Procedure A.—A mixture of 27.7 g (0.08 mole) of Ia, 50 ml of EtOH, and 3.3 g (0.082 equiv) of NaOH dissolved in 10 ml of H_2O was refluxed 1 hr, then cooled and poured into 500 ml of iced H_2O with stirring. A clear solution resulted which was assumed to indicate that saponification was completed. This solution was acidified to pH 1 with HCl producing Ib: recrystallized from EtOH, yield 23 g (90%), mp 170–170.5°; λ_{max}^{MeOH} 264 mμ (ε 441), 257.5 mμ (ε 677); no change in MeOH–HCl or MeOH–KOH; nmr (CF_3CO_2H), δ 2.99 (t, 2, CH_2CO), 4.14 (t, 2, $CH_2N(CO)_2$), 7.42 (s, 10), 7.83 ppm (s, 1, $NHCO$). *Anal.* ($C_{18}H_{16}N_2O_4$) C, H, N.

Procedure B.—A mixture of 5 g (16.4 mmoles) of Ic, 25 ml of H_2O, and 25 ml of concentrated H_2SO_4 was refluxed with stirring for 2 hr. After cooling and adding the solution to 1 l. of iced H_2O, the precipitate that formed was filtered, washed, and dried. This precipitate was ground fine and stirred in 500 ml of H_2O containing 10 g of $NaHCO_3$. Most of the precipitate dissolved leaving 0.3 g (6%) of unreacted Ic, as identified by mixture melting point. The slightly turbid bicarbonate filtrate was clarified with Norit and Celite, filtered, and then acidified to pH 1 with HCl. This produced 4.5 g (85%) of Ib, recrystallized from EtOH, yield 4 g (75%), mp 170–171°. Mixture melting point with Ib produced in procedure A above gave no depression.

In a similar manner a mixture of 5 g (16.4 mmoles) of Ic, 40 ml of absolute EtOH, and 10 ml of concentrated H_2SO_4 was refluxed 4 hr, then poured with stirring into 1 l. of iced H_2O to yield 5.3 g (91.5%) of Ia, recrystallized from EtOH, yield 4.9 g (84%), mp 91–92°, identified with an authentic sample of Ia by mixture melting point and ir.

3-(2,5-Dioxo-4-methyl-4-phenyl-1-imidazolidinyl)propanoic Acid (IIb). Procedure A.—A mixture of 11.2 g (0.04 mole) of IIa and 2 g (0.05 equiv) of NaOH (dissolved in 4.5 ml of H_2O) was dissolved in 100 ml of absolute EtOH and refluxed 8 hr. The reaction mixture was acidified and filtered, and the filtrate evaporated. The resulting oil was extracted with warm aqueous $NaHCO_3$, and this solution was then cooled and acidified. The oily product crystallized slowly to yield 4 g (41%) of acid IIb: recrystallized from H_2O, mp 123–123.5°; nmr (DMSO-d_6), δ 1.65 (s, 3), 2.53 (t, 2, CH_2CO), 3.62 (t, 2, $CH_2N(CO)_2$), 7.38 (m, 5), 8.83 ppm (s, 1, $NHCO$). *Anal.* ($C_{13}H_{14}N_2O_4$) C, H, N.

Procedure B.—Seven grams (0.03 mole) of IIc was refluxed in 35 ml of 6 *N* HCl for 5 hr. Upon cooling an oil settled out which crystallized slowly yielding after recrystallization from H_2O, 80% of IIb, identical with that produced from procedure A above as shown by mixture melting point and ir.

3-[2,5-Dioxo-4-methyl-4-(2-thienyl)-1-imidazolidinyl]propanoic Acid (IIIb).—In a manner similar to that described in procedure A above compound IIIa was saponified to yield 91% of IIIb: mp 122–122.5°, recrystallized from H_2O; reaction time 4.5 hr; nmr (CF_3CO_2H), δ 1.94 (s, 3), 2.85 (t, 2, CH_2CO), 3.96 (t, 2, $CH_2N(CO)_2$), 6.85–7.30 (m, 3, thiophene ring protons), 7.56 ppm (s, 1, $NHCO$); λ_{max}^{MeOH} 231.5 mμ (ε 7968); no change in MeOH–HCl or MeOH–KOH. *Anal.* ($C_{11}H_{12}N_2O_4S$) C, H, N. IIIb was prepared also by the acid hydrolysis of IIIc similar to that described in procedure B above.

3-(2,5-Dioxo-4,4-pentamethylene-1-imidazolidinyl)propanoic Acid (IVb).—In a similar manner IVa was saponified to yield 85% of acid IVb, recrystallized from aqueous EtOH, mp 214–215°. The ir spectrum was identical with that of an authentic

sample of IVb. The reaction time was 4.5 hr, and a large amount of precipitate formed during the course of the refluxing, presumably the sodium salt of IVb. Also, IVc was hydrolyzed in 50% H_2SO_4 to IVb in 90% yield; identified with an authentic sample by mixture melting point and ir. The reaction mixture was refluxed 2 hr.

3-(2,5-Dioxo-4,4-diphenyl-1-imidazolidinyl)propanamide (Id).—A mixture of 8.6 g (26.5 mmoles) of Ib and 7.5 g (63 mmoles) of $SOCl_2$ was refluxed 30 min. The resulting viscous solution of the acid chloride of Ib was poured slowly, with rapid stirring, into 42.5 ml (62.5 mmoles) of concentrated NH_4OH, while maintaining the temperature below 5° with an ice bath. After standing for 30 min the solution was filtered to yield 8 g (94%) of amide Id: recrystallized from EtOH, yield 7 g (82%), mp 181–182°; λ_{max}^{MeOH} 264 mμ (ε 437), 257.5 mμ (ε 673); no change in MeOH–HCl or MeOH–KOH; nmr (CF_3CO_2H), δ 3.00 (t, 2, CH_2CO), 4.19 (t, 2, $CH_2N(CO)_2$), 7.42 (s, 10), 7.86 ppm (s, 1, $NHCO$). *Anal.* ($C_{18}H_{17}N_3O_3$) C, H, N.

3-(2,5-Dioxo-4,4-pentamethylene-1-imidazolidinyl)propanamide (IVd).—One gram (4.5 mmoles) of IVc was added to 20 ml of concentrated H_2SO_4. The reaction mixture was held at 45–50° for 20 min, then poured over iced H_2O, and the pH was adjusted to 11, yielding 0.4 g (40%) of IVd, which, after recrystallization from H_2O, melted at 236–237°. *Anal.* ($C_9H_{17}N_3O_3$) N.

3-(2,5-Dioxo-4,4-pentamethylene-1-imidazolidinyl)propionanilide (IVe).—A mixture of 2.4 g (0.01 mole) of IVb, 0.93 g (0.01 mole) of aniline, and 2 g (0.013 mole) of $POCl_3$ in 75 ml of dioxane was heated on a water bath for 30 min. The mixture was then neutralized with $NaHCO_3$, diluted with H_2O to 400 ml, then concentrated until crystallization occurred upon cooling. The crude product was washed with aqueous $NaHCO_3$; recrystallized from aqueous MeOH, yield 0.8 g (25%), mp 195.5–197°. Acidification of the $NaHCO_3$ solution produced 0.9 g of unreacted IVb: nmr (CF_3CO_2H), δ 1.80 (m, 10, $(CH_2)_5$), 3.05 (t, 2, CH_2CO), 4.15 (t, 2, $CH_2N(CO)_2$), 7.41 (s, 5), 7.72 (s, 1, alicyclic $NHCO$), 9.00 ppm (s, 1, acyclic $NHCO$); λ_{max}^{MeOH} 241 mμ (ε 5727); no change in MeOH–HCl or MeOH–KOH. *Anal.* ($C_{15}H_{21}N_3O_3$) N.

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Analgetics Based on the Azetidine Ring

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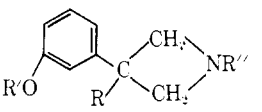
A series of azetidines of type I has been synthesized and examined for analgetic activity. The activity is comparable with that of pyrrolidines prepared previously. Relative activities within the azetidine series do not, however, closely parallel those of the corresponding pyrrolidines.

An earlier paper reported our discovery of a high level of analgesia in compounds based on the pyrrolidine ring[1] (*e.g.*, *m*-(1-methyl-3-propyl-3-pyrrolidinyl)phenol). We have now prepared several azetidines of type I.

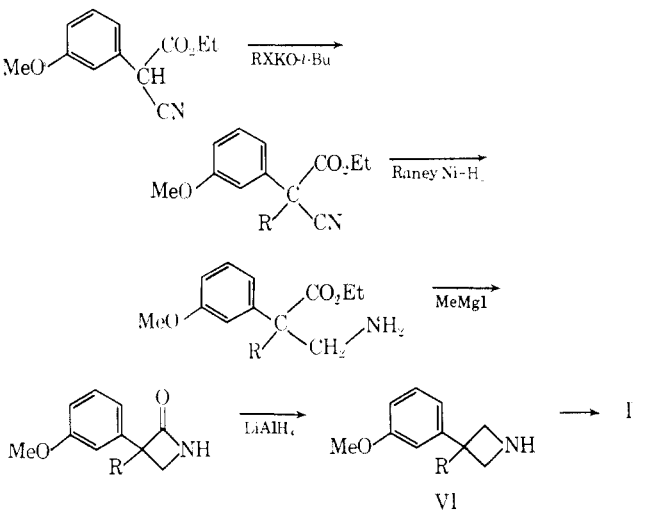


I

Even though lacking a two-carbon bridge between the basic center and the quaternary carbon atom, their relative activity as analgetics was developed to a level comparable with that of the earlier pyrrolidine compounds.

Chemistry.—Our synthetic route to key intermediates (Scheme I) closely follows that pioneered by Testa and his co-workers[2] with the exception of the method used to alkylate the aryl cyanoacetate II. It was found that using sodium ethoxide as the basic reagent[2] gave lower (~50%) yields of the C-alkylated ethyl α-(*m*-methoxyphenyl)cyanoacetate (III) than did sodium *t*-butoxide (~70%) or potassium *t*-butoxide (~90%). Ethyl α-alkyl-α-(*m*-methoxyphenyl)cyanoacetate (III) was catalytically reduced to the amine IV. An attempt

SCHEME I



VI

to prepare the azetidine by $LiAlH_4$ reduction of III and subsequent treatment of the amino alcohol with thionyl chloride and base, following our earlier method,[1] was not successful.

The catalytic reduction was markedly dependent upon the concentration of the reactants; for example, at a concentration of 5% w/v, the yield of IV (R = *n*-Pr) was 90%, at 40% w/v it was 50%. A smooth curve relating yield to concentration was obtained. These amino esters were readily cyclized to the azeti-

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