glass tube immersed in 3 ml. of radioactive hydrochloric acid solution (containing 10 microcuries of chlorine-36), a concentrated sulfuric acid bubbler, a fritted glass tube immersed in 6 ml. of chloroform in a heavy walled glass tube containing 1.6 g. (0.014*M*) of 2,5-dihydrothiophene-1,1-dioxide (m.p. 64–66°) chilled to −58 ± 3°C, and a calcium chloride drying tube.

Chlorine gas from the cylinder was slowly bubbled through the gas train. An immediate exchange occurred between the chlorine gas and the radioactive hydrochloric acid solution.[3,5] One gram (0.014*M*) of radioactive chlorine gas was collected and the glass tube was then sealed.

The sealed tube was heated to 60–70° for about 4 hr. The tube was chilled, opened, and the contents poured into an evaporating dish. After evaporating to dryness, the yield of crude 3,4-dichlorotetrahydrothiophene-1,1-dioxide was 2.4 g., or about 80%.

The dry crystals were dissolved in 20 ml. of hot water and filtered hot. The filtrate was then chilled in ice water for 3 hr. and the crystals filtered on a Büchner funnel. The recrystallization was repeated; the final purified material weighed 1.6 g., representing 65% of the theoretical yield.

Infrared analysis[6] showed that the final product contained 58% of the *trans* 3,4-dichlorotetrahydrothiophene-1,1-dioxide, 37% of the *cis* isomer, and 5% of 3-chloro-2,3-dihydrothiophene-1,1-dioxide. These values were obtained by comparing the infrared curves of the product with standards made from solutions of the pure *cis* and *trans* isomers in acetonitrile and a solution of pure 3-chloro-2,3-dihydrothiophene-1,1-dioxide in nitromethane. The *trans* isomer shows an absorption peak at 8.25 μ, the *cis* isomer at 8.33 μ, and 3-chloro-2,3-dihydrothiophene-1,1-dioxide at 13.03 μ.

The purified product was dissolved in acetone and aliquots were pipetted into stainless steel cup planchets. The acetone was evaporated and the radioactivity of the product was determined.

The measured activity in a windowless counter was 6.4 counts per minute per microgram.

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(5) F. A. Long and A. R. Olson, *J. Am. Chem. Soc.*, **58**, 2214 (1936).

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Some 3,3-Disubstituted-2-Pyrrolidinones

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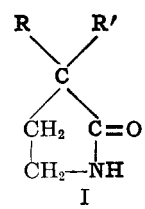
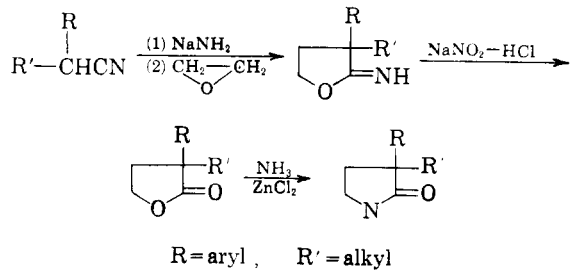
Certain barbituric acid derivatives have long been standard as hypnotics and for use as anticonvulsants. They offer a natural starting point for studies seeking other compounds possessing similar activities. 3,3-Disubstituted-2-pyrrolidinones (I) maintain part of the configuration of the barbiturates and seemed to offer a promising field for investigation.



I

Because of its relationship to phenobarbital (5-ethyl-5-phenylbarbituric acid), 3-ethyl-3-phenyl-2-pyrrolidinone was the first compound prepared. The synthetic scheme for this and related pyrrolidinones was as follows:



R = aryl, R′ = alkyl

The method of preparation of the lactones was a modification of the procedure used by Anker and Cook[1] for some related compounds.

Variations of the aryl-alkyl derivatives include 3-*n*-butyl-3-phenyl-, 3-ethyl-3-*p*-chlorophenyl-, and 3,3-diphenyl-2-pyrrolidinone. An *N*-methyl derivative was prepared by alkylation of 3-ethyl-3-phenyl-2-pyrrolidinone employing sodium hydride.

Attempts at preparation of dialkyl derivatives by the same methods failed when the aliphatic nitriles could not be alkylated in the presence of sodamide. No further investigation of other methods was made. Related compounds of this type, with *N*-alkyl substitution, have been prepared by Clarke, Mooradian, Lucas, and Slauson[2] using a different approach.

When tested orally in rats the best compound was 3-ethyl-3-phenyl-2-pyrrolidinone. The average protective dose against both electro- and metrazol shock was shown to be about 60 mg./kg. This was considerably below the average hypnotic dose of about 188 mg./kg. A limited clinical trial has shown that the anticonvulsant activity carries over to human use.

EXPERIMENTAL[3]

α-Ethyl-α-phenyl-γ-butyrolactone. To the sodamide prepared from 4.2 g. (0.187 g.-atom) of sodium in 200 ml. of liquid ammonia was added, at a dropwise rate, 27.38 g. (0.187 mole) of α-phenylbutyronitrile.[4] Stirring was continued for one hour and then there was added 8.25 g. (0.187 mole) of ethylene oxide in 50 ml. of dry ether. After stirring for 44 hr., 15 g. of ammonium chloride was added and then, cautiously, 5 ml. of water. The solids were separated by filtration, were washed with ether, and the ether was re-

(1) R. M. Anker and A. H. Cook, *J. Chem. Soc.*, 806 (1948).

(2) R. L. Clarke, A. Mooradian, P. Lucas, and T. J. Slauson, *J. Am. Chem. Soc.*, **71**, 2821 (1949).

(3) The Skelly B referred to throughout the Experimental is petroleum ether (b.p. 60–71°).

(4) F. Bodroux and F. Taboury, *Bull. soc. chim. France*, [4] **7**, 666 (1910).

moved by distillation. To the residual oil was added 200 ml. of 1*N* hydrochloric acid and the stirred mixture was cooled to 0° before dropwise addition of 12 g. (0.17 mole) of sodium nitrite dissolved in a small amount of water. The mixture was stirred for one hour and then, after removal of the ice salt bath, was allowed to stand overnight. The product was isolated by ether extraction, drying over magnesium sulfate, and removal of the ether by distillation. Fractionation gave 17.5 g. (49%) boiling at 123–125° (0.4 mm.), n_D^{25} 1.5254.

Anal. Calcd. for $C_{12}H_{14}O_2$: C, 75.75; H, 7.42. Found: C, 75.72; H, 7.49.

3-Ethyl-3-phenyl-2-pyrrolidinone.[5] A mixture of 100 g. (0.53 mole) of α-ethyl-α-phenyl-γ-butyrolactone and 2 g. of anhydrous zinc chloride in 200 ml. of liquid ammonia was heated in a bomb at 225° for 21 hr. After cooling and opening the bomb the ammonia was allowed to evaporate and the residue was removed by dissolving it in absolute ethanol. Most of the ethanol was removed under reduced pressure and the addition of Skelly B and chilling produced a crystalline mass. Subsequent to filtration, the solids were treated twice with boiling Skelly B. This separated the product, which crystallized from the solution, from an insoluble oil. The product from two runs was combined and recrystallized twice from Skelly B to give 157 g. (79%) of product melting at 88–90°.

Anal. Calcd. for $C_{12}H_{15}NO$: C, 76.23; H, 7.99. Found: C, 76.11; H, 7.76.

α-(p-Chlorophenyl)-α-ethyl-γ-butyrolactone. The procedure previously described was employed to convert 33.6 g. (0.187 mole) of α-(*p*-chlorophenyl)butyronitrile[6] to the lactone in a yield of 12 g. (29%) boiling at 136–145° (0.5 mm.), n_D^{25} 1.5402. In a subsequent run the yield was 41%.

Anal. Calcd. for $C_{12}H_{13}ClO_2$: C, 64.15; H, 5.83. Found: C, 64.22; H, 5.78.

3-(p-Chlorophenyl)-3-ethyl-2-pyrrolidinone. Twelve grams (0.053 mole) of the lactone was converted to the pyrrolidinone which, after one recrystallization from Skelly B, weighed 6.5 g. and melted at 67–70°. Two additional recrystallizations gave 3.7 g. (31%) melting at 69–70°.

Anal. Calcd. for $C_{12}H_{14}ClNO$: C, 64.49; H, 6.32. Found: C, 64.73; H, 6.18.

3-Ethyl-1-methyl-3-phenyl-2-pyrrolidinone. To 0.7 g. (0.029 mole) of sodium hydride in 10 ml. of dimethylformamide (purified by azeotropic distillation from benzene to a boiling point of 150–151°) was added, dropwise with the temperature at 15–20°, a solution of 5.5 g. (0.029 mole) of 3-ethyl-3-phenyl-2-pyrrolidinone in 15 ml. of purified dimethylformamide and 10 ml. of dry benzene. The mixture was stirred for 35 min. and there was then added 5 g. (0.035 mole) of methyl iodide. Sodium iodide began to appear immediately and the solution was neutral after stirring overnight. Five milliliters of water was added and the benzene layer was separated, washed with water and with sodium bisulfite solution, and dried over magnesium sulfate. Distillation gave 2.3 g. (39%) of product boiling at 130–132° (0.75 mm.), n_D^{25} 1.5430.

Anal. Calcd. for $C_{13}H_{17}NO$: C, 76.84; H, 8.43; N, 6.89. Found: C, 76.84; H, 8.43; N, 6.75.

3-Ethyl-1,3-diphenyl-2-pyrrolidinone. Based on a procedure of Pernot and Willemart,[7] a mixture of 4.2 g. (0.022 mole) of α-ethyl-α-phenyl-γ-butyrolactone, 8.8 g. (0.095 mole) of aniline, and 4.75 g. (0.037 mole) of aniline hydrochloride was heated at 180° for 4 hr. It was poured into 80 ml. of 2*N* hydrochloric acid and the oil which separated was extracted with chloroform. The extracts were washed with water and were dried over magnesium sulfate. Removal of the solvent and two distillations gave 1.8 g. (31%) of product which boiled at 150–160° (0.25 mm.), n_D^{25} 1.5789.

Anal. Calcd. for $C_{18}H_{19}NO$: C, 81.48; H, 7.23; N, 5.28. Found: C, 80.96; H, 7.75; N, 5.43.

3,3-Diphenyl-2-pyrrolidinone. α,α-Diphenyl-γ-butyrolactone[8] (40 g., 0.167 mole) was treated with ammonia as described. The product was recrystallized twice from 95% ethanol to give 20 g. (52%) melting at 208–210°. An analytical sample melted at 209–211°.

Anal. Calcd. for $C_{16}H_{15}NO$: C, 80.98; H, 6.37. Found: C, 80.84; H, 6.45.

α-(n-Butyl)-α-phenyl-γ-butyrolactone. The lactone was prepared from α-phenylhexanonitrile[9] (50 g., 0.29 mole). After completion of the initial reaction ammonium chloride and ether were added. The mixture was filtered and from the ether was obtained 39 g. of oil. The solids, after dissolving in water and extraction with ether, yielded an additional 16 g. of dark oil. The combined oils in 330 ml. of 1*N* hydrochloric acid were treated with 20.7 g. (0.3 mole) of sodium nitrite. Work-up gave 30.5 g. (48%) boiling at 144–147° (1 mm.), n_D^{25} 1.5146.

Anal. Calcd. for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 77.21; H, 8.38.

3-(n-Butyl)-3-phenylpyrrolidinone. This pyrrolidinone was prepared from 21.8 g. (0.1 mole) of the lactone. Purification from Skelly B gave 13 g. (60%) of product melting at 87.5–89.5°. An analytical sample melted at 88.5–90.5°.

Anal. Calcd. for $C_{14}H_{19}NO$: C, 77.38; H, 8.81; N, 6.45. Found: C, 77.38; H, 8.62; N, 6.51.

α-(2-Hydroxyethyl)-α-(p-chlorophenyl)-γ-butyrolactone. The procedure of Anker and Cook[1] for the synthesis of α-(2-hydroxyethyl)-α-phenyl-γ-butyrolactone was employed in the preparation of the corresponding *p*-chlorophenyl derivative from 57.9 g. (0.375 mole) of *p*-chlorophenylacetonitrile. At the iminolactone stage, 25 g. of ether soluble oil and 36 g. of solid, insoluble in both ether and water, were both used in the conversion to the lactone which distilled at 193–203° (1.5 mm.). The product solidified when stirred with Skelly B and a crystallization from a 1:3 mixture of chloroform and benzene gave 29.5 g. (33%) of colorless crystals melting at 85–88°. An analytical sample melted at 89–91°.

Anal. Calcd. for $C_{11}H_{13}ClO_3$: C, 59.85; H, 5.43. Found: C, 59.46; H, 5.30.

α-(2-Bromoethyl)-α-(p-chlorophenyl)-γ-butyrolactone. Twenty grams (0.083 mole) of the 2-hydroxyethyl derivative was converted to the 2-bromo compound by means of 48% hydrobromic acid and concentrated sulfuric acid according to the procedure of Anker and Cook[1] for the corresponding phenyl derivative. The crystals which separated from the ether extracts weighed 17 g. (68%) and melted at 90–93°. Removal of the ether gave 7 g. of usable but less pure material melting at 85–89°. An analytical sample was prepared from the higher melting product by recrystallization from benzene–Skelly B and melted at 92–94°.

Anal. Calcd. for $C_{12}H_{12}BrClO_2$: C, 47.50; H, 3.97. Found: C, 47.73; H, 3.98.

α-(2-Diethylaminoethyl)-α-p-chlorophenyl-γ-butyrolactone. To a warm solution of 17 g. (0.056 mole) of the 2-bromoethyl compound in 100 ml. of dry benzene was added 8 g. (0.112 mole) of diethylamine in 5 ml. of dry benzene. The mixture was stirred and refluxed for 24 hr. and was filtered to remove the diethylamine hydrochloride. The product was isolated from the benzene by extraction with 10% hydrochloric acid, followed by addition, with cooling, of ammonium hydroxide. Following ether extraction the extracts were dried over magnesium sulfate. Distillation gave 11.7 g. (71%) boiling at 169–171°, n_D^{25} 1.5311.

(5) The method of preparation of the pyrrolidinones was based on a procedure of E. Späth and J. Lintner, *Ber.*, **69**, 2727 (1936).

(6) M. A. Spielman, A. O. Geiszler, and W. J. Close, *J. Am. Chem. Soc.*, **70**, 4189 (1948).

(7) A. Pernot and A. Willemart, *Bull. soc. chim., France*, 324 (1953).

(8) J. Attenburrow, J. Elks, B. A. Hems, and K. N. Speyer, *J. Chem. Soc.*, 510 (1949).

(9) L. H. Baldinger and J. A. Nieuwland, *J. Am. Chem. Soc.*, **55**, 2851 (1933).

Anal. Calcd. for $C_{16}H_{22}ClNO_2$: Cl, 11.99; N, 4.74. Found: Cl, 12.29; N, 4.94.

3-p-Chlorophenyl-3-(β-diethylaminoethyl)-2-pyrrolidinone. Conversion of 4 g. (0.016 mole) of the lactone gave 2.2 g. (48%) of the pyrrolidinone which boiled at 175–180° (0.2 mm.).

Anal. Calcd. for $C_{16}H_{23}ClN_2O$: C, 65.23; H, 7.87; N, 9.50. Found: C, 64.95; H, 7.67; N, 9.11.

Acknowledgment. The author is grateful to Dr. H. L. Breunig for supplying some of the starting materials and to J. J. Traverso and W. B. Scanlon for carrying out the pressure reactions leading to the pyrrolidinones. Thanks also are due to W. L. Brown, H. L. Hunter, G. M. Maciak, and Miss Gloria Beckmann for the microanalyses.

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Derivatives of Ferrocene. V. The Preparation of Some *N*-Substituted Ferrocenecarboxamides[1]

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Many years ago Leuckart reported that the reaction of benzene with phenyl isocyanate in the presence of aluminum chloride produced good yields of benzanilide.[2] Leuckart extended the reaction to other benzene derivatives as well as to thiophene.[2,3] Since the original references, however, this convenient preparation of anilides has seldom been reported in the chemical literature.[4]

It was of interest to us to determine if this reaction of phenyl isocyanate with aluminum chloride could be applied to the aromatic-type compound ferrocene, and further, to determine if other alkyl and aryl isocyanates could be reacted in a similar manner. As is indicated in Table I, the reaction of ferrocene with various alkyl and aryl isocyanates in the presence of aluminum chloride appears to be a general method for the preparation of *N*-alkyl- and *N*-arylferrocenecarboxamides. The yields are very satisfactory when compared to other methods of synthesis (see below), especially the yields based on the readily recovered, unreacted ferrocene.

The reaction of ferrocenoyl chloride with aniline produced *N*-phenylferrocenecarboxamide in 19% yield. During the preparation of the acid chloride from carboxyferrocene and phosphorus pentachloride, however, appreciable decomposition occurred. This fact may be responsible for the low yield of the anilide. *N*-Phenylferrocenecarboxamide was also isolated in 9.7% yield from the reaction of lithioferrocene with phenyl isocyanate, followed by chromotography on alumina.

The stability of the *N*-substituted ferrocene carboxamides was determined under both basic and acidic conditions. Of the two possible methods for determining the stability, *i.e.* the determination of the amine produced or the determination of the amount of carboxamide remaining, the latter procedure was employed for convenience. The extensive decomposition of the carboxylic acid in the hydrolytic media precluded its use in a quantitative determination.

As can be seen from Table II, the *N*-aryl and the *N*-octadecyl compounds are quite stable under vigorous hydrolysis conditions, whereas the *N*-ethyl derivative was partially degraded in alkali, and no starting material was recovered from the acid treatment. The stability of these amides may be due in part to their insolubility in the hydrolytic medium; however, it was noted that all of the amides exhibited some solubility in the aqueous ethanol, and the *N*-ethyl derivative was nearly completely soluble at room temperature.

EXPERIMENTAL[5]

Starting materials. The phenyl, 4-bromophenyl, 4-biphenylyl, 1-naphthyl and ethyl isocyanates used were Eastman reagents. The *n*-octadecyl isocyanate was a gift from Mr. Milton Kosmin, Monsanto Chemical Company, Dayton, Ohio, and was distilled before use, b.p. 145–147°/0.045 mm. Ferrocene was generously supplied by Dr. R. L. Pruett, Linde Air Products Company, Tonawanda, N. Y. Carboxy- and 1,1′-dicarboxyferrocene were prepared by a modification[6] of the procedure originally reported by Benkeser *et. al.*[7]

Preparation of N-substituted ferrocenecarboxamides from ferrocene, aluminum chloride, and isocyanates. All compounds listed in Table I were prepared by essentially the same procedure, using a slight excess of both aluminum chloride and isocyanate to ferrocene. The preparation of *N*-4-bromophenylferrocenecarboxamide is given as a typical example.

A solution of 21.8 g. (0.11 mole) of 4-bromophenyl isocyanate and 14.7 g. (0.11 mole) of anhyd. aluminum chloride in 400 ml. of methylene chloride (dried over calcium hydride) was added with stirring under a nitrogen atmosphere and over a period of 30 min. to a solution of 18.6 g. (0.10 mole) of ferrocene in 200 ml. of the same solvent. The reaction mixture was stirred at room temperature for 20 hrs., hydrolyzed with 200 ml. of 10% hydrochloric acid and filtered, leaving 10.0 g. of a yellow-brown crystalline solid. The filtrate was separated into phases, the organic phase

(1) Presented in part before the Division of Organic Chemistry at the 131st Meeting of the American Chemical Society, Miami, Fla., April 10, 1957.

(2) R. Leuckart, *Ber.*, **18**, 873 (1885).

(3) R. Leuckart and M. Schmidt, *Ber.*, **18**, 2338 (1885).

(4) There has just appeared an article in which *N*-phenylferrocenecarboxamide (m.p. 205–207°) was prepared by this procedure, in order to prove that the Beckmann rearrangement product of the *p*-toluenesulfonate of benzoylferrocene oxime was this same anilide: N. Weliky and E. S. Gould, *J. Am. Chem. Soc.*, **79**, 2742 (1957).

(5) All analyses were performed by the Schwarzkopf Microanalytic Laboratory, Woodside 77, N. Y.

(6) D. W. Mayo, P. D. Shaw, and M. D. Rausch, *Chem. & Ind. (London)*, 1388 (1957).

(7) R. A. Benkeser, D. Goggin, and G. Schroll, *J. Am. Chem. Soc.*, **76**, 4025 (1954).