Synthesis of Peptides Containing Aminophosphonic Acids

W. FRANKLIN GILMORE[x] and HILMER A. McBRIDE

Abstract □ Dipeptides containing C-terminal α-aminobenzylphosphonic acid were prepared in both aqueous and nonaqueous media. The synthesis of intermediates necessary for the preparation of peptides containing α-aminophosphonic acids is also discussed. Similarities and differences in coupling aminophosphonic and aminocarboxylic acids by means of dicyclohexylcarbodiimide, acyl chlorides, and 1-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline are described.

Keyphrases □ Aminophosphonic acids—as terminal portion of synthesized peptides □ Peptides—synthesized containing terminal α-aminobenzylphosphonic acid in aqueous and nonaqueous media □ Coupling agents—evaluation of 1-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline and dicyclohexylcarbodiimide for esters of aminophosphonic acids and carbobenzoxyamino acids

In a program designed to prepare peptide hormones with altered biological activity, methods of incorporating α-aminophosphonic acids at the C-terminal position of peptides were investigated. α-Aminophosphonic acids are dibasic, having one pKa larger and one pKa smaller than aminocarboxylic acids; thus, it is anticipated that peptides containing these phosphonic acids will have altered isoelectric points, altered binding properties for biological molecules, altered metabolism, and other altered biological properties when compared to the corresponding peptides containing only aminocarboxylic acids.

Initial results of endeavors to incorporate an α-aminophosphonic acid into a peptide are reported. Despite the long existence of α-aminophosphonic acids, no simple broadly applicable method of preparation has been described. Satisfactory methods have been described (1–10) for the synthesis of phosphonic acid analogs of the simple aminocarboxylic acids. A recent report (11) described the synthesis of the optically active α-aminobenzylphosphonic acid, but this method does not appear to be broadly applicable. The synthesis of peptides containing an α-aminophosphonic acid has been explored only recently (12–15). Now a number of modern peptide methods have been examined in the synthesis of peptides containing aminophosphonic acids.

RESULTS

Addition of a dioxane solution of carbobenzoxyglycyl chloride to an aqueous alkaline solution of α-aminobenzylphosphonic acid (I) gave carbobenzoxyglycine and unchanged I. Despite the use of a number of bases such as magnesium oxide, triethylamine, and sodium hydroxide, peptide formation could not be detected. In contrast, addition of a dioxane solution of phthalylglycyl chloride to I in a cold aqueous solution, adjusted to pH 8.5 with sodium hydroxide and maintained at pH 8.5 by periodic addition of sodium hydroxide solution, gave peptide formation. Treatment of the blocked dipeptide with hydrazine hydrate in ethanol gave the dipeptide hydrochloride (II). The dipeptide (II) as the free base was also prepared in one step by an adaptation of the *N*-carboxyanhydride method (16).

Addition of a solution of carbobenzoxyglycine and triethylamine in acetonitrile to a solution of the hydrobromide salt of diethyl α-aminobenzylphosphonate (III) and dicyclohexylcarbodiimide failed to give peptide formation. Conversion of III to the free amine (IV) was accomplished by use of silver oxide in methylene chloride. The free amine and carbobenzoxyglycine in the presence of dicyclohexylcarbodiimide gave peptide formation. Peptide formation from carbobenzoxyglycine and IV was also efficiently accomplished using 1-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (17) in tetrahydrofuran. Treatment of the blocked dipeptide with hydrogen bromide in acetic acid removed the carbobenzoxy group and hydrolyzed the phosphonate to give VI. Hydrogenolysis of V in ethanol–hydrochloric acid removed only the carbobenzoxy group and gave VII (Scheme I).

DISCUSSION

From these results, it is apparent that 1-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline and dicyclohexylcarbodiimide are excellent coupling agents for esters of aminophosphonic acids and carbobenzoxyamino acids. Contrary to what has been found with salts of amino acid esters (18), the addition of a solution of a blocked amino acid and triethylamine to a solution of the hydrobromide salt of the aminophosphonic acid ester and dicyclohexylcarbodiimide was not satisfactory. From IR spectra, the formation of anhydride from the blocked amino acid was observed. However, peptide formation did not occur. Although without direct evidence, it is postulated that *N*-acylurea formation is faster than peptide formation. *N*-Acylurea formation in the dicyclohexylcarbodiimide coupling reaction is believed to be catalyzed by triethylamine (19, 20). In this case, it appears that *N*-acylurea or some other product is formed from the blocked amino acid anhydride. In retrospect, carbobenzoxyglycine was a poor choice since it is known that the corresponding anhydride rearranges in the presence of bases (20).

Perhaps one of the most surprising results and a major difference between the synthesis of peptides containing aminophosphonic acids and peptides containing only aminocarboxylic acids is that, at the dipeptide stage, treatment of the carbobenzoxyamino dipeptide ester with hydrogen bromide in acetic acid caused hydrolysis of both the carbobenzoxy group and the esters of the phosphonic acid. Preliminary evidence shows that the carbobenzoxy group is hydrolyzed faster than the esters. Thus, with a short reaction time, salts of the dipeptide esters should be obtained. The problem is best avoided by hydrogenolysis of the carbobenzoxy group. When the peptide acid is the desired product, treatment with hydrogen bromide in acetic acid is of considerable utility. This result is surprising since treatment of VIII with hydrogen bromide in acetic acid gave III. One explanation is that in the dipeptide, neighboring group participation through a six-membered transition state (IX and/or the intermediate X) is possible. This is not possible for VIII.

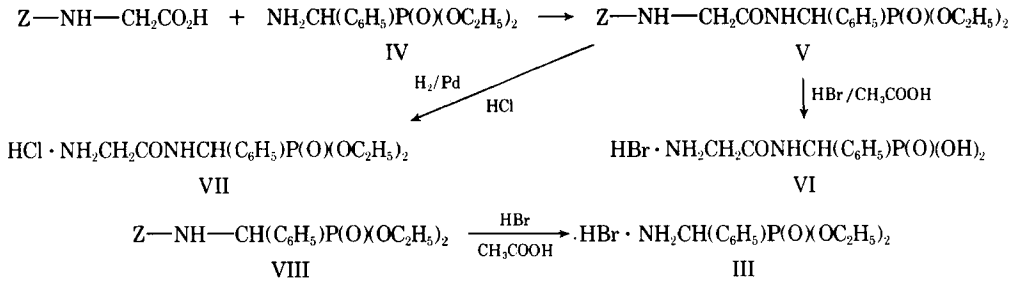
In IX and X, the phosphorus is pentacoordinate, thus having trigonal-bipyramidal geometry. In this case, at least one ethoxy group could occupy one of the longer apical bond positions. This would make hydrolysis easier than it would be in the case of the tetrahedral phosphorus of VIII.

The antimicrobial properties of II were investigated[1]. At a con-

$$HCl \cdot NH_2—CH_2—CONH—CH(C_6H_5)—P(O)(OH)_2$$

II

[1] Tests were performed by Dr. Larry Robertson and Mrs. Nanci Youngblood, Department of Pharmacognosy, University of Mississippi.



Z = carbobenzoxy

Scheme I

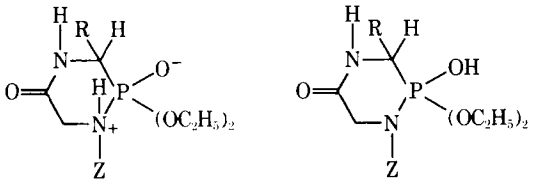
centration of 10 mg/ml, this compound was inactive against selected bacteria and fungi.

EXPERIMENTAL[2]

***N*-Phthalylglycyl-α-aminobenzylphosphonic Acid**—To a stirred suspension of 0.94 g (5 mmoles) of I in 30 ml of water was added 5.0 ml of 1 *N* NaOH, and the pH was adjusted to 8.0 with additional sodium hydroxide. The solution was cooled in an ice bath, and the pH was monitored by a pH electrode placed directly in the solution. To the cold alkaline solution, a solution of 1.18 g (5 mmoles) of phthalylglycyl chloride (21) in 20 ml of dry dioxane was added dropwise over 30 min. The pH was adjusted by periodic addition of sodium hydroxide during the reaction, and the pH stabilized in approximately 1 hr. The solution was stirred an additional 15 min, acidified to pH 1.0 with 6 *N* HCl to obtain a copious precipitate, collected by filtration, and dried (*in vacuo*, 80°). The crude solid was recrystallized from ethanol to yield 1.6 g (86%) of fine white needles, mp 253–254°; IR (KBr): 3275 (N—H), 1710 (glycine C=O), and 1725 and 1775 (phthalyl C=O) cm^{-1}; NMR (D_2O, NaOD): δ 4.32 (s, 2, CH_2CO), 5.01 (d, 1, J = 18 Hz, CH—P), 7.65 (s, 5, phenyl), and 7.81 (s, 4, phthalyl).

Anal.—Calc. for $C_{17}H_{15}N_2O_6P$: C, 54.55; H, 4.04; N, 7.48; P, 8.27. Found: C, 54.58; H, 4.14; N, 7.59; P, 8.13.

Carbobenzoxy-α-aminobenzylphosphonic Acid—A suspension of 8.4 g (0.047 mole) of I in 50 ml of water was treated dropwise with 4 *N* NaOH until solution was effected, and the pH was adjusted to 9.5. The solution was cooled to 0°, and 8.0 g (0.047 mole, 95% purity) of carbobenzoxy chloride was added dropwise over 45 min. The pH was maintained at 9.0–9.5 during the reaction by periodic addition of 4 *N* NaOH. The pH was monitored by a pH electrode in the solution and stabilized after 6 hr. The solution was warmed to 25°, stirred for 2 hr, and extracted with 50 ml of ether, which was discarded. The aqueous phase was added to a mixture of 30 ml of water, 20 ml of concentrated hydrochloric acid, and 100 g of crushed ice. The oil which separated was extracted into two 100-ml portions of ether and the two extracts were combined, dried (magnesium sulfate), and evaporated to yield the crude solid product. The crude solid was recrystallized from ethyl acetate–*n*-hexane to afford 12.7 g (84%) of long needles, mp 152–153°; IR (KBr): 1680 (C=O) and 1240 (P—O) cm^{-1}; NMR (CH_3OH-d_4): δ 5.20 (s, 2, CH_2), 5.22 (d, 1, J = 22 Hz, CH—P), and 7.50 (m, 10, aromatic).



IX X

[2] Melting points were determined with a Thomas–Hoover Unimelt melting-point apparatus and are corrected. NMR spectra were taken on a Jeol model C-60HL spectrometer using tetramethylsilane or sodium 2,2-dimethyl-2-silapentane-5-sulfonate as internal standards. IR spectra were taken on either a Perkin-Elmer 137 or 257 spectrophotometer. Microanalyses were performed by either Chemalytics, Inc., Tempe, Ariz., or Galbraith Laboratories, Knoxville, Tenn. The aminobenzylphosphonic acid was racemic.

Anal.—Calc. for $C_{15}H_{16}NO_5P$: C, 56.08; H, 5.02; N, 4.36; P, 9.65. Found: C, 56.30; H, 4.86; N, 4.13; P, 9.57.

Diethyl Carbobenzoxy-α-aminobenzylphosphonate (VIII)—Using a modified procedure described by Nicholson *et al.* (22), a suspension of 6.42 g (0.02 mole) of carbobenzoxy-α-aminobenzylphosphonic acid in 25 g of triethyl orthoformate was slowly heated at 80°. The ethanol and ethyl formate were continually removed by a Dean–Stark apparatus. When all of the acid had dissolved, the temperature rose from 80 to 145°. The solution was refluxed for 20 min and cooled. After standing for 12 hr, the diester precipitated and was collected by filtration. Recrystallization of the crude ester from ethyl acetate–*n*-hexane yielded 7.0 g (93%) of fine white needles, mp 118–119°. An analytical sample was recrystallized from methylene chloride–*n*-hexane to give fine needles, mp 118–118.5° [lit. (13) mp 108–109°]; IR (KBr): 1160 (P—OCH_2CH_3) and 1735 (C=O) cm^{-1}; NMR ($CDCl_3$): δ 1.15 (m, 6, CH_3), 4.00 (m, 5, CH_2—O), 5.22 (s, 2, benzyl CH_2), 5.25 (m, 1, CH—P), and 7.55 (m, 10, aromatic).

Anal.—Calc. for $C_{19}H_{24}NO_5P$; C, 60.47; H, 6.41; N, 3.71; P, 8.21. Found: C, 60.26; H, 6.21; N, 3.81; P, 8.09.

Diethyl α-Aminobenzylphosphonate Hydrobromide (III)—A solution of 6.8 g (18.3 mmoles) of VIII in 15 ml of acetic acid was treated with 11.0 g (5.5 mmoles/g) of 45% HBr in acetic acid and stirred at 25° for 45 min. The solution was diluted with dry ether until the hydrobromide precipitated. The suspension was stirred for 30 min and the crystals were collected by filtration and recrystallized from methanol–ether to yield 5.3 g (95%) of a fine white crystalline powder, mp 268–270°; IR (KBr): 1160 (P—OCH_2CH_3) cm^{-1}; NMR (D_2O): δ 1.38 (m, 6, CH_3), 4.36 (m, 4, CH_2—CH_3), 5.10 (d, 1, J = 18 Hz, CH—P), and 7.72 (s, 5, phenyl).

Anal.—Calc. for $C_{11}H_{19}BrNO_3P$: C, 40.77; H, 5.91; N, 4.32; P, 9.57. Found: C, 40.58; H, 5.71; N, 4.57; P, 9.66.

Diethyl *N*-Carbobenzoxyglycyl-α-aminobenzylphosphonate (V)—*Method A*—A suspension of 1.5 g (4.8 mmoles) of III in 40 ml of methylene chloride was treated with 30 ml of 10% K_2CO_3 solution. The organic phase was separated and the aqueous layer was extracted with an additional 30 ml of methylene chloride. The organic extracts were combined, dried (magnesium sulfate), and evaporated to dryness to yield 0.97 g (4.22 mmoles, 88% recovery) of IV. The ester was dissolved in 20 ml of tetrahydrofuran and added at once to a solution of 1.07 g (4.22 mmoles) of 1-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline and 0.88 g (4.22 mmoles) of carbobenzoxyglycine in 20 ml of tetrahydrofuran. The solution was stirred for 24 hr at 25° and evaporated to yield an orange-brown oil, which was dissolved in 30 ml of methylene chloride and extracted with two 25-ml portions of 0.1 *N* HCl, 30 ml of 10% K_2CO_3, and finally 30 ml of water. The organic phase was dried (magnesium sulfate), evaporated, and dried by high vacuum (0.10–0.05 mm) to yield 1.60 g (91%) of the crude dipeptide, which was recrystallized from ethyl acetate–*n*-hexane to give white needles, mp 89–91° [lit. (13) mp 88–89°]; IR (KBr): 1175 (P—O—C), 1680 (glycine C=O), and 1735 (carbamate C=O) cm^{-1}; NMR ($CDCl_3$): δ 1.18 (m, 6, CH_3), 4.03 (m, 6, CH_3—CH_2 and glycine CH_2), 5.16 (s, 2, benzyl CH_2), 5.65 (m, 1, CH—P), and 7.40 (s, 10, aromatic).

Anal.—Calc. for $C_{21}H_{27}N_2O_6P$: C, 58.06; H, 6.26; N, 6.45; P, 7.13. Found: C, 58.04; H, 6.16; N, 6.28; P, 6.86.

Method B—To a solution of 0.66 g (3.20 mmoles) of dicyclohexylcarbodiimide and 0.77 g (3.20 mmoles) of IV in 25 ml of methy-

lene chloride was added 0.67 g (3.20 mmoles) of carbobenzoxyglycine. Urea formation was noticed in 15 min. The suspension was stirred for 14 hr and the urea was removed by filtration (627 mg, 82%). The solution was extracted with 50 ml of 1 *N* HCl and two 25-ml portions of 10% Na_2CO_3, dried (magnesium sulfate), and evaporated to yield 1.40 g of a light-green oil which solidified upon standing. The solid was recrystallized from ethyl acetate–*n*-hexane to afford 1.00 g (72%) of the peptide as white needles, mp 89–91°; IR (KBr): 1175 (P—O—C), 1680 (glycine C=O), and 1735 (carbamate C=O) cm^{-1}; NMR ($CDCl_3$): δ 1.20 (m, 6, CH_3), 4.09 (m, 6, CH_3—CH_2 and glycine CH_2), 5.18 (s, 2, benzyl CH_2), 5.70 (m, 1, CH—P), and 7.47 (s, 10, aromatic).

Diethyl *N*-Glycyl-α-aminobenzylphosphonate (VII Free Amine)—To a solution of 1.00 g (2.32 mmoles) of V in 30 ml of 95% ethanol and 1.00 ml of concentrated hydrochloric acid was added 400 mg of 5% palladium-on-charcoal, and hydrolysis was performed at 1.4 kg/cm^2 of hydrogen for 18 hr. Removal of the catalyst followed by evaporation of the solvent yielded 0.79 g (100%) of a yellow crystalline solid. The solid was dissolved in 7 ml of absolute ethanol and treated with dry ether until clouding occurred. Stirring overnight at 25° failed to give a precipitate. The solvent was evaporated and the solid was dissolved in 30 ml of water and extracted with 20 ml of methylene chloride which was discarded. The aqueous layer was basified with 15 ml of 10% K_2CO_3 and extracted with three 20-ml portions of methylene chloride, dried (magnesium sulfate), and evaporated to yield a light-green oil which solidified in platelets on standing. The platelets were recrystallized from methylene chloride–*n*-hexane to give 0.41 g (60%) of white needles, mp 66–70°; IR (KBr): 1240 (P—O), 1160 (P—O—C), and 1680 (C=O) cm^{-1}; NMR ($CDCl_3$): δ 1.25 (m, 6, CH_3—CH_2—), 1.88 (s, 2, NH_2), 3.43 (s, 2, CH_2—CO), 4.07 (m, 4, CH_2—O), 5.67 (m, 1, NH—CH—P, collapses to a doublet with D_2O exchange), 7.58 (m, 5, phenyl), and 8.75 (s, 1, NH—CO).

Anal.—Calc. for $C_{13}H_{21}N_2O_4P$: C, 51.99; H, 7.05; N, 9.33; P, 10.31. Found: C, 51.86; H, 7.13; N, 9.19; P, 10.24.

***N*-Glycyl-α-aminobenzylphosphonic Acid (VI Free Amine)**—*Method A: From Deblocking* N-*Phthalylglycyl-α-aminobenzylphosphonic Acid*—An adaption of the procedure of Sheehan and Frank (21) was followed. To an ethanolic solution of 1.87 g (5 mmoles) of the phthalyl-blocked dipeptide was added 5.0 ml of 2 *N* hydrazine hydrate in ethanol, and the solution was refluxed for 1 hr. During this time, a flocculent precipitate formed. The ethanol was removed by evaporation and the solid residue was treated with 30 ml of 2 *N* HCl and warmed to 50° for 15 min; the insoluble phthalylhydrazide was removed by filtration. Evaporation of the acidic solution yielded a mixture of the dipeptide hydrochloride and hydrazine hydrochloride. Recrystallization of the crude solid from *n*-propanol afforded 1.3 g (93%) of the dipeptide hydrochloride as small white crystals, mp 119–122° dec. Elemental analysis of the hydrochloride gave unacceptable values for carbon and phosphorus. A solution of 0.75 g (3 mmoles) of the dipeptide hydrochloride was dissolved in a small volume of water and treated with 0.35 g (3 mEq) of silver oxide, and the silver chloride was removed by filtration. The filtrate was passed through an ion-exchange column[3] (1 × 10 cm). Evaporation of the eluate yielded 0.60 g of slightly brown crystals, which were recrystallized from water–acetonitrile, mp 234–239° dec.; IR (KBr): 1700 (C=O) and 3450 (N—H) cm^{-1}; NMR (D_2O): δ 3.81 (s, 2, CH_2—CO), 5.28 (d, 1, J = 18 Hz, CH—P), and 7.55 (s, 5, phenyl).

Anal.—Calc. for $C_9H_{13}N_2O_4P$: C, 44.27; H, 5.36; N, 11.47; P, 12.28. Found: C, 44.16; H, 5.66; N, 11.50; P, 11.97.

Method B: From Glycine N-*Carboxyanhydride*—Since the *N*-carboxyanhydride procedure is subject to a number of variables, it is described in detail. To a metal-jacketed blender[4] fitted with an ice water supply was added 80 ml of 1 *M* H_3BO_3, previously cooled at 0°. A pH electrode calibrated at pH 10.0 and 0° was placed directly in the solution, and the pH was adjusted to 10.2 with 4 *N* NaOH. To the moderately stirred buffer was added 1.87 g (10 mmoles) of I, and the pH was adjusted to 10.2. The blender was turned to high speed, 1.20 g (12 mmoles) of glycine *N*-carboxyanhydride was added in four portions, and the pH was rapidly adjusted to 10.2 after each addition. After the last addition, the solution was stirred for 1 min. With rapid stirring the solution was acidified to pH 2.0 with concentrated hydrochloric acid. Cooling at 0° for 12 hr did not give crystals. Evaporation of the solution *in vacuo* at 40° followed by extraction with 100 ml of hot methanol yielded 2.0 g of a white crystalline solid. The NMR spectrum in D_2O showed that the solid contained the product but was contaminated. The solid was dissolved in 50 ml of water and treated with excess silver oxide. The suspension was stirred for a few minutes and the silver chloride and excess silver oxide were removed. The filtrate was passed through an ion-exchange column[3] (1 × 10 cm) and the eluate evaporated to yield a slightly purple solid. The solid was dissolved in 30 ml of water and treated with hydrogen sulfide, 0.5 g of activated charcoal was added, and the suspension was stirred and filtered. Evaporation of the solution yielded 0.8 g (33%) of a crystalline solid, mp 228–238° dec. The spectra were identical to those given under *Method A*. Recrystallization from water–acetonitrile failed to give the pure dipeptide.

Method C: From Diethyl N-*Carbobenzoxy-α-aminobenzylphosphonate (V)*—Diethyl *N*-carbobenzoxy-α-aminobenzylphosphonate (1 g, 2.3 mmoles) was dissolved in 10 ml of acetic acid, treated with 2.0 g of 45% (5.5 mmoles/g) HBr in acetic acid, and stirred for 1 hr. Addition of dry ether gave a waxy solid which, upon recrystallization attempts from methanol–ether, yielded an oil. The solvent was evaporated and the solid residue was dissolved in 30 ml of water and extracted with 50 ml of methylene chloride and 30 ml of ether. Evaporation of the aqueous layer yielded 0.63 g (84%) of *N*-glycyl-α-aminobenzylphosphonic acid hydrobromide (VII). The hydrobromide was dissolved in a little water and treated with 0.134 g (1.61 mEq) of silver oxide. The silver chloride was removed by filtration and the filtrate was passed through an ion-exchange column[3]. Evaporation of the eluate to dryness yielded 0.48 g (97%) of the free dipeptide, mp 234–239° dec. The spectra were identical to those given under *Method A*.

[3] Amberlite IRC-50.
[4] Waring.

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Anticonvulsant Activity of 1-Alkyl-4-substituted 3,5-Pyrazolidinediones

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Abstract □ Methods were developed for the synthesis of 1-methyl-4-substituted 3,5-pyrazolidinediones. These compounds are related to phensuximide and diphenylhydantoin and were prepared as potential anticonvulsant agents. The reaction between substituted malonic esters and methylhydrazine in the presence of sodium methoxide was employed to prepare a series of 1-methyl-4,4-disubstituted 3,5-pyrazolidinediones. 1-Methyl-4-phenyl-3,5-pyrazolidinedione was prepared from diethyl phenylmalonate and methylhydrazine. 1,4-Diethyl-4-phenyl-3,5-pyrazolidinedione was obtained by the alkylation of 4-ethyl-4-phenyl-3,5-pyrazolidinedione with ethyl bromide in the presence of potassium *tert*-butoxide as the base. All compounds are novel and were characterized by elemental analysis and IR and PMR spectrometry. All products were evaluated by maximal electroshock seizure and pentylenetetrazol seizure threshold tests.

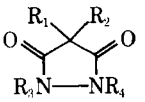
Keyphrases □ 1-Methyl-4,4-disubstituted 3,5-pyrazolidinediones —synthesis, evaluation of anticonvulsant activity □ 3,5-Pyrazolidinediones, 1-methyl-4,4-disubstituted—synthesis, evaluation of anticonvulsant activity □ Anticonvulsant activity—synthesis and evaluation of 1-methyl-4-substituted 3,5-pyrazolidinediones

It has been firmly established that an important pharmacophoric grouping among anticonvulsant agents is the imide group (1). Cyclic hydrazides, which may be represented by Structure I, have rarely been studied for their anticonvulsant properties. The two compounds (2, 3) of Structure I that were examined were found to be inactive; however, neither contains alkylated nitrogen atoms.

Cyclic imides and cyclic hydrazides have similar physical and chemical properties, and one might reasonably expect parallel pharmacological actions. The 3,5-pyrazolidinediones (I) are isomeric with the hydantoins, representing only a transposition of one CONR grouping. They represent the barbituric acids after removal of the urea carbonyl. The latter two observations were made more than 40 years ago (4).

DISCUSSION

In a program designed to synthesize molecular modifications of the imide grouping, the 3,5-pyrazolidinediones (I) were investigated. This report describes the preparation of a series of compounds in which R_3 = alkyl, R_4 = H, and R_1 and R_2 = a combination of H, alkyl, and aryl groups.



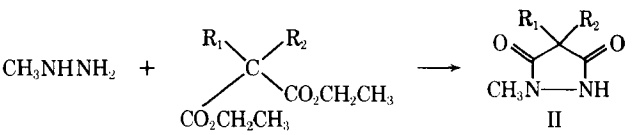
I

Although numerous 3,5-pyrazolidinediones containing aryl substituents on one or both nitrogens are known, the authors are unaware of *N*-monosubstituted compounds containing the simple methyl or ethyl substituents. The primary interest was in the *N*-methyl or *N*-ethyl compounds since the clinically useful succinimides and hydantoins containing *N*-substituents possess such alkyl groups. The synthesis of some *N*-*n*-hexyl-4-substituted 3,5-pyrazolidinediones was described previously (5).

The *N*-methyl-4-substituted 3,5-pyrazolidinediones (II) were obtained by the reaction of methylhydrazine with substituted diethyl malonates (Scheme I). Three distinct methods (A, B, and C) were developed because a given method was sometimes refractory with respect to the preparation of a specific compound. The details of each method are described in the *Experimental* section. The yields ranged from 16 to 74%. One product (II*g*) (R_1 = C_6H_5, R_2 = CH_3) was converted into its *N*-acetyl derivative (III) by treatment with acetyl chloride in pyridine.

The only *N*-ethyl compound prepared was 1,4-diethyl-4-phenyl-3,5-pyrazolidinedione. It was synthesized (Scheme II) by alkylating 4-ethyl-4-phenyl-3,5-pyrazolidinedione with ethyl bromide in the presence of potassium *tert*-butoxide as the base (Method D). This procedure proved unsuccessful as a general method for the preparation of other *N*-alkyl 3,5-pyrazolidinediones because it usually gave a complex mixture of *N*-alkyl, *N,O*-dialkyl, and *N,N*-dialkyl products. Such mixtures were not readily separated.

The single *N*-methyl-3,5-pyrazolidinedione containing one substituent at C-4 was 1-methyl-4-phenyl-3,5-pyrazolidinedione (II*f*). Support for the cyclic structure was obtained by dialkylation of the compound with excess methyl iodide in alcoholic potassium hydroxide and isolation of 1,2,4-trimethyl-4-phenyl-3,5-pyrazolidinedione (IV). The structure of the dialkylation product was established by an alternate synthesis from methyl sulfate and 4-methyl-4-phenyl-3,5-pyrazolidinedione (V). The latter was prepared, in turn, from diethyl methylphenylmalonate and anhydrous hydrazine (Scheme III). The TLC and IR spectra of the



II

Scheme I