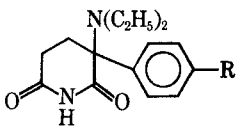
3-Aminopiperidones V: 2-Ethoxy and 2-Carbethoxy Derivatives of 2-*p*-Methoxyphenylglutarimide

B. H. MOON* and C. F. MARTIN

Abstract □ The syntheses of two new modifications of the model compound, 2-(*N*,*N*-diethylamino)-2-phenylglutarimide (I), bearing, in both instances, the methoxy substituent on the *para*-position of the phenyl group and, respectively, the ethoxy and the carbethoxy groups in place of the substituted amino function on carbon 2 are described. The preparation of these compounds is an extension of work designed to provide a basis for studies of structure *versus* potential anticonvulsant activity relationships among the 3-aminopiperidones.

Keyphrases □ 3-Aminopiperidones—2-ethoxy, 2-carbethoxy derivatives of 2-*p*-methoxyphenylglutarimide synthesized for structure–activity studies □ 2-*p*-Methoxyphenylglutarimide—synthesis of 2-ethoxy, 2-carbethoxy derivatives □ NMR—structure □ IR—structure

Pharmacological screening of the model compound, 2-(*N*,*N*-diethylamino)-2-phenylglutarimide (I) (1, 2), demonstrated that it possessed potential anticonvulsant activity but that it was detoxified rapidly in the biological system. Based upon pharmacological evaluations of similar compounds (3, 4), it was reasoned that of several possibilities, *para*-hydroxylation of the phenyl group, with subsequent glucuronide conjugation of I in the biological system, could account, at least in part, for its short duration of action. Therefore, routes to the synthesis of modifications I*a* and I*b* were developed, wherein the *para*-position of the phenyl group was occupied in one case by a chlorine atom and in the other by the methyl group (5). These compounds were designed to block the position noted from metabolic attack and also to provide a basis for studies of the effect on activity of substituents that would reasonably be expected to have opposite electronic influences on the phenyl group and, in turn, on the molecular stability, drug receptor interactions, and biotransportation of the compounds.



I: R = H
I*a*: R = Cl
I*b*: R = CH_3

DISCUSSION

During the present study, which has dealt with routes to the synthesis of other *para*-phenyl-substituted derivatives of the model compound (I), it was found (Scheme I) that in an attempted conversion of α-(*N*,*N*-diethylamino)-*p*-methoxyphenylacetonitrile (II) (6) to ethyl α-(*N*,*N*-diethylamino)-*p*-methoxyphenylacetate (III) by alcoholysis in the presence of sulfuric acid, the major product of the reaction was α-ethoxy-*p*-methoxyphenylacetonitrile (IV). Because the diethylaminomethoxyphenylacetonitrile and, in turn, the ethoxy derivative are both obtained in good yield by this route, it was determined that the synthesis of the corresponding ethoxy glutarimide would be worthy of investigation. This was accomplished by α-carbon alkylation of IV with methylacrylate in the presence of base to produce methyl 4-cyano-4-ethoxy-4-*p*-methoxyphenylbutyrate (VI), followed by cyclization of the cyano-ester in an acid system to yield 2-ethoxy-2-*p*-methoxyphenylglutarimide (VII).

As this work developed, it was proposed that for comparative purposes a corresponding carbethoxy derivative of the glutarimide system would be helpful to delineate further the relationships of structure to activity in the series. It was reasoned that relationships among molecules bearing the ester group, the ether group, and the tertiary amino group would provide bases for determining the importance of variations in polarity in this part of the glutarimide structure, along with information on the significance of the amino group, *per se*, in conferring pharmacological activity on the molecule. Synthesis of the desired carbethoxy derivative was accomplished, as shown in Scheme II, by the initial condensation of *p*-methoxyphenylacetonitrile (VIII) with diethylcarbonate in the presence of sodium to yield α-carbethoxy-*p*-methoxyphenylacetonitrile (IX) (7). This, in turn, was converted to methyl 4-carbethoxy-4-cyano-4-*p*-methoxyphenylbutyrate (X) by α-carbon alkylation with methylacrylate in the presence of base, followed by cyclization in acid to yield 2-carbethoxy-2-*p*-methoxyphenylglutarimide (XI).

EXPERIMENTAL[1]

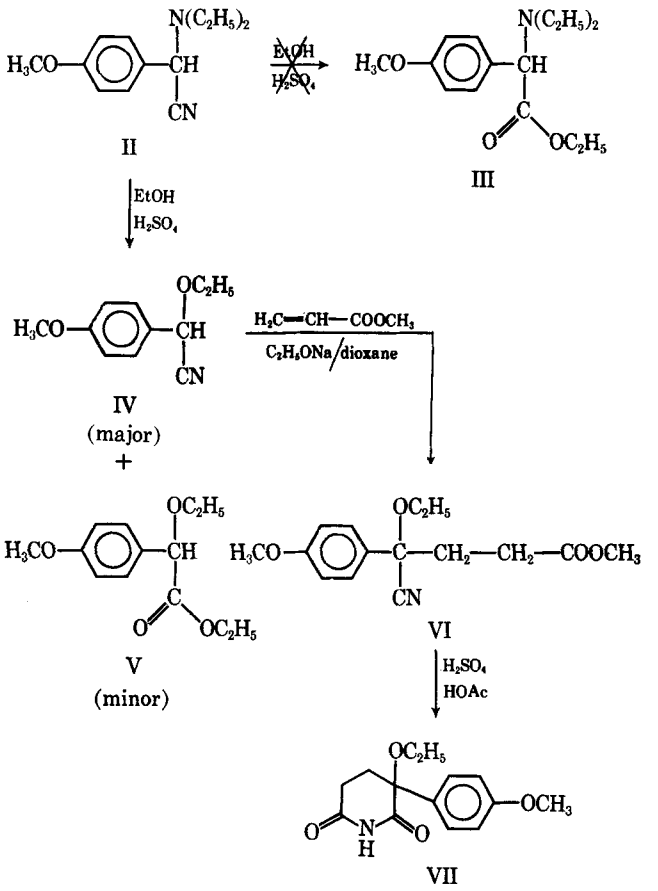
General—Melting points were determined on the Fisher-Johns melting-point block and in open capillary tubes using the Thomas-Hoover apparatus; they are uncorrected. IR spectra were recorded with Beckman IR-5 and IR-8 spectrophotometers. NMR spectra were determined on Varian A-60 and T-60 spectrometers using tetramethylsilane as the internal standard.

α-Ethoxy-*p*-methoxyphenylacetonitrile (IV)—To a stirred solution of ethanol (142 g.) and concentrated sulfuric acid (110 g.) was added α-(*N*,*N*-diethylamino)-*p*-methoxyphenylacetonitrile (II, 110 g.) at such a rate as to maintain gentle refluxing. The mixture was refluxed for an additional 10 hr., cooled, and poured into 300 ml. of ice water. The upper organic layer was separated and washed successively with Na_2CO_3 (10%) and water. After drying, the product was distilled to yield 57 g. (60%) of a 5:1 mixture of IV and V as a pale-yellow liquid, b.p. 110–115° (0.2 mm.). Separation of the mixture was accomplished chromatographically using acid-washed alumina and magnesium silicate gel[2] (60–200 mesh) (1:1) in a 25.4 × 2.54-cm. (10 × 1-in.) column with benzene–petroleum ether (10:1); b.p. (IV) 104° (0.2 mm.); IR (10% $CHCl_3$): 2250 (CN); 1120, 1145 (OC_2H_5 ethoxy); NMR (20% CCl_4): singlet 5.1 p.p.m. (methine proton); singlet 3.8 p.p.m. (methyl protons of *p*-methoxy group); quartet 3.6 p.p.m. (methylene protons of ethoxy group); triplet 1.2 p.p.m. (methyl protons of ethoxy group) with phenyl protons centered at 7.1 p.p.m.

Anal.—Calcd. for $C_{11}H_{13}NO_2$: C, 69.11; H, 6.80; N, 7.33. Found: C, 68.90; H, 6.82; N, 7.19.

Ethyl α-Ethoxy-*p*-methoxyphenylacetate (V)—This compound, b.p. 115° (0.2 mm.), obtained as a minor product from the reaction that yielded IV, was identified by the presence of the characteristic ester carbonyl stretching frequency in the IR (1730) and the absence of the nitrile peak (2250). NMR showed overlapping triplets at 1.2 p.p.m. (methyl protons of both the ester ethyl and the ethoxy groups), a quartet at 4.2 p.p.m. (methylene protons of ester ethyl), a quartet at 3.6 p.p.m. (methylene protons of ethoxy group), a

[1] Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn.
[2] Florisil.



Scheme I

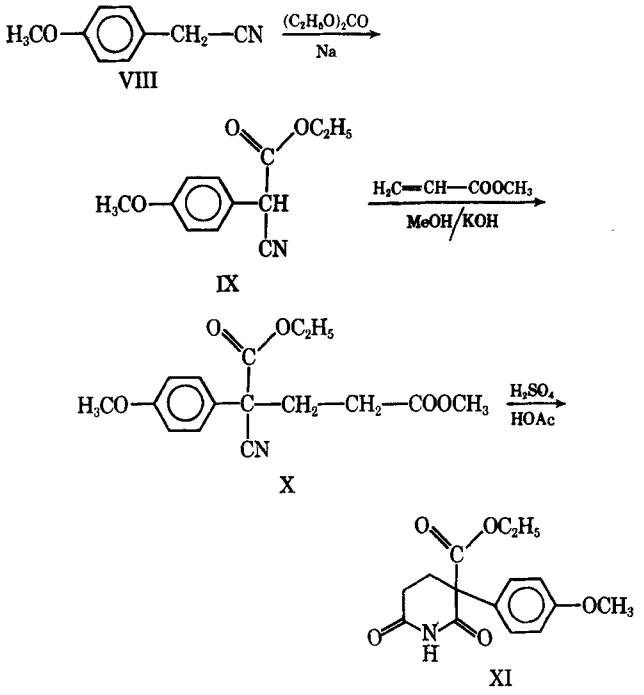
singlet at 4.8 p.p.m. (methine proton), and a singlet at 3.8 p.p.m. (methyl protons of *p*-methoxy group).

Anal.—Calcd. for $C_{13}H_{18}O_4$: C, 65.54; H, 7.56. Found: C, 65.57; H, 7.68.

Methyl 4-Cyano-4-ethoxy-4-*p*-methoxyphenylbutyrate (VI)—To a stirred solution of IV (19.1 g., 0.1 mole) and methylacrylate (10.4 g., 0.12 mole) in 70 ml. of dioxane at room temperature was added, dropwise, a solution of sodium (1 g.) in 20 ml. of ethanol. With this addition, the temperature of the reaction mixture gradually increased until it reached 50°, at which point it was maintained by cooling until all of the sodium ethoxide solution had been added. At the end of this period, the mixture was allowed to cool slowly to room temperature and was filtered; the filtrate was diluted with 70 ml. of water. After extraction with ether, the combined extracts were washed with water, dried, and flash evaporated; the residue was distilled to yield 15 g. (54%) of VI as a pale-yellow liquid, b.p. 132–135° (0.01 mm.); IR (10% $CHCl_3$): 1725 (C=O ester); 2250 (CN) was "quenched" (8); NMR (20% CCl_4): singlet 3.6 p.p.m. (methyl protons of ester methyl); singlet 3.8 p.p.m. (methyl protons of *p*-methoxy group); triplet 1.2 p.p.m. (methyl protons of ethoxy group); multiplets 2.4 p.p.m. (methylene protons of adjacent carbons in carbomethoxyethyl group).

Anal.—Calcd. for $C_{15}H_{19}NO_4$: C, 64.96; H, 6.91; N, 5.05. Found: C, 64.98; H, 7.23; N ,4.74.

2-Ethoxy-2-*p*-methoxyphenylglutarimide (VII)—To a stirred solution of concentrated sulfuric acid (65 ml.) in glacial acetic acid (130 ml.), VI (11.1 g., 0.04 mole) was added in small portions. The mixture was heated to 110° and maintained at this temperature for 30 min. After cooling, the mixture was poured into ice water, rendered alkaline with NH_4OH (28%) (cooling), and extracted with chloroform. The combined extracts were washed twice with water and dried. After flash evaporation of the solvent, the oily residue solidified to yield 0.5 g. (5%) of VII, m.p. 197°, after recrystallization from chloroform–ethanol; IR (KBr pellet): 3500 (NH imide); 1690 (C=O imide). NMR (20% CCl_4): singlet 3.8 p.p.m. (methyl protons of *p*-methoxy group); triplet 1.2 p.p.m. (methyl protons of ethoxy group); quartet 3.6 p.p.m. (methylene protons of ethoxy group); multiplets 2.4 p.p.m. (methylene protons of adjacent unsubstituted carbons in glutarimide ring system).



Scheme II

Anal.—Calcd. for $C_{14}H_{17}NO_4$: C, 63.86; H, 6.50; N, 5.32. Found: C, 63.38; H, 6.02; N, 5.24.

Methyl 4-Carbethoxy-4-cyano-4-*p*-methoxyphenylbutyrate (X)—To a solution of α-carbethoxy-*p*-methoxyphenylacetonitrile (IX, 21.9 g., 0.1 mole) in 40 ml. of tertiary butanol (warmed to 40°) was added 12.3 ml. of 30% methanolic KOH dropwise with stirring. This was followed immediately by the addition of methylacrylate (8.6 g., 0.1 mole) at a rate that permitted maintenance of reaction temperature between 35 and 40°. The mixture was stirred for an additional 3 hr., diluted with water (100 ml.), and neutralized (cooling) with HCl (10%). After extraction with ether, the extracts were washed with water, dried, and flash evaporated; the residue was distilled to yield 18 g. (59%) of X, b.p. 169–170° (0.1 mm.); IR (10% $CHCl_3$): 1750 (C=O ester); 2250 (CN); NMR (20% CCl_4): singlet 3.6 p.p.m. (methyl protons of ester methyl); singlet 3.8 p.p.m. (methyl protons of *p*-methoxy group); triplet 1.2 p.p.m. (methyl protons of ester ethyl); quartet 4.2 p.p.m. (methylene protons of ester ethyl); multiplets 2.4 p.p.m. (methylene protons of adjacent carbons in carbomethoxyethyl group).

Anal.—Calcd. for $C_{16}H_{19}NO_5$: C, 62.95; H, 6.23. Found: C, 62.79; H, 6.34.

2-Carbethoxy-2-*p*-methoxyphenylglutarimide (XI)—A mixture of methyl 4-carbethoxy-4-cyano-4-*p*-methoxyphenylbutyrate (X, 8.0 g., 0.03 mole) in 26 ml. of a 1:1 solution of glacial acetic and concentrated sulfuric acids was heated on the steam bath for 30 min. The reaction mixture was poured into an equal volume of ice water, neutralized with 6 *N* NaOH, and extracted with chloroform. The combined extracts were washed several times with water and dried. After evaporation of the solvent from the dried extract, the product solidified upon rubbing with a chloroform–hexane mixture to yield 3.5 g. (40%) of XI, m.p. 115–117°, after recrystallization from chloroform–hexane; IR (KBr pellet): 3200, 3400 (NH imide); 1725 (C=O ester) fused with 1710 (C=O imide); NMR (20% CCl_4): singlet 3.8 p.p.m. (methyl protons of *p*-methoxy group); triplet 1.2 p.p.m. (methyl protons of ester ethyl); quartet 4.2 p.p.m. (methylene protons of ester ethyl); multiplets 2.4 p.p.m. (methylene protons of adjacent unsubstituted carbons in glutarimide ring system).

Anal.—Calcd. for $C_{15}H_{17}NO_5$: C, 61.85; H, 5.84; N, 4.81. Found: C, 61.84; H, 5.77; N, 4.85.

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ACKNOWLEDGMENTS AND ADDRESSES

Received August 17, 1970, from the *College of Pharmacy, Washington State University, Pullman, WA 99163*

Accepted for publication October 6, 1970.

Abstracted in part from a thesis submitted by B. H. Moon to the Graduate School, Washington State University, in partial fulfillment of the Doctor of Philosophy degree requirements.

This investigation was supported in part by Grant NS 05032, National Institute of Neurological Diseases and Stroke, U. S. Public Health Service.

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N-Phenylacetylsulfamide: Sulfone Analog of Anticonvulsant Acylureas

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Abstract □ *N*-Phenylacetylsulfamide was synthesized under three different conditions. If ethyl acetate was used as a solvent, a higher yield of the monoacylated product was obtained than if pyridine was used as the solvent. If the lithium salt of sulfamide was used, a maximum yield of the diacylated product and a minimum yield of the monoacylated product were obtained. The *N*-phenylacetylsulfamide was less than half as active as trimethadione when tested as an anticonvulsant in the cat.

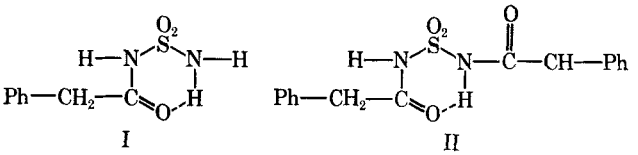
Keyphrases □ *N*-Phenylacetylsulfamide—synthesis, three methods □ Acylureas—synthesis of sulfone analog □ Anticonvulsant acylureas—synthesis of the sulfone analog *N*-phenylacetylsulfamide

The acylureas such as phenacemide[1], Ph—CH_2—CO—NH—CO—NH_2, represent a class of anticonvulsant drugs. Hence, it was desired to prepare the sulfone analog, Ph—CH_2—CO—NH—SO_2—NH_2, for comparison. A search of the literature revealed that only a few simple acyl derivatives of sulfamide have been prepared and characterized (1).

To prepare the desired compound, phenylacetyl chloride and sulfamide were condensed. Even though an equimolar ratio of the two chemicals was employed, an appreciable amount of *N,N'*-bis(phenylacetyl)sulfamide was obtained. If ethyl acetate was used as the solvent, a 40% yield of the monoacylated product and 15% yield of the diacylated product were obtained. If the reaction was run in pyridine, a 30% yield of the monosubstituted product and an 8% yield of the disubstituted product were obtained.

In an attempt to increase the yield of the monoacylated product and/or decrease the yield of the diacylated product, the reaction was run with the lithium salt of sulfamide. Unexpectedly, this reaction gave only a 10% yield of the monoacylated and a 42% yield of the diacylated products. The high yield of the diacylated product was probably the result of a transmetallation reaction between the *N*-lithiosulfamide and the monoacylated products.

Inspection of the NMR spectra of *N*-phenylacetylsulfamide and *N,N'*-bis(phenylacetyl)sulfamide revealed an unusually large chemical shift for one of the nitrogen-bonded protons of these compounds. These shifts are indicative of intramolecular hydrogen bonding (2). Based on these data, it is proposed that in solution the monosubstituted and disubstituted compounds exist as the following intramolecular hydrogen-bonded structures:



I II

These structures are compatible with most of the general rules governing the formation of intramolecular hydrogen-bonded rings set forth by Wheland (3). Also, the formation of an intramolecular hydrogen bond structure for *N*-phenylacetylsulfamide would explain the high incidence of disubstitution, especially in the reaction where *N*-lithiosulfamide was employed as the reactant.

An exchange reaction of *N*-phenylacetylsulfamide and deuterium oxide was conducted according to the procedures of Ouchi and Moeller (4). This was readily driven to completion by employing an excess of deuterium oxide. NMR analysis of the reaction product confirmed the structure assignment and revealed the location of all nitrogen-bound proton signals.

N-Phenylacetylsulfamide was studied for activity as a potential petit mal anticonvulsant by recording its protective ability, as compared to the standard anticonvulsant, trimethadione, against pentylenetetrazol-in-

[1] Phenurone.