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Synthesis and Anticonvulsant Screening of 3,3-Diphenyl-2-pyrrolidone Derivatives

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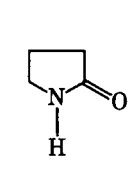
Abstract □ Six derivatives of 3,3-diphenyl-2-pyrrolidone were synthesized and screened for anticonvulsant activity. The synthetic route involved a mono-*N*-demethylation of an intermediate *N*,*N*-dimethylaminonitrile with methyl chloroformate followed by cleavage of the carbamate group. Of the six derivatives, (±)-2-imino-1,5-dimethyl-3,3-diphenylpyrrolidine hydrochloride was effective in protecting mice against maximal electroshock (MES) -induced seizures at a 30-mg/kg dose level.

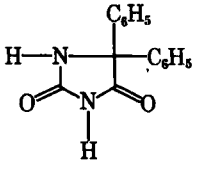
Keyphrases □ Anticonvulsant screening—synthesis of 3,3-diphenyl-2-pyrrolidone derivatives, maximal electroshock-induced seizures, mice □ 3,3-Diphenyl-2-pyrrolidone—synthesis and anticonvulsant screening, derivatives, maximal electroshock-induced seizures, mice

The reported (1) anticonvulsant activity of 2-pyrrolidone (I), the lactam of γ-aminobutyric acid, stimulated interest in 2-pyrrolidone derivatives as potential anticonvulsants. As it incorporated several features of the anticonvulsant diphenylhydantoin (II), the 3,3-diphenyl-2-pyrrolidone (III) system seemed a promising one for the study. When tested in rats, 3,3-diphenyl-2-pyrrolidone (III) itself was less effective than (±)-3-ethyl-3-phenyl-2-pyrrolidone against both pentylenetetrazol[1] and electrically-induced convulsions (2). Somewhat earlier, it was observed (3) that the structurally related α,α-diphenylsuccinimide (IVa) and its *N*-methyl derivative (IVb) ranked first and eighth in a series of 39 succinimides in protecting mice against electrically induced convulsions.

The work on 3,3-disubstituted-2-pyrrolidones (2) and α-phenylsuccinimides (3) showed that the presence of an asymmetric center at the 3-position often enhanced anticonvulsant activity. The present study was undertaken to determine if the introduction of an asymmetric center at the 4- or 5-position of the 3,3-diphenyl-2-pyrrolidone (III) system would have a similar beneficial effect. Accordingly, (±)-1,4-dimethyl-3,3-diphenyl-2-pyrrolidone (Va) and (±)-1,5-dimethyl-3,3-diphenyl-2-pyrrolidone (VIa) were synthesized and evaluated for anticonvulsant activity. The corresponding amidines, Vb and VIb, were also prepared to compare them with the neutral lactams. Moreover, the amidine functionality was expected to provide a handle for further structural modification as exemplified by the acyl derivatives, VIc and VId. The test compounds were prepared using modifications of previously reported (4–6) procedures.



I



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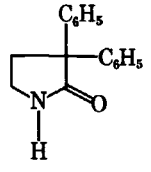
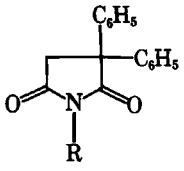
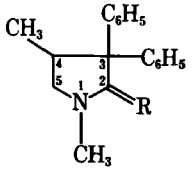


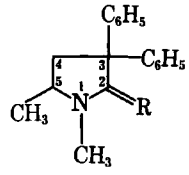
III



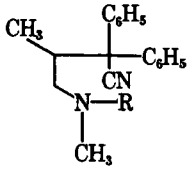
IVa: R = H
IVb: R = CH_3



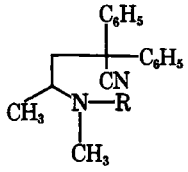
Va: R = O
Vb: R = NH



VIa: R = O
VIb: R = NH
VIc: R = $NCOCH_3$
VId: R = NCO_2CH_3



VIIa: R = CH_3
VIIb: R = CO_2CH_3



VIIIa: R = CH_3
VIIIb: R = CO_2CH_3

RESULTS AND DISCUSSION

Because of the interest in amidines Vb and VIb, the synthetic route (4–6) involving them as intermediates was preferred to other procedures (7, 8) for preparing (±)-1,4-dimethyl-3,3-diphenyl-2-pyrrolidone (Va) and (±)-1,5-dimethyl-3,3-diphenyl-2-pyrrolidone (VIa). The mono-*N*-demethylation of the *N*,*N*-dimethylaminonitriles VIIa and VIIIa was readily effected using excess methyl chloroformate. The subsequent conversion of carbamate VIIIb to VIb hydrochloride was carried out in refluxing hydrochloric acid. In contrast, carbamate VIIb failed to either dissolve or react in hydrochloric acid. Moreover, the compound was recovered essentially unchanged after 17 days of reflux in ethanol–hydrochloric acid (2:1). Ultimately, the transformation of VIIb to Vb was

[1] Metrazol.

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achieved using hydrogen bromide in glacial acetic acid. In addition, the nitrous acid reaction (4) was found to require a large excess of reagent added in portions in order to effect complete conversion of starting material to product. Throughout the synthesis, the geometric isomers were easily distinguished from each other by the ^{1}H-NMR chemical shifts of the various methyl groups.

The lactams Va and VIa were inactive in all tests at all dose levels. In contrast, amidine VIb was effective in protecting mice against maximal electroshock (MES)-induced seizures at a 30-mg/kg dose level, although it afforded no protection at lower dose levels (3, 10, and 20 mg/kg). Amidine Vb was inactive in all tests at 30 mg/kg. Both Vb and VIb were too toxic to be administered at dose levels >30 mg/kg. Of the acyl compounds derived from VIb, the carbomethoxyimino derivative VId was inactive at all dose levels. The acetimido derivative VIc, on the other hand, appeared to exacerbate the effects of MES and subcutaneous pentylenetetrazol treatment, thereby causing death. Furthermore, at dose levels of 300 and 600 mg/kg, compound VIc caused death through CNS depression.

Since the presence of an *N*-methyl group was shown to decrease the effectiveness of α-phenylsuccinimides against electrically induced convulsions (3), it was reasonable that *N*-demethylation of VIb might yield a compound with improved activity in the MES screen. However, compounds VIb and VIa were both unaffected by refluxing with 47% hydriodic acid. Treatment of compound VIc with excess methyl chloroformate also failed to effect an *N*-demethylation. Moreover, two attempts to further functionalize lactam VIa by nitration of an aromatic ring were unsuccessful.

In summary, the combination of *N*-methylation and the generation of an asymmetric center by introduction of a methyl group at the 4- or 5-position of the 3,3-diphenyl-2-pyrrolidone (III) system had no apparent beneficial effect on anticonvulsant activity. Although the amidine VIb was active in the MES screen at a low dose level, this activity was offset by the neurotoxicity of the compound at higher dose levels. Finally, the preparation of simple acyl derivatives failed to improve the activity, and the chemical inertness of the system made further structural modifications difficult.

EXPERIMENTAL[2]

(±)-4-Dimethylamino-2,2-diphenyl-3-methylbutyronitrile (VIIa) and (±)-4-Dimethylamino-2,2-diphenylvaleronitrile (VIIIa)—The isomeric nitriles were prepared by condensation of diphenylacetonitrile and 2-chloro-1-dimethylaminopropane in the presence of potassium *tert*-butoxide (7). The less soluble valeronitrile (VIIIa) was obtained in isomerically pure form by hexane trituration followed by recrystallization from absolute ethanol. Vacuum distillation of the hexane-soluble fraction afforded a 7:3 mixture of VIIa–VIIIa; bp 131–137° (0.15–0.20 mm). The total yield of nitriles was 58%.

(±) -4- (*N* - Carbomethoxy -*N*- methylamino)-2,2-diphenyl-3-butyronitrile (VIIb)—The 7:3 nitrile mixture (36 g, 0.13 mole), sodium bicarbonate (126 g, 1.5 moles), and methyl chloroformate (208 g, 2.2 moles) were refluxed for 26 hr in chloroform (1.4 liters). The reaction mixture was filtered and the filtrate washed with 3 *N* hydrochloric acid, 5% sodium bicarbonate, and water. Evaporation of the organic layer afforded a 7:3 mixture of VIIb–VIIIb (^{1}H-NMR analysis). Ether trituration removed the more soluble valeronitrile carbonate, VIIIb. Recrystallization of the residual solid from ethyl acetate–petroleum ether gave 19 g (45%) of VIIb as a white solid; mp 145–147°; IR 1697 cm^{-1} (C=O); ^{1}H-NMR δ 1.04 (d, 3, CHCH_3), 2.88 (s, 3, NCH_3), 3.70 ppm (s, 3, OCH_3). There was no detectable amount of the isomeric carbamate by ^{1}H-NMR.

(±) -4- (*N* - Carbomethoxy -*N*- methylamino)-2,2-diphenylvaleronitrile (VIIIb)—A mixture of VIIIa (5.0 g, 0.018 mole), sodium bicarbonate (10.0 g, 0.12 mole), and methyl chloroformate (36 g, 0.38 mole) in chloroform (260 ml) was refluxed for 48 hr with half of the methyl chloroformate being added after 24 hr. Workup as described above afforded 5.8 g (100%) of VIIIb as viscous oil; IR 1695 cm^{-1} (C=O); ^{1}H-NMR δ 1.16 (d, 3, CHCH_3), 2.28 (s, 3, NCH_3), 3.53 ppm (s, 3, OCH_3).

(±)-2-Imino-1,4-dimethyl-3,3-diphenylpyrrolidine (Vb) Hydrochloride—Hydrogen bromide gas was bubbled through a solution of VIIb (7.0 g, 0.022 mole) in glacial acetic acid (250 ml) for 30 min. The resultant mixture was stirred at room temperature for 4 days. Then it was diluted with water, basified with concentrated ammonium hydroxide, and extracted with methylene chloride. The residue obtained from evaporation of the organic extracts was partitioned between ether and 6 *N* hydrochloric acid. The resultant aqueous layer was extracted with chloroform and the extracts evaporated to obtain 5.8 g of crude product as a white foam. Crystallization from methanol–ethyl acetate gave 1.8 g (28%) of Vb hydrochloride as a white solid; mp 241–245° (hot stage) after *in vacuo* drying at 100° overnight [lit (4): mp 239°]; IR 3420, 1690 (C=N) cm^{-1}; ^{1}H-NMR δ 0.87 (d, 3, CHCH_3), 3.67 ppm (s, 3, NCH_3).

Anal.—Calc. for $C_{18}H_{21}ClN_2 \cdot \frac{1}{2} H_2O$: C, 69.75; H, 7.16; N, 9.04. Found: C, 69.69; H, 7.15; N, 8.98.

A subsequent preparation yielded material that had mp 239.5–242° (hot stage) and analyzed for $C_{18}H_{21}ClN_2 \cdot \frac{3}{4} H_2O$. Attempts to prepare Vb hydrochloride by refluxing VIIb in concentrated hydrochloric acid or in ethanol saturated with hydrogen chloride gas were unsuccessful.

(±)-1,4-Dimethyl-3,3-diphenyl-2-pyrrolidone (Va)—Compound Vb (1.5 g, 0.005 mole) was converted to Va using excess nitrous acid (4). Recrystallization of the crude product from 95% ethanol afforded 0.86 g (65%) of Va as clear crystals; mp 122–122.5° [lit. (8): mp 122–123°]; IR 1689 cm^{-1} (C=O); ^{1}H-NMR δ 0.80 (d, 3, CHCH_3), 2.98 ppm (s, 3, NCH_3).

(±)-2-Imino-1,5-dimethyl-3,3-diphenylpyrrolidine (VIb) Hydrochloride—A solution of VIIIb (5.8 g, 0.018 mole) in concentrated hydrochloric acid (150 ml) was refluxed for 43.5 hr under nitrogen. The mixture was cooled, diluted with water (300 ml), and extracted with chloroform. Evaporation of the organic extracts afforded the crude product as a white foam. Crystallization from 2-propanol–ether gave 4.6 g (85%) of VIb hydrochloride as a white solid; mp 281–283° [lit. (5): mp 279–281°]; IR 3420, 1690 (C=N) cm^{-1}; ^{1}H-NMR δ 1.30 (d, 3, CHCH_3), 3.45 ppm (s, 3, NCH_3).

(±)-1,5-Dimethyl-3,3-diphenyl-2-pyrrolidone (VIa)—Compound VIb (4.2 g, 0.015 mole) was converted to VIa using excess nitrous acid (4). Recrystallization from ethanol afforded 2.7 g (73%) of VIa as a white solid; mp 121–123° [lit. (8): mp 121–122°]; IR 1682 cm^{-1} (C=O); ^{1}H-NMR δ 1.25 (d, 3, CHCH_3), 2.88 ppm (s, 3, NCH_3).

(±)-2-Acetimido-1,5-dimethyl-3,3-diphenylpyrrolidine (VIc)—A solution of VIb hydrochloride (3.0 g, 0.01 mole) in pyridine (30 ml) and acetic anhydride (3 ml) was stirred at room temperature overnight. The solvents were removed *in vacuo* and the residue dissolved in chloroform. After washing with water, 10% sodium hydroxide, and saturated sodium chloride, the chloroform layer was evaporated to give an off-white solid. Recrystallization from cyclohexane–ethyl acetate provided 2.3 g (75%) of VIc as a white solid; mp 127–128° [lit. (4): mp 126.5–127.5°]; IR 1630, 1600 (sh) cm^{-1}; ^{1}H-NMR δ 1.27 (d, 3H, CHCH_3), 1.67 (s, 3H, COCH_3), 2.88 ppm (s, 3H, NCH_3).

Anal.—Calc. for $C_{20}H_{22}N_2O$: C, 78.40; H, 7.24; N, 9.14. Found: C, 78.37; H, 7.29; N, 9.08.

(±)-2-Carbomethoxyimino-1,5-dimethyl-3,3-diphenylpyrrolidine (VId)—A mixture of VIb (5.7 g, 0.022 mole), sodium bicarbonate (20 g, 0.24 mole), and methyl chloroformate (12 g, 0.13 mole) in chloroform was refluxed for 24 hr. The reaction mixture was filtered and the filtrate washed with 10% hydrochloric acid and saturated sodium chloride. Evaporation of the organic layer afforded a white solid which was recrystallized from ethyl acetate–petroleum ether to give 5.0 g (71%) of VId as a white solid; mp 166–167°; IR 1690, 1630 cm^{-1}; ^{1}H-NMR δ 1.22 (d, 3, CHCH_3); 2.88 (s, 3, NCH_3), 3.10 (s, 3, OCH_3).

Anal.—Calc. for $C_{20}H_{22}H_2O_2$: C, 74.51; H, 6.88; N, 8.69. Found: C, 74.46; H, 6.89; N, 8.67.

Screening Procedures—The test compounds underwent an anticonvulsant screening[3]. The compounds were screened at 30, 100, 300, and 600-mg/kg dose levels in adult male CF 1 mice (intraperitoneal injection). Compounds Vb hydrochloride and VIb hydrochloride were administered in 0.9% saline solution, other test compounds as suspensions in 30% aqueous polyethylene glycol 400. Each compound was screened in an MES test, a subcutaneous pentylenetetrazol seizure threshold test, and a rotorod test for neurotoxicity. Screening procedures, protocols, and data interpretation have been published (9).

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[2] Melting points were determined on either a Thomas-Hoover capillary tube apparatus or a Kofler hot stage apparatus and are uncorrected. IR spectra were obtained in methylene chloride solution on a Perkin-Elmer 467 spectrophotometer. ^{1}H-NMR spectra were obtained in deuteriochloroform solution on a Varian HA-100 spectrometer. Chemical shifts are reported in parts per million downfield from tetramethylsilane. Analyses were performed by Micro-Tech Laboratories, Inc., Skokie, Ill. Organic extracts and solutions were routinely dried over sodium sulfate prior to evaporation.

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Synthesis of Deuterium-Labeled Prochlorperazine

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Abstract □ The propylpiperazine side chain of prochlorperazine was labeled with two, four, or six deuterium atoms by lithium aluminum deuteride reduction of the appropriate amide. The isotopic purity of the products after correcting for chlorine isotopes was >95.7%.

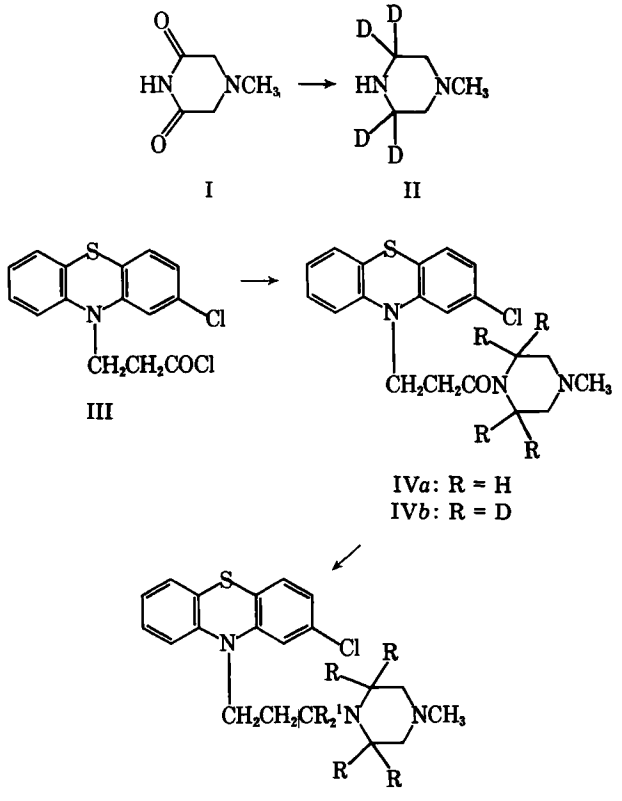
Keyphrases □ Prochlorperazine—deuterium-labeled synthesis □ Deuterium label—prochlorperazine synthesis

Prochlorperazine (V*a*), a piperazine-type phenothiazine, is primarily used as an antiemetic or antipsychotic. There are no literature reports that describe the usual plasma levels of this drug in patients under treatment, and, in fact, no suitable analytical methods have been described. The development of suitable analytical methods for the determination of the plasma concentrations of all piperazine-type phenothiazines has been slow, due to their instability in all stages of sample handling, as well as the extremely low plasma levels observed in the few studies involving humans.

BACKGROUND

The analytical procedures which have met the stringent sensitivity requirements of subnanogram determinations of these piperazine-type phenothiazines are either radioimmunoassay (RIA) or GLC–MS procedures (1, 2). In the case of prochlorperazine, an RIA method, which is capable of quantitating 0.125 ng/ml using 200-μl plasma aliquots, has been developed recently[1]. Following single 5-mg oral doses of prochlorperazine mesylate in healthy volunteers, the peak plasma concentrations were determined by RIA to be between 1–2 ng/ml. To verify the specificity of this sensitive biological procedure, a specific and sensitive chemical method such as GLC–MS is required. A stable isotope analogue of prochlorperazine was needed as a true internal standard for obtaining the required sensitivity by the chemical procedure. In addition, the availability of two other deuterium-labeled prochlorperazine standards will allow reliable pharmacokinetic studies to be carried out with fewer volunteers and animals, by administering these analogues by one or two routes and analyzing the plasma concentrations by GLC–MS using selected ion monitoring. Such studies will allow definitive pharmacokinetics of prochlorperazine to be obtained with far fewer administrations in volunteers.

The propylpiperazine side chain was chosen as the most suitable labeling site, since normally only the *N*-methyl group is lost during metabolism. It also offers adequate variation in the number of labeled atoms. Recently, the synthesis of labeled trifluoperazine, the 2-trifluoromethyl analogue of prochlorperazine, with two, four, or six deuterium atoms in the propylpiperazine side chain was successfully achieved (3). Similarly, this paper describes the synthesis of prochlorperazine with two, four, or six deuterium atoms.



Scheme I

RESULTS AND DISCUSSION

The synthesis (Scheme I) of the key tetradeuterated intermediate, 1-methyl(3,3,5,5-$^2H_4$)piperazine (II), from the lithium aluminum deuteride reduction of 1-methyl-3,5-piperazinedione (I) was previously described (3). Subsequent treatment of the unlabeled or labeled *N*-methylpiperazine in dry benzene with 3-[10-(2-chlorophenothiazinyl)]-

[1] K. K. Midha, E. M. Hawes, G. Rauw, J. McVittie, G. McKay, J. K. Cooper, and H. U. Shetty, unpublished work.

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