

3-Aminopiperidones IV.

2-(*N,N*-Diethylamino)-2-*p*-chlorophenylglutarimide and 2-(*N,N*-Diethylamino)-2-*p*-tolylglutarimide

By S. K. ARYA, K'UN CHANG, and C. F. MARTIN

The syntheses of two new modifications of the model compound, 2-(*N,N*-diethylamino)-2-phenylglutarimide (V) bearing chloro- and methyl-substituents on the *para* position of the phenyl group are described. The preparations of these compounds are extensions of work designed to provide a basis for studies of structure *versus* antiepileptic activity relationships among 3-aminopiperidones.

PREVIOUS WORK, which led to the synthesis and pharmacological screening of the model compound, 2-(*N,N*-diethylamino)-2-phenylglutarimide (V) (1, 2), suggested that of several possibilities, *p*-hydroxylation of the phenyl group, with subsequent glucuronide conjugation of the molecule in the biological system, could account in part for its short duration of action. The present communication deals, therefore, with routes to the synthesis of modifications Va and Vb of the model compound (V) designed not only to block this position from metabolic attack, but 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 ring and, in turn, on the molecular stability, drug-receptor interactions, and biotransportation of the compounds.

DISCUSSION

The syntheses of 2-(*N,N*-diethylamino)-2-*p*-chlorophenylglutarimide (Va) and of 2-(*N,N*-diethylamino)-2-*p*-tolylglutarimide (Vb) were accomplished by following the reaction sequence shown in Scheme I. In both instances, ethyl α -bromo-*p*-chlorophenylacetate (Ia) and ethyl α -bromo-*p*-tolylacetate (Ib) were prepared by modifications of the procedure of Anschütz (3). In the subsequent displacement reaction (I \rightarrow II) using diethylamine as the nucleophile, aminolysis of the ester was avoided by using a short-term, high-temperature procedure as reported in earlier work (1, 4).

Based upon experience in this laboratory with the unsubstituted phenyl compound of this series (1), the next step in the reaction sequence, that of adding the 3-carbon chain to the appropriate amino ester, was accomplished by employing the general procedure developed by Zaugg *et al.* (5) using β -bromopropionitrile. Treatment of IIIa and IIIb with a 1:1 mixture of concentrated sulfuric and glacial acetic acids at steam-bath temperature for 30 min. afforded a fair yield of the amido ester (IVa and IVb).

The cyclizations of IVa and IVb were accomplished by adaptations of the procedure used in the alkylation step (II \rightarrow III). It was observed in both instances that upon heating IVa and IVb in the sodium hydride-dimethylformamide system, hydrogen abstraction (as evidenced by cessation of gas evolution) was essentially complete after 2.5 hr. of heating at 55°. However, if the reaction was stopped at this point, the starting material was recovered. Continued heating of the reaction mixture beyond this point at a higher bath temperature (100–105°) did effect the desired cyclizations to Va and Vb.

As is the case with the unsubstituted phenyl derivative, it is expected that the imide portions of both Va and Vb are relatively flat (6), and as both the substituted phenyl and diethylamino groups are large, they will tend to assume quasi-equatorial and quasi-axial positions with respect to the adjacent carbonyl (7).

EXPERIMENTAL

Melting points were determined on a Fisher-Johns melting point block and are uncorrected. Infrared spectra were obtained with a Beckman IR-5 spectrophotometer; all were run on 10% solutions in a cell with a 0.1-mm. path length unless otherwise stated. Nuclear magnetic resonance spectra were determined on the 60 Mc. NMR manufactured by Varian Associates. The Beckman DB spectrophotometer was used for the ultraviolet absorption spectra reported. Microanalyses were performed by the Weiler and Strauss Microanalytical Laboratory, Oxford, England, or by the Galbraith Laboratories, Inc., Knoxville, Tenn.

Ethyl α -Bromo-*p*-chlorophenylacetate (Ia)—A modification of the procedure described by Anschütz (3) was used. To a stirred mixture of 34.1 Gm. (0.2 mole) of *p*-chlorophenylacetic acid and 1.2 Gm. of red phosphorus, 64.0 Gm. (0.4 mole) of bromine was added at 75–85° over a period of 5 hr. The mixture was stirred for an additional 5 hr. at 80°. After cooling, 12.5 Gm. (0.25 mole) of absolute ethanol was added slowly with stirring and the reaction mixture was heated at 75–80° for 10 hr. At the end of the period, the mixture was poured into ice water, the ester layer separated with ether, washed successively with 10% sodium bisulfite solution and water, and dried (Na₂SO₄). After filtering and flash evaporating the ether, the oil was distilled to yield 44.5 Gm. (80.5%) of liquid, b. p. 96° (0.06 mm.). Redistillation gave a center cut of product Ia, b. p. 94–95° (0.06 mm.); infrared (CHCl₃): 1732 (C=O ester); NMR (CCl₄): triplet 1.25 p.p.m. (methyl protons of ester ethyl); quartet 4.20 p.p.m.

Received April 14, 1967, from the College of Pharmacy, Washington State University, Pullman, WA 99163

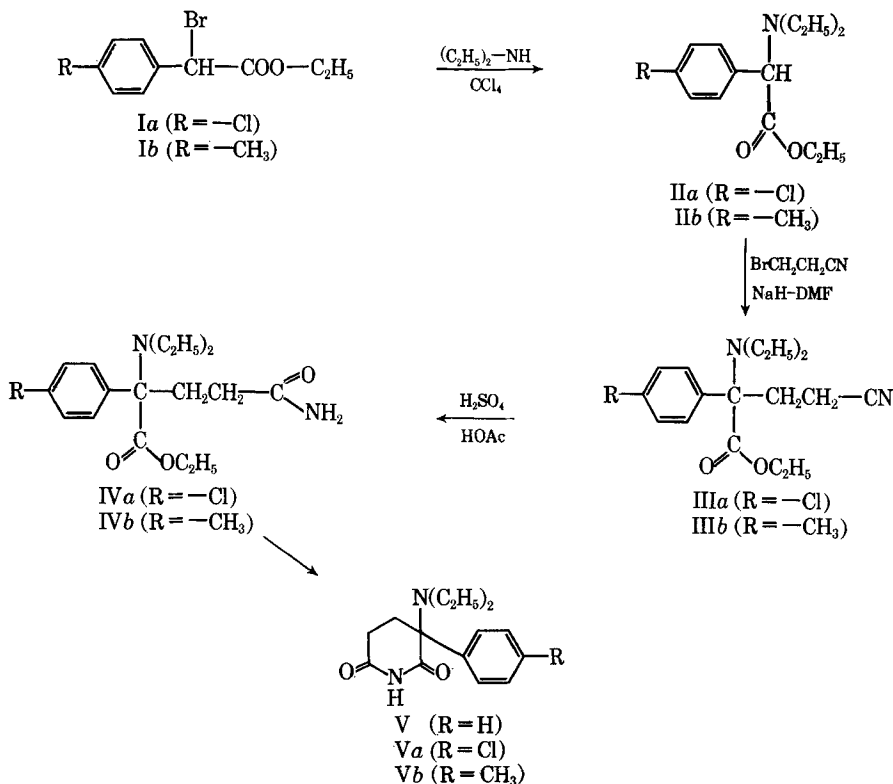
Accepted for publication August 1, 1967.

Presented to the Medicinal Chemistry Section, A. Ph. A. Academy of Pharmaceutical Sciences, Las Vegas meeting, April 1967.

This investigation was supported in part by funds provided for medical and biological research by the State of Washington Initiative Measure No. 171, and by research grant NB 05032-01 and -02, National Institutes of Health, U. S. Public Health Service, Bethesda, Md.

Abstracted from portions of theses submitted by S. K. Arya (1964) and K'un Chang (1966) to the Graduate School, Washington State University, in partial fulfillment of Master of Science degree requirements.

Previous paper: Narayanan, V. L., and Martin, C. F., *J. Med. Chem.*, **9**, 615 (1966).



Scheme I

(methylene protons of ester ethyl); singlet 5.15 p.p.m. (proton on α -carbon) with phenyl protons centered at 7.45 p.p.m.

Anal.—Calcd. for $\text{C}_{10}\text{H}_{10}\text{BrClO}_2$: C, 43.28; H, 3.63; Br, 28.54; Cl, 12.77. Found: C, 43.50; H, 3.82; Br, 28.54; Cl, 12.59.

Ethyl α -Bromo-*p*-tolylacetate (Ib)—To a stirred mixture of 150.2 Gm. (1.0 mole) of *p*-tolylacetic acid and 6.0 Gm. of red phosphorus, 320.0 Gm. (2.0 moles) of bromine was added at 60–70° over a period of 12 hr. The mixture was stirred for an additional 5 hr. at 70°. After cooling, 62.5 Gm. (1.25 moles) of absolute ethanol was added slowly with stirring and the reaction mixture was heated at 75–80° for 10 hr. At the end of the period, the mixture was poured into ice water, the ester layer separated with ether, washed successively with 10% sodium bicarbonate solution, water, 10% sodium bisulfite solution and water, and dried (Na_2SO_4). After filtering and flash evaporating the ether, the oil was distilled to yield 194.0 Gm. (75.4%) of liquid, b. p. 125–129° (2.1 mm.). Redistillation twice yielded product Ib, b.p. 124.5° (2.1 mm.); infrared (CHCl_3): 1745 ($\text{C}=\text{O}$ ester).

Anal.—Calcd. for $\text{C}_{11}\text{H}_{13}\text{BrO}_2$: C, 51.38; H, 5.09; Br, 31.08. Found: C, 51.59; H, 5.13; Br, 31.20.

Ethyl α -(*N,N*-Diethylamino)-*p*-chlorophenylacetate (IIa)—A well-stirred solution of 55.5 Gm. (0.2 mole) of freshly distilled Ia and 58.5 Gm. (0.8 mole) of diethylamine in 50 ml. of dry CCl_4 was heated gently under reflux for 10 hr. The mixture of precipitated hydrobromides was filtered, washed with CCl_4 , dissolved in water, the solution adjusted to pH

9.5 (cooling), and extracted with ether. The CCl_4 solution was extracted with 5% HCl, and after adjustment of the pH of the acidic extract to 9.5 (cooling), it was also extracted with ether. The ethereal extracts were combined and dried (Na_2SO_4). The solvent was flash evaporated and the product distilled to yield 48.5 Gm. (95%) of pale yellow mobile liquid, b. p. 102–105° (0.1 mm.). Redistillation twice yielded product IIa, b. p. 102° (0.1 mm.); infrared (CHCl_3): 2975 ($-\text{CH}$ arom.); 2800–2950 ($-\text{CH}$ aliph.); 1725 cm^{-1} ($\text{C}=\text{O}$ ester).

Anal.—Calcd. for $\text{C}_{14}\text{H}_{20}\text{ClNO}_2$: C, 62.34; H, 7.41; Cl, 13.14; N, 5.19. Found: C, 62.48; H, 7.39; Cl, 13.16; N, 5.18.

Ethyl α -(*N,N*-Diethylamino)-*p*-tolylacetate (IIb)—A well-stirred solution of 124.7 Gm. (0.5 mole) of freshly distilled Ib and 146.0 Gm. (2.0 moles) of diethylamine in 130 ml. of dry CCl_4 was heated gently under reflux for 10 hr. The mixture of precipitated hydrobromides was filtered, washed with CCl_4 , dissolved in water, the solution adjusted to pH 9.5 (cooling), and extracted with ether. The CCl_4 solution was extracted with 10% HCl, and after adjustment of the pH of the acidic extract to 9.5 (cooling), it was also extracted with ether. The ethereal extracts were combined and dried (Na_2SO_4). The solvent was flash evaporated and the product distilled to yield 80.9 Gm. (64.8%) of pale yellow mobile liquid, b. p. 104–107° (0.4 mm.). Redistillation twice yielded product IIb, b. p. 102° (0.35 mm.); infrared (CHCl_3): 2850–2970 ($-\text{CH}$ aliph.); 1730 ($\text{C}=\text{O}$ ester).

Anal.—Calcd. for $\text{C}_{15}\text{H}_{23}\text{NO}_2$: C, 72.25; H, 9.29;

N, 5.62. Found: C, 72.36; H, 9.40; N, 5.71.

4 - Carbethoxy - 4 - (N,N - diethylamino) - 4 - p-chlorophenylbutyronitrile (IIIa)—All of the glassware used in this reaction was flame-dried. Spectroquality dimethylformamide (DMF) was used, and the entire reaction was run under a blanket of dry nitrogen.

To a well-stirred suspension of 2.5 Gm. (0.11 mole) of sodium hydride in 50 ml. of dry DMF, 27.7 Gm. (0.1 mole) of freshly distilled IIa was added at such a rate as to maintain an internal temperature of 45–50° (addition time, 3 hr.). The resulting thick red liquid was cooled in ice (0–5°) and 15.5 Gm. (0.11 mole) of freshly distilled β -bromopropionitrile was added dropwise, with continuous stirring, over a period of 4 hr. The temperature was not allowed to exceed 5° during the addition. The mixture, containing the precipitated NaBr, was stirred overnight at room temperature under dry N₂. The residue left after removal of the solvent was taken up in 100 ml. of ice water and extracted with ether. The ether extract was washed with water and dried (MgSO₄). After removal of the ether, the residual product was fractionally distilled to yield 19.7 Gm. (60%) of IIIa as a pale yellow viscous liquid, b. p. 162° (0.01 mm.). An analytical sample was obtained by an additional distillation, b. p. 159–160° (0.01 mm.); infrared (CHCl₃): 2975 (—CH arom.); 2800–2950 (—CH aliph.); 2250 (—CN); 1720 cm.⁻¹ (C=O ester).

Anal.—Calcd. for C₁₇H₂₃ClN₂O₂: C, 63.25; H, 7.20; Cl, 10.99; N, 8.64. Found: C, 63.37; H, 7.25; Cl, 11.31; N, 8.43.

4 - Carbethoxy - 4 - (N,N - diethylamino) - 4 - p-tolylbutyronitrile (IIIb)—The use of flame-dried glassware, the maintenance of a dry, inert atmosphere, and the use of spectroquality dimethylformamide (DMF) were criteria for success in this reaction as they were for the synthesis of IIIa.

To a well-stirred suspension of 5.5 Gm. (0.23 mole) of sodium hydride in 100 ml. of dry DMF, 49.8 Gm. (0.20 mole) of freshly distilled IIb was added at such a rate as to maintain an internal temperature of 40–45° (addition time, 3 hr.). The resulting thick red liquid was cooled in ice (0–5°) and 29.5 Gm. (0.22 mole) of freshly distilled β -bromopropionitrile was added dropwise, with continuous stirring, over a period of 3 hr. The temperature was not allowed to exceed 5° during the addition. The mixture, containing the precipitated NaBr, was stirred overnight at room temperature under dry N₂. The mixture, in this case, instead of first being stripped of solvent was poured into 150 ml. of ice water and extracted with ether. The ether extract was washed with water and dried (MgSO₄). After removal of the ether, the residue was fractionally distilled to yield 20.8 Gm. (34.4%) of IIIb as a pale yellow viscous liquid, b. p. 136–139° (0.06 mm.). An analytical sample was obtained by an additional distillation, b. p. 135° (0.06 mm.); infrared (neat film): 2975 (—CH arom.); 2850–2950 (—CH aliph.); 2250 (—CN); 1720 cm.⁻¹ (C=O ester).

Anal.—Calcd. for C₁₈H₂₆N₂O₂: C, 71.49; H, 8.67; N, 9.27. Found: C, 71.44; H, 8.63; N, 9.44.

4 - Carbethoxy - 4 - (N,N - diethylamino) - 4 - p-chlorophenylbutyramide (IVa)—A mixture of 32.3 Gm. (0.1 mole) of IIIa and 30 ml. of glacial acetic

acid was stirred at room temperature for 20 min. Concentrated H₂SO₄ (30 ml.) was added slowly and the mixture heated on a steam bath with stirring for 30 min. The brownish-red liquid obtained was poured into stirred ice water, and 30% aqueous NaOH was added until the mixture was alkaline (pH 8.5). The product was extracted with chloroform, washed with water, dried (Na₂SO₄), and concentrated. Because attempts to solidify the resulting thick oil by rubbing with *n*-hexane and with ligroin were unsuccessful, the product was distilled to yield 23.8 Gm. (70.5%) of light yellow viscous liquid, b. p. 190° (0.05 mm.); infrared (CHCl₃): 3490, 3390, 3150 (NH amide, 2 free, 1 bonded); 1720 (C=O ester); 1680 (amide I); 1595 (amide II); no nitrile band at 2250 cm.⁻¹.

Anal.—Calcd. for C₁₇H₂₅ClN₂O₃: C, 59.94; H, 7.34; Cl, 10.42; N, 8.22. Found: C, 59.83; H, 7.19; Cl, 10.15; N, 8.41.

4 - Carbethoxy - 4 - (N,N - diethylamino) - 4 - p-tolylbutyramide (IVb)—A mixture of 30.2 Gm. (0.1 mole) of IIIb and 30 ml. of glacial acetic acid was stirred at room temperature for 20 min. Concentrated H₂SO₄ (30 ml.) was added slowly and the mixture heated on a steam bath for 30 min. The brownish-red liquid obtained was poured into stirred ice water, and 30% NaOH was added until the mixture was alkaline (pH 8.5). The product was extracted with chloroform, washed with water, dried (Na₂SO₄), and concentrated. The thick oil which could not be crystallized or distilled without decomposition, was obtained as a crude product in a yield of 31.8 Gm. (99.1%); infrared (CHCl₃): 3500, 3400, 3160 (NH amide, 2 free, 1 bonded); 1720 (C=O ester); 1680 (amide I); 1595 (amide II); no nitrile band at 2250 cm.⁻¹. It was used in the final step without further purification.

2 - (N,N - Diethylamino) - 2 - p - chlorophenylglutarimide (Va)—Spectroquality DMF was used. All glassware was flame-dried. The reaction was carried out under an atmosphere of dry nitrogen.

A solution of 10.0 Gm. (0.028 mole) of freshly distilled 4 - carbethoxy - 4 - (N,N - diethylamino) - 4 - p - chlorophenylbutyramide (IVa) in 25 ml. of dry DMF (warming aids the dissolution process) was added dropwise to a stirred suspension of 0.8 Gm. (0.03 mole) of NaH in 50 ml. of dry DMF. The mixture was stirred at 55° for 2.5 hr., by which time the formation of anion was complete as evidenced by the cessation of H₂ evolution. The bath temperature was raised to 105° and maintained at this point for 15 hr. The residue, left after distilling off the solvent under reduced pressure, was well stirred with ice water, the solution adjusted to pH 8.5 (cooling), and the product extracted with chloroform, washed with water, and dried (Na₂SO₄). Filtration and removal of the chloroform left a thick oil which was washed with *n*-hexane and ligroin. The partially purified product was redissolved in chloroform, extracted with 10% HCl, and the acid extract, upon evaporation on a steam bath, yielded a residue which, after rubbing with a chloroform-ether mixture, gave 4.2 Gm. (46.0%) of Va as the solid hydrochloride. Recrystallization of the product from hot chloroform yielded a white powder, m.p. 132–135°; infrared (Nujol): 3150, 3050 (NH); 1710 with shoulder at 1730 (C=O); 2535, 2450 cm.⁻¹ (amine salt); ultraviolet (95% ethanol): 220 m μ (flat shoulder) and evidence of peak below 200 m μ out of

range of instrument; ($10^{-3}M$ ethanolic KOH): bathochromic shift to 225 $m\mu$ (flat shoulder) and 215 $m\mu$ (peak).

Anal.—Calcd. for $C_{15}H_{20}Cl_2N_2O_2$: C, 53.39; H, 6.08; Cl, 21.20; N, 8.45. Found: C, 53.03; H, 5.96; Cl, 20.21; N, 8.81.

2-(N,N-Diethylamino)-2-p-tolylglutarimide (Vb)—Spectroquality DMF was used. All glassware was flame-dried, and the reaction was carried out under an atmosphere of dry nitrogen.

A solution of 16.0 Gm. (0.05 mole) of crude, but dried, 4-carbethoxy-4-(N,N-diethylamino)-4-p-tolylbutyramide (IVb) in 50 ml. of dry DMF was added dropwise to a stirred suspension of 1.4 Gm. (0.057 mole) of NaH in 100 ml. of dry DMF. The mixture was stirred at 55° for 2.5 hr., by which time the formation of anion was complete as evidenced by the cessation of H_2 evolution. The bath temperature was raised to 105° and maintained at this point for 15 hr. The residue, left after distilling off the solvent under reduced pressure, was well stirred with ice water, the solution adjusted to pH

8.5 (cooling), and the product extracted with chloroform, washed with water, and dried (Na_2SO_4). Filtration and removal of the chloroform left a thick oil which solidified on rubbing with dry *n*-hexane. Recrystallizations from dry chloroform-hexane¹ yielded 1.62 Gm. (11.8%) of Vb as white crystals, m. p. 112°; infrared (CHCl₃): 3375, 3200 (NH); 1720 cm^{-1} (C=O).

Anal.—Calcd. for $C_{16}H_{22}N_2O_2$: C, 70.04; H, 8.08; N, 10.21. Found: C 69.95; H, 8.04; N, 10.21.

REFERENCES

- (1) Narayanan, V. L., and Martin, C. F., *J. Med. Chem.*, **9**, 615(1966).
- (2) Fink, G. B., and Juchau, M. R., *J. Pharm. Sci.*, **53**, 325(1964).
- (3) Anschütz, R., *Ann.*, **354**, 127(1907).
- (4) Weizman, C. H., Sulzbacher, M., and Bergmann, E., *J. Am. Chem. Soc.* **70**, 1153(1948).
- (5) Zaugg, H. E., Horrom, B. W., and Borgwardt, S., *ibid.*, **82**, 2895(1960).
- (6) Lee, C. M., and Kumler, W. D., *ibid.*, **83**, 4586(1961).
- (7) Kumler, W. D., personal communication, 1962.

¹ Using decolorizing carbon (Norit).

Segregation Kinetics of Particulate Solids Systems IV. Effect of Particle Shape on Energy Requirements

By E. G. RIPPIE, M. D. FAIMAN*, and M. K. PRAMODA

The relative energy requirements of the processes of segregation and mixing, which occur in systems of particulate solids, are shown to be a function of the shape and size of the particles. These energy requirements, as reflected by agitation coefficients, have been determined for several idealized systems. Granular solids, as represented by crushed quartz and pyrite, were found to behave in conformity with predictions based on the idealized systems.

PARTICLE SHAPE is known to exert a marked influence on the behavior of particulate solids. This is true, moreover, when powdered or granular material is either in a dynamic state of flow or is at rest. Little is presently known regarding the specific cause and effect relationships between bulk behavior and particle shape, a situation which arises because of difficulties in expressing the latter as a single scalar quantity.

The problem is frequently approached by the use of shape factors as a quantitative expression of the average shape of particles in a system. The function of shape factors, however, is not to express shape, but rather to relate the results of particle size measurements which have been obtained by several different methods (1). Consequently, it is possible to have different particulate solids with quite different characteristic shapes, but which all possess a similar value of a given shape factor. Further complications result when average values are used to describe particulate variables without

regard for the deviation of individual values from the mean.

The present work is intended to give quantitative information on the effects of particle shape on segregation and mixing in idealized systems where an intuitive appraisal of shape is possible. Such idealized systems, which are made up of regularly shaped particles (spheres, paired spheres, cubes, rods, and hexagonal rods), have the advantage that they may be described exactly as to shape which is uniform from particle to particle. For purposes of comparison, crushed quartz and pyrite were also studied.

Results indicate that substantial differences in bulk behavior can result from relatively minor changes in particle shape. Particle size is also shown to influence the change in rate of segregation and mixing with a change in agitation intensity.

EXPERIMENTAL

Materials—Chrome steel balls of the type and grade commonly employed in the manufacture of commercial ball bearings were used. Paired balls were prepared by spot welding two similar sized balls together. The effective distance of separation of the centers of mass was reduced by approximately 1% by the welding operation. Steel cubes and cylinders of circular and hexagonal cross section were made of cold rolled steel and case hardened in

Received May 26, 1967, from the Department of Pharmaceutics, College of Pharmacy, University of Minnesota, Minneapolis, MN 55455

Accepted for publication July 21, 1967.

This investigation was supported by grants GP-1820 and GK-471 from the National Science Foundation.

Previous paper: Faiman, M. D., and Rippie, E. G., *J. Pharm. Sci.*, **54**, 719(1965).

* Present address: University of Kansas, Lawrence, KS 66044