(18) R. Shangraw, W. Grim, and A. M. Mattocks, *Trans. Soc. Rheol.*, **5**, 247(1961).
(19) I. M. Kreiger and S. H. Maron, *J. Appl. Phys.*, **25**, 72 (1954).
(20) C. G. Lindquist and W. C. Sierichs, *J. Colloid Sci.*, **6**, 33(1951).
(21) J. A. Lescarboura, F. J. Eichstadt, and G. W. Swift, *AIChE J.*, **13**, 169(1967).
(22) I. M. Kreiger and H. Elrod, *J. Appl. Phys.*, **24**, 134(1953).
(23) J. G. Brodnyan, F. H. Gaskins, and W. Philippoff, "Symposium on Non-Newtonian Viscometry," No. 299, American Society for Testing and Materials, Philadelphia, Pa., 1960, pp. 14–25.
(24) E. S. Swinbourne, *J. Chem. Soc.*, **1960**, 2371.
(25) P. J. Niebergall and E. T. Sugita, *J. Pharm. Sci.*, **57**, 1805(1968).

ACKNOWLEDGMENTS AND ADDRESSES

Received July 7, 1975, from the *Department of Pharmacy, Philadelphia College of Pharmacy and Science, Philadelphia, PA 19104*

Accepted for publication November 14, 1975.

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NOTES

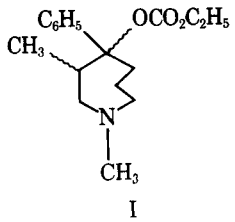
Epimeric 5-Hydroxy-5-phenyl-1-azabicyclo[5.4.0]undecanes

N. ABOUL-ENEIN and J. SAM ˣ

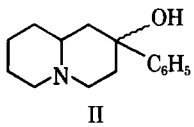
Abstract □ The preparation of epimeric 5-hydroxy-5-phenyl-1-azabicyclo[5.4.0]undecanes is described. One propionate ester exhibited weak analgesic activity.

Keyphrases □ Undecanes, substituted cyclic—epimers synthesized, analgesic activity evaluated □ 5-Hydroxy-5-phenyl-1-azabicyclo[5.4.0]undecanes epimers—synthesized, analgesic activity evaluated □ Analgesic agents, potential—epimers of 5-hydroxy-5-phenyl-1-azabicyclo[5.4.0]undecanes synthesized and screened

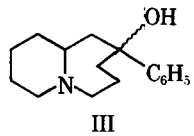
The potent analgesic activity exhibited by proheptazine (I) (1) and the esters of 2-hydroxy-2-phenylquinolizidines (II) (2) led to the investigation of epimeric 5-hydroxy-5-phenyl-1-azabicyclo[5.4.0]undecanes (III) and the corresponding propionate esters. The preparation and stereochemistry of 6-hydroxy-6-aryl-1-azabicyclo[5.4.0]undecanes and their structural relationship to biologically active phenethylamines and analgesic piperidines were reported previously (3).



I



II

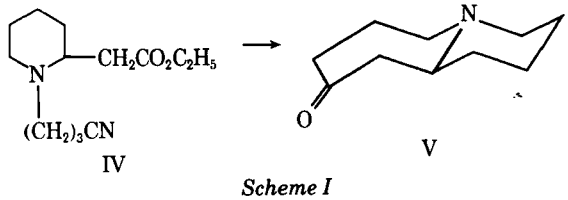


III

DISCUSSION

For the synthesis of III, 1-azabicyclo[5.4.0]undecan-5-one (V) was utilized. The procedure followed (Scheme I) for the preparation of V from ethyl 1-(3-cyanopropyl)piperidyl-2-acetate (IV) was similar to the method described (4) for the synthesis of 1-oxoquinolizidine.

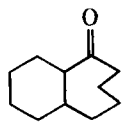
Published reports (3–9) describing the stereochemical structure of bicyclo[5.4.0]undecan-2-one (VI), II, and related quinolizidines



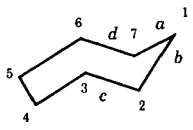
IV V

Scheme I

were utilized in determining the stereochemical nature of the ring in V. The IR spectra of V is consistent with published data (2–9) on *trans*-fused II and related *trans*-fused ring systems. Since TLC indicated the formation of only one isomer, *trans*-fused Structure V was assigned to the product.



VI



VII

The reaction of phenylmagnesium bromide with V provided an 8:1 mixture of epimeric 5-hydroxy-5-phenyl-1-azabicyclo[5.4.0]undecanes (III*a* and III*b*). Because of the lack of definitive information on the conformation of heterocyclic ring systems containing more than five carbons (10, 11) and the high flexibility of seven-membered rings (12), a conclusive delineation of the conformation of III*a* and III*b* could not be determined. Investigators noted previously (13–16) that the stable conformation of cycloheptane is in a deformed chair position (VII). Moreover, the cyclohexane chair can be fused at any one of the four bounds marked *a*, *b*, *c*, and *d* without affecting the original conformation. Structures resulting from *trans*-fusion of the cyclohexane chair at *a* or *b* are readily interconvertible by a slight manipulation of C-4 and are the most favored, while the other two structures fused at *c* or *d* are quite rigid (5, 16).

The IR spectra of both III*a* and III*b* are similar in the hydroxyl absorption region (both show absorption at 3300 cm^{-1} in carbon tetrachloride even on high dilutions) and in the aromatic region between 600 and 800 cm^{-1}. Bohlmann bands do not appear in the spectrum of III*a*; the spectrum of III*b* includes bands at 2765, 2795, and 2860 cm^{-1}, indicative of a *trans*-fused system. Sircar and Meyers

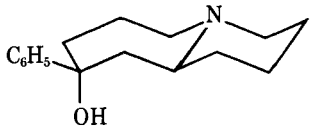
Table I—Analgesic Potency of Propionates of Phenylhydroxy-1-azabicyclo[5.4.0]undecanes

Compound	ED_{50}, mg/kg[a]	Activity, min		
		Onset	Peak	Duration
VIII	71.5 (62.5–81.8)	4.5	36.5	134.8
IX	65.9 (56.7–76.7)	2.0	39.1	160.2
Codeine	7.5 (6.8–82)	4.0	22.8	147.6

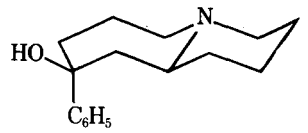
[a] Subcutaneous; numbers in parentheses are 95% confidence limits.

(17), however, reported that Bohlmann bands have not always been observed in systems known to possess *trans*-fused quinolizidine moieties. The NMR spectra of III*a* in deuterochloroform shows the hydroxyl group as a sharp peak at δ 5.33; for III*b*, it appears as a weak broad peak at δ 5.60. The aromatic nucleus appears as a multiplet centered at δ 7.48 in both III*a* and III*b*. The results are in agreement with data reported for related 1-, 2-, and 3-hydroxyquinolizidines (2, 18, 19) and 6-hydroxy-1-azabicyclo[5.4.0]undecanes (3).

On the basis of these data, Structures III*a* and III*b* are assigned to these epimers, respectively. *trans*-Fused rings are proposed for both epimers, with the hydroxyl group of III*a* in a quasiaxial position and the hydroxyl group of III*b* in a quasiequatorial position.

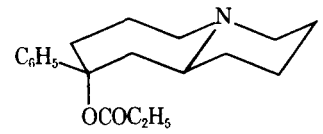


III*a*

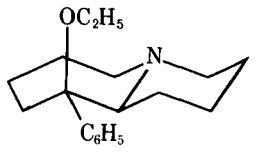


III*b*

The reaction of III*a* with propionyl chloride provided ester VIII. The IR spectrum of the ester showed the disappearance of the hydroxyl group; Bohlmann bands at 2700, 2780, 2820, and 2860 cm^{-1}, indicating *trans*-fusion of the rings; and carbonyl absorption at 1740 cm^{-1}. Because of difficulties encountered in the preparation of a sufficient quantity of III*b*, the corresponding ester was not prepared.



VIII



IX

The analgesic potency of VIII and the propionate ester IX of 6-hydroxy-6-phenyl-1-azabicyclo[5.4.0]undecanes, prepared in a previous study (3), was determined by the hot-plate method (20). As noted in Table I, both VIII and IX are considerably less potent than codeine. Studies are being conducted to obtain sufficient quantities of III*b* to permit biological evaluation of the corresponding propionate ester.

EXPERIMENTAL[1]

Ethyl 1-(3-Cyanopropyl)piperidyl-2-acetate (IV)—A mixture of 63.1 g (0.36 mole) of ethyl piperidyl-2-acetate (21), 43.5 g (0.29 mole) of δ-bromobutyronitrile, and 80 g of anhydrous potassium carbonate in 130 ml of dry toluene was stirred and refluxed for 24 hr. An additional 20 g of anhydrous potassium carbonate and 70 ml of dry toluene were added, and the mixture was refluxed another 24 hr. After cooling, the mixture was treated with 500 ml of benzene and with enough water to dissolve the precipitate.

The organic layer was separated and the aqueous layer was extracted with ether (2 × 300 ml). The combined organic extracts were dried over magnesium sulfate and evaporated. The oily residue was distilled at 140–142°/0.1 mm to give 60 g (69%) of IV, $n_D^{27.5}$ = 1.4686; IR (liquid film): 2240 (C≡N) and 1720 (C=O ester) cm^{-1}.

Anal.—Calc. for $C_{13}H_{22}N_2O_2$: C, 65.52; H, 9.30; N, 11.75. Found: C, 65.08; H, 9.34; N, 11.44.

1-Azabicyclo[5.4.0]undecan-5-one (V)—A solution of 54 g (0.226 mole) of the nitrile (IV) in 60 ml of dry xylene was added during 1.5 hr to a refluxing mixture of 20.5 g (0.439 mole) of a 50% dispersion of sodium hydride in mineral oil and 1000 ml of dry xylene. After the addition was completed, refluxing was continued for 5 hr. Then the mixture was cooled in ice and treated carefully with 90 ml of acetic acid. The xylene layer was extracted with concentrated hydrochloric acid (3 × 100 ml), and then the combined acidic extracts were refluxed for 24 hr.

The residue remaining after the excess acid was distilled *in vacuo* was basified with 20% sodium hydroxide solution, extracted with ether (3 × 100 ml), and dried over potassium carbonate. Distillation of the ether extract gave 14 g (36%) of V, bp 144–146°/30 mm, $n_D^{27.5}$ = 1.4959; IR (CCl_4): Bolhmann bands at 2690, 2775, 2810, and 2860 cm^{-1} and 1710 (C=O) cm^{-1}. The picrate was prepared in the usual manner and recrystallized from ethanol–acetone, mp 200–201°.

Anal.—Calc. for $C_{16}H_{20}N_4O_8$: C, 48.49; H, 5.09; N, 14.14. Found: C, 48.60; H, 5.11; N, 14.17.

5-Phenyl-5-hydroxy-1-azabicyclo[5.4.0]undecane (III*a* and III*b*)—The procedure described by England and Sam (18) was followed using 13 g (0.077 mole) of V. A viscous oil (16 g, 88%), which crystallized on standing, was obtained. The IR spectrum showed strong hydroxyl and weak carbonyl absorptions. Trituration of the mass with cold *n*-hexane and storage at 0–5° for 4 hr yielded crystalline needles, mp 116–117°. Recrystallization from *n*-hexane gave 7.8 g (44%) of III*a*, mp 117–118°. TLC, using petroleum ether (bp 30–60°)–ether (3:7) and 1-butanol–acetic acid–water (4:1:1), indicated the presence of a single component; IR (CCl_4): 3300 (—OH) cm^{-1} and no obvious Bohlmann bands; IR (KBr): 695, 730, and 765 cm^{-1} (monosubstituted aromatic absorption); NMR: δ 5.33 (s, —OH, exchangeable with D_2O) and 7.48 (m, 5H).

Anal.—Calc. for $C_{16}H_{23}NO$: C, 78.32; H, 9.45; N, 5.71. Found: C, 78.32; H, 9.64; N, 5.65.

Evaporation of the *n*-hexane from which III*a* was obtained yielded 6 g of a viscous oil, which was dissolved in a minimum amount of *n*-hexane and column chromatographed. Elution was performed with *n*-hexane at a flow rate of 7 ml/min. Fractions 4–25 yielded 1 g (6%) of crystalline III*b*, mp 65.5–67.5°. TLC showed one spot; IR (CCl_4): 3300 (—OH) cm^{-1} and Bohlmann bands at 2765, 2798, and 2860 cm^{-1}; IR (KBr): 700 and 760 (monosubstituted aromatic absorption) cm^{-1}; NMR: δ 5.60 (broad, weak, s, —OH, exchangeable with D_2O) and 7.48 (m, 5H).

Anal.—Calc. for $C_{16}H_{23}NO$: C, 78.32; H, 9.45; N, 5.71. Found: C, 78.34; H, 9.63; N, 5.70.

Further elution with *n*-hexane followed by ether yielded unreacted ketone (V).

5-Phenyl-5-propionoxy-1-azabicyclo[5.4.0]undecane (VIII)—To a solution of 7.5 g (0.031 mole) of III*a* and 15 g (0.150 mole) of triethylamine in 125 ml of dry toluene was added dropwise a solution of 7.5 g (0.081 mole) of propionyl chloride in 25 ml of dry toluene. The reaction mixture was stirred under reflux for 6–8 hr. After cooling, the mixture was filtered, and the filtrate was evaporated under reduced pressure. The residual brown oil was treated with ice-cold saturated potassium carbonate solution and extracted with ether (3 × 150 ml). The extract was dried over magnesium sulfate and evaporated.

A solution of the residue in 60 ml of 20% hydrochloric acid was extracted with ether (3 × 50 ml) and then basified under cooling with saturated potassium carbonate solution. An ether extract (3 × 150 ml) was dried over magnesium sulfate and then evaporated to give 8.5 g (94%) of brown oil. The oil was column chromatographed using *n*-hexane as the eluant, and 6.5 g (71%) of a yellow oil was obtained, $n_D^{27.5}$ = 1.5364; IR (CCl_4): no hydroxyl absorption, Bohlmann bands at 2700, 2780, 2820, and 2860 cm^{-1}, and 1740 (C=O) cm^{-1}.

Anal.—Calc. for $C_{19}H_{27}NO_2$: C, 75.71; H, 9.03; N, 4.65. Found: C, 75.91; H, 9.06; N, 4.57.

[1] Melting points were taken with a Thomas-Hoover Uni-Melt apparatus and are uncorrected. IR spectra were determined with a Perkin-Elmer 257 spectrophotometer. NMR spectra were obtained with a Jeolco C-60-HL spectrometer relative to an internal standard of tetramethylsilane. TLC and column chromatography were performed with Eastman alumina sheets and Woelm grade I neutral alumina, respectively. Elemental analyses were performed by the A. H. Robins Co., Richmond, Va.

REFERENCES

(1) R. A. Hardy, Jr., and G. Howell, in "Analgetics," vol. 5, G. DeStevens, Ed., Academic, New York, N.Y., 1965, p. 209.

(2) J. Sam, J. D. England, and D. Temple, *J. Med. Chem.*, **12**, 144(1969).
(3) M. N. Aboul-Enein and J. Sam, *J. Heterocycl. Chem.*, **8**, 7(1971).
(4) S. F. Mason, K. Schofield, and R. J. Wells, *J. Chem. Soc., C*, **1967**, 626.
(5) T. C. Joseph and S. Dev, *Tetrahedron*, **24**, 3841(1968).
(6) F. Bohlmann, *Angew. Chem.*, **69**, 641(1957); *Chem. Ber.*, **91**, 2157(1958).
(7) T. M. Moynehan, K. Schofield, R. A. Y. Jones, and A. R. Katritzky, *J. Chem. Soc.*, **1962**, 2637.
(8) H. S. Aaron and C. P. Ferguson, *Tetrahedron Lett.*, **1968**, 6191.
(9) P. J. Chivers, T. A. Crabb, and R. O. Williams, *Tetrahedron*, **24**, 4411(1968).
(10) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Wiley, New York, N.Y., 1965, p. 254.
(11) F. G. Riddell, *Quart. Rev.*, **21**, 364(1967).
(12) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Wiley, New York, N.Y., 1965, p. 207.
(13) S. Dev, *J. Indian Chem. Soc.*, **33**, 769(1956).
(14) N. L. Allinger, *J. Am. Chem. Soc.*, **81**, 5727(1959).
(15) R. Pauncz and D. Ginsburg, *Tetrahedron*, **9**, 40(1960).
(16) J. B. Hendrickson, *J. Am. Chem. Soc.*, **83**, 4537(1961).
(17) J. C. Sircar and A. I. Meyers, *J. Org. Chem.*, **32**, 1248(1967), and references cited therein.
(18) J. D. England and J. Sam, *J. Heterocycl. Chem.*, **3**, 582(1966).
(19) M. E. Rogers and J. Sam, *J. Med. Chem.*, **17**, 726(1974).
(20) A. E. Jacobson and E. L. May, *ibid.*, **8**, 563(1965); N. B. Eddy and D. Leimbach, *J. Pharmacol. Exp. Ther.*, **107**, 385(1953).
(21) H. J. Rhodes and T. O. Soine, *J. Am. Pharm. Assoc., Sci. Ed.*, **45**, 746(1956).

ACKNOWLEDGMENTS AND ADDRESSES

Received August 28, 1975, from the *Department of Medicinal Chemistry, School of Pharmacy, University of Mississippi, University, MS 38677*

Accepted for publication November 6, 1975.

The authors are grateful to Dr. E. L. May, National Institutes of Health, for the analgesic data.

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Differential Thermal Analysis of Aluminum Hydroxide Gel

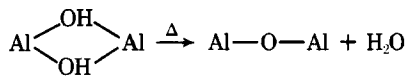
STEVEN L. NAIL [*], JOE L. WHITE [‡], and STANLEY L. HEM [*x]

Abstract □ The development of order during the aging of aluminum hydroxide gel prepared by the reaction of aluminum chloride and ammonium hydroxide to a final pH of 7.0 can be monitored by differential thermal analysis. The loss of acid reactivity upon aging is accompanied by an increase in the temperature and intensity of the dehydroxylation endotherm and an accompanying decrease in the intensity of the water of hydration endotherm. With continued aging, the thermogram develops the characteristics of a crystalline aluminum hydroxide.

Keyphrases □ Aluminum hydroxide gels—differential thermal analysis, development of order during aging □ Gels, aluminum hydroxide—differential thermal analysis, development of order during aging □ Aging—aluminum hydroxide gels, monitored by differential thermal analysis □ Differential thermal analysis—aging of aluminum hydroxide gels monitored

In previous investigations (1, 2), IR spectroscopy and X-ray diffraction were used to monitor the structural changes in aluminum hydroxide gel which occurred upon aging and were associated with a decreased rate of acid reactivity. The initial highly random structure changed during aging as the hydroxyls became part of an ordered structure. The degree of order increased until a crystalline form of aluminum hydroxide developed. This report demonstrates the utility of differential thermal analysis in monitoring the aging of aluminum hydroxide gel and relates the thermal behavior to a recently proposed structure of aluminum hydroxide gel (3, 4).

The physical changes detectable by differential thermal analysis when aluminum hydroxide gel is heated are the loss of water of hydration in the range of



Scheme I

100–120° and the loss of structural hydroxyl as water (Scheme I). The temperature at which the dehydroxylation of the double hydroxide bridges occurs is a characteristic that allows the identification of crystalline aluminum hydroxide (5–10), although the aluminum hydroxide polymorphs cannot be distinguished from one another. Gibbsite and bayerite both have dehydroxylation endotherms at about 300°. Pseudoboehmite and boehmite undergo dehydroxylation at about 450° (9).

EXPERIMENTAL

Materials—All chemicals used were either reagent or analytical grade.

Aluminum Hydroxide Gel Preparation—A 4-liter batch of gel was prepared by the addition of 13% (v/v) strong ammonia solution to a solution of 287.2 g of aluminum chloride hexahydrate in 3340 ml of distilled water. Strong ammonia solution was added, with continuous stirring, at a rate of approximately 120 ml/min to a final pH of 7.0. After precipitation, the gel was divided into equal portions prior to washing. The first portion (I) was washed with 1 liter of distilled water by draining through a canvas bag, the second (II), was washed with 3 liters of distilled water, and the third (III) was washed with 5 liters of distilled water. The three gels were diluted to 1 liter with distilled water and were then stored in tightly closed glass containers and aged at 25°.

Differential Thermal Analysis Thermograms—The differential thermal analysis thermogram[1] was recorded from room temperature

[1] Model III, Deltatherm Instrument Co., Denver, Colo.