

ethyl acetate was hydrogenated at 30 p.s.i. initial hydrogen pressure. The color of the suspension changed from red to yellow when the theoretical amount of hydrogen was consumed. The catalyst was removed by filtration¹⁰ and the filtrate washed with (a) three 20-ml. portions of 0.5 *N* hydrochloric acid, (b) three portions of water and (c) two portions of saturated sodium chloride solution, and then dried over Drierite. The solution was concentrated under reduced pressure and the solid residue recrystallized from 80 ml. of ethyl acetate. A yellow crystalline powder was obtained weighing 1.3 g. (57%) and melting at 192–193°.

Anal. Calcd. for $C_7H_8N_2O_4$: C, 45.66; H, 4.38; N, 15.21. Found: C, 45.88; H, 4.88; N, 15.41.

Ethyl 3-Amino-2,6-dihydroxy-4-pyridinecarboxylate (Ethyl 3-Aminocitrazinate, VII).—The ethyl ester VII was prepared from IV by the same method described for VI; yield ca. 45%, m.p. 206–208°.

Anal. Calcd. for $C_8H_{10}N_2O_4$: C, 48.48; H, 5.09; N, 14.14. Found: C, 48.73; H, 5.19; N, 14.15.

3-Diazo-2-oxy-6-hydroxy-4-pyridinecarboxylic Acid (3-Diazocitrazinic Acid, VIII).—A solution of 25 ml. of iso-amyl nitrite in 35 ml. of chloroform was added during ca. 1 hour to a well-stirred suspension of V (7.18 g., 0.042 mole), in 30 ml. of trifluoroacetic acid and 100 ml. of chloroform, cooled at 0°. After the addition was complete, the mixture was stirred in the cold for an additional 2 hours; then it was concentrated under reduced pressure to about half its original volume, and 100 ml. of ethyl ether was added. The yellow powder was separated by filtration, washed with ethyl ether, and dried under vacuum; yield 7.25 g. (92%), decomposes without melting at 250°; absorption in the ultraviolet: λ_{max}^{water} 330 $m\mu$ (ϵ 14.1 $\times 10^3$); $\lambda_{max}^{0.1N HCl}$ 335 $m\mu$ (ϵ 14.6 $\times 10^3$); $\lambda_{max}^{0.1N NaOH}$ 342 $m\mu$ (ϵ 12.3 $\times 10^3$); $\lambda_{max}^{(CH_3COCH_2)_2}$ 333 $m\mu$

(ϵ 14.0 $\times 10^3$); characteristic infrared absorption band: λ_{max} at 4.7 μ (diazo group).

Anal. Calcd. for $C_6H_5O_4$: C, 39.78; H, 1.67; N, 23.20. Found: C, 39.40; H, 1.97; N, 23.08.

Methyl 3-Diazo-2-oxy-6-hydroxy-4-pyridinecarboxylate (Methyl 3-Diazocitrazinate, IX).—A solution of 35 ml. of isoamyl nitrite in 100 ml. of ethyl acetate was added during ca. 90 minutes to a well-stirred solution of VI (5.5 g., 0.0295 mole), in 22 ml. of trifluoroacetic acid and 550 ml. of ethyl acetate, at 0°. The reaction mixture was stirred for an additional 30 minutes in the cold, and was then concentrated to ca. 75 ml. under vacuum. The precipitate formed was separated by filtration and washed with liberal amounts of ethyl ether. After being dried under high vacuum, the yellow crystalline precipitate weighed 4.2 g. (74%) and melted at 172–174° dec. An additional quantity of product, ca. 1.0 g., m.p. 170° dec., can be obtained by diluting the filtrate with 100 ml. of ethyl ether and 100 ml. of petroleum ether, with cooling; absorption in the ultraviolet: λ_{max}^{water} 337 $m\mu$ (ϵ 13.4 $\times 10^3$); $\lambda_{max}^{0.1N HCl}$ 335 $m\mu$ (ϵ 9.45 $\times 10^3$); $\lambda_{max}^{0.1N NaOH}$ 343 $m\mu$ (ϵ 13.2 $\times 10^3$); $\lambda_{max}^{(CH_3COCH_2)_2}$ 335 $m\mu$ (ϵ 13.0 $\times 10^3$); characteristic infrared absorption band: λ_{max} at 4.7 μ (diazo group).

Anal. Calcd. for $C_7H_8N_2O_4$: C, 43.08; H, 2.58; N, 21.53. Found: C, 43.45; H, 2.88; N, 21.92.

Ethyl 3-Diazo-2-oxy-6-hydroxy-4-pyridinecarboxylate (Ethyl 3-Diazocitrazinate, X).—The ethyl ester X, was prepared from VII by the general method used for IX; yield 85%, m.p. 162–164° dec. The ultraviolet and infrared spectra were similar to those of IX.

Anal. Calcd. for $C_8H_{10}N_2O_4$: C, 45.94; H, 3.37; N, 20.09. Found: C, 45.99; H, 3.62; N, 20.69.

CHICAGO 9, ILL.

[CONTRIBUTION NO. 1551 FROM THE STERLING CHEMISTRY LABORATORY, YALE UNIVERSITY]

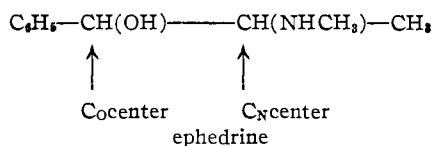
Nuclear Magnetic Resonance Spectra and Configuration. The N.m.r. Spectra of Diastereoisomeric Heterocyclic Derivatives of the Ephedrines

By J. B. HYNÉ¹

RECEIVED MAY 7, 1959

The n.m.r. spectra of derivatives of (–)-ephedrine and (+)- ψ -ephedrine synthesized by ring closure across the hydroxyl and amino functions of the amino-alcohols are analyzed in terms of the differing configurations in the molecules. The influence of the magnetic anisotropy of the phenyl group in the derivatives studied is the key factor which enables detailed interpretation of the spectra in terms of the relative spatial distribution of the various groups in the molecules.

Introduction.—The primary purpose of this work was to investigate the effect of configurational differences on the n.m.r. spectra of diastereoisomeric compounds. The ephedrines were chosen for this study since the configuration of the two asymmetric centers in the various isomers has been well established by previous work. It has been shown^{2a} by conversion of both (–)-ephedrine and (+)- ψ -ephedrine to (+)-deoxyephedrine that these



diastereoisomers differ in configuration at the C_o center and that the other asymmetric center in both forms has the (+)-alanine configuration.^{2b} In order to establish a fixed spatial disposition of the groups on the two asymmetric centers, several het-

erocyclic derivatives of the two ephedrines were prepared by bridging across the hydroxyl and amino groups. This bridging effectively restricts rotation about the asymmetric carbon linkage, and the relative spatial distribution of the various groups on both centers is known. Projection formula, systematic names and trivial names by which the structures will hereafter be identified are shown in Fig. 1. The configuration about the C_o center is drawn in anticipation of the n.m.r. spectral evidence.

N.m.r. Spectra.—All n.m.r. spectra were taken on a Varian V4300, 40 mc. machine with 5 mm. spinning sample tube at $20 \pm 1^\circ$. Chemical shifts were measured relative to benzene (external standard) by the side band technique. Peaks were identified with specific types of hydrogens by a combination of peak area, spin-coupling splitting and previously known chemical shifts for similar groups. Schematic presentations of the spectra for the six heterocyclic derivatives are shown in pairs in Fig. 2.

As different solvents were used for different pairs of diastereoisomers, discussion of the spectra will be

(1) Department of Chemistry, Dartmouth College, Hanover, N. H.
(2) (a) H. Emde, *Helv. Chim. Acta*, **12**, 365 (1929); (b) K. Freudenberg and F. Nikolai, *Ann.*, **510**, 223 (1934).

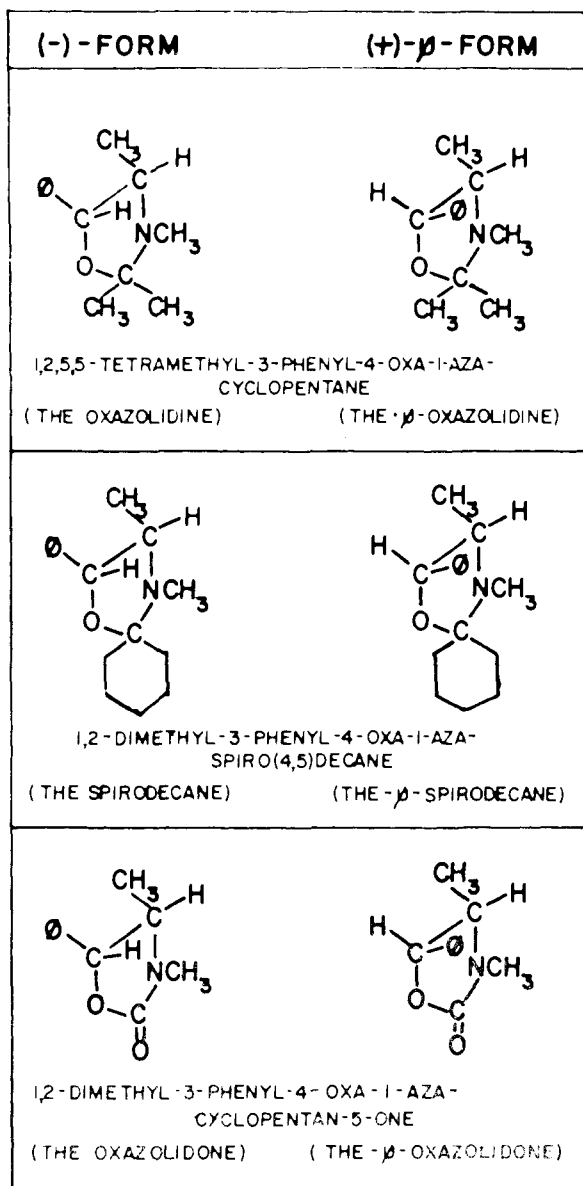


Fig. 1.—Projection formulas and nomenclature for ephedrine derivatives.

primarily restricted to comparisons of the spectra of each diastereoisomer within a pair. Since identical concentrations were used in each pair, any chemical shift contribution from the solvent effect alone is thus minimized. Inspection of Fig. 2 reveals that the relationship between the spectra for each pair is similar for all three types of heterocyclic derivative. The following detailed observations are notable: (a) The position of the NCH_3 peak is virtually identical in all cases, suggesting a very similar molecular environment for the NCH_3 group. (b) The position of the C_NCH_3 doublet is always lower on the frequency scale for the ψ -diastereoisomer of each pair. (c) The position of the C_NH quintuplet is always higher on the frequency scale for the ψ -diastereoisomer of each pair. (d) The position of the C_0H doublet is always higher on the frequency scale for the ψ -diastereoisomer of each pair. (e) The spirodecane and oxazolidine

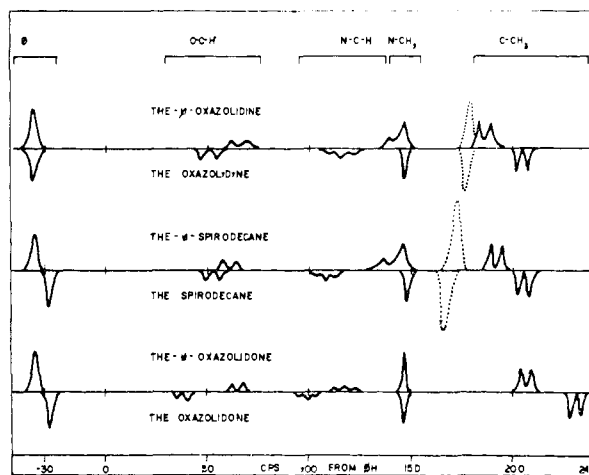


Fig. 2.—N.m.r. spectra of ephedrine derivatives; areas under peaks approximate only; dotted peaks are for hydrogens in bridging group; oxazolidines in chloroform solution; oxazolidones and spirodecanes in carbon tetrachloride. The $N-CH$ is a quintuplet in all cases, although when located close to $N-CH_3$ this multiplicity is not clear.

spectra are strikingly similar regarding peak positions, but that of the oxazolidone ($C=O$ bridge) is considerably different particularly regarding the position of the C_NCH_3 doublets.

Inspection of molecular models of any pair of the diastereoisomeric heterocycles immediately reveals that, accepting the identical configuration at the C_N center in both forms, in one of the two members of the pair the C_NCH_3 must lie in close proximity to the $C_0C_6H_5$. Furthermore the phenyl group is not free to rotate through a full 360° angle about its bond to the C_0 carbon but is constrained to a small angle of twist which results in the C_NCH_3 predominantly facing the plane of the phenyl ring rather than an edge (see Fig. 3). A considerable body of

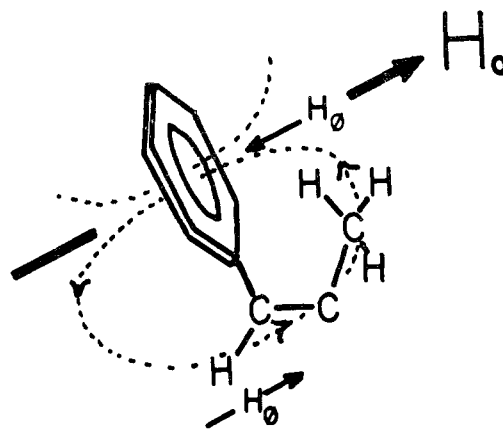


Fig. 3.—Anisotropic effect of benzene ring on adjacent groups.

both theoretical³ and experimental evidence^{4,5} is now available which indicates the considerable

(3) J. A. Pople, *J. Chem. Phys.*, **24**, 1111 (1956).

(4) J. S. Waugh and R. W. Fessenden, *THIS JOURNAL*, **79**, 846 (1957).

(5) H. Conroy, "Newer Methods of Organic Chemistry," Vol. I, Ed. R. A. Raphael and E. C. Taylor, Interscience Publishers, Inc. New York, N. Y., in press.

influence of the magnetic anisotropy of the benzene ring on the chemical shift of adjacent groups. As is shown in Fig. 3, the applied magnetic field H_0 induces a moment which augments the applied field by H_ϕ along the edges of the benzene ring but opposes the applied field at points above and below the plane of the ring. Very convincing evidence of the essential validity of this premise recently has been found by Griffin⁶ in the n.m.r. spectra of biduryl and bimesityl. The nonplanarity of the two rings, clearly shown in the ultraviolet spectrum, results in the *o*-methyl groups lying above and below the plane of the adjacent benzene ring. In the n.m.r. spectrum the *o*-methyl groups appear as a single peak some 20 c.p.s. higher on the frequency scale than the *p*-methyl groups. The phenomenon was also observed with biduryl.

In Fig. 3 it is clear that the diastereoisomer which has the C_NCH_3 and C_6H_5 adjacent will have an n.m.r. spectrum which shows the C_NCH_3 doublet at higher frequency, *i.e.*, higher field. The higher applied field is necessary to overcome the opposing effect of H_ϕ in the region above and below the plane of the ring. The spectra of the various derivatives clearly indicate that the diastereoisomers derived from (–)-ephedrine must be those with the phenyl and methyl adjacent as is shown in the projection formula of Fig. 1. In the ψ -diastereoisomers the C_NH must lie opposite the plane of the benzene ring and accordingly the C_NH frequency in the ψ -diastereoisomers will be higher than in the other member of the pair.

The recent work of Johnson and Bovey⁷ on the computation of the magnitude of the effect of the induced field H_ϕ on the chemical shift of protons in various positions relative to the ring suggests a comparison⁸ of the magnitude of the observed effects with those calculated using the data of Johnson and Bovey. Utilizing the X-ray crystallographic bond length and bond angle data⁹ for ephedrine hydrochloride, the average position of the C_NCH_3 and C_NH protons relative to the phenyl can be calculated for the derivatives in which the phenyl and methyl are eclipsed and also when the phenyl and C_N -hydrogen are eclipsed. Two simplifying assumptions were made in order to calculate the effect of H_ϕ on the various protons. The axis orthogonal to the basal plane of the phenyl group is assumed to be always in the same plane as the C_0 – C_N bond, that is, rotation of the phenyl around its bond to the C_0 carbon is restricted such that the C_NCH_3 or C_NH in the respective derivatives always "face" the plane of the ring. This assumption is clearly an approximation, but models show that the phenyl is constrained to a relatively small angle of twist about the C_0 –phenyl axis. The second assumption that the C_NCH_3 does rotate about the bond to the C_N carbon is in accord with the equivalence of all three protons as reflected in the n.m.r. spectra. On the basis of this model the calculations of H_ϕ reported by Johnson and Bovey predict

that the C_NCH_3 in one diastereoisomeric form experiences a diamagnetic field shift of +0.6 p.p.m. and in the other a paramagnetic field shift of –0.1 p.p.m. The difference in C_NCH_3 resonance frequency in a pair of diastereoisomers is therefore predicted as 28 c.p.s. (0.7 p.p.m. at 40 mc.). Similar calculations for the C_NH predict a diamagnetic shift of +0.15 p.p.m. in one form and a paramagnetic shift of –0.2 p.p.m. in the other. The calculated difference in C_NH resonance frequency is therefore 14 c.p.s. (0.35 p.p.m. at 40 mc.). The observed differences in resonance frequencies for the oxazolidones are $C_NCH_3 = 26$ c.p.s. and $C_NH = 18$ c.p.s. which are in good agreement with the calculated values. However for the oxazolidines and spirodecanes the differences are $C_NCH_3 = 15$ c.p.s. and $C_NH = 27$ c.p.s., that is, virtually the inverse of the predicted values. A possible explanation of the failure of the calculations based on the rigid model described above to predict the relative shifts of the C_NH and C_NCH_3 in the two sp^3 bridged derivatives may be that in these structures the heterocyclic ring is not rigid. This means that the relationship between the phenyl and the eclipsed group on the C_N -carbon is not fixed as postulated in the model. In the oxazolidone case, however, the sp^2 -carbonyl bridge constrains the ring to a much more rigid form and consequently the model is a closer approximation to reality.

The apparent insensitivity of the NCH_3 peak position is in keeping with the fact that this group is relatively far removed from the predominant perturbing influence of the phenyl ring in both configurations. Furthermore the rapid flipping of the $N-CH_3$ from one side of the ring to the other in the oxazolidine and spirodecane derivatives and the relatively coplanar restriction in the oxazolidone derivatives will average out any small anisotropy effect which may be present.

The relative position of the C_0H resonance in the spectra of diastereoisomeric pairs does not appear to be explicable on the basis of a single simple effect. At least two possible effects seem plausible in rationalizing the observed shifts (although neither is supported by other experimental data which is convincing). Firstly, due to the close proximity of the C_0H to the C_0 -phenyl, the magnitude and possibly the sign of the effect of the H_ϕ on this proton will be very sensitive to the angle between the basal plane of the phenyl and the C_0 -H bond. Since the phenyl rotation about its bond axis to C_0 -carbon is affected by the restricting influence of the eclipsing group, C_NCH_3 or C_NH , the over-all time averaged effect of H_ϕ on the C_0H would be expected to differ in the two diastereoisomers of a pair. The second possible effect is that resulting from the anisotropy of the carbon-carbon bond as suggested by Bothner-By and Naar-Colin.¹⁰ These authors suggest a diamagnetic anisotropy in the carbon-carbon bond which, along the axis transverse to the bond axis, would exert an upfield shift on protons. This would, in part, explain the higher resonance frequency of the C_0H in ψ -ephedrine derivatives where the C_N-CH_3 bond eclipses the C_0H and would also account for the higher $C_0C_6H_5$ resonance in

(6) G. Griffin, private communication.

(7) C. E. Johnson and F. A. Bovey, *J. Chem. Phys.*, **29**, 1012 (1958).

(8) This quantitative comparison was suggested by Dr. Aksel A. Bothner-By.

(9) G. D. Phillips, *Acta Cryst.*, **7**, 159 (1954).

(10) A. A. Bothner-By and C. Naar-Colin, *THIS JOURNAL*, **80**, 1728 (1958).

PHYSICAL PROPERTIES AND ANALYSIS OF EPHEDRINES AND DERIVATIVES

Compound	M.p., °C.	[α] ^{20D} (solvent)	Carbon, %		Hydrogen, %		Nitrogen, %	
			Calcd.	Found	Calcd.	Found	Calcd.	Found
Oxazolidine	39-43 (44-45) ¹²	+22.0°(EtOH) (+23.0) ¹²						
ψ -Oxazolidine	Oil	+38.0(EtOH)						
Spirodecane	77-77.5	+8.0(CHCl ₃)	78.4	78.5	9.5	9.4	5.7	6.0
ψ -Spirodecane	72-72.5	+41.3(CHCl ₃)	78.4	78.6	9.5	9.3	5.7	5.6
Oxazolidone	91-92	-110.6(CHCl ₃)	69.1	69.3	6.8	7.0	7.3	7.1
ψ -Oxazolidone	50-51 (50-51) ¹³	+29.9(CHCl ₃)	69.1	69.3	6.8	7.0	7.3	7.2
(-)-Ephedrine	39.7	-15.4(CHCl ₃)						
(+)- ψ -Ephedrine	117-118	+99.8(CHCl ₃)						

(-)-ephedrine derivatives where the C_N-CH₃ bond eclipses the C₆C₅H₅. No real significance can be attached to the identity of the C₆C₅H₅ resonance in the spectra of the oxazolidines since the strong chloroform solvent proton signal effectively masked the weaker phenyl proton signal.

Conclusion.—Differences in the n.m.r. spectra of diastereoisomeric pairs of compounds obtained under conditions of identical concentration and solvent can be interpreted in terms of the relative configuration of the asymmetric centers in the molecule. This is especially true when one of the centers contains a group such as phenyl which exerts a marked magnetic anisotropy effect upon adjacent groups.

Preparative

1,2-Dimethyl-3-phenyl-4-oxa-1-aza-cyclopentan-5-one.—The diastereoisomeric pair of oxazolidones were prepared from (-)-ephedrine (anhydrous) and (+)-ephedrine (method of Newman and Kutner¹¹): 13 g. of phosgene in 25 ml. of toluene was added to a solution of 5 g. of the ephedrine in 12.5% caustic soda solution. A yield of approximately 80% was obtained in both cases. Recrystallization was from alcohol.

(11) M. S. Newman and A. Kutner, *THIS JOURNAL*, **73**, 4199 (1951).

1,2,5,5-Tetramethyl-3-phenyl-4-oxa-1-aza-cyclopentane.—Two grams of the corresponding ephedrine were dissolved in 10 ml. of acetone and 25 ml. of benzene and refluxed for 3 days. Solvent then was evaporated and reflux continued for a further 24 hours with fresh acetone. On reducing the bulk of the solution an oily viscous layer separated in both cases. After drying over anhydrous potassium carbonate the oils were vacuum distilled. In the (-)-ephedrine case the distillate solidified on standing to yield oily crystals. Crystallization could not be induced in the (+)- ψ -ephedrine case.

1,2-Dimethyl-3-phenyl-4-oxa-1-aza-spiro(4,5)decane.—Three and five-tenths grams of the corresponding ephedrine were refluxed in 10 ml. of cyclohexanone and 30 ml. of benzene for 7 hours. The theoretical amount of water azeotroped out in each case. The reaction appeared to proceed much more readily than in the case with acetone. Excess cyclohexanone was removed under moderate vacuum (40 mm.) and the product distilled at between 150 and 160° at 8 mm. Both distillates solidified on cooling and were recrystallized from ethanol. Crude yields of 90% were obtained in both cases.

Acknowledgment.—The author expresses his thanks to Dr. Aksel A. Bothner-By for helpful comments and suggestions regarding the interpretation of the spectra.

(12) K. Freudenberg and J. Geiger, *Ann.*, **575**, 145 (1952).

(13) W. J. Close, *J. Org. Chem.*, **15**, 1131 (1950).

NEW HAVEN, CONN.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE FLORIDA STATE UNIVERSITY]

Constituents of Helenium Species. VIII. Isolation and Structure of Balduilin¹

BY WERNER HERZ, R. B. MITRA² AND P. JAYARAMAN

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A new sesquiterpene lactone, balduilin, has been isolated from *Balduina uniflora* Nutt. Conversion to derivatives of helenalin and tenulin establishes its gross structure as I or II (R = Ac). The new guaianolide is a C₈-epimer of the tenulin series and a C₈-epimer of the helenalin series of compounds. Helenalin and tenulin are therefore of opposite absolute configuration at C₆ and C₈, but not at C₇.

In an earlier paper³ the isolation of helenalin⁴ from *Balduina angustifolia* (Pursh) Robins.⁵ was reported. Since the genus *Balduina* is technically placed in a tribe of *Compositae* different from *Heleniæ* (the tribe containing the genus *Helenium*) further examination of *Balduina* species was expected to yield results of chemical and taxonomic interest. The findings reported in this paper fully substantiate this expectation.

(1) Previous paper, W. Herz, R. B. Mitra, K. Rabindran and W. A. Rohde, *THIS JOURNAL*, **81**, 1481 (1959).

(2) Recipient of a Fulbright Travel Award, 1957-1958.

(3) W. Herz and R. B. Mitra, *THIS JOURNAL*, **80**, 4876 (1958).

(4) R. Adams and W. Herz, *ibid.*, **71**, 2346, 2551, 2554 (1949); G. Büchi and D. Rosenthal, *ibid.*, **78**, 3860 (1956).

(5) This species is also referred to as *Actinospermum angustifolium* (Pursh) T and G.

Extraction of *Balduina uniflora* Nutt., a late summer and fall-flowering composite found in the low pinelands of the Southern coastal plain, gave in 0.15% yield a new sesquiterpene lactone C₁₇-H₂₀O₅, m.p. 231-232°, [α]^{24D} 57°, which we have named balduilin.

Balduilin was doubly unsaturated as suggested by the infrared spectrum (bands at 1655 and 1582 cm.⁻¹) and confirmed by quantitative hydrogenation to tetrahydrobalduilin. The double bond responsible for the relatively strong absorption at 1655 cm.⁻¹ is present as an exocyclic methylene group conjugated with a γ -lactone function (infrared band at 1755 cm.⁻¹) as in helenalin (I, R = H). The evidence for this is: Ozonolysis of balduilin which has a band in the near infrared