Stirring at 0° was continued for 30 min, then at 25° for 20 hr. The opaque solution was washed with EtOAc, cooled to 0°, and brought to pH ~2 with 6 *N* HCl. The oil that separated was extracted with EtOAc which was washed with saturated NaCl, dried (Na_2SO_4), and evaporated under reduced pressure, yield 7.9 g (70.5%), mp 62–64.5°; after recrystallization (C_6H_{12}, 6 ml/g; C_6H_6, 20 ml/g), yield 6.9 g (61.6%), mp 63.2–65.5°. Repeated recrystallization yielded 5.3 g (47.9%), mp 64.5–66°; $[\alpha]^{25}D$ −33.1° (*c* 2, AcOH). *Anal.* ($C_{12}H_{13}NO_4$) C, H, N.

N-Carbobenzoxy-N-methyl-L-alanine Dicyclohexylamine Salt.—A solution of 9.5 g of N-carbobenzoxy-N-methyl-L-alanine and 80 ml of EtOAc was cooled to 0° in an ice bath and 9.8 ml of redistilled dicyclohexylamine was added; after 12 hr at 25° and 5 hr at 5°, the white solid was filtered and washed with EtOAc, yield 16.7 g (100%), mp 141–142°; after recrystallization (Me_2CO, 25 ml/g), 16 g (95.6%), mp 141°, $[\alpha]^{25}D$ −13.8° (*c* 2, 95% EtOH). *Anal.* ($C_{26}H_{38}N_2O_4$) C, H, N.

***p*-Nitrophenyl N-(2-Quinoxaloyl)-L-isoleucinate.**—A solution of 2.9 g of N-(2-quinoxaloyl)-L-isoleucine[16] and 10 ml of pyridine was treated with 2.4 g of *p*-nitrophenyl trifluoroacetate (Aldrich Chemical Co.) in a flask protected with a drying tube. The solution was stirred for 1 hr and poured into 100 ml of H_2O, extracting the dark oil with $CHCl_3$. The $CHCl_3$ solution was washed successively with saturated NaCl, 5% citric acid, and saturated NaCl, then dried (Na_2SO_4) and evaporated under reduced pressure. The residual brown oil was dissolved in 50 ml of absolute EtOH, treated with decolorizing carbon and filter aid, and filtered. After the addition of 200 ml of ligroin (bp 30–60°), the solution was kept at 0° for 10 hr, yield 1 g (24.5%), mp 114–115° dec; after recrystallization (EtOH, 20 ml/g; ligroin, bp 30–60°, 70 ml/g); yield 0.8 g (19.5%); mp 115–116° dec; $[\alpha]^{25}D$ +7.6° (*c* 2, DMF); $\lambda_{max}^{95\%\ EtOH}$ 207 mμ (ε 25,940), 244 (35,290), 278 (9232), 318 (7516). *Anal.* ($C_{21}H_{20}N_4O_5$) C, H, N.

Epimeric 2-Hydroxy-2-phenylquinolizidines[1]

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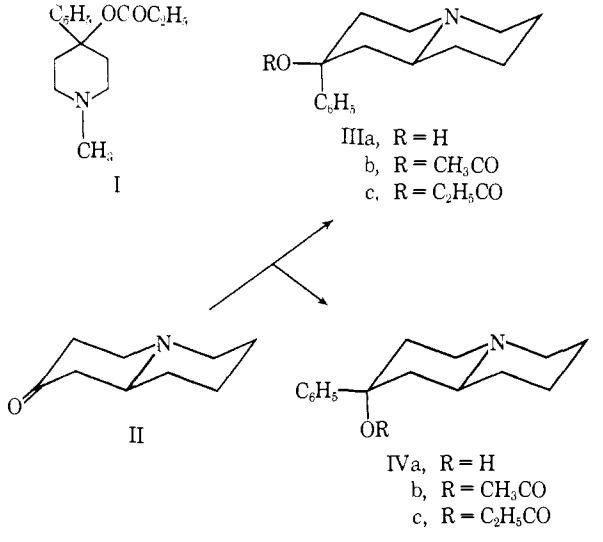
The preparation of epimeric 2-hydroxy-2-phenylquinolizidines and the corresponding acetates and propionates is described. Ir and nmr data were utilized for the elucidation of the stereochemical structures. Preliminary analgetic screening of the esters demonstrated marked activity in both axial and equatorial esters.

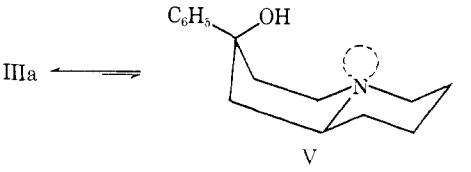
The potential biological properties inherent in substituted phenylhydroxyalkylamines[3] and the importance of stereochemical characteristics[4] on biological action led to the investigation of epimeric 2-hydroxy-2-phenylquinolizidines (IIIa, IVa) and their esters (IIIb, c, IVb, c). The preparation and structural relationship of epimeric 1-hydroxy-1-phenylquinolizidines to biologically active phenethylamines were reported earlier.[5]



The isomeric 2-substituted derivatives not only are related closely to the phenylalkylamines but also to the potent analgetic piperidines (I).[6]

The reaction of C_6H_5MgBr with 2-ketoquinolizidine (II) provided a 1:3 mixture of epimeric hydroxyphenylquinolizidines (IIIa, IVa). Elution chromatography provided first the 2(a)-hydroxy-2(e)-phenylquinolizidine (IVa) followed by 2(e)-hydroxy-2(a)-phenylquinolizidine (IIIa). The epimers were identified by means of ir and nmr spectroscopy (Tables I and II). The ir spectra of both IIIa and IVa are very similar; however, with high dilutions IIIa exhibits some intramolecular hydrogen bonding (broad weak band at 3350 cm^{-1} attributed to V). A distinguishing characteristic in the ir spectra is the absorption at higher wave numbers (770–762 cm^{-1}) in the monosubstituted aromatic region of the axial phenylquinolizidines (III, VI) in contrast to the absorption at lower wave numbers (762–750 cm^{-1}) of the corresponding equatorial phenylquinolizidines (IV, VII).

The similarity of the nmr spectra of both epimers did not provide features which could be used for the identification of either IIIa or IVa. Additional evidence for the configuration of the epimers, however, was provided by the nmr spectra (Table II) of the corresponding



V

acetates (IIIb, IVb). The methyl protons of the axial acetate (IVb) absorb downfield from the corresponding equatorial acetate (IIIb). This is consistent with ob-

(1) This work was done in part during the tenure of a Mississippi Heart Association Research Fellowship to James D. England.

(2) National Institutes of Health Predoctoral Fellow, 1966–.

(3) (a) J. Triggle, "Chemical Aspects of the Autonomic Nervous System," Academic Press, New York, N. Y., 1965, Chapter XIV; (b) J. Sam, *J. Pharm. Sci.*, **56**, 1344 (1967); (c) Symposium on Beta Adrenergic Receptor Blockade, *Am. J Cardiol.*, **18**, 303 (1966).

(4) (a) A. H. Beckett, *Progr. Drug. Res.*, **1**, 455 (1959); (b) R. B. Barlow, "Introduction to Chemical Pharmacology," 2nd ed, John Wiley and Sons, Inc., New York, N. Y., 1964; (c) P. S. Portoghese, *J. Pharm. Sci.*, **55**, 865 (1966).

(5) J. D. England and J. Sam, *J. Heterocyclic Chem.*, **3**, 482 (1966).

(6) R. A. Hardy, Jr., and M. G. Howell in "Analgesics," G. de Stevens, Ed., Academic Press, New York, N. Y., 1965, pp 181–222.

TABLE I
IR DILUTION STUDIES OF EPIMERIC 2-HYDROXY-2-PHENYLQUINOLIZIDINES IN $CHCl_3$[a]

		Ir spectra, cm^{-1}		
No.	% concn	Free hydroxyl absorp	Intramol H bonding	Intermol H bonding
IIIa	20	3605 (s)	3350 (w)	3080–3450 (s)
IIIa	10	3605 (m)	3350 (w)	3080–3450 (w)
IIIa	5	3605 (m)	3350 (w)	None
IIIa	0.053	3605 (m)	3350 (w)	None
IVa	20	3605 (s)	None	3075–3450 (s)
IVa	10	3605 (m)	None	3075–3450 (w)
IVa	5	3605 (w)	None	None

[a] At all concentrations the Bohlmann absorption bands [F. Bohlmann, *Chem. Ber.*, **91**, 2157 (1958)] were also present at 2770 and 2815 cm^{-1} indicating a *trans*-fused ring system; s = sharp, m = medium, and w = weak.

TABLE II
NMR SPECTRA OF QUINOLIZIDINES[a]

No.	δ values
IIIa[b]	2.6 (s)[c]
IVa[b]	2.0 (s)[c]
IIIb[d]	1.85 (s)[e]
IVb[d]	2.11 (s)[e]
IIIc[d]	0.09 (m)[e]
IVc[d]	1.05 (m)[e]
VI[b]	2.08 (s)[e]
VII[b]	2.30 (s)[e]

[a] s = singlet, m = multiplet; aromatic protons were as expected. [b] Determined in $CDCl_3$. [c] Hydroxy proton. [d] Hydrochloride, determined in D_2O. [e] Terminal ester methyl protons.

for analgetic activity by means of the Nilson electrical stimulation method.[8] The alcohols (IIIa, IVa) were inactive, whereas both epimeric acetates and propionates were active. Both equatorial (IIIc) and axial (IVc) propionates exhibited marked analgetic activity of about equal intensity. The equatorial acetate, however, was somewhat less active than the axial acetate. The LD_{50} and the ED_{50} of the esters and a standard for comparison are listed in Table IV.

Experimental Section[9]

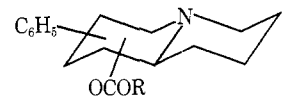
2-Hydroxy-2-phenylquinolizidine.—The procedure described by England and Sam[5] was followed using 25.5 g (0.166 mole) of 2-ketoquinolizidine.[10] A viscous yellow syrup (33 g, 85%) was obtained. The ir spectrum showed strong OH and weak C=O absorption. Trituration of the syrup with petroleum ether (30–60°) yielded a white powder, mp 114–115°. Recrystallization of the material from petroleum ether yielded 10.1 g (26%) of white needles, mp 116–117° identified as 2(a)-hydroxy-2(e)-phenylquinolizidine (IVa). *Anal.* ($C_{15}H_{21}NO$) C, H, N. Tlc on silica gel (*n*-BuOH–AcOH–H_2O 4:1:1) of this analytical sample indicated the presence of a single component.

Evaporation of the petroleum ether from which the above alcohol was obtained yielded 22.4 g of viscous yellow syrup. The syrup was dissolved in a minimum amount of petroleum ether and placed on a 54 × 2.7 cm column packed with 240 g of Woelm grade III neutral alumina. Elution was begun taking 25-ml cuts at a flow rate of 7 ml/min. Fractions 1–12, eluted with petroleum ether, yielded 897 mg of biphenyl, mp 65–66°. Spectra were consistent with the structure of biphenyl which is frequently a side product in phenyl Grignard reactions.[11]

Fractions 12–17, eluted with CCl_4, yielded 405 mg of biphenyl and unsaturated phenylquinolizidine. Fractions 18–21, eluted with CCl_4, yielded 78 mg of unsaturated phenylquinolizidine, identified by its ir spectrum. Fraction 22, eluted with CCl_4, yielded 99 mg of unreacted 2-ketoquinolizidine, identified by its ir spectrum. Fraction 23, eluted with CCl_4, yielded 656 mg of IVa. The ir spectrum showed weak C=O absorption indicating the presence of a small amount of unreacted 2-ketoquinolizidine.

Fractions 24–34, eluted with CCl_4, yielded 9.614 g (24%) of IVa. Recrystallization from petroleum ether yielded 6.27 g

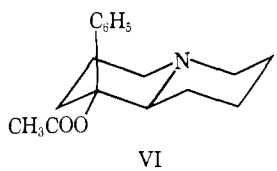
TABLE III
ESTERS OF HYDROXYPHENYLQUINOLIZIDINES



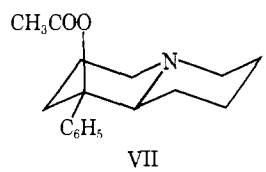
No.	R	Ester position	Phenyl position	Yield, %	Bp, °C (mm)	Mp, °C	Formula
IIIb	CH_3	2 (e)	2 (a)	49	120 (0.1)	204–205[a]	$C_{17}H_{24}ClNO_2$[a]
IIIc	C_2H_5	2 (e)	2 (a)	63	110–110 (0.1)	198–199[a]	$C_{18}H_{26}ClNO_2$[a,b]
IVb	CH_3	2 (a)	2 (e)	66	120 (0.1)	168–170[a]	$C_{17}H_{24}ClNO_2$[a]
IVc	C_2H_5	2 (a)	2 (e)	54	122 (0.15)	205–206[a]	$C_{18}H_{26}ClNO_2$[a]
VI	CH_3	1 (e)	1 (a)	75	...	158–160[b]	$C_{23}H_{26}N_4O_9$[c]
VII	CH_3	1 (a)	1 (e)	30	...	183–184[b]	$C_{23}H_{26}N_4O_9$[c]

[a] Hydrochloride, recrystallized from Me_2CO; analyzed for C, H, Cl, N. [b] C: calcd, 66.7; found, 67.4. [c] Picrate, recrystallized from EtOH; analyzed for C, H, N.

servations in other systems.[7] This characteristic shift of the methyl signals also occurred in the corresponding epimeric acetates (VI, VII) of 1-hydroxy-1-phenylquinolizidines (Table II). Since the latter structural characteristics are known,[5] this provided further evidence for structures III and IV. The esters (Table III) were prepared readily from the corresponding alcohols using an excess of the appropriate anhydride in pyridine.



VI



VII

The compounds described in this study were tested

(7) R. U. Lemieux, R. K. Kullnig, H. J. Bernstein, and W. G. Schneider *J. Amer. Chem. Soc.*, **79**, 1005 (1957); **80**, 6098 (1958).

(8) G. C. Helsley, J. A. Richman, C. D. Lunsford, H. Jenkins, R. P. Mays, W. H. Funderburk, and D. N. Johnson, *J. Med. Chem.*, **11**, 472 (1968); P. Nilsen, *Acta Pharmacol. Toxicol.*, **18**, 10 (1961).

(9) All melting points were taken on a Thomas–Hoover Uni-Melt melting point apparatus and are corrected. Ir spectra were determined on a Perkin-Elmer Model 257 ir spectrophotometer and were corrected against the 5.138-μ absorption band of polystyrene film. The nmr spectra were taken on a Varian Model A-60A instrument (TMS). Where analyses are indicated only by symbols of the elements, analytical results obtained were within ±0.4% of the theoretical values.

(10) R. E. Counsell and T. O. Soine, *J. Am. Pharm. Assoc., Sci. Ed.*, **49**, 289 (1960).

(11) L. F. Fieser, "Organic Experiments," D. C. Heath and Co., Boston, Mass., 1964, p 89.

TABLE IV

INTRAPERITONEAL ACUTE TOXICITY AND ANALGETIC ACTIVITY OF 2-QUINOLIZIDINYL ESTERS[a]

Compd[b]	ED_{50}, mg/kg 95% confidence limit(s)	Slope	LD_{50}, mg/kg[c] (95% confidence limits)	Slope
Axial acetate (IVb)	13.7 (10.0–18.8)	1.44	109.9 (76.3–158.3)	1.53
Equatorial acetate (IIIb)	20 (% at 20 mg/kg)		97.0 (78.3–120.3)	1.35
Equatorial propionate (IIIc)	3.0 (1.3–6.8)	3.14	69.1 (51.3–93.4)	1.63
			84.0 (65.8–107)	1.22
Axial propionate (IVc)	2.4 (1.4–4.1)	1.80	100 (64.1–156)	1.44
			124 (78.5–196)	1.90
Meperidine	6.4 (4.3–9.6)	1.39	145 (95–225)	1.19

[a] Five female mice (ICR strain) per dose. [b] Hydrochlorides. [c] LD_{50} observation period = 2 hr.

(15.6%) of white needles, mp 117–178°, bringing the total yield of IVa to 16.27 g (39.6%).

Fractions 36–46, eluted with 50:50 Me_2CO–anhydrous Et_2O, gave 7.31 g (19%) of product, mp 114–116°. The sample was recrystallized from petroleum ether to give 5.6 g (14.5%) of 2(e)-hydroxy-2(a)-phenylquinolizidine (IIIa), mp 119–120°. Admixture of the material with IVa showed a significant melting point depression (90–95°). *Anal.* ($C_{15}H_{21}NO$) C, H, N.

Esters of Hydroxyphenylquinolizidines (Table III).—A solution of 0.01 mole of the appropriate epimeric hydroxyphenylquinolizidine in 10 ml of Ac_2O or propionic anhydride and 40 ml of pyridine was refluxed for 18 hr. The mixture was cooled to room temperature and treated with crushed ice and excess solid K_2CO_3, respectively. The aqueous mixture was extracted with two 250-ml portions of Et_2O. The ethereal solution was evaporated and the residual oil either was distilled or converted to hydrochlorides or picrates in the usual manner and recrystallized. The ir spectra showed no OH but strong C=O absorption at 1725 cm^{-1}. Samples of the free bases of VI and VII for nmr studies were obtained by elution chromatography using Woelm grade I neutral alumina and petroleum ether as the eluent.

Acknowledgments.—The authors are grateful to Dr. Herbert S. Aaron, U. S. Army Chemical Research and Development Laboratories, Edgewood Arsenal, Md., for originally suggesting structure V confirming our infrared spectral data and assisting in the correlation of the data and to Dr. John Ward, A. H. Robins Co., Richmond, Va., for the pharmacological data.

Phosphorus Analogs of Nitrogenous Drugs. II.[1] 10H-Dibenzo[1,4]thiaphosphorins as Central Nervous System Depressants

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In an effort to delineate the electronic properties of the tricyclic nucleus which are important to chlorpromazine-type biological activity, 10-(3-dimethylaminopropyl)-10H-dibenzo[1,4]thiaphosphorin, its oxide, and three analogous oxides, substituted at the 2 position with Cl, SMe, and OMe groups, respectively, have been synthesized. Ultraviolet spectral data are presented to show that extensive delocalization of the 3p electrons on the phosphorus atom in the phosphine would be expected. The compounds are shown to depress spontaneous activity in mice in the 30–50-mg/kg dosage range, and a possible correlation between biological activity and electronic properties of the nucleus, as revealed by uv spectral data, are discussed.

The important biological properties associated with the phenothiazine tranquilizers, of which chlorpromazine is the prototype, are well known and have been reviewed extensively.[2] In an initial attempt aimed at definition of optimum stereoelectronic properties in the tricyclic nucleus the title compounds, of which **1** is the prototype, in which phosphorus replaces the ring nitrogen have been synthesized and submitted to preliminary biological evaluation. Several related oxides **2** have also been prepared and tested. We elected to insert phosphorus into these systems because its close chemical relationship to nitrogen would be expected to affect the chemical properties of the aromatic nucleus in a very subtle manner. These small changes should be observable chemically, by observing the spectroscopic properties of the system, as well as biologically.

Perusal of the uv spectral data for the first six compounds in Table I will show that the unshared electrons of nitrogen adjacent to an aromatic system interact with the aromatic π electrons to cause a bathochromic shift in the λ_{max} and a pronounced increase in the ϵ_{max}. The effect is more pronounced in Ph_2NH than in $PhNH_2$, but reduced in $Ph_2N(CH_2)_3NMe_2$, perhaps because the alkyl chain interferes with coplanarity of the two benzenoid rings. The 3p orbital accommodating the unshared electrons of phosphorus is much larger than the corresponding 2p orbital of nitrogen and, in some situations, this results in striking chemical differences between analogous nitrogen and phosphorus compounds. For example, the phosphorus analog of pyridine is not known,[3] apparently because in this sp^2-bonded system the overlap of the 3p phosphorus electrons with those in the carbon 2p orbitals is so poor that little or no resonance stabilization is afforded. However, in the present case, the uv data for Ph_3P in

(1) (a) Part I: R. A. Wiley and H. N. Godwin, *J. Pharm. Sci.*, **54**, 1063 (1965). (b) J. H. C. was a Predoctoral Fellow of the Public Health Service, 1963–1967. (c) The authors gratefully acknowledge the assistance of Dr. C. K. Erickson in the biological studies.

(2) (a) M. Gordon in "Psychopharmacological Agents," Vol. 2, M. Gordon, Ed., Academic Press, New York, N. Y., 1967, p 1; (b) K. Stach and W. Poldinger, *Fortsch. Arzneimittelforsch.*, **9**, 129 (1966); (c) P. B. Bradley in "Physiological Pharmacology, A Comprehensive Treatise," Vol. 1, W. S. Root and F. G. Hofmann, Ed., Academic Press, New York, N. Y., 1963, p 417.

(3) R. F. Hudson, "Structure and Mechanism in Organophosphorus Chemistry," Academic Press, New York, N. Y., 1965, p 3.