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THE CONFIGURATIONS AT C-9 OF THE CINCHONA ALKALOIDS

NMR SPECTRAL STUDY OF THE DERIVED OXIRANES[1a]

G. G. LYLE and L. K. KEEFER[1b]

Department of Chemistry, University of New Hampshire, Durham, New Hampshire 03824

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Abstract—The existing ambiguity regarding the configurations of quinine, quinidine, cinchonine, cinchonidine, and their C-9 epimers has been resolved by stereospecifically converting quaternary salts of the dihydro derivatives of quinine, quinidine, quinidine-9*d*, and epiquinidine to derivatives containing the conformationally rigid oxirane ring. The configurations of the oxiranes were determined by NMR spectroscopy, and the stereochemistry of the alkaloid precursors was deduced on the basis of the known stereochemical course of the reactions used in the preparation of the oxiranes. In this way, it has unequivocally been demonstrated that the natural *cinchona* alkaloids are all of the *erythro* configuration with respect to their C-8,C-9 systems and that the epi-bases are *threo*.

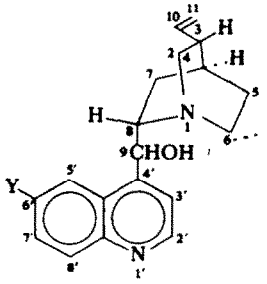
QUININE (Ia), quinidine (IIIa), cinchonine (IIIb), and cinchonidine (Ib) are the most important members of the *cinchona* series of alkaloids (Fig. 1), and elucidation of the structures of these compounds has been the aim of a vast number of investigators during the past 150 years. The wealth of experimental data that can be cited in support of the assigned structures, including the absolute configurations at C-3, C-4 and C-8, has been the subject of several excellent reviews[2] and will not be discussed here; for the purposes of the present investigation this evidence has been regarded as conclusive.

The configuration of the remaining asymmetric carbon atom, C-9, may be adequately defined for a given compound by designation of the C-8,C-9 system as *erythro* or *threo*. Thus, Prelog and Häfliger[3] have argued that the naturally occurring *cinchona* alkaloids must have the *erythro* configuration while the relatively more basic C-9 epimers must be *threo*, an argument which they based on the postulate that the increased basicity of the *threo* isomers might be due to the presumedly larger concentration of conformers in which H-bonding between the OH group and the adjacent nitrogen function is possible. In particular, they concluded that the OH oxygen atom is involved in stabilization of the conjugate acid of the amino group, probably with the interposition of a molecule of solvent to form a 7-membered

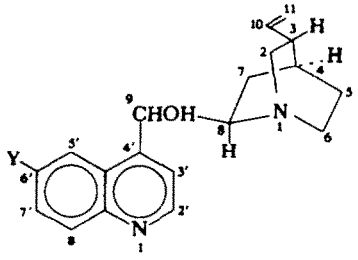
[1] *a* Taken in part from the thesis of L. K. Keefer submitted to the graduate School of the University of New Hampshire in partial fulfillment of the requirements for the Ph.D. degree. A portion of this work was presented before the Organic Division of the American Chemical Society at the 149th meeting, Detroit, Michigan, 9 April 1965, Abstracts P119. Support of this study by the Public Health Service, GM 07239, is gratefully acknowledged; *b* NIH Predoctoral Fellow, 1963–1965.

[2] R. B. Turner and R. B. Woodward in *The Alkaloids* (Edited by R. H. F. Manske and H. L. Holmes), Vol. 3; pp. 1–63. Academic Press, New York (1953); T. A. Henry, *The Plant Alkaloids* (3*rd* Edition) pp. 394–446. Blakiston's, Philadelphia (1939); K. W. Bentley, *The Alkaloids* pp. 132–142. Interscience, New York (1957).

[3] V. Prelog and O. Häfliger, *Helv. Chim. Acta* 33, 2021 (1950).



I and II



III and IV

	Compound	Y	C-9 configuration[a]	$[\alpha]D^{b,c}$	m.p.[b]
Ia	Quinine	-OMe	R(or S)	−158°	177°
IIa	Epiquinine	-OMe	S(or R)	+43°	oil
IIIa	Quinidine	-OMe	R(or S)	+243°	168°
IVa	Epiquinidine	-OMe	S(or R)	+102°	113°
Ib	Cinchonidine	-H	R(or S)	−111°	202°
IIb	Epicinchonidine	-H	S(or R)	+63°	103–104°
IIIb	Cinchonine	-H	R(or S)	+224°	260°
IVb	Epinchonine	-H	S(or R)	+120°	82–83°

[a] Configurational system according to R. S. Cahn, C. K. Ingold and V. Prelog, *Experientia* **12**, 81 (1956).
[b] T. A. Henry, *The Plant Alkaloids* (4th Edition) p. 446. Churchill, London (1949).
[c] In EtOH.

FIG. 1. The *Cinchona* Alkaloids.

chelate ring. However, although such correlations of basicity with configuration have been used to great advantage in many stereochemical investigations,[4] it should be pointed out that, in at least one case, the above reasoning has led to the wrong assignment. Tropine[5] is significantly more basic than pseudotropine, even though intramolecular H-bonding is a possibility only in the latter.

Further support for this conclusion was offered by Földi, *et al.*,[6] who found that the C-9 epimers of the cinchona alkaloids readily formed copper chelates with the formula $(C_{20}H_{23}N_2O_2)_2Cu \cdot xH_2O$ when heated with copper sulfate, whereas the natural bases gave only unreacted starting material under the same conditons. Since inspection of models suggested that a 5-membered ring could form only with great difficulty in the *erythro* alkaloids, the epibases were assigned the *threo* configuration, for which such a chelate would be expected to form easily. The force of this argument

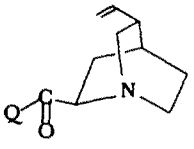
[4] J. F. King, *Elucidation of Structures by Physical and Chemical Methods* (Edited by K. W. Bentley) Part 1; pp. 317–371. Interscience, New York (1963).
[5] T. A. Geissman, B. D. Wilson and R. B. Medz, *J. Am. Chem. Soc.* **76**, 4182 (1954).
[6] Z. Földi, T. Földi and A. Földi, *Chem. & Ind.* 465 (1957); Z. Földi, T. Földi and A. Földi, *Acta Chim. Acad. Sci. Hung.* **16**, 185 (1958); *Chem. Abstr.* **53**, 5945 (1959).

is diminished, however, by reports[7] of the apparently spontaneous closure of such 5-membered rings in the *cinchona* boroxazolidines which demonstrated that the N–C–C–O system can, under certain circumstances, easily assume the conformation necessary for ring closure in the natural alkaloids.

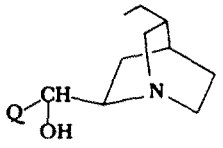
A third line of evidence in support of the *erythro* assignment was advanced by Kobayashi,[8] who observed that N-benzoylepihydroniquine (an amide of a secondary amine derived from epiquinine which possesses the same relative configuration of the aminoalcohol moiety as epiquinine) was converted in acidic medium to O-benzoyl-epihydroniquine, whereas its C-9 epimer (derived from quinine) was unchanged after subjection to the same conditions. In view of the fact that such N → O acyl migration is much slower in the N-acyl ephedrines than it is in the corresponding pseudo-ephedrine derivatives, Kobayashi concluded that the niquine bases, and hence the *cinchona* alkaloids themselves, must have the *erythro* configuration and that the epi-bases possess the *threo* stereochemistry. This type of N → O acyl migration has been employed in other stereochemical investigations, perhaps most successfully in the unequivocal assignment of configuration to the tropines.[9] The use of such reasoning in the case of non-cyclic systems such as the niquines, however, necessarily suffers from the disadvantage (as do the arguments cited above) that reasonable but as yet unverified assumptions must be imposed regarding the relative populations of the various possible conformations of the molecule.

In contrast to the investigations discussed above, Lyle and Gaffield have recently come to the opposite conclusion on the basis of ORD studies of certain *cinchona* alkaloids.[10] These authors found that the curves for the naturally occurring bases had characteristics in common with those of model compounds of the *threo* series, while the curves for derivatives of the C-9 epimer IVa more closely resembled those of the *erythro* models.

These results thus offer support for the earlier conclusions of Doering *et al.*,[11] who attempted to apply a modification of Linstead's theory[12] to the catalytic hydrogenation of quinidinone (Va). They argued that the observed,[13] major product of



Va



HC

VIa Hydroquinidine
VIb Hydrocinchonine
VIIa Epihydroquinidine

[7] H. J. Roth, *Habilitationsschrift*, Würzburg (1960); H. J. Roth, *Pharmazie* **16**, 257 (1961); *Chem. Abstr.* **61**, 9547 (1964).

[8] Y. Kobayashi, *Chem. Pharm. Bull. Tokyo* **7**, 209 (1959).

[9] G. Fodor and K. Nádor, *Nature, Lond.* **169**, 462 (1952); G. Fodor and K. Nádor, *J. Chem. Soc.* 721 (1953); A. Nickon and L. F. Fieser, *J. Am. Chem. Soc.* **74**, 5566 (1952).

[10] G. G. Lyle and W. Gaffield, *Tetrahedron Letters* 1371 (1963).

[11] W. E. Doering, G. Cortes and L. H. Knox, *J. Am. Chem. Soc.* **69**, 1700 (1947).

[12] B. Belleau and S. McLean, *Elucidation of Structures by Physical and Chemical Methods* (Edited by K. W. Bentley) Part 2; pp. 1023–1026. Interscience, New York (1963).

[13] R. B. Woodward, N. L. Wendler and F. J. Brutschy, *J. Am. Chem. Soc.* **67**, 1425 (1945).

the reduction, hydroquinidine (VIa), should have the *threo* configuration, since it was expected that that conformer of Va which yielded the *threo* isomer would be preferentially adsorbed at the catalytic surface. Epihydroquinidine (VIIa) should thus have the *erythro* configuration.

It is apparent that there is some disagreement regarding the configurations of the *cinchona* alkaloids at C-9. Inasmuch as none of the evidence cited above can be regarded as conclusive, the present investigation was undertaken in an effort to resolve this ambiguity in a rigorous fashion.[14]

Since a major source of difficulty in the previous work arose from the fact that C-9 is potentially free to rotate with respect to C-8, it was sought to incorporate both atoms into the same rigid ring system. This approach would render unnecessary any problematical assumptions regarding the conformation of the molecule.

The formation of oxiranes from quaternary salts of β-aminoethanols is a stereospecific reaction involving retention of configuration at the carbinol center and inversion at the carbon atom to which the ammonium function was originally bonded.[15] Furthermore, it is possible, at least in principle, to make an unambiguous assignment of the stereochemistry of the cyclic product using NMR spectroscopy. The oxirane protons have been shown to have coupling constants of different magnitude for the *cis* and *trans* isomers, J_{cis} being significantly larger than J_{trans} for a given pair of epoxides.[16] That this is true in general is fully consistent with the considerations of the Karplus correlation[17] of dihedral angle with coupling constant. Since, however, J_{cis} for certain compounds is less than J_{trans} for some other epoxides,[16] it must be emphasized that the absolute value of J cannot be used to determine the ring stereochemistry. A fully rigorous assignment of stereochemistry to an isomeric pair of epoxides may be made, however, on the basis of coupling constant data alone, providing the data for both compounds are available.

Unlike many β-hydroxy ammonium compounds, salts of the *cinchona* alkaloids characteristically undergo base-initiated elimination to ketone derivatives or "toxines".[18] Despite this complicating factor, however, the work of Rabe[19] and of Claus[20] has demonstrated that epoxide formation can predominate under certain conditions.

By way of preliminary investigation, hydrocinchonine benzochloride (VIIIb) was converted to the oxirane derivative IXb according to the procedure of Rabe *et al.*[19] Fully consistent with the assigned structure was the compound's infrared absorption spectrum, the most characteristic features of which included the oxirane C–H stretching vibrations[21] (3080, 3060, and/or 3020 cm^{-1}), the "Bohlmann"

[14] Shortly before the submission of this manuscript, Dr. G. A. Sim announced at the Oxford meeting of the Chemical Society, 29 March 1966, that in the course of an X-ray crystallographic study, he had determined that the C-9 configuration of quinidine was (S), i.e. the relative configuration of the C-8,C-9 centers of quinidine was *erythro*.

[15] A. C. Cope and E. R. Trumbull, *Organic Reactions* **11**, 352–355, 389–390 (1960).

[16] G. G. Lyle and L. K. Keefer, *J. Org. Chem.* **31**, 3921 (1966); and Refs therein.

[17] *a* M. Karplus, *J. Chem. Phys.* **30**, 11 (1959); *b* M. Karplus, *J. Am. Chem. Soc.* **85**, 2870 (1963).

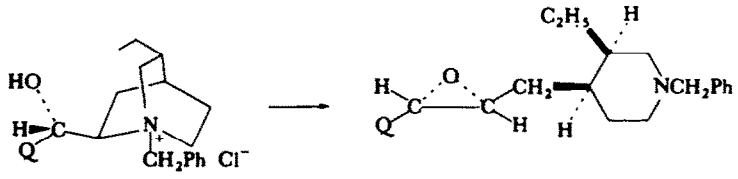
[18] L. Pasteur, *Alembic Club Reprints No. 14*, p. 41. The Alembic Club, Edingburgh (1905).

[19] P. Rabe, K. Dussel and R. Teske-Guttmann, *Liebig's Ann.* **561**, 159 (1949).

[20] A. Claus and Kemperdick, *Chem. Ber.* **13**, 2286 (1880); A. Claus and H. Müller, *Ibid.* 2290 (1880); A. Claus and W. Treupel, *Ibid.* 2294 (1880).

[21] A. R. Katritzky and A. P. Ambler, *Physical Methods in Heterocyclic Chemistry* (Edited by A. R. Katritzky), Vol. 2; p. 179. Academic Press, New York (1963).

C–H[22] stretching vibrations (2795 and 2745 cm^{-1}), absorptions due to the mono-substituted benzene ring (760 and 700 cm^{-1}), and the total absence of peaks due to CO, OH, or secondary NH functionalities.[23]



VIII IX

The NMR spectrum of IXb (Fig. 2), which was also consistent with the assigned structure, showed considerable promise as a tool for the elucidation of the stereochemistry of this epoxide. Particularly fortunate was the fact that the one-proton doublet (Table 1) believed to be due to the proton at C-2 on the epoxide ring was sufficiently isolated from other regions of absorption that it could be examined without difficulty. The coupling constant determined for this peak was 2 c/s.

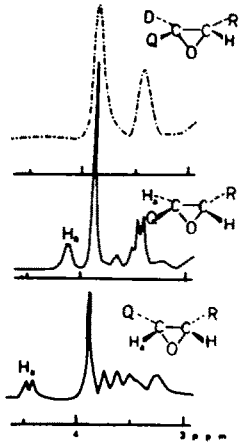


FIG. 2. The NMR spectra from 3–4·5 ppm of the isomeric oxiranes XIa (bottom curve), IXa (middle curve) and the deutero derivative XV (top curve). The peak labeled H_a in the spectrum of IXa is absent in the spectrum of XV. The 3-proton peak is that of the C-6′ methoxyl hydrogens at about 3·9 ppm.

Because epiquinidine (IVa) is much more efficiently prepared than epicinchonine (IVb), however, it was decided that work in the quinidine series might lead with greater facility to the production of the required stereomeric pair of epoxides. Thus hydroquinidine (VIa) was prepared by catalytic hydrogenation of quinidine (IIIa) and quaternized with one mole of benzyl chloride. The salt VIIIa was purified by recrystallization from acetone and apparently contained one tenaciously bound

[22] F. Bohlmann, *Chem. Ber.* **91**, 2157 (1958).

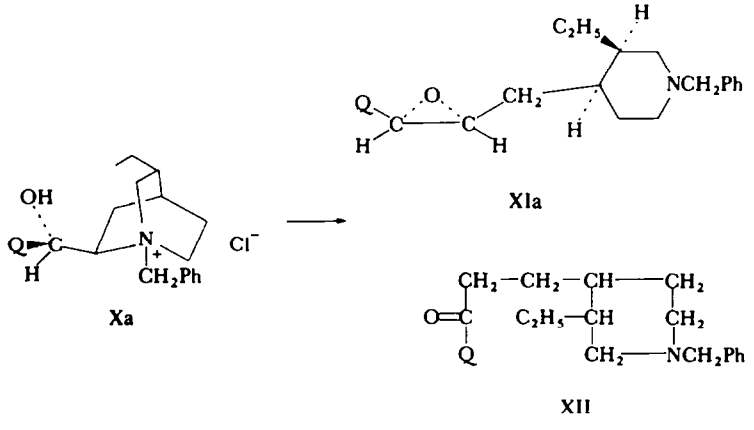
[23] A. D. Cross, *An Introduction to Practical Infrared Spectroscopy*. Butterworths, London (1960).

equivalent of acetone of crystallization (cf. the analytical data and presence of strong IR peak at 1700 cm^{-1}).

Hydroquinidine benzochloride (VIIIa) was treated with potassium t-butoxide in t-butyl alcohol. The product obtained from the reaction was a viscous yellow oil which darkened noticeably on exposure to light or on hea ing. Diagnostic thin layer chromatography (TLC) indicated that the material was composed of a single compound. Attempts to crystallize the oil from such solvents as ethanol, cyclohexane, and ether resulted in failure, and, when treated with CCl_4 or $HCCl_3$ a solid decomposition product was formed. By taking advantage of the fact that the compound exhibited a blue fluorescence under the influence of UV light, however, the oily product was purified by column chromatography on Florisil.

Epihydroquinidine benzochloride (Xa) was prepared by an analogous route. When this salt was similarly treated with potassium t-butoxide, TLC revealed the presence of a significant amount of a yellow-fluorescent product in addition to the major product, a blue-fluorescent substance which was eluted first from a Florisil column. The former material was presumed to be N-benzyl hydroquinotoxine (XII) and was not further characterized.

That the major products of these two reactions were in fact the desired epoxides IXa and XIa was substantiated by several observations. The IR spectra of the two were quite similar to that of IXb, the only profound difference being the presence of the pair of peaks (1610 and 1595 cm^{-1}) characteristic of the 6-methoxy-4-quinolyl ring system. The UV spectra of the two compounds were nearly identical, and the elemental analytical data were in agreement with expectation for each compound, but IXa was dextrorotatory and XIa was levorotatory. Finally, the NMR spectra

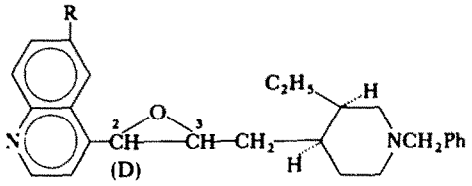


(Fig. 2) offer compelling support, not only for the assigned structures, but also for the conclusion that IXa is of the *trans* stereochemistry, whereas the epimer XIa is of the *cis*, since the coupling constants for the one-proton doublets (Table 1) at 4–5 ppm are 2 and 4 c/s, respectively.

In order to strengthen this stereochemical conclusion, however, it would seem desirable to verify a major assumption upon which it is based, i.e. that the one-proton doublets referred to above are due to the C-2 protons of the oxirane rings. In an

effort to prove this tentative assignment, experiments were undertaken to prepare the analog of one of the epoxides bearing a deuteron at C-2. The NMR spectrum of such a deuterated analog would not be expected to contain the peak in question, provided the assumption regarding its origin is correct.

TABLE 1. COUPLING CONSTANT DATA FOR THE *Cinchona* OXIRANES

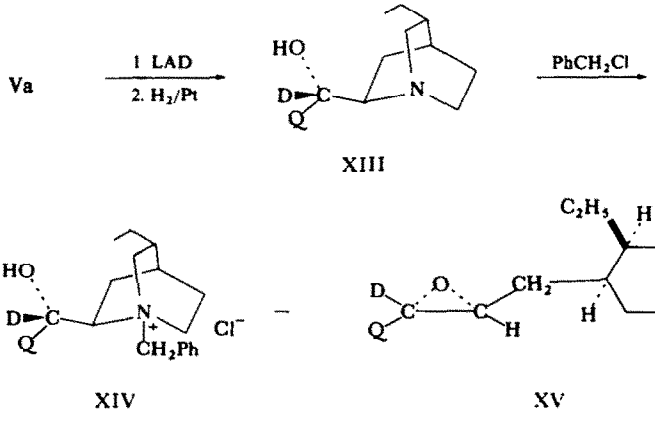


(D)

Alkaloid	Derived oxirane	R	Chemical shift of C-2 Proton (ppm)	*J*	Ring stereochemistry
Quinidine	IXa	OCH_3	4·11	2 c/s	*trans*
Epiquinidine	XIa	OCH_3	4·48	4 c/s	*cis*
Quinidine-9*d*	XV	OCH_3	Peak absent		*trans*
Quinine	XVII	OCH_3	4·09	2 c/s	*trans*
Cinchonine	IXb	H	4·17	2 c/s	*trans*

As a starting point in the synthesis of the deuterated series, quinidine-9*d* (IIIa-9*d*) was prepared in 49% yield by the LAD reduction of quinidinone (Va). Except for the expected difference in the NMR spectra, the product and its acid tartrate salt were identical in all respects to the nondeuterated materials.

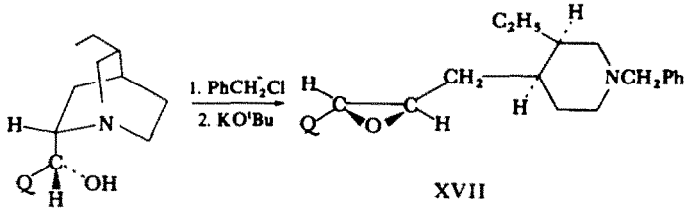
When quinidine-9*d* was subjected to the conditions of hydrogenation over a colloidal platinum catalyst for a period of 35 min, the product gave a negative Baeyer test indicating that reduction of the vinyl group was complete. The NMR



spectrum of the product was identical to that of VIa except for the complete absence of the C-9 doublet found at 5·63 ppm in the spectrum of hydroquinidine. This fact demonstrated that no protium, within the limits of accuracy of the NMR analytical method, had been introduced at C-9, and that the product was hydroquinidine-9*d* (XIII).

Treatment of XIII with benzyl chloride gave the expected quaternary salt XIV which was converted to the epoxide XV using potassium t-butoxide in refluxing t-butyl alcohol. Available spectral and analytical data were found to support the assigned structure. Particularly important, however, was the fact that the one-proton doublet (Table 1) located at 4·11 ppm in the NMR spectrum of its nondeuterated analog IXa was completely absent (Fig. 2). This observation offered conclusive proof that the C-2 oxirane proton was responsible for this peak.

As a final proof of the stereochemical relationship of quinine (Ia) and quinidine (IIIa), hydroquinine (XVI) was quaternized and converted to the corresponding epoxide XVII. Its NMR spectrum displayed a one-proton doublet (Table 1) at 4·09 ppm assigned to the C-2 hydrogen, and the coupling constant of 2 c/s for this peak indicated that the stereochemistry of the oxirane ring was *trans*, the same as that of the epoxide IXa derived from quinidine.



XVI XVII

From the known stereochemical course of the reaction sequence by which the epoxy derivatives were produced (*vide supra*), the *erythro* configurations of quinidine and quinine can be shown to follow from the *trans* stereochemistry of the oxiranes. Furthermore, in view of the established stereochemical interrelationships among the *cinchona* alkaloids,[2, 24] it can be seen that the configurations of all 8 compounds are quite adequately defined in terms of this information. These data are summarized in Table 2.

[24] Each of the alkaloids (Ia, Ib, IIIa, IIIb) may be converted, by reactions involving only C-9, to an epi-base of the same name. (J. Fiedzuiszko and J. Suszko, *Bull. intern. acad. polonaise. classe sci. math. nat.* **1934a**, 412; *Chem. Abstr.* **29**, 2961 (1935); see also reference 2). Therefore, Ia and IIa are epimeric at C-9, as are Ib and IIb, IIIa and IVa, and IIIb and IVb. Furthermore, it has been shown chemically (H. King, *J. Chem. Soc.* 523 (1946)) that cinchonine and cinchonidine are the demethoxy derivatives of quinidine and quinine, respectively, *i.e.* that Ia and Ib are stereochemically identical, as are IIIa and IIIb. It follows that IIa and IIb are likewise of identical configuration as are IVa and IVb. (The principle of optical superposition has been used to support the further contention that Ia and IIIa (etc.) are of the opposite configuration at C-9. Although this type of evidence usually furnishes a reliable indication of stereochemistry, there are exceptions to the rule (T. S. Patterson and J. Kaye, *J. Chem. Soc.* **91**, 705 (1907); T. S. Patterson and C. Buchanan, *Ibid.* **125**, 1475 (1924)), and the question of the stereochemical relationship between Ia and IIIa has been considered an open one for the purposes of this discussion.

TABLE 2. CONFIGURATIONS OF THE *Cinchona* ALKALOIDS

Alkaloid	Relative stereochemistry of C-8,C-9 system	Configuration at C-9
Quinine (Ia)	*erythro*	R
Epiquinine (IIa)	*threo*	S
Quinidine (IIIa)	*erythro*	S
Epiquinidine (IVa)	*threo*	R
Cinchonidine (Ib)	*erythro*	R
Epicinchonidine (IIb)	*threo*	S
Cinchonine (IIIb)	*erythro*	S
Epicinchonine (IVb)	*threo*	R

EXPERIMENTAL

NMR spectra were determined at concentrations of 8–25% (w/v) in $CDCl_3$ using a Varian A-60 instrument. Specific rotations were measured in 95% EtOH in 2 dm tubes. Microanalyses were performed by Schwarzkopf Microanalytical Laboratory, Woodside, New York. The adsorbent for TLC analysis was a 250 μ layer of unactivated Silica Gel H, and the developer was 50:50 (v:v) $CHCl_3$:MeOH; the chromatograms were visualized using a Blak-Ray UVL-22 light. IR spectra were determined on a Perkin–Elmer 337 spectrophotometer, and the solid samples were run as mulls and oils were run neat. M.ps were determined in capillaries and are corrected; decomposition points were generally variable and indistinct and were observed on a Kofler micro hot stage.

Quinidine-9d *acid tartrate*. To a slurry of 794 mg of LAD in 100 ml of anhyd ether was added 6·377 g crystalline Va, m.p. 91–98° (lit.[13] m.p. 106–108°). The mixture was stirred magnetically for 8 hr and the excess reducing agent was decomposed with wet ether. After addition of a few drops of water, the suspension was separated by filtration. Evaporation of the filtrate under reduced press left an oily residue which was dissolved in a soln of (+)-tartaric acid in 40 ml of hot water. The acid tartrate of quinidine-9*d* (5·02 g, 49%) was collected by filtration and recrystallized from water, m.p. 123–127° (dec.), $[\alpha]_D^{24}$ +186° (*c* 0·24). (Found: C, 59·52; H, 6·38. $C_{20}H_{23}DN_2O_2 \cdot C_4H_6O_6 \cdot \frac{1}{2}H_2O$ requires: C, 59·49; H, 6·66%).

Quinidine-9d (IIIa-9*d*). The tartrate salt of quinidine-9*d* was dissolved in water and neutralized with excess Na_2CO_3. The base was extracted into ether, and the combined ether extracts were dried over $MgSO_4$ and concentrated. Crystallization was induced by seeding with a minute amount of commercial quinidine. The crude base was recrystallized successively from ether and EtOH, m.p. 172–173°, $[\alpha]_D^{23}$ +230° (*c* 0·22). (Found: C, 73·98; H, 7·80. $C_{20}H_{23}DN_2O_2$ requires: C, 73·82; H, 7·74%). The NMR spectrum was essentially identical to that of quinidine except that the doublet at 5·63 ppm (J = 3 c/s) for the C-9 proton was absent.

Hydroquinidine-9d (XIII). A soln of 941 mg of quinidine-9*d* in HCl was stirred magnetically in an atmosphere of H gas at room temp in the presence of colloidal Pt for 35 min. After removal of the catalyst by filtration, the base was regenerated with Na_2CO_3 and extracted into ether. The ether extracts were concentrated and the crystalline product collected in 80% yield. Recrystallization from ether yielded an analytical sample, m.p. 170–171°, $[\alpha]_D^{23}$ +218° (*c* 0·20). (Found: C, 73·08; H, 8·01. $C_{20}H_{25}DN_2O_2$ requires: C, 73·36; H, 8·31%). The NMR spectrum showed no bands between 4 and 7 ppm indicating that no protium, within the limits of accuracy of the instrument, had been introduced at C-9. Otherwise, the spectrum was identical to that of VIa.

Preparation of benzochloride salts. The base to be quaternized was dissolved in a convenient volume of abs EtOH and treated with 1 equiv benzyl chloride in EtOH. After heating under reflux for 1–8 hr, the deep red, green-fluorescent soln was concentrated under reduced press, leaving a brown glassy residue which was worked up as indicated for each compound.

Hydroquinidine benzochloride (VIIIa). Compound VIa (6·8 g) was treated with 2·7 g benzyl chloride yielding 6·4 g (60%) crude benzochloride salt, m.p. 163–166° (dec.). After recrystallization from acetone,

$[\alpha]_D^{25}$ +191° (*c* 0·23) (Found: C, 70·53; H, 7·43. $C_{27}H_{33}ClN_2O_2 \cdot C_3H_6O$ requires: C, 70·50; H, 7·69%). The IR spectrum showed a strong band at 1700 cm^{-1} which indicated the presence of the occluded acetone.

Epihydroquinidine benzochloride (Xa). The quaternary salt was prepared from 1·11 g of VIIa. The crude product (1·00 g) was recrystallized from acetone to yield an analytical sample, m.p. 170–173° (dec.), $[\alpha]_D^{25}$ +35° (*c* 0·16). (Found: C, 70·65; H, 7·90. $C_{27}H_{33}ClN_2O_2 \cdot C_3H_6O$ requires: C, 70·50; H, 7·69%). The IR spectrum showed strong absorption at 1705 cm^{-1} indicative of the occluded acetone.

Hydroquinidine-9d benzochloride (XIV). Hydroquinidine-9*d* (750 mg) was quaternized with $PhCH_2Cl$ yielding 655 mg of the salt XIV. After recrystallization from acetone, the product melted at 163–166° (dec.), $[\alpha]_D^{24}$ +185% (*c* 0·26). (Found: C, 70·06; H, 7·73. $C_{27}H_{32}ClDN_2O_2 \cdot C_3H_6O$ requires: C, 70·36; H, 8·87%). The IR spectrum supported the presence of the occluded acetone by the band at 1705 cm^{-1}.

Hydroquinine benzochloride. Hydroquinine (446 mg) was quaternized with 191 mg of $PhCH_2Cl$ and crystallization of the glassy product was induced by treating its anhyd methanolic soln with anhyd ether. Recrystallization from acetone yielded an analytical sample, m.p. 184–189° (dec). lit.[25] m.p. 202–204° (dec), $[\alpha]_D^{21}$ −155° (*c*, 0·090). (Found: C, 68·78; H, 7·58. $C_{27}H_{33}ClN_2O_2 \cdot H_2O$ requires: C, 68·85; H, 7·49%). This salt did not crystallize with a molecule of acetone as did the quinidine derivatives. The IR spectrum showed only moderate absorption at 1705 cm^{-1} and the analysis indicated water but not acetone was present.

Preparation of oxiranes. A soln (or slurry) of the appropriate benzochloride salt in anhydrous t-butyl alcohol was added to a boiling soln of freshly prepared potassium t-butoxide (3–6 fold excess by wt) in a convenient volume of the anhyd solvent. TLC indicated that in each case the salt was completely consumed within the first minute of reaction and that the products were relatively stable to the conditions of the reactions. Upon completion of the reaction, the mixture was cooled, a slight excess of water was added, and the soln was evaporated under reduced press. The residual material was triturated with ether or low-boiling pet. ether and the extracts were applied to a Florisil column and chromatographed with anhyd ether or pet. ether. Collection of fractions continued until TLC analysis of the eluate revealed either (a) the absence of the blue-fluorescent epoxide or (b) the presence of an additional substance. Evaporation of the eluate left a viscous, yellow oil which decomposed on attempted distillation, on exposure to light, or upon being dissolved in CCl_4, $CHCl_3$ or other slightly acidic solvent. Although it could in no case be induced to crystallize, this material could be rendered analytically pure by repetition of the chromatographic technique described above.

trans-2(S)-(6-*Methoxy-4-quinolyl*)-3-(1-*benzyl*-3(R)-*ethyl*-4-cis-*piperidyl*) *methyl oxirane* (IXa).* VIIIa (68 mg) was treated with 390 mg potassium t-butoxide. The total volume of the resulting t-butyl alcohol soln was 10 ml. The product had $[\alpha]_D^{25}$ +73° (*c* 0·22). (Found: C, 77·63; H, 7·45; N, 6·82. $C_{27}H_{32}N_2O_2$ requires: C, 77·85; H, 7·74; N, 6·72%). There was no absorption in the CO or OH regions of the IR spectrum. The NMR spectrum showed the C–CH_3 triplet at 0·82 ppm (J = 6 c/s), two peaks of the expected AB quartet due to the non-equivalent N-benzyl protons at 3·41 and 3·47 ppm, the O-Me singlet at 3·87 ppm, a doublet due to the C-2 oxirane proton (J = 2 c/s), and the Ph resonance at 7·29 ppm.

cis-2(R)-(6-*Methoxy-4-quinolyl*)-3-(1-*benzyl*-3(R)-*ethyl*-4-cis-*piperidyl*) *methyl oxirane* (XIa).* Xa (89 mg) was treated with 285 mg of potassium t-butoxide, resulting in the production of a substantial amount of yellow-fluorescent oil in addition to the major product XIa which gave $[\alpha]_D^{24}$ −243° (*c* 0·18). (Found: C, 78·02; H, 7·85; N, 6·97. $C_{27}H_{32}N_2O_2$ requires: C, 77·85; H, 7·74; N, 6·72%). The IR spectrum showed no OH or CO absorption bands. The NMR spectrum showed the O–Me singlet at 3·92 ppm, C—Me triplet at 1·22 ppm (J = 6 c/s), Ph resonance at 7·25 ppm, and a doublet at 4·48 ppm (J = 4 c/s) due to the epoxy proton adjacent to the aromatic ring.

trans-2(S)-(6-*Methoxy-4-quinolyl*)-3-(1-*benzyl*-3(R)-*ethyl*-4-cis-*piperidyl*) *methyl oxirane*-2d (XV).* Compound XIV (172 mg) was converted to 150 mg (95%) of the corresponding deuterated epoxide XV, $[\alpha]_D^{24}$ +91° (*c* 0·17). (Found: C, 77·84; H, 7·91; N, 6·50. $C_{27}H_{31}DN_2O_2$ requires: C, 77·66; H, 7·97; N, 6·71%).

* The names of the oxiranes have been selected with the intent of showing the geometrical relationships of the substituents on the heterocyclic rings. The correct names according to the Sequence Rule system[26] would be (2*S*, 3*S*, 3″*R*, 4″*S*)-2-(6′-methoxy-4′-quinolyl)-3-(1″-benzyl-3-″-ethyl-4″-piperidyl)methyl oxirane for IXa, the (2*R*, 3*S*, 3″*R*, 4″*S*)-isomer for XIa. The former prefix would also apply to the deutero derivative XV, while the oxirane XVII from quinine would have the prefix (2*R*, 3*R*, 3″*R*, 4″*S*).

[25] W. A. Jacobs and M. Heidelberger, *J. Am. Chem. Soc.* **41**, 2090 (1919).

[26] R. S. Cahn, C. K. Ingold and V. Prelog, *Experientia* **12**, 81 (1956).

The IR spectrum showed a weak band at 2200 cm^{-1} which was attributed to the C–D stretching frequency, and no OH or CO absorption was evident. The NMR gave a spectrum essentially identical to that of the non-deuterated epoxide IXa except for the absence of the doublet at 4·11 ppm.

trans-2(R)-(6-*Methoxy-4-quinolyl*)-3-(1-*benzyl*-3(R)-*ethyl*-4-cis-*piperidyl*) *methyl oxirane* (XVII).* By treatment with 480 mg of potassium t-butoxide, 114 mg of hydroquinine benzochloride was converted to the corresponding epoxide XVII, $[\alpha]_D^{22}$ −55° (*c* 0·16). (Found: C, 77·68; H, 7·97; N, 6·51. $C_{27}H_{32}N_2O_2$ requires: C, 77·85; H, 7·74; N, 6·72%). The IR spectrum gave no absorption bands due to CO or OH groups. In the NMR spectrum, the doublet at 4·09 ppm (J = 2 c/s) was not well-resolved but was present as in the other epoxides. There was a singlet at 3·90 ppm due to the O–Me group, an AB quartet corresponding to the N-benzyl protons centered at 3·43 ppm (J = 13·6 c/s, $\Delta\delta$ = 8·5 c/s), C–Me triplet at 0·80 ppm (J = 6 c/s), and the Ph resonance at 7·19 ppm.

* See footnote on previous page.