tion, vigorous stirring was continued for an additional 5 min. Then the upper layer was separated, and the lower aqueous layer was extracted with two 15-ml portions of ether. The combined ether extracts were washed once with 5% sodium carbonate and then four times with water. Gas chromatographic analysis on a Carbowax 20M column with benzil as internal standard showed 74% yield of 1-phenylnorcamphor in the absence of any starting alcohol. After the solvent was removed, the remaining oil was carefully fractionally distilled through a 10-cm Vigreux column and the ketone, bp 132–135° (1.5 mm), solidified in the receiver. The yield of this glpc homogeneous 1-phenylnorboranone, mp 41–42° (lit.[25] 40.2–41.0), was 6.37 g (68%).

Other alcohols listed in Table III were oxidized in the same way.

Registry No.—3-Methyl-2-butanol, 598-75-4; cyclopentanol, 96-41-3; cyclohexanol, 108-93-0; cyclooctanol, 696-71-9; *cis*-2-methylcyclohexanol, 7443-70-1; *trans*-2-methylcyclohexanol, 7443-52-9; *l*-menthol, 2216-51-5; isopinocampheol, 1196-00-5; *exo*-norbornanol, 497-37-0; *endo*-norbornanol, 497-36-9; 1-methyl-*exo*-norbornanol, 766-25-6; 1-methyl-*endo*-norbornanol, 3588-21-4; 1-phenyl-*exo*-norbornanol, 14182-93-5; 7,7-dimethyl-*exo*-norbornanol, 26908-71-4; isoborneol, 124-76-5; borneol, 507-70-0; *endo*-fenchyl alcohol, 14575-74-7; chromic acid, 7738-94-5.

Acknowledgment.—Financial support from the Office of Ordnance Research (Contracts DA-33-008-ORD-992 and -2002) and the National Science Foundation (Grant G 19878) is gratefully acknowledged.

Frangomeric and Anchimeric Processes in the Preparation and Reactions of α,β-Epoxy Ketones[1]

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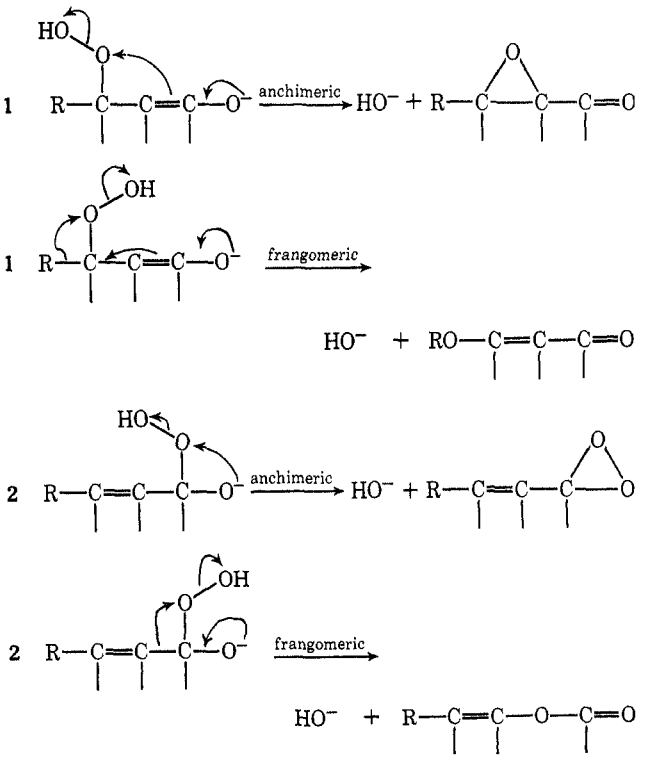
Four pathways are considered for the reaction of the hydrogen peroxide anion with α,β-unsaturated ketones. One of these pathways leading to α,β-epoxy ketones is well known. Examples of a second pathway, Baeyer–Villiger oxidation, are described with 2-arylmethylene-3-quinuclidinones. The reactions of hydrazine with α,β-epoxy ketones yield either hydroxypyrazolines or allylic alcohols depending on whether the intermediate epoxyhydrazones follow an anchimeric process or a frangomeric process. The former is shown to be preferred with α,β-epoxy ketones in which the β-carbon atom is benzylic and in which a cisoidal conformation of epoxide and ketone functions is accessible.

Heterolytic processes involving interaction between two functional groups may formally proceed by either of two pathways. Electron pairs may shift through an existing framework of chemical bonds or they may move through space, forming a new bond in the process. These two pathways have been described as frangomeric and anchimeric processes, respectively,[2] as an extension of the concept of frangomeric[3] and anchimeric[4] effects. In a formal sense, four reaction pathways could be defined for the reaction of alkaline hydrogen peroxide[5] with an α,β-unsaturated ketone.[6] The hydrogen peroxide anion could add in either the conjugate or direct mode giving either intermediate **1** or **2** and each of these could collapse to products *via* an anchimeric or a frangomeric process (Scheme I).

The first of these pathways leading to α,β-epoxy ketones is familiar and clearly preferred in most systems. The second pathway corresponds to a vinylogous Baeyer–Villiger oxidation but has never, to our knowledge, been observed. The migration of the group R formally entails heterolysis of the R—C bond whence the analogy with the generalized frangomeric process is valid. The third pathway leading to a dioxirane is unknown. The fourth pathway is a normal Baeyer–Villiger oxidation which virtually never occurs under these conditions.[7] However, one possible exception and some low-yield Baeyer–Villiger oxidations of simple ketones under these conditions have been reported.[8] The pathway is

SCHEME I



(1) Synthetic Quinine Analogs. III. Supported by the U. S. Army Medical Research and Development Command, Contract DADA-17-68-C-80-45. Part II: D. L. Coffen and T. E. McEntee, *J. Org. Chem.*, **35**, 503 (1970).

(2) J. W. Wilt and W. J. Wagner, *J. Amer. Chem. Soc.*, **90**, 6135 (1968).

(3) C. A. Grob, *Bull. Soc. Chim. Fr.*, 1360 (1960); *Angew. Chem., Int. Ed. Engl.*, **8**, 535 (1969).

(4) E. S. Gould, "Mechanism and Structure in Organic Chemistry," Holt-Dryden, New York, N.Y., 1959, Chapter 14.

(5) (a) E. Weitz and A. Scheffer, *Chem. Ber.*, **54**, 2327 (1921); (b) for recent discussion, see R. D. Temple, *J. Org. Chem.*, **35**, 1275 (1970).

(6) With care the reagent can be used to epoxidize base sensitive unsaturated aldehydes: G. B. Payne, *J. Amer. Chem. Soc.*, **81**, 4901 (1959).

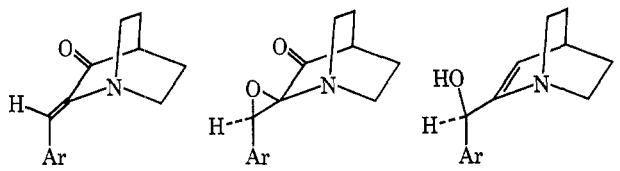
(7) C. H. Hassall, *Org. React.*, **9**, 81 (1957).

(8) H. O. House and R. L. Wasson, *J. Org. Chem.*, **22**, 1157 (1957).

labeled frangomeric purely for the convenience of this discussion.

Although all four of these reaction pathways are feasible, only the first is well known. In the course of a project involving *dl*-quinine and related synthetic antimalarials, we have studied the epoxidation of several α-amino-α,β-unsaturated ketones and have found some clear-cut[9] examples of the fourth pathway.

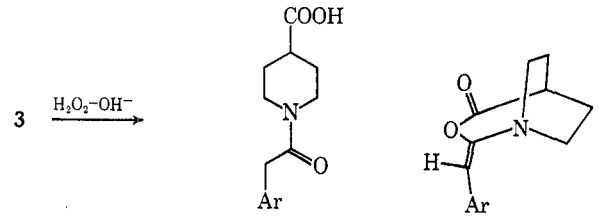
The ketones examined were those with general formula **3**. These compounds are easily prepared by condensing aryl aldehydes with 3-quinuclidinone[10] and could, in principle, be easily converted to antimalarials of the "desvinylquinine type" **5** by epoxidation and reduction with hydrazine.[11]



3 **4** **5**

a, Ar = phenyl
b, Ar = 9-anthryl
c, Ar = 9-phenanthryl
d, Ar = 6-methoxy-4-quinolyl

Although epoxides bearing nitrogen functions on the epoxide ring are known,[12] the epoxidation of α-amino-α,β-unsaturated ketones has not been described previously. β-Amino-α,β-unsaturated ketones respond as vinylogous amides to most reagents and are accordingly inert to alkaline hydrogen peroxide.[13] When the ketones **3a–c** were treated with alkaline hydrogen peroxide in aqueous ethanol, they were smoothly transformed into the *N*-arylacetylisonipecotic acids, **6a–c**, and gave



6a, Ar = phenyl **7**
b, Ar = 9-anthryl
c, Ar = 9-phenanthryl

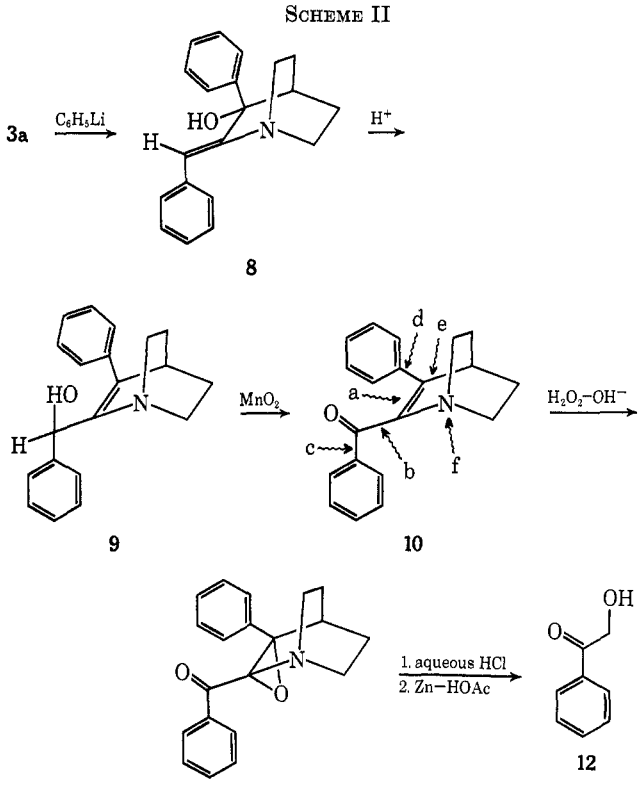
no trace of epoxy ketones **4**. Similar oxidation of **3d** gave only a water-soluble product, presumed to be an amino acid and not isolated. The structures of products **6a–c** were deduced from their analytic and spectroscopic data and were confirmed by synthesizing **6a** and **6b** from isonipecotic acid and the corresponding arylacetyl chlorides.

Thus the hydrogen peroxide anion adds in the direct modes to ketones **3a–c** (and by inference, **d**) giving an intermediate of type **2** which collapses to give the primary products **7** *via* the fourth pathway. Alkaline hydrolysis of the Baeyer–Villiger products **7** yields the isonipecotic acids **6** directly.[14]

The reaction affords an efficient method of transforming aromatic aldehydes into their homologous acids and may, in that respect, have some synthetic utility.

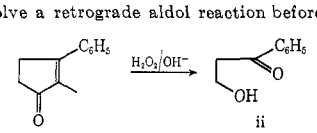
The reaction of the structurally related α-amino-α,β-unsaturated ketone **10** with alkaline hydrogen peroxide was also examined, principally because the fourth pathway would, in this instance, provide ready access to 2-quinuclidinones. 2-Quinuclidinones are rather interesting substances but can only be obtained by a lengthy synthesis.[15] Compound **10** was synthesized from the unsaturated ketone **3a** by sequential treatment of the latter with phenyllithium, hot 10% hydrochloric acid, and manganese dioxide (Scheme II). The allylic rear-

SCHEME II



8 **9** **10** **11** **12**

(9) The alkaline peroxide oxidation of i to ii described by House and Wasson[8] may involve a retrograde aldol reaction before the oxidation step.



ii

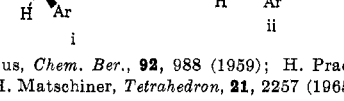
(10) (a) G. R. Clemo and E. Hoggarth, *J. Chem. Soc.*, 1241 (1939); (b) C. A. Grob and A. Kaiser, *Helv. Chim. Acta*, **46**, 2646 (1963); (c) D. R. Bender and D. L. Coffen, *J. Org. Chem.*, **33**, 2504 (1968).

(11) (a) P. S. Wharton and D. H. Bohlen, *ibid.*, **26**, 3615 (1961); (b) Huang-Minlon and Chung-Tungshun, *Tetrahedron Lett.*, 666 (1961).

(12) Aminoepoxide: C. L. Stevens and P. M. Pillai, *J. Amer. Chem. Soc.*, **89**, 3084 (1967). *N*-Acylaminoepoxide: H. Smith, P. Wegfahrt, and H. Rapoport, *ibid.*, **90**, 1668 (1968). Nitroepoxide: H. Newman and R. B. Angier, *Chem. Commun.*, 369 (1969).

(13) For example, 3-amino-5,5-dimethyl-2-cyclohexenone is recovered unchanged after 48-hr exposure to the reagent.

(14) An alternative mechanism involving the epoxy ketones **4** as intermediates was also considered. Attack on the carbonyl group of **4** by a hydroxide ion would produce intermediate i which could fragment to ii in the indicated manner [*cf.* decarboxylation of glycidic acids discussed by E. P. Blanchard and G. Büchi, *J. Amer. Chem. Soc.*, **85**, 955 (1963)]. This mechanism was rejected both because the epoxy ketone **4d**, described later, is inert to alkaline hydrogen peroxide and because, in contradistinction to the rigid stereoelectronic requirements established for such fragmentation processes,[8] the C–C and C–O bonds undergoing cleavage in the process i → ii are virtually orthogonal.



i ii

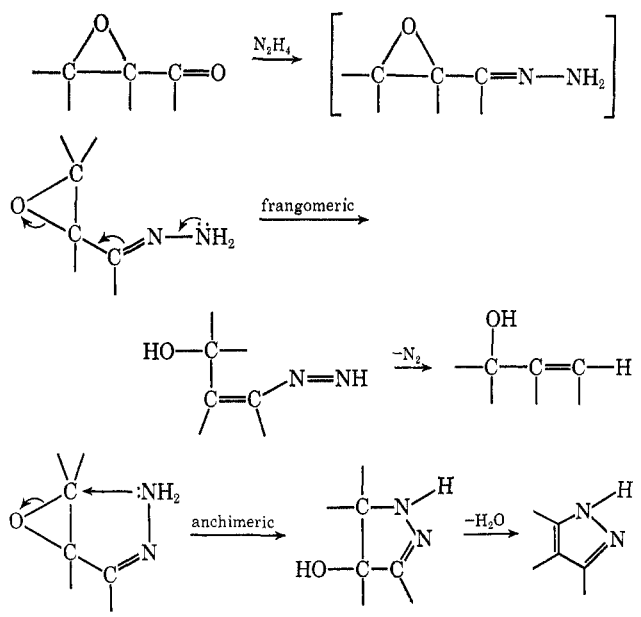
(15) H. Pracejus, *Chem. Ber.*, **92**, 988 (1959); H. Pracejus, M. Kehlen, H. Kehlen, and H. Matschiner, *Tetrahedron*, **21**, 2257 (1965).

rangement of alcohol **8** proceeds readily in high yield and this reaction has subsequently been applied to the synthesis of phenanthrenemethanol antimalarials.[16] Oxidation of ketone **10** proceeded sluggishly but cleanly giving a single product. Analysis and the molecular weight of this product established that the transformation corresponded to the addition of one oxygen atom. This could have been added at any one of the positions indicated with arrows a–f. Acid hydrolysis followed by reduction with zinc in hot acetic acid afforded a low yield of 2-hydroxyacetophenone (**12**). The oxidation product must therefore be the α,β-epoxy ketone **11**.

Since the α-amino-α,β-unsaturated ketone **10** reacts "normally" (first pathway) with alkaline hydrogen peroxide, the preference for the fourth pathway exhibited by the ketones **3** cannot be a consequence of the α-amino group. It is not at present possible to define the structural parameters which determine the choice between these two pathways.

The preference for oxidation *via* the fourth pathway over the first pathway exhibited by ketone **3d** can be reversed by changing (principally the steric bulk) of the oxidizing agent. By using *tert*-butyl hydroperoxide rather than hydrogen peroxide, and acetonitrile and Triton-B as the solvent and base,[17] the oxidation of ketone **3d** proceeded cleanly *via* the first pathway to the epoxy ketone **4d**. Since ketone **3d** is readily available,[10c] a short synthesis of devinylquinine[18] was anticipated at this stage but was thwarted by the subsequent realization that both frangomeric and anchimeric pathways are possible in the reaction of hydrazine with α,β-epoxy ketones (Scheme III). Since the reduction of an

SCHEME III



α,β-epoxy ketone to an allylic alcohol with hydrazine constituted a vital step in our effort to synthesize *dl*-quinine and devinyl analogs, we undertook to establish the structural factors which cause the anchimeric process of Scheme III to prevail in some instances while the frangomeric process prevailed in others.

The results of this investigation permit us to draw the following conclusion. *The anchimeric process leading to a hydroxypyrazoline will prevail with any α,β-epoxy ketone which satisfies both of the following conditions: (a) the ketone and epoxide functions must be cisoidal or have access to the cisoidal conformation; (b) the β-carbon atom must be benzylic. In all other cases the frangomeric process leading to an allylic alcohol will prevail.*

This conclusion was drawn after examination of all available literature[19] on the reactions of hydrazine with α,β-epoxy ketones and after carrying out a series of experiments designed to test it while in the form of a premise. The results with substrates examined during this work and key examples from the literature are presented in Table I.

The reason for the cisoidal conformational requirement is obvious since the anchimeric process is otherwise impossible. Syn–anti isomerism of the hydrazone function could play an important role in this context but there is no evidence that it does. The necessity of having the β-carbon atom benzylic is undoubtedly related to the enhanced SN2 reactivity of groups in a benzylic position.[24] Substituted hydrazines will show different selectivity for the frangomeric and anchimeric processes. Thus, for example, tosylhydrazine gives mainly the anchimeric product with the epoxide of mesityl oxide.[25]

Since both reaction pathways of Scheme III are of synthetic value, the conclusions offered here can con-

(16) Unpublished results.

(17) Conditions described by N. C. Yang and R. A. Finnegan, *J. Amer. Chem. Soc.*, **80**, 5845 (1958).

(18) P. Rabe, *et al.*, *Justus Liebigs Ann. Chem.*, **496**, 151 (1932); *Chem. Ber.*, **74**, 636 (1941); *ibid.*, **76**, 318 (1943). V. Prelog, *et al.*, *ibid.*, **74**, 647 (1941).

(19) The results of reacting hydrazine with epoxy ketones appear to have been first described in 1916.[20] Chalcone oxide and substituted derivatives were observed to give 3,5-diarylpyrazoles *via* diarylhydroxypyrazolines. Several additional examples and analogous reactions were described in subsequent years.[21] In 1961 Wharton and Huang-Minlon[11] independently described the preparation of allylic alcohols by reacting hydrazine with α,β-epoxy ketones. Numerous examples of this reaction have been described since,[22] particularly with steroids and monoterpenes. The frangomeric process delineated in Scheme III was first suggested by Huang-Minlon[11b] as the mechanism leading to allylic alcohols. The manner in which hydrazines react with α-halo ketones[23] makes it highly probable that the epoxyhydrazone is an intermediate and, moreover, vinyl diimides are now known to lose nitrogen spontaneously at room temperature.[23d] Thus this mechanism is probably correct. An alternative reaction pathway, the anchimeric process in Scheme III, is also possible for epoxyhydrazones, this pathway being the one that leads to hydroxypyrazolines and pyrazoles. Since identical reaction conditions can be used, it is reasonable to assume that this same primary intermediate is involved for those substrates which give hydroxypyrazolines and pyrazoles as well. The structures of pyrazoles formed with substituted hydrazines[21] support this assumption.

(20) (a) O. Widman, *ibid.*, **49**, 477 (1916); (b) H. Jörlander, *ibid.*, **49**, 2782 (1916); (c) S. Bodforss, *ibid.*, **49**, 2795 (1916).

(21) W. A. Hutchins, D. C. Motwani, K. D. Mudbhatkal, and T. S. Wheeler, *J. Chem. Soc.*, 1882 (1938); P. P. Dodwadmath and T. S. Wheeler, *Proc. Indian Acad. Sci., Sect. A*, 438 (1935); N. H. Cromwell and R. A. Setterquist, *J. Amer. Chem. Soc.*, **76**, 5752 (1954); A. Padwa, *J. Org. Chem.*, **30**, 1274 (1965).

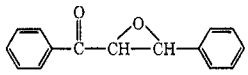
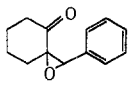
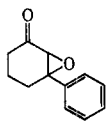
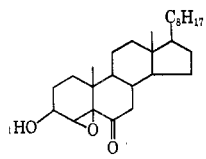
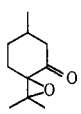
(22) (a) P. S. Wharton, *ibid.*, **26**, 4781 (1961); (b) C. Djerassi, D. H. Williams, and B. Berko, *ibid.*, **27**, 2205 (1962); (c) C. Beard, J. M. Wilson, H. Budzikiewicz, and C. Djerassi, *J. Amer. Chem. Soc.*, **86**, 269 (1964); (d) K. Klein and G. Ohloff, *Tetrahedron*, **19**, 1091 (1963); (e) W. R. Benn and R. M. Dobson, *J. Org. Chem.*, **29**, 1142 (1964); (f) R. Sciaky and F. Facciano, *Gazz. Chim. Ital.*, **93**, 1014, (1963); (g) S. V. Kessar, Y. P. Gupta, and A. L. Rampal, *Tetrahedron Lett.*, 4319 (1966); (h) G. V. Nair and G. D. Pandit, *ibid.*, 5097 (1966).

(23) (a) P. S. Wharton, S. Dunny, and L. S. Krebs, *J. Org. Chem.*, **29**, 958 (1964); (b) V. R. Mattox and E. C. Kendall, *J. Amer. Chem. Soc.*, **72**, 2290 (1950); (c) B. T. Gillis and J. D. Hagarty, *ibid.*, **87**, 4576 (1965); (d) T. Tsuji and E. M. Kosower, *ibid.*, **91**, 3375 (1969).

(24) A. Streitwieser, "Solvolytic Displacement Reactions," McGraw-Hill, New York, N.Y., 1962, p 13.

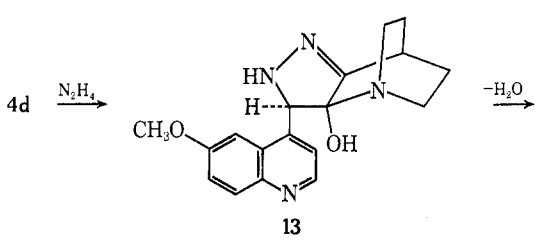
(25) D. P. G. Hamon and L. J. Holding, *Chem. Commun.*, 1330 (1970).

TABLE I
REACTIONS OF SELECTED α,β-EPOXY KETONES WITH HYDRAZINE

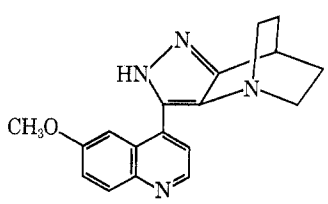
α,β-Epoxy ketone	Cisoidal (accessible)	β carbon benzylic	Product	Yield, %	Ref
	Yes	Yes	Pyrazole		20a
 15	Yes	Yes	Pyrazole (16)	65	This work
 17	No	Yes	Allylic alcohol (18)	92	This work
 19	Yes	No	Allylic alcohol (20)	48	This work
	Yes	No	Allylic alcohol	71.5	22d
	Yes	No	Allylic alcohol	75	22d
	No	No	Allylic alcohol	75	11a

siderably enhance the utility of the reactions of hydrazine with epoxy ketones.[26]

The epoxy ketone **4d**, from which the allylic alcohol was desired, is cleanly transformed into the hydroxypyrazoline **13** with hydrazine in ethanol or into the pyrazole **14**[10c] with hydrazine in hot acetic acid.

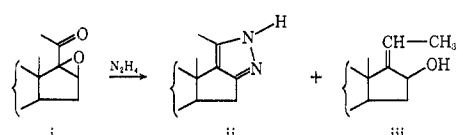


13



14

(26) It should be noted that this, like most generalizations in organic chemistry, has it exceptions. Benzalacetone oxide reacts with hydrazine to give a mixture of allylic alcohol and the expected pyrazole. The steroidal epoxy ketone i gives a small amount of pyrazole ii in addition to the expected allylic alcohol iii.[22e]



i ii iii

Experimental Section[27]

***N*-Phenylacetylisonipecotic Acid (6a). A. From 2-Phenylmethylene-3-quinuclidinone.**[10b]—Compound **3a** (1.455 g, 6.8 mmol) was placed in 150 ml of ethanol and cooled to 5°. Hydrogen peroxide (4.5 ml, 30%) was added, followed by 10 ml of 5% sodium hydroxide, and the suspension was stirred for 15 hr. Water (30 ml) was then added and the aqueous layer washed with methylene chloride. The aqueous layer was then acidified with dilute hydrochloric acid and extracted three times with methylene chloride. The organic phase was dried over sodium sulfate and evaporated, yielding a clear oil. The pure product (680 mg, 40%) was obtained from ethyl ether as colorless crystals: mp 124–125.5°; ν_{max} (Nujol) 3400, 1705, 1690, 1405, 1300, 1270, 1240, 1210, 1185, 1150, 1030, 945, 925, 723, and 711 cm^{-1}. The nmr spectra of compounds **6a–c** were composed of poorly resolved multiplets which were consistent with the respective structures.

Anal. Calcd for $C_{14}H_{17}NO_3$: C, 67.99; H, 6.93; N, 5.66. Found: C, 67.81; H, 7.02; N, 5.51.

B. From Phenylacetyl Chloride.—The reaction of phenylacetyl chloride with isonipecotic acid using the Schotten–Baumann procedure yielded (41%) material identical (ir, tlc, melting point) with that produced by method A.

2-(9-Anthrylmethylene)-3-quinuclidinone (3b).—A slurry of 4.12 g of 9-anthracene carboxaldehyde and 3.23 g of 3-quinuclidinone hydrochloride (20 mmol each) in 50 ml of absolute ethanol was treated with a solution of 1.0 of sodium in 30 ml of absolute ethanol. The mixture was warmed at 50° for 30 min and cooled, with resulting formation of yellow crystals. Addition of water and subsequent filtration afforded 5.77 g

(27) Melting points are uncorrected. Nmr spectra were recorded on Varian A-60A and HA-100 instruments using deuteriochloroform as solvent and tetramethylsilane as internal standard. Infrared and mass spectra were recorded on Perkin-Elmer 137 and Atlas CH-5 instruments, respectively. Analyses were carried out by Galbraith Laboratories, Inc., Knoxville, Tenn.

(92%) of yellow powder. Recrystallization from ethanol–chloroform gave yellow needles: mp 284–285°; ν_{max} 1715, 1650, 1325, 1235, 1170, 1100, 993, 887, 850, 842, 812, 783, 738, and 732 cm^{-1}. The nmr spectrum shows quinuclidine proton signals (9 H, multiplet) from 1.9 to 3.1 ppm, aromatic proton signals (9 H, multiplet) from 7.2 to 8.4 ppm, and a vinyl proton signal (1 H, singlet) at 7.52 ppm.

Anal. Calcd for $C_{22}H_{19}NO$: C, 84.31; H, 6.11; N, 4.47. Found: C, 84.40; H, 6.15; N, 4.37.

N-(**9-Anthrylacetyl**)**isonipecotic Acid** (**6b**). A. **From 2-(9-Anthrylmethylene)-3-quinuclidinone** (**3b**).—Compound **3b** (1.00 g) was placed in 150 ml of ethanol and cooled to 5°. Hydrogen peroxide (3 ml, 30%) was added, followed by 5 ml of 5% sodium hydroxide. The suspension was stirred at room temperature for 40 hr with concomitant disappearance of all solid. The ethanol was evaporated and the residue was taken up in a 1:1 water–methylene chloride mixture. The aqueous phase was separated, acidified, and extracted with methylene chloride, which was dried and evaporated. The colorless product (901 mg, 82%) was recrystallized from benzene–methylene chloride: mp 212–214°; ν_{max} 1720, 1595, 1270, 1255, 1195, 1155, 1025, 1015, 925, 895, 870, 732, and 673 cm^{-1}. The product is apparently dimorphic, a form exhibiting a slightly altered infrared spectrum being obtained from some recrystallizations.

Anal. Calcd for $C_{22}H_{21}NO_3$: C, 76.06; H, 6.09; N, 4.03. Found: C, 76.03; H, 5.86; N, 3.95.

B. From 9-Anthrylacetyl Chloride.—The reaction of 9-anthrylacetyl chloride[28] with isonipecotic acid in *N*-methyl-2-pyrrolidone using triethylamine as the base yielded (64%) material identical (ir, tlc, melting point) with that produced by method A.

2-(9-Phenanthrylmethylene)-3-quinuclidinone (**3c**).—Sodium (0.805 g, 0.035 g-atom) was dissolved in 100 ml of absolute ethanol and was followed by addition of 9-phenanthrene carboxaldehyde (5.15 g, 25 mmol) and 3-quinuclidinone hydrochloride (4.03 g, 25 mmol). The suspension was heated at reflux for 19 hr then cooled and diluted with water. Filtration afforded 7.29 g (92%) of yellow needles: mp 169–171°; ν_{max} 1690, 1615, 1600, 1480, 1320, 1240, 1170, 1095, 928, 885, 850, 764, and 745 cm^{-1}. The nmr spectrum shows quinuclidine proton signals (9 H, multiplet) from 1.9 to 3.3, aromatic proton signals (9 H, multiplet) from 7.3 to 8.8, and a vinyl proton signal (1 H, singlet) at 6.27 ppm.

Anal. Calcd for $C_{22}H_{19}NO$: C, 84.31; H, 6.11; N, 4.47. Found: C, 84.58; H, 6.31; N, 4.56.

N-(**9-Phenanthrylacetyl**)**isonipecotic Acid** (**6c**).—A slurry of compound **3c** (995 mg, 3.2 mmol) in 70 ml of 95% ethanol was cooled to 5°. Hydrogen peroxide (3 ml, 30%) was then added followed by 5 ml of 5% sodium hydroxide, and the mixture was stirred for 15 hr. The residue, after evaporation of the solvent, was taken up in 30 ml of water, acidified with dilute hydrochloric acid, and extracted with methylene chloride. The extract was dried and evaporated, and the resulting solid was recrystallized as colorless prisms (677 mg, 60%) from benzene–methylene chloride: mp 199–201°; ν_{max} 1725, 1595, 1275, 1255, 1195, 1165, 1100, 1025, 948, 927, 810, 747, and 674 cm^{-1}.

Anal. Calcd for $C_{22}H_{21}NO_3$: C, 76.06; H, 6.09; N, 4.03. Found: C, 76.22; H, 6.16; N, 3.91.

2-Phenylmethylene-3-phenyl-3-hydroxyquinuclidine (**8**).—A suspension of 2-phenylmethylene-3-quinuclidinone[10b] (12.0 g, 0.056 mol) in ether (240 ml) was slowly treated with 1.91 *M* phenyllithium (40 ml, 0.066 mol) in 1:1 ether–benzene. The resulting solution was immediately quenched by the dropwise addition of water (50 ml). The organic layer was separated and combined with three ether extracts of the aqueous layer. The combined organic layers were dried over anhydrous Na_2SO_4 and evaporated giving a pale yellow oil. Crystallization from Skellysolve B afforded colorless crystals (8.80 g, 54%): mp 105–106°; ν_{max} 3540, 1650, 1600, 1480, 1225, 1190, 1035, 1015, 973, 896, 881, 858, and 821 cm^{-1}; nmr 1.2–3.3 (9 H, multiplet, quinuclidine H), 6.2 (1 H, singlet, vinyl H), and 7.2–8.0 ppm (10 H, multiplet, aromatic H); mol wt 291 (mass spectrum).

2-Phenylhydroxymethyl-3-phenyl-2-quinuclidinene (**9**).—A suspension of alcohol **8** (8.80 g, 0.03 mol) in 10% hydrochloric acid (90 ml) was heated at reflux for 1 hr and then refrigerated overnight. The hydrochloride of alcohol **9** which crystallized out was filtered and dried giving 9.22 g (96%) of colorless crystals. The free base was obtained by shaking the hydrochloride with saturated sodium bicarbonate solution followed by threefold extraction with methylene chloride. The organic phase was dried and evaporated yielding 8.81 g of colorless solid. A sample recrystallized from ethanol had mp 122–122.5°: ν_{max} 3050, 1600, 1485, 1315, 1295, 1185, 1135, 1118, 1015, 970, 800, 778, and 736 cm^{-1}; nmr 1.5–2.0 and 2.7–3.0 (9 H, multiplets, quinuclidine H), 5.6 (1 H, singlet, secondary alcohol), and 7.3 ppm (10 H, broad singlet, aromatic H); mol wt 291 (mass spectrum).

2-Benzoyl-3-phenyl-2-quinuclidinene (**10**).—A solution of alcohol **9** (3 g, 10.4 mmol) in methylene chloride (200 ml) was treated with activated manganese dioxide (30 g) and stirred vigorously for 3 days. The solid was filtered out and washed with more methylene chloride. The filtrate and washings were evaporated leaving a colorless solid (100%). Recrystallization from ethanol gave colorless crystals: mp 142–143°; ν_{max} 1650, 1600, 1580, 1260, 1240, 1143, 933, 925, 760, and 740 cm^{-1}; nmr 1.6–2.0 and 2.7–3.3 (9 H, multiplets, quinuclidine H), 7.0–7.4 and 7.6–7.8 ppm (10 H, multiplets, aromatic H); mol wt 289 (mass spectrum).

Anal. Calcd for $C_{20}H_{19}NO$: C, 83.01; H, 6.62; N, 4.84. Found: C, 83.30; H, 6.59; N, 4.80.

2-Benzoyl-3-phenyl-2,3-oxidoquinuclidine (**11**).—A solution of ketone **10** (250 mg) in methanol (12 ml) was treated with 30% hydrogen peroxide (0.85 ml). Sodium hydroxide solution (1.2 ml, 4 *N*) was added and the resulting solution heated at reflux for 62 hr. Water was added slowly with swirling until crystallization commenced and 107 mg (40%) of colorless crystals were collected by filtration. An analytical sample recrystallized from ethanol, had mp 137–138°: ν_{max} 1680, 1600, 1575, 1490, 1310, 1265, 1235, 1122, 1010, 924, 873, 854, and 762 cm^{-1}; nmr 1.4–3.6 (9 H, multiplets, quinuclidine H), 7.2–7.6 and 7.9–8.2 ppm (10 H, multiplet, aromatic H); mol wt 305 (mass spectrum).

Anal. Calcd for $C_{20}H_{19}NO_2$: C, 78.66; H, 6.27; N, 4.59. Found: C, 78.82; H, 6.41; N, 4.41.

Degradation of Epoxide 11.—A solution of epoxide **11** (2.00 g, 6.6 mmol) in 10% hydrochloric acid (300 ml) was heated at reflux for 1 hr. Overnight refrigeration yielded a light yellow solid which was separated by filtration and washed with water (1.05 g, 44%). A solution of this solid in methanolic silver nitrate (1%) gave a colorless precipitate, indicating an amine hydrochloride. An analytical sample recrystallized from methanol had mp 181–186°: ν_{max} 3300, 1710, 1680, 1620, 1595, 1265, 1140, 942, 910, and 710 cm^{-1}. Neutralization with aqueous sodium bicarbonate gave an oil containing three compounds. This mixture was reconvertible to amine hydrochloride by treatment with 10% hydrochloric acid in the manner described above.

Anal. Calcd for $C_{20}H_{22}NO_3Cl$: C, 66.75; H, 6.16; N, 3.89. Found: C, 66.92; H, 6.23; N, 3.91.

A solution of this amine hydrochloride (320 mg, 0.90 mmol) in glacial acetic acid (30 ml) was cooled in an ice bath and activated zinc (3.0 g, 0.046 g-atom) was added. The resulting suspension was stirred vigorously for 20 hr at room temperature. Most of the acetic acid was evaporated *in vacuo* and 10% hydrochloric acid (30 ml) was added. Threefold extraction was carried out with methylene chloride and the organic phase was dried over anhydrous sodium sulfate and evaporated, yielding a yellow oil (241 mg). Distillation of this oil in a Kugelrohr apparatus [100° (0.1 mm)] gave a colorless solid (6 mg) which was collected on a cooled portion of the glass receiver. The crystals, which had mp 85–87°, exhibited ν_{max} 3400, 1690, 1600, 1580, 1320, 1290, 1235, 1105, 762, 753, and 687 cm^{-1}; the mass spectrum (mol wt 136) exhibited major peaks at *m/e* 136, 122, 105, and 77. All obtainable data agreed with those of an authentic sample of α-hydroxyacetophenone (mp 86–87°). A thin layer chromatographic comparison, using two different solvent systems (1% methanol–chloroform and 5% ether–chloroform), confirmed that the product is α-hydroxyacetophenone.

6′-Methoxy-8,9-oxido-7-ketorubane (**4d**).—To a solution of α,β-unsaturated ketone **3d** (1.00 g, 3.40 mmol) in acetonitrile (50 ml) was added 0.44 ml of *tert*-butyl hydroperoxide and four drops of Triton B (35% methanolic). After 20 hr at room temperature, yellowish crystals (466 mg, 45%) formed, which were separated by filtration. Unoxidized starting material was recrystallized from the mother liquor (367 mg). Small amounts of starting material were removed from the pulverized product by leaching with boiling tetrahydrofuran. The resulting colorless powder had mp 159–161°: ν_{max} 1735, 1615, 1590, 1500,

(28) F. H. C. Stewart, *Aust. J. Chem.*, **13**, 478 (1960).

1225, 1023, 993, 860, 845, 817, and 716 cm^{-1}; nmr[29] 0.75–3.9 (multiplet, quinuclidine H), 4.9 (singlet, methoxy H), 5.27 (singlet, HCO), 6.9–7.8 (3 multiplets, aromatic H); mol wt 310 (mass spectrum).

Anal. Calcd for $C_{18}H_{18}N_2O_3$: C, 69.66; H, 5.85; N, 9.03. Found: C, 69.88; H, 5.92; N, 8.91.

5-(6-Methoxy-4-quinolyl)-3,4-(1,4-piperidylidene)-4-hydroxy-2-pyrazoline (13).—A solution of epoxy ketone **4d** (50 mg, 0.16 mmol) and anhydrous hydrazine (0.1 ml) in absolute ethanol (2 ml) was heated at reflux for 2 hr. The solution was diluted with water (5 ml) and extracted three times with methylene chloride. The extracts gave, when dried and evaporated, 53 mg (100%) of a tan solid. This was recrystallized from benzene to give a sample with mp 173–175°: ν_{max} 3310, 1645, 1625, 1535, 1505, 1345, 1255, 1168, 1110, 1035, 865, and 817 cm^{-1}; nmr 1.5–2.0 and 2.4–3.0 (9 H, multiplets, quinuclidine H), 3.87 (3 H, singlet, methoxy H), 4.05 (1 H, singlet, pyrazoline CH), 7.3 (3 H, multiplet quinoline H), 7.97 and 8.73 ppm (2 H, doublets, quinoline H); mol wt 324 (mass spectrum). Attempts to prepare an analytically pure sample caused partial dehydration to the pyrazole **14**.

5-(6-Methoxy-4-quinolyl)-3,4-(1,4-piperidylidene)pyrazole (14).—A solution of epoxy ketone **4d** (50 mg, 0.161 mmol) and anhydrous hydrazine (0.1 ml) in glacial acetic acid (3 ml) was heated at reflux for 2 hr. The solvent was evaporated *in vacuo* and the colorless residue was treated with saturated sodium carbonate solution. Threefold extraction with methylene chloride followed by drying and evaporation of the extract gave 55 mg (100%) of a light brown solid. Recrystallization from methylene chloride–ether gave brownish-white crystals with mp 230–234° (lit.[10c] mp 239–243°). The infrared spectrum and tlc behavior of this product were identical with those of an authentic sample prepared from ketone **3d** by sequential treatment with hydrazine and mercuric acetate.[10c]

2-Phenylmethylenecyclohexanone Oxide (15).—A solution of 2-phenylmethylenecyclohexanone[30] (2.00 g, 0.01 mol) and 30% hydrogen peroxide (1.5 ml) in ethanol (50 ml) was treated with 20% sodium hydroxide solution (1.0 ml) and kept at room temperature for 6 hr. Water was then added slowly until the solution became cloudy. The mixture was refrigerated overnight then filtered to give 1.19 g (56%) of pale yellow needles. Recrystallization from ethanol gave colorless needles with mp 125–126°: ν_{max} 1710, 1600, 1265, 1152, 1130, 1118, 938, 878, 846, 777, and 750 cm^{-1}; nmr 1.4–2.7 (8 H, multiplet, alicyclic H), 4.1 (1 H, singlet, epoxide H), and 7.3 ppm (5 H, singlet, aromatic H); mol wt 202 (mass spectrum).

Anal. Calcd for $C_{13}H_{14}O_2$: C, 77.20; H, 6.98. Found: C, 77.45; H, 7.03.

3,4-Tetramethylene-5-phenylpyrazole (16).—Anhydrous hydrazine (0.6 ml) was added to a solution of epoxy ketone **15** (305 mg) in absolute ethanol (12 ml). The solution was heated at reflux for 2 hr and water was then added slowly with swirling causing the product to precipitate. This was filtered out giving 201 mg (65%) of colorless solid. Recrystallization from ethanol afforded a sample with mp 123–126°: ν_{max} 3150, 1600, 1365, 1263, 1145, 1045, 983, 933, and 768 cm^{-1}; nmr 1.5–1.9 (4 H, multiplet), 2.3–2.8 (4 H, multiplet), and 7.1–7.8 ppm (5 H, multiplet, aromatic H); mol wt 198 (mass spectrum).

Anal. Calcd for $C_{13}H_{14}N_2$: C, 78.75; H, 7.12; N, 14.13. Found: C, 78.93; H, 7.19; N, 14.25.

3-Phenyl-2,3-oxidocyclohexanone (17).—A solution of 3-phenyl-2-cyclohexenone[31] (2.00 g, 0.01 mol) in methanol (30 ml) was treated with 30% hydrogen peroxide (4.0 ml), cooled to 5° and treated dropwise with 4 *N* sodium hydroxide solution (4.0 ml). After stirring for 24 hr, the solution was filtered, diluted with water, and extracted three times with ether. The residue from the dried extract was distilled [125° (2 mm)] giving 502 mg (23%) of a colorless oil which crystallized when chilled. The product had mp 49–50°: ν_{max} 1705, 1485, 1320, 1260, 975, 805, 790, and 750 cm^{-1}; nmr 1.7–2.6 (6 H, multiplet, alicyclic H), 3.26 (1 H, singlet, epoxide H), and 7.35 (5 H, singlet, aromatic H); mol wt 188 (mass spectrum).

Anal. Calcd for $C_{12}H_{12}O_2$: C, 76.57; H, 6.43; O, 17.00. Found: C, 76.36; H, 6.54; O, 17.27.

1-Phenyl-2-cyclohexenol (18).—Anhydrous hydrazine (0.5 ml) was added to a solution of epoxy ketone **17** (250 mg, 1.23 mmol) in absolute ethanol (10 ml) and the solution was heated at reflux for 2 hr. Dilution with water (75 ml) followed by threefold extraction with ether afforded 213 mg (92%) of colorless oil. Distillation [110° (1 mm)] gave a product which crystallized. Recrystallization from Skellysolve B gave a sample with mp 42–43°: ν_{max} 3360, 1600, 1485, 1310, 1080, 1045, 1005, 960, 760, and 736 cm^{-1}; nmr 1.3–2.2 (6 H, multiplet, aliphatic H), 5.5–6.1 (2 H, multiplet, vinyl H), and 6.9–7.6 ppm (5 H, multiplet, aromatic H); mol wt 174 (mass spectrum). This material deteriorated rather quickly at room temperature precluding analysis.

3-Hydroxy-4,5-epoxycholestan-6-one (19).—A solution of 3β-acetoxy-Δ^4-cholesten-6-one[32] (500 mg, 1.25 mmol) in methanol (20 ml) was treated with 5% methanolic sodium hydroxide (1.0 ml) and 30% hydrogen peroxide (0.5 ml). The solution was kept at room temperature for 24 hr and then diluted with water (50 ml) and extracted three times with methylene chloride. Evaporation of the dried extract left 467 mg (91%) of colorless oil which solidified on standing. This product showed ν_{max} 3480, 1715, 1262, 1225, 1175, 1070, 975, 898, 867, 818, and 798 cm^{-1}; nmr 0.6–2.3 (39 H, multiplet), 3.2–3.4 (2 H, multiplet), and 3.6–4.2 (2 H, multiplet); mol wt 416 (mass spectrum).

3β,4β-Dihydroxy-Δ^5-cholestene (20).—Anhydrous hydrazine (0.5 ml) was added to a solution of epoxy ketone **19** (300 mg) in absolute ethanol (10 ml) and the resulting solution was heated at reflux for 2 hr. Water was then added gradually to the solution and the product extracted into methylene chloride. Evaporation of the dried extract left 345 mg of pale yellow solid which showed a single spot on tlc. This product was purified by recrystallization from ethanol. The resulting colorless crystals (140 mg, 48%) had mp 175–176° (lit.[33] mp 174–176°): ν_{max} 3400, 1670, 1070, 1040, 965, 916, 903, 855, 838, and 757 cm^{-1}; nmr 0.7–2.4 (41 H, multiplet), 4.0–4.2 (2 H, multiplet), and 5.65 ppm (1 H, multiplet, vinyl H); mol wt 402 (mass spectrum).

Anal. Calcd for $C_{27}H_{46}O_2$: C, 80.54; H, 11.52. Found: C, 80.46; H, 11.63.

Registry No.—**3b**, 26965-30-0; **3c**, 26965-31-1; **4d**, 27006-04-8; **6a**, 26965-32-2; **6b**, 26965-33-3; **6c**, 26965-34-4; **8**, 26965-35-5; **9**, 26965-36-6; **10**, 27005-95-4; **11**, 26965-37-7; **13**, 26965-38-8; **15**, 13243-58-8; **16**, 27005-96-5; **17**, 27005-97-6; **18**, 26965-40-2; **19**, 20951-85-3; **20**, 17320-10-4.

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(29) This nmr spectrum was recorded with a CAT because of poor solubility and was not integrated.

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