On the Stereochemistry of Conjugate Addition. II. Hydrocyanation of 1-Acetyl-$\Delta^{1,8}$-hydrindene[1,2a]

WALTER L. MEYER AND JAMES F. WOLFE[2b]

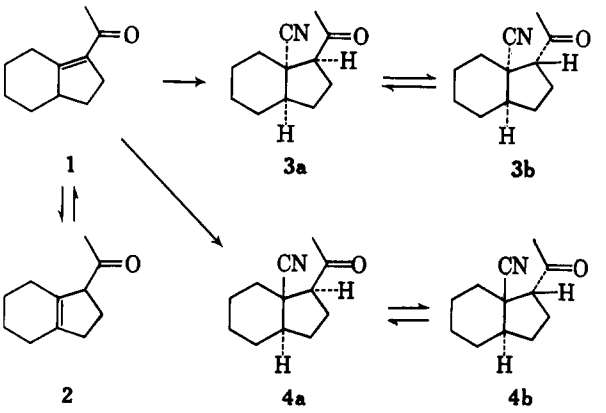
Department of Chemistry, Indiana University, Bloomington, Indiana[2c]

Received July 29, 1963

Reaction of 1-acetyl-$\Delta^{1,8}$-hydrindene (**1**) with potassium cyanide and ammonium chloride in aqueous dimethylformamide produces a mixture of the four racemic 1-acetyl-8-cyanohydrindanes. The *cis*-fused products (**3**) of this kinetically controlled addition predominate over the *trans* isomers (**4**) in a 63:37 ratio. Relative configurations of these products at the ring-junction positions were determined by degradation of two of them to the known *cis*- and *trans*-hydrindane-8-carboxamides, respectively, the degradative sequence involving conversion of the cyano ketones to their C-1 enol acetates, ozonolysis to the 8-cyano-1-hydrindanones, hydrolysis to the corresponding ketoamides, formation of the ethylene thioketals, and Raney nickel desulfurization of the latter. The significance of the observed stereoselectivity of the conjugate addition reaction with respect to steroid synthesis and the mechanism of 1,4-addition of hydrogen cyanide is discussed.

As part of a study of the stereoselectivity of conjugate nucleophilic additions to α,β-unsaturated carbonyl compounds and the utility of such reactions for introduction of angular functional groups in natural product total synthesis,[1] we examined addition of hydrogen cyanide to 1-acetyl-$\Delta^{1,8}$-hydrindene (**1**). This ketone provides an excellent model for the C/D ring system of the 20-keto steroids. Consequently, if it proved possible in this way to introduce an angular cyano group with the correct (*trans*) configuration, due to the synthetic versatility of the nitrile function the technique promised to be of considerable significance in affording a new route to synthesis of various important 18-functional steroids (aldosterone, conessine, etc.) as well as the angularly methylated hormones (progesterone, etc.). The crucial question, of course, was whether the reaction would result in the necessary stereoselectivity at the angular position.

Exposure of the enone[3] **1** to potassium cyanide in aqueous dimethylformamide containing ammonium chloride[4] smoothly produced a mixture of the four racemates[5] of the desired 1-acetyl-8-cyanohydrindane (**3** and **4**).[6] Two of these, a liquid *trans*-fused cyano ketone (**4a** or **4b**) and a crystalline *cis* isomer, m.p. 65–65.5° (**3a** or **3b**), were isolated in pure form by chromatography over Florisil, and a small amount of a third isomer was obtained in approximately 70% purity according to gas–liquid chromatographic (g.l.c.) analysis. The functionality of each cyano ketone was attested by its infrared spectrum, which like that of the crude mixture contained absorption characteristic of nitrile (4.5 μ) and saturated ketone (5.85 μ) but no other functional groups. Further, the n.m.r. spectrum of each pure isomer showed the sharp singlet resonance of an acetyl group (7.83 τ for the oil **4** and 7.72 τ for the solid **3**).



Formation of more than two cyano ketone adducts was not unanticipated, for during conjugate addition a new asymmetric center is introduced not only at the angular C-8 position but also at C-1, and thus there is a possibility of producing a total of four 1-acetyl-8-cyanohydrindanes, two *cis*-fused (**3a** and **3b**) and two *trans*-fused C-1 epimers (**4a** and **4b**). From the standpoint of assessing the stereoselectivity of the conjugate addition reaction, the configurations at C-1 are unimportant, for configurations at that center are determined by protonation of the C-1 enolates (or ketonization of the corresponding enols) and this step follows determination of the angular configuration by attachment of cyanide at C-8. While the cyanide addition step is irreversible under the reaction conditions used, C-1 protonation is reversible, and thus the relative proportions of the two C-1 epimers in each series are determined subsequent to and independent of the cyanide addition.

Gas chromatography of the total reaction product was the method of choice for determination of the ratio of *cis*-fused (**3**) and *trans*-fused (**4**) products from the addition, but before this could be successfully applied it was necessary to relate the two pure isomers, whose ring-fusion configurations were determined by degradation, to the remaining two isomers, which were not readily isolable in pure form. Furthermore, only *three* cyano ketone peaks were present in gas chromatograms of the crude mixture. These represented 6%, 37%, and 56% (±2%) of the total material, and corre-

(1) Part I, W. L. Meyer and N. G. Schnautz, *J. Org. Chem.*, **27**, 2011 (1962).

(2) (a) Abstracted from the Ph.D. dissertation of James F. Wolfe, Indiana University, 1963; (b) U. S. Public Health Service Predoctoral Fellow, 1961–1963; (c) Communication no. 1158.

(3) W. L. Meyer and J. F. Wolfe, *J. Org. Chem.*, **27**, 3263 (1962).

(4) W. Nagata, S. Hirai, H. Itazaki, and K. Takeda, *ibid.*, **26**, 2411 (1961); W. Nagata, T. Terasawa, T. Aoki, and K. Takeda, *Chem. Pharm. Bull.* (Tokyo), **9**, 783 (1961).

(5) All synthetic compounds discussed are *racemic*, although the prefix *dl* is omitted and only one enantiomer of each is depicted in the structural formulas.

(6) Use of aqueous-methanolic potassium cyanide for the hydrocyanation was a considerably less efficient alternative. Under these more basic conditions partial hydrolysis of the nitrile, tautomerization of the starting enone, and other side reactions also occurred, and in addition to cyano ketones the product mixture contained significant amounts of the corresponding ketoamides, the $\Delta^{8,9}$-double bond tautomer (**2**) of the starting ketone, and high-melting products apparently similar to those previously encountered from cyanide additions under analogous conditions; *cf.* ref. 1, 4, and A. Bowers, *J. Org. Chem.*, **26**, 2043 (1961).

sponded in retention times to the cyano ketone obtained in 70% purity by chromatography, the pure crystalline *cis* isomer, and the pure liquid *trans* isomer, respectively. However, to the extent that angular cyanation led to both C-8 configurations, production of all four rather than only three isomers was expected, since inspection of molecular (Dreiding) models did not reveal any apparent steric reason for absence of either C-1 epimer from a C-1 equilibrium mixture in either the *cis* or the *trans* series. Indeed, although the n.m.r. spectrum contained three sharp singlets in the acetyl region (7.72, 7.75, and 7.83 τ), each of them was much more intense than could be accounted for by a 6% component of the mixture. This suggested that all four racemates were in fact present and that the gas chromatographic technique failed to reveal the presence of one of them because its retention time was coincident with that of another on all columns examined.

In order to interrelate the two *cis* and the two *trans* C-1 epimers and also to confirm that the fourth racemate had been present in the initial mixture but was concealed to g.l.c. assay, the two pure isomers were converted to their corresponding C-1 epimeric equilibrium mixtures by treatment with *p*-toluenesulfonic acid in diethylene glycol dimethyl ether at room temperature. Under these conditions each cyano ketone produced a different mixture of only two components according to gas–liquid chromatography, and after 72 hr. the ratios of components became constant. The liquid *trans*-cyano ketone (56% original g.l.c. component) afforded itself and the 6% initial component in a ratio of 86:14 ± 2%, with no trace of the 37% initial component appearing in the chromatogram. The solid *cis*-cyano ketone (the 37% initial component), on the other hand, was converted to a 61:39 ± 2% mixture of itself and a substance with the same retention time as the 56% initial component, no trace of the 6% original component being visible in the chromatogram. These results established three crucial points. First, such acid-catalyzed equilibration does not alter the ring-fusion configuration in addition to that of the side chain, for if it had, both the solid (*cis*) and the liquid (*trans*) cyano ketones would have produced the same equilibrium mixture. Secondly, the minor (6%) cyano ketone in the reaction mixture, like the liquid cyano ketone with which it equilibrates, corresponds to a *trans*-fused structure. Thirdly, the *cis*-fused C-1 epimer of the 65° cyano ketone has the same g.l.c. retention time as does the major *trans*-cyano ketone, and it is distinctly possible that the 56% peak in the crude cyano ketone mixture represents both of these products.

With these results in hand, the ratio of *cis*-fused and *trans*-fused products could be ascertained by subjecting the crude conjugate addition product mixture to acid-catalyzed side-chain equilibration followed by g.l.c. analysis, for it had been established that under these conditions no interconversion of ring-fusion isomers occurred. After such treatment the ratio of areas of the three g.l.c. peaks due to the four cyano ketones was 9:40:51% ± 2%. Combination of this result with the previously determined equilibrium ratios of the *cis*- and the *trans*-fused epimers shows that the ratio of total *cis*- to total *trans*-locked compounds is 63:37 ± 4%. Consideration of the relative intensities of the 4 acetyl proton resonances in the n.m.r. spectrum of the crude product leads to exactly the same result.

This ratio is clearly the result of kinetically controlled attack of cyanide ion on the enone **1** rather than a subsequent equilibration of the ring-fusion stereoisomers by reversal of the addition reaction,[4] for treatment of either the pure *cis*- or the pure *trans*-cyano ketone with potassium cyanide and ammonium chloride under conditions of the reaction produces C-1 epimerization but *no* interconversion of *cis* and *trans* isomers. Whether the selectivity results from "steric approach control" or "product development control"[7] is not clear, however, for it is difficult to assess the structural factors involved in terms of the small energy difference (0.5 kcal.) between the two transition states. It does appear that approach of cyanide ion from that side of the enone **1** which leads to a *trans*-fused product is somewhat more hindered (particularly by the axial hydrogens at C-4 and C-6) than is approach from the other side. It seems that stereoelectronic effects resulting from efficient overlap between the developing carbon–cyanide bond and the enolate π-system[1,4] might not be so significant in this instance as they probably are with endocyclic enones like $\Delta^{1,9}$-2-octalone, for the exocyclic location of the developing enolate allows nearly as efficient overlap in the transition state leading to the *cis*-fused product as in that leading to the *trans* isomer, so far as one can judge from models. Neither transition state appears to suffer exceptional crowding in order to attain such orbital overlap, but that leading to the *trans* adduct may be of slightly higher energy due to deformation of the five-membered ring and eclipsing of the acetyl group with the equatorial C-7 hydrogen.

From the standpoint of steroid synthesis, the stereochemical result of this cyanide addition is of considerable interest, for although the *trans*-fused isomer is the minor product of the reaction, it is formed in sufficient quantity to make the process synthetically practical. Indeed, since this work was initiated, two laboratories have utilized such an approach to steroid total synthesis, syntheses of 3-hydrox-19-norpregna-1,3,5(10)-trien-20-one,[8a] conessine,[8b,9] progesterone,[10] 5α-pregnan-3β-ol-20-one,[8b] and latifoline[8b] having thus far appeared. The steric results of addition of cyanide to the tetracyclic analogs of **1** used in those programs were quite similar to those we have observed, yields of *cis*-fused products exceeding[8] or approximately equalling[9] those of the *trans* forms when similar reaction conditions were used.[11] However, at least in the bicyclic series the reaction can in practice be made completely stereospecific in either desired sense, for we have found that exposure of either cyano ketone (**3** or **4**) to sodium methoxide reverses the addition, giving a mixture of the starting enone **1** and its

(7) W. G. Dauben, G. J. Fonken, and D. S. Noyce, *J. Am. Chem. Soc.*, **78**, 2579 (1956).

(8)(a) W. Nagata, I. Kikkawa, and K. Takeda, *Chem. Pharm. Bull.* (Tokyo), **9**, 79 (1961); (b) W. Nagata, T. Terasawa, and T. Aoki, *Tetrahedron Letters*, 865, 869 (1963).

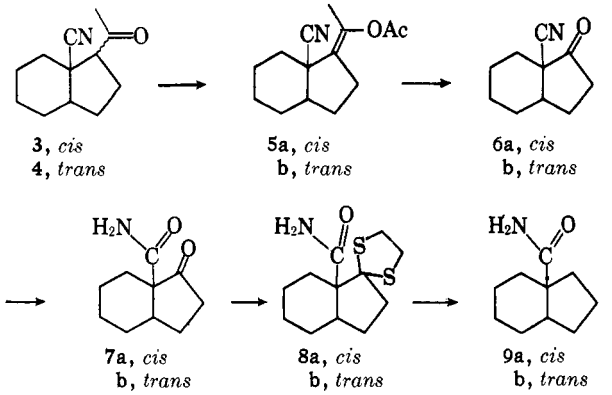
(9) J. A. Marshall and W. S. Johnson, *J. Am. Chem. Soc.*, **84**, 1485 (1962).

(10) W. S. Johnson, J. F. W. Keana, and J. A. Marshall, *Tetrahedron Letters*, 193 (1963).

(11) See W. Nagata, M. Yoshioka, and S. Hirai, *ibid.*, 461 (1962), and ref. 8b for quite different conditions which lead predominantly to a *trans* product.

$\Delta^{8,9}$ tautomer 2. Elimination of hydrogen cyanide to form the conjugated ketone is more rapid under these conditions than is the equilibration of the acetylhydrindenes (1 and 2), because after 12 hr. at room temperature no cyano ketone remained but the two enones were present in a 43:57 ratio (conjugated–nonjugated) compared with the equilibrium ratio of 20:80.[3] Presumably suitable conditions of basicity could thus be found for conversion of the undesired *cis* adduct (corresponding to **3**) only to the starting enone (corresponding to **1**) and this could be recycled. Marshall and Johnson[9] achieved a similar regeneration of enone in a tetracyclic series by heating the corresponding *cis*-fused adduct.

Configurations of the 1-Acetyl-8-cyanohydrindanes. —In order to ascertain which 1-acetyl-8-cyanohydrindane possessed the *trans* fusion and which the *cis*, both were degraded to the corresponding hydrindane-8-carboxamides of known configuration. On treatment with acetic anhydride and *p*-toluenesulfonic acid,[12] each cyano ketone (**3** and **4**) was converted to a corresponding enol acetate (**5a** and **5b**, respectively). That these were indeed tetrasubstituted olefinic derivatives was apparent from the absence of vinyl proton resonance from their n.m.r. spectra, but to which of the geometric isomers about the double bond they correspond is not known. In each case, however, g.l.c. showed only one product peak, and the n.m.r. spectrum had only one strong acetyl proton resonance and one strong allylic methyl proton resonance, suggesting the presence of a significant amount of only one isomer. The conditions of enol acetylation were rather vigorous, but the original ring-junction configuration must have been retained in each instance, for when each isomeric cyano ketone was heated at 140–150° in diethylene glycol dimethyl ether with *p*-toluenesulfonic acid, conditions of temperature and acidity equivalent to those of enol acetylation, only side-chain epimerization occurred. Further, although the two enol acetates were but poorly resolved by gas chromatography and had similar infrared spectra, ozonolysis of each provided a distinctly different 8-cyano-1-hydrindanone, the solid 1-acetyl-8-cyanohydrindane (**3**) leading to a crystalline cyanohydrindanone (**6a**), m.p. 75–76°, and the liquid acetylcyanohydrindane (**4**) affording an oily derivative (**6b**). These two cyanohydrindanones were well resolved by gas chromatography, and neither was contaminated by its isomer, even in the crude ozonolysis product.



3, *cis*; **4**, *trans* — **5a**, *cis*; **b**, *trans* — **6a**, *cis*; **b**, *trans*

7a, *cis*; **b**, *trans* — **8a**, *cis*; **b**, *trans* — **9a**, *cis*; **b**, *trans*

With the intent of removing the nuclear carbonyl group, the solid (**6a**) and liquid (**6b**) cyanohydrindanones were converted to the corresponding thioketals, m.p. 137–139° and 88–90°, respectively. Attempted desulfurizations with W-2 Raney nickel were hampered by concomitant reduction of the nitrile function, however, and use of deactivated nickel[13] produced considerable amounts of carbonyl-containing by-products. Attempted Clemmensen reduction[14] of the crystalline cyano hydrindanone resulted in formation of a complex mixture, and the method was not explored in the other series.

Since the strongly basic conditions of the Wolff–Kishner reduction rendered its use inadvisable because the angular nitrile might have been saponified and decarboxylatively lost or the β-ketonitrile system might have undergone reverse Claisen ring opening, further efforts to remove the ketone were preceded by conversion of the nitrile to a group more stable toward reduction. The cyano groups of the cyanothioketals were unaltered by attempted alkaline hydrolysis, no doubt for steric reasons, but the cyanohydrindanones (**6a** and **6b**) themselves were readily converted by concentrated sulfuric acid at 80° [15] to the corresponding 1-hydrindanone-8-carboxamides, **7a** (m.p. 129–130.5°) and **7b** (m.p. 178–179.5°), respectively. Infrared spectra and thin layer chromatograms of these derivatives showed them to be different and uncontaminated by one another. The keto amides (**7a** and **7b**) were readily transformed[16] into their thioketals, **8a** (m.p. 223–224°) and **8b** (m.p. 148–149°), which were smoothly desulfurized by Raney nickel to the respective hydrindane-8-carboxamides, **9a** and **9b**. Like the other intermediates in the degradation, these products were clearly different and uncontaminated by each other as demonstrated by infrared spectroscopy and gas and thin layer chromatography.

The hydrindane-8-carboxamide with m.p. 114–115° (**9a**) was identical in all respects with a sample of the authentic *cis* amide.[17] Infrared spectra (chloroform solution) of the two samples were superimposable, and a mixture melting point was undepressed, although admixture with the *trans* amide produced a depression of some 20° in melting point. Since this amide was derived from the crystalline 1-acetyl-8-cyanohydrindane (**3**) and no step in the degradation altered the ring-fusion configuration, that cyano ketone and all of its progeny (**5**–**9a**) have the *cis* configuration. The liquid 1-acetyl-8-cyanohydrindane (**4**) and its derivatives (**5**–**9b**) accordingly are in the *trans*-fused series. The latter conclusion is substantiated by identity of the thence-derived hydrindane-8-carboxamide (**9b**), m.p. 123.5–125°, with the authentic *trans* isomer.[18]

(12) C. W. Marshall, T. H. Kritchevsky, S. Lieberman, and T. F. Gallagher, *J. Am. Chem. Soc.*, **70**, 1837 (1948).

(13) G. B. Spero and A. W. McIntosh, *ibid.*, **70**, 1907 (1948).

(14) R. D. Haworth, B. G. Hutley, R. G. Leach, and G. Rogers, *J. Chem. Soc.*, 2720 (1962).

(15) L. T. Tsai, T. Miva, and M. S. Newman, *J. Am. Chem. Soc.*, **79**, 2530 (1957).

(16) L. F. Fieser, *ibid.*, **76**, 1945 (1954).

(17) W. G. Dauben, J. W. MacFarland, and J. B. Rogan, *J. Org. Chem.*, **26**, 297 (1961). We are grateful to Professor Dauben for samples of the two amides with which ours were compared.

(18) W. G. Dauben, unpublished work.

Experimental[19]

Addition of Potassium Cyanide to 1-Acetyl-$\Delta^{1,8}$-hydrindene.—To a 3.99-g. (0.0243 mole) sample of 1-acetyl-$\Delta^{1,8}$-hydrindene (**1**),[3] b.p. 102° at 8 mm. (90% pure by g.l.c., contaminated only by the β,γ-unsaturated isomer **2**), in 60 ml. of dimethylformamide was added a solution of 3.20 g. (0.0492 mole) of potassium cyanide and 1.98 g. (0.0370 mole) of ammonium chloride in 20 ml. of water.[4] The resulting cloudy solution was stirred at 100° for 6 hr.,[20] during which time aliquots were analyzed by gas chromatography. The reaction mixture was concentrated *in vacuo* to approximately one-fourth of its original volume and poured into 200 ml. of water which was extracted with methylene chloride. The extracts were dried over sodium sulfate and concentrated to afford 4.30 g. (92% as $C_{12}H_{17}NO$) of crude products as a dark red oil; λ_{max}^{film} 4.5 and 5.85 μ; n.m.r. (CCl_4), 7.72 (s), 7.75 (s), 7.78 (s, very small), and 7.83 τ (s). The intensities of the acetyl resonances were in the ratio 37:30:32 if the 7.78-τ peak is excluded and 36:29:4:31 if it is included.

Gas chromatograms (Z, 200°) of the crude product mixture showed three peaks which represented, in order of elution from the column, 6% (peak A), 37% (peak B), and 56% (peak C) ± 2% of the total material (average of four preparations). The entire unrefined sample was chromatographed on 120 g. of Florisil. Elution with 1 l. of benzene–cyclohexane (7:3 through 4:1) furnished 1.216 g. (26%) of crude 1-acetyl-8-cyano-*cis*-hydrindane (**3**), m.p. 60–65°, the 35% component (g.l.c. peak B). Further elution with 1.4 l. of pure benzene afforded 1.053 g. (23%) of intermediate (mixed) fractions, g.l.c. of which showed approximately 40% of peak B and 60% of peak C (these fractions appear to be mainly a mixture of the two *cis* adducts **3a** and **3b**). Elution with 1.6 l. of benzene–ether (9:1) yielded 1.375 g. (30%) of 1-acetyl-8-cyano-*trans*-hydrindane (**4**, g.l.c. peak C) as a colorless oil; $\lambda_{max}^{CHCl_3}$ 4.5 and 5.85 μ; b.p. 120° (oil bath) at 1.5 mm.; $n^{27}D$ 1.4919; n.m.r. ($CDCl_3$), 7.83 τ (s).

Anal. Calcd. for $C_{12}H_{17}NO$: C, 75.35; H, 8.96; N, 7.32. Found: C, 75.0; H, 8.8; N, 7.4.

Recrystallization of the combined fractions of the solid isomer from petroleum ether (b.p. 30–60°) afforded 1.150 g. (25%) of the pure *cis* adduct (**3**) as stout prisms, m.p. 65–65.5°; $\lambda_{max}^{CHCl_3}$ 4.5 and 5.85 μ; n.m.r. ($CDCl_3$), 7.72 τ (s).

Anal. Calcd. for $C_{12}H_{17}NO$: C, 75.35; H, 8.96; N, 7.32. Found: C, 75.4; H, 8.8; N, 7.6.

Rechromatography of the mother liquors from recrystallization of **3** and the mixed fractions obtained from the first chromatogram resulted in isolation of 55 mg. of an oily fraction rich (70% by g.l.c.) in the 7% component (g.l.c. peak A) which had λ_{max}^{film} 4.5 and 5.85 μ. However, for the most part the intermediate fractions from the first chromatography were not resolved but were eluted from the column together in approximately the same 1.5:1 ratio. Chromatography on neutral activity I alumina resulted in no better separation of components.

The total isolated yield of *cis* ketonitrile (**3**) was 25% while the yield of *trans* product (**4**) was 30%. The intermediate fractions, consisting primarily of the two *cis* isomers **3a** and **3b**, amounted to 1.119 g. (24%). The total yield of adducts amounted to 3.644 g. (79%).

Acid-Catalyzed Equilibration of Cyano Ketones 3, 4, and a Crude Cyanation Reaction Mixture. Determination of the Ratio of Total *cis* and *trans* Adducts. A.—A mixture of 26.0 mg. (0.136 mmole) of *cis* ketone **3**, m.p. 64–65° (g.l.c. peak B) and 23 mg. (0.136 mmole) of *p*-toluenesulfonic acid in 2 ml. of diethylene glycol dimethyl ether was allowed to stand at room temperature under a nitrogen atmosphere. Aliquots were examined by gas chromatography at 6-hr. intervals for the first 24 hr. and at 12-hr. intervals thereafter for a period of 192 hr. After 72 hr. the mixture had come to equilibrium, g.l.c. showing 61 ± 2% of peak B and 39 ± 2% of peak C.

B.—A 24-mg. sample of the oily *trans* ketone **4** (chromatographed and pure by g.l.c., peak C) was added to a solution of 22 mg. (0.125 mmole) of *p*-toluenesulfonic acid in 2 ml. of diethylene glycol dimethyl ether. Aliquots were analyzed as in A and after 72 hr. equilibrium had been attained, g.l.c. showing 86 ± 2% of peak C and 14 ± 2% of peak A.

C.—A 172-mg. sample of the crude conjugate addition product mixture, g.l.c. of which showed 6 ± 2% of peak A, 37 ± 2% of peak B, and 57 ± 2% of peak C, was added to 8 ml. of diethylene glycol dimethyl ether containing 155 mg. of *p*-toluenesulfonic acid. After 72 hr. at room temperature the ratios of isomers ceased to change and equilibrium was attained with g.l.c. showing 9 ± 2% of peak A, 40 ± 2% of peak B, and 51 ± 2% of peak C. On the basis of this equilibria the ratio of total *cis*-(**3a** and **3b**) to total *trans*-1-acetyl-8-cyanohydrindanes (**4a** and **4b**) in the crude reaction mixture was calculated to be 1.7 ± 0.3 to 1.

Treatment of Acetylcyanohydrindanes 3 and 4 with Sodium Methoxide. A.—A 36-mg. sample of *cis*-cyano ketone **3** was allowed to stand at room temperature with 3 ml. of 1 *N* methanolic sodium methoxide. After 24 hr. a gas chromatogram (Z, 200°) of the reaction mixture showed the presence of two peaks corresponding to 43% of 1-acetyl-$\Delta^{1,8}$-hydrindene (**1**) and 57% of 1-acetyl-$\Delta^{8,9}$-hydrindene (**2**) but no residual cyano ketone. After 48 hr. the 4 to 1 equilibrium mixture of enones **2** and **1** was obtained.

B.—A 44-mg. sample of pure (g.l.c.) *trans*-cyano ketone **4** was treated with 4 ml. of 1 *N* sodium methoxide solution as in A. After 24 hr. an identical mixture of enones **1** (43%) and **2** (57%) was obtained, and after 48 hr. the equilibrium mixture of the enones **1** and **2** was observed by g.l.c.

Treatment of Acetylcyanohydrindanes 3 and 4 with Potassium Cyanide and Ammonium Chloride. A.—A 27.7-mg. (0.145 mmole) sample of the pure *cis* adduct (**3**), m.p. 64–65° (g.l.c. peak B), 9.0 mg. (0.145 mmole) of potassium cyanide, and 4.0 mg. (0.075 mmole) of ammonium chloride in 0.5 ml. of dimethylformamide and 0.2 ml. of water was heated at 100° for 24 hr. Gas chromatographic analysis (Z, 200°) of the crude reaction mixture showed the presence of both *cis*-fused C-1 epimers in a 65:35 ratio (peak B–peak C) but no *trans* isomer (peak A).

B.—A mixture consisting of 42.6 mg. (0.22 mmole) of the pure (g.l.c. peak C) *trans*-cyano ketone (**4**), 14 mg. (0.21 mmole) of potassium cyanide, and 6.0 mg. (0.11 mmole) of ammonium chloride in 0.5 ml. of dimethylformamide and 0.2 ml. of water was heated at 100° under a nitrogen atmosphere for a total of 24 hr. A gas chromatogram (Z, 200°) of an aliquot of the reaction mixture after this time showed the presence of both *trans*-fused C-1 epimers in a 10:90 ratio (peak A–peak C) but no *cis* isomer (peak B).

Enol Acetate of 1-Acetyl-8-cyano-*cis*-hydrindane (5a).—A solution of 880 mg. (0.0046 mole) of 1-acetyl-8-cyano-*cis*-hydrindane (**3**), m.p. 65–66°, and 790 mg. (0.0046 mole) of *p*-toluenesulfonic acid in 155 ml. of acetic anhydride[12] was distilled over a period of 7 hr. The residue was diluted with water and extracted into ether. Concentration of the ether extracts yielded 1.07 g. of the crude *cis*-enol acetate as a dark viscous oil; $\lambda_{max}^{CHCl_3}$ 4.5, 5.7, 5.85 (weak) and 6.0 μ; n.m.r. ($CDCl_3$), 7.87 (s), 8.16 τ (poorly resolved triplet, $J < 1$ c.p.s., probably long range). The unrefined product had a gas chromatogram (Z, 225°) similar to that of the *trans*-enol acetate, and a mixture of *cis*- and *trans*-enol acetates was poorly resolved. Subsequent experiments demonstrated their nonidentity.

Enol Acetate of 1-Acetyl-8-cyano-*trans*-hydrindane (5b).—A solution of 870 mg. (0.00455 mole) of 1-acetyl-8-cyano-*trans*-hydrindane (**4**, pure by g.l.c.) and 780 mg. (0.00455 mole) of *p*-toluenesulfonic acid in 90 ml. of acetic anhydride was distilled slowly[12] at 150–160° until approximately 10 ml. of acetic anhydride remained (11 hr.). The residue was cooled, poured into 100 ml. of ice–water, and the resulting solution was extracted with ether. The extracts were washed with 5% sodium hydroxide solution and water and dried over sodium sulfate. Removal of

(19) Infrared spectra were obtained on Perkin-Elmer Models 21, 137, and 137G spectrophotometers, ultraviolet spectra were taken using a Cary Model 14 ultraviolet spectrophotometer, and n.m.r. spectra were obtained from dilute solutions with tetramethylsilane as internal standard using a Varian A-60 spectrometer or a Varian DP-60 spectrometer operating at 60 Mc. and equipped with a Model 3506 flux stabilizer. Band positions in DP-60 spectra were determined by the audio sideband technique. Chemical shifts are expressed in τ-units, the designation (s) indicating a singlet resonance. Gas–liquid chromatograms (g.l.c.) were run on a Perkin-Elmer Model 154D vapor fractometer with helium as the carrier gas and a thermal conductivity detector or on an F & M Model 609 chromatograph using nitrogen as the carrier gas with a hydrogen flame ionization detector. A 2-m. 20% Apiezon L grease column, designated Q, or a 2-m. 9% silicone gum (SE30) on Chromosorb W column, designated Z, was employed. Compositions of mixtures were estimated as the ratios of peak areas, *cf.* M. Dimbat, P. E. Porter, and F. H. Stross, *Anal. Chem.*, **28**, 290 (1956). That the isomeric acetylcyanohydrindanes indeed gave identical detector responses was confirmed with known mixtures. Melting points (microscope hot stage) are corrected for stem exposure. Boiling points are uncorrected. Microanalyses were by Alfred Bernhardt, Mulheim (Ruhr), Germany.

(20) Reaction times up to 14 hr. at 100° did not change the ratio of products appreciably but resulted in formation of some polymeric material which was not characterized.

the ether afforded 929 mg. of crude *trans*-enol acetate as a dark red oil; $\lambda_{max}^{CHCl_3}$ 4.5, 5.7, 5.8 (weak) and 6.0 μ; n.m.r. ($CDCl_3$), 7.87 (s), 8.13 τ (poorly resolved triplet, $J < 1$ c.p.s., probably long range). The gas chromatogram (Z, 225°) had a single major peak less volatile than starting material which was also present as a minor contaminant.

8-Cyano-*cis*-1-hydrindanone (6a).—The 1.07-g. sample of crude *cis*-enol acetate (**5a**) prepared before was dissolved in 75 ml. of methylene chloride and treated with excess ozone at −75°. The reaction mixture was allowed to warm to room temperature, 10 ml. of acetic acid, 5 ml. of water, and 1.5 g. of powdered zinc were added, and the resulting heterogeneous mixture was refluxed for 4 hr. The zinc was removed by filtration and the methylene chloride was washed with sodium bicarbonate solution and water. Evaporation of the solvent after drying over sodium sulfate afforded an orange oil which was chromatographed on 30 g. of Florisil. Elution with benzene–cyclohexane (4:1), benzene, and benzene–ether (9:1) afforded 286 mg. of crystalline material, m.p. 70–73°. After repeated recrystallization from hexane, 200 mg. (38% from **3**) of the *cis* ketone (**6a**) was obtained as colorless needles, m.p. 75–76°, $\lambda_{max}^{CHCl_3}$ 4.5 and 5.75 μ.

Anal. Calcd. for $C_{10}H_{13}NO$: C, 73.59; H, 8.03; N, 8.58. Found: C, 73.7; H, 7.8; N, 8.6.

The gas chromatogram of the crude material showed it to be completely without contamination by the *trans* isomer.

The *cis* ketone was converted to its thioketal as in the case of the *trans* isomer. Recrystallization from methanol afforded the analytical sample, m.p. 137–139°, $\lambda_{max}^{CHCl_3}$ 4.5 μ.

Anal. Calcd. for $C_{12}H_{17}NS_2$: C, 60.24; H, 7.16; N, 5.85; S, 26.75. Found: C, 60.1; H, 7.0; N, 6.3; S, 26.4.

8-Cyano-*trans*-1-hydrindanone (6b).—The entire 929-mg. sample of crude *trans*-enol acetate (**5b**) prepared as described before was dissolved in 60 ml. of methylene chloride and treated with excess ozone at −75°. The ozonide was decomposed as in the preceding experiment with 10 ml. of acetic acid, 5 ml. of water, and 1.5 g. of powdered zinc. Filtration and concentration of the methylene chloride resulted in isolation of a dark viscous oil which was chromatographed on 20 g. of Florisil. Elution with benzene–cyclohexane (7:3) and benzene furnished 176 mg. (24% from **4**) of the desired *trans* ketone (**6b**) as a colorless oil, $\lambda_{max}^{CHCl_3}$ 4.5 and 5.75 μ. The gas chromatogram (Z, 225°) was indicative of a single product.

Reaction of **6b** with 1,2-ethanedithiol and boron trifluoride etherate in acetic acid[16] afforded the expected 8-cyano-1,1-ethylenedithio-*trans*-hydrindane as colorless prisms from methanol, m.p. 88–90°, $\lambda_{max}^{CHCl_3}$ 4.5 μ.

Anal. Calcd. for $C_{12}H_{17}NS_2$: C, 60.21; H, 7.16; N, 5.85; S, 26.75. Found: C, 60.4; H, 7.3; N, 5.95; S, 26.5.

***cis*-1-Hydrindanone-8-carboxamide (7a).**—A solution of 146 mg. (0.895 mmole) of 8-cyano-*cis*-1-hydrindanone (**6a**), m.p. 74–76°, in 0.4 ml. of concentrated sulfuric acid was heated at 80–90° for 2 hr. under nitrogen.[15] The resulting dark red solution was poured into 5 ml. of cold water and the crude keto amide was extracted with methylene chloride. The extracts were washed with sodium bicarbonate and water, dried over sodium sulfate, and concentrated to furnish 128 mg. of crude yellow crystals, m.p. 129–130°. Repeated recrystallization from cyclohexane–ethyl acetate yielded 108 mg. (67%) of *cis*-keto amide (**7a**), m.p. 129–130.5°; $\lambda_{max}^{CHCl_3}$ 2.85, 2.95, 5.8, 6.0, and 6.3 μ.

Anal. Calcd. for $C_{10}H_{15}NO_2$: C, 66.27; H, 8.34; N, 7.73. Found: C, 66.3; H, 8.4; N, 8.0.

***trans*-1-Hydrindanone-8-carboxamide (7b).**—A 123-mg. (0.755 mmole) sample of the liquid 8-cyano-*trans*-1-hydrindanone (**6b**) was heated with 0.4 ml. of concentrated sulfuric acid at 80° for 2 hr. under a nitrogen atmosphere.[15] The acid solution was poured into 5 ml. of cold water and the resulting cloudy solution was extracted with methylene chloride. Washing of the extracts with sodium bicarbonate solution and water was followed by drying over sodium sulfate and removal of the solvent. The 95 mg. of light yellow crystals, m.p. 167–175°, thus obtained was recrystallized from cyclohexane–ethyl acetate to afford 68 mg. (50%) of the desired *trans*-keto amide (**7b**), m.p. 178–179.5°; $\lambda_{max}^{CHCl_3}$ 2.85, 2.95, 5.80, 6.0, and 6.3 μ.

Anal. Calcd. for $C_{10}H_{15}NO_2$: C, 66.27; H, 8.34; N, 7.73. Found: C, 66.2; H, 8.4; N, 8.2.

Gas chromatographic analysis (Z, 225°) of the *cis*- and *trans*-keto amides failed. However, they were well resolved by thin layer chromatography which with solution infrared spectra established their nonidentity. The same methods showed neither isomer to be contaminated by the other even in the crude state.

8-Carboxamido-1,1-ethylenedithio-*cis*-hydrindane (8a).—A solution consisting of 86.9 mg. (0.480 mmole) of *cis*-1-hydrindanone-8-carboxamide (**7a**), m.p. 148–150°, 0.75 ml. of glacial acetic acid, 0.2 ml. of 1,2-ethanedithiol, and 0.2 ml. of boron fluoride etherate[16] was allowed to stand at room temperature for 25 hr. The reaction mixture was poured into 5 ml. of water and the thioketal was extracted with methylene chloride. The extracts were washed with sodium bicarbonate solution and water, and dried over sodium sulfate. Evaporation of the solvent resulted in isolation of 130 mg. of a colorless solid, m.p. 222–223°. Recrystallization from methanol gave 93 mg. (72%) of the *cis* thioketal (**8a**) as colorless prisms, m.p. 223–224°; λ_{max}^{KBr} 2.92, 3.04 (weak), 3.16, 6.0, and 6.24 μ.

Anal. Calcd. for $C_{12}H_{19}NOS_2$: C, 56.02; H, 7.44; N, 5.44; S, 24.88. Found: C, 55.8; H, 7.3; N, 5.5; S, 24.7.

8-Carboxamido-1,1-ethylenedithio-*trans*-hydrindane (8b).—Reaction conditions and isolation were similar to those used with the *cis*-keto amide. Reaction of a 38.6 mg. (0.213 mmole) sample of *trans*-1-hydrindanone-8-carboxamide (**7a**), m.p. 178–179°, in 0.4 ml. of glacial acetic acid with 0.1 ml. of 1,2-ethanedithiol and 0.1 ml. of boron fluoride etherate yielded 48 mg. of crude thioketal, m.p. 146–155°. Recrystallization from cyclohexane afforded 36 mg. (65%) of pure *trans* thioketal (**8b**) as colorless prisms, m.p. 148–149°; $\lambda_{max}^{CHCl_3}$ 2.82, 2.92, 6.0, and 6.31 μ.

Anal. Calcd. for $C_{12}H_{19}NOS_2$: C, 56.02; H, 7.44; N, 5.44; S, 24.88. Found: C, 56.1; H, 7.3; N, 5.5; S, 24.7.

Nonsuperimposable infrared spectra (KBr mull) and thin layer chromatography established the nonidentity of the isomeric thioketals.

***cis*-Hydrindane-8-carboxamide (9a).**—A mixture of 53 mg. (0.206 mmole) of 8-carboxamido-1,1-ethylenedithio-*cis*-hydrindane, m.p. 222–223°, and 0.75 g. of Raney nickel in 10 ml. of absolute ethanol was refluxed gently for 20 hr. Evaporation of the ethanol after repeated washing of the nickel resulted in isolation of 30 mg. of crude white crystalline solid, m.p. 110–112°. Repeated recrystallization from *n*-hexane afforded 21.6 mg. (63%) of pure *cis* amide (**9a**) as colorless needles, m.p. 114–115° (lit.[17] 111–112°); $\lambda_{max}^{CHCl_3}$ 2.82, 2.92, 6.0, and 6.32 μ. A mixture melting point with an authentic sample of *cis* amide[17] was undepressed. However, on admixture with the *trans* amide (**9b**), the melting point was depressed more than 20°. The solution infrared spectrum of **9a** was identical with that of the authentic sample of *cis* amide. A mixture of the crude *cis* and *trans* amides was resolved by gas chromatography (Z, 225°) and thin layer chromatography on silica gel. Examination of each amide in the crude state by the same methods provided their nonintercontamination.

***trans*-Hydrindane-8-carboxamide (9b).**—A mixture consisting of 25 mg. (0.097 mmole) of 8-carboxamido-1,1-ethylenedithio-*trans*-hydrindane, m.p. 148–149°, 0.5 g. of Raney nickel, and 3 ml. of absolute ethanol was refluxed for 17 hr. The reaction mixture was cooled and the Raney nickel was removed by centrifugation and washed with 50 ml. of hot absolute ethanol. The ethanol was evaporated *in vacuo* and the solid residue was dissolved in ether. The ether solution was centrifuged to remove turbidity and evaporated to dryness to afford 13.6 mg. of crude *trans* amide (**9b**), m.p. 118–126°. Four recrystallizations from *n*-hexane yielded 7.0 mg. (43%) of pure amide as colorless prisms, m.p. 123.5–125°[21] (reported[18] 123–124°); $\lambda_{max}^{CHCl_3}$ 2.82, 2.92, 6.0, and 6.32 μ. The gas chromatogram (Z, 225°) had a single peak and a thin layer chromatogram on silica gel G showed a single spot when developed with iodine. No melting point depression was observed on admixture with an authentic sample.[18] The infrared spectrum of a chloroform solution was identical in every respect with that of the authentic amide.

Acknowledgment.—We thank the National Science Foundation for a grant (G-18744) which supported this work and the Division of General Medical Sciences, U. S. Public Health Service, for a predoctoral fellowship for J. F. W.

(21) Melting of this material, as well as Professor Dauben's sample, was characterized by softening of the original rather poorly defined crystals at 114–115° with the rapid formation of sharp prisms which then melted at 123.5–125°.