Experimental

The pure *cis*- and *trans*-4-*t*-butylcyclohexanecarbonitriles used in this study were prepared by phosphorus pentoxide dehydration of the corresponding amides.[18] The experimental procedures and properties of these materials have been reported elsewhere.[19]

Equilibration of the Nitriles.—Stock base solutions were prepared by dissolving sublimed potassium *t*-butoxide (MSA Research Corp.) in *t*-butyl alcohol which had been dried by distillation from Linde Molecular Sieves, type 4A.

The appropriate amount of either *cis*- or *trans*-4-*t*-butylcyclohexanecarbonitrile then was added to this stock base, so that the final solution was 1.0 *M* in potassium *t*-butoxide and 0.30 *M* in nitrile. Aliquots (2 ml.) of this solution in sealed Pyrex tubes were placed in the constant temperature baths, and removed after equilibrium had been established. The time required for equilibration was determined by prior kinetic experiments under the same conditions.

The samples from the equilibration at 25° were quenched by pouring into water. The higher temperature sealed tubes were cooled by immersion in Dry Ice–acetone before the contents were poured into water. The aqueous solution was extracted three times with pentane, and the pentane was washed with water and evaporated on a steam bath. The residual nitrile (high recovery) was used directly for analysis.

Equilibrium was attained from each isomer at each temperature, and the individual constants shown in Table I are based on eight to fifteen determinations.

Analysis of Isomer Distribution.—The *cis*- and *trans*-4-*t*-butylcyclohexanecarbonitriles were easily separable by vapor phase chromatography; a 20-ft., $^1/_4$-in. diethylene glycol succinate polyester column used at 150°, 20 p.s.i., gave complete peak separation. Relative areas were determined by planimetry. No correction factor was necessary for calculation of the equilibrium constants, as shown by measurement of a known mixture prepared from weighed samples of the pure nitriles.

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α-Carbon Isomerization in Amide Dehydrations[1]

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Received June 22, 1962

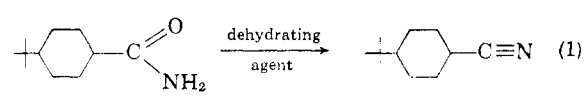
The extent of α-carbon isomerization in the dehydration of *cis*- and *trans*-4-*t*-butylcyclohexanecarboxamide has been determined, using phosphorus pentoxide, thionyl chloride, and phosphorus oxychloride as the dehydrating agents. No detectable isomerization was observed with the first two reagents, but some isomerization occurred with phosphorus oxychloride.

Although many dehydrating agents have been employed for the conversion of amides to nitriles, no investigations have been reported which allow a precise determination of the extent of isomerization of the α-carbon atom. Reagents which have been used include phosphorus pentoxide,[3] phosphorus oxychloride,[4] thionyl chloride,[5] phosphorus pentachloride,[6] sulfamic acid,[7] aluminum chloride,[8] and various organosulfonyl chlorides.[9] Of these reagents, the first three mentioned are the most commonly used, and these were employed in the present study.

Kenyon and Ross[10] examined the phosphorus pentoxide dehydration of optically active 2-methyl-3-phenylpropanamide to the corresponding nitrile, and their results indicated that no extensive racemization occurred during this process. Although the acid obtained on hydrolysis of the nitrile had essentially the same rotation as the material from which the amide was prepared, the amide had been recrystallized, and the possibility of optical fractionation at this step cannot be excluded.

Preparations of optically active nitriles by amide dehydration have recently been reported by Cram and coworkers[11–13]; the rotational values obtained were higher with phosphorus pentoxide than with phosphorus oxychloride, but the results pointed to some racemization in most cases.

In the present study, the pure *cis*- and *trans*-4-*t*-butylcyclohexanecarboxamides, readily prepared from the corresponding acids,[14] were used. The extent of geometrical interconversion in the product nitrile gave a measure of the stereochemical integrity of the dehydration reaction.



(1)

Analysis of geometrical isomers [*e.g.*, by vapor phase chromatography (v.p.c.) methods] offers a distinct advantage over polarimetric analysis, as

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(10) J. Kenyon and W. A. Ross, *J. Chem. Soc.*, 3407 (1951).
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(14) The authors are indebted to Mr. James Rogers for samples of these acids.

the latter is subject to the vagaries of various impurities, both optically active and inactive. The *cis*- and *trans*-4-*t*-butylcyclohexanecarbonitriles are easily separable by v.p.c., and it was demonstrated that <1% of the alternate isomer could be detected by this method.

Although all three dehydrating agents are formally acidic, the experimental procedures cause both product and reactant to be subjected to a different environment in each case. With phosphorus pentoxide, the solid amide and powdered reagent were intimately mixed and heated in a distillation apparatus under reduced pressure. The pressure was regulated so that, as the amide melted and reacted, the product was rapidly removed from the acidic medium.

Thionyl chloride and phosphorus oxychloride were used as both reactant and solvent. The reactions were carried out under reflux for "reasonable" periods of time. These procedures differ in that the acidic by-products of the thionyl chloride reaction are volatile, while with phosphorus oxychloride the reaction temperature is higher.

The results, summarized in Table I, show that no detectable amount of α-carbon isomerization occurred with either the thionyl chloride or the phosphorus pentoxide procedure. This high stereochemical integrity was shown by both the *cis* and the *trans* isomers.

The use of phosphorus oxychloride resulted in some isomerization; it was suspected that this isomerization was due to acid-catalyzed enolization of the product nitrile. In order to test this hypothesis, a sample of the pure *cis* nitrile was subjected to the dehydration reaction conditions, *i.e.*, heated with phosphorus oxychloride containing a small amount of phosphoric acid. The extent of isomerization was comparable to that found in the dehydration product. In this respect, it is worthwhile noting that the *cis* and *trans* nitriles are of about the same stability;[15] thus, the similar degree of isomerization found for both the *cis* and *trans* nitriles (Table I) is not unexpected.

TABLE I

DISTRIBUTION OF NITRILES FROM THE DEHYDRATION OF *cis*- AND *trans*-4-*t*-BUTYLCYCLOHEXANECARBOXAMIDES

Starting amide	Dehydrating agent	Approx. reaction temp., °C.	*trans* Nitrile,[a] %	M.p., °C.
cis	$SOCl_2$	80	0	52–55.2
trans	$SOCl_2$	80	100	29.4–37.7
cis	$POCl_3$	106	2.3	47–54
trans	$POCl_3$	106	97.6	27.8–30.8
cis	P_4O_{10}	145	0	56.3–57.3[b]
trans	P_4O_{10}	145	100	33.4–34.7[b]

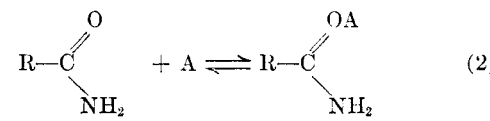
[a] Samples were analyzed on a 20-ft. polydiethylene glycol succinate column at 150°. [b] The melting point was the same as that of a sample collected from v.p.c., and the mixed melting point was not depressed.

(15) The equilibrium constant for the *cis* ⇌ *trans* interconversion of the nitrile is $K = 1.30$, [*t*-butoxide] = 1.0 *M* in *t*-butyl alcohol solvent. *J. Org. Chem.*, **27**, 4606 (1962).

It is possible that careful control of reaction time and conditions would allow the phosphorus oxychloride dehydration to be carried out with negligible isomerization of the α-carbon. The work of Kenyon and Ross[10] illustrates this point. Optically active 2-methyl-3-phenylpropanonitrile was hydrolyzed to the corresponding acid by treatment with concentrated hydrochloric acid at room temperature for several months, with little or no racemization.

Although the 4-*t*-butylcyclohexanecarbonitriles obtained from the phosphorus pentoxide and thionyl chloride procedures showed no detectable isomerization, the melting points of the products (distilled but not recrystallized) of the thionyl chloride treatment were depressed, indicating the presence of an impurity. Taking this and the procedural simplicity into consideration, the phosphorus pentoxide treatment is regarded as the method of choice for amide dehydration when feasible.

A reasonable general mechanism for the dehydration involves the formation of imido ester as intermediate



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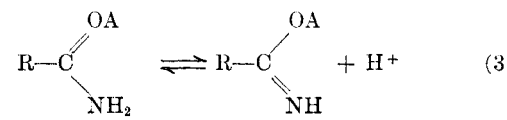

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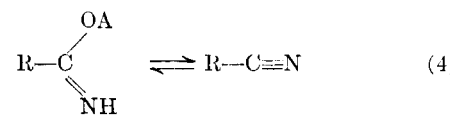
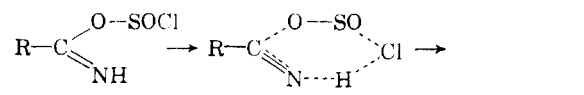


(4)

Reaction 4 may be a two-step (E1) or one-step (E2) reaction, or the formation of a six-ring may be involved in the transition state, *e.g.*, with thionyl chloride



$$R{-}C{\equiv}N + SO_2 + HCl \quad (5)$$

For α-carbon isomerization to occur with the amide, it is necessary that enolization (to α-carbon) occurs with the oxonium compound formed in equation 2. However, it is well known that proton transfer from nitrogen (equation 3) is much faster than from carbon, and it is to be expected that reaction 3 is not reversible under these reaction conditions. Therefore, with the reagents utilized in the present study, it is not surprising to find that isomerization of the amide does not occur.

Experimental

cis-4-*t*-Butylcyclohexanecarboxamide.—Pure *cis*-4-*t*-butylcyclohexanecarboxylic acid,[16] m.p. 117–118°, 6.7 g. (0.036 mole), was added to thionyl chloride and the mixture was stirred overnight at room temperature. The excess thionyl chloride was removed on a rotary film evaporator, and the residue was cooled in Dry Ice–acetone. Rapid addition of 60 ml. of concentrated ammonium hydroxide gave a slurry which was allowed to warm slowly with stirring. The mixture was filtered, and the resultant solid was dissolved in boiling ethanol. This solution was filtered while hot, and water was added dropwise to the cloud point. After cooling, 5.0 g. (75%) of the *cis* amide, m.p. 162.7–163.9° (lit.,[16] 161°) was collected.

trans-4-*t*-Butylcyclohexanecarboxamide.—Similar treatment of the pure *trans* acid,[16] m.p. 174.2–175.8°, 3.7 (0.02 mole), gave on recrystallization from cyclohexane 3.3 g. (90%) of the *trans* amide, m.p. 134.2–135.8° (lit.,[16] 134–135°).

Dehydration with Phosphorus Pentoxide.—In a typical experiment, 1.00 g. (0.0054 mole) of *cis*-4-*t*-butylcyclohexanecarboxamide was thoroughly dispersed in 1.2 g. of phosphorus pentoxide in a simple distillation apparatus. The system was subjected to reduced pressure (20–25 mm.), and placed in an oil bath preheated to 145°. Distillation commenced rapidly to yield 0.83 g. (93%) of the pure crystalline *cis* nitrile, m.p. 56.3–57.3.°

Dehydration with Thionyl Chloride.—*cis* Amide, 0.70 g. (0.0038 mole), was dissolved in 1.0 ml. of thionyl chloride, and the mixture was refluxed for 1 hr. The excess thionyl chloride was removed on a rotary film evaporator; distillation (6 mm.) gave 0.61 g. (97%) of product, m.p. 52–55.2.°

Dehydration with Phosphorus Oxychloride.—A sample of the same *cis* amide, 0.70 g. (0.0038 mole), used in the above procedures, was added to 2.0 ml. of phosphorus oxychloride and the mixture was refluxed for 1.5 hr. Ten milliliters of methylene chloride and 50 ml. of water were added and the mixture extracted. The aqueous phase was extracted with another portion of methylene chloride, and the combined organic extracts were washed with water, then heated on a steam bath with water until the methylene chloride boiled. After cooling the mixture was neutralized with dilute sodium hydroxide, the organic phase separated, dried, and evaporated. Distillation of the residue (6 mm.) gave 0.50 g. (80%) of product, m.p. 47–54.°

cis-4-*t*-Butylcyclohexanecarbonitrile, a nitrile sample collected by v.p.c., had a melting point of 56.3–57.3.°

Anal. Calcd. for $C_{11}H_{19}N$: C, 79.94; H, 11.59. Found: C, 80.14; H, 11.48.

Trans-4-*t*-Butylcyclohexanecarbonitrile, a nitrile sample collected by v.p.c., had a melting point of 33.4–34.7°.

Anal. Found: C, 80.05; H, 11.55.

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Configurational Assignment to C-6 Epimeric 3α,5α-Cyclosteroid Alcohols and Amines by Means of N.m.r.

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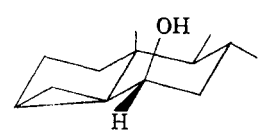
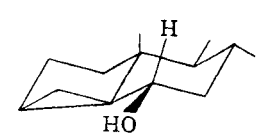
Received July 9, 1962

Interpretation by the first order approximation of the multiplet absorption patterns of the C-6 protons of acetoxy and *p*-nitrobenzoyloxy derivatives of the C-6 epimeric 6-hydroxy-17-ethylenedioxy-3α,5α-cycloandrostanes provides strong evidence for their configurations. These products have been related to the C-6 epimeric 6-hydroxy-3α,5α-cyclocholestanes by the methods of preparation and correlations of optical rotation. The 3α,5α-cyclo-6-substituted steroids provide an example of an exception to the generalization that, for rigid six-membered ring systems, axial ring protons absorb at higher field than the epimeric equatorial protons. Configurational assignments have been made to the C-6 epimeric 6-amino-3α,5α-cycloandrostan-17-ones based on the chemical shifts of the C-6 protons of acetamido and *p*-nitrobenzamido derivatives.

The criteria on which the accepted configurations of the epimeric 6-hydroxy-3α,5α-cyclocholestanes have been based are described in detail by Kosower and Winstein.[1] These authors concluded from examination of models that the 3α,5α-cyclo bond does not greatly affect the conformation of the B-ring and, thus, that both of the epimers have chair-form *B*-rings. From relationships of optical rotation, chromatographic behavior, and relative rates of solvolysis of derivatives, it was deduced that the epimer (*i*-cholesterol) resulting from hydrolysis of the *p*-toluenesulfonate of 3β-hydroxycholest-5-ene (cholesterol) has the 6β-axial hydroxyl (I), while the epimer (epi-*i*-cholesterol) resulting from reduction of 3α,5α-cyclocholestan-6-one has the 6α-equatorial hydroxyl group (II). Further evidence for these assignments was reported by Evans and Summers,[2] who found that *i*-cholesterol was epimerized to the extent of 37% on treatment with sodium ethoxide in ethanol at 190°, while no change occurred on similar treatment of epi-*i*-cholesterol. The results were interpreted as reflecting the greater stability of the 6α-equatorial hydroxyl of II.



I



II

By analogy with the configurations assigned to 3α,5α-cyclo 6-alcohols obtained by hydrolysis of steroid Δ^5-3β *p*-toluenesulfonates, the 3α,5α-cyclo 6-amines formed by ammonolysis have been assigned the 6β-amino configuration.[3] It was reported[2] that sodium–ethanol reduction of 6-oximino-

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