infrared spectra indicated that the filtrate contained isocyanate and that the crude solid was a mixture of sulfonyloxamide and sulfonylparabanate. The solid was boiled with methanol and the insoluble oxamide, 5 g. (41%), was recovered by filtration. Recrystallization from dimethyl acetamide–methanol gave m.p. 291° dec.

Anal. Calcd. for $C_4H_8N_2O_6S_2$: C, 19.67; H, 3.30; S, 26.26. Found: C, 19.4; H, 3.1; S, 25.9.

Concentration of the methanol filtrate yielded 4.0 g. of a mixture from which methyl methanesulfonylcarbamate, m.p. 120.6–121.3°, was isolated.

Anal. Calcd. for $C_3H_7NO_4S$: C, 23.53; H, 4.61; N, 9.15. Found: C, 23.61; H, 4.47; N, 9.09.

Methyl methanesulfonyloxamate, m.p. 103–105°, and a little N,N′-bis(methanesulfonyl)oxamide were also found in the mixture. The yield of methyl esters corresponds to a yield of 26% of N,N′-bis(methanesulfonyl)parabanate in the initial crude reaction product.

Preparation of Methanesulfonyloxamoyl Chloride (IIIc).—Methanesulfonamide, 9.5 g. (0.10 mole), and 63.5 g. (0.50 mole) of oxalyl chloride were refluxed for 0.5 hr., and the mixture was then allowed to remain at room temperature for 1 day. An equal volume of hexane was added, and the precipitate was recovered by filtration. The yield of off-white crystalline product, m.p. 95–100° dec., was 16 g. (86%). The crude product (0.8 g.) was warmed with methanol and 0.05 g. of bis(methanesulfonyl)-oxamide was removed by centrifugation. The methyl ester recovered from the methanol solution melted at 104.5–105.5° after recrystallization from benzene–methanol–petroleum ether.

Anal. Calcd. for $C_4H_7NO_5S$: C, 26.52; H, 3.89; N, 7.73. Found: C, 26.63; H, 4.08; N, 7.79.

Pyrolysis of Methanesulfonyloxamoyl Chloride.—When 9.3 g. (0.05 mole) of methanesulfonyloxamoyl chloride was heated with 50 ml. of trichlorobenzene to 150°, vigorous gas evolution occurred. A solid which appeared during the decomposition remained present even at the maximum temperature reached. Distillation of the entire reaction mixture through a Holzmann column gave 4.3 g. of a mixture of trichlorobenzene and methyl sulfonyl isocyanate which was identified by its infrared spectrum.

The distillation residue was cooled and filtered to give a tan powder, 3.9 g., m.p. 200–220° dec., which appeared, from the infrared spectrum, to contain oxamide (Ic) and parabanate (IVc). Treatment with methanol enabled separation of the oxamide, 19% of theory, m.p. 285–290°. The mixture of esters obtained from the alcohol-soluble portion corresponded to 2.73 g. of parabanate, 41% of theory.

Preparation of N,N′-Bis(methanesulfonyl)parabanate (IVc).—A mixture of 4.76 g. (0.05 mole) of methanesulfonamide, 12.2 g. (0.10 mole) of oxalyl chloride, 100 ml. of ethylene chloride, and 3 drops of pyridine was refluxed for 5.5 hr. After cooling and filtering, there was recovered 4.1 g. of product. The infrared spectrum indicated the major constituent was parabanate contaminated with some oxamide. Methanol treatment of a portion indicated that about 13% of this product was oxamide. The parabanate, m.p. 215° dec., was extracted from the mixture with acetonitrile and precipitated with ether.

Anal. Calcd. for $C_5H_6N_2O_7S_2$: C, 22.22; H, 2.24; S, 23.73. Found: C, 22.18; H, 2.28; S, 23.82.

Reaction of Octanesulfonamide with Oxalyl Chloride.—A mixture of 4.7 g. (0.024 mole) of *n*-octanesulfonamide and 17 g. (0.134 mole) of oxalyl chloride was refluxed 7 hr. *o*-Dichlorobenzene (10 ml.) was added and excess oxalyl chloride was removed by distillation. The mixture was then distilled under reduced pressure. The infrared spectrum of the product, 4.5 g., b.p. 102–104° (1.0 mm.), indicated an equimolar mixture of *n*-octanesulfonyl isocyanate and *n*-octanesulfonyl chloride.[16]

Anal. Calcd.: Cl, 8.1. Found: Cl, 8.5.

(16) R. B. Scott, Jr., and R. E. Lutz [*J. Org. Chem.*, **19**, 830 (1954)] reported this sulfonyl chloride, b.p. 94° at 1 mm.

The Synthesis of Dehydrocycloheximide and the Conversion of *cis*-2,4-Dimethylcyclohexanone to Its *trans* Isomer[1,2]

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The synthesis of dehydrocycloheximide has been accomplished by the condensation of the enamine of (+)-*trans*-2,4-dimethylcyclohexanone with glutarimide-β-acetyl chloride. It is inferred that, when *cis*-2,4-dimethylcyclohexanone was converted into its enamine, an isomerization occurred with the result that the methyl groups assumed a *trans* relationship. A proposal is presented in an attempt to explain this isomerization.

The determination of the stereochemistry and the attempted syntheses of the glutarimide antibiotics related to cycloheximide have been under investigation in a number of laboratories.[3–6] We now wish to give the complete details of our previously announced synthesis of dehydocycloheximide[7] and to describe certain isomerizations which appear to occur during the preparation of enamines from substituted cyclic ketones.

For the synthesis of dehydrocycloheximide, we elected to combine the two fragments, 2,4-dimethylcyclohexanone (I) and glutarimide-β-acetyl chloride (III). The ketone was activated for condensation by converting it into either the pyrrolidine or piperidine enamine according to the elegant procedure of Stork and co-workers.[8] Thus, when (+)-*trans*-2,4-dimethylcyclohexanone was allowed to react with pyrrolidine in benzene solution, a 78% yield of the desired enamine (II) was obtained. Condensation of II in dioxane solution with glutarimide-β-acetyl chloride (III), followed by hydrolysis with dilute hydrochloric acid gave dehydrocycloheximide in a 25% yield. The fact that the synthetic dehydrocycloheximide (IV) was identical with an authentic sample of dehydrocycloheximide[9] was established by comparison of the optical rotation, ultraviolet and infrared spectra, R_f on thin layer chromatography, and the melting and mixture melting points of the two samples. As reported earlier,[7] when a similar condensation was performed in which the piperidine enamine of (+)-*trans*-2,4-dimethylcyclohexanone was allowed to react with III, a 19% yield of IV was obtained. In addition, the synthesis of (±)-norde-

(1) The research described in this paper was submitted by V. K. Jain in partial fulfillment of the Ph.D. requirements.

(2) This investigation was supported in part by Research Grant CY-4812 from the National Institutes of Health and in part by a Public Health Service research career program award CA-K6-18718 from the National Institutes of Health.

(3) H. J. Schaeffer and V. K. Jain, *J. Pharm. Sci.*, in press.

(4) B. C. Lawes, *J. Am. Chem. Soc.*, **82**, 6413 (1960).

(5) T. Okuda, M. Suzuki, and Y. Egawa, *J. Antibiotics* (Tokyo), **14A**, 158 (1961); *Chem. Pharm. Bull.* (Tokyo), **11**, 582 (1963).

(6) F. Johnson, W. D. Gurowitz, and N. A. Starkovsky, *Tetrahedron Letters*, 1167 (1962).

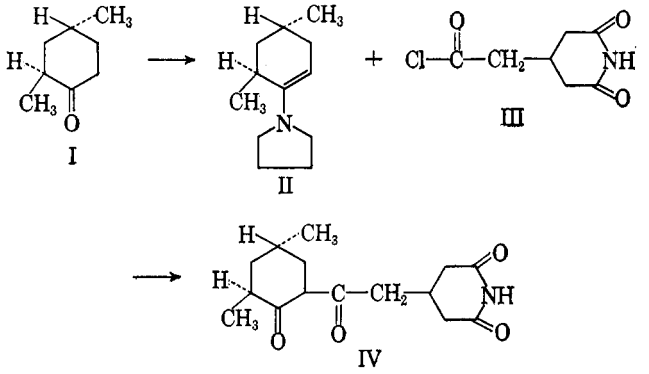
(7) H. J. Schaeffer and V. K. Jain, *J. Pharm. Sci.*, **52**, 509 (1963).

(8) G. Stork, A. Brizzolara, H. Landesmann, J. Szmuszkovicz, and R. Terrell, *J. Am. Chem. Soc.*, **85**, 207 (1963).

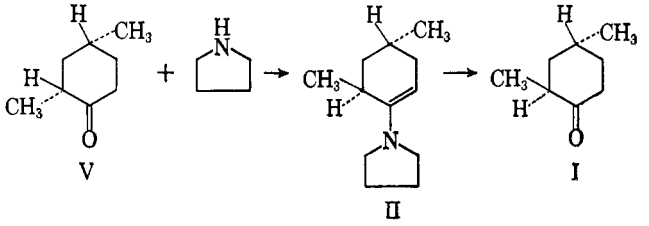
(9) E. C. Kornfeld, R. J. Jones, and T. V. Parke, *ibid.*, **71**, 150 (1949).

hydrocycloheximide was accomplished by allowing the piperidine enamine of 2-methylcyclohexanone to react with glutarimide-β-acetyl chloride (III).

The synthesis of IV establishes that the methyl groups in IV are *trans* because the compound was synthesized from an enamine (I) that gives, after acidic hydrolysis, (+)-*trans*-2,4-dimethylcyclohexanone (I) with 73% retention of configuration.



Since it is known that isocycloheximide[10] has *cis*-methyl groups,[11,12] it was felt that dehydroisocycloheximide could be synthesized by condensation of the enamine prepared from *cis*-2,4-dimethylcyclohexanone with III. Therefore, cycloheximide was degraded with sodium hydroxide solution to give the known *cis*-2,4-dimethylcyclohexanone.[9] When *cis*-2,4-dimethylcyclohexanone (V) was allowed to react with pyrrolidine in benzene solution, an enamine was obtained but the enamine was identical with the one prepared from the *trans* ketone (I). The identity of the enamines was



shown by comparison of their optical rotation, infrared and n.m.r. spectra, boiling points, retention time on v.p.c., and by the fact that the enamine prepared from *cis*-2,4-dimethylcyclohexanone (V) on hydrolysis gave *trans*-2,4-dimethylcyclohexanone (I) and on reaction with glutarimide-β-acetyl chloride (III) gave dehydrocycloheximide (IV). Thus, by the simple procedure of preparation of an enamine followed by hydrolysis of that enamine, it has been possible to convert, in good yield, the thermodynamically stable *cis* ketone (V) into the thermodynamically less stable *trans* ketone (I).[13,14]

(10) A. J. Lemin and J. H. Ford, *J. Org. Chem.*, **25**, 344 (1960).

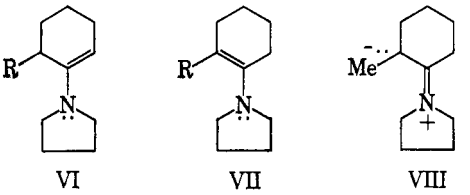
(11) T. Okuda, M. Suzuki, T. Furumai, and H. Takahashi, *Chem. Pharm. Bull.* (Tokyo), **11**, 730 (1963).

(12) F. Johnson and N. A. Starkovsky, *Tetrahedron Letters*, 1173 (1962).

(13) After this work was completed, F. Johnson, N. A. Starkovsky, A. C. Paton, and A. A. Carlson reported in a recent communication [*J. Am. Chem. Soc.*, **86**, 118 (1964)] the synthesis of cycloheximide. In their synthesis of cycloheximide, dehydrocycloheximide was one of their key intermediates and it was prepared essentially by our procedure except that the morpholine enamine was used. These authors also reported that *cis*-2,4-dimethylcyclohexanone yielded the morpholine enamine with *trans*-methyl groups.

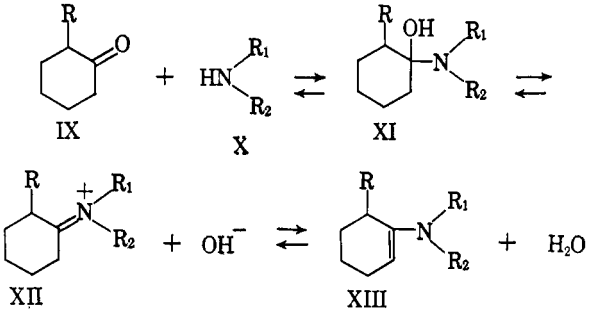
(14) The thermodynamic stability of 2,4-dimethylcyclohexanone has been established; for example, B. C. Lawes [*J. Am. Chem. Soc.*, **84**, 239 (1962)] has shown that the *trans* ketone (I) is rapidly isomerized to the *cis* ketone (V) with aqueous sodium hydroxide. The final equilibrium concentration was 89.5% V and 10.5% I.

In an attempt to find an explanation for the isomerization of the *cis* ketone (V) to the *trans* ketone (I) *via* the enamine II, several observations concerning the structure and reactivity of enamines appear to be pertinent. Two investigators[8,15] have stated that, when enamines are prepared from 2-alkylcyclohexanones, the less substituted enamine is formed; *i.e.*, VI and not VII is the product of reaction, and it was suggested that VII



is not the product of the reaction because of steric interaction of the R group with the α-methylene group of the pyrrolidine ring.[8] Williamson in a discussion concerning the inability of the pyrrolidine enamine of 2-methylcyclohexanone to undergo C-methylation with methyl iodide has suggested that the severe steric interference which occurs in VIII when the methyl group is equatorial is relieved by the methyl group assuming an axial conformation in the dipolar form of the enamine (VIII).[16] It was further suggested that, after the methyl group had assumed an axial conformation, further reaction at the 6-position is blocked, presumably by a 1,3-effect. A similar argument was used to explain the lack of dialkylation of the enamines of cyclohexanone and other related cyclic ketones.[16]

Stork has discussed the factors which influence the rate of formation of enamines and has postulated that three reversible reactions are involved as shown below.



It was found that the over-all rate of enamine formation could not be ascribed solely to any one of the reversible steps.[8]

We wish to point out that the previously discussed interaction between an equatorial R group in an enamine derived from a 2-alkylcyclohexanone and the methylene group α to the nitrogen of the enamine is much more severe in the intermediate XII than in the product XIII. This interaction should force the alkyl group of simple 2-alkylcyclohexanones to assume the axial orientation in the intermediate XII. The rate of enamine formation should therefore decrease as the energy required to cause the 2-alkyl group to assume the axial orientation, in XII, increases.

Our observations on enamine formation are readily explained on the basis of the above postulate. Thus, *trans*-2,4-dimethylcyclohexanone (I) exists as a mobile

(15) M. E. Kuehne, *ibid.*, **81**, 5400 (1959).

(16) W. R. N. Williamson, *Tetrahedron*, **3**, 314 (1958).

equilibrium mixture of two energetically similar forms in which the respective methyl groups are axial and equatorial or *vice versa*. This substance can therefore readily form the enamine in which the 2-methyl group is quasi-axial and the 4-methyl group is quasi-equatorial. In contrast, in the chair form of *cis*-2,4-dimethylcyclohexanone (V) both methyl groups should be equatorial and a relatively large amount of energy would be required to change the conformation of the 2-methyl group to axial. This substance therefore cannot form the enamine at a rate comparable with that of I. Consequently, an isomerization occurs and an equilibrium mixture of the *cis* and *trans* ketones is established. Even though the equilibrium is greatly in favor of the *cis* ketone (V),[14] the rate of reaction of the *trans* ketone (I) with pyrrolidine is higher than that of the *cis* ketone (V); in this way, the *cis* ketone (V) gradually is converted into the enamine (II) with *trans*-methyl groups *via* a common intermediate similar to XII.[17,18] In addition, it may be possible to use this enamine procedure to isomerize other substituted cyclic ketones into the less thermodynamically stable isomers. For example, *trans*-2,3-disubstituted cyclohexanones and *trans*-2,5-disubstituted cyclohexanones might be isomerized to the corresponding *cis* derivatives *via* their enamines. This concept is currently under investigation in our laboratory.

Experimental

(+)-*trans*-2,4-Dimethylcyclohexanone (I).—This compound was prepared by the method of Lawes[14] in a 41% yield, b.p. 73–75° (18 mm.); ν (film) 1720 cm.$^{-1}$ (C=O); $[\alpha]^{20}D$ +60.1° (*c* 4.35, $CHCl_3$). The reported constants are b.p. 69° (17 mm.) and $[\alpha]^{24}D$ +64.8° (*c* 6.0, EtOH).

N-(*trans*-2,4-Dimethylcyclohex-6-enyl)pyrrolidine (II).—To a solution of 10.2 g. (79.2 mmoles) of *trans*-2,4-dimethylcyclohexanone in 60 ml. of benzene was added 13.2 ml. (158 mmoles) of pyrrolidine. The reaction solution was refluxed under a constant water separator until no more water was collected (2.0 ml., 36 hr.). The solvent was removed by distillation at atmospheric pressure, and the residue was distilled *in vacuo;* yield of N-(*trans*-2,4-dimethylcyclohex-6-enyl)pyrrolidine was 11.1 g. (78.8%), b.p. 82–85° (1.8 mm.). One redistillation of the crude product gave the analytical sample, b.p. 83–85° (1.8 mm.); ν (film) 1720 (weak C=O) and 1645 cm.$^{-1}$ (C=C); $[\alpha]^{21}D$ −42.9° (*c* 2.3, benzene).

Anal. Calcd. for $C_{12}H_{21}N$: C, 30.38; H, 11.80; N, 7.81. Found: C, 80.54; H, 11.97; N, 7.68.

Dehydrocycloheximide (IV).—To a solution of 3.50 g. (19.5 mmoles) of N-(*trans*-2,4-dimethylcyclohex-6-enyl)pyrrolidine (II) in 25 ml. of *p*-dioxane was added triethylamine (25 ml.) and a solution of glutarimide-β-acetyl chloride[19,20] (5.60 g., 29.3 mmoles) in 60 ml. of *p*-dioxane. The reaction solution was stirred for 22 hr. at room temperature, chilled in an ice bath and then was made acidic with 60 ml. of 20% hydrochloric acid. After stirring the mixture for 4 hr. at room temperature, it was extracted with five 50-ml. portions of chloroform. The chloroform extracts were washed with three 80-ml. portions of a saturated solution of sodium bicarbonate and water (100 ml.); the aqueous washings were re-extracted with chloroform (100 ml.), and the combined organic portions were dried with anhydrous magnesium sulfate. After filtration, the volatile materials were removed *in vacuo* from the filtrate, and the semisolid residue on crystallization from acetone and water gave 1.35 g. (25.0%) of dehydrocycloheximide, m.p. 152–155°. Three recrystallizations of the crude product from hot acetone gave the analytical sample, m.p. 177–179°; m.m.p. 176–178° with an authentic sample of dehydrocycloheximide[9]; $[\alpha]^{21}D$ −30.4° (*c* 1.0, $CHCl_3$)[21]; ν (KBr) 3200 and 3120 (NH), 1700 (C=O), and 1560 cm.$^{-1}$ (enolic β-diketone); R_f 0.82, chloroform containing 1.0% of methanol on silica gel G; $\lambda_{max}^{EtOH-NaOH}$ 315 mμ (ε 17,620).

Anal. Calcd. for $C_{15}H_{21}NO_4$: C, 64.49; H, 7.58; N, 5.02. Found: C, 64.30; H, 7.37; N, 5.22.

Dehydrocycloheximide was also synthesized by condensation of N-(*trans*-2,4-dimethylcyclohex-6-enyl)piperidine with glutarimide-β-acetyl chloride under similar experimental conditions; yield 19%; m.p. 177–179°; m.m.p. 176–178° with the authentic sample of dehydrocycloheximide; lit.[9] m.p. 177–180°; $[\alpha]^{21}D$ −30.9° (*c* 1, $CHCl_3$).

Nordehydrocycloheximide.—To a solution of 5.38 g. (30.0 mmoles) of N-(2-methylcyclohex-6-enyl)piperidine in 30 ml. of *p*-dioxane was added triethylamine (25 ml.) and a solution of glutarimide-β-acetyl chloride (8.46 g. 44.9 mmoles) in 50 ml. of *p*-dioxane. The reaction mixture was stirred for 18 hr. at room temperature, cooled in an ice bath, and then made acidic with 20% hydrochloric acid (50 ml.). After stirring for 3.5 hr. at room temperature, the reaction mixture was concentrated *in vacuo* to about half of its volume and then extracted with four 100-ml. portions of chloroform. The organic portion was washed with three 100-ml. portions of a saturated solution of sodium bicarbonate and water (100 ml.). The aqueous portion was re-extracted with chloroform (100 ml.), and the combined organic portions were concentrated *in vacuo*. The residue was dissolved in 40 ml. of acetone and an aqueous solution of copper acetate (2.0 g.) was added. The reaction mixture was stirred overnight at room temperature, and the crystals which formed were collected by filtration; yield, 1.12 g. (12.6%) of the copper chelate of nordehydrocycloheximide; m.p. 205–209° dec. After two recrystallizations from acetone and water, the crude material gave the analytical sample, m.p. 230–233° dec.; ν (KBr) 3220 and 3110 (NH), 1745 and 1690 (C=O), and 1560 cm.$^{-1}$ (enolic β-diketone).

Anal. Calcd. for $C_{28}H_{36}CuN_2O_8$: C, 56.79; H, 6.13; Cu, 10.7; N, 4.73. Found: C, 56.46; H, 6.07; Cu, 10.9; N, 4.71.

To a solution of 0.62 g. (1.05 mmoles) of the copper chelate of nordehydrocycloheximide in 15 ml. of chloroform was added 25 ml. of 10% sulfuric acid, and the reaction mixture was stirred at room temperature for 2 hr. The organic layer was separated, and the aqueous portion was extracted with two 25-ml. portions of chloroform. The combined organic extract was washed with two 25-ml. portions of a saturated solution of sodium bicarbonate and water (25 ml.), and dried with anhydrous magnesium sulfate. After filtration, the volatile materials were removed *in vacuo*, and the residue on crystallization from acetone and water gave 0.43 g. (75.0%) of nordehydrocycloheximide, m.p. 125–127°. Two recrystallizations of the crude material from acetone and water gave the analytical sample, m.p. 140–142°; ν (KBr) 3220 and 3110 (NH), 1745 and 1690 (C=O), and 1590 cm.$^{-1}$ (enolic β-diketone); $\lambda_{max}^{EtOH-NaOH}$ 315 mμ (ε 18,850).

Anal. Calcd. for $C_{14}H_{19}NO_4$: C, 63.38; H, 7.22; N, 5.28. Found: C, 63.15; H, 7.32; N, 5.04.

Hydrolysis of N-(*trans*-2,4-dimethyl-cyclohex-6-enyl)pyrrolidine(II).—To a solution of 1.04 g. (5.80 mmoles) of N-(*trans*-2,4-cyclohex-6-enyl)pyrrolidine in 20 ml. of chloroform was added 20 ml. of 20% hydrochloric acid. The reaction mixture was stirred at room temperature for 90 min. and the chloroform layer was separated. The aqueous portion was extracted with 15 ml. of chloroform, and the combined organic portions were washed with two 20-ml. portions of a saturated solution of sodium bicarbonate and water (10 ml.), and dried with anhydrous magnesium sulfate. After filtration, the volatile materials were removed from the filtrate, and the residue on distillation gave 0.23 g. (31.5%) of *trans*-2,4-dimethylcyclohexanone, b.p. 80° (23 mm.); ν (film) 1720 cm.$^{-1}$ (C=O); $[\alpha]^{22}D$ +43.9° (*c* 4.2, $CHCl_3$). The observed optical rotation corresponds to 73% retention of configuration.

(17) The possibility does exist that the hydrolysis of II is under kinetic control and gives the thermodynamically less stable isomer (I).

(18) Distillation of the crude pyrrolidine enamine prepared from *trans*-2,4-dimethylcyclohexanone resulted in a forerun which was shown to be *cis*-2,4-dimethylcyclohexanone with an $[\alpha]^{23}D$ of +2.55° (*c* 4.4, $CHCl_3$). Thus, when the *trans* ketone (I) is exposed to the basic pyrrolidine it is, in fact, isomerized to the *cis* ketone (V).

(19) D. D. Phillips, M. A. Acitelli, and J. Meinwald, *J. Am. Chem. Soc.*, **79**, 3517 (1957).

(20) Y. Egawa, M. Suzuki, and T. Okuda, *Chem. Pharm. Bull.* (Tokyo), **11**, 589 (1963).

(21) When dehydrocycloheximide was prepared from cycloheximide according to the published procedure,[9] it was found to have $[\alpha]^{23}D$ −31.1° (*c* 1.0, $CHCl_3$).

cis-2,4-Dimethylcyclohexanone (V).—This ketone was prepared by the alkaline degradation of cycloheximide according to a known procedure; yield, 44.7%; b.p. 73–74° (20 mm.); ν (film) 1720 cm.$^{-1}$ (C=O); $[\alpha]^{22}D$ +3.4° (*c* 7.0, $CHCl_3$). The reported constants for this compound are b.p. 69.5° (17 mm.), $[\alpha]^{25}D$ + 4.3° (*c* 6, EtOH).

Preparation of the Pyrrolidine Enamine from *cis*-2,4-Dimethylcyclohexanone.—The enamine was prepared from *cis*-2,4-dimethylcyclohexanone and pyrrolidine under the same conditions that were used for the *trans* enamine (II). The product that was isolated in a 62.4% yield was N-(*trans*-2,4-dimethylcyclohex-6-enyl)pyrrolidine (II), b.p. 72–74° (1.4 mm.); ν (film) 1720 (weak, C=O) and 1645 cm.$^{-1}$ (C=C); $[\alpha]^{21}D$ −44.6° (*c* 2.3, benzene).

Anal. Calcd. for $C_{12}H_{21}N$: C, 80.38; H, 11.80; N, 7.81. Found: C, 80.16; H, 11.67; N, 7.58.

Vapor phase chromatography using an 8 ft × 4 mm. column, 200°, helium inlet pressure 15 p.s.i., established that the pyrrolidine enamine from the *cis* ketone (V) and from the *trans* ketone (I) were identical; each enamine exhibited a single peak having 200-sec. retention time with respect to air.

Hydrolysis of the Pyrrolidine Enamine Prepared from *cis*-2,4-Dimethylcyclohexanone.—This enamine was hydrolyzed in a manner similar to that described for II; thus, *trans*-2,4-dimethylcyclohexanone was obtained with $[\alpha]^{22}D$ +40.8° (*c* 1.8, $CHCl_3$). The observed optical rotation corresponds to 68% retention of configuration.

Attempted Isomerization of (+)-*trans*-2,4-Dimethylcyclohexanone (I).—To a solution of 3.11 g. (24.6 mmoles) of I in 30 ml. of chloroform was added 4 ml. of 20% hydrochloric acid, and the mixture was stirred for 45 min. at room temperature. The organic layer was separated, washed with water (20 ml.), and dried over anhydrous magnesium sulfate. After filtration the chloroform was removed *in vacuo* from the filtrate, and the residue on distillation gave 1.54 g. (50.0%) of (+)-*trans*-2,4-dimethylcyclohexanone, b.p. 80° (20 mm.), $[\alpha]^{24}D$ +55.5° (*c* 6.1, $CHCl_3$). Thus, treatment of II with hydrochloric acid gave 92.5% retention of configuration.

Acknowledgment.—The authors wish to express their appreciation to Drs. A. J. Solo and H. Tieckelmann for their helpful discussion and suggestions during the preparation of this paper.

The Furanoquinoline Alkaloids. II.[1] Synthetic Approaches to Demethoxylunacrine

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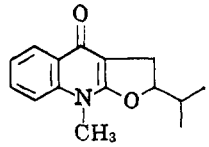
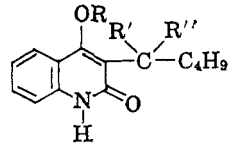
Two new synthetic approaches to the furoquinoline alkaloids have been explored. In the first, 3-isovaleryl-4-hydroxy-2-quinolone is converted to 2-isopropyl-3,4-dioxo-2,3,4,5-tetrahydrofuro[3.2-*c*]quinoline. This compound on reduction, dehydration and hydrogenation gave 2-isopropyl-4-oxo-2,3,4,5-tetrahydro[3,2-*c*]quinoline. In contrast to compounds lacking the 2-isopropyl group, the dihydro furan ring was inert to phosphorous oxychloride. In a second approach 3-isovaleryl-4-methoxy-2-quinolone was reduced to the alcohol and upon reaction with either dimethyl sulfoxide or phosphorus oxychloride–pyridine gave 2-isopropyl-4-methoxy-2,3-dihydrofuro[2,3-*b*]quinoline. This compound with methyl iodide gave the N-methyl derivative, which was converted to demethoxylunacrine upon treatment with lithium bromide–acetonitrile.

Although the general synthesis of furoquinoline alkaloids devised by Grundon and co-workers[3] has been applied to the synthesis of several furoquinoline alkaloids, the scope of this synthesis is limited by the availability of appropriately substituted malonic esters. Since many of these malonic esters are not easily obtainable, and in the Grundon synthesis they are employed in large excess in the first step, we felt it was desirable to devise an alternative general synthesis employing more readily available starting materials. The initial goal of our synthetic efforts was demethoxylunacrine (I), the parent compound of the series of furoquinoline alkaloids containing an isopropyl group in the α-position of the furan ring. Although this compound has not yet been obtained from natural sources, it bears the same relationship to an N-methyl platydesmine[4] as lunacrine does to balfourodine,[5] and it is quite possible that it will ultimately prove to be a naturally occurring substance.



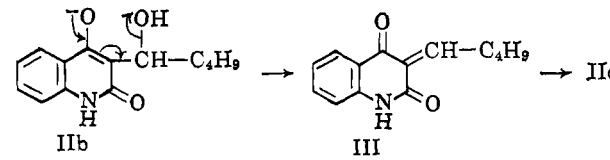
I



IIa, R = H; R′, R″ = O
b, R = H; R′ = H; R″ = OH
c, R, R′, R″ = H
d, R = CH_3; R′, R″ = O
e, R = CH_3; R′ = H; R″ = OH
f, R = CH_3; R′, R″ = H

The starting material chosen for the synthesis of I was 3-isovaleryl-4-hydroxy-2-quinolone[6] (IIa), readily obtainable from the Friedel–Crafts reaction of isovaleryl chloride and 4-hydroxy-2-quinolone.[7]

In an effort to introduce a double bond in the side chain, IIa was reduced with sodium borohydride, but, rather than the expected alcohol IIb, 3-isoamyl-4-hydroxy-2-quinolone (IIc) was obtained. Although the hydrogenolysis of a benzyl alcohol with sodium borohydride appears unprecedented, it seems probable



IIb III IIc

(1) Part I of this series: J. W. Huffman, *J. Org. Chem.*, **26**, 1470 (1961).

(2) Abstracted from the thesis presented by L. E. Browder in partial fulfillment of the requirements for the Ph.D. degree, Jan., 1964.

(3) (a) M. F. Grundon and N. J. McCorkindale, *J. Chem. Soc.*, 2177 (1957); (b) M. F. Grundon and E. A. Clarke, *Chem. Ind.* (London), 559 (1962); (c) J. R. Price ("Fortschritte der Chemie Organischer Naturstoff," Vol. XIII, L. Zechmeister, Ed., Springer, Vienna, 1956, pp. 317–330) has reviewed the earlier synthetic work in this area.

(4) P. J. Scheuer and F. Werny, *Tetrahedron*, **19**, 1293 (1963).

(5) H. Rapoport and K. G. Holden, *J. Am. Chem. Soc.*, **81**, 3738 (1959).

(6) K. Tomita, *J. Pharm. Soc. Japan*, **71**, 1100 (1951); *Chem. Abstr.*, **46**, 5044 (1952).

(7) 3-Acyl hydroxyquinolones are equally readily available *via* the well-known reaction of anilines and acylmalonic esters.