zene in a 1:1 ratio with the solvent. In order to check this, 965.2 mg. of benzenated radical was heated to 100° and pumped to constant weight (80 hr.); the weight loss was 98.3% of theoretical. The spectral maximum at 860 mμ (ε 1.62 × 10³) was used for analysis, as the maximum at 489 mμ (ε 2.81 × 10⁴) (lit.⁸ 490 mμ (ε 2.63 × 10⁴)) was inconveniently intense, and the products were found to absorb slightly at this wave length. The Koelsch radical is unstable in solution, even at −25°, in the presence of air, and solutions were prepared immediately before degassing.

N.m.r. analysis was used to find cage effects in the thiophenol-scavenged reactions. It is not possible to separate the methyl peak of dicumyl (δ 1.19 in carbon tetrachloride) from the downfield peak of the cumene doublet (δ 1.07 and 1.20); the two peaks of the cumene doublet are of slightly different area, and this depended on the direction of integration sweep in standard mixtures. Best results were obtained using upfield integration

$$\text{area } \% \text{ dicumyl} = (A(1) - 1.17A(2))/(A(1) + A(2))$$

and downfield integration

$$\text{area } \% \text{ dicumyl} = (A(1) - 1.27A(2))/(A(1) + A(2))$$

where $A(1) = A$(dicumyl) + A(cumene, δ 1.20), $A(2) = A$(cumene, δ 1.07). Cage effects found in this manner were reproducible to *ca.* ±2% in the cage effect. Thiophenol (3 *M*) in benzene was used as the solvent; cutting the thiophenol concentration to 1.5 *M* did not affect the cage effects found. Since azocumene itself has its methyl peak at δ 1.5, it was possible to analyze for completeness of decomposition without disturbing the system. Decompositions were run in sealed, degassed n.m.r. tubes. The high-temperature decompositions were done in Y tubes and the solvent was heated to temperature before the azocumene was added.

Radical-scavenged decompositions were run in degassed, sealed, square Pyrex cuvettes, absorbancies being measured on a thermostated Beckman DU spectrophotometer. Photodecompositions at 366 mμ were run in similar tubes, those at 313 mμ in quartz cuvettes sealed to Pyrex test tubes in which the degassing was done. A Bausch and Lomb high-intensity monochromator was used for a light source.

Acknowledgment. This work was supported by grants from the National Science Foundation, the National Institutes of Health, and the Petroleum Research Fund, administered by the American Chemical Society. We also thank the National Science Foundation for predoctoral fellowships in 1962–1965 to S. F. N., and Drs. John R. Thomas and John D. Baldeschwieler for helpful discussions.

The Total Synthesis of Cycloheximide[1]

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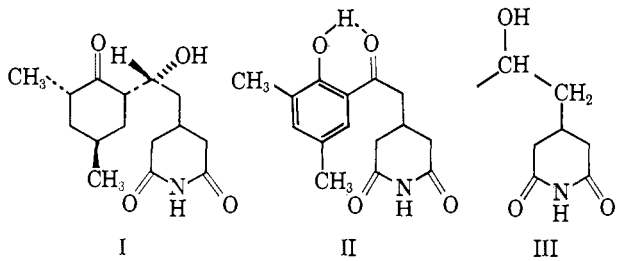
Contribution from The Dow Chemical Company, Eastern Research Laboratory, Wayland, Massachusetts. *Received September 3, 1965*

Abstract: The stereoselective synthesis of both *dl*- and *l*-cycloheximide (I) is described.

Cycloheximide (I) was first reported in 1946 by Whiffen, Bohonas, and Emerson[2] who isolated it from *Streptomyces griseus* and gave to it the name Actidione.[3] Although at that time it represented a



I II III

unique type of natural product, other strains of *Streptomyces* have since yielded related compounds. With the exception of actiphenol[4,5] (II) they all have in common the 1-hydroxy-2-[3-glutarimidyl]ethyl group (III), and most of them display biological activity of one type or another. I itself possesses antitumor,[6–8] amebicidal,[9] and powerful systemic fungicidal properties[2,10–12] in phytological systems. Besides this it is the most potent rodent repellent known,[13] rats preferring to die from thirst than to drink water containing 4–5 p.p.m. The correct gross structure of I was elucidated at an early date by Kornfeld, *et al.*[14] Later, in 1958, Djerassi and co-workers[15] reported the determination of the absolute configuration of the methyl group at C-4, by means of both chemical degradation and optical rotatory dispersion analysis. Thereafter followed several abortive at-

(1) This work, which is to be regarded as part X of the series Glutarimide Antibiotics, has been published in preliminary form: F. Johnson, N. A. Starkovsky, A. C. Paton, and A. A. Carlson, *J. Am. Chem. Soc.*, **86**, 118 (1964).

(2) A. J. Whiffen, J. N. Bohonas, and R. L. Emerson, J. *Bacteriol.*, **52**, 610 (1946); B. E. Leach, J. H. Ford, and A. J. Whiffen, *J. Am. Chem. Soc.*, **69**, 474 (1947).

(3) This name has been retained as the trade name for the compound by the Upjohn Co.

(4) R. H. Highet and V. Prelog, *Helv. Chim. Acta*, **42**, 1523 (1959); K. V. Rao, *J. Org. Chem.*, **25**, 661 (1960).

(5) F. Johnson, *ibid.*, **27**, 3658 (1962).

(6) J. C. Bateman and C. T. Klopp, *Proc. Am. Assoc. Cancer Research*, **1**, 3 (1953).

(7) H. C. Reilly, C. C. Stock, S. M. Buckley, and D. A. Clark, *Cancer Research*, **13**, 684 (1953).

(8) B. Sokoloff and F. Homburger, "Progress in Experimental Tumor Research," Vol. 1, J. B. Lippencott Co., Philadelphia, Pa., 1960, p. 360.

(9) J. B. Loefer and T. S. Matney, *Physiol. Zool.*, **25**, 272 (1952).

(10) J. R. Vaughn, *Phytopathology*, **41**, 36 (1951); T. L. McLure, *ibid.*, **42**, 114 (1952).

(11) H. D. Wells and B. P. Robinson, *ibid.*, **44**, 509 (1954).

(12) D. Cation, *Am. Fruit Grower*, **74**, 29 (1954); J. M. Hamilton and M. Szkolnik, *Proc. N. Y. State Hort. Soc.*, 58 (1955).

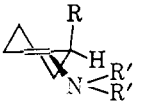
(13) J. F. Welch, *J. Agr. Food Chem.*, **2**, 142 (1954).

(14) E. C. Kornfeld and R. G. Jones, *Science*, 108, 437 (1948); E. C. Kornfeld, R. G. Jones, and T. V. Parke, *J. Am. Chem. Soc.*, **71**, 150 (1949).

(15) E. J. Eisenbraun, J. Osiecki, and C. Djerassi, *ibid.*, **80**, 1261 (1958); see also C. Beard, C. Djerassi, J. Sicher, F. Šipoš, and M. Tichý, *Tetrahedron*, **19**, 919 (1963).

tempts at synthesis[16-18] but these were necessarily doomed to failure because of the lack of an exact knowledge of the correct stereochemistry of I. Subsequent clarification of the orientation of the cyclohexanone-ring substituents both by Japanese work[19] and by investigations[20] in our own laboratory set the stage for a more educated approach to the problem of synthesis.[21] At first glance the structure of I appears relatively simple, but from a stereoselective synthetic point of view it presents certain difficulties. One of these springs from the sensitivity of the molecule to both acidic and basic conditions. The former cause dehydration and isomerization to anhydroisocycloheximide,[24] whereas the latter lead to isomerization,[25] opening of the imide ring,[14] or, at worst, reverse aldol cleavage.[14] Without citing specific details we were to find that outside the pH range of 3–10 one or other of these transformations occurs fairly rapidly.

A second difficulty which presents itself is that of stereoselectively introducing the ostensibly aliphatic hydroxyl of the side chain. The third and most important problem is the difficulty of building into the system the axial methyl group at C-4, a position equally inaccessible from all other functional groups in the molecule. This is especially the case when it is considered that the logical method of putting I together must involve the combination of a cyclohexanone derivative and a close relative of III. With respect to the latter we had on hand an ample supply of 3-carboxymethylglutarimide,[8,16,17,26] but unfortunately no suitable derivative of *trans*-2,4-dimethylcyclohexanone appeared readily available. Nevertheless a brief publication by Williamson,[27] speculating on the nature of certain enamines, threw a faint glimmer of light on the situation. Williamson suggested that enamines of 2-substituted cyclohexanones have the 2-substituent in the quasi-axial orientation[28] (as in IV). He reasoned that in this way it would be possible to explain the difficulty of alkylating such enamines since any reagent approaching the 6-position of IV axially (*i.e.*, under stereoelectronic control) must necessarily be involved in a nonbonded interaction with the substituent at C-2.[29]



IV

With this in mind we elected to examine the acylation of an enamine of 2,4-dimethylcyclohexanone with 3-glutarimidylacetyl chloride (V) in the hope of at least obtaining a compound with *trans*-related methyl groups. The subsequent problem of conformationally freezing the methyl substituents in the 2e,4a orientations necessarily had to be ignored for the present.

Before proceeding with a description of the synthesis, it is convenient to mention at this point that considerable experimental difference between the racemic and optically active series of compounds was encountered. Despite this both syntheses will be considered simultaneously for the sake of a unified presentation, and because in many ways the two are inextricably related, experimentally.

Synthesis

Reduction of 2,4-dimethylphenol over a 10% palladium-on-charcoal catalyst under 70 kg./cm.^{2} of hydrogen pressure until 2 equiv. of hydrogen had been absorbed afforded *cis*-2,4-dimethylcyclohexanone[30] (VI) in high yield. Conversion of the latter to the morpholine enamine (VII) (in which we anticipate the stereochemistry) was accomplished in good yield by refluxing the components in toluene over a Dowex-50W catalyst (acid form) and removing water azeotropically over a period of 2 days. Acylation of VII with 3-glutarimidylacetyl chloride (V) was carried out in rigorously dry chloroform[31] in the presence of dry triethylamine at room temperature. Removal of the solvent then led to a mixture of viscous liquid and crystalline material from which it was impossible to separate any pure compound except triethylamine hydrochloride. The crude reaction product therefore was hydrolyzed directly using a sodium acetate buffered solution of acetic acid in aqueous methanol, and crude *dl*-dehydrocycloheximide (VIII) spontaneously crystallized from the medium. This material, obtained in 30% yield (based on acid chloride), proved to be spectroscopically identical with an optically active specimen prepared by the oxidation of *l*-cycloheximide; their infrared and n.m.r. spectra in chloroform were superimposable. It was characterized as its copper chelate. The optically active form of VIII was also prepared synthetically by the same route using 2,4-dimethylcyclohexanone, derived from cycloheximide by base-catalyzed cleavage, as the starting material. Thus not only did we now have access to a compound closely related to cycloheximide but the synthetic sequence provided the first evidence that Williamson's speculations were correct.[32,33]

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

(17) T. Okuda, M. Suzuki, and Y. Egawa, *J. Antibiotics* (Tokyo), **A14**, 158 (1961); Y. Egawa, M. Suzuki, and T. Okuda, *Chem. Pharm. Bull.* (Tokyo), **11**, 589 (1963); M. Suzuki, Y. Egawa, and T. Okuda, *ibid.*, 11, 582 (1963).

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

(19) T. Okuda and M. Suzuki, *Chem. Pharm. Bull.* (Tokyo), **9**, 1014 (1961).

(20) F. Johnson, W. D. Gurowitz, and N. A. Starkovsky, *Tetrahedron Letters*, 1173 (1962); *J. Am. Chem. Soc.*, 87, 3492 (1965).

(21) Early work by Okuda[22] had indicated that the asymmetric center of the side chain had the (*S*) configuration. We had by this time, however, proven the evidence for this conclusion untenable but had not been able to solve the problem ourselves. Subsequent work[23] was to show that the (*R*) configuration is in fact the correct assignment. This situation however did not discourage us from attempting the synthesis of I at this stage.

(22) T. Okuda, *Chem. Pharm. Bull.* (Tokyo), 7, 259 (1959); *ibid*, 7, 671 (1959).

(23) N. A. Starkovsky and F. Johnson, *Tetrahedron Letters*, 919 (1964); F. Johnson, N. A. Starkovsky, and A. A. Carlson, *J. Am. Chem. Soc.*, 87, 4612 (1965).

(24) K. V. Rao, *ibid.*, **82**, 1129 (1960).

(25) A. J. Lemin and J. H. Ford, *J. Org. Chem.*, **25**, 344 (1960); T. Okuda, M. Suzuki, T. Furamai, and H. Takahashi, *Chem. Pharm. Bull.* (Tokyo), 10, 639 (1962); *ibid.*, **11**, 730 (1963).

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

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

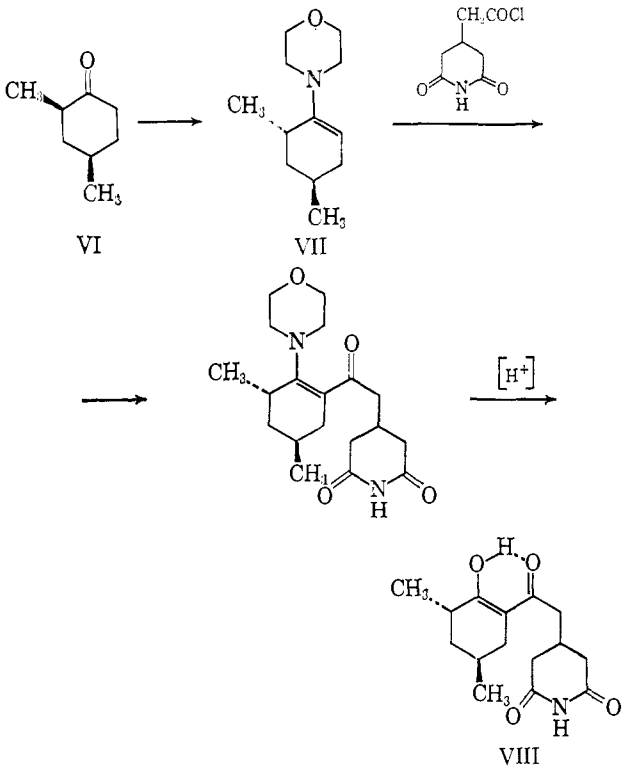
(28) That this is the case, for pyrrolidine enamines at least, has recently been demonstrated by other work from this laboratory: F. Johnson and A. Whitehead, *Tetrahedron Letters*, 3825 (1964).

(29) This should be particularly true when the carbon atom at C-6 is approaching the sp^3 state since at this point the C-2 substituent is changing from a quasi-axial to a truly axial position.

(30) This, after treatment with base to remove traces of the phenol, is the equilibrated mixture and contains about 7–9% of the *trans* isomer.

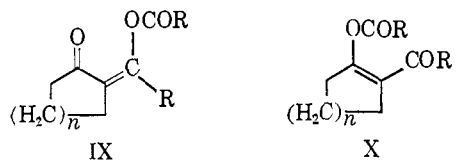
(31) The use of other solvents such as dimethylformamide, dioxane, tetrahydrofuran, ether, acetone, benzene, or petroleum ether reduced the yield in this preparation.

(32) The possibility that VIII could be produced in a kinetic process by hydrolysis of a molecule such as i was originally entertained by the



VI VII VIII

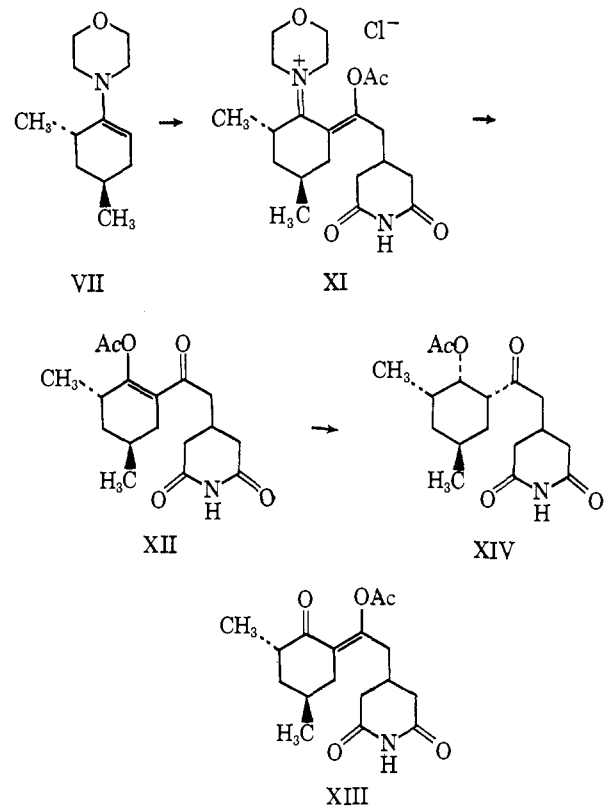
The problem of further modifying VIII now presented itself and the work of Hunig, *et al.*,[34] suggested a line of attack. They had found that the double acylation of enamines of cyclic ketones by acyl chlorides led to products of type IX (n = 2) after hydrolysis. Later, on the basis of ultraviolet spectral data, it was suggested,[35] but not conclusively proved, that the product was X in



IX X

the case of six-membered rings (n = 2) and essentially IX in the case of five-membered rings (n = 1). We elected to investigate this avenue using VII.

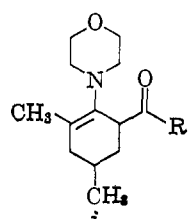
Acylation of VII by V as before was followed by the addition of 1 equiv. of the second acid chloride. In experiments where the latter was either formyl fluoride or carbobenzoxy chloride a copious evolution of carbon monoxide occurred and only VIII could be isolated after hydrolysis. However, when acetyl chloride was used a glassy product was obtained which on chromatography over silica gel afforded XII[36] in 40% over-all yield with no sign of the isomeric compound XIII.



VII XI XII XIV XIII

Some evidence for the structure of XII was secured when it was found that XIV, obtained by hydrogenation of XII over a rhodium-on-alumina catalyst in ethyl acetate, did not give 2,4-dimethylcyclohexanone on treatment with base. The structure of XII was completely proved when it was observed that the solution infrared spectrum was identical with that of optically

authors.[1] This viewpoint was not favored however, largely because the decomposition step would have to involve the unlikely, but not impossible equatorial protonation. Subsequent work[28] and more recently, deuterium isotope studies, to be reported later, have confirmed our views.



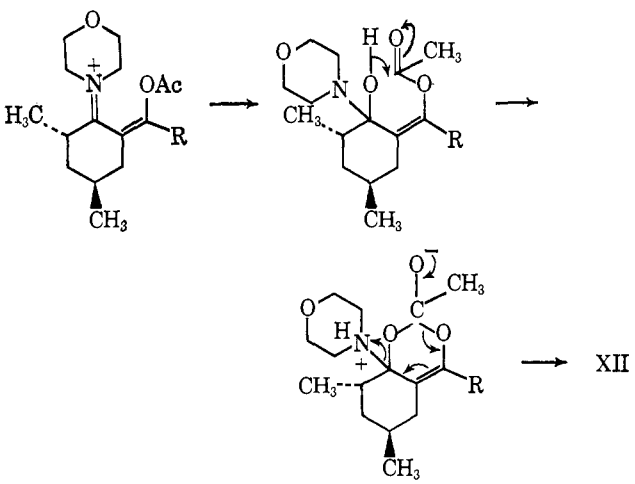
i

(33) After this work was complete H. J. Schaeffer and V. K. Jain (*J. Pharm. Sci.*, **52**, 509 (1963); *J. Org. Chem.*, **29**, 2595 (1964)) reported the preparation of VIII by essentially this method. They however originally used *trans*-2,4-dimethylcyclohexanone from the thermal decomposition of cycloheximide, in the belief that only this isomer would give rise to the enamine VII.

(34) S. Hunig, E. Benzing, and E. Lücke, *Ber.*, **90**, 2833 (1957).

(35) S. Hunig and E. Lücke, *ibid.*, **92**, 652 (1959); S. Hunig and W. Lendle, *ibid.*, **93**, 909 (1960).

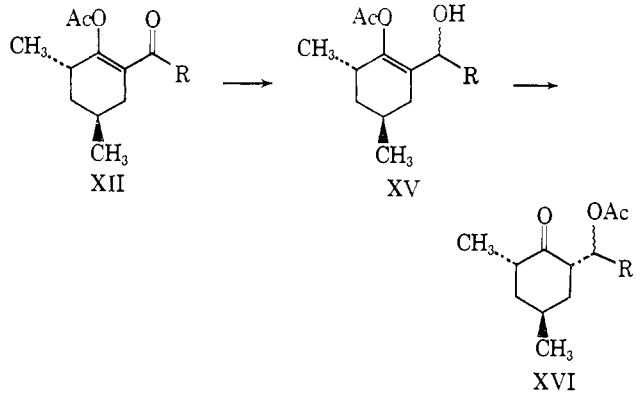
(36) XI is, without doubt, the product of diacylation of VII, but a six-membered cyclic mechanism can be written to explain the ester transfer in the formation of XII, in which the protonated form of the carbinolamine permits morpholine to behave as a good leaving group.



XII

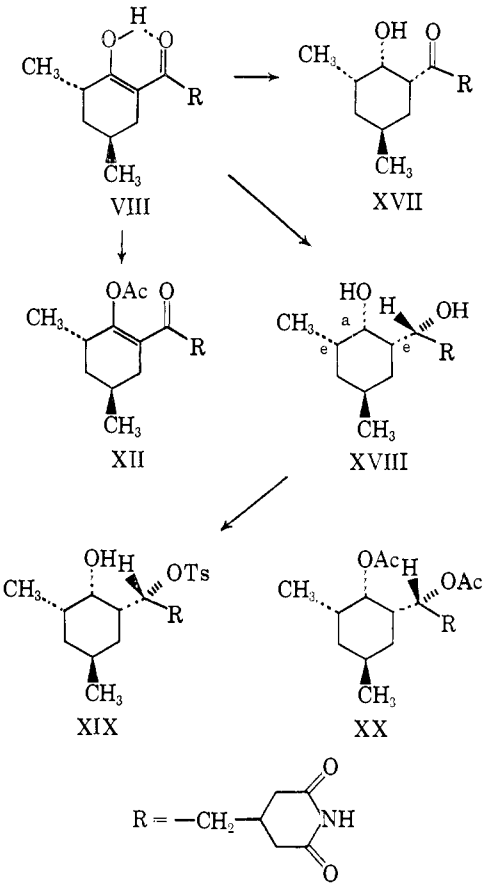
We thank Dr. W. D. Gurowitz who suggested this pathway. Undoubtedly the related products obtained recently by R. F. Struck, H. J. Schaeffer, C. A. Krauth, R. J. Kemp, Y. F. Shealy, and J. A. Montgomery, *J. Med. Chem.*, 7, 646 (1964), have the same structure, being of type XII.

active ψ-cycloheximide-I acetate[37] whose stereochemistry we had already demonstrated.[23] Thus this synthetic tack appeared unprofitable but in an effort to salvage something from the route we attempted to reduce the ketonic group of XII with diphenyltin dihydride in ether with the idea that the ester transfer would be reversed as shown below. However, this



hope was dashed when it was found that the procedure led only to a complex mixture whose infrared spectrum suggested that extensive hydrogenolysis had taken place. Further work then in this direction was abandoned. Nevertheless we had learned that on hydrogenation XII *did give rise to a product with the desired ring stereochemistry* (*i.e.*, XIV), a most encouraging finding. With the observation that acid-catalyzed enol acetylation of VIII with isopropenyl acetate at 100° also afforded XII,[38] we concluded that VIII probably existed largely in the enolic form depicted.[39] Consequently we attempted to reduce VIII to the dihydro derivative XVII using a platinum catalyst in acetic acid, by analogy with the reduction of XII. This yielded a complex mixture from which it was possible to isolate a small sample of the desired compound. It was still impure, however, and could not be used for further work. What was truly surprising was the finding that when the hydrogenation was forced to completion by renewing the catalyst several times, *dl-dihydrocycloheximide* (*XVIII*) *itself was obtained in 60% yield.* This compound was too insoluble in solvents where a comparison of its infrared spectrum with the optically active form would be meaningful. Therefore the monotosylate XIX and the diacetate XX were prepared and their solution infrared spectra were found to be identical with those of the optically active forms.[23]

Thus in three relatively simple steps we were able to establish stereoselectively, five asymmetric centers. Four of these were those desired in the final product including that in the side chain. The problem then, of establishing the axial methyl group at C-4, was solved. The hydrogenation step, however, bears further scrutiny and it is perhaps axiomatic to state that hydrogenation of VIII to XVIII occurs in two discrete steps involving XVII as an intermediate since (a) the latter (in the optically active series) can be isolated half-way through the reduction as noted above, and (b) the rate of reduction exhibits a break, becoming very slow after the introduction of 1 equiv. of hydrogen. In the ground state, however, VIII can be expected to exist as a conformational mixture of VIIIa and VIIIb with the latter in slight predominance because it contains a quasi-axial methyl group (at C-2) whereas the former has essentially a fully axial methyl group (at C-4).



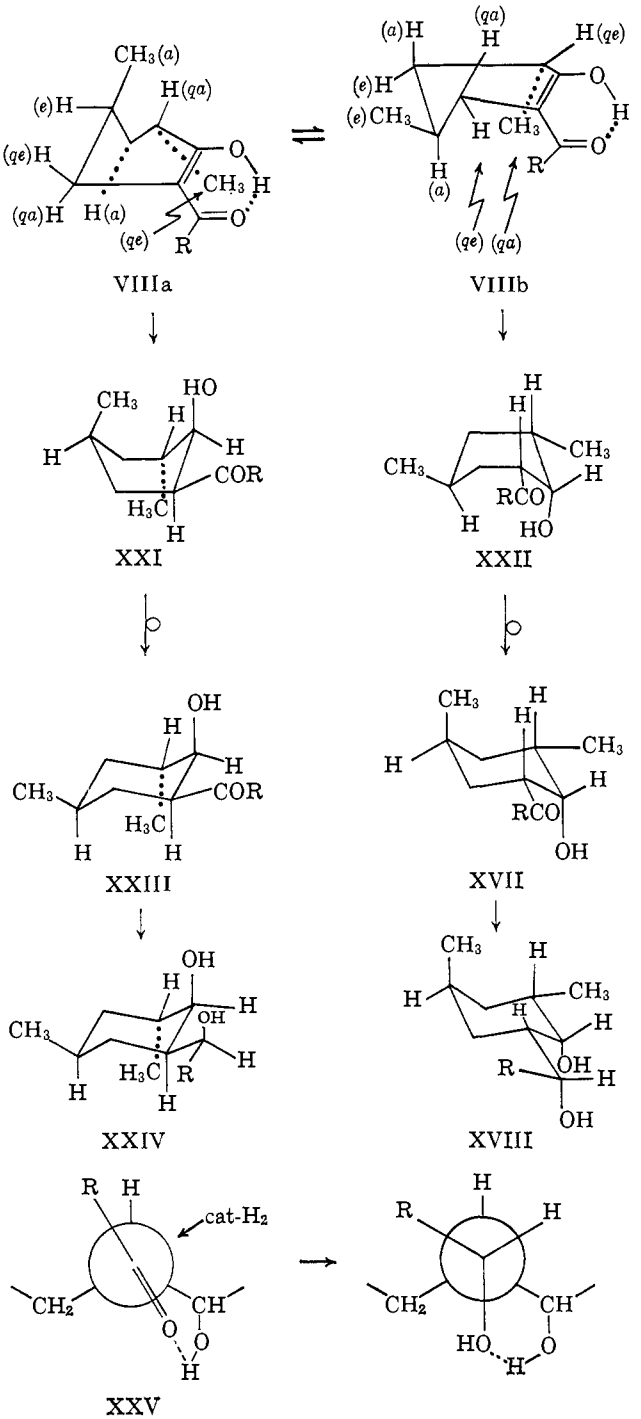
From the point of view of steric hindrance to catalyst approach the α face of VIIIa is more accessible than the β face (1*a*-H + 1*qa*-H + 1*qe*-CH_3 *vs.* 1*qa*-H + 1*a*-CH_3; where *a* = axial, *e* = equatorial, *qa* = quasi-axial, and *qe* = quasi-equatorial). On the other hand the α face of VIIIb appears more sterically hindered than the β face (1*a*-H + *qa*-CH_3 *vs.* 1*a*-H + 1*qa*-H + *qe*-H). As most of the hindrance comes from axial and quasi-axial groups, hydrogenation of VIII can be expected to involve largely the β face of the conformer VIIIb and to a lesser extent the α face of VIIIa. Under these circumstances both conformers would be converted to the boat forms of potential products, *i.e.*, XXII and XXI, respectively, which would flip immediately into the chair forms XVII and XXIII. The further reduction of XVII to XVIII with induction of the correction orientation of the side-chain hydroxyl was not anticipated and can only be classified as that type of good fortune which often attends the synthesis of polyasymmetric molecules, and is so aptly described by Ginsberg in his monograph on the opium alkaloids.[40] Its preferential formation perhaps can be rationalized on the basis of reduction of the conformer XXV by frontal approach of the catalyst, as shown. It might be expected that XXV would be the most stable of the six possible conformers both from the point of view of

(37) M. Suzuki, *Chem. Pharm. Bull.* (Tokyo), 8, 778 (1960).

(38) We thank Dr. W. D. Gurowitz who performed this experiment.

(39) This is not perhaps surprising since it is a well documented fact that endocyclic double bonds are more stable than their exocyclic counterparts in six-membered rings: H. C. Brown, J. A. Brewster, and and H. Schechter, *J. Am. Chem. Soc.*, 76, 467 (1954).

(40) D. Ginsberg "The Opium Alkaloids," Interscience Publishers, Inc., New York, N. Y., 1962, p. 62.



hydrogen bonding and the skew interactions of the R group. It is interesting to note that this reduction in the side chain corresponds to the production of an axial hydroxyl group in a ring. The alternative possibility that this reduction is controlled by a nonsteric directive effect, involving the ring hydroxyl group, cannot be overlooked. Such effects have been described recently.[41]

In an attempt to find the expected second hydrogenation product XXIV, the glassy residue from the mother liquors of the reaction were chromatographed extensively but to no avail. No crystalline material could be isolated. Much to our surprise, however, when the optically active form of VIII was hydrogenated under the same conditions as those used for the racemic compound, dihydrocycloheximide (XVIII) was not obtained initially. Instead a new highly crystalline diol was isolated in about 20% yield by direct crystallization. Its infrared spectrum was entirely different from that of XVIII and its n.m.r. spectrum in pyridine had a *sharp absorption* at 234 c.p.s. (half-height width ~7 c.p.s.) indicative of a ring C*H*OH proton with the hydroxyl axially oriented.[23] In confirmation of this its O,O,N-triacetyl derivative showed a *sharp* hydrogen absorption for the ring C*H*OCOCH$_3$ function at 301 c.p.s., a value to be expected for equatorial hydrogen at such a location.[23] *This diol afforded an acetonide* (whose n.m.r. spectrum showed sharp and broad absorption peaks for the ring and side-chain C*H*O protons, respectively). This fact, together with the knowledge that its ring hydroxyl is axially oriented, permits us, on the basis of previous work, unequivocally to assign this diol, structure XXIV; *i.e.*, it is optically active dihydro-α-epinaramycin-B.[42] It is interesting to note that in this isomer the side-chain hydroxyl group has the (*S*) configuration, which conforms in a mirror image sense to the mechanism of reduction suggested for XXV.

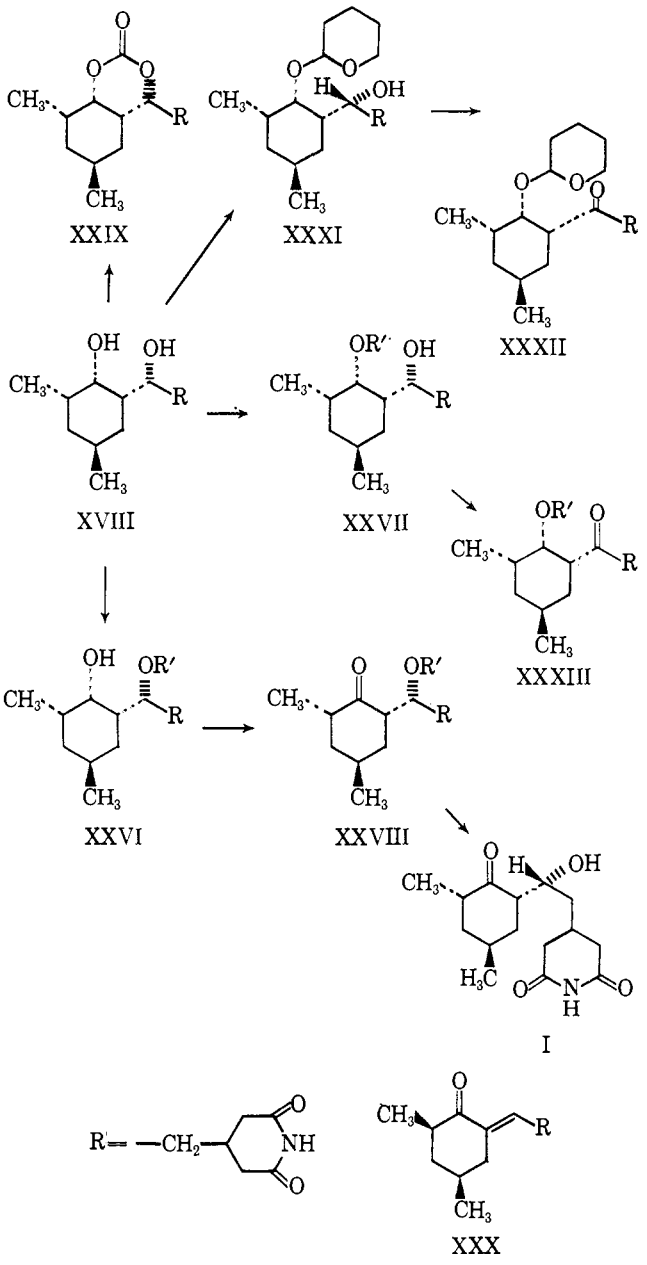
This assignment then reinforces our previous arguments concerning the mechanism of hydrogenation of VIII, both with respect to the production of the ring stereochemistry and to the relative orientation of the side-chain hydroxyl group.

Despite the fact that XXIV was the initial crystalline product from the catalytic reduction of optically active VIII, it was also possible to isolate moderate amounts (~30%) of dihydrocycloheximide but only after very extensive chromatography of the glassy residue from the mother liquors of XXIV.

Returning now to the synthesis of I we found it possible to obtain traces of *dl*-cycloheximide by the oxidation of XVIII with 1 equiv. of chromic acid. However, this could be accomplished only in the case of racemic XVIII. The optically active form of XVIII when oxidized in this way afforded only impure ψ-cycloheximide[23,37] (XVII) and the cycloheximide could not be isolated from the mother liquors by crystallization or chromatography. The isolation and purification of *dl*-I by this method also left a great deal to be desired and we looked for a more satisfactory route. The most logical approach appeared to be through protection of the side-chain hydroxyl group. With this in mind XVIII was treated with 1 equiv. of acetyl chloride in pyridine. This led to a mixture of the two hydroxy acetates XXVI (R′ = Ac) and XXVII (R′ = Ac) in the ratio of 9:1 from which the former could be isolated pure in 65–80% yield. Oxidation of XXVI (R′ = Ac) then afforded *dl*-cycloheximide acetate (XXVIII, R′ = Ac) in excellent yield. However, all attempts to hydrolyze XXVIII (R′ = Ac) to cycloheximide failed. Only further transformation products of I were obtained or starting material was recovered. Oxidation of XXVII (R′ = Ac), which was obtained in only small amounts, led as expected to the previously prepared XIV (*i.e.*, XXXIII, R′ = Ac). The use of other protecting groups was then examined, but for the

(41) T. J. Howard, *Rec. trav. chim.*, 83, 992 (1964); *Chem. Ind.* (London), 1899 (1963); S. Nishimura and K. Mori, *Bull. Chem. Soc. Japan*, 36, 318 (1963).

(42) A detailed discussion of the validity of making this assignment in this way can be found in part IX of this series.[23]



sake of economy optically active dihydrocycloheximide was used in most of these experiments.

A logical choice appeared to be the carbobenzoxy group but all attempts to obtain the desired ester were futile. Even a preformed anion prepared from XVIII and 1 mole of methylmagnesium bromide in tetrahydrofuran did not react with carbobenzoxy chloride in the expected manner. Treatment of optically active XVIII with *p*-nitrophenyl chlorocarbonate did not lead to the anticipated hydroxy ester but gave instead the highly crystalline carbonate XXIX which was of little use for further work. Reaction of XVIII with tetrahydropyran did afford an hydroxy tetrahydropyranyl derivative in excellent yield which appeared to be a single compound.[43] Oxidation of this substance with chromium trioxide in pyridine led to a crystalline product which by virtue of its infrared spectrum and elemental analysis had to be a ketotetrahydropyranyl ether. Its n.m.r. spectrum showed a band for a single proton at 274 c.p.s. for $\begin{matrix}O\\O\end{matrix}>CHR$, a complex multiplet at ~220 c.p.s. corresponding to the OCH_2 of the tetrahydropyran ring, and a $>CHOR$ proton resonance. The component of the multiplet due to the latter proton was not sufficiently well defined to permit a decision to be made as to whether this hydrogen should be assigned to the cyclohexanone ring or the side chain.

Attempts to cleave the tetrahydropyranyl ether with mild acid were unsuccessful and strong acid gave only an oily product. This approach was abandoned when it was found that 1-cycloheximide itself was converted to anhydroisocycloheximide XXX when treated with aqueous methanolic oxalic acid at room temperature. In addition it seemed likely that the initial tetrahydropyranyl derivative must be formulated as XXXI (and its oxidation product as XXXII) since it is produced under conditions where thermodynamic control might be expected to operate. Previously we had found[23] that reduction of the ketone in cycloheximide acetate under acidic or basic conditions leads to considerable ester transfer from the side-chain hydroxyl to that being produced in the ring. Presuming that in both cases this transfer involves an equilibrium process, it seemed likely, if somewhat surprising, that the acyl group preferred largely to reside on the axial hydroxyl function of the ring. These impressions were completely confirmed when we found that the reaction of optically active XVIII with trifluoroacetic anhydride alone led exclusively to the amorphous hydroxytrifluoroacetate XXVII (R′ = $COCF_3$).[44] Proof of the structure of this compound was obtained by oxidation to the keto ester XXXIII (R′ = $COCF_3$), whose n.m.r. spectrum in deuteriochloroform showed a *sharp* peak at 331.5 c.p.s. (half-height width 4.5 c.p.s.) which could only be characteristic of an equatorial $CHOCOCF_3$ proton in a cyclohexanol ring.[23] Confirmation of this was obtained by hydrolysis of XXXIII (R′ = $COCF_3$) with potassium bicarbonate solution which afforded ψ-cycloheximide-I (XVII) in its optically active form. This was judged to be spectroscopically identical with the somewhat impure sample obtained above by partial catalytic reduction of VIII. Its acetate was also identical with that (XIV) obtained earlier by reduction of XII as well as with an optically active sample prepared previously.[23]

Thus we were faced with a dilemma. On the one hand the use of an acylating agent, which would lead to an unreactive ester, permitted acylation of the side-chain hydroxyl, but by the same token the ester could not be subsequently hydrolyzed without destroying the molecule. On the other hand the use of a reagent which afforded an easily hydrolyzable ester led only to ring-hydroxyl acylation. Thus an impasse appeared to have been reached. In the meantime, however, experiments indicated that the chloroacetate of 1-cycloheximide could be hydrolyzed back to I in reasonable yield. The chloroacetyl group then appeared a likely candidate for protection of the side-chain hydroxyl group of XVIII. This proved to be true only when 1 equiv. of chloroacetyl chloride was added in one portion (as fast as possible) to XVIII in dioxane con-

(43) This implies that the formation of the tetrahydropyranyl ether is accompanied by asymmetric induction at the new optically active center in the ether ring. A similar effect was noted by A. C. Ott, M. F. Murray, and R. L. Pederson, *J. Am. Chem. Soc.*, 74, 1239 (1952), when they treated androstenolone with dihydropyran.

(44) Undoubtedly this acylation occurs first on the side-chain hydroxyl group and is then rapidly transferred by an ester exchange process to the ring hydroxyl.

taining 1 equiv. of pyridine. Under these circumstances pyridine hydrochloride precipitates, thus removing both acid and base from the sphere of reaction, and reasonable yields of the desired ester (XXVI, R′ = $COCH_2Cl$) were produced. Any excess of base (*i.e.*, pyridine) led to a complete reversal of the situation and large amounts of the isomeric ester (XXVII, R′ = $COCH_2Cl$) were obtained as could be expected. Oxidation of XXVI (R′ = $COCH_2Cl$) with chromium trioxide in aqueous acetone containing a little acetic acid afforded XXVIII (R′ = $COCH_2Cl$) in good yield and hydrolysis of the latter with aqueous methanolic potassium bicarbonate then gave *dl*-cycloheximide, m.p. 139–140°. Its solution infrared and n.m.r. spectra were identical with those of the naturally occurring material and its biological activity[45] against *Saccharomyces pastorianus* was 50% of that of the *l* form. Thus against this organism the *d* isomer has no activity as was anticipated.

The same reaction sequence was also applied to optically active dihydrocycloheximide with the exception that the intermediate hydroxychloroacetate (XXVI, R′ = $COCH_2Cl$) was not isolated but was oxidized directly to the ketochloroacetate (XXVIII, R′ = $COCH_2Cl$). Hydrolysis of the latter using above specified conditions then afforded pure *l*-cycloheximide (I) identical in all respects with the natural product. This constitutes a total stereoselective synthesis of cycloheximide since *cis*-2,4-dimethylcyclohexanone has been resolved previously.[14] It also constitutes a total synthesis of naramycin-B and of isocycloheximide as both of these compounds have been produced[25] by base-catalyzed isomerization of I.

In conclusion, the synthetic methods described above, in making available compounds of the stereochemistry of I, now open the door to synthetic work on the streptovitacins[46] (hydroxycycloheximides) and inactone.[47]

Experimental Section

Melting points are uncorrected. Infrared spectra were obtained with a Baird Model 4-55 recording spectrometer and, where not stated, as Nujol mulls. N.m.r. spectra were recorded in deuteriochloroform unless otherwise stated and peaks were measured downfield from TMS taken at 0 c.p.s. A Varian 60-Mc. instrument (A-60) was used to obtain the latter spectra.

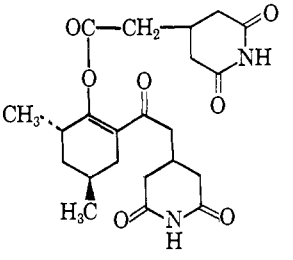
N-(*trans*-4,6-Dimethyl-1-cyclohexenyl)morpholine (VII). *dl-cis*-2,4-Dimethylcyclohexanone (200 g.) was added to a mixture of morpholine (280 g.) and toluene (1.2 l.) containing Dowex-50W resin (2.5 g.). The mixture was refluxed in an apparatus fitted with an efficient water separator, until water ceased to be removed azeotropically from the system (about 48 hr.). The yellowish solution was then filtered to remove the resin and evaporated under reduced pressure to separate the solvent. The residual liquid was fractionally distilled under reduced pressure (3 mm.) and that portion boiling at 95–105° was refractionated to give pure *dl*-VII (214 g.), b.p. 97–98° (3 mm.), $n^{25}D$ 1.4930. *Anal.* Calcd. for $C_{12}H_{21}NO$: C, 73.8; H, 10.8; N, 7.2. Found: C, 73.8; H, 10.7; N, 7.3.

When optically active *cis*-2,4-dimethylcyclohexanone ($[\alpha]^{25}D$ +5° (EtOH)) was used in this experiment, a similar yield of the optically active form of VII was obtained, $[\alpha]^{25}D$ +45° (*c* 2.0, $CHCl_3$).

dl- and *l*-Dehydrocycloheximide (VIII). A 12-l., three-necked, round-bottom flask equipped with a magnetic stirring bar, a nitrogen inlet, and a 500-ml. addition funnel was charged with triethylamine (75 g.) dried over sodium, chloroform (3.5 l.) dried over phosphorus pentoxide, and the morpholine enamine VII (150 g.). 3-Glutarimidylacetyl chloride (122 g.) in *p*-dioxane (600 ml.), previously dried over calcium hydride, was added with good stirring under dry nitrogen over a period of 6 hr. The mixture then was allowed to stand in the refrigerator overnight. A brown, sandy solid (27 g.) which had deposited was removed by filtration (this is discussed below), and the filtrate was then concentrated to a dark oily sludge (600 g.) by removal of the bulk of the solvents under reduced pressure. The residual material was treated with a buffer solution (pH 5.5) made up from water (1.32 l.), methanol (0.5 l.), acetic acid (0.33 l.), and sodium acetate (396 g.). After stirring for about 2.5 hr. a highly crystalline precipitate had appeared, but for maximum recovery of product the total mixture of liquid and solid was extracted several times with methylene chloride. The combined extracts (1500 ml.) were washed with sodium bicarbonate solution (two 100-ml. portions) followed by water (two 100-ml. portions). The methylene chloride solution then was dried over anhydrous magnesium sulfate and evaporated under reduced pressure. The gummy residue readily crystallized from methylene chloride–alcohol to give almost pure *dl*-dehydrocycloheximide (37.5 g.) as white nacreous crystals, m.p. 173–175°. An additional 15 g. of this material was obtained by concentrating the mother liquors. A sample recrystallized several times from the same solvent pair afforded the pure compound, m.p. 176–178°. Its infrared spectrum in chloroform (5% solution) showed bands at 2.99, 5.85, 6.21, 6.35, 8.00, and 8.70 μ, and was identical with that of a specimen prepared by the oxidation of *l*-cycloheximide. In Nujol mull, absorption peaks appeared at 3.11, 3.22, 5.85, 6.21, 7.10, 7.72, 7.85, 8.10, 8.74, 9.16, 10.50, and 11.25 μ. *Anal.* Calcd. for $C_{15}H_{21}NO_4$: C, 64.5; H, 7.6; N, 5.0. Found: C, 64.5; H, 7.6; N, 5.0.

A sample (70 mg.) of VIII was dissolved in ethanol (10 ml.) and added hot to cupric acetate monohydrate (152 mg.) in water (5 ml.). After standing overnight the green precipitate was collected and recrystallized from methylene chloride–methanol to give the pure copper chelate of VIII, m.p. 232–233°. Its 5% solution in chloroform showed characteristic infrared absorption at 6.39 μ for a chelate of this type. *Anal.* Calcd. for $C_{30}H_{40}CuN_2O_8$: C, 58.1; H, 6.5; Cu, 10.3; N, 4.5. Found: C, 57.8; H, 6.5; Cu, 10.3; N, 4.6.

The tan colored solid which precipitated from the acylation reaction mixture was investigated only at a late stage in the synthetic work. When a sample was stirred with aqueous methanolic hydrochloric acid (10%) a white solid was obtained which on repeated crystallization from ethyl acetate, then methylene chloride–methanol, afforded a product, m.p. 188–189°, undoubtedly of structure i in view of the analytical and spectral data. Its infrared spectrum showed bands at 3.08, 3.21, 5.68, 5.76, 5.90, 6.07, 7.93, 8.71, 9.09



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and 9.38 μ in Nujol mull. *Anal.* Calcd. for $C_{22}H_{23}N_2O_7$: C, 61.1; H, 6.5; N, 6.5. Found: C, 60.9; H, 6.5; N, 6.6.

l-Dehydrocycloheximide was prepared in similar yield by the above procedure using the optically active form of the enamine VII. The product, m.p. 173–174°, $[\alpha]^{25}D$ −34.9° (*c* 1.0, $CHCl_3$), did not depress the melting point of an authentic sample, m.p. and m.m.p. 173–176°, $[\alpha]^{25}D$ −34.5° (*c* 1.0, $CHCl_3$), prepared by the oxidation of naturally occurring cycloheximide. *Anal.* Found: C, 64.7; H, 7.6; N, 5.0.

dl-Enol Acetate of Dehydrocycloheximide (XII). A. By Double Acylation of VII. 3-Glutarimidylacetyl chloride (1.9 g.) was suspended in dry chloroform (50 ml.) under an atmosphere of nitrogen and then treated with a solution of dry triethylamine (2.0 g.) in chloroform (25 ml.). The latter addition was carried out dropwise with stirring at ice-bath temperatures over a period of 20 min. The *dl*-enamine (VII; 3.5 g.) was added during 30 min. with stirring at room temperature and stirring was continued thereafter overnight. The reaction mixture was then cooled to 5°, and a solution

(45) We gratefully acknowledge that biological testing of this material was carried out by Drs. M. Siegel and H. Sisler of the University of Maryland.

(46) R. R. Herr, *J. Am. Chem. Soc.*, **81**, 2595 (1959).

(47) R. Paul and S. Tchelitcheff, *Bull. soc. chim. France*, 1316 (1955).

of acetyl chloride (2.5 g.) in dry chloroform (10 ml.) was added dropwise. Stirring was prolonged for 3 hr. and a small quantity (~0.4 g.) of a precipitate was removed by filtration. The filtrate was poured into a buffer solution made up from sodium acetate (25 g.), acetic acid (20 ml.), and water (100 ml.). After stirring vigorously for 2.5 hr. the chloroform layer which had separated was removed and the aqueous phase was extracted with methylene chloride (50 ml.). The combined organic extracts were washed with 1 *N* HCl acid (100 ml.) and 5% sodium bicarbonate solution, and then dried over anhydrous magnesium sulfate. Removal of the solvents under reduced pressure afforded a viscous glass (4.4 g.) which was dissolved in 80 ml. of a 1:1 mixture of methylene chloride–petroleum ether (b.p. 30–60°) and absorbed on a column of silica gel (90 g., 80–200 mesh). Elution of the column with methylene chloride–petroleum ether mixtures, methylene chloride, and methylene chloride containing up to 10% ethyl acetate gave only small amounts of material which were not the desired product. Washing the column with methylene chloride containing 20% ethyl acetate (16 50-ml. portions) afforded material which crystallized when triturated with ether. These fractions were combined (1.71 g.) and crystallized from ether–petroleum ether (b.p. 30–60°) to give a nicely crystalline solid (1.25 g.), m.p. 112–115°. A second crop (75 mg.) had m.p. 109–112°. These were combined and recrystallized to give pure material (1.08 g.), m.p. 115–116°. Its infrared spectrum showed bands at 3.10, 3.21, 5.66, 5.72, 5.79, 5.92, 6.04, 7.09, 7.40, 7.84, 7.92, 8.31, 8.69, 9.05, and 9.19 μ in Nujol mull and at 2.97, 5.85, 7.24, 8.03, 8.72, and 9.95 μ in 2% chloroform solution. *Anal.* Calcd. for $C_{17}H_{23}NO_5$: C, 63.5; H, 7.2; N, 4.4. Found: C, 63.4; H, 7.3; N, 4.3.

B. By Enol Acetylation of *dl*-Dehydrocycloheximide. *dl*-Dehydrocycloheximide (1.0 g.) was added to isopropenyl acetate (20 ml.) containing a trace of sulfuric acid and the mixture was refluxed overnight. The liquid then was stirred with aqueous sodium acetate solution and the product, a dark brown oil (1.73 g.), was isolated by methylene chloride extraction in the usual way. The infrared spectrum of the oil showed no NH absorption and it was assumed that both O- and N-acylation had taken place. The oil was dissolved therefore in methylene chloride and this solution then was treated with a stream of gaseous ammonia for 2 hr., after which it was allowed to stand overnight. The solution was washed with water, dried over anhydrous magnesium sulfate, and evaporated to dryness. Because the residual oil (1.07 g.) could not be recrystallized, it was redissolved in methylene chloride and chromatographed over silica gel. Elution with methylene chloride containing up to 10% ethyl acetate (38 50-ml. portions) afforded some starting material whereas when the ethyl acetate content of the eluting solvent was raised slowly to 25% (30 50-ml. portions) crude enol acetate (0.49 g.) was eluted from the column. Crystallization from methylene chloride–ether afforded material, m.p. 103–107° (168 mg.). A further crystallization from the same solvent pair gave the pure enol acetate, m.p. 116–117°. When mixed with a sample prepared according to A above no melting point depression was observed (m.m.p. 115–116.5°). Both the solid-state and solution infrared spectra of the two samples were identical. A close examination of the mother liquors from this reaction failed to reveal the presence of any isomeric enol acetate.

***dl*-Dihydrocycloheximide (XVIII).** *dl*-Dehydrocycloheximide (30 g., m.p. 174–176°) was dissolved in hot glacial acetic acid (400 ml.) and the solution was allowed to cool to room temperature. Platinum oxide catalyst (3 g.) was added, and the mixture then was stirred with hydrogen gas at normal temperature and pressure until gas absorption ceased (2 days). The catalyst then was replaced by fresh platinum oxide (2 g.) and stirring with hydrogen was continued for an additional day. Total hydrogen absorption amounted to 5086 ml. (97% of 2 equiv.). The catalyst was removed by filtration and the acetic acid was taken off as completely as possible under reduced pressure. A colorless glass (37 g.) remained. This was dissolved in methylene chloride and then ether was added gradually to the boiling solution (steam bath) until the methylene chloride had almost been replaced completely by this solvent. On cooling, chunky white crystals (18 g.) were deposited, m.p. 150–155°. This was recrystallized by repeating the above process, 1 l. of methylene chloride being needed to dissolve the crude product. The material thus obtained had m.p. 158–160° (14.9 g.) and was suitable for further work. The analytical sample was obtained by recrystallization from acetone–ether, m.p. 164–165°. Its infrared spectrum showed bands at 2.88, 3.14, 3.25, 5.81, 5.95, 7.80–7.85, 8.50, 8.56, 8.69, 9.30, 10.78, 11.17, and 12.30 μ, in Nujol mull. *Anal.* Calcd. for $C_{15}H_{25}NO_4$: C, 63.6; H, 8.9; N, 4.9. Found: C, 63.3; H, 8.9; N, 4.9.

***dl*-Dihydrocycloheximide Diacetate (XX).** A solution of *dl*-XVIII (0.5 g.) in a mixture of acetic anhydride (5 ml.) and pyridine was allowed to stand at room temperature for 24 hr. Evaporation of the volatile materials *in vacuo* led to a glassy, brown product which was dissolved in methylene chloride and chromatographed on a column of silica gel (15 g.). Elution of the column with methylene chloride containing 20% ethyl acetate led to crude XX which afforded colorless platelets, m.p. 155–156° on recrystallization from ether. The infrared spectrum of XX in Nujol mull was characterized by bands at 3.07, (strong) 3.27 (weak), 5.76, 5.85, 7.90, 8.00, 8.05, 8.61, 9.39, 9.55, 9.80, 10.21, 10.61, 11.40, and and 12.18 μ. Its chloroform solution infrared and n.m.r. spectra were identical with those of an optically active specimen, described in an earlier paper.[23] *Anal.* Calcd. for $C_{19}H_{29}NO_6$: C, 62.1; H, 8.0; N, 3.8. Found: C, 62.2; H, 8.0; N, 3.9.

***dl*-Dihydrocycloheximide *p*-Toluenesulfonate (XIX).** *dl*-Dihydrocycloheximide (1.0 g.) was added to a cooled solution of *p*-toluenesulfonyl chloride (1.1 g.) in pyridine (5 ml.) and the solution was allowed to stand at room temperature for 48 hr. Isolation of the product in the usual way afforded a viscous oil which crystallized from ether–petroleum ether (b.p. 30–60°) as rosettes of hard, colorless crystals (0.5 g.) m.p. 135–137°. Two further crystallizations from methylene chloride–ether gave pure XIX, m.p. 139–140°. Its chloroform solution infrared spectrum was identical with that of an optically active sample prepared according to Okuda.[22] *Anal.* Calcd. for $C_{22}H_{31}NO_6S$: C, 60.3; H, 7.1; N, 3.2; S, 7.3. Found: C, 60.1; H, 7.9; N, 3.1; S, 6.8.

***d*-Dihydrocycloheximide (XVIII) and *l*-Diol XXIV from the Reduction of *l*-Dehydrocycloheximide.** *l*-Dehydrocycloheximide (obtained by chromic acid oxidation of *l*-cycloheximide), m.p. 177–179° (3.0 g.), was dissolved in warm acetic acid (74 ml.). Platinum oxide (0.5 g.) was added and the solution then was stirred at normal pressure and temperature with hydrogen until gas absorption ceased. This amounted to 91% and required 12 hr. The catalyst was removed by filtration and the solvent was removed by evaporation under reduced pressure. The residual gum (3.1 g.) was dissolved in methylene chloride and the solution was boiled, ether being added periodically until all of the methylene chloride had been replaced. On cooling a crystalline solid (1.0 g.) deposited, m.p. 130–139°. Repeated crystallization of this material from the same solvents afforded pure diol XXIV, m.p. 138.5–139.5°, $[\alpha]^{25}D$ −8.0° (*c* 1.0, $CHCl_3$). The solid-state infrared spectrum of this material showed bands at 2.88, 2.94, 3.13, 3.24, 5.77, 5.91, 7.74, 7.84, 8.64, 10.13, 10.79, and 11.18 μ whereas the chloroform solution spectrum had absorptions at 2.88, 2.97, 5.85, 7.26, 7.41, 8.73, 9.30, 9.70, 9.99, 10.27, 10.52, 10.85, and 11.20 μ. Its n.m.r. spectrum in pyridine showed CH_3 doublets at 63 (J = 6 to ~7 c.p.s.) and 60 c.p.s. (J = 5 to ~6 c.p.s.) and >C*H*OH absorptions at 234 (sharp) and 245 c.p.s. (broad). *Anal.* Calcd. for $C_{15}H_{25}NO_4$: C, 63.6; H, 8.9; N, 4.9. Found: C, 63.4; H, 9.0; N, 5.0.

The mother liquors from the above reduction were evaporated to dryness and the residual gum (2.1 g.) was dissolved in methylene chloride and chromatographed over silica gel (75 g.). Elution of the column with methylene chloride containing up to 50% ethyl acetate (30 50-ml. portions) gave only a trace of a crystalline material (32 mg.) which was not investigated. Further elution with methylene chloride–ethyl acetate (45:55; eight 50-ml. portions) afforded a second crystalline material (93 mg.) which when recrystallized had m.p. 151–154°. Its infrared spectrum indicated it to be a new diol which was not investigated at this point. Further washing of the column with the same solvent (38 50-ml. portions) gave a viscous gum (1.142 g.) as did subsequent washing with mixtures containing up to 100% ethyl acetate (20 50-ml. portions). The total material (1.38 g.) from these fractions was combined and from its solution infrared spectrum judged to be crude *d*-dihydrocycloheximide. Crystallization from methanol–water led to the pure compound (0.7 g.) as its dihydrate, m.p. 125–132° (effervescing). *Anal.* Calcd. for $C_{15}H_{25}NO_5 \cdot 2H_2O$: C, 56.4; H, 9.2; N, 4.4. Found: C, 56.2; H, 9.1; N, 4.6.

When a sample of this material was dried at 100° for 3 hr. the pure diol was obtained, m.p. 132–133°, $[\alpha]^{26}D$ +10.4° (*c* 2.0, $CHCl_3$), which did not depress the melting point (m.m.p. 132–133°) of a specimen, m.p. 131–133°, $[\alpha]^{26}D$ +10.7° (*c* 2.0, $CHCl_3$), prepared[14] by the platinum-catalyzed hydrogenation of cycloheximide. The infrared spectra of the two samples were also identical. *Anal.* Calcd. for $C_{15}H_{25}NO_4$: C, 63.6; H, 8.9; N, 4.9. Found: C, 63.6; H, 8.9; N, 5.0.

***l*-O,O,N-Triacetyl Derivative of XXIV.** The diol XXIV (100 mg.) was refluxed in acetic anhydride (2 ml.) containing sodium acetate (50 mg.) for 4 hr. The mixture was evaporated to dryness

under reduced pressure, and the residue was diluted with water. Extraction with methylene chloride followed by the usual isolation procedure afforded a brown solid which crystallized from ether–petroleum ether (b.p. 30–60°) as yellow plates (50 mg.), m.p. 120–125°. Further purification was effected by percolating the crude product in methylene chloride solution through a column of silica gel (2 g.). Recrystallization of the product isolated from the methylene chloride eluates led to the pure triacetyl derivative of XXIV, m.p. 132.5–133.5°, $[\alpha]^{24}D$ −3.5° (*c* 1.0, $CHCl_3$). It showed characteristic infrared bands in Nujol mull at 5.58, 5.79, 5.95, 7.91, 8.05–8.10, 8.54, and 9.72 μ whereas in chloroform solution bands appeared at 5.58, 5.79, 5.90, 7.32, 7.90–7.95, 8.60–8.65, and 9.80 μ. Its n.m.r. spectrum in chloroform showed doublets at 47.0 (*J* = 6.0 c.p.s.) and 59.0 c.p.s. (*J* = 7.0 c.p.s.) for >CHC*H*$_3$ absorption while >C*H*OAc peaks appeared as sharp and broad absorptions at 301 (ring) and 287 c.p.s. (side chain), respectively. In addition COC*H*$_3$ signals appeared at 146 and 121–126 c.p.s. *Anal.* Calcd. for $C_{21}H_{31}NO_7$: C, 61.6; H, 7.6; N, 3.4. Found: C, 61.8; H, 7.8; N, 3.7

Acetonide of Diol XXIV. A sample (0.2 g.) of the diol in acetone (20 ml.) was added to a freshly prepared solution of sulfuric acid (1 ml.) in the same solvent (20 ml.). The solution was allowed to stand for 2 hr., then diluted with a large excess of water, and extracted with methylene chloride. The extract was washed with water, dilute sodium bicarbonate solution, and water again; finally after drying over anhydrous sodium sulfate, it was evaporated to dryness. The residue was crystallized from water and afforded the desired acetonide in good yield, m.p. 120°. Its infrared spectrum showed characteristic bands at 3.09, 3.21, 5.76, 5.87, 7.72, 7.90, 8.30, 8.51, and 8.65 μ. In the n.m.r. spectrum in deuteriochloroform, acetonide–methyl hydrogen absorption was evident at 81–82.6 c.p.s. whereas the cyclohexane ring methyl groups showed doublets at 56 (*J* = 7 c.p.s.) and 51 c.p.s. (*J* = 6.5 c.p.s.). The spectrum also displayed a sharp peak at 225 c.p.s. indicative of the equatorially oriented C*H*OR ring proton and a broad absorption at 237 c.p.s. corresponding to the C*H*OR proton of the side chain. In pyridine solution these peaks appeared at 222 and 239 c.p.s., respectively. *Anal.* Calcd. for $C_{18}H_{29}NO_4$: C, 66.8; H, 9.0; N, 4.3. Found: C, 66.6; H, 9.3; N, 4.0.

***dl*-Dihydrocycloheximide Acetate (XXVI, R′ = Ac) and *dl*-Dihydro-ψ-cycloheximide-I Acetate (XXVII, R′ = Ac).** *dl*-Dihydrocycloheximide (1.6 g.) was dissolved in dry pyridine (16 ml.) and the solution was cooled to 0°. It then was treated dropwise, while stirring and cooling with acetyl chloride (0.6 ml.) in methylene chloride (25 ml.). After stirring at 0° for 2 hr., the resulting solution was poured on ice and water (~100 g.) and extracted with methylene chloride (three 40-ml. portions). The combined organic extracts were washed with water twice and evaporated to dryness. The residue was crystallized from methylene chloride–ether to give *dl*-dihydrocycloheximide acetate (1.2 g.) as long shiny needles, m.p. 177.5–178°. Its infrared spectrum (Nujol mull) showed bands at 2.81 (OH), 3.10, 3.21, 5.77, 5.90, 7.90, 8.70, and 12.01 μ, and its n.m.r. spectrum showed methyl doublets in deuteriochloroform at 58.6 (*J* = 6.8 c.p.s.) and 55.2 c.p.s. (*J* = 5.7 c.p.s.). The latter spectrum was identical with that of the optically active form.[23] *Anal.* Calcd. for $C_{17}H_{27}NO_5$: C, 62.8; H, 8.4; N, 4.3. Found: C, 63.1; H, 8.3; N, 4.3. On a larger scale better yields (80%) of XXVI (R′ = Ac) were obtained.

Dilution of the mother liquor from above with an equal volume of ether and allowing it to stand at 0° overnight gave a second crop of XXVI (0.1 g.) which was removed by filtration. The filtrate was diluted with its own volume of petroleum ether (b.p. 60–80°) and again allowed to stand overnight at room temperature. A colorless precipitate (80 mg.) of XXVII (R′ = Ac) formed which, after recrystallization, had m.p. 145–146°. Its infrared spectrum showed bands at 2.92 (OH), 3.07 and 3.23 (NH), 5.79, 5.85, 5.91, 7.96–8.00, 8.70, 9.31, 9.69, 10.20, 11.50, and 11.98 μ. Its n.m.r. spectrum in deuteriochloroform displayed methyl hydrogen doublets at 46.7 (*J* = 5.9 c.p.s.) and 60.1 c.p.s. (*J* = 6.8 c.p.s.) and was identical with that of the optically active form described previously. *Anal.* Calcd. for $C_{17}H_{27}NO_5$: C, 62.8; H, 8.4; N, 4.3. Found: C, 63.0; H, 8.2; N, 4.5.

***dl*-Cycloheximide Acetate (XXVIII, R′ = Ac).** The hydroxy acetate XXVI (R′ = Ac; 1.0 g.) was added to 100 ml. of a cold 2% solution of chromium trioxide in 96% acetic acid and the solution was set aside at 25° for 3 hr. Dilution with ice-cold water (300 ml.), followed by extraction with methylene chloride (three 50-ml. portions) and isolation of the product in the usual way, led to a crystalline residue. Crystallization of the latter from aqueous alcohol afforded *dl*-cycloheximide acetate as colorless prisms (0.8 g.), m.p. 180–181°. The infrared spectrum in Nujol mull displayed characteristic bands at 3.11, 3.22, 5.73, 5.77, 5.86, 7.88, 8.12, and 11.45 μ. Its solution infrared spectrum in chloroform and its n.m.r. spectrum in the same solvent were exactly superimposable on those of cycloheximide acetate prepared[14] from naturally occurring cycloheximide. *Anal.* Calcd. for $C_{17}H_{25}NO_5$: C, 63.1; H, 7.8; N, 4.3. Found: C, 62.9; H, 7.7; N, 4.2.

***dl*-ψ-Cycloheximide-I Acetate (XIV). A. By Oxidation of XXVII (R′ = Ac).** *dl*-Dihydro-ψ-cycloheximide-I acetate (XXVII, R′ = Ac; 0.2 g.) was oxidized as described in the experiment above. Crystallization of the solid product (146 mg.) from methylene chloride–ether afforded XIV as colorless needles, m.p. 144°. Its infrared spectrum (Nujol mull) was characterized by bands at 3.14, 3.24, 5.79, 5.90, 7.75, 7.99, 8.71, and 9.76 μ. Its n.m.r. spectrum showed methyl peaks at 50.5 (*J* = 5.9 c.p.s.) and 58.2 c.p.s. (*J* = 6.9 c.p.s.). Both of these spectra, taken in chloroform, were identical with those of an optically active specimen described[23] previously. *Anal.* Calcd. for $C_{17}H_{25}NO_5$: C, 63.1; H, 7.8; N, 4.3. Found: C, 63.0; H, 7.8; N, 4.5.

B. By Hydrogenation of XII. A solution of the racemic enol acetate XII (0.3 g.) in ethyl acetate (20 ml.) was stirred with hydrogen in the presence of a 5% rhodium-on-alumina catalyst (120 mg.) for 45 min. at 25° and normal pressure. At the end of this time gas absorption (~110% of theoretical) ceased. The catalyst was removed by filtration and the solvent was removed under reduced pressure. Trituration of the residue with ether afforded a solid which when recrystallized several times from ether–petroleum ether had m.p. 138–140° (125 mg.). Repeated recrystallization or chromatography did not improve the melting point, but its identity with both the product obtained by method A above and the optically active form[23,27] was proven by comparison of infrared spectra and by mixture melting point (138–140°). *Anal.* Found: C, 63.1; H, 7.8; N, 4.3. When 200 mg. of XIV was added to 2 *N* sodium hydroxide (20 ml.) and the mixture was steam distilled, no organic material could be isolated from the distillate. On the other hand, cycloheximide acetate under the same conditions afforded small amounts of *cis*-2,4-dimethylcyclohexanone in keeping with earlier reports.[14]

***d*-Dihydrocycloheximide Carbonate (XXIX).** *d*-Dihydrocycloheximide (XVIII, 0.84 g.) in pyridine (2 ml.) was cooled to 0° in an ice–salt bath and stirred while a solution of *p*-nitrophenyl chloroformate (0.8 g.) in methylene chloride (4 ml.) was added dropwise during 10 min. The pasty mixture was stirred for 5 min. longer then stored at 5° for 2 days. The solvents then were removed at reduced pressure and the residue, which did not crystallize readily, was dissolved in methylene chloride (50 ml.). This solution was passed through a column of silica gel (30 g.) and the column then was washed with methylene chloride (150 ml.). Further washing with the same solvent containing 10% ethyl acetate (250 ml.) led to *p*-nitrophenyl carbonate (0.5 g.), m.p. 143°. Elution of the column with pure ethyl acetate (500 ml.) then gave a glassy material (0.6 g.) which crystallized overnight from ether–ethyl acetate as small hard prisms, m.p. 203–205°, $[\alpha]^{25}D$ +0.4° (*c* 1.0, $CHCl_3$). Its infrared spectrum showed bands at 3.10, 3.21, 5.71, 5.76, 5.89, 7.39, 7.70, 7.91, 8.16, 8.26, 8.59, 8.79, 9.14, 9.26, 11.2–12.2, 12.91, and 13.40 μ. *Anal.* Calcd. for $C_{16}H_{23}NO_5$: C, 62.1; H, 7.5; N, 4.5. Found: C, 61.9; H, 7.4; N, 4.5.

ψ-Dihydrocycloheximide-I Tetrahydropyranyl Ether (XXXI). *d*-Dihydrocycloheximide (2.0 g., m.p. 131–132°) was dissolved in methylene chloride (20 ml.) and added to a solution of dihydropyran (0.6 g.) in methylene chloride (30 ml.). Dowex-50W resin (1.0 g.) was added to the mixture which was then stirred overnight. The resin was removed by filtration and the solvent was removed under reduced pressure. The residual gum solidified and was recrystallized from methylene chloride–ether to give the hydroxy ether (1.0 g.), m.p. 167–170°. A sample recrystallized twice from the same solvents afforded the pure material, m.p. 171–172°, $[\alpha]^{26}D$ 0° (*c* 1.0, $CHCl_3$). The infrared spectrum showed bands at 2.85, 2.98, 3.11, 3.25, 5.84, 5.91, 7.89, 8.44, 8.56, 8.75, 9.02, 9.16, 9.42, 10.26, 10.64, 11.23, and 12.00 μ. *Anal.* Calcd. for $C_{20}H_{33}NO_5$: C, 65.4; H, 9.1; N, 3.8. Found: C, 65.3; H, 9.1; N, 3.7.

Oxidation of ψ-Dihydrocycloheximide-I Tetrahydropyranyl Ether (XXXI). An oxidizing mixture of chromium trioxide (1.0 g.) and pyridine (10 ml.) was prepared according to Poos, Arth, Beyler, and Sarett.[48] To this was added a solution of ψ-dihydrocycloheximide tetrahydropyranyl ether (XXXI, 1.0 g.) in dry pyridine (20 ml.) with stirring. No heat was evolved and the mixture was stirred

(48) G. I. Poos, G. E. Arth, R. E. Beyler, and L. H. Sarett, *J. Am. Chem. Soc.*, 75, 422 (1953).

overnight at room temperature. Isopropyl alcohol (2 ml.) then was added and stirring was continued for 1 hr. All of the volatile materials then were removed under reduced pressure at room temperature (vacuum pump) and the brown solid which remained was extracted with ether. This extract was washed twice with water, dried over anhydrous sodium sulfate, and evaporated to dryness *in vacuo*. A glass (0.76 g.) remained which was dissolved in methylene chloride and chromatographed over silica gel (30 g.). Elution of the column with methylene chloride containing up to 25% ethyl acetate (12 50-ml. portions) did not yield any product, but washing the column with methylene chloride–ethyl acetate (7:3, 20 50-ml. portions) afforded a partially crystalline material (0.54 g.) which was recrystallized twice from ether–petroleum ether (b.p. 30–60°) to yield a powdery material (0.35 g.) whose crystalline character was poorly defined. Its melting point (135–143°) could not be improved by further crystallization; $[\alpha]^{24}D$ +1.1° (*c* 1.0, $CHCl_3$). Its infrared spectrum in Nujol mull showed a complete lack of hydroxyl absorption, and had bands at 3.15, 3.25, 5.78, 5.85, 5.98, 7.65, 8.28, 8.45, 8.65, 8.81, and 10.07 μ. *Anal.* Calcd. for $C_{20}H_{31}NO_5$: C, 65.7; H, 8.6; N, 3.8. Found: C, 65.6; H, 8.5; N, 4.0. No crystalline material could be obtained when a sample (0.2 g.) of this compound was heated for 20 min. on the steam bath with methanol (2 ml.) and 6 *N* hydrochloric acid (4 ml.). At room temperature in methanol containing a trace of hydrochloric acid no loss of the tetrahydropyranyl group occurred.

Dihydro-ψ-cycloheximide-I Trifluoroacetate (XXVII, R′ = $COCF_3$). Dihydrocycloheximide (1.0 g., $[\alpha]^{25}D$ + 10.7°) in dry methylene chloride (20 ml.) was treated dropwise at 0° with trifluoroacetic anhydride (1.0 g.) in the same solvent (10 ml.). The mixture was stirred for 2 hr., washed with ice–water, dried over anhydrous sodium sulfate, and evaporated to dryness under reduced pressure. The residue, a hard friable foam, resisted all attempts at crystallization. It showed infrared bands at 2.87 (OH), 3.11 and 3.21 (NH), 5.60, 5.78–5.92, 7.90, 8.20, 8.40–8.70, 11.46, 12.85, and 13.70 μ. The crude product was used as such in the succeeding experiment.

ψ-Cycloheximide-I Trifluoroacetate (XXXIII, R′ = $COCF_3$). A solution of XXVII (R′ = $COCF_3$; 1.49 g.) in glacial acetic acid (10 ml.) was treated, while cooling in a cold water bath, with a solution of chromium trioxide (0.75 g.) in 80% aqueous acetic acid (10 ml.). After stirring for 2.5 hr. at 5–10° the reaction mixture was diluted with water and extracted with methylene chloride (100 ml.). Isolation of the product from the extract in the usual way afforded crude ψ-cycloheximide-I trifluoroacetate as a white, amorphous solid. Repeated crystallization of the latter from ether–petroleum ether (b.p. 30–60°) gave the pure substance (0.6 g.), m.p. 145–146°, $[\alpha]^{25}D$ −7.2° (*c* 2.5, $CHCl_3$). Its infrared spectrum showed absorption at 3.12 and 3.23 (NH), 5.59, 5.77–5.85, 7.25, 7.85, 8.07–8.10, 8.40–8.60, 8.92, 9.40, 11.31, 11.44, 12.85, and 13.70 μ, and its n.m.r. spectrum showed doublets for CH_3 hydrogen at 53.1 ($J \sim 6.3$ c.p.s.) and 63.3 c.p.s. ($J \sim 6.8$ c.p.s.). *Anal.* Calcd. for $C_{17}H_{20}F_3NO_7$: C, 54.1; H, 5.8; F, 15.1; N, 3.7. Found: C, 54.1; H, 5.8; F, 15.8; N, 4.2.

ψ-Cycloheximide-I (XXXIII, R′ = H). A. By Hydrolysis of XXXIII (R′ = $COCF_3$). A solution of XXXIII (R′ = $COCF_3$; 0.4 g.) in methanol (12 ml.) was mixed with potassium bicarbonate (0.5 g.) dissolved in water (6 ml.). After stirring overnight at room temperature the solution which resulted was concentrated under reduced pressure below 40°, treated with water, and extracted with methylene chloride. The extract was washed with water and dried over magnesium sulfate, and then the solvent was removed under reduced pressure. The gummy residue was crystallized several times from ether–petroleum ether (b.p. 30–60°) to give colorless crystals of optically active ψ-cycloheximide (80 mg.), m.p. 127–128° (lit.[37] m.p. 135–136°),[49] $[\alpha]^{25}D$ +30° (*c* 1.0, $CHCl_3$). It showed characteristic bands at 2.85 (OH), 3.12 and 3.21 (NH), 5.85, 7.89, 7.63, 9.74, and 10.74 μ in the infrared spectrum. *Anal.* Calcd. for $C_{15}H_{23}NO_4$: C, 64.0; H, 8.2; N, 5.0. Found: C, 64.0; H, 8.2; N, 5.0. A sample of this material (20 mg.) was treated with 2 drops of acetic anhydride and 3 drops of pyridine. The product, after isolation in the usual way, crystallized from ether as fine needles, m.p. 149–150°. It did not depress the melting point of an authentic sample[23] (m.m.p. 149–150°) and its identity was further confirmed by comparison of their infrared spectra.

(49) This material was originally prepared by Suzuki[37] by the partial oxidation of dihydrocycloheximide. Repetition of this work has shown that the high melting point of this sample is due to contamination with cycloheximide. Complete separation of the two isomers by crystallization is virtually impossible.

B. By Hydrogenation of Dehydrocycloheximide. Dehydrocycloheximide[14] (m.p. 176–178°, 2.43 g.) in acetic acid (60 ml.) was hydrogenated at room temperature and atmospheric pressure using a preformed platinum catalyst. After the absorption of 1 equiv. of hydrogen the reaction was stopped. Filtration to remove the catalyst followed by evaporation under reduced pressure afforded a glassy residue. Trituration with ether gave a crystalline solid (1.2 g.) which was purified further by chromatography of its methylene chloride solution over silica gel (30 g.). Elution of the column with 10% ethyl acetate in methylene chloride (200 ml.) gave starting material (120 mg.); further elution afforded crude ψ-cycloheximide-I (0.9 g.), m.p. 125–127°, whose melting point was raised to 127–128° on recrystallization from ether–petroleum ether (b.p. 30–60°). The purified material did not depress the melting point of a sample prepared according to method A above, and their infrared spectra were identical. When this experiment was performed using racemic dehydrocycloheximide only an impure sample of *dl*-XXXIII (R′ = H) could be obtained. Its solution infrared spectrum was however essentially the same as that of the optically active form.

***dl*-Dihydrocycloheximide Chloroacetate (XXVIII, R′ = $COCH_2Cl$).** *dl*-Dihydrocycloheximide (1.5 g.) was dissolved in dry *p*-dioxane (8 ml.) containing dry pyridine (0.8 g.). To this solution maintained at 0°, was added in one portion chloroacetyl chloride (0.78 g.) in dry dioxane (4 ml.) with vigorous stirring. Stirring was continued for 1 hr. at 0° and 15 hr. at room temperature. Methylene chloride (75 ml.) was then added and the solution was washed with cold 1 *N* hydrochloric acid and water. After drying over anhydrous sodium sulfate the solution was evaporated to dryness and the solid residue was recrystallized from tetrahydrofuran–ether. The chloroacetate thus obtained (0.894 g.) had m.p. 183.5–184.5° and showed infrared absorption at 2.81, 3.08, 3.21, 5.76, 5.91, 7.14, 7.56, 7.63, 7.92, 8.27, 8.72, 9.45, 10.15, 10.80, and 12.00 μ. *Anal.* Calcd. for $C_{17}H_{26}ClNO_5$: C, 56.8; H, 7.2; Cl, 9.9; N, 3.9. Found: C, 56.5; H, 7.0; Cl, 10.1; N, 4.1.

***dl*-Cycloheximide Chloroacetate (XXVIII, R′ = $COCH_2Cl$).** To a solution of *dl*-dihydrocycloheximide chloroacetate (1.2 g.) in acetone (25 ml.) cooled to 0° there was added with good stirring a solution of chromium trioxide (1.08 g.) in water (5 ml.) and acetic acid (2.5 ml.) over a period of 5 min. After the addition was complete the mixture was set aside for 4 hr. at room temperature. Most of the acetone then was removed under reduced pressure at 25° and water (100 ml.) was added. The product (1.3 g.), isolated by extraction with methylene chloride in the usual way, was crystallized from methylene chloride–ether and afforded the desired material (0.81 g.), m.p. 136–138°. Its infrared spectrum showed bands at 3.14, 3.24, 5.80, 5.89, 7.79, 7.90, 8.06, 8.76, and 9.43 μ in Nujol mull and at 2.95, 5.76, 5.85, 7.41, 8.70, and 10.60 μ in chloroform solution. *Anal.* Calcd. for $C_{17}H_{24}ClNO_5$: C, 57.1; H, 6.7; Cl, 9.9; N, 3.9. Found: C, 56.8; H, 6.6; Cl, 10.2; N, 3.9.

***d*-Cycloheximide Chloroacetate (XXVIII, R′ = $COCH_2Cl$).** Dihydrocycloheximide (1.0 g., m.p. 131–132°, $[\alpha]_{26}$ +10.7°) was chloroacetylated as described above for the racemic case. The crude chloroacetate (1.45 g.) failed to crystallize and thus was dissolved in methylene chloride and chromatographed over silica gel (30 g.). The column was eluted with mixtures of methylene chloride and ethyl acetate. Those fractions obtained from solvent mixtures (18 50-ml. portions) containing up to 50% ethyl acetate were combined and afforded a glassy material (0.8 g.) which again could not be crystallized. This was therefore oxidized as described for the racemic compound, above. The product (688 mg.) crystallized from methylene chloride–ether and afforded cycloheximide chloroacetate, m.p. 135.5–137°, $[\alpha]^{26}D$ +7.5° (*c* 1.0, $CHCl_3$). Its infrared spectrum was identical with that of a specimen prepared[23] by the direct chloroacetylation of *l*-cycloheximide.

***dl*-Cycloheximide (I). A. By Hydrolysis of *dl*-Cycloheximide Chloroacetate.** *dl*-Cycloheximide chloroacetate (0.75 g.) in methanol (25 ml.) was treated with potassium bicarbonate (1.26 g.) in water (8 ml.) and the mixture was stirred at room temperature for 24 hr. It was then diluted with water and extracted with methylene chloride. Evaporation of the dried ($MgSO_4$) extract under reduced pressure gave a gum (0.574 g.) which was dissolved in methylene chloride and chromatographed over silica gel (12 g.). Elution of the column with methylene chloride containing from 2 to 15% ethyl acetate (25 25-ml. portions) afforded a noncrystallizable glass (86 mg.) which was discarded. Further elution with the same solvent containing 20 to 50% ethyl acetate (32 25-ml. portions) gave fractions which crystallized when triturated with ether. These were combined (0.275 g.) and recrystallized from methylene

chloride–ether to give *dl*-cycloheximide, m.p. 137–139° (0.2 g.). A specimen recrystallized from the same solvent pair afforded the pure material, m.p. 139–140.5°. It showed infrared absorption peaks (Nujol mull) at 2.86, 3.12, 3.24, 5.81, 5.92, 7.10, 7.83, 7.90, 8.63, 8.82, 9.02, 9.67, and 11.80 μ. In chloroform solution (1%) it showed bands at 2.81, 2.96, 5.85, 7.23, 8.70, 8.99, 9.68, 10.85, and 11.08 μ and its n.m.r. spectrum in deuteriochloroform showed two methyl doublets at 58.2 (J = 6.1 c.p.s.) and 73.6 c.p.s. (J = 6.7 c.p.s.). The latter two solution spectra were indistinguishable from the corresponding spectra of *l*-cycloheximide, recorded under the same conditions. *Anal.* Calcd. for $C_{15}H_{23}NO_4$: C, 64.0; H, 8.2; N, 5.0. Found: C, 64.3; H, 8.1; N, 5.0.

B. By Oxidation of *dl*-Dihydrocycloheximide (XVIII). An aqueous solution of 1 *N* chromium trioxide (9.3 ml.) containing sulfuric acid (60 ml./l. of solution) was added dropwise with stirring to the diol XVIII (1.1 g.) in acetone distilled from potassium permanganate (30 ml.) at 0–2° during 15 min. The mixture was then allowed to stand in the refrigerator for 48 hr. at 0°. The product, isolated in the usual, was triturated with ether and the solid (0.4 g.) removed by filtration. This was recrystallized from a dilute solution in ether and afforded large hard crystals, m.p. 110–120° (150 mg.). Three further crystallizations from aqueous acetone then afforded essentially pure *dl*-cycloheximide (45 mg.), m.p. 138–139°, which did not depress the melting point of a specimen prepared according to method A above, m.m.p. 138–140°. The infrared spectra of the two specimens were also identical.

l-Cycloheximide (I). *d*-Cycloheximide chloroacetate (0.5 g.) was stirred overnight at room temperature with a solution of methanol (10 ml.) and water (4 ml.) containing potassium bicarbonate (0.84 g.). The methanol then was removed under reduced pressure and the organic product was isolated in the usual way. This material (0.39 g.) could not be crystallized and therefore was dissolved in methylene chloride and chromatographed on a silica gel (10 g.) column. Elution of the column with methylene chloride containing 35% ethyl acetate initially gave starting material (51 mg.) but later fractions (14 25-ml. portions) yielded crude *l*-cycloheximide (190 mg.). Recrystallization of this material from methylene chloride–ether then afforded the pure material, m.p. 115–116°, $[\alpha]^{24}D$ −33° (*c* 1.0, $CHCl_3$), whose infrared spectrum was identical with an authentic sample, m.p. 114–115°, $[\alpha]^{24}D$ −33.8° (*c* 1.0, $CHCl_3$). No depression in melting point was observed when these two samples were mixed, m.m.p. 114–115°. *Anal.* Calcd. for $C_{15}H_{23}NO_4$: C, 64.0; H, 8.2; N, 5.0. Found: C, 63.8; H, 8.2; N, 5.1.

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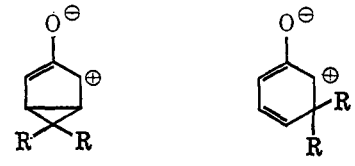
Communications to the Editor

The Relation of Cyclohexenone to Cyclohexadienone Rearrangements. Mechanistic Organic Photochemistry. XIV[1]

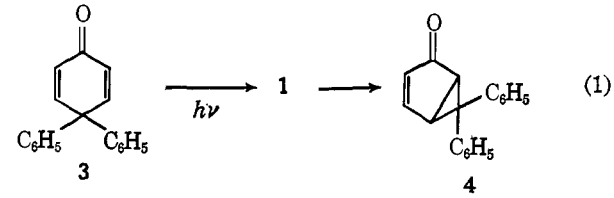
Sir:

The photochemical rearrangements of 4,4-disubstituted cyclohexadienones are well known, and mechanisms involving the mesoionic zwitterions **1** and **2** have been proposed in our earlier publications.[2,3]



1 **2**

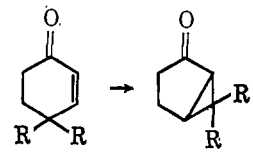
One such rearrangement, conveniently termed type A, is typified by the 4,4-diphenylcyclohexadienone (**3**) to 6,6-diphenylbicyclo[3.1.0]hex-3-en-2-one (**4**) conversion.[3] We suggested this to proceed *via* zwitterion **1** (R = C_6H_5).



3 **4**

Type A dienone rearrangement

Although our proposal of the intermediacy of **1** and **2** in dienone photochemistry seems accepted,[4,5] doubt is cast by the occurrence of type A skeletal changes on irradiation of 4,4-dialkylcyclohexenones.[6] In the



5 **6**

Type A enone rearrangement

monoenones there is no second double bond to par-

(1) For Paper XIII of the series note: H. E. Zimmerman, *Pure Appl. Chem.*, **9**, 493 (1964).

(2) H. E. Zimmerman, 17th National Organic Chemistry Symposium, June 1961, Abstracts, p 31.

(3) (a) H. E. Zimmerman and D. I. Schuster, *J. Am. Chem. Soc.*, **83**, 4486 (1961); (b) *ibid.*, **84**, 4527 (1962).

(4) O. L. Chapman, *Advan. Photochem.*, **1**, 323 (1963).

(5) P. J. Kropp, *J. Am. Chem. Soc.*, **85**, 3779 (1963).

(6) (a) W. W. Kwie, B. A. Shoulders, and P. D. Gardner, *ibid.*, **84**, 2268 (1962); (b) O. L. Chapman, T. A. Rettig, A. I. Dutton, and P. Fitton, *Tetrahedron Letters*, 2049 (1963); (c) B. Nann, D. Gravel, R. Schorta, H. Wehrli, K. Schaffner, and O. Jeger, *Helv. Chim. Acta*, **46**, 2473 (1963).