Glutarimide Antibiotics. XI. A Total Synthesis of *dl*-α-Epiisocycloheximide[1]

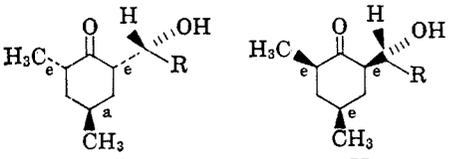
FRANCIS JOHNSON, A. A. CARLSON, AND N. A. STARKOVSKY

Eastern Research Laboratory, The Dow Chemical Company, Wayland, Massachusetts

Received December 6, 1965

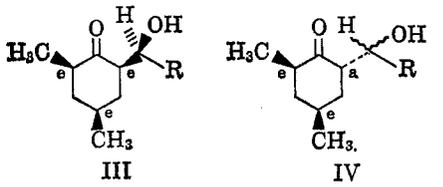
A stereoselective synthesis of *dl*-α-epiisocycloheximide (III) is described. Oxalylation of *dl-cis*-2,4-dimethylcyclohexanone gave the 6-oxalyl ester which spontaneously decarbonylated on distillation. The product ethyl *cis*-2,4-dimethylcyclohexanone-6-carboxylate was transformed into the benzyl ester and the latter was then converted to its magnesiobromide salt. Acylation of this salt with 3-glutarimidylacetyl chloride, followed by reductive debenzylation and decarboxylation, afforded *dl*-dehydroisocycloheximide (V). Catalytic reduction of this compound led to the diol XIII which was selectively chloroacetylated at its side-chain hydroxyl group. Oxidation of the ring hydroxyl of the resulting hydroxy chloroacetate (XIV, R′ = $COCH_2Cl$) yielded the ketone XV (R′ = $COCH_2Cl$) and mild saponification of the latter afforded *dl*-α-epiisocycloheximide (III). The stereochemistry of the intermediates was proved largely by nmr spectroscopy. The relative orientation of the side-chain hydroxyl group of III was deduced by a stereochemical argument involving the facts that diol XIII forms an acetonide, whereas the diol XXIV obtained from III by lithium aluminum tri-*t*-butoxyhydride reduction does not.

The successful synthesis[2] of cycloheximide (I) in a stereoselective fashion has opened the door to the preparation of homologous compounds having *trans*-related substituents at C-2 and C-4. Despite this, the methods employed do not lend themselves readily to the synthesis of the more thermodynamically stable isomers having *cis*-methyl groups at these two positions. The only procedures available for the synthesis of such compounds are (a) base-catalysed isomerization of cycloheximide[3] or (b) aldol condensation of 3-glutarimidylacetaldehyde with *cis*-2,4-dimethylcyclohexanone.[4-6] In the former case, the product, isocycloheximide (II) is obtained in poor yield and is difficult to purify. In the latter, the Japanese[5] workers obtained complex mixtures which ultimately yielded about 12% each of isocycloheximide (II) and α-epiisocycloheximide[7] (III),



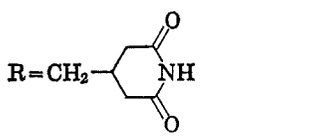
I

II



III

IV



whereas Lawes[4] observed only the products of further dehydration of these hydroxy ketones. We have obtained the racemic form of neocycloheximide (IV; only one optical isomer shown here) from such an aldol condensation,[6] but again in low yield. These methods obviously did not recommend themselves for the preparation of reasonable quantities of pure substances having *cis*-methyl groups. With both a practical need of, and a vested academic interest in, such materials, we elected to investigate an alternate route to the gross skeleton of I. We now describe a synthesis which stereoselectively leads to α-epiisocycloheximide. For the sake of clarity, most of the stereochemical discussion is deferred to a later section.

Synthesis.—Success in this endeavor hinged initially on finding a stereoselective method of preparing dehydroisocycloheximide (V). This was accomplished as follows.

Oxalylation of *dl-cis*-2,4-dimethylcyclohexanone (VI) according to the usual procedure gave good yields of the acylation product (VII) which on distillation underwent spontaneous decarbonylation to the ester VIII (Chart I). Further distillation over soft-glass powder and a trace of iron, as is usual in such decarbonylations, is probably not necessary and in this case, while it was carried out, it appeared merely to reduce the yield of VIII, markedly. When VIII was heated with benzyl alcohol, ethanol distilled and IX could be isolated in good yield. However, glpc analysis using QF-1 on Celite showed the presence of two materials in the ratio of ~60:40. These we regard as the *cis* (IXa) and *trans* (IXb) forms of IX, respectively, since neither ethyl acetoacetate nor the ethyl or benzyl esters of cyclohexanone-2-carboxylic acid showed comparable resolution on the same substrate. This eliminates the possibility of their being the ketonic and enolic forms of IX. It did, however, introduce a discordant note as far as the attempted stereoselective synthesis was concerned. Notwithstanding this, IX was treated in dry tetrahydrofuran with 1 equiv of phenylmagnesium bromide followed by 1 equiv of 3-glutarimidylacetyl chloride. The product presumed to be X proved to be a thick viscous oil and no attempt was made to

(1) A preliminary account of this work has been published: F. Johnson and A. A. Carlson, *Tetrahedron Letters*, 885 (1965).

(2) F. Johnson, N. A. Starkovsky, A. C. Paton, and A. A. Carlson, *J. Am. Chem. Soc.*, **88**, 149 (1966).

(3) 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); **11**, 730 (1963).

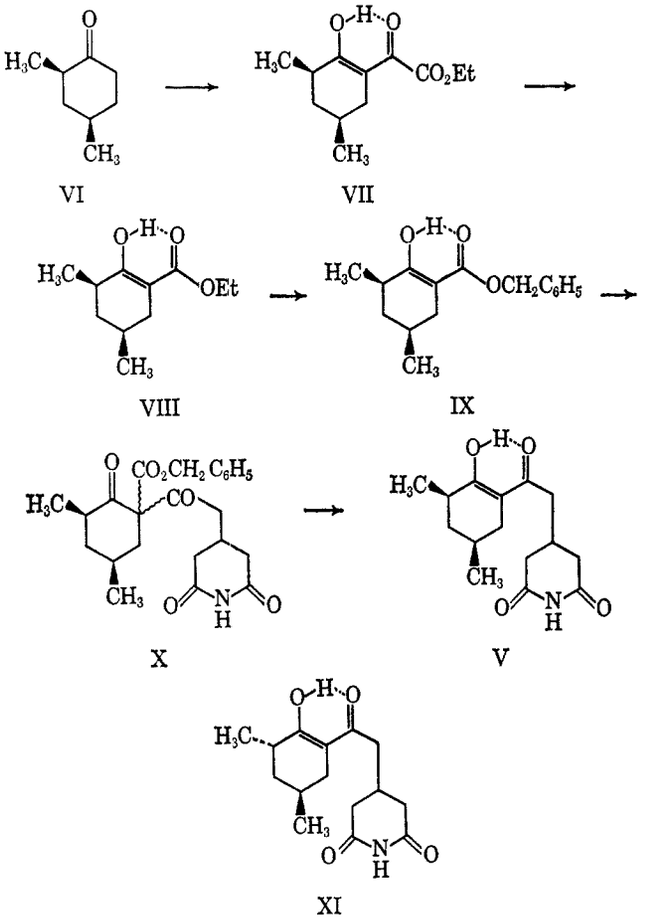
(4) B. C. Lawes, *J. Am. Chem. Soc.*, **82**, 6413 (1960).

(5) 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).

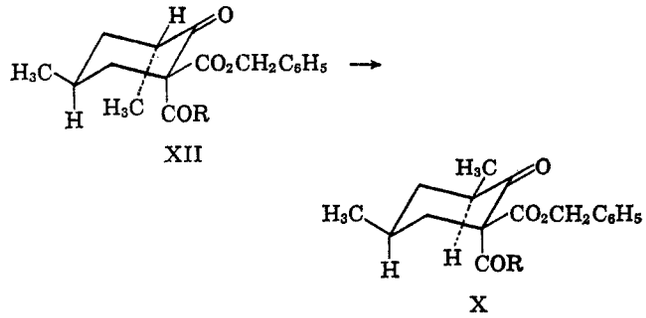
(6) F. Johnson, W. D. Gurowitz, and N. A. Starkovsky, *Tetrahedron Letters*, 1173 (1962); *J. Am. Chem. Soc.*, **87**, 3492 (1965).

(7) This name originally was chosen[5] to represent the optically active isomer having the absolute structure III, since it differs from II only in the relative orientation of the hydroxyl group. The mirror image of III being identical with cycloheximide except for the equatorial nature of the 4-methyl group cannot logically be regarded as an "α-epi" compound. Thus the choice of the name for III was unfortunate and some more trivial designation would have been better. However bearing this in mind we have elected to preserve the name *dl*-α-epiisocycloheximide for the racemic form of III in order to maintain continuity.

CHART I



characterize it other than by infrared spectroscopy. It was hydrogenated in ethyl acetate using a 10% palladium-on-charcoal catalyst to effect debenzylation. Hydrogen absorption ceased at 85% of theory and the filtered solution was boiled to decarboxylate the intermediate β-keto acid. Evaporation of the solvent then afforded the required enolic ketone V as a partially crystalline mass in 50–70% yield after recrystallization. V was characterized as its copper chelate. V was the only substance that could be isolated despite chromatography of the mother liquors. No trace of the isomeric compound XI,[2] from which it is difficult to separate V by chromatography or crystallization, could be found. This perhaps is not surprising for if we consider that acylation of IXb occurs at a rate comparable to IXa, then the product from the former (say XII) would be very sensitive to acid- or base-catalyzed[8] isomerization, this as a direct result of there being considerable non-



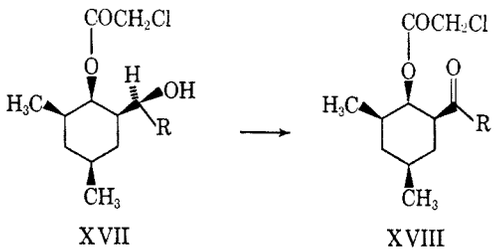
(8) The base or acid required for this isomerization is inherent in the reaction since it involves a carbanion, and magnesium halides are known to behave as Lewis acids.

bonded steric strain between the axial substituents at the 2 and 6 positions of the cyclohexanone ring in XII. A facile synthesis of V had thus been secured.

The remainder of the synthesis (Chart II) was accomplished by much the same procedures as we had employed for cycloheximide. Hydrogenation of V in acetic acid over a platinum catalyst led to 70% of a single crystalline diol (XIII), and once again *it had proved possible to elaborate stereoselectively a molecule having five asymmetric centers in essentially four steps.* When XIII was monoacetylated with acetic anhydride, it afforded XIV (R′ = Ac) in good yield. Oxidation of the latter with chromium trioxide in aqueous acetic acid containing sulfuric acid then led to *dl*-α-epiisocycloheximide acetate (XV, R′ = Ac) whose solution infrared and nmr spectra were identical with those of an optically active specimen.

Hydrolysis of this acetate to the free alcohol did not prove feasible because of competing side reactions such as imide ring opening or reverse aldol cleavage. The reaction sequence thus was repeated using chloroacetyl chloride to protect[2] the side-chain hydroxyl of XIII. Here once again, as in the cycloheximide series, the desired monochloroacetate (XIV, R′ = $COCH_2Cl$) could be obtained only when the reaction was carried out using exactly 1 equiv of pyridine in dioxane solution, with very rapid mixing of the reactants. This technique removes both acid and base from the immediate sphere of the initially produced monochloroacetate (by precipitation of the pyridine hydrochloride) and thus prevents the facile migration of the chloroacetyl groups from the side-chain hydroxyl group to that on the ring. Oxidation of XIV (R′ = $COCH_2Cl$) was easily accomplished as before to give XV (R′ = $COCH_2Cl$) and hydrolysis of the latter by means of potassium bicarbonate in aqueous methanol led to pure *dl*-α-epiisocycloheximide (I), mp 153–155°. Acetylation of the latter regenerated XIV (R′ = Ac).

When the above monochloroacetylation of XIII was carried out by a very slow addition of chloroacetyl chloride to XIII in dioxane–pyridine the product was contaminated with a considerable amount of the isomeric chloroacetate XVII. After chromatographic separation of XVII, it led on oxidation to the keto chloroacetate (XVIII), a compound which can be regarded as belonging to the (ψ)-α-epiisocycloheximide series.[9]



Stereochemistry.—The stereochemical course of the sequence described above needs further comment. Hydrogenation of V to XIII proceeded rapidly and with even greater selectivity than it had done in the case of XI.[2] With respect to the former compound the only sensible conformer available for reduction is Va (Chart III) and its upper and lower faces differ in steric hin-

(9) M. Suzuki, *Chem. Pharm. Bull.* (Tokyo), **8**, 788 (1960).

CHART II

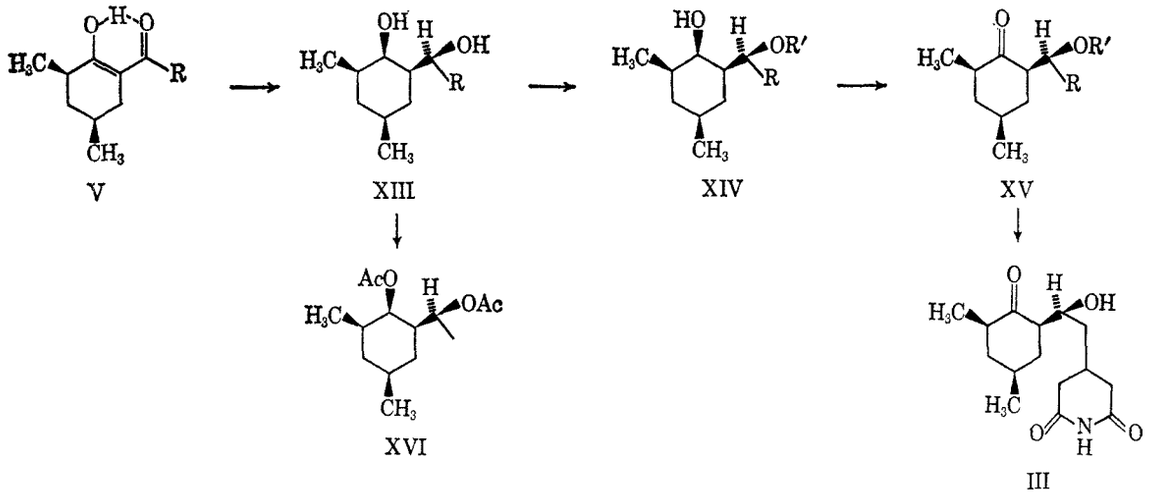
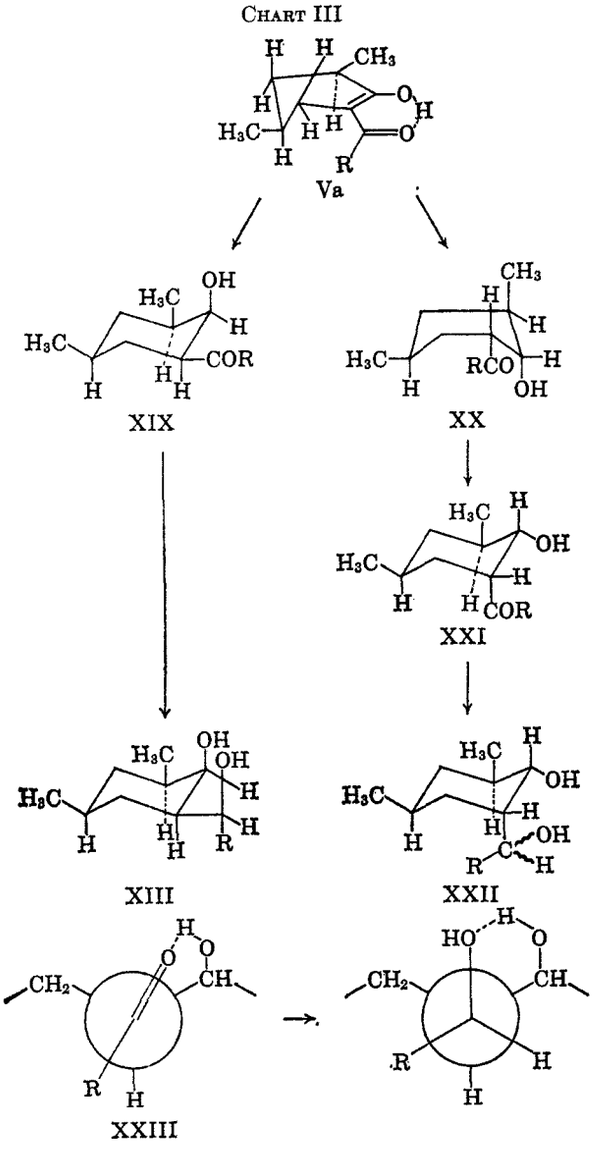
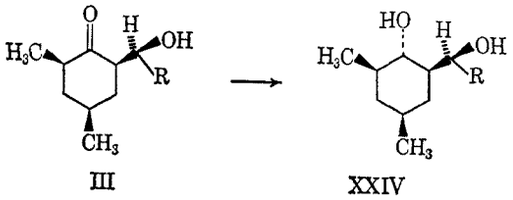


CHART III



drance to approach of the catalyst by only a quasi-equatorial methyl group. This, however, appears to be sufficient to cause reduction to occur almost entirely by attack on the lower face to give XIX, a result which was quite surprising but nevertheless gratifying. The further stereoselective reduction of XIX to XIII might be predicted on the basis of previous synthetic work with cycloheximide.[2] Undoubtedly the most stable of the six possible rotational conformers about C-6 and the α-carbon atom of the large side chain is that shown in XXIII; a result of both hydrogen bonding and the minimal skew interactions it contains. Frontal approach of the catalyst would then give the product obtained. It was disappointing that despite careful chromatography of the residual mother liquor material from XIII, no trace of a crystalline diol corresponding to the structure XXII (neocycloheximide series) could be isolated. We had expected to find a little XXII as a result of some reduction of the upper face of Va.

The stereochemistry of the ring hydroxyl group of the diol XIII was confirmed by measuring the width at half-height (W_H) of the ring C*H*OH proton absorption in its nmr spectrum and those of its derivatives XIV (R′ = Ac or $COCH_2Cl$) and XVI. The latter was prepared by diacetylation of XIII. As was shown in the cycloheximide series it could be expected that, if the ring hydroxyl group were axial, the W_H for the proton in question should be ~6–8 cps and the absorption band sharp (s), whereas if the hydroxyl were equatorial the W_H should be ~16–20 cps and the peak broad (b). The side-chain C*H*OR proton should have a broad absorption band no matter what since it is split by three other hydrogen atoms. Table I lists the results[10] of this study confirming the axial nature of the ring hydroxyl of XIII. In this connection it is interesting to note that reduction of α-epiisocycloheximide with lithium tri-*t*-butoxyaluminum hydride afforded a new diol XXIV, mp 214–216°, both of whose C*H*OH proton absorptions were broad, thus allowing the equatorial assignment to be made to the ring hydroxyl.



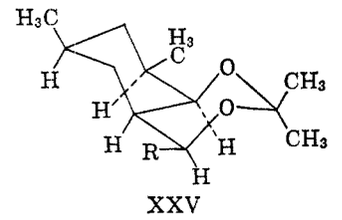
(10) A detailed analysis of these results is not given here since a very comprehensive treatment of similar results was discussed[11] previously in the determination of the stereochemistry of the diols of cycloheximide and certain of its isomers.

TABLE I

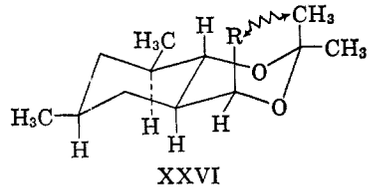
Compd	Spectra[a] in deuteriochloroform: Ring CHOR	Spectra[a] in deuteriochloroform: Side-chain CHOR	Spectra[a] in pyridine: Ring CHOR	Spectra[a] in pyridine: Side-chain CHOR
α-Epiisocycloheximide (III)	...	252 b	...	...
α-Epiisocycloheximide acetate (XV, R = Ac)	...	324 b	...	346 b
Dihydro-α-epiisocycloheximide (XIII)	...	...	235 s	249 b
Dihydro-α-epiisocycloheximide chloroacetate (XIV, R′ = $COCH_2Cl$)	222 s	309 b	232 s	342 b
Dihydro-α-epiisocycloheximide diacetate (XVI)	305 s	285 b	310 s	275 b
Hydroxy chloroacetate XVII	314 s	222 b	325 s	226 b
Keto chloroacetate XVIII	325 s	...	...	...
Dihydro-α-epiisocycloheximide (XXIV)	...	...	210 b	270 b

[a] Measurements made using a 60-Mc instrument and the results are quoted in cycles per second downfield from tetramethylsilane (TMS) taken at 0 cps.

Having at hand the epimeric pair of diols XIII and XXIV now allowed us to test an earlier prediction[11] that the former should give an acetonide easily, whereas the latter should not. This proved to be the case, XIII giving XXV, and XXIV being recovered unchanged when each was separately treated with acetone and anhydrous copper sulfate. The failure of XXIV to yield an acetonide is readily understood in terms of



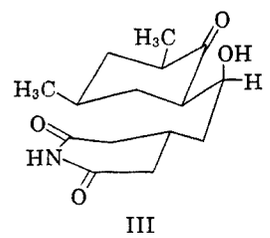
XXV



XXVI

increasing steric strain in the transition state leading to the potential product XXVI. The latter would have a large nonbonded interaction between two axial substituents (R and CH_3) in the acetonide ring.

Finally, these results dovetail completely with the similar experiments carried out with the two diols derived from isocycloheximide (II).[11] In so doing they show unequivocally that II and III differ only in the relative orientation of their hydroxyl groups. By conventional nomenclature, in II the hydroxyl group is α, whereas in III it is β. Thus the known[5] optically active form of III, which displays a positive Cotton effect, must now be represented in the absolute sense as shown below, in which the hydroxyl group has the (*S*) configuration, an assignment opposite to that originally made by the Japanese workers.[5]



III

(11) F. Johnson, N. A. Starkovsky, and A. A. Carlson, *J. Am. Chem. Soc.*, **87**, 4612 (1965).

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. Nmr spectra were recorded in deuteriochloroform unless otherwise stated and peaks were measured downfield from TMS taken at 0 cps. A Varian 60-Mc instrument (A-60) was used to obtain the latter spectra.

Ethyl 2,4-Dimethylcyclohexanone-6-carboxylate.—To a solution of sodium metal (18.4 g) in ethanol (300 ml) under an atmosphere of nitrogen, there was added a mixture of diethyl oxalate (116.8 g) and *dl-cis*-2,4-dimethylcyclohexanone (100.8 g) over a period of 1 hr, the reaction flask being immersed in an ice bath. After an additional 1 hr of stirring the ice bath was removed and the reaction mixture was allowed to stand at room temperature overnight. It was then reimmersed in an ice bath and sulfuric acid (22.4 ml) in ice water (175 ml) was added slowly with rapid stirring. Water (300 ml) was then added to aid stirring. The organic layer was separated and the aqueous phase was extracted with five 100-ml portions of benzene. These extracts were combined with the previous organic phase, this was then washed with six 100-ml portions of water and dried over anhydrous Na_2SO_4, and volatile organic material was removed on the steam bath under reduced pressure. The residual liquid was distilled with considerable decarbonylation taking place and that portion (91 g) boiling at 130–135° (10 mm) was collected. This material was again distilled from powdered glass (0.6 g) containing a trace of iron powder. The total distillate (77.6 g), collected at 130–145° (17 mm), was fractionally distilled with care to yield ethyl 2,4-dimethylcyclohexanone-6-carboxylate (68.5 g), $n^{25}D$ 1.4687. The infrared spectrum (film) of this material showed bands at 5.74, 5.82, 6.05, 6.18, 7.12, 7.25–7.45, 7.65, 7.84, 7.97, 8.14, 8.22, 8.46, 8.58, 8.87, 9.01, 9.74, and 12.00 (broad) μ, and was no different from that of the product of the initial distillation. Thus, although the point was not investigated, it seems likely that the subsequent distillation from soft glass and iron powder might conveniently be omitted.

Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.6; H, 9.2. Found: C, 66.5; H, 9.3.

Benzyl 2,4-Dimethylcyclohexanone-6-carboxylate.—Ethyl 2,4-dimethylcyclohexanone-6-carboxylate (68.5 g) and benzyl alcohol (150 ml) were placed in a flask and heated to boiling. This was maintained until no more ethanol distilled from the reaction mixture. The excess benzyl alcohol was then removed under reduced pressure, and the residue was distilled fractionally to give benzyl 2,4-dimethylcyclohexanone-6-carboxylate, bp 155° (0.3 mm) (61.6 g), $n^{25}D$ 1.5244. Its infrared spectrum (film) showed bands at 5.73, 5.82, 6.04, 6.19, 6.65, 6.84, 7.16, 7.65, 7.85, 7.97, 8.13–8.26, 8.88, 9.01, 10.04 (broad), 12.10 (broad), 13.45 (broad), and 14.37 μ.

Anal. Calcd for $C_{16}H_{20}O_3$: C, 73.8; H, 7.7. Found: C, 74.0; H, 7.8.

***dl*-Dehydroisocycloheximide.**—In a dry, three-necked, 1-l. flask, equipped with nitrogen inlet, addition funnel, condenser, and a magnetic stirring bar, was placed benzyl 2,4-dimethylcyclohexanone-6-carboxylate (26 g, 0.02 mole) in dry tetrahydrofuran (200 ml, distilled from calcium hydride) under a dry nitrogen atmosphere. With good-stirring and with the flask immersed in an ice bath, an ether–tetrahydrofuran solution (100 ml) of phenylmagnesium bromide (1 *N*) was added dropwise during 30 min. After this was complete (15 min) a solution of 3-glutarimidylacetyl chloride (19.0 g, 0.1 mole) in dry tetrahydrofuran (250 ml) was added to the reaction mixture over a 1-hr

period. The mixture was stirred for an extra hour, then allowed to stand overnight.

The bulk of the solvents was then removed under reduced pressure on a warm water bath. The residual liquid was mixed with ice–water (250 ml) and dilute sulfuric acid (100 ml, 1*N*), and the organic material was extracted with seven 50-ml portions of methylene chloride. The organic extract was washed with saturated sodium bicarbonate solution, then water, and dried over anhydrous sodium sulfate. Removal of the methylene chloride under reduced pressure furnished a viscous oil (46.8 g) which was dissolved in ethyl acetate (400 ml). A palladium-on-charcoal catalyst (2 g, 10% Pd) was added and the mixture was reduced at atmospheric pressure and room temperature in an atmosphere of hydrogen. After 8 hr, hydrogen absorption (81% of theory) ceased, and the solution was allowed to stand overnight. The catalyst which was coated with product was removed by filtration and the organic material was washed free by means of methylene chloride. This extract when evaporated to dryness afforded almost pure dehydroisocycloheximide (8.8 g), mp 145–149°. The bulk of the reaction mixture, after removal of the coated catalyst, was hydrogenated again using new catalyst (1 g). After 2.5 hr, absorption of gas ceased (87 ml of H_2, total 85% of theory). The catalyst was removed and the solution was boiled for 1 hr to effect decarboxylation and then concentrated to small volume. On cooling, crude *dl*-dehydroisocycloheximide (11.2 g), mp 140–147°, deposited as white nacreous plates, total yield (20 g) 75%. Recrystallization from alcohol gave the pure compound (15.0 g), mp 150–151°. The infrared spectrum showed bands at 3.12, 3.23, 5.78, 5.85, 6.25, 7.12, 7.55, 7.60, 7.75, 7.88, 8.05, 8.65, and 11.30 μ, and was identical with that of an optically active specimen prepared previously.[6]

Anal. Calcd for $C_{15}H_{21}H_{21}NO_4$: C, 64.5; H, 7.6; N, 5.0. Found: C, 64.6; H, 7.6; N, 5.0.

A specimen of dehydroisocycloheximide (150 mg) was dissolved in ethanol (5 ml) and added to a warm solution of copper acetate (0.2 g) in ethanol (5 ml) and water (2 ml). After standing at room temperature for 3 hr the olive drab colored needles were removed and twice recrystallized from ethanol–dimethylformamide to give the pure copper chelate of V as fine needles, mp 253–255° (decomposing if placed on hot stage below 230°).

Anal. Calcd for $C_{30}H_{40}CuN_2O_8$: C, 58.1; H, 6.5; Cu, 10.3; N, 4.5. Found: C, 57.9; H, 6.4; Cu, 10.0; N, 4.5.

***dl*-Dihydro-α-epiisocycloheximide (XIII).**—A solution of *dl*-dehydro-α-epiisocycloheximide (14.8 g) in glacial acetic acid (300 ml) was stirred in a hydrogen atmosphere at normal temperature and pressure, over prereduced platinum oxide (2.0 g) catalyst. After stirring overnight absorption of gas (2655 ml, 98% of theory) had ceased and the catalyst was removed by filtration and the acetic acid evaporated under reduced pressure at ~80°. The residual solid was recrystallized from ethyl acetate to give pure XIII as white flaky crystals (9.3 g), mp 169–174°. Further processing of the mother liquors yielded an additional 1.2 g of the same quality: total yield, 70%. The substance exists in dimorphic forms with melting points of 174–176° and 163–165°. The melting point of the lower melting form occurs at 163–165° partially solidifying at 166–168° then remelting at 174°. The infrared spectrum of the higher melting form showed bands at 2.91, 3.11, 3.24, 5.78, 5.91, 7.72, 7.90, 8.69, 8.98, 9.30, 9.50, 10.15, 10.53, 10.69, and 11.30 μ, whereas the lower melting form showed bands at 3.09 (broad), 3.20, 5.78, 5.88, 7.75, 7.95, 8.66, 8.95, 9.31, 9.47, 10.21, 10.53, 10.71, and 11.30 μ. In chloroform solution both showed identical spectra having bands at 2.89, 2.97, 5.85, 7.29, 7.40, 8.72, 9.72, 10.20, 10.52, 10.83, and 11.35 μ.

Anal. Calcd for $C_{15}H_{25}NO_4$: C, 63.6; H, 8.9; N, 4.9. Found: C, 63.6; H, 9.0; N, 5.0.

***dl*-Dihydro-α-epiisocycloheximide Diacetate (XVI).**—The diol (XIII, 120 mg) was dissolved in acetic anhydride (1 ml) and pyridine (1.5 ml) and the mixture was allowed to stand overnight at room temperature. The product was isolated in the usual way by dilution of the mixture with ice water, followed by extraction with methylene chloride. It crystallized easily from ether–petroleum ether (bp 30–60°) as fluffy needles, mp 129–130°. Its infrared spectrum showed bands at 3.01, 3.22, 5.74, 5.86, 7.72, 7.85, 7.92, 8.08, 8.55, 8.65, 9.42, 9.49, 9.78, 10.14, 10.50, 10.59, 11.36, 11.50, and 13.84 μ.

Anal. Calcd for $C_{19}H_{29}NO_6$: C, 62.1; H, 8.0; N, 3.8. Found: C, 61.8; H, 8.0; N, 3.9.

***dl*-Dihydro-α-epiisocycloheximide Monoacetate (XIV, R′ = Ac).**—A solution of the diol (XIII, 1.12 g) in dry pyridine (3 ml) was cooled to 5° in an ice bath, and acetic anhydride (0.53 g, 1.3 equiv) in methylene chloride (1 ml) was added dropwise with stirring during 3 min. After standing 2 days at room temperature the solvents were removed under reduced pressure using a vacuum pump. The residue was crystallized from ether to give the monoacetate (0.65 g) as plates, mp 168–170°. A specimen recrystallized for analysis had mp 173–174°.

Chromatography over alumina of the material from the mother liquors afforded additional pure monoacetate (0.2 g) together with some diacetate XVI (180 mg), mp 125–127°. The infrared spectrum of XIV (R′ = Ac) exhibited significant bands at 2.85, 2.90, 3.10, 5.75–5.95, 7.90, 8.64, 9.53, 9.63, 10.05, 10.65, 10.76, 12.00, and 13.80 μ.

Anal. Calcd for $C_{17}H_{27}NO_5$: C, 62.8; H, 8.4; N, 4.6. Found: C, 63.1; H, 8.3; N, 4.6.

***dl*-α-Epiisocycloheximide Acetate (XV, R′ = Ac).**—A solution of XIV (R′ = Ac, 0.52 g) in acetone (20 ml, distilled from $KMnO_4$) was cooled to 5° and treated dropwise with a solution of chromium trioxide (0.41 g) in water (6 ml) containing sulfuric acid (0.34 g) during 10 min. Stirring was continued for 2 hr, isopropyl alcohol (2 ml) was added, and after stirring for an additional hour the volatile solvents were removed under reduced pressure at room temperature. Extraction of the residue with methylene chloride afforded a solid (0.45 g) which when recrystallized from ether led to *dl*-α-epiisocycloheximide acetate (0.38 g), mp 166–168°. Further crystallization sharpened the melting point to 167–168°. Its infrared spectrum showed bands at 3.12, 2.23, 5.75, 5.83, 5.92, 7.71, 7.84, 8.09, 8.14, 8.58, 8.66, 8.84, 9.42, 9.53, 10.66, and 11.18 μ. Its infrared spectrum taken in chloroform solution was identical with that of an optically active sample,[5] mp 177–178°, supplied by Dr. T. Okuda and had bands at 2.96, 5.70–5.90, 6.83, 7.16, 7.26, 7.40, 7.76, 7.90–8.40, 8.70, 8.85, 9.42, 9.60, 9.76, 10.62, 11.21, and 11.65 μ. This was quite different from the spectrum of isocycloheximide acetate which showed significant differences above 9.0 μ having bands at 9.80, 10.22 (weak), 10.59, 11.50, and 11.65 μ.

Anal. Calcd for $C_{17}H_{25}NO_5$: C, 63.1; H, 7.8; N, 4.3. Found: C, 63.1; H, 7.7; N, 4.6.

***dl*-Dihydro-α-epiisocycloheximide Chloroacetate (XIV, R′ = $COCH_2Cl$) and Its Isomer XVII.**—Diol XIII (1.1 g) in 8 ml of dioxane was treated at 0° with 0.57 g of dry pyridine followed by a solution of chloroacetyl chloride (0.56 g) in 3 ml of dioxane, added in one portion, with high-speed stirring. After standing for 2 hr at room temperature, the mixture was filtered and poured into 100 ml of methylene chloride. The solution thus obtained was washed with cold dilute hydrochloric acid, water, and sodium bicarbonate solution. After washing once more with water and drying over anhydrous sodium sulfate, the solution was evaporated *in vacuo* giving a glassy residue, which crystallized from ether giving the desired product as colorless needles, mp 166–168° (0.92 g). It showed characteristic absorptions at 2.77 (OH), 3.06 (NH), 5.74 (ester), 5.89 (imide C=O), 7.61, 7.75, 7.92, 8.25, 8.35, 8.68, 9.66, 10.06, 10.68, 11.50, 11.96, and 12.32 μ.

Anal. Calcd for $C_{17}H_{26}ClNO_5$: C, 56.8; H, 7.2; Cl, 9.9. Found: C, 56.9; H, 7.1; Cl, 10.0.

When the above reaction was carried out using excess pyridine and the chloroacetyl chloride was added dropwise over 15 min, a mixture of products was obtained. Chromatography of the mixture over silica gel afforded XIV (R′ = $COCH_2Cl$) in 50% yield which was eluted with 30–50% ethyl acetate in methylene chloride. Elution of the column with pure ethyl acetate afforded crude XVII (20% yield) which, when recrystallized from methylene chloride–ether, furnished the pure material, mp 180–181°. Its infrared spectrum showed absorption bands at 2.85 and 2.90 (OH), 3.05 and 3.24 (NH), 5.85, 5.91, 7.63, 7.85, 7.95, 8.07, 8,30, 8.61, 8.71, 10.28, and 11.34 μ.

Anal. Calcd for $C_{17}H_{26}ClNO_5$: C, 56.8; H, 7.2; Cl, 9.9. Found: C, 56.9; H, 7.1; Cl, 10.0.

***dl*-α-Epiisocycloheximide Chloroacetate (XV, R′ = $COCH_2Cl$).**—XIV (R′ = $COCH_2Cl$, 0.8 g) dissolved in a mixture of purified acetone (16 ml) and water (3 ml) was treated, at 0°, with a solution of chromic anhydride (0.45 g) in a mixture of water (6 ml) and concentrated sulfuric acid (0.35 ml). The reaction mixture was stirred at room temperature overnight. After addition of 2 ml of isopropyl alcohol, the mixture was stirred for 20 min, the acetone was evaporated *in vacuo* at room temperature, and the resulting aqueous solution was diluted with water and extracted with two 35-ml portions of methylene chloride. Evaporation of the combined methylene chloride extracts gave a gum which crystallized from methylene chloride–ether as feathery

colorless crystals of the desired product, mp 149–150° (0.42 g). The chloroacetate was characterized by infrared absorption bands (Nujol mull) at 3.04 (NH), 5.78–5.90 (C=O), 7.51, 7.70, 7.88, 7.95, 8.05, 8.75, 9.58, 10.38, and 12.40–12.45 μ.

Anal. Calcd for $C_{17}H_{24}ClNO_5$: C, 57.1; H, 6.7; Cl, 9.9. Found: C, 57.2; H, 6.6; Cl, 9.9.

Oxidation of XVII. (ψ)-α-Epiisocycloheximide Chloroacetate XVIII.—A solution of XVII (2 g) was oxidized by the method described for the preparation of XV (R′ = $COCH_2Cl$). The crude keto chloroacetate thus obtained (1.66 g) was crystallized first from methylene chloride–ether, and then from aqueous methanol giving flaky colorless crystals of pure XVIII, mp 108–109°. XVIII showed characteristic infrared bands at 3.06 (NH), 5.77–5.90 (C=O), 7.71, 8.00, 8.75, 10.20, and 10.51 μ.

Anal. Calcd for $C_{17}H_{24}ClNO_5$: C, 57.1; H, 6.7; Cl, 9.9; N, 3.9. Found: C, 56.5; H, 6.4; Cl, 9.0; N, 4.0.

dl-α-Epiisocycloheximide (III).—XV (R′ = $COCH_2Cl$, 0.32 g) in 15 ml of methanol was treated at room temperature with a solution of 0.5 g of potassium bicarbonate in 5 ml of water. After stirring overnight, the methanol was removed *in vacuo*, and the resulting aqueous mixture was extracted with methylene chloride. Evaporation of the methylene chloride extract previously washed with water and dried over anhydrous sodium sulfate gave a glassy material which was dissolved in 10 ml of methylene chloride and adsorbed on a column of silica gel (8 g). After washing the column with 100 ml of methylene chloride and 100 ml of 10% ethyl acetate in methylene chloride (this eluted about 40 mg of the starting material), crude III (80 mg) was obtained by elution with 200 ml of 20% ethyl acetate in methylene chloride. After recrystallization from methylene chloride, III appeared as colorless crystals, mp 153–153.5°. It was soluble in alcohol and acetone and sparingly soluble in water and ether. Its characteristic infrared bands (Nujol mull) were at 2.90 (OH), 3.11 and 3.24 (NH), 5.77, 5.85, and 5.99 (C=O), 7.78, 7.88, 8.00, 8.62, 9.30, 10.82, and 11.51 μ.

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, 5.1.

Acetylation of III with acetic anhydride in pyridine for 24 hr at room temperature gave *dl*-α-epiisocycloheximide acetate (XIV, R′ = Ac), mp 165–167°, which was identical with the specimen obtained previously (mmp 165–167°).

dl-Dihydro-α-Epiisocycloheximide (XXIV). Reduction of dl-α-Epiisocycloheximide.—A mixture of lithium aluminum hydride (132 mg) in 15 ml of dry tetrahydrofuran was treated, slowly, with 770 mg of dry *t*-butyl alcohol, and the mixture was stirred at 0° for 30 min. It was then treated dropwise, with external cooling and efficient stirring, with a solution of III (300 mg) in 10 ml of tetrahydrofuran. After stirring for 2 hr at 0–5°, the mixture was treated dropwise with 5 ml of cold water and 5 ml of 20% acetic acid. The mixture was stirred for a few minutes longer and filtered from the precipitated inorganic salts, and the filtrate was freed from tetrahydrofuran *in vacuo*. The residual aqueous mixture was extracted with five 50-ml portions of methylene chloride. Evaporation of the combined organic extracts (washed with water and sodium bicarbonate solution and dried over anhydrous sodium sulfate) gave a white solid which was crystallized from ethyl acetate to give crystalline XXIV, mp 214–216° (about 100 mg). XXIV was very sparingly soluble in methylene chloride, chloroform, and water, and practically insoluble in ether. Its infrared spectrum showed characteristic bands (Nujol mull) at 2.90 (OH), 3.10 and 3.23 (NH), 5.73 and 5.99 (C=O), 7.74, 7.93, 8.59, 8.94, 9.32, 9.42, and 9.54 μ, and its solution spectrum (in acetonitrile, 2.5 mg/ml) was characterized by bands at 2.78 (OH), 2.94 (NH), 5.85 (C=O), and 8.68 μ.

Anal. Calcd for $C_{15}H_{25}NO_4$: C, 63.6; H, 8.9; N, 4.9. Found: C, 63.8; H, 8.8; N, 5.3.

Acetonide of Diol XIII.—The diol XIII (0.2 g) was refluxed in acetone (20 ml) in the presence of anydrous copper sulfate (1.0 g) for 16 hr. After filtration to remove copper sulfate and evaporation of the solvent the residue was crystallized from aqueous alcohol to give the acetonide XXV quantitatively, mp 102°. The infrared spectrum of this material showed significant absorption at 3.12, 3.22, 5.79, 5.81, 7.74, 7.90, 8.30, 8.54, and 8.72 μ, while its nmr spectrum in deuteriochloroform exhibited peaks at 81.8 and 83.9 (acetonide methyls), at 54.3 (J = 5.4 cps) and 54.9 (J = 4.5 cps) for the cyclohexane methyl groups, and at 226 (sharp) and 237 cps (broad) for C*H*–O protons. In pyridine solution these peaks occurred at 83.6, 85.4, 58.2, 58.1, 216 (sharp), and 230 (broad) cps, respectively.

Anal. Calcd for $C_{18}H_{29}NO_4$: C, 66.9; H, 9.0; N, 4.3. Found: C, 66.8, H, 9.1; N, 4.4.

Under the same conditions as described above diol XXIV was recovered unchanged.

Acknowledgment.—We are grateful to Dr. T. Okuda (Tanabe Seiyaku Company, Tokyo) who supplied us with an optically active synthetic sample of α-epiisocycloheximide acetate for comparison purposes.

The Formation of a Cyclopropane Ring by Hydride Reduction of a Bridged Imidate[1]

H. E. ZAUGG AND R. J. MICHAELS

Organic Chemistry Department, Research Division, Abbott Laboratories, North Chicago, Illinois

Received November 2, 1965

Treatment of the bridged imidates Ia and Ib with lithium aluminum hydride in refluxing 1,2-dimethoxyethane results in fragmentation of the molecule with production of the cyclopropane derivative II in 47 and 43% yields, respectively. At the same time the cyclopropane ring originally present in Ia is opened and the cleaved fragment appears in the product as N-methyl-*n*-propylamine. The cyclization is limited in scope and apparently depends on the coincidence of several structural features in the imidates I. These are partially defined.

The bridged cyclic imidates I[2] were treated with excess lithium aluminum hydride in refluxing 1,2-dimethoxyethane in an effort to secure the corresponding amino alcohol III for pharmacological testing. Although a poor yield (24%) of III was formed from Ib, the main product obtained from both imidates was a neutral substance lacking nitrogen. The elemental analysis combined with the presence of absorption at 1.63 μ in its near-infrared spectrum, characteristic of a CH_2-group in a three-membered ring,[3] suggested assignment of structure II to this product. This was confirmed by its nmr spectrum (Table I). The possibility that II was formed spontaneously as a result of some structural instability in the cyclic imidates was ruled out by the observation that Ia is unaffected by heat (225°) and by ultraviolet irradiation. Likewise, Ia was inert to lithium aluminum hydride in refluxing ether.

(1) Paper XIII in the series, "Neighboring Group Reactions."

(2) H. E. Zaugg and R. J. Michaels, *J. Org. Chem.*, **28**, 1801 (1963).

(3) W. H. Washburn and M. J. Mahoney, *J. Am. Chem. Soc.*, **80**, 450 (1958); P. G. Gassman, *Chem. Ind.* (London), 740 (1962); H. Weitkamp and F. Korte, *Tetrahedron*, **20**, 2125 (1964).