Addition of Iodine Isocyanate to Olefins. Scope and Synthetic Utility[1]

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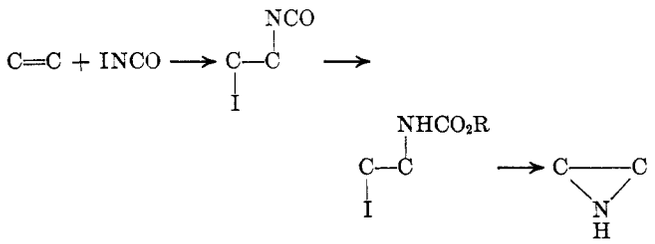
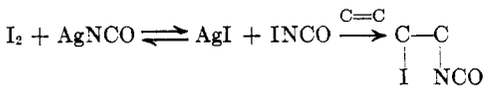
The stereospecific introduction of nitrogen functions *via* additions of iodine isocyanate to olefins is discussed with emphasis on the reagent, solvent effects, the scope of the reaction, the formation of carbamates, and synthetic routes to heterocyclic compounds and amino alcohols. Additions of iodine isocyanate generally proceed well with mono-, di-, and some trisubstituted olefins and can also be carried out with acetylenes. Conjugated unsaturated acids, esters, ketones, and nitriles are unreactive toward the reagent. Conjugated and nonconjugated dienes can yield monoaddition products. The β-iodo isocyanates can be characterized as carbamates, amine salts, or bisulfite addition compounds all of which can be transformed into aziridines. In this manner fused and spiroaziridines may be synthesized. The conversion of the isocyanate adducts to carbamates by exposure to alcohols can be sped up considerably by catalytic amounts of lithium or sodium alkoxide. The addition reaction may be employed for the stereospecific synthesis of *cis*-β-amino alcohols.

The modern synthetic chemist has at his disposal a variety of methods for introducing oxygen functions stereospecifically into organic molecules, notably *via* epoxides and ketones. For the introduction of nitrogen functions, in particular for the stereospecific formation of bifunctional compounds, the available repertory is much more limited. Since electrophilic additions to olefins usually occur with a high degree of stereospecificity and olefins are readily available starting materials, we investigated the suitability of additions to olefins for the introduction of nitrogen functions.

The method of choice became the addition of iodine isocyanate (INCO) to olefins. This reaction has been successfully utilized in recent years[2-7] after it lay dormant following the initial investigation by Birckenbach and co-workers 35 years ago.[8] It has been demonstrated that the additions generally occur in a stereospecific manner and that the iodine and isocyanate functions are introduced *trans* to each other and diaxially in rigid, fused cyclohexanes.[6] The isocyanate function can usually be converted to a carbamate and the resulting β-iodo carbamates serve as convenient precursors to aziridines.[5]



The Reagent and Work-Up Procedure.—In 1929 and 1930, Birckenbach and Lindhard reported the preparation of the pseudohalogens chlorine isocyanate, bromine isocyanate, and iodine isocyanate.[9] They showed that, even at −80°, the first two pseudo-halogens exist in a dimeric form, presumably $X_2NC(=O)NCO$. On the other hand, INCO was found to exist as a monomer even at higher temperatures. It was never isolated as such but an ethereal solution of INCO can be prepared from iodine and silver cyanate in ether. In our work we found it essential to prepare silver cyanate freshly. The white or light gray silver cyanate can be stored in a desiccator in the dark for a period of up to 1 year without losing its effectiveness appreciably, but usually we use material that is less than 3 months old. Iodine reacts only slowly with silver cyanate at 0° in ether (within *ca.* 3 hr) but, if an olefin is present in the mixture, the INCO generated *in situ* will react rapidly with the olefin, shifting the equilibrium of the reaction of iodine and silver cyanate toward INCO. In the latter case the over-all reaction with olefin often is complete within 30 min. One concludes that in ether the formation of INCO is slower than its addition to most olefins.



The procedure used for preparing β-iodo isocyanates has been to generate INCO *in situ* at −15 to 25° by adding 1 equiv of iodine to an ether suspension of silver cyanate (in 30% excess) and olefin. Depending on the olefin used the reaction is usually complete within 0.5–3 hr and this can be recognized by the disappearance or paling of the brown iodine color. Alternatively, iodine can be allowed to react with a large excess of silver cyanate in a variety of solvents and the formed silver iodide can be filtered off. Olefins can then be added to the preformed solution of INCO and reaction usually takes place within minutes. We have kept solutions of iodine isocyanate in ether at −20° in the dark for 48 hr and found it still suitable for reaction with olefins, although some decomposition had taken place during that period. Since iodine isocyanate in ether solution does undergo decomposition even at 0°, and because less silver cyanate is required than for preformed solutions, we prefer to use the *in situ* method for the reaction of INCO with unsaturated compounds.

In some instances it does appear more advantageous to add the unsaturated compound to a preformed solution of INCO. For instance, phenylacetylene adds iodine when exposed to INCO formed *in situ* (because of the presence of iodine in the solution),

(1) (a) Stereochemistry. XX. Chemistry of Carbamates. V. For paper IV, see A. Hassner and C. Heathcock, *J. Org. Chem.*, **29**, 3640 (1964). (b) Presented in part before the Symposium on Electrophilic Additions to Olefins, 148th National Meeting of the American Chemical Society, Chicago, Ill., Sept 1964; (c) National Institute of Health Predoctoral Fellow.

(2) G. Drefahl and K. Ponsold, *Ber.*, **93**, 519 (1960).

(3) R. R. Wittekind, J. D. Rosenau, and G. I. Poos, *J. Org. Chem.*, **26**, 444 (1961).

(4) For a preliminary communication of part of this work, see C. Heathcock and A. Hassner, *Angew. Chem. Intern. Ed. Engl.*, **2**, 213 (1963).

(5) A. Hassner and C. Heathcock, *Tetrahedron*, **20**, 1037 (1964).

(6) A. Hassner and C. Heathcock, *J. Org. Chem.*, **30**, 1748 (1965).

(7) C. G. Gebelein and D. Swern, *Chem. Ind.* (London), 1462 (1965).

(8) L. Birckenbach and M. Lindhard, *Ber.*, **64B**, 961, 1076 (1931).

(9) L. Birckenbach and M. Lindhard, *ibid.*, **63B**, 2528 (1930); **62B**, 2261 (1929); **63**, 2544 (1930).

but does give an INCO adduct when treated with a preformed solution of iodine isocyanate. The presence of silver salts does not seem to influence the reaction, so that filtration of the silver salt is unnecessary either in the *in situ* or the preformed INCO reaction.

The INCO addition to olefins proceeds by formation of a three-membered ring iodonium ion intermediate[6] and consequently one can expect such electrophilic additions to proceed faster in polar than in nonpolar solvents. It was therefore not surprising to find that both the reaction of iodine with silver cyanate, as well as the addition reaction to olefins, proceeded faster in acetonitrile than in tetrahydrofuran than in ether.

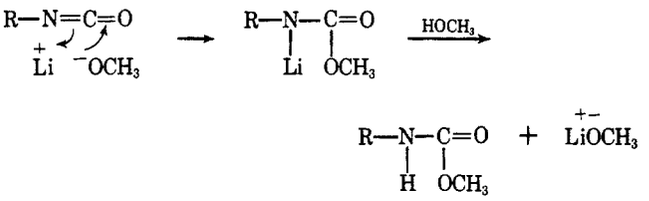
Whereas in ether the reaction of iodine with a threefold excess of silver cyanate (in the absence of olefin) is nearly complete in 2 hr, in tetrahydrofuran the reaction is complete within 30 min at −15° and in acetonitrile within 1 min, as indicated by the change of color of the slurry from brown to yellow. The reaction is faster in the presence of olefin. However, in the more polar solvents side reactions seem to occur and work-up is more difficult; consequently, if the reaction can be carried out in ether, this still remains the solvent of choice.

It is possible to generate INCO in solution by treating iodine or iodine monochloride with other metal cyanates but the yields are usually inferior to the silver cyanate–iodine reaction. When cyclohexene was added to a solution of INCO prepared from iodine monochloride and potassium cyanate the yield of iodoisocyanate adduct was only 15 to 20%. In the reaction of olefin with the iodine–silver cyanate system, the yield of adduct is usually 60 to 90%.

Birckenbach and co-workers[9] have shown that bromine isocyanate and chlorine isocyanate can be obtained only as polymeric material and do not give addition products with olefins. We find that bromine isocyanate apparently can be added to olefins (as indicated by infrared spectra), but no pure product could be isolated. The elements of chlorine isocyanate have been added to olefins by exposing an olefin to an excess of trichloro cyanurate in the presence of cyanic acid.[10]

Two problems are encountered in the work-up of INCO adducts to olefins. Iodoalkanes are often unstable being susceptible to thermolysis, photolysis, or solvolysis. Isocyanates are commonly known to be unstable to hydrolysis and often trimerize or polymerize. Therefore, purification of the iodoisocyanates themselves is usually difficult and it is necessary to convert them to derivatives which are easier to purify and which are at the same time useful intermediates for further synthesis.

Three work-up procedures have been found most useful: (1) conversion to a carbamate, (2) formation of a sodium bisulfite addition product, and (3) acid hydrolysis to an amine salt. Carbamates can be readily prepared by warming an isocyanate with the appropriate alcohol. Tertiary or hindered isocyanates react only sluggishly with alcohol and require either prolonged heating or base catalysis. Since in the addition of INCO to olefins the isocyanate functions usually appear at the more substituted carbon, one is often faced with the problem of a sluggishly reacting isocyanate group in these adducts. Heating of the iodo isocyanate adducts with alcohol is undesirable because the resulting β-iodocarbamates cyclize readily on heating to an oxazolidone. An excess of base cannot be employed to speed up the addition of the alcohol to the isocyanate because the resulting iodocarbamate is converted in basic medium to aziridine derivatives. A method for achieving the formation of carbamate at room temperature was suggested by the work of others who had used various inorganic salts as catalysts to speed up the addition of alcohols to isocyanates.[11] A catalyst not previously used was lithium alkoxide. It was expected to be quite effective at room temperature in catalyzing the formation of carbamates possibly by a path as suggested below. Indeed, the presence of



0.01 equiv of lithium methoxide or sodium methoxide proved to be a catalyst almost as efficient (see Table I) and more convenient than dibutyltin dilaurate. The latter had been shown to be 7000 times as active as triethylamine.[11] In this manner it was possible to effect the conversion of β-iodo isocyanates to methyl β-iodocarbamates in good yield at room temperature even for more hindered isocyanates.

TABLE I

CATALYZED CONVERSION OF 1-(IODOMETHYL)CYCLOHEXYL ISOCYANATE AT 25° IN METHANOL TO CARBAMATE 16

Catalyst[a]	Time, min	% conversion
$LiOCH_3$	30	17
$NaOCH_3$	30	24
Bu_2SnLau_2[b]	30	30
$LiOCH_3$	120	33
$NaOCH_3$	120	39
Bu_2SnLau_2	120	63

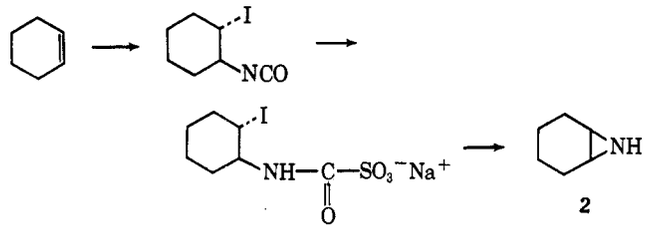
[a] Mole ratio of catalyst to isocyanate, 0.012. [b] Dibutyltin dilaurate.

The second method for the purification of iodoisocyanates is the reaction of these compounds with sodium bisulfite to give adducts which sometimes can be obtained in crystalline form and which serve to separate isocyanates from nonisocyanate materials. The advantage of this method is that the sodium bisulfite adducts can be converted back to isocyanates by heat[12] or into aziridines in the presence of base. This is particularly applicable if the iodo isocyanates are to be used as intermediates in the synthesis of aziridines. Thus, when the INCO addition product to cyclohexene was treated with a saturated aqueous solution of sodium bisulfite, a solid adduct (1) was obtained which could be crystallized carefully from water and was converted by base to 1,2-iminocyclohexane (2).

(10) J. Harper, private communication.

(11) F. Hosteller and E. F. Cox, *Ind. Eng. Chem.*, **52**, 609 (1960); A. Davies and G. J. D. Peddle, *Chem. Commun.*, 96 (1965).

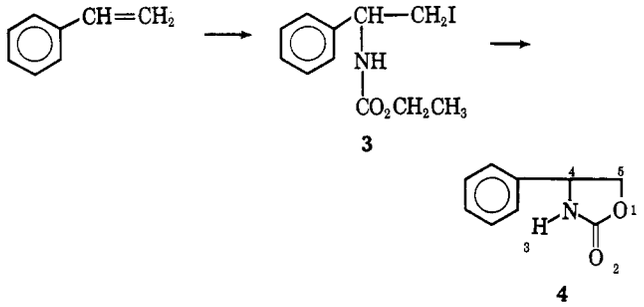
(12) S. Petersen, *Ann.*, **562**, 205 (1949).



1

In the synthesis of **10**, heating of the INCO adduct with methanol led to ring closure to an oxazolidone. The carbamate **10** can, however, be obtained in 80% yield on treatment of the isocyanate with hydrogen chloride followed by methanol.

The Scope of INCO Additions.—The addition of INCO has been studied to date with a large enough variety of olefins to allow the statement that the reaction has general applicability. We have used successfully cyclic olefins of various ring size. Most of these yield crystalline β-iodocarbamates, some of which have been converted to fused bicyclic aziridines. The rate of addition of INCO decreases in the following order: cyclopentene > cycloheptene > cyclohexene > cyclooctene > cyclododecene. Methylene cycloalkanes react readily and so do styrenes. In these cases the direction of the addition is such that the isocyanate function appears at the more substituted carbon. Styrene gives an INCO adduct which with ethanol produces ethyl N-(2-iodo-1-phenylethyl)carbamate (**3**) in 65% over-all yield. The structure of **3** was established by its conversion (on heating) to the known 4-phenyl-2-



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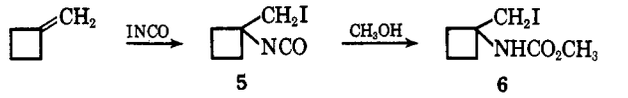
oxazolidone (**4**).[13a] An isomeric α-iodo-β-carbomethoxyaminoethylbenzene structure would have yielded 5-phenyl-2-oxazolidone.[13b] The nmr spectrum of **3** indicates a doublet at τ 6.6 (2 H, *CH₂I*) and a multiplet at 5.3 (H, *CH*N) owing to additional splitting by NH.

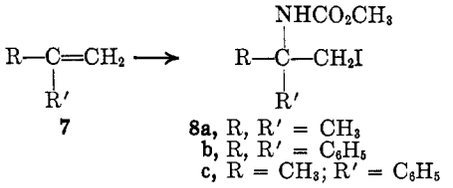
INCO addition product **5** to methylenecyclobutane shows singlet absorption in the nmr at τ 6.5 characteristic of the CH_2I grouping. A similar absorption (τ 6.32) is found for iodocarbamate **6**.



5 6

Isobutylene (**7**, R = R′ = CH_3) yields iodocarbamate **8a** as the only isolable product. Its nmr spectrum exhibits a singlet at τ 6.40 (CH_2I). α-Substituted styrenes (**7**, R = C_6H_5) behave analogously. In carbamate **8c**, the absorption for the methylene hydrogens coincides with that of the methoxy hydro-

(13) (a) M. S. Newman and W. Edwards, *J. Am. Chem. Soc.*, **76**, 1840 (1954); (b) M. S. Newman and A. Kutner, *ibid.*, **73**, 4199 (1951).



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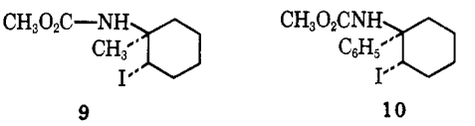
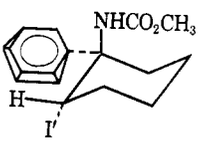
8a, R, R′ = CH_3
b, R, R′ = C_6H_5
c, R = CH_3; R′ = C_6H_5

gens. In this case the INCO adduct was isolated and its nmr spectrum (singlet at τ 6.52) confirmed its structure.

The effect of a β-phenyl group on the chemical shift of protons geminal to the iodine function can be one of considerable deshielding if, in the predominant conformation of the molecule, these protons are in the periphery of the field induced by aromatic π cloud. In adducts **3**, **8a**, and **8c** the protons of the *CH₂I* group absorb at τ 6.6, 6.3, and 6.15, respectively. In **8b** these protons cannot escape deshielding by one of the phenyl groups and absorb at τ 5.52. Similarly, the chemical shift of the proton geminal to iodine in INCO adduct **9** derived from methylcyclohexene occurs at τ 5.35 while the corresponding proton in phenyl analog **10** absorbs at 4.85. The large (*ca.* 0.5 ppm) deshielding of the β hydrogen by the phenyl group tends to indicate that the preferred conformation of **10** is that with the phenyl group equatorial (see **11**) and the other two groups axial.



9 10

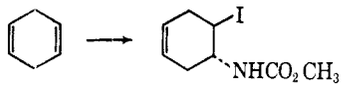


11

In simple terminal olefins such as 1-hexene, addition takes place readily but a mixture of products is obtained with the isocyanate at the terminal as well as at the secondary carbon. This is recognizable from the nmr spectrum of the product. Although INCO addition has all the markings of electrophilic additions to olefins, and presumably proceeds *via* a three-membered-ring iodonium-ion intermediate, the reaction seems to have definite steric requirements. For instance, one would expect alkyl substitution on an olefin to increase the electron density and make the olefin more susceptible to electrophilic addition. We found that, whereas 2-cholestene (a 1,2-disubstituted olefin) readily reacts with INCO to give an addition product, 5-cholestene or cholesterol acetate (trisubstituted olefins) are recovered largely unchanged upon exposure to this reagent. Similarly, in a competition experiment using equimolar amounts of cyclohexene and 1-methylcyclohexene the preference of reaction of methylcyclohexene to cyclohexene is less than 6 to 4. This ratio is not changed appreciably when the olefins are treated either with INCO *in situ* in ether or with a preformed tetrahydrofuran solution of INCO. Tetramethylethylene reacts readily with INCO formed *in situ* but the iodocarbamate is obtained only as an oil.

Monoaddition to di- or triolefins can be achieved. Thus, 1,4-cyclohexadiene reacts with 1 molar equiv

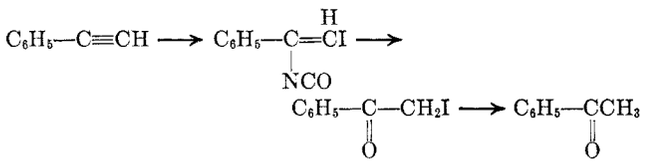
of INCO to give a monoaddition product (**12**), and 1,5,9-cyclododecatriene reacts with 1 equiv of INCO to give a mono iodo isocyanate. Conjugated dienes such as 1,3-cyclohexadiene are also capable of yielding a monoaddition product although, as will be discussed elsewhere, 1,4 addition seems to have taken place.[14] On the other hand 1,4-diphenyl-1,3-butadiene was left unreacted.



12

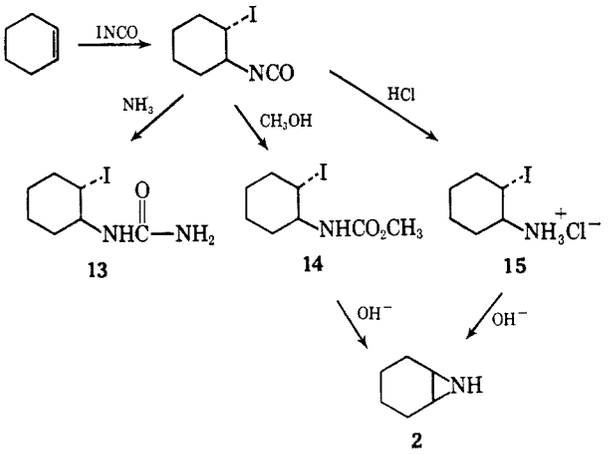
Conjugated unsaturated carbonyl compounds are recovered unchanged on exposure to INCO. Among the compounds to show this behavior were cyclohexenone, 2-methylenenorbornanone, methyl acrylate, acrylonitrile, cinnamic acid, and chalcone. Stilbene and diphenylacetylene are essentially unreactive to INCO. It appears that conjugated electron-withdrawing groups deactivate the double bond sufficiently to prevent electrophilic addition to these olefins.

Phenylacetylene when exposed to INCO prepared *in situ* gives α,β-diiodostyrene in 70% yield—the same product obtained by the addition of iodine to phenylacetylene. On the other hand, when a solution of INCO is prepared in tetrahydrofuran and phenylacetylene is added, addition of INCO does take place, and the product upon hydrochloric acid work-up yields acetophenone. This indicates that in phenylacetylene as in styrene the direction of addition follows the Markovnikov rule.



In a number of cases it was observed that addition of INCO to the olefins studied had taken place, as evidenced by a strong absorption at 2250 cm^{-1} characteristic of isocyanate groups in the product. Upon work-up with alcohol the products were obtained as oils and could not be crystallized. The infrared spectrum of the product indicated the presence of carbamate; however, other impurities possibly including products resulting from trimerization or polymerization of the isocyanate were also present, and purification procedures attempted were of no avail. Such is the case with norbornene, benzonorbornene, norbornadiene, 2-methylbutadiene, cyclopentadiene, dihydropyran, 2,4-hexadiene, and cycloheptatriene. Also, in the case of limonene, a mixture of products was obtained, so that it appears that INCO adds with equal ease to each of the two double bonds. The isolation of oily rather than crystalline carbamate products from reactions of INCO with olefins, when the disappearance of the iodine color and the consumption of the olefin indicated that addition had taken place, can be attributed to the formation of several products in the reaction. A few examples are given. In the addition of INCO to 1-hexene the oily product proved to be an inseparable mixture of Markovnikov and anti-Markovnikov addition products. The addition product from norbornene or from α-pinene proved to be a mixture of at least three components by vpc; presumably rearrangement had taken place during addition. When the INCO addition product of methylenecyclohexane is heated with methanol, an oil is obtained which proved to be a mixture of iodoisocyanate (tertiary isocyanate) and iodocarbamate (by infrared). Warming of this product with methanol–lithium methoxide led to complete conversion to a crystalline iodocarbamate. 1-Methyl-1,4-cyclohexadiene, ethylallene, 5,7-cholestadiene, 2-methyl-1,5-hexadiene, and limonene all gave mixtures of products (oils) that are difficult to separate.

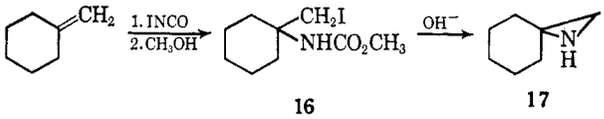
Synthetic Utility of the Reaction.—The β-iodo isocyanates obtained by addition of INCO to olefins display the normal reactions characteristic of isocyanates. Treatment with aqueous ammonia gives urea derivatives (*e.g.*, **13**).[3] Similar reactions are observed with aniline to give a phenylurea or with phenylhydrazine to give a semicarbazide. Hydrolysis of an INCO adduct with aqueous hydrochloric acid to give a β-iodamine salt (**15**) and the reaction with alcohol to produce carbamate (**14**) has already been discussed. The high degree of stereoselectivity of the addition reaction enables the introduction of the iodo and the isocyanate functions in a *trans* manner and this has been used to advantage in the formation of aziridines, since ring closure to such compounds requires a *trans* arrangement of a halogen and amino function. In this



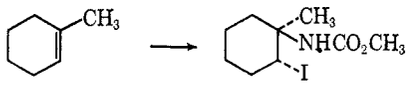
13 **14** **15** **2**

manner a variety of aziridines has been synthesized, including some spiroaziridines and steroidal fused aziridines which are difficult to obtain by other methods.

The conversion of methylenecyclohexene to spiroaziridine **17** in essentially two steps and in 60% overall yield can be contrasted with the known conversion of nitrocyclohexane to **17** in four steps and 20% over-



16 **17**



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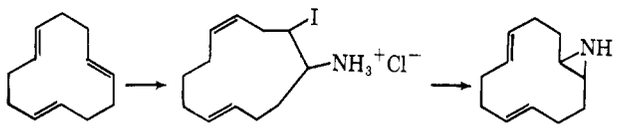
(14) A future paper will discuss possible rearrangements during INCO additions.

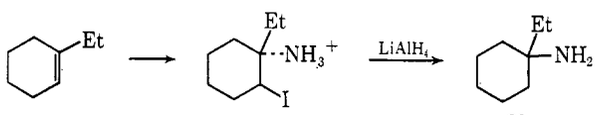
all yield.[15] It should be noted that 1-methylcyclohexene and methylenecyclohexane gave different INCO addition products isolated as carbamates **16** and **9**. Though interconversion of these olefins under acid condition takes place readily, no isomerization had occurred during the reaction with INCO.

All-*trans* 1,5,9-cyclododecatriene **18** gave an adduct which can be converted into an iodamine salt. By the known criterion of *trans* addition of INCO and of conformational mobility in this system it can be assigned *cis* structure **19**. Treatment of **19** with base gave aziridine **20**. Since formation of an aziridine requires a *trans* (and if possible coplanar) arrangement of a β-aminoalkyl halide or a β-aminoalkyl sulfate,[16] ring closure must have taken place through a *trans* conformation of **19**; hence **20** is a *trans*-fused aziridine. The



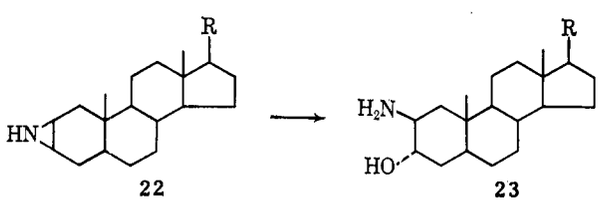
18 19 20

iodine function in β-iodamine salts may be removed by reduction with lithium aluminum hydride. In this manner tertiary amines such as **21** can be obtained from olefins.[17] Since ring opening of aziridines occurs



21

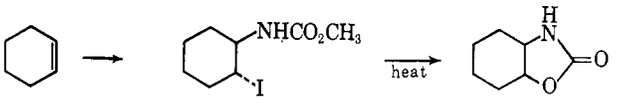
in a stereospecific *trans* manner, a useful method is at hand for the conversion of olefins into bifunctional amino compounds of well-defined stereochemistry. For instance, 2-cholestene was converted *via* aziridine **22** to *trans*-amino alcohol **23**.[6]



22 23

R = C_8H_{17}

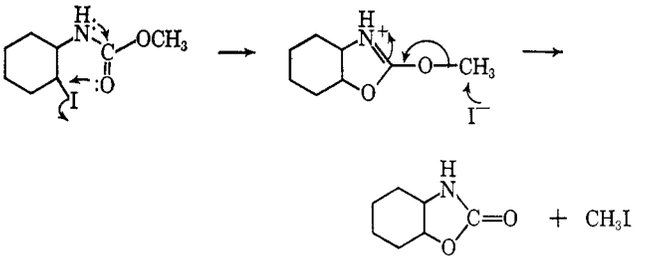
During the course of our study we found that β-iodocarbamates, which resulted from iodo isocyanate adducts on treatment with alcohol, can be readily converted on heating to oxazolidones with the expulsion of 1 mole of alkyl iodide. These pyrolyses can be carried out either neat or in a variety of inert solvents and the yield of the product is between 50 and 80%. Although 2-oxazolidones are well-known heterocyclic compounds, the most common synthesis available requires that one starts with the corresponding *cis*-amino alcohols, which are often rather difficult to obtain. Katchalsky and Ben Ishai[18] have shown that β-halocarbamates may be converted to 2-oxazolidones by pyrolysis at 120 to 200°, but they had to resort to rather complicated methods to obtain their β-halocarbamates. Since these are now readily available, by the addition of INCO to olefins followed by treatment of the intermediate iodo isocyanates with alcohol, the sequence of reactions shown below represents an attractive synthesis of 2-oxazolidones from olefins.



14 25

trans-β-Iodocarbamates obtained from cyclic olefins give rise on pyrolysis to *cis*-fused 2-oxazolidones. It is known that the latter may be hydrolyzed by base to corresponding β-amino alcohols and the hydrolytic transformation occurs without breakage of the R–O or R–N bonds. Hence, the above sequence permits the stereospecific introduction of *cis*-β-amino alcohol functions into cyclic systems starting with readily available olefins. The most general method presently available for the preparation of *cis*-β-amino alcohols involves treatment of an acyl derivative of a *trans*-β-amino alcohol with thionyl chloride to give the corresponding chloroamide. This is usually not isolated but cyclized to an oxazoline salt which on hydrolysis gives the *cis*-β-amino alcohol. The required *trans*-amino alcohol is usually obtained by aminolysis of the corresponding epoxide a reaction which often proceeds in poor yield.[16] The alternative reduction of α-keto oximes usually leads to a mixture of *cis*- and *trans*-amino alcohol.

Methyl N-(*trans*-2-iodocyclohexyl)carbamate (**14**), on pyrolysis in refluxing tetrachloroethylene, gives an oxazolidone melting at 55–56°. The reported melting point for *cis*-cyclohexano[*b*]-2-oxazolidone (**25**) is 55°; the isomeric *trans*-cyclohexano[*b*]-2-oxazolidone melts at 110°.[19] This reaction establishes the fact that an inversion of the iodine-bearing carbon is involved in the pyrolitic conversion of β-iodocarbamates to 2-oxazolidones which is best explained as shown below.



25

Neat pyrolysis of **3** at 150° (2 mm) affords **4** in 85% yield. In this reaction ethyl iodide is isolated in 91% yield. Oxazolidone **4** is hydrolyzed by methanolic potassium hydroxide to 2-phenyl-2-aminoethanol, isolated as its hydrochloride salt (**24**). When methyl (3α-iodo-2β-cholestanyl)carbamate (**27**) was heated at 190° for 5 min, oxazolidone **28** was obtained in 63% yield. The same compound is also obtained by re-

(15) P. B. Talukdar and P. E. Fanta, *J. Org. Chem.*, **24**, 526 (1959); W. E. Noland, J. F. Kneller, and D. E. Rice, *ibid.*, **22**, 695 (1957).

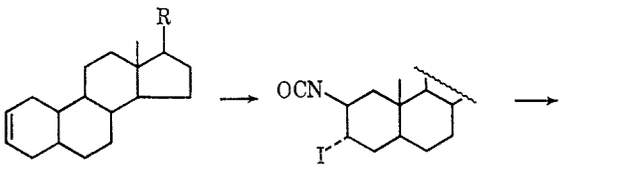
(16) *cis*-β-Aminoalkyl sulfates with base led to unsaturated amines and/or ketones: P. E. Fanta, L. J. Pandya, W. R. Oroskopf, and H. J. Su, *ibid.*, **28**, 413 (1963).

(17) G. Drefahl and K. Ponsold, *J. Prakt. Chem.*, **23**, 136 (1964).

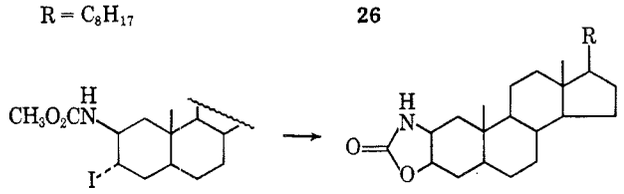
(18) E. Katchalsky and D. Ben Ishai, *J. Org. Chem.*, **15**, 1067 (1950).

(19) M. Mousseron, F. Winternitz, and M. Mousseron Canet, *Bull. Soc. Chim. France*, 737 (1953).

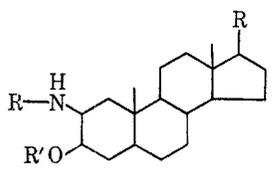
fluxing 3α-iodo-2β-cholestanyl isocyanate (**26**) in isopropyl alcohol (56% yield) or in ethanolic hydrochloric acid (50% yield). The latter two transformations undoubtedly proceed *via* the isopropyl and ethyl carbamate corresponding to **27**. Oxazolidone **28** was hydrolyzed in 93% yield to an amino alcohol by potassium hydroxide in aqueous methanol. Amino alcohol **29a** was converted to its diacetyl derivative **29b** by acetic anhydride in pyridine. Mild hydrolysis of diacetate **29b** with methanolic base gives amido alcohol **29c**. It has been shown earlier that iodocarbamate **27** has the carbomethoxyamino group at the 2β position.[6] It follows that oxazolidone **28** and *cis*-amino alcohol **29a** must be either the 2β,3α or the 2β,3β isomer. Amino alcohol **29a**, is different from 2β-aminocholestan-3α-ol prepared in an unequivocal manner[6] and must necessarily be the isomeric 2β-aminocholestan-3β-ol. It follows that oxazolidone **28** is the *cis*-fused cholestano-[2′β,3′β-*d*]-2-oxazolidone.



R = C_8H_{17} **26**

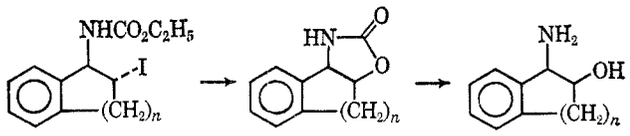


27 **28**



29a, R, R′ = H
b, R, R′ = Ac
c, R = Ac; R′ = H

Iodocarbamates **30a** and **30b** obtained from indene and 1,2-dihydronaphthalene were pyrolyzed in refluxing diglyme to give the oxazolidones **31a** and **31b** in 87 and 45%, respectively (see Table II). That these oxazolidones are the *cis* isomers is shown by the fact that they are hydrolyzed by alcoholic base to give the known *cis*-1-amino-2-indanol (**32a**) and *cis*-1-amino-2-tetralol (**32b**).[20]



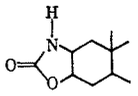
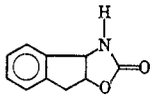
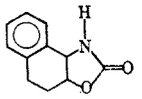
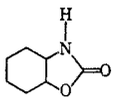
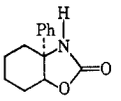
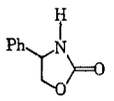
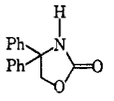
30a, $n = 1$ **31a**, $n = 1$ **32a**, $n = 1$
b, $n = 2$ **b**, $n = 2$ **b**, $n = 2$

The reaction with INCO thus provides a convenient stereospecific route to the synthesis of *cis*-2-amino alcohols (*e.g.*, **29a**) as well as of *trans*-2-amino alcohols (*e.g.* **23**) from olefins.

(20) G. Drefahl and K. Ponsold, *Ber.*, **91**, 266 (1958).

TABLE II

PREPARATION OF 2-OXAZOLIDONES BY PYROLYSIS OF β-IODOCARBAMATES AVAILABLE FROM OLEFINS

Starting olefin	2-Oxazolidone	Pyrolysis solvent	Temp, °C	Time, min	% yield
2-Cholestene		Neat	190	5	63
		i-PrOH	76	225	55
		EtOH–HCl	75	180	50
Indene		Diglyme	155	120	87
1,2-Dihydronaphthalene		Diglyme	155	120	45
		Neat	150	15	44[a]
		Neat	135	20	42
Cyclohexene		TCE[b]	115	1530	41
Phenylcyclohexene		TCE[b]	115	6600	59
Styrene		Neat	100	240	62
		Neat	145	15	85[c]
		Neat	142	15	90
1,1-Diphenylethylene		EtOH	75	1000	64

[a] Ethyl iodide isolated in 71% yield. [b] Tetrachloroethylene. [c] Ethyl iodide isolated in 91% yield.

Experimental Section

Addition of Iodine Isocyanate to Olefins. General Procedure.—To 200 ml of anhydrous ether in a three-necked flask equipped with a mechanical stirrer and a drying tube was added 25.4 g (0.1 mole) of solid I_2 and 20 g (0.13 mole) of fresh silver cyanate.[6] The slurry was stirred for 30 min after which time 0.1 mole of the olefin was added in three equal portions over a 30-min period. If on addition a vigorous reaction was observed an ice–salt bath was used. Then the reaction mixture was stirred at room temperature from 1 to 5 hr depending on how long the iodine color persisted. In some cases, *e.g.*, cyclododecene, the iodine color was still strong after 8 hr but monotoring of the reaction by vapor phase chromatography indicated that 95% of the olefin had been consumed within 5 hr. The inorganic salts (silver iodide and isocyanate) were filtered off over Celite 512. At this point the solution can be evaporated under vacuum and the iodoisocyanate in some cases can be isolated and characterized by its strong infrared absorption at 2250 cm^{-1} and/or by nmr.

When these reactions were run under identical conditions except with anhydrous acetonitrile substituting for ether, the iodine color was discharged within seconds of the addition of iodine. Olefin was added and work-up was continued as above.

Alternatively, the slurry obtained on addition of iodine to silver cyanate (threefold excess) in ether or tetrahydrofuran can be filtered after 30 min and the filtrate can be stored in the refrigerator in the dark for 2–3 days and then used in additions to olefins.

Proceedure for Obtaining Nmr Spectra of Iodo Isocyanates.—A mixture of 20 g of silver cyanate, 24.5 g of iodine, and 12.8 g of 1-phenylpropene in 100 ml of ether was stirred for several hours and filtered over Celite. Five milliliters of the filtered solution was placed in a 50-ml, round-bottom flask and to this was added 3 ml of Spectrograde carbon tetrachloride. The ether was removed under vacuum at 25° on a Roto-vac. Gentle heating can be used without causing decomposition. The solution was taken down to

a volume of 2 ml and tetramethylsilane was added. The sample was ready for an nmr spectrum. (2-Iodo-1-phenyl)propyl isocyanate showed a singlet at τ 2.6 (5 H phenyl), a doublet at 5.0 (CHN), an octet at 5.5 (CHI), and a doublet at 8.33 (CH_3).

β-Iodoalkanecarbamates.—To the solution of β-iodoalkyl isocyanate, obtained as above after removal of the silver salts by filtration, was added 200 ml of anhydrous methanol (or another alcohol) and 3 drops of a dilute solution of lithium methoxide (prepared by dissolving 25 mg of lithium in 50 ml of of anhydrous methanol). The solution was swirled and left to stand in the dark for 24 hr; then the ether was stripped off on a Roto-vac at room temperature. If no iodine color or only a very slight color has appeared by that time, most of the methanol can also be stripped off under vacuum on a steam bath (*do not evaporate to dryness*). The remaining solution was then poured onto 400 ml of ice–water containing a trace of sodium sulfite to remove residual iodine color. The solution was stirred for a few minutes and allowed to stand until all the ice melted. At this point either a solid product resulted, which could be filtered off, or the product oiled out and was extracted with ether. The ether extract was washed with sodium chloride solution and dried over sodium sulfate, and the product was collected upon evaporation of the ether.

In some cases the oily product was found to be a mixture of the iodocarbamate and the iodo isocyanate as evidenced by infrared spectra. This occurred with molecules containing a tertiary or hindered isocyanate function, and was averted by refluxing the solution of the iodo isocyanate with methanol and lithium methoxide (0.01 equiv). In all cases so far this modification has been successful and upon work-up a solid was obtained free of iodo isocyanate.

Methyl N-(*trans*-2-iodocyclopentane)carbamate was prepared from cyclopentene: yield 74%; mp 85–87° (from methanol); ν_{max} 3300, 1712, 1550 cm^{-1}. *Anal.* Calcd for $C_7H_{12}INO_2$: C, 31.24; H, 4.49. Found: C, 31.41; H, 4.63.

Methyl N-(*trans*-2-iodocyclohexane)carbamate (14) was prepared from cyclohexene: yield 80%; mp 130–131°.[5] The decoupled nmr spectrum indicates axial protons at τ 5.58 (CHI, doublet, J = 10 cps) and 6.08 (CHN, doublet, J = 10 cps), and a OCH_3 singlet at 6.3.

Cyclohexene (15 ml) was added to a solution of 10 g of iodine monochloride and 10 g of potassium cyanate in 200 ml of acetonitrile that had been maintained at 0° for 30 min. Stirring was continued for 3 hr at 0° and then 100 ml of methanol was added. Usual work-up and crystallization from ether–pentane gave 4.1 g of methyl N-(*trans*-2-iodocyclohexane)carbamate, mp 125–128°, identical with an authentic sample.

Phenyl N-(*trans*-2-iodocyclohexane) carbamate was prepared from cyclohexene using phenol and pyridine: yield 60%; mp 125–127° (from methanol); ν_{max} 3350, 1715, 1500 cm^{-1}. *Anal.* Calcd for $C_{13}H_{16}INO_2$: C, 45.20; H, 4.67. Found: C, 45.43, H, 4.75.

Methyl N-(*trans*-2-iodocycloheptane)carbamate was prepared from cycloheptene: yield 72%; mp 103–104°; ν_{max} 3300, 1695, 1550 cm^{-1} (from methanol). *Anal.* Calcd for $C_9H_{16}INO_2$: C, 36.88; H, 5.43. Found: C, 37.17; H, 5.47.

Methyl N-(*trans*-2-iodocyclooctane)carbamate was prepared from cyclooctene: yield 70%; mp 115–116.5° (from methanol); ν_{max} 3300, 1700, 1555 cm^{-1}. *Anal.* Calcd for $C_{10}H_{18}INO_2$: C, 38.59; H, 5.83. Found: C, 38.75; H, 5.92.

Methyl N-(*cis*-2-iodocyclododecane)carbamate was prepared from *trans*-cyclododecene: crude yield 65%; mp 102–104° (from methanol); ν_{max} 3300, 1710, 1540 cm^{-1}. *Anal.* Calcd for $C_{14}H_{26}INO_2$: C, 45.78; H, 7.13. Found: C, 45.96; H, 7.32.

Methyl N-(1-methyl-*trans*-2-iodocyclohexane)carbamate (9) was prepared from 1-methylcyclohexene. Before addition of methanol an nmr spectrum of the 2-iodo-1-methylcyclohexyl isocyanate in carbon tetrachloride was taken: τ 5.6 (quartet, J = 4 and 8 cps, CHI indicating an axial H), 8.0 (multiplet), 8.49 (singlet, CH_3). The yield of iodocarbamate was 69%; mp 68–69° (from methanol); ν_{max} 3350, 1700, 1510 cm^{-1}; nmr τ 5.0 (CHI, multiplet), 6.35 (OCH_3 singlet), 7.9 (broad multiplet), 8.6 (CH_3 singlet). *Anal.* Calcd for $C_9H_{16}INO_2$: C, 36.87; H, 5.21. Found: C, 36.76; H, 5.39.

Methyl N-(1-phenyl-*trans*-2-iodo-1-cyclohexane)carbamate (10) was prepared from 1-phenylcyclohexene using the following modification of the above procedure. After the inorganic salts were filtered off, dry hydrogen chloride gas was bubbled through the ether solution for several minutes. Methanol was added and the ether was boiled off on a steam bath (15 min). The work-up was carried out as usual. The yield of product obtained in this manner was 58%, mp 126–128°. On recrystallization from benzene–pentane, the melting point was raised to 143–144°. The purified material was unstable and turned to a black tar after standing several weeks at room temperature. The crude product, mp 126–128°, was much more stable. When the normal procedure was used, the yield of product was 32%; ν_{max} 3380, 3050, 1725 sh, 1711, 1527, 1267, 1248, 1010 cm^{-1}. *Anal.* Calcd for $C_{14}H_{18}INO_2$ (mp 143–144°): C, 46.81; H, 5.05; N, 3.90. Found: C, 46.58; H, 4.92; N, 3.94.

Methyl N-(*trans*-2-iodo-4-cyclohexene)carbamate (12) was prepared from 1,4-cyclohexadiene: yield 72%; mp 93–95° (from methanol); ν_{max} 3300, 3100, 1700, 1545, 850 cm^{-1}; nmr τ 7.1 (4 H, allylic, broad band), 6.38 (OCH_3, singlet), 5.7 (2 H, CHN and CHI, multiplet), 5.0 (NH broad), 4.2 (2 H, vinyl, broad split band). *Anal.* Calcd for $C_8H_{12}INO_2$: C, 34.14; H, 4.38. Found: C, 34.27; H, 4.23.

Methyl N-(1-iodomethyl-1-cyclobutane)carbamate (6) was prepared from methylenecyclobutane: yield 67%, mp 69–71° (from methanol); ν_{max} 3300, 1710, 1540 cm^{-1}; nmr τ 5.1 (NH, broad), 6.32 (CH_2I, singlet), 6.4 (OCH_3, singlet), 7.9 (6 H, multiplet). *Anal.* Calcd for $C_7H_{12}INO_2$: C, 31.24: H, 4.49. Found: C, 31.41: H, 4.61.

Methyl N-(1-iodomethyl-1-cyclohexane)carbamate (16) was prepared from methylenecyclohexane: yield 72%; mp 92–93° (from methanol–water); ν_{max} 3300, 1710, 1530, 780 cm^{-1}; nmr τ 5.15 (NH, broad), 6.32 (CH_2I, singlet), 6.38 (OCH_3, singlet), 8.5 (10 H, multiplet). *Anal.* Calcd for $C_9H_{16}INO_2$: C, 36.87; H, 5.43. Found: C, 36.79; H, 5.63.

Methyl N-(*trans*-1-iodo-2-methyl-2-propane)carbamate (8a) was prepared from isobutene: yield 71%; mp 35–36° (from methanol); ν_{max} (neat) 3400, 1710, 1520 cm^{-1}; nmr τ 6.34 (CH_2I, OCH_3, singlet, with shoulder), 8.52 [$(CH_3)_2$, singlet]. *Anal.* Calcd for $C_6H_{12}INO_2$: C, 28.01; H, 4.70. Found: C, 28.10; H, 4.88.

Methyl N-(*trans*-1-iodo-2-phenyl-2-propane)carbamate (8c) was prepared from α-methylstyrene: yield 62%; mp 83–84.5° (from methanol); ν_{max} 3350, 1710, 1520 cm^{-1}; nmr τ 2.68 (singlet), 4.7 (broad peak), 6.2 (CH_2I, doublet, J = 6 cps), 6.36 (OCH_3, singlet), 8.2 (CH_3, singlet). *Anal.* Calcd for $C_{10}H_{14}INO_2$: C, 41.39; H, 4.41. Found: C, 41.48; H, 4.56.

Methyl N-(2-iodo-1,1-diphenylethane)carbamate (8b) was prepared from 1,1-diphenylethylene: yield 89%; mp 135–137° (from methanol); ν_{max} 3350, 1705, 1550 cm^{-1}; nmr τ 2.7 (10 H, phenyl, singlet broad), 4.2 (NH, singlet broad), 5.52 (CH_2I, singlet), 6.4 (OCH_3, singlet). *Anal.* Calcd for $C_{16}H_{16}INO_2$: C, 50.40; H, 4.23. Found: C, 50.59; H, 4.18.

Methyl N-(2-iodo-1-phenylpropane)carbamate was prepared from 1-phenyl-1-propene: yield 64%; mp 103–104° (from methanol); ν_{max} 3300, 3100, 1700, 1525 cm^{-1}; nmr τ 2.65 (phenyl, singlet), 4.4 (NH broad peak), 5.4 (CHI multiplet), 5.56 (CHN multiplet), 6.4 (OCH_3 singlet), 8.25 (CH_3 doublet, J = 7 cps). *Anal.* Calcd for $C_{11}H_{14}INO_2$: C, 41.39; H, 4.42. Found: C, 41.52; H, 4.41.

Bisulfite Addition to *trans*-2-Iodocyclohexyl Isocyanate.—To an ether solution of 6 g of *trans*-2-iodocyclohexyl isocyanate obtained by INCO addition to cyclohexene was added 20 ml of 40% aqueous sodium bisulfite solution and 12 ml of dioxane. The solution was stirred at room temperature for 20 hr. After 3 hr a fluffy, white solid began to appear. The ether was stripped down, the mixture was filtered, and the product was air dried. A white solid was obtained which weighed 6.9 g and melted at 145–147°. The yield of crude product 1 was 80%. It was recrystallized from water without change in melting point: ν_{max} 3280, 1645, 1540 cm^{-1}. *Anal.* Calcd for $C_7H_{11}INNaO_4S$: C, 23.68; H, 3.12. Found: C, 23.52; H, 3.16.

Conversion of Bisulfite Addition Compound 1 to 1,2-Iminocyclohexane (2).—One gram of bisulfite addition product 1 was added to 50 ml of a 1.5 *N* solution of potassium hydroxide in methanol. The mixture was refluxed for 3 hr, poured into 50 ml of sodium chloride solution, and extracted with hexane (three 20-ml portions). The hexane layer was washed with water (three 20-ml portions) and dried over anhydrous sodium sulfate and the volume was reduced to about 10 ml. Phenyl isocyanate (2 ml) was added and the solution was warmed on a steam bath and then placed in the refrigerator. A white solid formed which weighed 0.475 g and melted at 144–148°. Upon recrystallization from acetone (65% yield) it melted at 150–152°. This product was shown to be identical by infrared and mixture

melting point with an authentic sample of N-phenylcarbamoyl-1,2-iminocyclohexane:[5] ν_{max} 3300, 1650, 1590, 1440, 755 cm^{-1}.

1-(N-Phenylcarbamoyl)-2,2-pentamethyleneaziridine.—Methyl N-(1-iodomethyl-1-cyclohexane)carbamate (**16**, 1.0 g) was added to a 1.5 *N* solution of potassium hydroxide in methanol and the solution was refluxed on the steam bath for 5 hr. The reaction mixture was allowed to cool and 50 ml of sodium chloride was added. The mixture was extracted with hexane (three 30-ml portions), washed with water (three 20-ml portions), and dried over anhydrous sodium sulfate. The hexane solution was evaporated to a volume of 10 ml, and 2 ml of phenyl isocyanate was added. A white solid was filtered off after 10 min of standing in the refrigerator (64% yield). On recrystallization from acetone, the urea melted at 149.5–150.5°: ν_{max} 3300, 1635, 1590, 770 cm^{-1}. *Anal.* Calcd for $C_{14}H_{18}N_2O$: C, 73.01; H, 7.88. Found: C, 73.07; H, 7.73.

N-Phenylcarbamoyl-1,2-iminocycloheptane.—A solution of 1.0 g of the methyl (*trans*-2-iodocycloheptane)carbamate in 50 ml of methanolic potassium hydroxide was refluxed on the steam bath for 3 hr. The mixture was poured onto 30 ml of saturated sodium chloride solution and extracted with hexane (three 15-ml portions). The hexane layer was washed with water (three 15-ml portions) and dried over anhydrous sodium sulfate. All but 2–3 ml of hexane was removed on the Roto-vac and then 1.5 ml of phenylisocyanate was added. The solution was warmed on a steam bath and then placed in the refrigerator for 24 hr. The resulting solid mass was filtered off, air dried (56%), and recrystallized from acetone–water: mp 104–105.5°; ν_{max} 3370, 1655, 1590, 1440, 785 cm^{-1}. *Anal.* Calcd for $C_{14}H_{18}N_2O$: C, 73.01; H, 7.88. Found: C, 72.88; H, 7.85.

trans-**1,2-Imino-***trans,trans*-**5.9-cyclododecadiene** (**20**) was prepared by INCO addition to all-*trans*-1,5,9-cyclododecatriene using the following modification. After the inorganic salts were filtered off, 6 *N* hydrochloric acid was added to the solution and stirring was continued for 24 hr. The ether and most of the water were stripped off on the Roto-vac leaving amine salt **19** as a dark solid. The solid was refluxed in methanolic potassium hydroxide for 3 hr. The solution was extracted with ether, washed with water, and dried over magnesium sulfate. The ether was removed leaving **20** as a tan solid: mp 72–75°; ν_{max} 3200, 1440, 1350, 980, 850 cm^{-1}. *Anal.* Calcd for $C_{12}H_{19}N$: C, 81.30; H, 10.80. Found: C, 81.55; H, 10.93.

Competitive Experiments between Cyclohexene and 1-Methylcyclohexene.—To ether at 18° there was added 3.125 g of iodine, 3 g of silver cyanate, 2.48 g of 1-methylcyclohexene, and 2.058 g of cyclohexene. The solution was stirred for 100 min and aliquots were removed for vpc measurements to determine the ratio of unreacted olefins. The amount of unreacted cyclohexene and 1-methylcyclohexene was 54 and 46%, respectively. An aliquot removed after 150 min showed the same ratio (53:45). The experiment was repeated except that this time the ether solution of iodine and silver cyanate was allowed to stir for 90 min before the olefins were added. After 2 hr of stirring with the olefins, vpc measurements were taken and the ratio of unreacted cyclohexene to 1-methylcyclohexene was again 54:46.

The olefins were correlated with their retention times by injecting pure olefin into some of the runs and observing which peak increased. A 2% SE-30 on Chromosorb W column maintained at 65° was used.

Addition of Iodine Isocyanate to Phenyl Acetylene.—A solution containing 0.025 mole of iodine isocyanate was formed by adding 6.25 g (0.025 mole) of iodine to 10 g (0.066 mole) of silver cyanate in 100 ml of dry tetrahydrofuran maintained at −18° with stirring for 3 hr. The inorganic salts were filtered, 2.58 (0.025 mole) of phenylacetylene was added, and the solution was stirred for 12 hr. At this point an infrared spectrum of the mixture showed a strong absorption at 2250 cm^{-1} (isocyanate). Hydrochloric acid (100 ml, 6 *N*) was added. Within minutes after addition of hydrochloric acid, a pungent odor of a lachrymator was detectable. This was attributed to the formation of ω-iodoacetophenone. Stirring was continued for 12 hr at room temperature. An orange solution over a dark oil was obtained. The mixture was extracted with ether, washed with water, and dried over magnesium sulfate. An infrared spectrum at this time showed a mixture of isocyanate, ketone, and imine. Another 50-ml portion of 6 *N* hydrochloric acid was added and the solution was stirred and heated gently for 3 hr. An infrared spectrum of the material extracted with ether indicated that all isocyanate had disappeared and only carbonyl absorption was present. The dark solution was cleared up by addition of metallic mercury. An nmr spectrum in carbon tetrachloride showed a sharp singlet at τ 7.5 as well as peaks centered at 2.5. The methyl protons of acetophenone absorb at τ 7.5 and the solution had an odor characteristic of this ketone. A 2,4-dinitrophenylhydrazone derivative formed readily and melted at 242–246° after several crystallizations from ethanol and ethyl acetate. This material was identical by infrared and melting point with the derivative prepared from authentic acetophenone.

When INCO was formed *in situ* in the presence of phenylacetylene, the only product isolated in 70% yield was α,β-diiodostyrene, mp 72–73°, identical with material obtained from addition of iodine to phenylacetylene.

Catalyzed Conversion of Isocyanates to Carbamates.—The conversion of isocyanates to the corresponding carbamates utilizing lithium methoxide, sodium methoxide, and di-*n*-butyltin dilaurate as catalysts was studied on the Beckman Infracord 5, by analyzing the peak heights at 2250 (isocyanate) and at 1710 cm^{-1} (carbamate) at different time intervals after addition of catalyst.

Standard solutions were made up with different ratios of cyclohexyl isocyanate and methyl cyclohexanecarbamate. Infrared investigation of these solutions showed that the intensity of the isocyanate and carbamate absorption was close to equal and calibration curves were prepared. With this information four solutions of 0.77 g (0.00625 mole) of cyclohexyl isocyanate in 10 ml of methanol were prepared and labeled A, B, C, and D. To solution A 0.33 ml of a 1% by weight solution of lithium methoxide was added, to B 0.5 ml of 1% sodium methoxide was added, and to C 1.0 ml of a 5.5% by weight solution of di-*n*-butyltin dilaurate was added.[21] Solution D was left as a reference.

The flasks were stoppered and swirled by hand. Infrared spectra of solutions A, B, and C were taken after 5 min and all showed essentially no absorption at 2250 cm^{-1} indicating complete conversion to the carbamate. An infrared spectrum of solution D after 15 min showed only 4% conversion to the carbamate. Subsequent infrared spectra of solution D at intervals up to 2 hr showed the following per cent conversion as calculated from log differences of the peak heights: after 15 min, 4%; 30 min, 11%; 60 min, 16%; 120 min, 26%.

From this information it was decided that a hindered isocyanate should be used in order to detect rate differences with these catalysts. The iodo isocyanate formed by the addition of iodine and silver isocyanate to methylene cyclohexane was chosen because the isocyanate function is tertiary and was found to react very slowly with methanol. An ether solution containing 0.025 mole of the INCO adduct of methylenecyclohexane was divided into four equal parts. To each was added 10.0 ml of reagent grade methanol and the same amounts of the three catalyst solutions previously mentioned so that the resulting molar ratio of catalyst to isocyanate was approximately 0.012 in all cases. The solutions were swirled by hand and allowed to stand at 25°. Infrared spectra were taken at 30- and 120-min intervals and the results are summarized in Table I.

Cholestano[2′β,3′β-*d*]-2-oxazolidone (**28**). **A. By Neat Pyrolysis.**—Methyl N-(3α-iodo-2β-cholestane)carbamate[5] (100 mg) was placed in a small test tube and immersed in a Woods metal bath at 190–195° for 5 min. Extraction with 15 ml of boiling hexane left 38 mg of oxazolidone **28** as fluffy, white needles, mp 223–226°. Concentration of the hexane solution gave an additional 10 mg of product, mp 225–227°. The total yield was 63%.

An analytical sample was prepared by two crystallizations from benzene–Skellysolve F (bp 40–60°), followed by one recrystallization from ether. The product was obtained as white needles: mp 226–227°; ν_{max} 3300, 1749, 1725, 1700 cm^{-1}; (in CCl_4) 1772 cm^{-1}; the nmr spectrum had bands at τ 3.0 (NH), 5.58 (3 H), 5.93 (2 H), 8.97 (C-19, singlet), 9.13 (C-26 and C-27, doublet, J = 6.5 cps), and 9.35 (C-18, singlet). *Anal.* Calcd for $C_{28}H_{47}NO_2$: C, 78.27; H, 11.03; N, 3.26. Found: C, 78.34; H, 11.08; N, 3.57.

B. In Isopropyl Alcohol.—3α-Iodo-2β-cholestanyl isocyanate (**26**, 1.01 g) was refluxed for 3.75 hr in 50 ml of isopropyl alcohol. The solvent was removed and the resulting amorphous solid was crystallized from *n*-hexane. There was obtained 440 mg of product (56%) melting at 223–224°.

(21) A. Castro, D. Brain, H. Fischer, and R. Fuller, *J. Org. Chem.*, **19**, 1444 (1954).

C. In Ethanol–Hydrochloric Acid.—A solution of 320 mg of 3α-iodo-2β-cholestanyl isocyanate (**26**) (in 15 ml of absolute ethanol was refluxed for 20 min while dry hydrogen chloride gas was passed through; then boiling was continued for 2.5 hr. The solution was poured into 50 ml of water and extracted with ether. The ether layer was washed with water and dried over anhydrous magnesium sulfate. Removal of solvent gave a yellow oil which crystallized on trituration with cold hexane. The yield of **28** was 125 mg (50%), mp 225–228°.

2β-Aminocholestan-3β-ol (29a).—Cholestano[2β,3β-*d*]-2-oxazolidone (**28**, 48 mg) was dissolved in a solution of 5 ml of methanol and 0.5 ml of water containing 1.0 g of potassium hydroxide. The solution was refluxed under an atmosphere of nitrogen for 20 hr, then diluted with water and filtered. The product weighed 39 mg (89%) and melted at 166–169°.

Upon crystallization from methanol–water, the material melted at 153–155°. After drying overnight at 80° (2 mm) the melting point was 148–149°; ν_{max} 3280, 1077, 1054 cm^{-1}. This material was subjected to elemental analysis. *Anal.* Calcd for $C_{27}H_{49}NO$: C, 80.33; H, 12.24. Found: C, 80.08; H, 12.20.

2β-Acetamidocholestan-3β-ol Acetate (29b).—Crude 2β-aminocholestan-3β-ol (**29a**, 300 mg) was acetylated by heating with 5 ml of acetic anhydride and 5 ml of pyridine on a steam bath for 45 min. The solution was poured into ice water and allowed to stand for 1 hr. The acetic acid was neutralized with sodium carbonate, then dried over anhydrous magnesium sulfate. Removal of solvent gave a white solid which was crystallized from methanol. The product obtained as 160 mg (44%) of white needles, had mp 193–194°.

The analytical sample, mp 194–195°, was obtained by recrystallization from methanol: ν_{max} 3590 (water of crystallization), 3480, 1745, 1673, 1535, 1254, 1045 cm^{-1}. *Anal.* Calcd for $C_{31}H_{53}NO_3 \cdot 0.5H_2O$: C, 75.00; H, 10.96; N, 2.82. Found: C, 75.32; H, 10.67; N, 3.24.

2β-Acetamidocholestan-3β-ol (29c).—Diacetate **29b** (45 mg) was dissolved in a solution of 7 ml of methanol and 1.5 ml of water containing 0.55 g of potassium hydroxide. The solution was refluxed for 2 hr, cooled, and filtered. The product melted at 248–253°, or at 258–260° when the block was preheated to 240°.

An analytical sample was obtained by recrystallization from methanol: mp 265–269° (block preheated to 240°); ν_{max} 3340, 3100, 1650, 1563, 1087, 1060 cm^{-1}. *Anal.* Calcd for $C_{29}H_{51}NO_2$: C, 78.14; H, 11.53; N, 3.14. Found: C, 78.31; H, 11.44; N, 3.04.

***cis*-Indano[1,2-*d*]-2-oxazolidone (31a).**—Ethyl N-(*trans*-2-iodo-1-indan)carbamate[5] (**30a**, 500 mg) was dissolved in 10 ml of anhydrous diglyme. The solution was refluxed for 14 hr, then diluted with hexane, and cooled to 5°. The resulting light tan solid was collected and washed with hexane. After drying, it weighed 230 mg (87%) and melted at 155–156°. An analytical sample, mp 159.5–160°, was prepared by three recrystallizations from benzene, followed by one recrystallization from acetone–hexane: ν_{max} 3300, 1774, 1707 sh, 1233, 1054 cm^{-1}. *Anal.* Calcd for $C_{10}H_9NO_2$: C, 68.56; H, 5.18; N, 8.00. Found: C, 68.72; H, 5.28; N, 8.09.

***cis*-Tetralino[1,2-*d*]-2-oxazolidone (31b).**—Ethyl N-(*trans*-2-iodo-1-tetralin)carbamate[5] (**30b**, 4.0 g) was dissolved in 20 ml of anhydrous diglyme. On refluxing, the solution turned deep red-brown. After 2 hr, hexane was added and the mixture was filtered. The resulting tan solid was dissolved in acetone and treated twice with decolorizing charcoal. The acetone solution was diluted with hexane and cooled. There was obtained 795 mg (36%) of product, mp 141.5–144°. A second crop, weighing 185 mg (9%) and melting at 138–139.5°, was obtained by concentration of the mother liquor.

An analytical sample, mp 140.5–142°, was prepared by two recrystallizations from acetone–hexane: ν_{max} 3280, 1755, 1730 (very broad), 1233, 1073, 1048 cm^{-1}; ν_{max} (in tetrachloroethylene) 3480, 3240, 3150, 1790 sh, 1772, 1228, 1055 cm^{-1}. *Anal.* Calcd for $C_{11}H_{11}NO_2$: C, 69.82; H, 5.86; N, 7.40. Found: C, 69.32; H, 5.77; N, 7.33.

***cis*-Cyclohexano[*d*]-2-oxazolidone (25).**—Methyl N-(*trans*-2-iodo-1-cyclohexane)carbamate (2.0 g) was dissolved in 10 ml of tetrachloroethylene. The solution was refluxed for 24 hr. Removal of solvent under reduced pressure gave a brown oil. This oil was dissolved in ether and chromatographed on 20 g of Woelm neutral alumina, activity grade I. Fractions 8–11 (ether, 25 ml each) gave an oil which solidified on cooling. On recrystallization from ether–hexane, there was obtained 433 mg of product (41.3%), mp 55.5–56°. The reported melting point for the *cis* isomer is 55° and for the *trans* isomer is 110°;[19] ν_{max} 3280, 1740, 1220, 1080, 994, 952, cm^{-1}; ν_{max} (in tetrachloroethylene) 3490, 3280, 1793 sh, 1773, 1753 sh, 1220 cm^{-1}.

4-Phenyl-2-oxazolidone (4).—Ethyl N-(2-iodo-1-phenylethane)-carbamate[5] (**3**, 3.19 g) was placed in a 30-ml, one-necked, pear-shaped flask equipped with a 6-in. Vigreux column. The top of the column was connected to a vacuum pump through an adapter. The system was equipped with a tared trap which was cooled to −80°.

The flask was heated 15 min in an oil bath maintained at 143–146°, while the pressure in the system was 2 mm. The trap contained 1.41 g of ethyl iodide (91%), identified by comparison of its infrared and nmr spectra with those of the authentic material.

The solid residue in the reaction flask was dissolved in hot chloroform. On cooling there was obtained 821 mg (50.4% of precipitate, mp 138–139.5°. An additional 555 mg (34.1%), mp 137–138°, was obtained by concentration of the mother liquor. The total yield was 1.376 g (84.5%). The reported melting point for this compound is 136.8–137.8°; for 5-phenyl-2-oxazolidone the melting point is 88.8–90.2°.[18]

4,4-Diphenyl-2-oxazolidone.—The standard procedure was used to add iodine isocyanate to 1,1-diphenylethylene. The inorganic salts were filtered off and 50 ml of ethanol was added to the solution. The ether was removed on the Roto-vac. The ethanol solution was refluxed for 18 hr on a steam bath. Upon work-up, a high-melting solid was obtained which proved to be 4,4-diphenyl-2-oxazolidone: yield 64%; mp 175–177° (from methanol); ν_{max} 3250, 1740, 1400, 1060, 1040, 950, 760, 730, 700 cm^{-1}; nmr τ 2.68 (10 H, multiplet); 5.1 (2 H, singlet). *Anal.* Calcd for $C_{15}H_{13}NO_2$: C, 75.30; H, 5.48. Found: C, 75.01; H, 5.64.

4-Phenyl-*cis*-cyclohexano[*d*]-2-oxazolidone.—Methyl N-(1-phenyl-*trans*-2-iodo-1-cyclohexane)carbamate (**10**, 2.0 g) was dissolved in 20 ml of tetrachloroethylene and the solution was refluxed for 11 hr. The solvent was removed *in vacuo*, leaving a brown oil. This oil was chromatographed on 22 g of neutral alumina, activity grade II. Fractions 4–8 (1:1 pentane–ether, 25 ml each) yielded 709 mg (59%) of the oxazolidone, mp 115–119°.

An analytical sample, mp 123–125° (white prisms), was obtained by recrystallization from ether–pentane, followed by two recrystallizations from acetone–pentane: ν_{max} 3360, 3030, 2930, 2855, 1780, 1745 sh, 1027, 1002, 931, 763, 733, 701 cm^{-1}. *Anal.* Calcd for $C_{13}H_{15}NO_2$: C, 71.86; H, 6.96; N, 6.45. Found: C, 72.02; H, 6.93; N, 6.33.

2-Hydroxy-1-phenylethylamine Hydrochloride (24).—4-Phenyl-2-oxazolidone (**4**, 772 mg) was dissolved in 20 ml of 0.85 *N* methanolic potassium hydroxide; 5 ml of water was added. After refluxing the solution under nitrogen for 24 hr, the solvent was removed under reduced pressure. The remaining solid was partitioned between ether and water. The ether solution was separated and dried. Anhydrous hydrogen chloride gas was bubbled into the dried ether solution until no more precipitate appeared. The resulting white solid was filtered off and recrystallized from ethanol–ether to yield 425 mg (52%) of the pure salt, mp 150–151° (lit.[21] mp 149–150°).

***cis*-1-Amino-2-indanol (32a).**—*cis*-Indano[1,2-*d*]-2-oxazolidone (**31a**, 360 mg) was dissolved in 20 ml of 0.85 *N* methanolic potassium hydroxide; 5 ml of water was added. The solution was refluxed under nitrogen for 18 hr, the methanol was evaporated under reduced pressure, and the resulting solid was extracted with ether. After drying the ethereal solution, part of the solvent was evaporated and the solution was cooled to −12°. There was obtained 135 mg of product as white plates, mp 134–135° (lit.[20] mp 131°). Further concentration and cooling gave an additional 105 mg, mp 133–134°. The total yield of amino alcohol was 240 mg (79%).

***cis*-1-Amino-2-tetralol (32b).**—*cis*-Tetralino[1,2-*d*]-2-oxazolidone (**31b**, 1.0 g) was hydrolyzed as described for the indan analog. The product obtained as white plates, 450 mg, mp 109–110°, and an additional 201 mg, had mp 108–109°. The total yield was 75%. The reported melting point is 107°.[20]

After recrystallization from methanol–ether, the hydrochloride salt melted at 220°–221° (lit.[20] mp 215°).

Registry No.—Iodine isocyanate, 3607-48-5; (2-iodo-1-phenyl)propyl isocyanate, 7480-08-2; methyl N-(*trans*-2-iodocyclopentanecarbamate, 7480-09-3;

methyl N-(*trans*-2-iodocyclohexane)carbamate, 1199-15-1; phenyl N-(*trans*-2-iodocyclohexanecarbamate, 7480-11-7; methyl N-(*trans*-2-iodocycloheptane), 7480-12-8; methyl N-(*trans*-2-iodocyclooctane)carbamate, 7480-13-9; methyl N-(*cis*-2-iodocyclododecane)carbamate, 7492-93-5; **9**, 7480-14-0; **10**, 7480-15-1; **12**, 7480-16-2; **6**, 7480-17-3; **16**, 7480-18-4; **8a**, 7540-56-9; **8c**, 7480-19-5; **8b**, 7492-91-3; methyl N-(2-iodo-1-phenylpropane)carbamate, 7480-20-8; **1**, 7540-57-0; N-phenylcarbamoyl-1,2-iminocyclohexane, 4714-51-6; 1-(N-phenylcarbamoyl)-2,2-pentamethyleneaziridine, 7541-69-7; N-phenylcarbamoyl-1,2-iminocycloheptene, 7480-22-0; **20**, 7480-23-1; **28**, 7480-24-2; **29**, 1896-38-4; **29b**, 7480-26-4; **29c**, 1896-39-5; **31a**, 7480-28-6; **31b**, 7480-29-7; *cis*-cyclohexano[*d*]-2-oxazolidone, 7480-30-0; *trans*-cyclohexano[*d*]-2-oxazolidone, 7480-31-1; **4**, 7480-32-2; 4,4-diphenyl-2-oxazolidine, 7480-33-3; **25**, 7480-34-4; 2-hydroxy-1-phenylethylamine hydrochloride, 4561-44-8; **32a**, 7480-35-5; **32b**, 7480-36-6.

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The Reaction of Bromo Epoxides and Acetoxy Epoxides with Amines[1]

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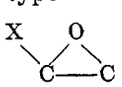
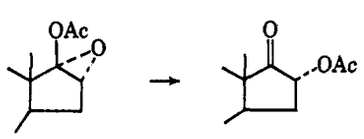
The synthesis of negatively substituted epoxides, such as 3β-acetoxy-17β-bromo-16α,17α-oxidoandrostane (I), and their reactions with amines are described. The resulting amino ketones (II) were identical with those obtained in a substitution reaction from the 16α-bromo 17-ketone IV with amines. Reduction of amino ketones II leads to the corresponding amino alcohols. 16β-Alkylamino 17-ketones (II) also resulted from the interaction of acetoxy epoxide VIII with amines. The opening of the three-membered ring is interpreted as a concerted process. The synthesis of 2-alkylamino-3-cholestanones cannot be effected *via* 2-bromo-3-cholestanone but was accomplished by ring opening of acetoxy epoxide IX with amines.

Little is known about the chemistry of negatively substituted epoxides of type

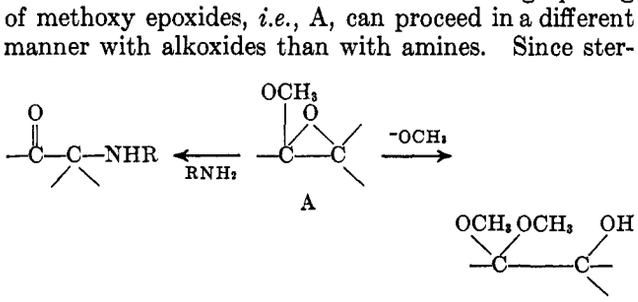


in particular about the stereochemistry of their reactions. Such compounds are of theoretical interest as possible precursors of highly strained oxirenes, as well as of synthetic interest leading to stereospecific introduction of functional groups. Acetoxy epoxides, such as VIII, are known to rearrange on heating or in the



VIII

presence of catalysts[2] and chloro epoxides apparently undergo similar transformations.[3] The investigations of Stevens and co-workers[4] indicate that ring opening of methoxy epoxides, *i.e.*, A, can proceed in a different manner with alkoxides than with amines. Since steroids provide an excellent testing ground for stereochemical principles and because of our interest in steroidal small-ring compounds[5] and amino ketones,[6] we investigated the reaction of bromo epoxides I and Ia and of acetoxy epoxides VIII and IX with amines.



Epoxide I was readily prepared by per acid oxidation of 3β-acetoxy-17-bromo-16-androstene, which was in turn obtained from epiandrosterone hydrazone as outlined by Mori and Tsuneda.[7] The assignment of the α configuration for epoxide I is based on the well-known approach of reagents from the α side of steroids and has analogy in the formation of other 16α,17α-oxido compounds on epoxidation of steroid 16-enes.[2,8]

The reaction of bromo epoxides such as I with amines can potentially proceed by a variety of pathways which include elimination to oxirene intermediates B or C. (See Scheme I.)

We found that I reacts readily at room temperature with primary or secondary amines to give amino ketones. These products are identical with those obtained upon heating of 16α-bromo-17-keto steroid IV with amines and are assigned 16β-amino-17-keto structure II. The structures of IIc and IId have been recently established.[9] It was disquieting to find that 16β-bromoandrostan-17-on-3β-ol acetate reacted with piperidine to give IIc, the same product obtained from I or IV. Attempts to isolate a 16α-amino 17-ketone intermediate under milder reaction conditions were unsuccessful. Nevertheless, we feel that the 16β configuration for the amino group in II, though not unequivocally established, can be considered correct in view of the recent work of Hewett and Savage.[9]

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