1,2-Cycloaddition of Dichloroketen to Cyclo-olefins and the Aza-ring Expansion of Cyclobutanones. Conformational Features of *cis*-Octahydrobenzo[*b*]furanones and *cis*-Octahydroindolones

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Summary The syntheses of the *cis*-octahydroindoles (**11**)—(**13**) and the *cis*-octahydrobenzo[*b*]furanones (**2**), (**5**), and (**8**) are described; the conformational features of the *cis*-fused 6/5 ring system present in the octahydroindoles and octahydrobenzo[*b*]furanones are discussed.

The unusual axial aryl conformation exhibited by mesembrine and related alkaloids[1] of the *cis*-octahydroindole series prompted an investigation of a synthetic route to some simple analogues containing a variety of 3a substituents. We report here an efficient synthesis[2] of several examples of this group.

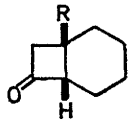
Previous studies indicated that alkyl- or aryl-substituted mono-olefins are unreactive towards keten and the use of the more reactive dichloroketen was required to obtain 1,2-cycloaddition products.[3] A recent survey[4] of the reactivity of olefins towards 1,2-cycloaddition with dichloroketen discussed their behaviour in terms of decreasing reactivity with increasing substitution of the olefin. In keeping with this was the observation that no examples of 1,2-cycloadducts of dichloroketen and tri- or tetra-substituted mono-olefins have been reported.

Despite these previous findings we found that 1-methylcyclohexene reacts in ether solution with trichloroacetyl bromide in the presence of activated zinc[5] to afford a single dichlorocyclobutanone (ν_{max} 1800 cm^{-1}) which on reduction (Zn–HOAc, 120°) gives (**1**)† (ν_{max} 1780 cm^{-1}) (59%). The structure and stereochemistry of (**1**) was established by oxidation of the ketone with trifluoroperacetic acid to the lactone (**2**) (ν_{max} 1773 cm^{-1}) (90%). The ^{1}H n.m.r. spectrum of (**2**) confirmed its structure.

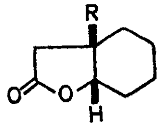
The generality of this reaction was demonstrated by the transformation of 1-phenylcyclohexene and 1-methylcyclopentene into the respective cyclobutanones (**3**) and (**4**),[6] which were the only products formed in each of these individual reactions.‡ Conversion of these cyclobutanones and the ketone (**7**)[4] into the corresponding lactones (**5**), (**6**),[7] and (**8**)[8] was accomplished by a Baeyer–Villiger reaction.

Attempted synthesis of the desired octahydroindoles from the bicyclo[4,2,0]octanones (**1**) and (**3**) employing the Beckman rearrangement gave a single amide in each case. The characterisation of these compounds as the octahydroisoindolones (**9**) and (**10**) followed from their spectral properties and by a comparison of their *N*-methyl derivatives with the isomeric amides (**11**) and (**12**) (*vide infra*).

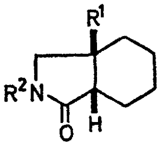
Since a recent report[12] has indicated that the *N*-methyl nitrones derived from several ketones undergo aza-ring expansion in the opposite sense to that found for the Beckman rearrangement of the analogous oxime derivatives, we examined this reaction with the cyclobutanones (**1**), (**3**), (**7**) and (**4**). Reaction of each of these ketones with *N*-methylhydroxylamine in pyridine and subsequent addition of tosyl chloride followed by water gave (**11**)—(**14**) respectively. Reduction of the amide (**12**) with lithium aluminium hydride provided the known 3a-phenyl-*cis*-octahydroindole (**15**)[13] and a similar reduction of (**11**) provided the corresponding 3a-methyl compound (**16**).



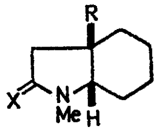
(**1**) R = Me
(**3**) R = Ph
(**7**) R = H



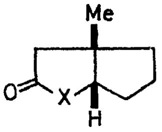
(**2**) R = Me
(**5**) R = Ph
(**8**) R = H



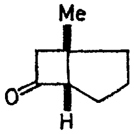
(**9**) R^1=Me, R^2=H
(**10**) R^1=Ph, R^2=H



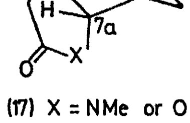
(**11**) R = Me, X = O
(**12**) R = Ph, X = O
(**13**) R = H, X = O
(**15**) R = Ph, X = H$_2$
(**16**) R = Me, X = H$_2$



(**6**) X = O
(**14**) X = NMe



(**4**)



(**17**) X = NMe or O

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† Satisfactory analytical and spectral data have been obtained for all new compounds.

‡ Although the high regio- and stereo-selectivity observed in the formation of the αα-dichloro-derivatives of (**1**), (**3**), and (**4**) may be a consequence of orbital symmetry control in a concerted reaction proceeding through a highly polarized transition state,[9] the fact that 1-phenylcyclohexene is essentially inert to dichloroketen generated *in situ* by dehydrohalogenation of $Cl_2CHCOBr$ suggests that a step-wise[10] process involving a discrete dipolar intermediate originating from a zinc-complexed dichloroketen[11] is a more likely possibility for these reactions.

The synthetic sequence described thus provides an expeditious route to 3a-substituted *cis*-octahydroindoles and the method lends itself to the synthesis of complex *cis*-fused 2,3-pyrrolidines such as those which occur in alkaloids of the crinine, mesembrine,[2] and hasubanine groups.

Examination of the ^{1}H n.m.r. spectra of (**2**), (**5**), (**8**), and (**11**)—(**15**), shows from the narrow appearance of the 7a hydrogen signal that the equivalent conformation of the *cis*-fused 6/5 ring system persists in all seven compounds. The $w_{\frac{1}{2}}$ values of the 7a hydrogen signal (7·5—9·0 Hz) indicate the equatorial disposition of this hydrogen and establish that the predominant conformer in both series is represented by structure (**17**) in which the substituent at 3a (H, Me, or Ph) occupies a quasi-axial position. Although the reasons for the observed conformational preference in these compounds is not yet clear, recent calculations[16] employing the force-field method have shown that the equivalent conformation of 1-methyl-*cis*-hydrindan-3-one, possessing an axial methyl, is 1·1 kcal more stable than the conformer having an equatorial methyl group.

We thank the National Institutes of Health for a research grant for support of this work and for a Career Development Award (P.W.J.). A fellowship from the U.S. Public Health Service (G.M.) is acknowledged.

(*Received, 2nd October* 1972; *Com.* 1679.)

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