TRANSFORMATIONS OF ISOQUINOLONE-DICHLOROCARBENE ADDUCT. Synthesis of 2-Benzazepinones.

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N-methylisoquinolone reacts with dichlorocarbene to give an 1:1 adduct which upon treatment with alcohols yields 2-benzazepinone derivatives.

Reactions of carbenes with enamines provide a versatile approach for the insertion of functionalized one-carbon units between the carbon atoms of the (enamine) olefinic linkage[2]. The synthetic utility of this transformation has been illustrated in the preparation of several modified steroids[3] and nucleosides[4]. We now report a facile procedure for the conversion of isoquinolone (1) to benzazepine derivatives, via its dichlorocarbene adduct (2).

When dichlorocarbene was generated by phase-transfer catalyzed decomposition of chloroform, in the presence of N-methylisoquinolone 1, 4,4-dichloro-2-methylbicyclo[4,1,$0^{3,5}$]-2-benzazepin-1-one (2) (Scheme A) was obtained, as a crystalline product, in 83% yield. Significant in the PMR spectrum of 2 was the AB pattern of the C_3- and C_5-protons [δ 3.08(H_3), 3.58(H_5),

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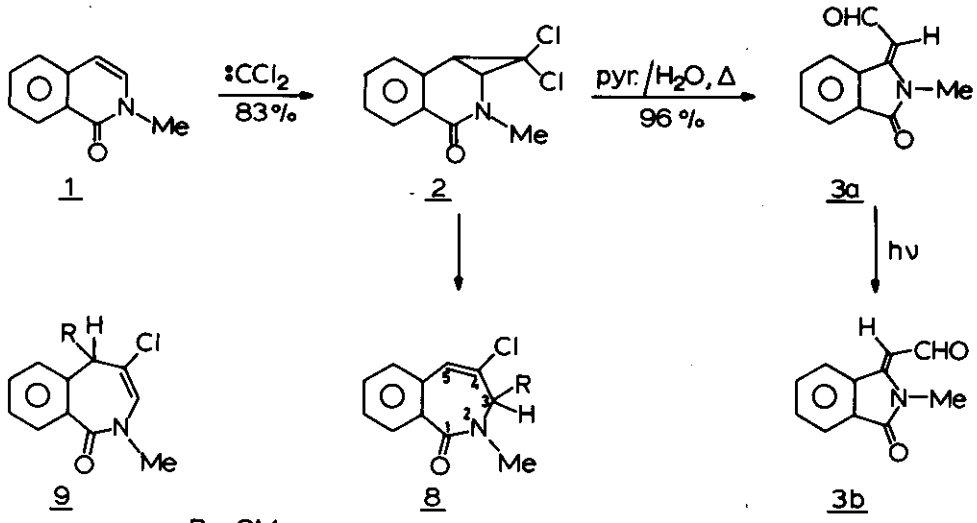
Dedicated to Prof. T. Nozoe on the occasion of his 77th birthday.

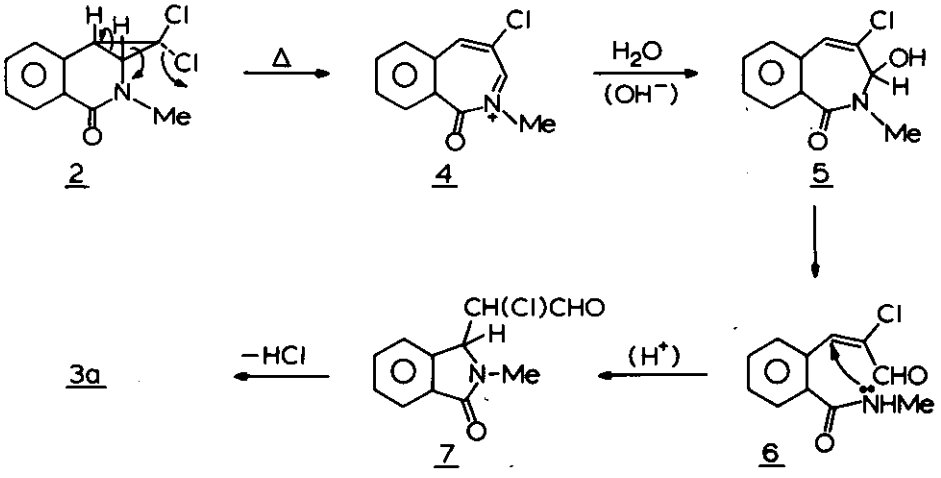
$J_{3,5}$=17 Hz]. Reaction of 1 with dibromocarbene, generated by an analogous base-catalyzed decomposition of bromoform led to the formation of a product which, while resembling the adduct, however, proved to be too unstable to be characterized unambiguously. Ethoxycarbonylcarbene ($N_2CHCOOEt$, Cu, Δ) readily added to 1 to yield a mixture of 1:1 isomeric adducts, which have been described elsewhere[5].

Transformations of Adduct 2.

When adduct 2 was refluxed in a water-pyridine mixture for 18 h, workup of the reaction mixture gave exclusively E-3-formylmethine-2-methylisoindolinone (3a, 96%, Scheme A). The structure of 3a followed from its PMR spectrum [δ 3.25 s (NCH_3), 5.95 d (H_8), 10.54 d (H_9), $J_{8,9}$=7.5 Hz] and comparison of the spectral data with that reported for the compound in the literature[6]. The E stereochemistry was further established by its photochemical transformation [300 nm, c=27 mmol/l in ethanol/water (2:1)] into the Z-isomer (3b)[6]. This transformation could be conveniently recognized by observing the shift of the N-methyl signal from δ 3.25 (in 3a) to δ 3.65 in 3b. The formation of 3a from 1 is visualized to proceed according to the sequence of reactions described in Scheme B. A thermal disrotatory ring-opening - involving a loss of the endo-chlorine atom - of the cyclopropane system in 1, results in the acylimmonium cation 4. Attack of the latter species by water (addition of OH^-) followed by ring-opening of aminal 5 gives the unsaturated aldehyde 6. An intramolecular Michael addition of the amide moiety to the α,β-unsaturated carbonyl function, leads to the isoindolinone 7, which dehydrohalogenates, under the conditions of the reaction, to the observed product 3a. The mechanism proposed in



Scheme A



Scheme B

Scheme B involves steps which are well precedented. Further support for it is derived from the following observations: (a) reaction of 1 in scrupulously dried pyridine leads to decomposition, without any formation of 3a; (b) when ^{18}O-labelled water was employed - in conjunction with pyridine - in the reaction, the product 3a was found to contain the oxygen label in the aldehyde carbonyl (mass spectral analysis) and (c) the benzazepinone cation 4 could be trapped, as discussed in the sequel. While the exclusive formation of the E-isomer (3a) is noteworthy, it is consistent with the known thermodynamic stability of the latter configuration in analogous isoindolinones[7]. This stability is associated with a release of the steric strain involving proximity of the N-methyl group and the bulkier substituent in the Z-orientation.

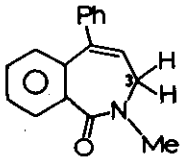
The recognition of the pathway for the transformation of 2 to 3a suggested that if the cationic intermediate 4 were quenched with suitable nucleophiles, a convenient general procedure for the synthesis of benzazepinones would become available. This concept has been tested by the reaction of adduct 2 with alcohols and hydride donating reagents, under conditions which are known to cause the opening of the cyclopropane moiety in 2. Thus, when the dichlorocarbene adduct was heated to reflux in thoroughly dried alcohols MeOH, EtOH, i-PrOH and t-BuOH, the benzazepinones 8a-d and 9d were obtained in excellent yields (Table). In the case of methanol, ethanol and isopropanol, none of the isomeric products 9a-c were observed. Since, in the case of the reaction of 2 with t-butanol, both isomers were formed, a study of the Aromatic Solvent Induced Shift (ASIS) of the PMR spectra provided the basis for discrimination between structures 8d and

TABLE

Compound	Yield	δ^a-NC$\underline{H}_3$	$\Delta\delta^b$NC$\underline{H}_3$	δ^aC$\underline{H}_3$	$\Delta\delta$C$\underline{H}_3$
8a	>95%	3.28	+0.26	3.26[c]	+0.53
8b	>95%	3.25	+0.20	1.03[d]	+0.31
8c	>95%	3.29	+0.24	1.06[d]	+0.36
8d	65%[e]	3.10	+0.07	1.20[d]	+0.44
9d	33%[e]	3.30	+0.35	1.06[d]	+0.01
8e	30%	3.26	+0.44	-	-

a. δ $CDCl_3$. b. $\Delta\delta=\delta CDCl_3 - \delta C_6D_6$. c. OCH_3. d. CCH_3.

e. Analysis is based upon PMR spectrum of the isomeric mixture.



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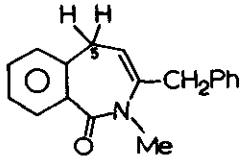

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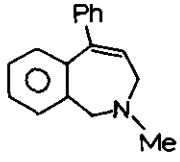

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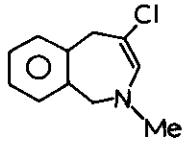

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9d. Pertinent to the discussion is the magnitude of the induced shifts (ASIS) of the tertiary methyl groups in 8d and 9d. It is highly significant that while for 8d there is a large shift ($\Delta\delta$=+0.44) for the tertiary methyl and a small one for the N-methyl ($\Delta\delta$=+0.07), the magnitude of these is reversed in isomer 9d. The low $\Delta\delta$ for the N-CH_3 in 8d is most adequately rationalized in terms of the presence of a sterically bulky group in the immediate vicinity of the solvent-association centre[8], namely the amide carbonyl. The latter reasoning is further supported by the fact that the tertiary methyl signal in the same compound (8d) is subjected to a large displacement, presumably due to the proximity of the associative solvent (benzene molecules). An opposite ASIS effect for the N-CH_3 and the tertiary methyl groups would be expected for structure 9d where the t-butoxy group is far removed from the carbonyl function. This is consistent with the displacements observed for the compound to which structure 9d has been assigned. The arguments used for the assignment of the structures 8d and 9d may be extrapolated to the product(s) of the reaction of 2 with other alcohols. The significant positive values of $\Delta\delta$ for the N-CH_3 and the O-CH_3 or C-CH_3 groups (in 8a-c) indicate that both substituents are shielded by the association of benzene. This phenomenon is related to the presence of modest-sized substituents at the 3-position, a fact in agreement with the assigned structures.

When 2 was refluxed in DME and thereafter treated with $LiBH_4$, a product was isolated from the reaction mixture which, according to its spectral data, corresponded to a benzazepinone derivative. The methylene protons for this substance showed a signal at $\delta(CDCl_3)$ 3.87 and a solvent (benzene) induced shift of

+ 0.65. The assignment of structure 8e to the $LiBH_4$-reduction product rests upon the following arguments. The chemical shifts of the methylene protons in the known benzazepinones 10[9] and 11[10] - corresponding to the structures 8e and 9e - exhibit a pronounced difference, [10, $C(3)H_2$ = δ 3.70, d, J=7.4 Hz; 11, $C(5)H_2$ = δ 3.16 m]. While the substituents in 10 and 11 are identical and differ from that in the product 8e, the δ value of 3.87 for the methylene protons in the latter compound strongly suggests its structural analogy with 10. Furthermore, the observed ASIS effect for 8e (+ 0.65) is very similar to that found for the C_7-protons of 1-methylazepin-2-one[11].

Ring-opening of 2, followed by reduction with $LiAlH_4$ results in a single isolable product in which the amide group is absent. On the basis of the fact that the signal for the $N-CH_3$ (δ 2.68) in the compound is at a considerably lower field than for the $N-CH_3$ (δ 2.30) in the benzazpine 12[12], structure 13 has been tentatively assigned to this product. The scope of the benzazepine synthesis and in particular its extension to the synthesis of polyheterocyclic systems via intramolecular nucleophilic quenching of the cationic species corresponding to 4, is under investigation.

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