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FUNCTIONALIZED ENAMINES—XVII[1]

RING EXPANSION OF α,β-UNSATURATED CYCLIC KETONES BY REACTION OF PYRROLIDINE DIENAMINES WITH DIHALOCARBENES; SYNTHESIS OF A-HOMO-STEROIDS

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Abstract—Reaction of pyrrolidine dienamine **2b** with carbenes **3a** and **3b** leads to the formation of ring expanded ketones **4a** and a mixture of **4a** and **4b**, respectively. The ring-expansion reaction has been utilized in a two-step conversion of Δ^4-cholestenone and testoterone acetate into the A-homo-steroids **7a-c**. Structure assignments and the mechanism of formation of the reaction products are discussed.

In a preceeding paper[2] we have described the patterns of carbene addition to the morpholine dienamine **2a** (Fig 1). With halocarbenes generated via several different procedures, **2a** reacted to give cyclopropane derivatives (1 : 1 adducts) as principle products. This communication reports the behavior of pyrrolidine dienamine **2b** towards dihalocarbenes; the results of the reaction emphasize the influence of the base-component upon the reactivity pattern. Reaction of pyrrolidine dienamine **2b** (derived from ketone **1b**) with dichlorocarbene **3a**, generated by the thermal decomposition of sodium trichloroacetate in refluxing DME,[4,5] gave, after hydrolysis and chromatography of the mixture, a crystalline product which was identified as chloroketone **4a**. Structure of **4a** is based upon its spectroanalytical data. The IR spectrum of **4a** possessed a pattern of four strong bands 1700 cm^{-1}: C=O, 1650 cm^{-1}: α,β-unsaturated C=O, 1600 and 1565 cm^{-1}: –CCl=C–C=C–); and the NMR spectrum exhibited two olefinic proton signals (δ 6·35; distorted triplet and δ 7·27, doublet, J = 1Hz). The UV spectrum showed a maximum at 295 nm (ε 13,800). The formation of the ring-expansion product can be visualized to proceed via the intermediacy of the 1 : 1 adduct a (Fig 2), which can subsequently undergo a ring opening[5] of the cyclopropane system. Such a process would be especially facilitated owing to the additional stabilization of the initially formed allylic cation (**b**), due to participation of the nitrogen electron pair (**b** ↔ **c**). In fact, a concerted elimination of the chloride ion and relay of the nitrogen electron pair may more closely represent the transition-state for the formation of cation **c**. The overall experimental results are, however, also consistent with a mechanism—differing in a subtle fashion from the aforementioned one—in which the heterolytic fragmentation of **a** is triggered by the free electron pair on the nitrogen. Intermediate **c**, formed in both cases, would be recognized as the precursor of the ring expanded product of **4a**. The fact that **4a** is isolated exclusively under conditions which do not result in the ring opening of adduct **5a**, obtained by reaction of **2a** with dichlorocarbene,[2] may be, *à priori*, attributed to the greater basicity of pyrrolidine in comparison with that of morpholine (pK_a 11·27 and 8·36 respectively[7,8]) and/or the energetically favoured location of the double bond, namely, exocyclic to the 5-membered ring base,[9,10] in the intermediate iminium salt. Both factors can, in principle, contribute to the facility of the ring opening. An experiment which provides information as to which of the two aforementioned factors is dominant in causing the ring opening, is the reaction of piperidine dienamine **2c** with carbene **3a**. The only isolable product of this reaction was the cyclopropane derivative **5b**, obtained as a crystalline substance. Since the basicity of piperidine (pK_a 11·29[7]) is very similar to that of pyrrolidine, and the reactions of **2a** and **2c** are comprable,† it is reasonable to suggest that the ease of formation of an exocyclic double bond to the pyrrolidine (5-membered) ring determines the course of the reaction of the pyrrolidine dienamines with dihalocarbenes. Reaction of dienamine **2b** with chlorofluorocarbene (**3b**), generated by decomposition of

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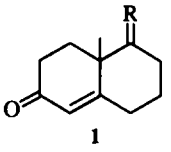
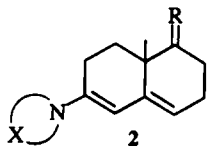
†That the nature of the substituent(s) at C_1 is (are) not critical to the reactivity pattern is confirmed by the fact that the morphiline enamine of **1b** behaves analogously to **2a**.



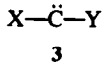
1

a: R = β-OAc, α-H
b: R = O



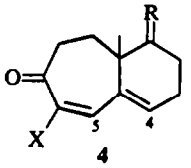
2

a: R = β-OAc, α-H; X = —$(CH_2)_2$—O—$(CH_2)_2$—
b: R = O; X = —$(CH_2)_4$—
c: R = O; X = —$(CH_2)_5$—



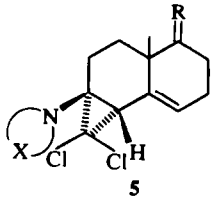
3

a: X = Y = Cl
b: X = Cl; Y = F



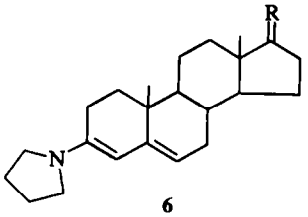
4

a: R = O; X = Cl
b: R = O; X = F



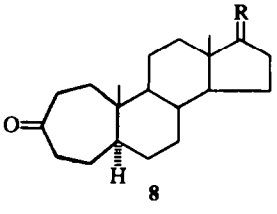
5

a: R = β-OAc, α-H;
X = —$(CH_2)_2$—O—$(CH_2)_2$—
b: R = O; X = —$(CH_2)_5$—



6

a: R = β-C_8H_{17}, α-H
b: R = β-OAc, α-H



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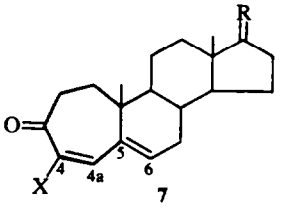


7

a: R = β-C_8H_{17}, α-H; X = Cl
b: R = β-OAc, α-H; X = Cl
c: R = β-OAc, α-H; X = F

Fig 1.

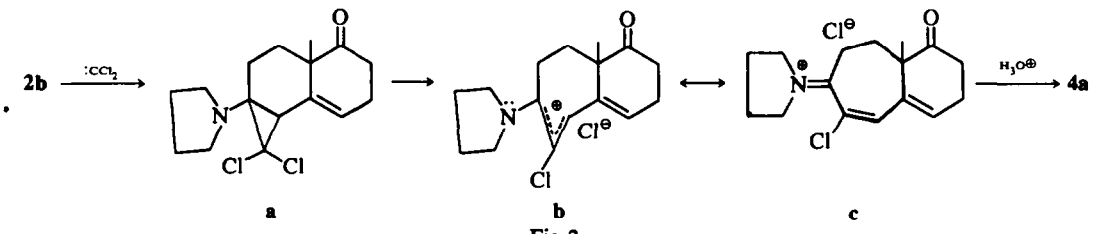


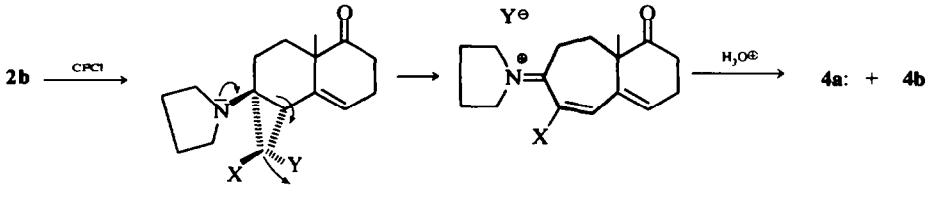
Fig 2.

phenyldichlorofluoromethylmercury[11,12] gave, after hydrolysis and chromatography, two crystalline products. One of them was found to be identical to **4a** (same spectroanalytical data and m.p.). The structure of the second compound, **4b**, followed from its spectroanalytical data. IR spectrum: 1705 cm^{-1} (C=O), 1665 cm^{-1} (α,β-unsat C=O) and 1615 cm^{-1} (–CF=C–C=C–); NMR spectrum: two olefinic proton signals, δ 6·30 (distorted trt) and δ 6·63 (d of doublets; $J_{HF} = 23$ Hz, $J_{5,4} = 1$Hz). The formation of both ketones **4a** and **4b** can be rationalized in terms of the mechanism suggested earlier. The addition of the unsymmetrical carbene **3b** to the first double bond of the dienamine **2b** would give a mixture of the isomeric *endo*-fluoro and *exo*-fluoro adducts **d** and **e**, respectively, (Fig 3) as intermediates. Ring opening of these intermediates would involve the elimination of the *endo*-halogen, in each case, to result in iminium salts **f** and **g**, which would subsequently hydrolyse to **4a** and **4b**, respectively. While cyclopropane ring opening involving the expulsion of an *endo*-halogen, as a halide ion, is in accord with the Woodward–Hoffmann rules and has been documented for 7,7-dihalobicyclo [4, 1, 0] heptanes,[6] the cleavage of a C–F bond in such an electrocyclic process is normally not encountered;[13] presumably owing to the high C–F bond strength. The recently reported case of the loss of a fluoroide ion, in the reaction of chlorofluorocarbene-bicyclo [4, 1, 0] heptene adduct[14] with formic acid, has been explained on the basis of a partial C–O bond formation (with the formate anion) in the transition state of the reaction. The facility with which the fluoride ion is lost from intermediate **d**, emphasizes the important role of the "pyrrolidine" nitrogen in lowering the energy of the transition state of the ring opening process.

The above mentioned ring expansion reaction was applied to the conversion of Δ^4 - 3 - keto - steroids into their corresponding 3 - keto - A - homo - steroidal systems. Reaction of dienamine **6a** with dichlorocarbene (generated from sodium trichloroacetate) in refluxing DME, gave, after hydrolysis and chromatography, crystalline A - homo - 4 - chloro - 4,5 - cholestadine - 3 - one (**7a**). The structure of **7a** followed from its spectroanalytical data. The IR spectrum of the product showed absorptions at 1650 cm^{-1} (C=O), 1600 and 1560 cm^{-1} (–CCl=C–C=C–). In the NMR spectrum, the signals of the pyrrolidine ring were absent, while two olefinic proton signals were present at δ 6·03 (mt) and δ 7·08 (st). The UV spectrum exhibited a maximum at 303 nm (ϵ 15,000). The structure of **7a** was further established by its conversion (H_2/Pd) into the known A - homo (5α) - cholestanone - 3(**8**).[15] Reaction of dienamine **6b** with **3a** gave, in a similar fashion, A - homo - 4 - chloro - 4,5 - testostadien - 3 - one - 17 - acetate (**7b**); IR: 1710 cm^{-1} (–OAc), 1650 cm^{-1} (C=O), 1600 and 1560 cm^{-1} (–CCl=C–C=C–); NMR: two olefinic protons at δ 6·04 (multiplet) and δ 7·09 (singlet); UV: λ_{max} 303 nm (ϵ 16,000). When chlorofluorocarbene **3b** was allowed to react with steroidal dienamine **6b**, in contrast to its reaction with dienamine **2b**, the only product isolated (albeit in poor yield) was the A - homo - 4 - fluoro - steroid **7c**. The structure of **7c** was attested by its spectroanalytical data: IR: 1720 cm^{-1} (–OAc), 1660 cm^{-1} (C=O) and 1615 cm^{-1} (–CF=C–C=C–); NMR: two olefinic protons at δ 6·04 (multiplet) and δ 6·49 (doublet, $J_{HF} = 25$ Hz).

EXPERIMENTAL

All m.ps are uncorrected. Analysis were carried out by Mr. H. Pieters of the Microanalytical Department of this laboratory. IR-spectra were recorded on a Unicam SP 200



d: X = CL; Y = F
e: X = F; Y = Cl
f: X = Cl; Y = F
g: X = F; Y = Cl

Fig 3.

spectrometer and NMR-spectra were run in $CDCl_3$ on Varian Associates Model A-60D and HA-100 instruments using TMS as an internal standard. UV spectra were recorded on a Cary-14 spectrophotometer. Mass spectra were obtained with a Varian Mat-711 spectrometer and ORD-spectra were recorded on a Spectropol-1 apparatus at 25°. All reactions were carried out with dry reagents under N_2.

Reaction of pyrrolidine dienamine **2b** *with dichlorocarbene.* To a refluxing soln of **2b** (1·16 g, 0·005 mole) in 20 ml DME was added dropwise a soln of $NaOOCCCl_3$ (3·71 g, 0·02 mole) in 35 ml DME. After the addition was complete, the refluxing was continued for 2h. The mixture was hydrolysed by addition of 10 ml of 2% HCl/H_2O. This mixture was heated to reflux for 30 min after which it was neutralised with $NaHCO_3$. The solvent was removed and the residue was dissolved in $CHCl_3$. This soln was washed with H_2O, sat NaCl aq and dried over $MgSO_4$. Removal of the solvent gave a brown oil, which was chromatographed on a silicagel comumn. Elution with $CHCl_3$/EtOAc 5:1 gave product **4a**, yield (after recrystallization from MeOH) 385 mg (34%), m.p. 104–106°; IR(KBr) 1700 cm^{-1} (C=O), 1650 cm^{-1} (unsat C=O), 1600 and 1565 cm^{-1} (–CCl=C–C=C–); NMR δ 1·25, s(-Me), 6·35 distorted t (=CH–), 7·27, t, J = 1 Hz (–CCl=CH–); UV (EtOH) λ_{max} 295 (ϵ 13,800); MS calculated for M^+: 189·09155, found: 189·09360.

Reaction of pyrrolidine dienamine **2b** *with chlorofluorocarbene.* The $PhHgCCl_2F$, used to generate :CClF, was prepared according to the method of Seyferth.[10]

Dienamine **2b** (1·16 g, 0·005 mole), $PhHgCCl_2F/Ph_2Hg$ (2·38 g, containing approx 0·005 mole $PhHgCCl_2F$) and NaI (0·91 g, 0·006 mole) were dissolved in 20 ml of DME. This soln was kept at room temp for 2hr, after which the ppt was filtered off. After removal of the solvent, the residue was dissolved in 20 ml $CHCl_3$. To this soln was added 20 ml 2% HCl/H_2O. The resulting mixture was stirred for 3 h, after which it was neutralized with $NaHCO_3$. The organic layer was separated, washed with H_2O, sat NaCl aq and dried over $MgSO_4$. Evaporation of the solvent gave a dark gum, which was chromatographed on a silicagel column. Elution with $CHCl_3$/EtOAc 6:1 gave products **4a** (124 mg, 11%) and **4b** (94 mg, 9%). Spectroanalytical data of **4b**: IR($CHCl_3$) 1705 cm^{-1} (C=O), 1665 cm^{-1} (unsat C=O), 1615 cm^{-1} (—CF=C—C=C—); NMR δ 1·26, s (—Me), 6·30, m (=CH—), 6·63, dxt, J_{HF} = 23 Hz, $J_{3,4}$ = 1 Hz (—CF=CH—). (Found: C, 69·1; H, 6·2; F, 9·1. Calc. for $C_{12}H_{13}O_2F$: C, 69·21; H, 6·29; F, 9·12.)

Reaction of dienamine **6a** *with dichlorocarbene.* The same procedure as described for the reaction of **2b** with **3a** was followed. Starting with **6a** (2·18 g, 0·005 mole) in 25 ml DME and $NaOOCCCl_3$ (3·71 g, 0·02 mole) in 40 ml DME, a dark mixture was obtained which was chromatographed on a silicagel column. Elution with benzene gave **7a**, yield (after recrystallisation from MeOH) 660 mg (31%), m.p. 137·5–140°; IR(KBr) 1650 cm^{-1} (unsat C=O), 1600 and 1560 cm^{-1} (—CCl=C—C=C—); NMR δ 0·71, s (Me_{18}); δ 0·86, d (Me_{26} + Me_{27}); δ 0·91, d (Me_{21}), δ 0·99, s (Me_{19}), δ 6·03, m (H_6), δ 7·08, s (H_{4a}); UV (EtOH) λ_{max} 303 nm (ϵ 15,200). (Found: C, 78·0; H, 9·9; Cl, 8·1. Calc. for $C_{28}H_{43}OCl$: C, 78·01; H, 10·05; Cl, 8·23.)

Catalytic hydrogenation of **7a**. A-homo-steroid **7a** (90 mg, 0·2 mmole) was dissolved in 20 ml EtOH. To this soln was added 10% Pd on charcoal (45 mg) and a soln of NaOAc (45 mg) in a very small amount of H_2O. Hydrogenation was accomplished at atm pressure (3 h). The mixture was filtered and the filtrate was concentrated to give 80 mg of an oil, which was chromatographed on a florisil column. Elution with successively benzene, benzene/$CHCl_3$ 9:1 and benzene/$CHCl_3$ 1:1 afforded, beside **7a**, 30 mg of **8**. After repeated recrystallization from MeOH, the A-homo-steroid **8** was obtained in a colourless, crystalline form, m.p. 81–82·5° (lit.[14] 83–85°); IR($CHCl_3$) 1700 cm^{-1} (C=O); NMR δ 0·66, s(Me_{18}), δ 0·81, s(Me_{19}), δ 0·88, d (Me_{26} + Me_{27}), δ 0·91, d (Me_{21}); ORD(MeOH) Φ-3540° (305) min, Φ + 4400° (261) max; ORD (dioxane) Φ – 1832° (320) sh, Φ – 2044° (311) min, Φ + 3664° (269) max.

Reaction of dienamine **6b** *with dichlorocarbene.* The same procedure as described for the reaction of **2b** with **3a** was followed. Starting with **6b** (1·28 g, 3·3 mmole) and $NaOOCCCl_3$ (2·5 g, 13·2 mmole) and, following the same working up procedure, a brown solid was obtained, which was chromatographed on a silicagel column. Elution with benzene/ether 3:1 gave **7b**, yield (after recrystallization from n-hexane/benzene) 413 mg (34%) colourless, crystalline product, m.p. 158–161°; IR(KBr) 1710 cm^{-1} (—OAc), 1650 cm^{-1} (unsat C=O), 1600 and 1560 cm^{-1} (—CCl=C—C=C—); NMR δ 0·84, s (Me_{19}), δ 2·03, s (—OAc), δ 4·63, m (H_{17}), δ 6·04, m (H_6), δ 7·09, s (H_{4a}); UV (EtOH) λ_{max} 303 (ϵ 16,200). (Found: C, 69·9; H, 7·7; Cl, 9·2. Calc. for $C_{22}H_{29}O_3Cl$: C, 70·11; H, 7·76; Cl, 9·41.)

Reaction of dienamine **6b** *with chlorofluorocarbene.* The same procedure as described for the reaction of **2b** with **3b** was followed. Starting with **6b** (1·9 g, 5 mmole), $PhHgCCl_2F/HgPh_2$ (2·4 g, 5 mmole $PhHgCCl_2F$) and NaI (0·91 g, 6 mmole) in 35 ml DME, a red oil was obtained, which was chromatographed on a silicagel column. Elution with $CHCl_3$/EtOAc 9:1 gave **7c**, yield 90 mg (5%) colourless oil, IR ($CHCl_3$) 1720 cm^{-1} (—OAc), 1660 cm^{-1} (unsat —C=O), 1615 cm^{-1} (—CF=C—C=C—); NMR δ 0·83, s (Me_{18}), δ 1·01, s (Me_{19}), δ 2·01, s (—OAc), δ 4·42–4·81, m (H_{17}), δ 6·04, *m* (H_6), δ 6·49, d, J_{HF} = 25 Hz (H_{4a}).

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