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ON THE REACTION OF BICYCLOBUTANES WITH CARBONYL COMPOUNDS*

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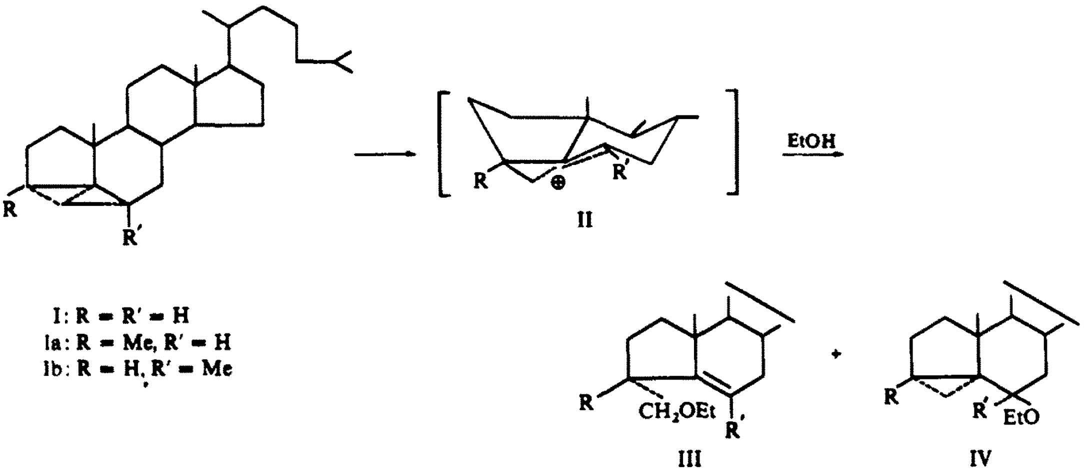
Abstract—Reactions of steroidal bicyclobutanes I with aldehydes give the A-norketones IX. The hydride shift involved is shown to be stereoselective and a mechanism for the reaction is proposed.

STEROIDAL bicyclobutanes I are known to react with protic solvents in the following manner.[1]



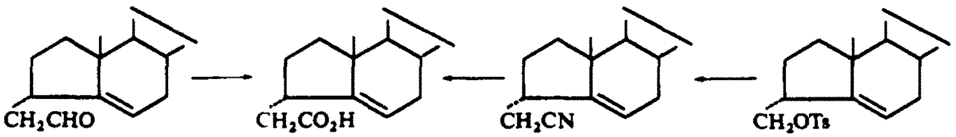
II

I: R = R' = H
Ia: R = Me, R' = H
Ib: R = H, R' = Me

III + IV

It was of interest to see if this reaction could be extended to other electrophiles, such as aldehydes, ketones and anhydrides.

Treatment of a pentane solution of bicyclobutane I‡ with gaseous formaldehyde gave aldehyde V.



V VI VII VIII

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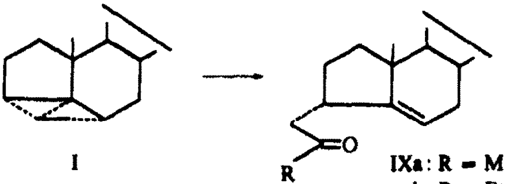
‡ The bicyclobutanes were generated by irradiating a 0·2% pentane soln of the appropriate cholesta-3,5-diene in a helium atmosphere. The presence of I was determined by treatment of an aliquot with ethanol. Products III and IV were detected by TLC.

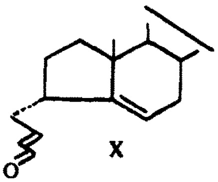
A mass spectrum of V showed a parent peak corresponding to a 1,1-adduct of I and formaldehyde. The NMR spectrum showed an aldehydic proton at 9·8 ppm (unsymmetrical triplet with small coupling constants), a vinylic proton at 5·15 ppm, signals due to the non-equivalent protons α to the carbonyl group at 2·4 ppm, and a broad signal at 3·0 ppm corresponding to the allylic C-3 proton. The structure of V was conclusively proven by oxidation to acid VI. Acid VI was synthesized from the known tosylate VIII[2] by the sequence shown (VIII → VII → VI).

It was found that bicyclobutane I reacted in an analogous fashion with acetaldehyde, propionaldehyde isobutyraldehyde, pivaldehyde, benzaldehyde, anisaldehyde and *p*-nitrobenzaldehyde to give ketones of type IX.



I

IXa: R = Me
b: R = Et
c: R = $-CHMe_2$
d: R = $-CMe_3$
e: R = Ph
f: R = *p*-MeO$-C_6H_4$
g: R = *p*-$NO_2-C_6H_4$
h: R = $CH=CH_2$

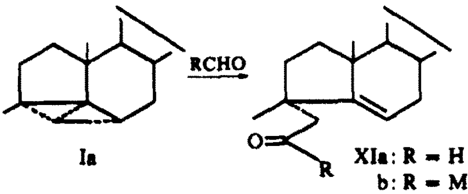


X

The NMR spectra of ketones IX all showed a vinylic proton around 5·0 to 5·3 ppm, the AB portion of an ABX-system due to the protons α to the ketone group and a broad signal around 3·0 ppm due to the allylic C-3 proton (Table 1).

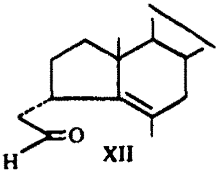
Reaction of I with acrolein gave, in addition to ketone IXh, the product of 1,4-addition X. The latter product showed a UV absorption at 224 mμ in ethanol and 216 mμ in pentane (ε = 7900). In addition peaks (2715 and 1695 cm^{-1}) corresponding to an α,β-unsaturated aldehyde were observed in the IR. The NMR spectrum showed a quartet centered at 6·3 ppm (*J* = 7 c/s, 23 c/s, 1H) and broad signals between 5·0 and 5·4 ppm integrating to two protons. In addition a doublet centered at 9·4 ppm (*J* = 7 c/s) was observed corresponding to the aldehydic proton.

The reaction was extended to bicyclobutane Ia, which reacted with formaldehyde and with acetaldehyde, to give XIa and XIb, respectively. The NMR spectrum of ketone XIb showed all the appropriate signals, and in particular a very clean AB quartet due to the two hydrogens adjacent to the carbonyl group. Bicyclobutane Ib also reacted with formaldehyde, giving aldehyde XII.



Ia

XIa: R = H
b: R = Me



XII

Reaction of a pentane solution of bicyclobutane I with excess acetic anhydride gave 25% of a keto acetate XIII. The NMR spectrum of XIII showed a vinyl proton

TABLE 1

Compound	Yield[b]	Reaction[a] completed after (hours)	Eluent solvent mixture for preparative TLC separations (% volume benzene/hexane)	NMR[c]		
				C_6—H	C_3—H	C_3—CH_2—C=O
V	70	0·25	70	5·15	3·0	2·4
V-D_2	70	0·25	70	5·15	3·0	2·55
IXa	35	2	60	5·0	2·9	2·3
IXb	33	5	60	5·1	3·0	2·35
IXc	21	30	50	5·15	3·0	2·5
IXd[d]	15	60	50	5·3	3·0	2·3
IXe	19	24	60	5·15	3·3	3·2
IXf	23	55	70	5·15	3·3	3·3
IXg	30	3	60	5·2	3·1	2·9
IXh	31	6	70	5·0	2·9	2·5
X	24	6	70	5·15	2·7	2·2
XIa	33	1	70	5·2	—	2·35
XIb	18	24	60	5·15	—	2·3
XII	25	1	70	—	3·25	2·35
XIII	20	24	80	5·2	3·2	5·3

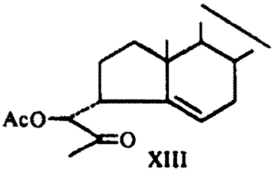
[a] See Experimental.

[b] Based on starting diene. The bicyclobutane generated was 75% pure.

[c] ppm in CCl_4 solns from external TMS.

[d] Compound IXd could not be crystallized and no satisfactory analysis was obtained. IXd also resisted formation of an oxime or a hydrazone derivative.

at 5·2 ppm, the allylic C-3 hydrogen at 3·15 ppm, two low-field Me signals due to the acetate and methyl ketone functions at 1·89 and 1·99 ppm, and a doublet at 5·3 ppm (J = 2·5 c/s).

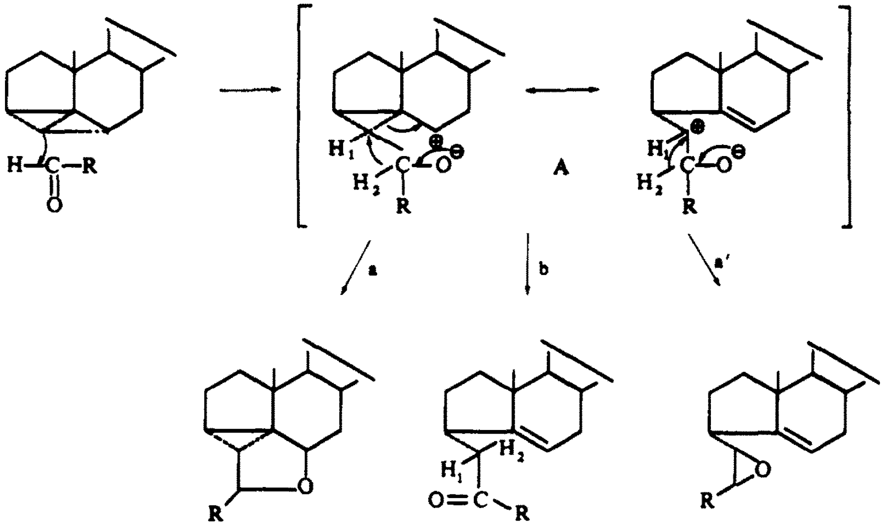


XIII

DISCUSSION

The following reaction sequence is envisaged to explain the reaction of bicyclobutanes I with aldehydes. It is known[3] that reaction of I with a proton (or deuteron) leads to incorporation of the proton (or deuteron) at the 4β-portion with formation of a homoallylic ion. In the reaction with an aldehyde, it could be expected that a similar attack would lead to the formation of zwitterion A. This zwitterion could stabilize itself either (a) by formation of a tetrahydrofuran or epoxide ring, or (b) by hydride or alkyl (aryl) shift.

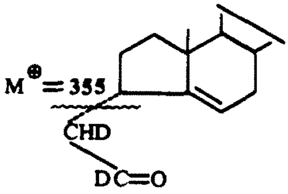
In all the examples hitherto studied, pathway (b) seemed to account for the products formed, and no ethers or epoxides derived from pathway (a) or (a′) could be detected. The nature of the aldehyde influenced the rate at which the reaction proceeded. In



the reaction with aliphatic aldehydes, the rate of reaction diminished with increasing alkyl substitution. With the aromatic aldehydes, the reaction with *p*-nitrobenzaldehyde was approximately 20–30 times faster than that with anisaldehyde. The rough rate data are summarized in Table 1.

In order to establish if the hydride shift postulated in mechanism (b) did occur stereospecifically, bicyclobutane I was treated with gaseous formaldehyde-d_2.

The aldehyde V-d_2 was obtained in the same yield as V. Comparison of the mass spectra of V and V-d_2 indicated incorporation of two deuterium atoms per molecule of V. The spectra of V and V-d_2 both showed a strong peak at M = 355, corresponding to the loss of C_2H_3O and C_2HD_2O, respectively. Both deuterium atoms



were therefore still incorporated in the side-chain. In the IR spectrum of V-d_2 the aldehydic C—H vibration, normally found at 2715 cm^{-1}, had shifted to 2060 cm^{-1}. In addition, a shoulder at 2150 cm^{-1} characteristic of a methylene C–D stretching frequency was present. The NMR spectrum confirmed these findings, and proved that the deuteride shift was stereospecific. Whereas the two protons α to the carbonyl group in V appeared as a complex signal resembling the AB portion of an ABX system (the coupling to aldehydic proton was small), the same group of signals in V-d_2 appeared as a broad doublet at the centre of gravity of the low field proton of the AB-system. Irradiation of the allylic C-3 proton led to collapse of the broad doublet which then appeared as a singlet.

Analysis of the coupling constants of the C_4–methylene proton(s), in the ketones obtained, showed that $J_{AX} = 2–4·5$ c/s and $J_{BX} = 9–11$ c/s. The coupling constant of the C-4 proton in aldehyde V-d_2 was 4·0 c/s, and in acetate XII, 2·5 c/s. These results are in agreement with a mechanism, in which deuteride ion shifts stereospecifically as indicated in Fig. 1. For the formation of XIII, a stereospecific attack by acetate ion is postulated (Fig. 2). There is no reason to believe that the other hydride shifts leading to the formation of ketones IX should proceed with a stereochemistry different from than that described for aldehyde V.

The formation of the zwitterion A from the bicyclobutane must give rise to two diastereomers A′ and A″. Since the hydride shift is stereospecific, we must conclude that the conformations of A′ and A″ prior to hydride shift must be such that the hydrogen is lined up with the vacant orbital into which the hydride is going to transfer, and that any interaction between the negatively charged oxygen and the cationic centre at C-6 favouring other conformations is more than compensated by the better migratory aptitude of hydride as compared to alkyl or aryl groups.

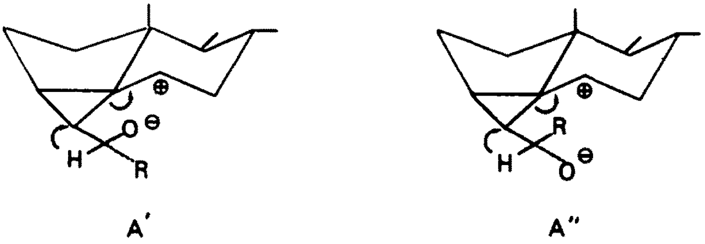


FIG. 1.

In no case did we find any evidence for alkyl or aryl shift.

The mechanism of addition of bicyclobutane to acetic anhydride can be formulated in a similar manner. In that instance, the incorporation of acetate at the position α to the carbonyl function was also stereospecific, since the hydrogen α to the carbonyl and acetate group appeared as a clean doublet at 5·3 ppm.

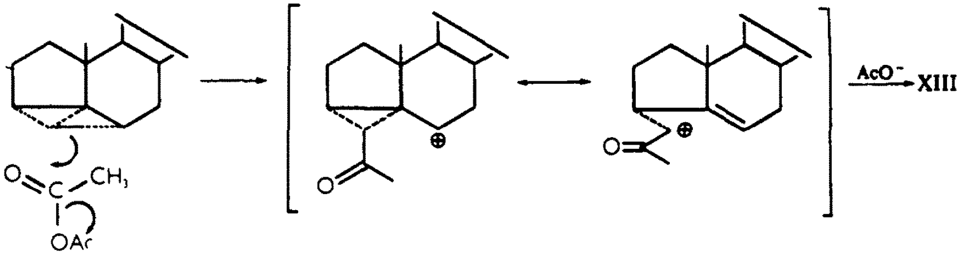
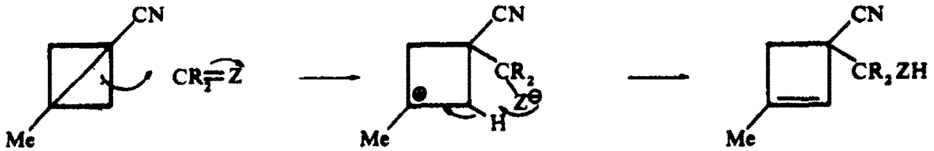
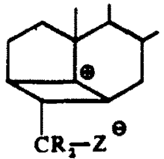


FIG. 2.

No significant reaction was observed when bicyclobutane I was treated with acetone after five days. We are, however, continuing these investigations using more electrophilic ketones such as the polyhalogenated ketones.

Blanchard and Cairncross,[4] observed that reaction of 3-methylbicyclo[1,1,0]-butane carbonitrile with such ketones proceeded by 1,2-fission of the diagonal bond with the formation of cyclobutane carbinol derivatives as depicted below:





XIV

However, these results cannot be compared with ours since the resultant tertiary cyclobutane zwitterion XIV formed from steroid bicyclobutanes would be expected to be less stable than the homoallylic zwitterion A′, A″.

EXPERIMENTAL

All m.ps were taken in a Gallenkamp m.p. apparatus and are uncorrected. The IR spectra were taken in a Perkin–Elmer 337 spectrophotometer. The NMR spectra were recorded on a Varian A-60 instrument as CCl_4 solns using TMS as an external standard. All preparative TLC separations were performed with glass plates (20 × 20 cm) covered with silica gel (0·5 mm, E. Merck A.G.). Bicyclobutanes I, Ia and Ib were obtained by irradiating a 0·2% pentane soln of cholesta-3,5-dienes in a Rayonet photochemical reactor using lamps having peak intensity at 253 mμ. The photolysis tubes (25 mm ID, 1 ft length) were equipped with drying tubes at the inlet and outlet.

TABLE 2

Compound	m.p. (°C)	Analyses[a]					
		Theoretical			Found		
		C	H	N	C	H	N
V	65–68	—	—	—	—	—	—
V-oxime	141–143	81·29	11·45	3·39	81·24	11·28	3·47
IXa	79–81	84·40	11·72	—	84·34	11·75	—
IXb	87–88	84·44	11·81	—	84·55	11·82	—
IXc	75–76	84·48	11·89	—	84·17	11·80	—
IXe-oxime	159–162	83·38	10·50	2·86	83·22	10·56	2·80
IXf	126–130	83·28	10·38	—	83·34	10·11	—
IXg	137–138	78·57	9·50	2·70	78·67	9·43	2·79
IXh	87–88	84·84	11·39	—	84·85	11·23	—
X-oxime	138–141	81·94	11·23	3·19	81·97	11·27	3·21
XIa	71–73	—	—	—	—	—	—
XIa-oxime	153–155	81·44	11·55	3·28	81·46	11·63	3·20
XIb-oxime	74–76	81·57	11·64	3·17	81·30	11·73	3·08
XII	74–75	—	—	—	—	—	—
XII-oxime	109–111	81·44	11·55	3·28	81·42	11·51	3·32
XIII	95–96	79·10	10·71	—	79·25	10·81	—

[a] Unsatisfactory analyses were obtained for the steroid aldehydes.

Reactions of the bicyclobutanes were carried out using the following general experimental procedures: A pentane soln (90 ml) of 200 mg of the diene was irradiated in a He atmosphere until no UV absorption was detected. Aldehyde (0·2 ml in the case of aliphatic aldehydes and one equiv in the case of aromatic aldehydes) was added. The soln was stirred at room temp until no bicyclobutane was detected.[3] The pentane was evaporated under reduced press and the residue was chromatographed on two TLC plates. The eluting solvent systems for each case are recorded in Table 1.

Oxidation of aldehyde V. To an acetone soln (2 ml) of V (120 mg) was added dropwise a soln of 100 mg of chromic acid in 5 ml AcOH and 1 ml water. The soln was stirred for 15 min at room temp. The resulting ppt (60 mg) was filtered off and recrystallized from ether–pentane giving VI, m.p. 182–184°, ν 1720 cm^{-1}. The NMR spectrum showed a signal at 10·1 ppm integrating to one proton and exchangeable with D_2O. (Found: C, 80·98; H, 11·18. $C_{28}H_{46}O_2$ requires: C, 81·10; H, 11·18%.)

3α-*Cyanomethyl*-A-*norcholest*-5-*ene* (VII). A soln of 100 mg of VIII in 5 ml of N-methylpyrrolidone and 300 mg of KCN was heated at 90° for 2 days. The cooled soln was extracted with 50 ml ether and the ether extract washed with water, dried over $MgSO_4$ and evaporated under reduced press to give 98·5 mg of nitrile VII. This was recrystallized from MeOH–ether, m.p. 110–111°, ν 2240 cm^{-1}. (Found: C, 85·16; H, 11·29; N, 3·55. $C_{28}H_{45}N$ requires: C, 84·99; H, 11·46; N, 3·54%.)

Hydrolysis of nitrile VII. A soln of 95 mg of VII in 5 ml ethylene glycol and 500 mg of NaOH was stirred at 140° for 2 days. To the mixture was added 50 ml ether and 10 ml water. The aqueous extract was acidified with conc HCl and extracted with ether. The ether extract was washed neutral with water, dried and evaporated under reduced press to give an amorphous solid which was crystallized from an ether–pentane. The crystalline product was identical in all respect with VI (IR; NMR; TLC; m.p. and mixed m.p.).

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