Addition Reactions of Heterocyclic Compounds. Part 72.[1] Dimethyl Acetylenedicarboxylate with 1,2,6,7,8,9-Hexahydropyrrolo[3,2,1-*jk*]carbazole

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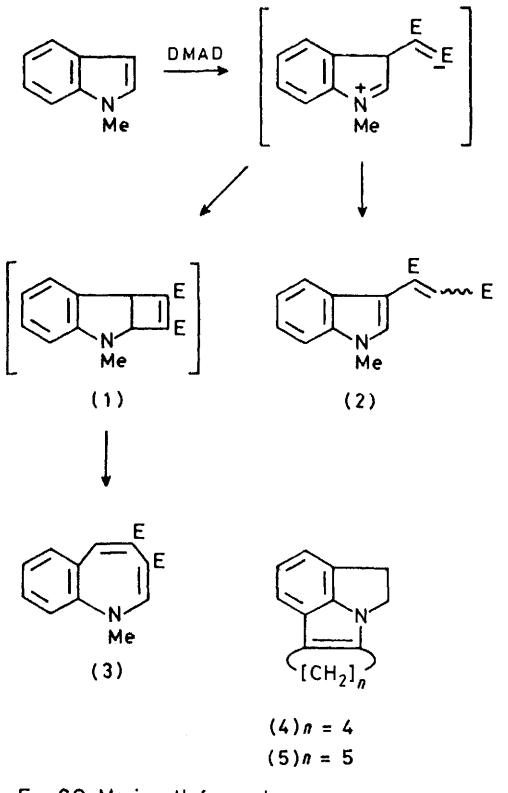
1,2,6,7,8,9-Hexahydropyrrolo[3,2,1-*jk*]carbazole with dimethyl acetylenedicarboxylate in aqueous acetic acid gave four complex products, the structures of which have been correlated with their ^{13}C n.m.r. and other spectra. The carbazole was hydrolysed as an enamine to the corresponding amino-ketone, and the reactions of the latter with the acetylenic ester examined. It is concluded that the acetylene first attacks the carbazole at position 5b, and ring-opening to an amino-ketone and conversion to the complex products follow. An intramolecular dehydrogenation of a cyclohexanone to a cyclohex-2-enone grouping by an enamine residue which is itself converted to the corresponding amine is discussed.

ELECTROPHILIC substitution of indoles takes place [2] almost invariably at position 3 as does attack by acetylenes with electron-attracting substituents.[3] Despite the variety of products, for example indole itself gives fourteen characterised products with dimethyl acetylenedicarboxylate,[4] these all appear to arise from the initial formation of a zwitterion leading to a maleate



(4) $n = 4$
(5) $n = 5$

E = CO_2Me in all formulae

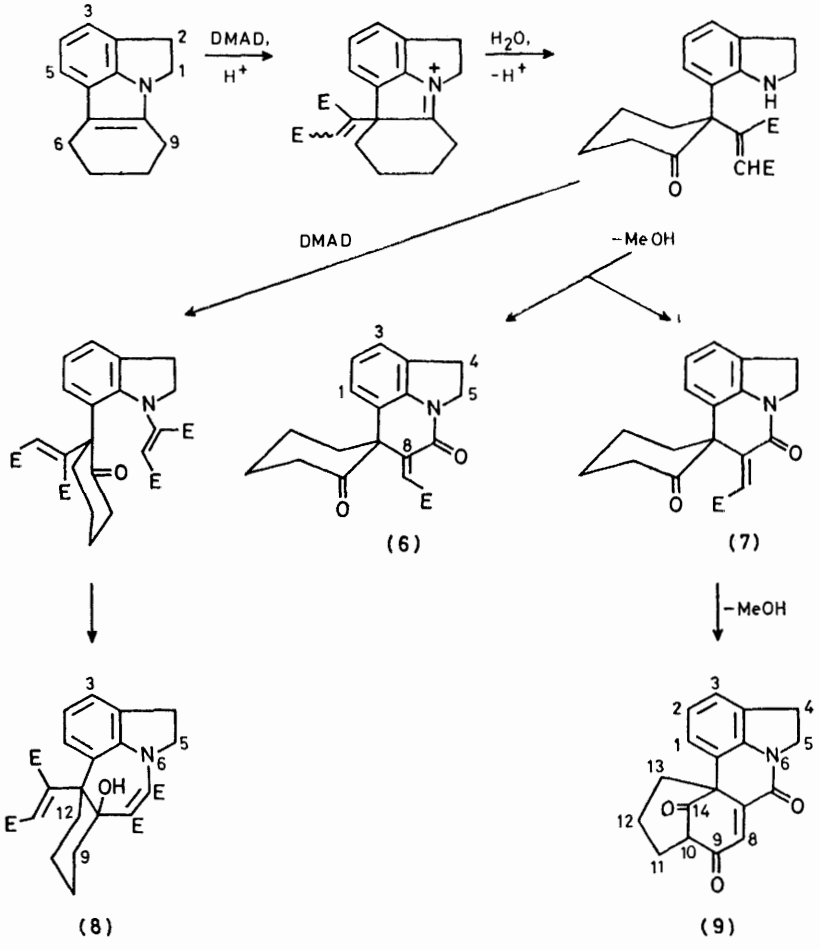
or fumarate [*e.g.* (2)], or a 4-membered ring [*e.g.* (1)] which expands to an azocine [*e.g.* (3)]; other products are formed subsequently.[3] Bailey and his co-workers have recently studied the reactions of the strained indoles (4) and (5) with sulphonyl azides, and have shown that various rearrangements take place.[5,6] We therefore began [7] to examine the reactions of (4), (5), and related indoles with dimethyl acetylenedicarboxylate (DMAD) where structures analogous to (2) cannot form without extensive rearrangement of the molecule and ring expansions might be inhibited. The results of treating DMAD with (4) are now described.

No products could be characterised from the reaction of (4) with DMAD in dimethylformamide, methanol, acetonitrile, or toluene, but with aqueous acetic acid as solvent four crystalline products were isolated. Their structures were difficult to deduce from analytical and spectral data and two of these compounds were identified by *X*-ray crystallography [8] as (9) and (13). From these structures it was obvious that hydrolysis of the indole had occurred somewhere along the reaction paths; almost no reaction, apart from a little tar formation, took place in acetic anhydride solutions where hydrolysis could hardly occur. One of the other compounds possessed a composition corresponding to (9) plus 1 mol of methanol. It was assigned structure (6) because the ^1H and ^{13}C n.m.r. spectra showed the expected correspondences to and differences from those of (9), and its mass, u.v., and i.r. spectra were in agreement. The ^{13}C n.m.r. spectrum of (9) is noteworthy in that one of the methylene resonances is at even higher field than any of the methylene resonances for cyclohexanone.[9] The resonance has been assigned to C-12 as only this atom is joined by short bonds (1.520 and 1.517 Å respectively) to C-11 and -13. Such upfield shifts have been observed [10] in systems with short non-bonded H · · · H interactions although interactions of this type are absent in (9). No such high-field carbon resonance is present in the spectrum of (6). However, one is present in (13) and this might be due to C-10, as the C-9–C-10 bond (1.502 Å) is significantly shorter than the C-8a–C-12a bond (1.521), and the C-10–C-11 bond (1.525) is also short. The structure of the fourth compound is probably (8) which accounts well for the spectra and its formation is easily rationalised. It is perhaps surprising that it does not spontaneously dehydrate to yield an analogue of (13).

The effects were examined of increasing concentrations of the lanthanide shift reagent $Eu(fod)_3$ on the ^1H n.m.r.

spectra of the tricarbonyl compound (9) and the ester (6) for solutions in deuteriochloroform. The fastest downfield shifts for (9) were shown by the 8-proton followed by the 5-protons, suggesting complexation at the amide oxygen atom. A similar picture was shown by (6), the rates of change of resonance positions being vinyl-H > ester-methyl > 5-CH_2 > other protons, showing that complexation could involve the amide, or ester oxygen atoms.

The adducts (6), (8), and (9) may arise as shown in



SCHEME 1

Scheme 1. The suggested addition of the acetylene before hydrolysis is supported by the observations that (i) 2-phenylcyclohexanone does not react with DMAD under conditions which yield these adducts and (ii) that under the reaction conditions employed (10) gives only (13). The ready formation of (9) must be due to the proximity of the activated methylene group and the ester group of (7). The maleic acid derivative (6), where cyclisation is sterically impossible, is stable under the reaction conditions and is therefore not a precursor of (9).

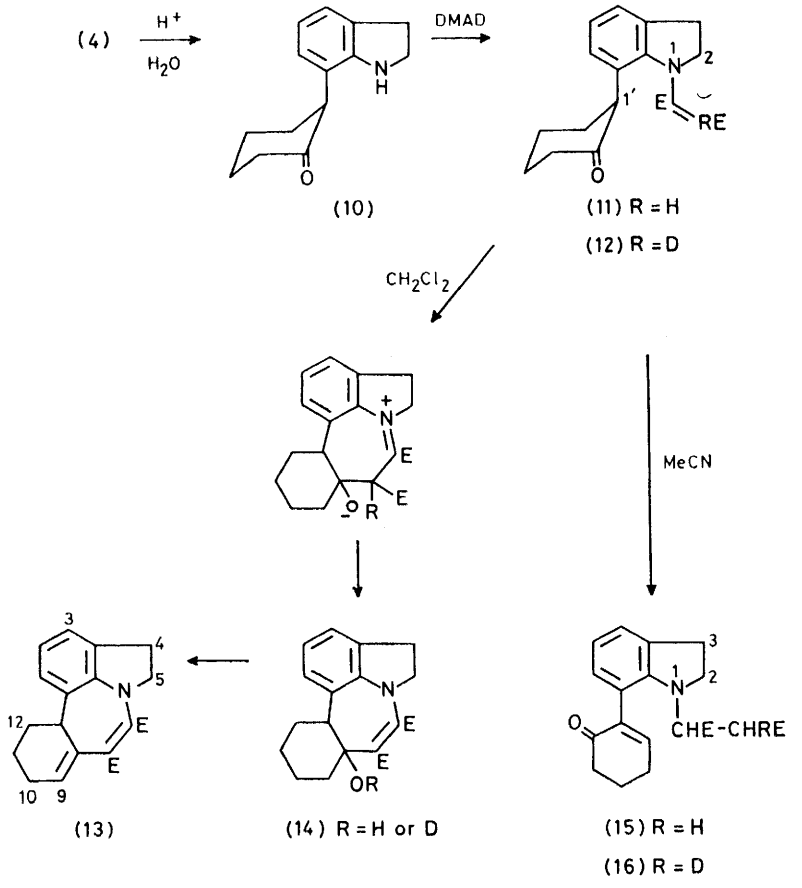
It is difficult to rationalise the formation of (13) without assuming an initial hydrolysis of the indole to the amino-ketone (10), and this has in fact been achieved in 91% yield using 6M-sulphuric acid, previously employed by Rapoport *et al.*[11] for the hydrolysis of other strained indoles. With DMAD in acetic acid the amino-ketone (10) gave a 91% yield of the azepine (13). The postulated intermediate (11) was later isolated when the reaction was carried out in dichloromethane; it was converted to (13) on attempted crystallisation or dissolution in acetic acid. Dehydration of the postulated intermediate (14) might be expected to give the isomer with the newly formed double bond conjugated with the aromatic ring; however, models suggest that doing this would introduce extra strain into the molecule. The amino-hydrogen atom was replaced by deuterium when (10) was shaken with deuterium oxide, and the product, with DMAD, gave (12). On cyclisation all the deuterium was eliminated in accordance with Scheme 2.

The amino-ketone (10) with DMAD in refluxing acetonitrile, or the enaminic ketone (11) on refluxing in the same solvent, gave (15), identified from its ^{13}C and ^{1}H n.m.r., i.r., and mass spectra. We are not aware of any other reactions of this type where an enamine system dehydrogenates a saturated ketone to an αβ-unsaturated ketone, and the remarkable effect of the solvent change has not yet been explained. Attempts to

exchange the protons activated by the carbonyl group in (10) by deuteriated methanol containing a trace of dissolved sodium resulted in extensive decomposition. Refluxing (12) in acetonitrile gave (16) which was identified by comparisons of its ^{1}H n.m.r. and mass spectra with those of (15). For example all the deuterium was lost with the ' $CH_2CO_2CH_3$ ' fragment. No reaction took place between 2-phenylcyclohexanone and dimethyl indolin-1-ylmaleate, so it is clear that the close

coated (1 mm) with Merck silica gel GF_{254} using solvent systems A (chloroform–ethyl acetate, 9 : 1 v/v) or B [toluene–ethyl acetate–light petroleum (b.p. 60—80°), 4 : 1 : 1 v/v/v].

1,2,6,7,8,9-*Hexahydropyrrolo*[3,2,1-jk]*carbazole* (4).—1-Aminoindoline [11] with cyclohexanone, using the method of Kost [12] modified by Bailey,[6] gave the carbazole in 55% yield, m.p. 155—157° (from ethanol) (lit.,[6] 157—158°), $\lambda_{max.}$ 235 ($\varepsilon \times 10^{-4}$ 3.36) and 292 nm (0.815), *m/e* 197 (M^+, 58%) and 169 ($M - C_2H_4^+$, 100).



SCHEME 2

proximity of the interacting groups in (11) is largely responsible for the hydrogen transfer taking place. There are various ionic (*e.g.* hydride transfer from the enolic tautomer of the ketone to the activated ethylenic bond), radical, and concerted processes which could account for this internal oxidation–reduction, but we have no experimental evidence clearly supporting any one of the possibilities.

EXPERIMENTAL

The instruments and procedures have been noted [1] except that some of the u.v. spectra (all for solutions in methanol) were recorded with a Beckman Acta CIII spectrophotometer. N.m.r. spectra were measured for solutions in $CDCl_3$ with tetramethylsilane as internal standard; ^{13}C resonances are shown in the Table. I.r. spectra were for Nujol mulls. Preparative t.l.c. was done on 20-cm^2 plates

Reaction of the Hexahydropyrrolocarbazole (4) *with Dimethyl Acetylenedicarboxylate* (*DMAD*).—The carbazole (4) (2.0 g) and DMAD (3.0 g) were mixed in acetic acid (30 ml) and left at room temperature for 28 days. Evaporation and preparative t.l.c. (30 plates; solvent A) gave back almost no (4) (R_F 0.9) and numerous bands of which three yielded crystalline materials. (i) A band with R_F 0.7 (blue fluorescence using 254 nm radiation) gave *dimethyl* 4,5,10,11,12,12a-*hexahydroindolo*[1,7-cd][3]*benzazepine*-7,8-*dicarboxylate* (13) (0.4 g) as pale yellow crystals, m.p. 123—124.5° (from chloroform–light petroleum) (Found: C, 70.7; H, 6.2; N, 4.3. $C_{20}H_{21}NO_4$ requires C, 70.8; H, 6.3; N, 4.2%), $\nu_{max.}$ 1 725, 1 690, and 1 648 cm^{-1}, $\lambda_{max.}$ 233 ($\varepsilon \times 10^{-4}$ 1.40), 307 (0.535), and 355 nm (1.76) unchanged by 70% aqueous $HClO_4$ (1 drop); *m/e* 339 (M^+, 100%) and 280 (86); δ 1.5—4.2 (m, 11-H), 3.64 (OMe), 3.91 (OMe), 5.82 (t, J 3.4 Hz, collapsed to s on irradiating at 2.15, 9-H), and 6.93 (m, ArH).

(ii) A yellow band, R_F 0.4, gave a gum which crystallised from ethanol or ethyl acetate giving 4,5,10,11,12,13-*hexahydro*-10,13a-*methanocyclo-octa*[c]*pyrrolo*[3,2,1-ij]-*quinoline*-7,9,14-*trione* (9) (0.34 g) as yellow crystals, m.p. 223—224° (Found: C, 73.6; H, 5.2; N, 4.8. $C_{18}H_{15}NO_3$ requires C, 73.7; H, 5.2; N, 4.8%), $\nu_{max.}$ (Nujol) 1 741, 1 733, and 1 660 cm^{-1}; $\lambda_{max.}$ 240 ($\varepsilon \times 10^{-4}$ 1.72), 274infl. (0.46), and 375 nm (0.33), unchanged by 70% aqueous $HClO_4$ (1 drop); *m/e* 293 (M^+, 27%), 237 (66), 222 (26), and 209 (100) with *m** 184.3 for 237 ⟶ 209; δ 1.45—2.5 (m, 11-, 12-, and 13-H_6), 3.34 (t, *J* 7 Hz, 4-H_2), 3.42 (10-H), 4.12 (t, 5-H_2), and 6.9—7.65 (m, 1-, 2-, 3-, and 8-H) (no change on shaking with D_2O).

(iii) A pale brown band, R_F 0.2, gave a solid which yielded two products on recrystallisation from ethanol. The lesser soluble was the *adduct* (6) (0.30 g), pale yellow crystals, m.p. 239—241° (Found: C, 70.2; H, 5.8; N, 4.3. $C_{19}H_{19}NO_4$ requires C, 70.2; H, 5.9; N, 4.3%), $\nu_{max.}$ (Nujol) 1 735—1 715, 1 700, 1 667, and 1 620 cm^{-1}; $\lambda_{max.}$ 233 ($\varepsilon \times 10^{-4}$ 1.52) and 326 nm (0.35), unchanged by 70% aqueous $HClO_4$ (1 drop); *m/e* 325 (M^+, 30%), 265 (42), 238 (88), 225 (71), 224 (100), 197 (23), and 196 (23); δ 1.55—2.7 (m, aliphatic H_8), 3.12 (t, 4-H_2), 3.75 (s, OMe), 4.05 (t, $J_{4.5}$ 8 Hz, irradiation caused signal at 3.12 to collapse to s, 5-H_2), 6.12 (s, 8-CH=), and 6.9—7.2 (m, ArH_3); (no change with D_2O).

The filtrate from (6) on standing deposited *dimethyl* 12a-(1,2-*bismethoxycarbonylvinyl*)-4,5,8a,9,10,11,12,12a-*octa-hydro*-8a-*hydroxyindolo*[1,7-cd]-3-*benzazepine*-7,8-*dicarb-oxylate* (8) (0.7 g) as colourless plates, m.p. 158—160° (from ethanol) (Found: C, 62.7; H, 6.0; N, 2.9. $C_{26}H_{29}NO_9$ requires C, 62.5; H, 5.9; N, 2.8%), $\nu_{max.}$ 3 350br, 1 735infl. 1 728, 1 665, and 1 622 cm^{-1}; $\lambda_{max.}$ 250infl. ($\varepsilon \times 10^{-4}$ 1.08), 303 (0.92), and 346 nm (1.15) (unchanged by 1 drop of $HClO_4$); *m/e* 499 (M^+, 60%), 481 (11), 467 (31), 440 (63), 436 (19), 422 (26), 408 (68), 380 (57), 364 (26), and 296 (100); δ 0.95—4.1 (m, aliphatic-H_{12}) 3.58, 3.62, 3.68, and 3.78 (4 s, 4OMe), 5.43 (s, olefinic), 5.54 (position concentration dependent and exchanges rapidly with D_2O, 8a-OH), and 6.85—7.33 (Ar-H_3).

^{13}C N.m.r. spectra for solutions in $CDCl_3$ measured at 22.63 MHz and recorded in δ values from internal tetramethylsilane. The multiplicities observed on off-resonance decoupling are noted

Compound	Carbon resonances (position assigned)	*CO*	OCH_3
(6)	21.3t; 25.7t; 27.9t; 35.2t; 39.8t; 45.0t (5); 58.1s (8a); 123.6d; 124.0s; 124.0d; 124.7d; 127.5d; 129.8s; 140.5s; 141.6s; 159.5s (*C*O—N); 207.8s (ketone)	167.6s	52.4q
(8)	20.5t; 20.5t; 27.5t; 32.0t; 35.0t; 51.0t (5); 57.5s (12a); 76.2s (8a); 114.5s; 122.6d; 123.9d; 123.9d; 124.4s; 129.7d; 132.3s; 140.4s; 142.7s; 157.7s	165.3s 165.8s 169.0s 169.2s	51.6q 52.0q 52.1q 52.7q
(9)	16.7t (12); 27.4t; 33.1t; 41.2t; 45.8t (5); 55.7s (13a); 62.2d; 119.1s; 124.3d; 124.9d; 127.2d; 130.1s; 134.1d; 137.8s; 147.5s; 157.1s (7); 197.5s(9); 203.6s (14)		
(13)	16.8t (10); 24.6t; 25.6t; 27.6t; 39.0d(13); 51.5t (5); 108.9s; 122.8d; 122.8d; 124.1d; 127.8d; 128.3s; 131.3s; 132.5s; 142.4s; 142.8s	166.7s 167.9s	51.7q 52.6q
(15)	22.8t; 26.4t; 28.4t; 34.4t (3); 38.6t (2); 48.2t (*C*H_2E); 56.7d (*C*HE); 118.8d (5); 119.2s (7); 124.2d (6); 130.4d (4); 130.7s (3a); 140.0s (1′); 147.5s (7a); 149.3d (6′); 197.6s (2′)	171.5s 171.6s	51.8q 52.1q

Hydrolysis of the Carbazole (4).—The carbazole (1.0 g) was added to 6M-sulphuric acid (15 ml), refluxed for 5 min, poured into cold water (100 ml), neutralised with sodium hydrogencarbonate, and extracted with dichloromethane (3 × 50 ml). The extract, after drying and evaporation, gave 2-(indolin-7-yl)cyclohexanone (1.0 g) as a pale bown viscous liquid, $\nu_{max.}$ (film) 3 380, 3 060, 2 920, 2 870, 1 720, and 1 610 cm^{-1}. This ketone (10) (0.90 g) was dissolved in acetic anhydride (20 ml) and evaporated after 1 h at room temperature. Crystallisation of the residue from methanol gave 2-(N-*acetylindolin*-7-*yl*)*cyclohexanone* (0.90 g) as colourless crystals, m.p. 146—147° (Found: C, 74.5; H, 7.5; N, 5.6. $C_{16}H_{19}NO_2$ requires C, 74.7; H, 7.4; N, 5.5%), $\nu_{max.}$ 1 820, 1 665, 1 655, and 1 590 cm^{-1}.

Reaction of 2-(*Indolin*-7-*yl*)*cyclohexanone* (10) *with DMAD*.—(i) The ester (1.00 g) was added to a solution of the freshly prepared ketone (10) (1.20 g) in acetic acid. After 18 h at room temperature evaporation and crystallisation (from methanol) gave the azepine (13) (1.71 g, 90.5%), identical with authentic material.

(ii) The reaction was carried out using dichloromethane instead of acetic acid. Evaporation gave a yellow gum which on preparative t.l.c. (15 plates), developed with solvent B, gave 2-[*N*-(1,2-bismethoxycarbonylvinyl)indolin-7-yl]cyclohexanone (11) (R_F 0.4) (1.10 g) as a pale yellow gum, which gave poor analytical data. Attempted fractional crystallisation from methanol at room temperature gave a 55% yield of the azepine (13) which was also obtained if the reaction was allowed to proceed for two weeks.

(iii) The reaction was carried out as in (ii) except that the solution of the ketone (10) was shaken with D_2O (3 × 1 ml), and the ester was added to the solution 'wet' with D_2O. The dried reaction solution was evaporated and chromatographed as in (ii) to give (12) (1.00 g), containing *ca.* 0.9 atom deuterium/mole (mass spectrometry).

(iv) The ester (0.75 g) was added to a solution of freshly prepared ketone (10) (1.00 g) in acetonitrile (150 ml) and the mixture refluxed for 24 h. Evaporation gave a tar which was chromatographed on a silica gel column (150 ml) made up in chloroform–toluene (1 : 1, v/v). Elution with this solvent gave the azepine (13) (0.024 g), and elution of the major orange band with chloroform gave a gum (1.34 g). This gum was purified by preparative t.l.c. (25 plates) using solvent B and was crystallised from dichloromethane–ether at −20 °C to give 2-[N-(1,2-*bismethoxy-carbonylethyl*)*indolin*-7-*yl*]*cyclohex*-2-*enone* (15) (R_F 0.35) (0.95 g) as colourless crystals, m.p. 80—81° (Found: C, 67.3; H, 6.6; N, 3.9. $C_{20}H_{23}NO_5$ requires C, 67.2; H, 6.4; N, 3.9%), $\nu_{max.}$ 1 735, 1 680, and 1 580 cm^{-1}.

Reactions of the Cyclohexanone (11).—The reactions were carried out using samples of (11) which had been purified twice by preparative t.l.c. (solvent B, *ca.* 0.10 g per plate).

(i) The ketone (11) (0.30 g) in acetic acid (20 ml) was left at room temperature for 18 h. Evaporation followed by crystallisation from methanol gave the azepine (13) (0.22 g), identical with authentic material.

(ii) The ketone (11) (0.30 g) in acetonitrile (25 ml) was refluxed for 24 h. Evaporation followed by preparative t.l.c. (solvent B, 5 plates) gave the cyclohexenone (15) (R_F 0.35) (0.18 g), identical with authentic material.

(iii) The reaction was carried out as in (ii) except that deuteriated ketone (12) (0.10 g) was used. Isolation as

above gave (16) (0.04 g) containing *ca.* 0.70 atom deuterium/mole (mass spectrometry).

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