Addition Reactions of Heterocyclic Compounds. Part 71.¹ The Formation of 1,3a,3b,4,6a,6b-Hexahydrocyclopenta[3,4]cyclobuta[1,2-*b*]pyrroles from Dimethyl Acetylenedicarboxylate and 1-Aryl-1,4-dihydropyridines

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1-Aryl-1,4-dihydropyridines combine with dimethyl acetylenedicarboxylate to form tetramethyl 1-aryl-1,3a,3b,4,-6a,6b-hexahydrocyclopenta[3,4]cyclobuta[1,2-*b*]pyrrole-3,3a,6,6a-tetracarboxylates, the structures of which were deduced from their ¹H, ¹³C n.m.r., and mass spectra. The mode of formation of the adducts is discussed.

DIHYDROPYRIDINES undergo several types of reaction with dimethyl acetylenedicarboxylate (DMAD) which may be exemplified as follows. 1-Phenyl-1,2-dihydropyridine yields the azocine (1), via an intermediate cyclobutapyridine (cf. 5; $\mathbf{R}' = \mathbf{H}$) which was detected but not isolated.² Several 3-substituted-1,6-dihydropyridines add the ester across the 2,5-positions and follow with a retro-Diels-Alder reaction to give phthalic esters.³ 1,4-Dihydropyridines with DMAD give initially a zwitterion (4) which can be trapped in some cases by proton addition leading to (2),³ but in the absence of a



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proton donor cyclisation to a cyclobutapyridine [e.g. (5; R = Ph)] occurs and a number of these compounds possessing 3-substituents have been isolated. Although several attempts to open the 4-membered rings of these compounds by heat or photolysis have failed,⁴ 1-methyl-1,4-dihydroquinoline does give the corresponding cyclobuta[b]quinoline which spontaneously ring-opens to the expected benzo[b]azocine.⁵ In contrast to this a new type of product has now been obtained from 1-aryl-1,4-dihydropyridines and DMAD, and is the subject of the present investigation.

1-Phenyl-1,4-dihydropyridine ⁶ with DMAD in refluxing chloroform or acetonitrile gave a mixture of two 1:2 molar adducts, A and B, from which only A could be obtained pure, while in chloroform at room temperature only A was formed (n.m.r.). Compound A has been identified as the *cis-anti-cis* product (12) while B appears to be the *cis-syn-cis* isomer. Using 1-(4-methoxyphenyl)-1,4-dihydropyridine and either solvent only one 1:2 molar adduct (C) was isolable, considered to have the *cis-syn-cis* structure (13), and corresponding in \dagger Present address; Department of Biochemistry, South Parks Road, Oxford OX1 3QU. its ¹H n.m.r. spectrum to B except for the differences caused by replacement of the aromatic proton by a methoxy-group. 1-(4-Chlorophenyl)-1,4-dihydropyridine gave a mixture of compounds, identified (n.m.r.) as 4'-chloro-derivatives of A and B which could not be separated. Attempts to isomerise A or C, and to alter the proportions of A and B in mixtures by refluxing in



SCHEME 1

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methanol, acetonitrile, or acetonitrile-trifluoroacetic acid failed.

The ¹H n.m.r. spectra of both A and C showed the expected aromatic signals, four ester-methyl resonances, one low-field one-proton singlet, and 4-spin systems involving a second low-field proton. In the case of adduct A this low-field proton coupled weakly and asymmetrically to a methylene group with non-equivalent protons, which were again coupled non-equivalently with a high-field proton. In contrast the otherwise similar 4-spin system of C possessed equivalent methylene protons. The relationships between these protons were established by double-resonance experiments. In addition, adduct A possessed an ester resonance at τ 6.63 and a proton singlet at τ 4.40, while for C the corresponding resonances were at τ 6.87 and 4.97 respectively. The n.m.r. spectra of both adducts were unchanged between -60 and +50 °C, in contrast to that of (1), thereby rendering the possibility of flexible dihydroazocine structures unlikely. The ¹³C n.m.r. spectra (Table) were particularly helpful as they confirmed the presence of the methylene groups and also showed that both compounds contained two sp^3 CH groupings and two sp^3 quaternary carbon atoms, thus enabling us to discard many otherwise possible structures not possessing the aromatic plus three additional rings. Nevertheless the u.v. spectra showed more conjugation than in the present starting materials.

The original dihydropyridines each contained six coupled protons, while one uncoupled low-field proton for each of A and C can be associated with one sp^{2-13} C resonance in each case. These low-field protons appear at very similar positions to that (2.12) ² of the 2-proton of (1). This suggests that the ArN-CH=C(CO₂Me) feature

 13 C N.m.r. spectra for solutions in CDCl₃ measured at 22.63 MHz downfield from internal tetramethylsilane. All assignments were confirmed by proton off-resonance decoupling experiments.

Position	Resonances (8)	
	(12)	(13)
2	149.3	152.2
3	110.4	105.9
3a	63.7	61.7
3b	50.9	48.7
4	34.8	35.2
5	145.2	148.8
6	140.5	155.2
6a	55.4	56.2
6b	70.9	69.6
3-CO	164.5 ª	163.2 ^b
3a-CO	170.4 4	172.0
6-CO	164.8 ª	165.5 ^b
6a-CO	169.9 *	172.0
1′	134.2	133.6 °
2'.6'	129.4	116.5 d
31.51	115.5	114.6^{d}
4	122.1	133.1 °
OCH,		55.6
CO ₄ CH	52.2	52.7
CO, CH,	52.2	52.5
CO,CH,	52.2	51.1
$CO_{2}CH_{3}$	51.7	51.0

a-d Assignments may be interchanged.

of (1) is present also in A and C, and it could be formed as it is for this azocine (1). A also possesses an uncoupled proton (τ 4.97) attached to an sp^3 carbon atom, while the corresponding proton for C (4.40) showed a much broader resonance which suggested some weak coupling. It therefore seemed likely that these last two protons had also been disconnected from the original chain of six, possibly by the same route, and that they were still attached to the carbon atom adjacent to the nitrogen atom because of their relatively low-field positions. This led us to structures (12) and (13) for A and C respectively.

All the key carbon resonances (Table) can be assigned unambiguously although some of the other assignments are interchangeable, and are in the expected ranges.⁷ The *cis-syn-cis* arrangement for the fixed rings of (13) was allocated to compound C because it possessed an unusually high-field ester-methyl resonance, absent in A, and which could be due to the 1-aryl group shielding the 6-ester group. Dreiding models show that these groups are close enough for this phenomenon to be likely as rotation of the aryl group is severely hindered. When the ring junctions are cis-anti-cis much less esteraryl interaction is possible and the 6a-ester group may be shielded a little. Confusion with the resonance due to the aryl-methoxy-group is very unlikely for this resonates at τ 6.28 in the original 1,4-dihydropyridine and would not be expected to change position significantly in (13). Although the methylene groups are diastereotopic in both (12) and (13) the protons are equivalent in compound C. The coupling constant for the non-equivalent methylene protons of A is not typical of the geminal coupling in cyclopentene or cyclohexene systems (J 11-14 Hz),⁸ or of the methylene group in certain cyclobutanes (J ca. 13 Hz).9 However it resembles that of cyclopent-4-ene-1,3-dione (J 21.5 Hz)¹⁰ and of other high geminal couplings such as in bromosuccinic anhydride (J 19.8 Hz) and ethyl cyanoacetate (J 18.7 Hz) which are associated with the π -bonds interacting with the geminal centre.¹⁰ Long-range coupling between the trans hydrogens of one isomer of 3,4-dichlorocyclobutane-1,2-dicarboxylic acid has ¹¹ the value of 1.5 Hz, but for other cyclobutanes it was not possible to identify^{9,11} which coupling, in the 0-2 Hz range, was 1,3-cis or 1,3-trans. The two 1,3-couplings for cyclobutanone have been reported ¹² as 1.9 and 1.1 Hz for the cis and trans interactions and this has been recorded in a review⁸ which failed to observe a footnote¹² stating that the assignments could be interchanged. No structural deduction can therefore be made from the fact that the 6b-proton signal of (13) is significantly broader than that of (12).

The mass spectra of (12) and (13) show the molecular ions (5 and 8% intensity respectively) and large fragments corresponding to the splitting of the 4membered ring (Scheme 2) and subsequent loss of one methoxy-radical. A positive ion corresponding to the cyclopentadiene was not detected. Similar scissions of cyclobutane rings are known.¹³

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Introducing a 4'-methoxy-group into 1-phenyl-1,4dihydropyridine causes a 9-nm bathochromic shift of the long-wavelength u.v. absorption, as is also observed for (13) compared with (12); however the extinction coefficient for (12) is double that for (13). This is consistent with the fact that Dreiding models show less steric interference with conjugation of the aryl group and the conjugated system in (12) than in (13). There may be some interaction between all the double bonds in these adducts as they show more conjugation than in 1phenyl-1,4-dihydropyridine [λ_{max} . 286 nm (10 ⁴ ε 1.58)],⁶ methyl 3-(*N*-methylanilino)acrylate [220 (0.68), 297 (2.95)],¹⁴ or (1) [253 (1.40), 297 (1.90)] and its reduced derivatives.

Hydrogenation of (13) gave the 5,6-dihydro-derivative (14), the enaminic double bond behaving as in the similar reduction of (1). The ¹H n.m.r. spectrum showed the expected changes from that of (13) but it is noteworthy



that the high-field ester group moved significantly up-field. This could be because hydrogenation of the 5,6-double bond takes place from the less-hindered side forcing the 6-ester group into even closer association with the 1-aryl substituent. The mass spectrum of (14) shows a fragmentation pattern exactly analogous to that of (13), the cyclobutane ring being split and an uncharged cyclopentene moiety being lost.

Only one fused 5:4:5 ring-system (15) is found in the literature from which spectral comparisons can be made with (12) and (13). Tsuda *et al.*¹⁵ obtained (15), along with other products, from cyclopentadiene and



ethyl 4,5-dioxo-2-phenyl-2-pyrroline-3-carboxylate (16) under both thermal and photochemical conditions. The protons of the methylene group were equivalent, and their chemical shift (7.40) and that of the adjacent 3b-proton (5.88, but the double irradiation experiment described ¹⁵ would not in fact enable it to be differentiated from the

6a-proton assigned to a resonance at 6.12) are similar to those of (13).

Various routes (Scheme 1) can be postulated for the formation of (12) and (13). When the benzo[b]-derivative of (5; R = Me) opens to form a benzo[b]azocine⁵ the newly formed double bonds must be cis-cis, as is also the case for (1)² If this type of non-concerted disrotatory ring-opening is followed then (9) will have all cis double bonds. The most stable conformation for this molecule is a folded one close to the shape of (13) and a sterically easy non-concerted cyclisation can be envisaged. In order to get a comparable cyclisation to (12), alternating *cis* and *trans* double bonds round (9)would be required and this arrangement would be produced by the very unlikely conrotatory (concerted)¹⁶ opening of both 4-membered rings of (8). However if (7) was formed with *cis-cis* conjugated double bonds, by either route indicated, then the 4-membered ring would now have the possibility to open by a conrotatory mode leading to (9) with one double bond trans. This bond is now roughly orthogonal to a cis double bond on the other side of the molecule, and a concerted [2s + 2a] cyclisation 16 with inversion of one of the carbon centres would lead to the geometry of (12) or (13). However an ionic pathway can hardly be excluded, and as the proportions of A (12) and B [de-methoxy (13)] formed from 1-phenyl-1,4-dihydropyridine vary with the temperature and the solvent there must be significant differences in the details of their formation.

EXPERIMENTAL

Instruments and procedures have been described previously.¹ Thoroughly dry reactants were essential for the reactions involving the 1,4-dihydropyridines. U.v. spectra are for solutions in methanol and n.m.r. spectra for solutions in CDCl₃ with tetramethylsilane as internal standard.

1-Phenyl-1,4-dihydropyridine.—This was prepared as described ⁶ but purified by sublimation at 30 °C and 0.1 Torr or recrystallised by dissolving in methanol at room temperature, cooling in acetone–dry-ice, filtering, and drying *in vacuo* over concentrated sulphuric acid; yield 61% with the literature ⁶ properties. The 1-(4-methoxyphenyl)-(59% yield, m.p. 77—78°) and 1-(4-chlorophenyl)-analogues (15% yield, m.p. 70—78°) were obtained similarly, τ ca. 3.75 (2-H), ca. 5.4 (3-H), and 7.02 (4-H₂) ($f_{2,3}$ 8.7, $f_{2,4}$ 1.3, $f_{3,4}$ 3.3 Hz), and 6.28 (OCH₃); no signals due to 1,6-dihydro-isomers were observed.

Reaction of 1-Phenyl-1,4-dihydropyridine with Dimethyl Acetylenedicarboxylate.—(i) The dihydropyridine (0.9 g) in chloroform (2.0 ml) with dimethyl acetylenedicarboxylate (1.2 ml) was left at room temperature for 36 h when ether (5 ml) was added and the mixture cooled to -19 °C. Recrystallisation from methanol gave tetramethyl 1-phenyl-1,3a,3b,4,6a,6b-hexahydro-cis-anti-cis-cyclopenta[3,4]-

cyclobuta[1,2-b]pyrrole-3,3a,6,6a-tetracarboxylate (12) as needles (179 mg), m.p. 184—186° (Found: C, 62.5; H, 5.2; N, 3.3. $C_{23}H_{23}NO_8$ requires C, 62.6; H, 5.3; N, 3.2%), λ_{max} 204 (10⁻⁴ ε 1.80), 297 (0.70), and 345 (2.20), m/e 441 (M^+ , 5%), 409 (3), 318 (6), 290 (2), 259 (79), 228 (100), 204 (3), and 170 (3), τ (100 MHz) 2.12 (s, 2-H), 2.6—2.8 (m, Ar-H₅), 2.98 [5-H; irradiating simplified 4-H_B resonance to a quartet (J 20 and 8 Hz), 4-H_A resonance

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loses a 3 Hz coupling], 4.97 (s, 6b-H), 6.19 and 6.29 (2 \times OMe), 6.32 [3b-H, under OMe resonance; irradiating collapsed 4-H_B resonance to a doublet (J 20 Hz) with a small additional coupling, and simplified 4-H_A resonance], 6.35 and $6.63~(2 \times \text{OMe})$, and $6.72~(4\text{-H}_{\text{A}}$, partially obscured by OMe resonance; spin-tickling affected 5-H) ($J_{3b, 4A}$ 1.3, $J_{3b, 4B}$ 8.5, $J_{4A,4B}$ 20.0, $J_{4A,5}$ 3.0, $J_{4B,5}$ 2.2 Hz).

(ii) Refluxing the reactants in acetonitrile for 3 h, removal of solvent, and chromatography of the residue dissolved in the minimum chloroform on an alumina column, eluting with ether, gave a 20% yield of a mixture, m.p. $154-181^\circ$, containing (12) with its cis-syn-cis isomer in a ca. 1:4 ratio (n.m.r.). The cis-syn-cis isomer was identified by comparison (^{1}H n.m.r.) to (13).

Tetramethyl 1-(4-Methoxyphenyl)-1,3a,3b,4,6a,6b-hexa-

hydro-cis-syn-cis-cyclopenta[3,4]cyclobuta[1,2-b]pyrrole-

3,3a,6,6a-tetracarboxylate (13).—1-(4-Methoxyphenyl)-1,4dihydropyridine (1.0 g), dimethyl acetylenedicarboxylate (1 ml), and dry acetonitrile (2 ml) were refluxed for 3 h, the solvent was removed, and the residue, in the minimum volume of methanol, was chromatographed on an alumina (150 g) column made up in ether. Elution with ether gave the adduct (13), as colourless needles (480 mg) from methanol, m.p. 186-188° (Found: C, 61.0; H, 5.4; N, 2.9. $C_{24}H_{25}NO_9$ requires C, 61.1; H, 5.3; N, 3.0%), λ_{max} 206 $(10^{-4}\varepsilon 2.30)$, 234 (1.30), 309 (0.64), and 354 (1.10); m/e 471 $(M^+, 8\%), 439$ (3), 348 (9), 320 (2), 289 (100), 258 (54), 230 (7), 228 (8), 215 (2), and 200 (2), τ (60 MHz) 2.20 (s, 2-H), 2.89 (5-H), 3.00-3.26 (m, A_2B_2 , $Ar-H_4$), 4.40br (s, 6b-H), 5.92 (3b-H), 6.19–6.35 (4 \times OMe), 6.87 (OMe), and 7.20 (4-H₂; irradiating collapsed 3b-H and 5-H resonances to singlets) ($J_{3b,4}$ 5.3, J_{45} 2.7 Hz). A similar experiment leaving the reactants in chloroform for 5 days at 18 °C gave a 7% yield of (13).

The adduct (13) (150 mg) in methanol (25 ml) was hydrogenated (5 atm.) over freshly prepared W-2 Raney nickel ¹⁷ for 18 h (shorter times or Pd-C were ineffective), and the product was boiled, filtered hot, and evaporated to ca. 5 ml. Cooling to -19 °C gave the *dihydro-compound* (14) as fluffy

crystals, m.p. 157-159° (from methanol) (Found: C, 60.8; H, 5.8; N, 3.0. C₂₄H₂₇NO₉ requires C, 60.9; H, 5.8; N, 3.0%), m/e 473 (M^+ , 2%), 322 (2), 289 (100), 258 (50), and 230 (3), τ (60 MHz) 2.17 (s, 2-H), 2.9-3.2 (m, A₂B₂, Ar-H₄), 4.43 (d, J 1.7 Hz, 6b-H), 6.13, 6.23, 6.29, and 6.29 (4 \times OMe), 6.62 (m, 3b-H), 7.20 (OMe), and 7.3—8.5 $(m, 4, 5, 6-H_5)$.

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