Tetrahedron. Vol. 26, pp. 1561–1567. Pergamon Press 1970. Printed in Great Britain

SYNTHESIS OF DITERPENOID ACIDS—X[1]

STEREOCHEMISTRY OF MARRUBIIN, THE C_8 AND C_9 POSITIONS

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(*Received in the USA* 5 *May* 1969; *Received in the UK for publication* 16 *December* 1969)

Abstract—Anhydrotetrahydromarrubiin (**2b**) has been reconverted into tetrahydromarrubiin (**1b**). Ozonolysis of **2b** to the trimethyl keto lactone (**5b**) does not involve change of the C_8 configuration. Reduction of **5b** with borohydride gave the trimethylhydroxy lactones **7a** and **7b**; the epimeric keto lactone **5c** was reduced to **8a**. Studies of NMR spectra show that the C_8 Me in **1a** is α and also that ring B is a twist boat in some derivatives of marrubiin though not in the parent compound itself.

As part of our work on the synthesis of diterpenoid acids we have been interested in determining the stereochemistry of marrubiin (**1a**),[2,3] one of the diterpenoid acids that are oxygenated at 6.[4,5a] Structure **1a** summarises the results of our own[3] and other groups.[5–10] The stereochemistry shown at C_8 was proposed after comparing shifts in the NMR peaks of C_8 and C_{10} methyls in several derivatives of marrubiin[3,5b] (cf. also[9,10]); that at C_9 followed from the partial synthesis of two degradation products obtained from marrubiin.[9–11] We proposed[3] that ring B of marrubiin was distorted to a twist boat to explain the isolation of only exocyclic product (in yields of up to 40%) from the dehydration of tetrahydromarrubiin.* Subsequently we reported that such distortion is characteristic of lactones of the type **5a** and results from the closure of the lactone ring.[12] Our present work and recent results of other groups[11,13,14] (discussed below) confirm the stereochemistry at positions 8 and 9; but we also find that distortion of ring B requires another factor besides the presence of the lactone.

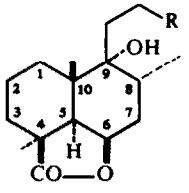
The C_8 *position.* As it had been suggested[7] that ozonolysis of **2b** to give the keto lactone **5b** might be accompanied by a change in configuration at 8 we carried out the reaction in MeOD and decomposed the ozonide with methyl sulphide.[15] The NMR spectrum of the keto lactone obtained in this way showed that deuterium had not been incorporated at C_8; this result establishes that the configuration of the Me group in **5b** is the same as in **1a**. The hydroxy acid **6a**, obtained by hydrolysis of **5b**, is recyclized to **5b** under mild conditions (in our work dicyclohexylcarbodiimide at room temperature, or in Mangoni's,[11] ethyl chloroformate in triethylamine at 0°); this indicates that the C_8 Me group in both **5b** and **6a** has the same configuration. The positions of the NMR signals for the Me groups in **5b** and **6b** (obtained from **6a** with diazomethane) in various solvents are shown in Table 1.

The solvent shifts (deuteriochloroform to benzene) shown by the C_8 Me group in **5b** and **6b** are consistent with the group being axial in **5b** and equatorial in **6b**.[16] These NMR results combined with the interconversion of **5b** and **6a** lead to the deduction that the C_8 Me group is α in both **5b** and **6b** but that the lactone ring in **5b** dis-

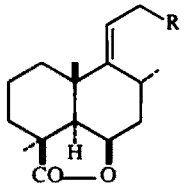
* Recently McCrindle and his coworkers[5] have shown that under appropriate conditions dehydration gives an endocyclic product, and have accounted for the anomalous exocyclic dehydration.

torts ring B to a twist boat form. Mangoni and Adinolfi[11] independently assigned the same stereochemistry to **5b** and (mainly on the basis of ORD studies) concluded that ring B in **5b** and its C_8 epimer **5c** is in a twist boat form. The recent[14] correlation of solidagenone with marrubiin also confirms the α configuration at C_8.

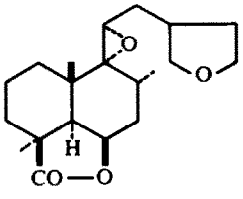
Our criterion[12] for detecting distortion in ring B of lactones of the type **5a** was based on the widths at half height and at the base of the NMR peak corresponding to the C_6 (diterpene numbering) proton. The widths of the corresponding peaks in a number of marrubiin derivatives are shown in Table 2. The figures shown for **5b** and **5c**, in agreement with the independent evidence discussed above, show that ring B in these compounds is distorted. We also conclude that similar distortion exists for **3** and **8a** (see below) but is not present in **1a**, **1b**, **7a** (see below) and **7b** (see below). McCrindle *et al.* also recently concluded that ring B of **1a** is a chair but that of **2a** is distorted.[5a]



1a: R = β-furan
1b: R = β-tetrahydrofuran



2a: R = β-furan
2b: R = β-tetrahydrofuran



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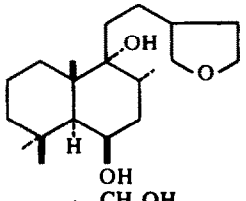

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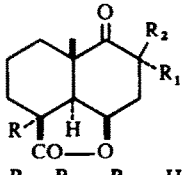
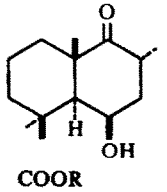
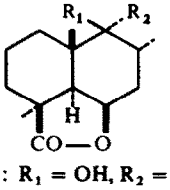


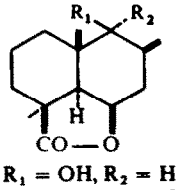
5a: R = R_1 = R_2 = H
5b: R = R_1 = CH_3, R_2 = H
5c: R = R_2 = CH_3, R_1 = H



COOR
6a R = H
6b R = CH_3



7a: R_1 = OH, R_2 = H
7b: R_1 = H, R_2 = OH



8a: R_1 = OH, R_2 = H
8b: R_1 = H, R_2 = OH

Reduction products of the keto lactones. Reduction of the keto lactone **5b** with sodium borohydride gave two hydroxy lactones, X, m.p. 133° and Y, m.p. 80–82° in amounts 3:7 respectively. Product X showed a broad singlet ($W_{1/2}$ = 4 c/s) in the NMR at δ = 3·13 ppm; product Y showed a doublet, δ = 2·95 ppm (J = 9 c/s). Since the reduction products from **5c** (discussed below) are different from X and Y, the formation of the latter compounds has not involved initial epimerization of **5b** at C_8 and so they have structures **7a** and **7b**.

TABLE 1. NMR SIGNALS OF C METHYL PEAKS[a]

	$CDCl_3$			C_6H_6			C_5H_5N		
	C_4	C_{10}	C_8[b]	C_4	C_{10}	C_8[b]	C_4	C_{10}	C_8[b]
5b	81	73	73·5	56	52	52	74	68	68
5c	81	68	70	57	55	58	75	65	68
6b	79	72	60	73	59	67	80	77	66

[a] Shifts (obtained on Varian A-60 and A-60D spectrometers) are given in c/s downfield from TMS.
[b] Doublet.

From Table 2 we conclude that ring B in X and Y (**7a** and **7b**) is in a chair conformation. Three independent lines of evidence lead us to assign structure **7b** to X and **7a** to Y: (a) The major product of the reduction (Y) of **5b** should be the equatorial epimer **7a**;* (b) the coupling constants for the C_9 proton with that at C_8 fit the assignment but not the reverse one; (c) the chemical shift for the C_9 proton in X appears at lower field than that for Y; this is consistent with X being the axial alcohol (**7b**) and Y the equatorial one (**7a**).[18]

Reduction of the ketolactone **5c** with borohydride also gave a mixture of products (approximately 4 to 1); the NMR of this mixture indicated that the major product had its C_9 proton peak at higher field than that of the minor product. We were only able to purify the major product; the signal corresponding to the C_9 proton appeared as a broad peak at δ = 3·55 ppm, which in benzene was resolved to a doublet (J = 7 c/s). The possible structures of this compound are **8a** and **8b**.

TABLE 2. WIDTHS OF NMR SIGNALS OF C_6 PROTONS

	1a	**1b**	**3**	**5b**	**5c**	**7a**	**7b**	**8a**
W[a]	16	15	26	23	23	15	13	20
$W_{1/2}$[b]	13	13	23	20	18	12	11	20

[a] Width (c/s) at base.
[b] Width (c/s) at half height.

* If ring B of **5b** were not distorted, attack by hydride from the α side is clearly favored and one would expect almost exclusive formation of the 9β alcohol. With ring B distorted attack from the α and β sides appears equally favored and one then expects the major product to be the equatorial alcohol.[17] The partial syntheses of marrubiin and some derivatives mentioned below also confirm that even when ring B is distorted reagents attack mainly from the α side.

The width of the C_6 proton peak in this reduction product (Table 2, **8a**) shows that ring B is distorted. The structure **8a** (rather than **8b**) is assigned for the following reasons: (a) as indicated for the discussion of X and Y the major reduction product should be the equatorial one; (b) the relative positions of the NMR signals for the C_9 protons in the major and minor products indicate that the OH group in the major product is equatorial.[18] The coupling constant for the C_8 proton with that at C_9 fits **8a** (ring B distorted) but would also agree with **8b** (ring B distorted).

The structures and conformations assigned to the hydroxy lactones are consistent with the shifts induced in NMR signals in changing the solvent from deuteriochloroform to pyridine.[19] In compound **7a** there is a downfield shift of 0·12 ppm for the C_8 Me and 0·21 ppm for the C_{10} Me. Shifts of this magnitude for both Me groups would not be expected if the OH were α. The small shifts observed for the C_8 and C_{10} Me groups in **7b** support the assignment of the OH as α and ring B as a chair. Similar small shifts (0·05 and 0·06 ppm.) are observed for the C_8 and C_{10} peaks in marrubiin and support the assignment of the α configuration to its OH group.

Partial synthesis of tetrahydromarrubiin. We converted the anhydro compound (**2b**) into the epoxide (**3**). The epoxide was reduced with LAH to a triol (**4**) which should be either marrubanol or 9-epimarrubanol. The triol we isolated had a m.p. of 137–147° not improved by repeated attempts at purification. Reduction of **1b** with LAH gave a product with the same broad m.p.* and a similar IR spectrum to that obtained from **3**. We then reoxidized the triol from **3** with manganese dioxide in acetonitrile[21] and obtained **1b**.

DISCUSSION

The best evidence for the stereochemistry at C_9 in **1a** is that based on the correlations of marrubiin with isoambreinolide[9] and solidagenone.[14] In these experiments insertion of oxygen at C_9 involved epoxidation of a C_8–C_9 double bond in a compound having no lactone linking C_4 and C_6. In such compounds it seems safe to assume that attack from the α side is less hindered. In other work such as our conversion of **2b** into **1b**, the parallel conversion of **2a** into **1a**[13] and the partial synthesis of marrubiin derivatives from **5a**,[11] introduction of the substituent at C_9 was done on compounds in which ring B is distorted and it is not clear *a priori* that α attack is more favored than β attack. However once the stereochemistry at C_9 is established it follows that even with the derivatives in which ring B is distorted the reagents approach predominantly from the α side.

Our results show that a lactone ring of the type in marrubiin may produce distortion of ring B. However, in compounds such as **1a**, **7a** and **7b** distortion would give eclipsed interactions between the C_8 and C_9 substitutents. Apparently these unfavorable energy interactions are sufficient to keep the ring in the chair conformation. Such an interaction is not present when C_9 is in an sp^2 hybrid state (as in **5a**, **5b** and **5c**) nor when the α C_9 substituent is pulled out of the axial orientation (as in **3**). Further when the C_8 Me is β (as in **8a**) it is not surprising that the 1–3 axial interactions between the C_8 and C_{10} methyls destabilize the chair form in **8a**.

* Attempts have been made by several members of our group to obtain marrubanol (lit.[20] m.p. 175°) either by reduction of **1b** or by hydrogenation of marrubenol; no product with better m.p. than 137–147° has been obtained.

EXPERIMENTAL*

Epoxide of anhydrotetrahydromarrubiin (3). A soln of *m*-chloroperbenzoic acid (0·574 g) in dichloromethane (30 ml) was added to a soln of **2b** (0·503 g) in dichloromethane (30 ml) and the mixture was kept at 0° for 21 days, and room temp for 4 days. It was then treated with aq 10% Na_2SO_3 until the starch-iodide test was negative. The soln was washed with 10% $NaHCO_3$ aq and with water and dried (Na_2SO_4). Evaporation of the solvent yielded a crude product (0·573 g) which upon recrystallization from ether–light petroleum gave the epoxide m.p. 108–110° (0·300 g). (lit.[22] 115°): ν_{max} 1780 cm^{-1}. NMR peaks at: δ = 1·00 (d, 3H J = 5 c/s), 1·07 (s, 3H), 1·27 (s, 3H), 1·42–2·50 (m, 15H), 2·83 (qu, 1H), 3·23–4·07 (m, 4H) and 4·77–5·02 (m, 1H) ppm.

Reduction of the epoxide (3). LAH (1·2 g) in ether (100 ml) was added to a soln of **3** (1·09 g) in ether (100 ml). The mixture was refluxed for 3 days, cooled, and the excess hydride destroyed by addition of water. The ethereal soln was washed with water and sat NaCl aq and dried (Na_2SO_4). Evaporation of the solvent yielded the crude triol (0·71 g). Recrystallization from MeOH–water and then EtOAc–light petroleum gave crude **4** m.p. 137–147° (lit.[20] 175°); $\nu_{max}^{CH_2Cl_2}$, 3675, 3610, 3400, 2925, 1610, 1410, 1120, and 1055 cm^{-1}. Further crystallization did not improve the m.p.

Oxidation of triol m.p. 137–147°. Manganese dioxide (1·5 g)[21] was added to a soln of crude triol from **3** (0·073 g) in acetonitrile (20 ml). The mixture was stirred for one day and the solid removed by filtration. Evaporation of the solvent under vacuum gave crude product (0·220 g), which was chromatographed on alumina. Elution with 30% EtOAc–70% benzene gave crude **1b** (0·061 g), which on recrystallization had m.p. 117–121° (0·037 g) identified with authentic **1b** by m.p., mixed m.p. and IR spectrum.

Keto lactone **5b**. (a) The keto lactone **5b** prepared by ozonolysis in MeOH and dichloromethane (see b) had m.p. 199–202° (lit. m.p. 195°[20], 196°[11, 22]); $\nu_{max}^{CS_2Cl_2}$ 1775 and 1715 cm^{-1}; and NMR peaks at δ = 1·22 (s, 3H), 1·23 (d, 3H, J = 7·5 c/s), 1·35 (s, 3H), 1·52–1·82 (m, 4H), 1·93–2·90 (m, 6H), and 4·90–5·28 (m, 1H) ppm.

(b) *By ozonolysis in* MeOD. A stirred soln of **2b** (0·344 g) in MeOD (10 ml) and dichloromethane (15 ml), cooled in a dry ice–acetone bath, was treated with a current of ozone until the soln was blue (about 30 min). The system was flushed with N_2 for 15 min. Me_2S (2 ml) was added; the soln was stirred in an ice–salt bath for 1 hr, at 0° for a further hr, and then at room temp for 1 hr. When the soln was concentrated to a small volume, the product crystallized to give keto lactone m.p. 195–199° (0·198 g). The NMR of this product showed a doublet corresponding to the C_8 Me.

trans-1β-*Carboxy*-8β-*hydroxy*-1α,4a,6α-*trimethyl*-5-*oxodecahydronaphthalene* (**6a**). A soln of **5b** (0·120 g) in 10% methanolic KOH (10 ml) was refluxed for 2 hr, and after cooling, the solvent was removed under vacuum. Water was added and the soln was acidified with conc HCl aq and extracted with dichloromethane which was then washed with water and sat NaCl aq and dried (Na_2SO_4). Removal of the solvent under vacuum yielded crude **6a** (0·096 g), which on recrystallization from MeOH–water had m.p. 173–174° (0·051 g), (lit. m.p. 177–178°[11] 172–174°,[20] 178°[22]), ν_{max} 3325, 3000, 2510, 2250, 1900, 1720 and 1690 cm^{-1}.

The ester **6b** (prepared by treatment of **6a** with diazomethane) had after crystallization from hexane m.p. 104–106° (lit.[11] m.p. 106–107°), ν_{max} 3400, 3000, 1705 and 1162 cm^{-1}; NMR peaks at δ = 1·00 (d, 3H, J = 6 c/s), 1·20 (s, 3H), 1·33 (s, 3H), 1·37–1·75 (m, 6H), 1·95–2·47 (m, 3H), 2·87–3·55 (m, 1H), 3·77 (s, 3H), 4·42 (broad s, 1H), and 5·83–6·00 (m, 1H) ppm.

Lactonization of trans-1β-*carboxy*-8β-*hydroxy*-1α,4a,6α-*trimethyl*-5-*oxodecahydronaphthalene*. A soln of N,N′-dicyclohexylcarbodiimide (0·124 g) in MeOH (5 ml) was added to a soln of **6a** (0·107 g) in MeOH (5 ml) and the mixture was kept overnight at room temp. The solvent was removed at room temp and the resulting solid was taken up in dichloromethane. The soln was washed with water, dil HCl aq, again with water, and with sat NaCl aq and then dried (Na_2SO_4). The solvent was removed and the solid was chromatographed on Florisil to yield **5b** m.p. 197–200° (0·090 g), identified as the original lactone **5b** by m.p., mixed m.p. and comparison of IR spectra.

Borohydride reduction of keto-lactone **5b**. $NaBH_4$ (1·5 g) was added to a soln of lactone **5b** (0·819 g) in MeOH (75 ml) and the soln was stirred at room temp for 5 hr. The soln at 0° was then neutralized with 10% HCl aq. After concentration to a small volume under reduced press the soln was saturated with salt and extracted with EtOAc. The EtOAc soln was washed with sat NaCl aq and dried (Na_2SO_4). Removal of the solvent under reduced press yielded the crude product (0·777 g), which was separated into two hydroxy-lactones by chromatography on Florisil, and elution with EtOAc-benzene, (5:95).

* Unless otherwise specified infrared spectra were determined for KBr pellets, and NMR spectra for $CDCl_3$ solutions. The NMR data (obtained on A-60 and A-60D spectrometers) are given in ppm downfield from TMS. $W_{1/2}$ is width at half-height in c/s.

The hydroxy lactone X, eluted first, which had m.p. 131–133° (**7b**, 0·175 g), recrystallized from hexane in needles, m.p. 133° (0·125 g): (Found: C, 70·77; H, 9·49. $C_{14}H_{22}O_3$ requires: C, 70·59; H, 9·24%); ν_{max} 3475, 3010 and 1750 cm^{-1}; NMR peaks at δ = 0·97 (d, 3H, J = 5 c/s), 1·02 (s, 3H), 1·27 (s, 3H), 1·43–2·38 (m, 11H), 3·13 (s, 1H $W_{1/2}$ = 4), and 4·53–4·82 (m, 1H) ppm; and in pyridine at 1·00 (d, 3H, J = 6 c/s) 1·05 (s, 3H), 1·20 (s, 3H), 1·28–2·33 (m, 10H), 3·15 (s, 1H, $W_{1/2}$ = 8), 4·68 (t, 1H, J = 5 c/s) and 5·95 (m, 1H) ppm.

The hydroxy lactone Y, (**7a**, 0·442 g) crystallized from hexane in long needles, m.p. 80–82°, (Found: C, 70·64; H, 9·36; O, 20·06. $C_{14}H_{22}O_3$ requires: C, 70·59; H, 9·24; O, 20·17%), ν_{max} 3475 and 1750 cm^{-1}; NMR peaks at 0·98 (d, 3H, J = 5 c/s), 1·02 (s, 3H), 1·27 (s, 3H), 1·33–2·63 (m, 11H), 2·95 (d, 1H, J = 9 c/s), and 4·50–4·75 (m, 1H) ppm; in pyridine at 1·10 (d, 3H, J = 6 c/s), 1·23 (s, 3H), 1·25 (s, 3H) 1·35–2·58 (m, 10H), 2·95 (d, 1H, J = 9 c/s), 4·58 (t, 1H, J = 5 c/s) and 4·83 (s, 1H) ppm.

Hydroxy lactone X was assigned structure **7b**; Y structure **7a**.

trans-1β-*Carboxy*-5β,8β-*dihydroxy*-1α,4a,6α-*trimethyldecahydronaphthalene*. A soln of lactone **7a** (0·145 g) and KOH (1·0 g) in MeOH (20 ml) was refluxed for 3 hr. The soln was cooled and most of the solvent evaporated under reduced press. Water was added to the concentrated soln and it was acidified (conc HCl). The product was extracted with EtOAc. The combined EtOAc solns were washed with sat NaCl aq and dried (Na_2SO_4). Removal of the solvent and crystallization of the solid residue yielded the dihydroxy acid m.p. 200–202° (0·028 g): (Found: C, 65·40; H, 9·65; O, 24·86. $C_{14}H_{24}O_4$ requires: C, 65·59; H, 9·44; O, 24·97%), ν_{max} 3400, 3000, 2975, 2950, 2885, 2600 and 1735 cm^{-1}.

trans-1β-*Carboxy*-8β-*hydroxy*-1α,4a,6β-*trimethyl*-5-*oxodecahydronaphthalene lactone* (**5c**). The C_6 keto-lactone **5c**, which was prepared from **5b**,[11] after crystallization from hexane had m.p. 115–117° (lit.[11] 113–115°) ν_{max} 1775 and 1720 cm^{-1}; NMR peaks at: δ = 1·13 (s, 3H), 1·17 (d, 3H, J = 7 c/s), 1·33 (s, 3H), 1·47–2·78 (m, 10H), and 4·88–5·28 (m, 1H) ppm.

Borohydride reduction of trans-1β-*carboxy*-8β-*hydroxy*-1α,4a,6β-*trimethyl*-5-*oxodecahydronaphthalene lactone*. $NaBH_4$ (0·5 g) was added to a soln of the C_6-epi keto lactone **5c** (0·155 g) in MeOH (30 ml). The mixture was stirred at room temp for 5 hr, and then, at 0°, neutralized with 10% HCl aq. The solvent was concentrated and water was added. The soln was saturated with NaCl and extracted with EtOAc (3 times). The combined EtOAc extracts were washed with 10% $NaHCO_3$ aq and with sat NaCl aq and dried (Na_2SO_4). Evaporation of the solvent yielded a crystalline solid (0·151 g) which on the basis of the NMR spectrum appeared to be a mixture of C_9 epimers, about 80% being the epimer with the C_9 OH equatorial. Recrystallization from hexane gave the lactone **8a** m.p. 119–120°: (Found: C, 70·67; H, 9·39; O, 20·13. $C_{14}H_{22}O_3$ requires: C, 70·59; H, 9·24; O, 20·17%), ν_{max} 3550, 3485, and 1775 cm^{-1}; NMR peaks at δ = 0·95–2·45 (m, 20H), 3·45–3·67 (m, 1H, broad; – this peak was resolved in benzene solution to a d, J = 7 c/s), and 4·68–5·02 (m, 1H) ppm.

Acknowledgments—This work was supported by the U.S. Public Health Service Grant CA05796 from the National Cancer Institute. L.J.S. was supported by a Texaco Fellowship (1967–68), MMM Fellowship (1965–66), an Avery Fellowship (1966–67), a Monsanto Summer Fellowship (1965), an NSF Summer Fellowship (1966) and an NSF Summer Traineeship (1967), and thanks the donors of these funds. We thank Prof. L. Mangoni for communicating results before publication and Dr. Margaret M. Wheeler for help.

REFERENCES

[1] Part IX, T. L. Eggerichs, A. C. Ghosh, R. C. Matejka and D. M. S. Wheeler, *J. Chem. Soc.* (C), 1632 (1969).
[2] A. C. Ghosh, S. K. Roy, K. Mori, A. C. Rieke and D. M. S. Wheeler, *J. Org. Chem.* **32**, 722 (1967).
[3] D. M. S. Wheeler, M. M. Wheeler, M. Fetizon, and W. H. Castine, *Tetrahedron* **23**, 3909 (1967).
[4] For related compounds see: S. Ito, M. Kodama, M. Sunagawa, T. Takahashi, H. Imamura, and O. Honda, *Tetrahedron Letters* 2065 (1968); Y. Hayashi, S. Takahashi, H. Ona, and T. Sakan, *Ibid.* 2071 (1968); L. Canonica, B. Rindone, C. Scolastico, G. Ferrari, and C. Casagrande, *Ibid.* 3149 (1968); C. Tabacik-Wlotzka, and Y. Laporthe, *Ibid.* 2531 (1968); E. P. Kaplan and D. E. A. Rivett, *J. Chem. Soc.* C, 262 (1968).
[5] [a] J. W. B. Fulke, M. S. Henderson and R. McCrindle, *Ibid.* (C) 807 (1968).
[b] R. A. Appleton, J. W. B. Fulke, M. S. Henderson and R. McCrindle, *Ibid.* (C), 1943 (1967).
[6] W. Cocker, J. T. Edward and T. F. Holley, *Chem. & Ind.* 772, (1955).
[7] D. Burn and W. Rigby, *J. Chem. Soc.* 2964 (1957).
[8] C. Djerassi and W. Klyne, *Ibid.* 4929 (1962).
[9] L. Mangoni and M. Belardini, *Gazz. Ital.* **93**, 465 (1963).

[10] L. Mangoni and M. Adinolfi, *Ibid.* **97**, 66 (1967).
[11] L. Mangoni and M. Adinolfi, *Tetrahedron Letters* 269 (1968); *Gazz. Ital.* **98**, 122 (1968).
[12] G. A. Gallup, M. L. Maheshwari, S. K. Roy and D. M. S. Wheeler, *Tetrahedron* **24**, 5769 (1968).
[13] L. Mangoni, M. Adinolfi, G. Laonigro and E. Doria, *Tetrahedron Letters* 4167 (1968).
[14] T. Anthonsen, P. H. McCabe, R. McCrindle and R. D. H. Murray, *Tetrahedron* **25**, 2233 (1969).
[15] J. J. Pappas, W. P. Keaveney, E. Gancher and M. Berger, *Tetrahedron Letters* 4273 (1966).
[16] J. D. Connolly and R. McCrindle, *Chem. & Ind.* 379 (1965); D. H. Williams and N. S. Bhacca, *Tetrahedron* **21**, 1641 (1965); *Ibid.* 2021; D. H. Williams, *Tetrahedron Letters* 2305 (1965); D. H. Williams and D. A. Wilson, *J. Chem. Soc.* (B), 144 (1966).
[17] D. M. S. Wheeler and M. M. Wheeler *Steroid Syntheses* (Edited by J. H. Fried and J. A. Edwards), Vol. I. Holden-Day, in press.
[18] N. S. Bhacca and D. H. Williams, *Applications of NMR Spectroscopy in Organic Chemistry*, pp. 47–48. Holden-Day, San Francisco (1964).
[19] P. V. Demarco, E. Farkas, D. Doddrell, B. L. Mylari and E. Wenkert, *J. Am. Chem. Soc.* **90**, 5480 (1968).
[20] W. Cocker, B. E. Cross, S. R. Duff, J. T. Edward and T. F. Holley, *J. Chem. Soc.* 2540 (1953).
[21] P. Johnston, R. C. Sheppard, C. E. Stehr and S. Turner, *Ibid.* (C), 1847 (1966).
[22] D. G. Hardy, W. Rigby and D. P. Moody, *Ibid.* 2955 (1957).