Tetrahedron. Vol. 25, pp. 1749 to 1756. Pergamon Press 1969. Printed in Great Britain

STUDIES IN TERPENOIDS—XIII[1]

MAGNETIC ANISOTROPY[2] IN AND STEREOCHEMISTRY OF SOME *GEM*-DIMETHYLCYCLOBUTANOIDS RELATED TO PINONIC ACID*

L. R. SUBRAMANIAN and G. S. KRISHNA RAO

Department of Organic Chemistry, Indian Institute of Science, Bangalore-12, India

(*Received in the UK* 15 *November* 1968; *accepted for publication* 22 *November* 1968)

Abstract—The chemical shifts of "axial" *vs* "equatorial" Me protons of some *gem*-dimethylcyclobutanoids derived from α-pinene, arising from magnetic anisotropy of the ring and as influenced by vicinal substituents, are discussed. Conformational aspects of some *cis*- and *trans*-pinonic, pinononic and pinic acids have been elucidated on the basis of NMR evidence.

FROM a recent study of the NMR spectroscopy of *cis*- and *trans*-pinane and related compounds Nakagawa *et al.*[3] and later Mühlstädt *et al.*[4] observed magnetic anisotropy in the puckered bridged cyclobutane systems. The conclusions drawn by the Japanese workers[3] were found to be valid even in the case of unbridged cyclobutanoids as revealed from the preliminary findings of the present authors who furnished additional NMR data[2] on essentially four cyclobutanoids derived from α-pinene (**1**) by rupture of the cyclohexene bridge.[5] Besides bringing to light further factors to be taken into consideration in the interpretation of the observed chemical shifts for the *gem*-dimethyl protons, the present study helped to demonstrate for the first time the successful use of NMR spectroscopy in arriving at the stereochemistry of pinonic, pinononic and pinic acids and their esters.

In Tables 1 and 2 are assembled the NMR data for the *gem*-dimethylcyclobutanoids **2**–**15**.† An examination of the chemical shifts of the "axially"[6d] oriented α-Me protons *vs* the "equatorially"[6d] oriented β-Me protons in compounds **8**‡ to **15** (Table 1) and **2** to **7** (Table 2) revealed the following features.

Firstly, the signal for the equatorial Me protons usually occurs at higher field than the corresponding signal for the axial Me protons as also observed in bridged cyclobutanes.[3,4] However, the equatorial Me protons signal is shifted even further downfield, relative to axial Me protons signal, in the presence of an adjacent trigonal carbon (compounds **9** to **11**; Table 1) or *cis*-oriented electron withdrawing groups (compounds **3a**, **5a**, and **7a**; Table 2).

* Taken from the Ph.D. Thesis (Indian Institute of Science, 1968) of L. R. Subramanian.

† These cyclobutanes (with no implication of absolute configurations) are presented by puckered conformations,[6] shown in the sequel to be consistent with the NMR data.

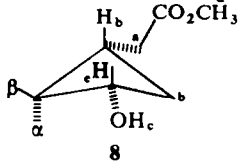
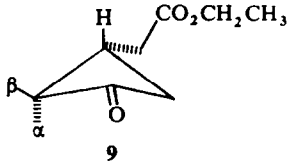
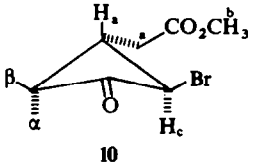
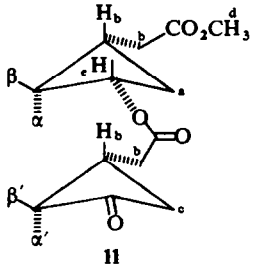
‡ The hydroxy ester (**8**) derived from **2c** by Baeyer–Villiger cleavage[7] was represented wrongly by the 1,3-*cis*-diaxial conformation in our preliminary communication,[2] which led to the wrong conformational representation of other related structures too. Though the opening of the cyclohexene bridge in α-pinene during its oxidation would initially give the less stable 1,3-*cis*-diaxial pinonic acid (**2a**), the cyclobutane ring of **2a** would immediately flip over to the corresponding more stable 1,3-*cis*-diequatorial conformation (**2b**), for which chemical evidence was adduced.[8]

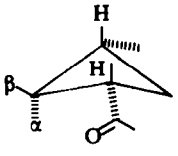
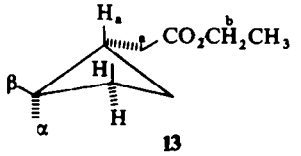
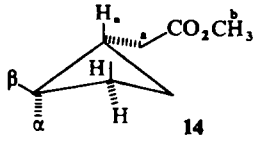
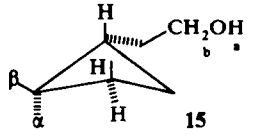
Secondly, the statement[2,3] that the chemical shift of the axial Me protons (occurring at 63–64 Hz[2] or 71–80 Hz[3]) is not affected by substituents elsewhere is to be qualified. We have observed in our present study that the axial Me protons signal also, like its equatorial counterpart, is remarkably affected by vicinal electron withdrawing functions and is shifted downfield (up to 87 Hz; compounds **2b**, **2c**, **4**, **5a**, **6a**, **6b** and **12**). However, an adjacent ketonic carbonyl does not appear to shift the axial Me protons signal to lower field (compounds **9** to **11**) as it does with the equatorial Me protons signal.

The value of the secondary Me protons resonance signal (50 Hz; Table 1) in pinonone (**12**) is consistent with its equatorial nature, in agreement with its formation[1] from **2b** in which the equatorial —CH_2CO_2H was converted to —Me by the Hunsdiecker procedure.

In compounds **13**, **14** and **15** (homogeneous by TLC and GLC; Table 1) on the higher field side of the equatorial Me protons signals (59–61 Hz) another signal is noticed (52–53 Hz, J = 7–8 Hz) which gives it the appearance of a doublet. In our

TABLE 1.* NMR DATA OF *GEM*-DIMETHYLCYCLOBUTANOIDS **8** TO **15**

Compound	*gem*-Dimethyl signals centered at (in Hz)	Other proton signals (in Hz)
 **8**	α-63 (3H, s); β-54 (3H, s)	95 (2H, m) ...a 136 (3H, m) ...b 183 (1H, br.s) ...c 217, 222 (4H, merged) d, e
 **9**	α-63 (3H, s); β-72 (3H, s) —$CO_2CH_2CH_3$-74 (6H) (t, J = 7 Hz)	See Ref. 11
 **10**	α-69 (3H, s); β-78 (3H, s)	152–175 (3H, m) ...a 220 (3H, s) ...b 293 (d, J = 7 Hz) ...c(*cis*) 322 (d, J = 9 Hz) ...c(*trans*)
 **11**	α-69 (3H, s); β-55 (3H, s) α′-63 (3H, s); β′-72 (3H, s)	104 (2H, m) ...a 142 (6H, m) ...b 185 (2H, m) ...c 217 (3H, s) ...d 280 (1H, m) ...e

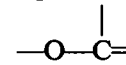
 12	α-74 (3H, s); β-47 (3H, s); >CH—C<u>H</u>$_3$—5O (3H, d, J = 6 Hz)	See Ref. 1	
 13	α-64 (3H, s); β-61 (3H, s)†	90–121 130–149 242 (2H, q)	... Ring methylenes ... a ... b
 14	α-63 (3H, s); β-59 (3H, s)†	88–123 128–146 212 (3H, s)	... Ring methylenes ... a ... b
 15	α-63 (3H, s); β-60 (3H, s)†	84–128 111 (s) 208 (t)	... Ring methylenes ... a ... b

* The NMR spectra of all the compounds reported in this Table were taken on a Varian A-60 spectrometer in CCl_4 soln with TMS as the internal standard.

† The equatorial β-Me protons signal (compounds **13**, **14** and **15**) is not centered with respect to the observed "doublet", as the authors are not sure of the long range coupling involving this Me.

preliminary communication[2] a suggestion was made of a possible long range (4σ) coupling between the equatorial Me protons and the vicinal axial *cis*-protons on the wrong assumption of the absence of such axial *cis*-protons in **8** and **9** in which the equatorial Me protons occurred as a singlet only. However, as already explained, this wrong assumption arose from assigning the less stable 1,3-diaxial conformation **2a** to *cis*-pinonic acid from which followed the other wrong conformations. We are however, unable to explain the observed high field signal.

In the diester **11** which incorporates both the hydroxy ester moiety (**8**) and the keto-ester moiety (**9**), the NMR signals for the *gem*-dimethyl groups (α, β, α′ and β′) are reminiscent of **8** and **9**. The lower field shift from 63 Hz in **8** to 69 Hz in **11** for the signal of the axial Me protons may be due to the introduction in **11** of the grouping



in *cis*-disposition with respect to the axial Me group.

An account is now given of the stereochemical information gleaned from an examination of the NMR spectra of pinonic, pinononic and pinic acids and their esters (Fig. 1 and Table 2). The stereochemical data obtained earlier were based on chemical transformations[9] (involving laborious degradations and syntheses) of compounds, the stereochemical structures of which were sometimes wrongly assumed, leading at times to inaccuracy of arguments and conclusions.*

* Details of these and other controversial aspects will be dealt with elsewhere.

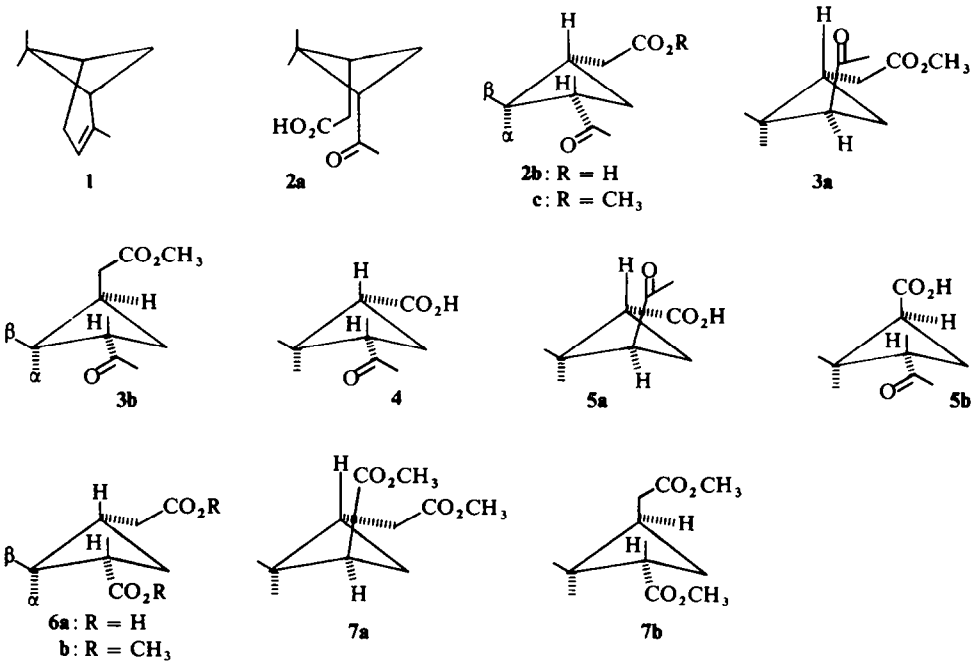
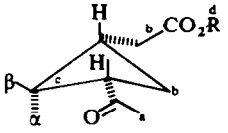
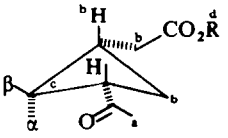
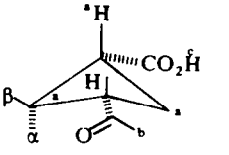
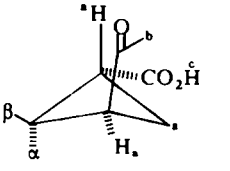
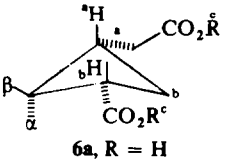


FIG. 1.

The low field signals (82 Hz and 87 Hz respectively) for the axial Me protons in *cis*-(±)-pinonic acid (**2b**) and *cis*-(+)-pinononic acid (**4**) compared to the normal value of 63 Hz may be explained on the basis of the deshielding influence of the *cis*-ketomethyl function in **2b** and of both the adjacent *cis*-ketomethyl and *cis*-carboxyl functions in **4**. The signals for the equatorial Me protons in **2b**, **2c** and **4** occur as usual at the high field (54–58 Hz), since there are no *cis*-deshielding groups with respect to the equatorial Me. A slight high field shift in both the axial and equatorial Me signals may be observed in **2c** compared to **2b**. This trend, on esterification, is also reflected in the *gem*-dimethyl signals of pinic acid and its ester, **6a** and **6b** respectively. In the equilibrium mixture of methyl *cis*- and *trans*-pinonate (**2c** and **3a**) the high intensity signals (axial 79, and equatorial 50 Hz) corresponds to 75% of the *cis*-isomer. In the *trans*-isomer (**3a**) the influence of the adjacent *cis*-ketomethyl on the equatorial Me is clearly seen as reflected by the displacement of its signal to 71 Hz (from 50 Hz in the *cis*-isomer), while the axial Me signal retains its normal value (60 Hz) (cf. **8** to **11** and **13** to **15**). Apart from mechanistic considerations (*vide infra*), these values conclusively rule out the alternative conformation **3b** for the methyl *trans*-pinonate present in the equilibrium mixture. The axial and equatorial Me signals for *trans*-pinonic acid (**5a**) demonstrate the *cis*-disposition of (i) the equatorial Me and the axial ketomethyl groups and (ii) the axial Me and the equatorial carboxyl groups. The alternative conformation **5b** is not considered both from the point of view of the observed magnitude of the downfield shift of the equatorial Me signal (80 Hz) and the manner of obtaining it[8] [aqueous alkali isomerization of *cis*-pinononic acid (**4**) fixes the carboxyl as its anion while enolizing the ring hydrogen adjacent to the ketonic carbonyl].

TABLE 2.* NMR DATA OF PINONIC, PINONONIC AND PINIC ACIDS AND ESTERS

Compound	*gem*-Dimethyl Signals centered at (in Hz)	Other proton signals (in Hz)
 **2b**, R = H	α-82 (3H, s); β-54 (3H, s)	125 (3H, s) ...a 108–160 ...b 178 (1H, t) ...c 698 (1H, s) ...d
 **2c**, R = CH_3	α-78 (3H, s); β-50 (3H, s)	118 (3H, s) ...a 102–145 ...b 171 (1H, t) ...c 216 (3H, s) ...d
Equilibrium mixture of **2c** and **3a**	**2c**: α-79; β-50 **3a** α-60; β-71	Complex
 **4**	α-87 (3H, s); β-58 (3H, s)	101–186 (4H)...a 124 (3H, s) ...b 643 (1H, s) ...c
 **5a**	α-70 (3H, s); β-80 (3H, s)	97–196 (4H)...a 125 (3H, s) ...b 652 (1H, s) ...c
 **6a**, R = H	α-74 (3H, s); β-61 (3H, s)	76–148 ...a 167 (1H, m) ...b 686 (2H, s) ...c
Dimethyl Pinate (**6b** + **7a**)	**6b**: α-72; β-53 **7a**: α-60; β-66	103–142 ...a 160 (1H, m) ...b 216 (6H, s) ...c

* The NMR spectra of **2c**, equilibrium mixture of **2c** and **3a** and equilibrium mixture of **6b** and **7a** were taken on a Varian A-60 spectrometer in CCl_4 solution with TMS as the internal standard. $CDCl_3$ was used as the solvent for compounds **2b**, **4** and **5a**. The NMR spectrum of compound **2b** was taken on a Perkin–Elmer Model R-12 spectrometer.

The *cis*-stereochemistry for pinic acid (**6a**), m.p. 101–102°, and its dimethyl ester (**6b**) finds support from the present study of their NMR spectra. The axial methyl proton signals in **6a** and **6b** are shifted downfield from the normal value 63 to 72–74 Hz because of the vicinal *cis*-O=C(|)—OR functions. In dimethyl *trans*-pinate (**7a**) obtained as a 20% mixture along with dimethyl *cis*-pinate (**6b**, 80%; calculated on the basis of intensities of the *gem*-dimethyl signals) by the esterification of **6a** involving equilibrating conditions the normal value (60 Hz) of the signal for the axial Me protons is restored, while that of equatorial Me is displaced downfield (66 Hz) because of the vicinal *cis* O=C(|)—OMe function. The alternative conformation **7b** for dimethyl *trans*-pinate is ruled out for the same reasons as **5b** was ruled out (*vide supra*) for *trans*-pinononic acid. From these data it is clear that *cis*-pinic acid (**6a**),m.p. 101–102°, like *cis*-pinonic acid (**2b**) and *cis*-pinononic acid (**4**), takes up the *cis*-1,3-diequatorial conformation, which also explains the difficulty in obtaining the anhydride and other cyclization reactions of **6a**.[10] A similar difficulty was experienced in converting the *cis*-diequatorial hydroxy acid (corresponding to **8**) to the δ-lactone,[11] the formation of which would involve a flip over to the more energy demanding *cis*-1,3-diaxial conformer.

The above account thus establishes (i) the 1,3-*cis*-diequatorial nature of (±)-pinonic acid, m.p. 105°, (+)-pinononic acid, m.p. 131° and (±)-pinic acid, m.p. 101–102° and (ii) the preferred conformation of their *trans*-compounds (acids or esters), arising in a minor amount along with the more stable *cis*-diequatorial isomers as a result of alkali equilibration.

A few other applications arising from an analysis of the chemical shifts of Me protons, notably in the assignment of configuration of β-bergamotene based on its NMR spectrum, were already mentioned in our earlier communication.[2]

EXPERIMENTAL*

Ethyl (−)-2,2-dimethylcyclobutyl acetate (**13**)

Preparation of the thioketal of **9**. The ketoester (**9**,[11] 1·84 g) was mixed with $BF_3 \cdot Et_2O$ (5 ml) and ethanedithiol (5 ml) in dry conditions and left aside for 6 hr. It was then diluted with water and the organic material was extracted with ether. The ether layer was thrice washed with 5% NaOH aq, water and dried. Evaporation of solvent and distillation of crude material yielded 2·07 g of the thioketal, b.p. 135°/1 mm, n_D^{26} 1·5210, $[\alpha]_D$ −7·44°; IR (neat): 1730 cm^{-1} (ester >C=O). The IR spectrum showed complete absence of the cyclobutanone peak. (Found: C, 55·5; H, 8·0. $C_{12}H_{20}O_2S_2$ requires: C, 55·4; H, 7·7%).

Raney-nickel desulphurization of the thioketal of **9**. The above thioketal (2 g) in EtOH (200 ml) was refluxed with Raney-Ni W-2 (20 g) for 8 hr. Filtration and removal of solvent yielded 1·3 g of the crude ester. Distillation gave **13**, b.p. 158°/690 mm, n_D^{26} 1·4292, $[\alpha]_D$ −3·76. TLC showed a single spot; IR (neat): 1739 cm^{-1} ester >C=O). (Found: C, 70·1; H, 10·5. $C_{10}H_{18}O_2$ requires: C, 70·5; H, 10·7%).

Methyl (−)-2,2-dimethylcyclobutyl acetate (**14**)

The ethyl ester **13** was hydrolysed with aqueous alkali (10%) to give 2,2-dimethylcyclobutylacetic acid,

* All m.ps and b.ps are uncorrected. B.t. refers to bath temperature. Optical rotations were measured as neat liquids at 25 ± 2°. The IR spectra were recorded on a Perkin–Elmer 137 instrument. All organic extracts were washed neutral and dried over anhydrous Na_2SO_4 prior to removal of the solvent unless otherwise stated.

b.t. 68–70°/45 mm, n_D^{27} 1·4258; IR (neat): 1704 (acid >C=O). (Found: C, 68·2; H, 9·8. $C_8H_{14}O_2$ requires: C, 67·6; H, 9·9%).

The above acid on esterification with ethereal diazomethane gave **14**, b.p. 70°/45 mm, n_D^{26} 1·4253; IR (neat): 1742 cm^{-1} (ester >C=O). The VPC analysis of the methyl ester (column SF 97, 140°) gave a single peak. (Found: C, 70·3; H, 10·4. $C_9H_{16}O_2$ requires: C, 70·6; H, 10·3%).

β-2,2-*Dimethylcyclobutylmethanol* (**15**)

The methyl ester **14** (0·7 g) in ether (10 ml) was added to a powdered suspension of LAH (0·8 g) in ether (20 ml) while stirring the contents vigorously. After the addition was over, it was gently refluxed for 2 hr and the product decomposed with sat NH_4Cl aq under cooling. Extraction with ether gave **15**; b.t. 130–140°/130 mm, IR (neat): 3500 cm^{-1} (—OH). (Found: C, 75·5; H, 12·6. $C_8H_{16}O$ requires: C, 75·0; H, 12·4%).

Pinonic, pinononic and pinic acids

cis-(±)-*Pinonic acid* (**2b**). Oxidation of α-pinene (16 g) isolated[11] from the essential oil of *Pinus wallichiana*, with $KMnO_4$ soln in buffered $(NH_4)_2SO_4$ medium[12] and work up as reported furnished a crude acidic product (14 g) which was stirred with CCl_4 for 5 min. The separated crystals of (±)-*pinonic acid* (2·4 g) were filtered off and crystallized from CCl_4, m.p. 105° [Lit.[13] reported for (±)-pinonic acid, m.p. 104–105°].

The *cis*-(±)-pinonic acid was esterified with distilled diazomethane as usual to furnish methyl cis-(±)-*pinonate* (**2c**), b.p. 125°/10 mm.

Equilibrium mixture of methyl (±)-cis- *and* trans-*pinonate*

Compound **2c** (0·5 g) in MeOH (5 ml) containing Na (0·25 g) was refluxed for 4 hr. The product was worked up and distilled to furnish the *cis*-**2c**, *trans*-**3a** equilibrium mixture of methyl pinonate.

Esterification[14] of **2b** also gave an equilibrium mixture of **2c** and **3a** of similar composition (3:1) as revealed by their NMR spectra.

cis-(±)-*Pinic acid* (**6a**). To a cooled soln of NaOH (15 g) in water (250 ml), Br_2 (20 g) was added in small portions agitating well after each addition, *cis*-(±)-Pinonic acid (**2b**, 15 g) dissolved in satd Na_2CO_3 (10 ml) was added at one time to the hypobromite soln. The mixture was stirred well and the separated bromoform was removed and the soln was acidified with H_2SO_4 (10 ml in 50 ml of water) containing $NaHSO_3$ (2·5 g). Extraction with ether after saturating the soln with NaCl followed by removal of solvent gave *cis*-**6a**,[15] m.p. 102° (water) (Lit.[16] m.p. 102°). IR (Nujol): 1701, 1689 cm^{-1} (acid >C=O).

Acknowledgements—We wish to express our gratitude for the NMR spectra to Dr. Sukh Dev (Samples: **8**, **9**, **11**, **12**, **13** and **15**), Prof. J.-M. Conia (sample **10**), Dr. H. G. Crout (sample **2b**), and Dr. T. R. Govindachari [samples: **2c**, (**2c** + **3a**), **4**, **5a**, **6a** and (**6b** + **7a**)]. We are also indebted to Prof. Horeau for authentic samples of *cis*- and *trans*-pinononic acids. We thank Prof. D. K. Banerjee of this Department for his keen interest in this work.

REFERENCES

[1] Part XII. L. R. Subramanian and G. S. Krishna Rao, *Can. J. Chem.* in press.
[2] Preliminary report: L. R. Subramanian and G. S. Krishna Rao, *Tetrahedron Letters* 3693 (1967).
[3] N. Nakagawa, S. Saito, A. Suzuki and M. Ito, *Ibid.* 1003 (1967).
[4] M. Mühlstädt, M. Hermann and A. Zschunke, *Tetrahedron* **24**, 1611 (1968).
[5] D. V. Banthorpe and D. Whittaker, *Chem. Rev.* **66**, 643 (1966).
[6] [a] J.-M. Conia and J. Gore, *Bull. Soc. Chim. Fr.* 1968 (1964);
[b] I. L. Karle, J. Karle and K. Britts, *J. Am. Chem. Soc.* **88**, 2918 (1966);
[c] J. B. Lambert and J. D. Roberts, *Ibid.* **87**, 3884, 3891 (1965);
[d] N. L. Allinger and L. A. Tushaus, *J. Org. Chem.* **30**, 1945 (1965);
[e] J.-M. Conia, *Ind. Chim. Belge*, **31**, 981 (1966).
[7] K. Mislow and J. Brenner, *J. Am. Chem. Soc.* **75**, 2318 (1953).
[8] M. Harispe, D. Mea and A. Horeau, *Bull. Soc. Chim. Fr.* 1035 (1964).
[9] J. L. Simonsen, *The Terpenes* Vol. II, p. 128, Cambridge University (1932); J. L. Simonsen and L. N. Owen, *The Terpenes* Vol. II, pp. 151–153. Cambridge University (1949).

[10] M. Grandperrin, *Ann. Chim.* **6(xi)**, 5 (1936).
[11] L. R. Subramanian and G. S. Krishna Rao, *Tetrahedron* **23**, 4167 (1967).
[12] M. Delepine, *Bull. Soc. Chim. Fr.* 1369 (1936).
[13] Le-Van-Thoi, *Ann. Chim.* **10(xii)**, 43 (1955); M. Harispe and D. Mea, *Bull. Soc. Chim. Fr.* 1340 (1962).
[14] W. D. Lloyd and G. W. Hedrick, *Ind. Engng Chem.* (Suppl.) **2**, 143 (1963).
[15] R. Trave and L. Garanti, *Gazz. Chim. Ital.* **93**, 549 (1963); H. Francois and Le-Van-Thoi, *Bull. Soc. Chim. Fr.* 535, 539, 542 (1967).
[16] A. Baeyer, *Ber. Dtsch. Chem. Ges.* **29**, 3 (1896).