Tetrahedron. Vol. 27, pp. 4983 to 4989. Pergamon Press 1971. Printed in Great Britain

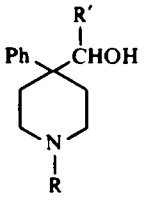
MOLECULAR REARRANGEMENT AND ELIMINATION OF 4-(α-HYDROXYALKYL (OR ARALKYL))-4-PHENYLPIPERIDINES

M. A. IORIO and M. MIRAGLIA
Istituto Superiore di Sanità, Laboratories of Therapeutical Chemistry, 00161 Rome, Italy

(*Received in the UK* 13 *April* 1971; *Accepted for publication* 24 *May* 1971)

Abstract—This paper reports the behaviour of some 4-(α-hydroxyalkyl(or aralkyl))-4-phenylpiperidines undergoing solvolysis under acidic conditions. The carbonium ions produced from 4-(α-hydroxyalkyl)-4-phenylpiperidines, by phenyl migration and loss of a proton from a ring methylene, give the corresponding 4-aralkyl-1,2,5,6-tetrahydropyridines. The 4-(α-hydroxyaralkyl)-4-phenylpiperidines, by phenyl migration and loss of a methine proton, rearrange to the corresponding benzhydrylidenepiperidines. The UV and NMR spectra of these compounds are reported and discussed.

IN AN attempt to prepare the corresponding halo-derivatives of **1** it was found that this compound underwent solvolysis under the acidic conditions used. In view of this result a number of 4-(α-hydroxyalkyl)- and 4-(α-hydroxyaralkyl)-4-phenylpiperidines was synthesized and their mechanism of solvolysis investigated. This paper reports the rearrangements of the carbonium ions produced.



1: R and R′ = H
2: R = Me; R′ = H
3: R = H; R′ = Me
4: R and R′ = Me
5: R = H; R′ = Ph
6: R = Me; R′ = Ph

Compounds **1**, **3** and **5** adopt preferentially the boat form: in fact the strong absorption band appearing in the region of 2200–2600 cm^{-1} (ammonium $>NH_2^+$), indicated the presence of transannular interaction (intramolecular H-bonding) between the OH group and the secondary nitrogen atom (Fig. 1a). Compounds **2**, **4** and **6** exist prevalently in the chair form: the IR spectra of **2** and **4** exhibited two sharp, concentration independent, peaks at 3638 cm^{-1} (free O—H) and 3600 cm^{-1} (O—H ... π intramolecular bonded[1]), and a broad band at *ca.* 3300 cm^{-1} (intermolecular H-bonding) which disappeared at high dilution, indicating that no transannular interaction occurred in these cases (Fig. 1b). The IR spectrum of **6** showed bands at 3618 and 3580 cm^{-1} both concentration independent and a broad band in the range 3300–3400 cm^{-1} which disappeared at high dilution, again indicating the absence of transannular interaction.

Treatment of **1** with $SOCl_2$ or HBr (d 1·49), gave the starting alcohol and a second product, identified as 4-benzyl-1,2,5,6-tetrahydropyridine (**7**) from elemental analysis, UV and NMR evidence. It was assumed that a heterolytic reaction leading to a primary carbonium ion was the first step of the sequence to **7** (Scheme I). By Ph migration the ion rearranges to a more stable tertiary carbonium ion; which, by abstraction of a proton

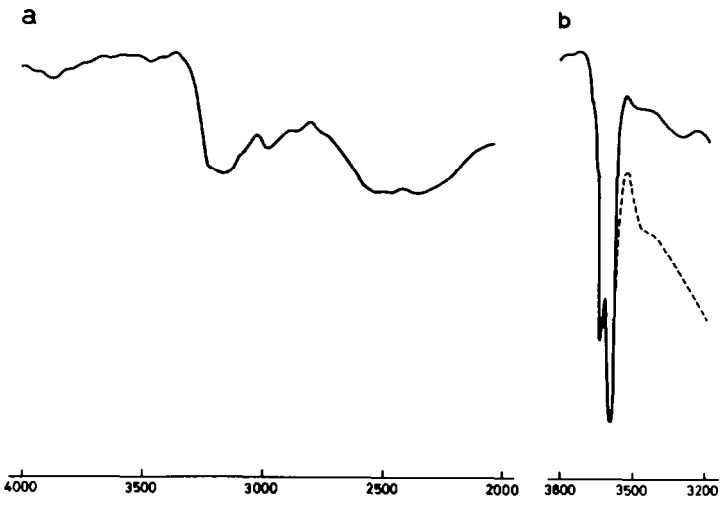
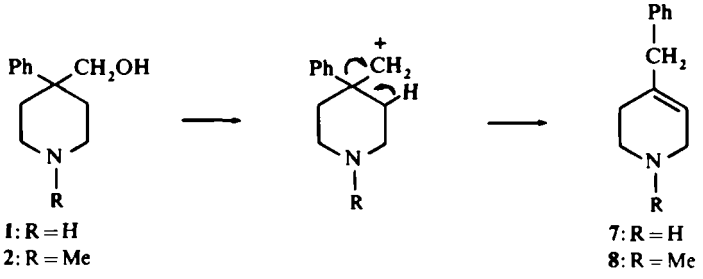
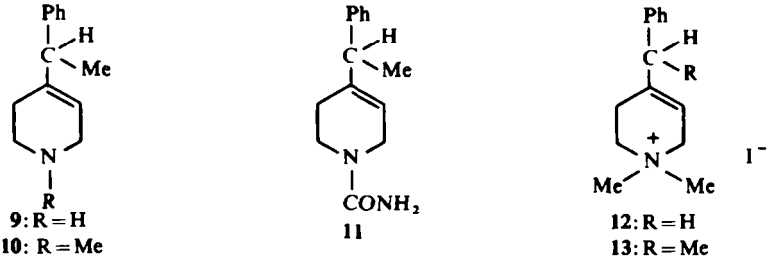


FIG 1. IR spectra of (a) **1** in $CHCl_3$ 0·005 M; (b) **2** and **4** in CCl_4: ——— 0·005 M, - - - 0·05 M

SCHEME I

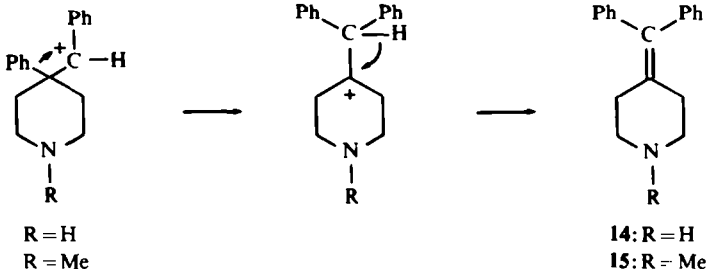


from C-3 or C-5 gives **7**. Ph migration and loss of a proton could be a concerted process with slightly charge-separated intermediate. By treatment of **2**, **3** and **4** with HBr under reflux for 6 hr or more, compounds **8**, **9** and **10** were obtained respectively. Compound **2** gave no significant reaction either with $SOCl_2$ or HCl (d 1·18), while **9** and **10** were obtained from **3** and **4** respectively by treatment with $SOCl_2$. 1-Cyano-4-(α-hydroxyethyl)-4-phenylpiperidine heated for 6 hr with 18% HCl gave 1-carbamyl-4-(α-phenethyl)-1,2,5,6-tetrahydropyridine (**11**) which by further heating under reflux with 1N HCl was hydrolyzed to **9**.



The two hydroxybenzylpiperidines **5** and **6**, when heated with HBr undergo a similar molecular rearrangement and the tertiary carbonium ion produced by loss of the methine proton gave the observed products, **14** and **15** (Scheme II).

SCHEME II



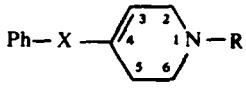
Compound **8** was obtained by Diamond *et al.*[2] from 1-methyl-4-aminomethyl-4-phenylpiperidine by the Demjanov rearrangement with HNO_2. The m.p. reported for the picrate and methiodide were identical to those found here for the picrate of **8** and the methiodide **12**. **14** and **15** were previously prepared by dehydration with aqueous H_2SO_4 from 4-piperidyldiphenylcarbinol[3] and N-methyl-4-piperidyldiphenylcarbinol[4] respectively.

Structural assignment

The lack of any strong absorption band in the 240–250 mμ region, characteristic of a styrene chromophore, in the UV spectra of **7–10** in EtOH, supports the fact that the Ph ring is separated from the olefinic bond by one methylene group. In this region **7–10** exhibited a weak absorption band, the extinction coefficients being 270, 235, 507 and 300 respectively for **7–10**. This fact excludes that the carbonium ion, produced from **1–4**, rearranges, by ring expansion and proton loss, to the isomeric Δ^3 or Δ^4-phenylazacycloheptenes, which were reported[5, 6] to exhibit a strong absorption band at 245 mμ (ε from 10,500 to 12,400). Also the 4-phenyl-1,2,5,6-tetrahydropyridines[7] absorb at 247–248 mμ with an extinction coefficient near 12,500.

Table I reports the NMR spectrum of **7** which agrees with the assigned structure. Double resonance experiments showed that the splitting observed in the C-3 vinylic hydrogen was due to coupling with a pair of the four protons appearing as an apparent singlet at 3·30 δ and the splitting of the signal of the C-6 protons was due to coupling with C-5 protons which resonate at 1·93 δ. The assignment of chemical shifts to the C-2 and C-6 protons is unambiguous. It is well known that the chemical shifts of the protons α to the nitrogen atom in the piperidine salts are downfield with respect to those of the corresponding bases as a result of increased deshielding by the positively charged nitrogen.[8] In the spectrum of the hydrochloride of **7**, the singlet (four protons), was split into two signals: one moving downfield 22 Hz due to the C-2 protons; the other, which is not shifted was due to the C-4 methylene protons. The triplet assigned to the C-6 protons also moved downfield 19 Hz. The NMR spectrum of **8** showed two distinct signals for the C-2 and the C-4 (methylene) protons: the former being upfield with respect to that of the corresponding nor-derivative as a consequence of shielding of the α-protons by the N-Me group.[8] Also the triplet signal of the C-6 protons was shifted 26 Hz upfield. Again

TABLE 1. NMR CHARACTERISTICS[a] OF SOME 1,2,5,6-TETRAHYDROPYRIDINES



Compound	N—R	C-2	C-3	C-4—X	C-4—Ph	C-5	C-6
7	1·70[b] s	3·30[c] m	5·50 m	3·30[c] s	7·23 s	1·93 m	2·90 t[d]
7-HCl	9·37 s W_H 24	3·67 m	5·38 m	3·33 s	7·23 s	2·33 m	3·22 t[d]
8	2·33 s	2·95 m	5·40 m	3·33 s	7·27[e] m	2·10 m	2·47 t[d]
12	3·43 s	4·25 m	5·43 m	3·43 s	7·22 s	2·35 m	3·78 t[d]
9	1·83[b] s	3·40 m	5·57 m	1·37[f] d[g]	7·26 s	1·87 m	2·87 t[d]
10	2·33 s	3·00 m	5·53 m	1·37[f] d[g] 3·37[h] q[g]	7·22 s	2·00 m	2·43 t[d]
13[i]	3·23[j] s 3·26 s	4·00 m	5·57 m	1·33[f] d[g]	7·27 s	2·16 m	3·43 t[d]
11	4·67[b] s W_H 12	3·92 m	5·53 m	1·37[f] d[g]	7·25[e] m	2·00 m	3·40 t[d]

[a] Chemical shifts in δ (ppm) from internal TMS in $CDCl_3$ (s: singlet, d: doublet, t: triplet, q: quartet, m: multiplet). Coupling constants (J) and half width (W_H) in Hz.

[b] Disappeared with D_2O

[c] Overlapping signals

[d] $J=6$

[e] Main peak

[f] Sec-Me

[g] $J=7$

[h] The methine signal of **9** is overlapped by the C-2 protons peak, that of **11** and **13** by the C-6 protons triplet

[i] In DMSO-d_6

[j] Separate signals for axial and equatorial N-Me

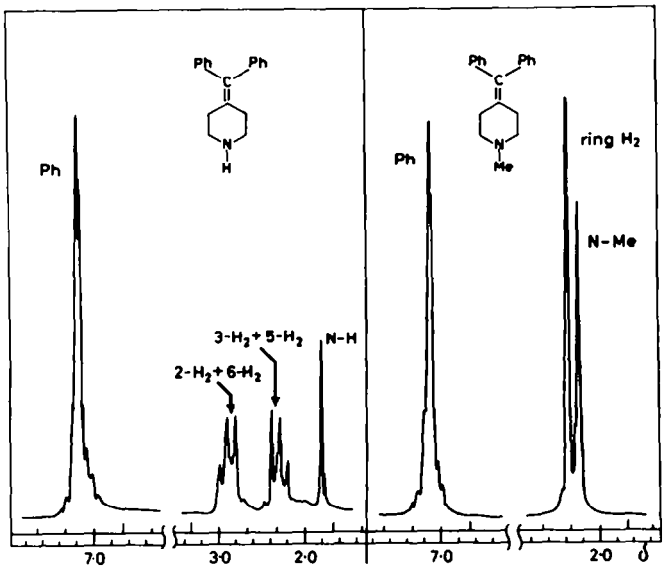


FIG 2

the positively charged nitrogen of **12** shifted the signals of the C-2 and C-6 protons downfield. A similar analysis of the NMR spectra of **9**, **10** and **13** provided clear evidence that the C-2 and C-6 protons were shielded by N-methylation and deshielded by N-quaternization. The C-5 protons signal, in all the tetrahydropyridines examined, appeared as a broad ill defined multiplet showing evidence of a further small coupling with the vinylic hydrogen.

The UV spectra of **14** and **15** in EtOH showed strong absorption bands at 246 mμ ($\varepsilon = 11{,}650$) and 244 mμ ($\varepsilon = 11{,}560$) respectively, indicating that the Ph groups are conjugated with the double bond. The NMR spectra of **14** and **15** in $CDCl_3$ (Fig. 2) are consistent with the assigned structures. In **14** the ring protons give rise to two A_2X_2 patterns: the C-2 and C-6 protons appearing downfield with respect to those α to the double bond. In **15** the protons α to the nitrogen atom experienced the shielding of the N-Me group and became magnetically equivalent to the C-3 and C-5 protons which combined to give a sharp singlet at 2·43 δ (a mean upfield shift of 0·38 ±0·025 ppm was observed in the N-methylation of tetrahydropyridine series (Table I)). The spectrum of **15** is comparable to that reported by Lee *et al.*[9] for the analogous N-benzyl derivative.

EXPERIMENTAL

M.ps were determined in open glass capillaries, using a Büchi–Tottoli apparatus and are uncorrected. UV spectra were recorded with a Perkin–Elmer Model 402 spectrometer. IR spectra were run routinely with an Unicam SP 200 spectrometer; the OH absorption region of the reported IR spectra were measured with a Perkin–Elmer Model 125 spectrometer, with infrared silica cells (path-length 1–4 cm). NMR spectra were recorded with a Varian T-60 spectrometer using TMS as internal standard. The purity of the compounds isolated was checked by TLC on silica gel G (Merck) or by chromatography on Whatman No. 1 paper, solvent was BuOH–AcOH–H_2O, 4:1:5, spots detected by Dragendorff's reagent.

1-*Methyl*-4-*hydroxymethyl*-4-*phenylpiperidine* (**2**) was prepared from **1** by methylation with 40% aqueous formaldehyde and formic acid; m.p. 132–133° (from EtOH–Et_2O), (lit.[10] 137°).

1-*Benzyl*-4-(α-*hydroxyethyl*)-4-*phenylpiperidine* was prepared from 1-benzyl-4-formyl-4-phenylpiperidine[11] and MeLi as reported[12]; b.p. 130–133°/0·05 mm; picrate, m.p. 168° (from EtOH). (Found: C, 59·54; H, 5·51; N, 10·53. Calc. for $C_{26}H_{28}N_4O_8$: C, 59·53; H, 5·38; N, 10·68%).

4-(α-*Hydroxyethyl*)-4-*phenylpiperidine* (**3**) was obtained by reductive debenzylation of the corresponding benzyl derivative in EtOH with H_2 over 5% Pd/C at 60° and 2 atm during 6 hr; m.p. 133–134° (from Et_2O–light petroleum (b.p. 40°)). (Found: C, 75·65; H, 9·31; N, 6·81. $C_{13}H_{19}NO$ requires: C, 76·05; H, 9·33; N, 6·82%); hydrochloride, m.p. 252–254° (from EtOH). (Found: C, 64·40; H, 8·34; N, 5·81. $C_{13}H_{20}ClNO$ requires: C, 64·59; H, 8·34; N, 5·79%).

1-*Benzyl*-4-(α-*hydroxybenzyl*)-4-*phenylpiperidine* was prepared from 1-benzyl-4-formyl-4-phenylpiperidine[11] and PhLi as reported.[13] The base was characterized as the hydrochloride, m.p. 269–270° (from EtOH). (Found: C, 75·90; H, 7·17; N, 3·18. Calc. for $C_{25}H_{28}ClNO$: C, 76·22; H, 7·16; N, 3·56%).

4-(α-*Hydroxybenzyl*)-4-*phenylpiperidine* (**5**) was obtained by reductive debenzylation of the corresponding benzyl derivative, as reported for **3**. The base was crystallized from EtOH, m.p. 174–175°. (Found: C, 79·86; H, 7·79; N, 4·91. $C_{18}H_{21}NO$ requires: C, 80·86; H, 7·02; N, 5·24%).

1-*Methyl*-4-(α-*hydroxybenzyl*)-4-*phenylpiperidine* (**6**) was obtained by treatment of 1-methyl-4-benzoyl-4-phenylpiperidine[14] with $LiAlH_4$; m.p. 152–153° (from Me_2CO–Et_2O). (Found: C, 81·14; H, 8·34; N, 5·13. Calc. for $C_{19}H_{23}NO$: C, 81·10; H, 8·24; N, 4·98%).

4-*Benzyl*-1,2,5,6-*tetrahydropyridine* (**7**). (A) $SOCl_2$ (15 ml) was added dropwise to a stirred soln of **1** (5 g, 25 mmoles) in 20 ml of dry $CHCl_3$ at 0°. After 24 hr stirring at room temp, the soln was poured onto crushed ice, basified with 40% NaOH and extracted with successive portions of $CHCl_3$. The combined extracts were dried (Na_2SO_4), evaporated to give an oil, triturated with ether. The residual solid after trituration was characterized as the starting alcohol **1**. The ethereal soln was evaporated and the base neutralized with ethereal HCl. Crystallization from EtOH–Et_2O gave the hydrochloride of **7** (1·6 g, 30%), m.p. 177°. (Found: C, 68·60; H, 7·75; N, 6·95; Cl, 16·76. $C_{12}H_{16}ClN$ requires: C, 68·73; H, 7·69; N,

6·69; Cl, 16·90%). The free base, **7**, m.p. 87–90° (from light petroleum) darkened at room temp; (it must be kept under 0° or stored as hydrochloride).

7 was converted into the methiodide **12** by treatment with excess MeI after heating under reflux for 3 hr. The solid which separated was crystallized from EtOH–Et_2O; m.p. 163° (lit.[2] 161–163°). (Found: C, 51·09; H, 6·17; N, 4·21. Calc. for $C_{14}H_{20}NI$: C, 51·05; H, 6·12; N, 4·25%).

(B). A mixture of **1** (5 g, 25 mmoles) and HBr (d 1·49) (20 ml) was heated under reflux for 6 hr, cooled in ice, basified with 40% NaOH and extracted with Et_2O. The ethereal soln was dried (Na_2SO_4), evaporated and the oily residue distilled. The fraction collected at 70–80°/0·05 mm was treated with ethanolic HCl and diluted with Et_2O. The hydrochloride which separated was crystallized to give the pure hydrochloride of **7** (1·8 g, 33%).

1-*Methyl*-4-*benzyl*-1,2,5,6-*tetrahydropyridine* (**8**) was prepared following method B. The fraction collected at 70–80°/0·05 mm was purified through its picrate; m.p. 132–134° (from EtOH) (lit.[2] 132–134°), yield 30%. (Found: C, 55·04; H, 4·84; N, 13·36. Calc for $C_{19}H_{20}N_4O_7$; C, 54·80; H, 4·84; N, 13·46%). The base was liberated using anionic-exchanger III (Merck). The ethanolic soln of the picrate was allowed to exchange with the resin (previously treated with 2N NaOH for 1 hr, then washed with CO_2-free water until the washing were at pH 6 and finally with EtOH) overnight, filtered and concentrated *in vacuo*. Hydrochloride, m.p. 143–145° (from Me_2CO). (Found: C, 69·65; H, 8·08; N, 6·20. $C_{13}H_{18}ClN$ requires: C, 69·78; H, 8·10; N, 6·25%). Methiodide (**12**), m.p. and m.m.p. with the methiodide obtained by the action of MeI on **7**, 163°.

4-(α-*Phenethyl*)-1,2,5,6-*tetrahydropyridine* (**9**) was obtained by method B. The fraction collected between 75–85°/0·05 mm was converted to the hydrochloride by reacting with ethereal HCl; yield 35%; m.p. 146–147°. (Found: C, 69·68; H, 8·12; N, 6·32. $C_{13}H_{18}ClN$ requires: C, 69·78; H, 8·10; N, 6·25%).

1-*Methyl*-(α-*phenethyl*)-1,2,5,6-*tetrahydropyridine* (**10**) was prepared by method A and B. The base was distilled and the fraction collected at 65–70°/0·05 mm converted to the oxalate with ethanolic oxalic acid; yield 45%; m.p. 160–170° (from EtOH). (Found: C, 65·91; H, 7·38; N, 4·74. $C_{16}H_{21}NO_4$ requires: C, 65·95; H, 7·27; N, 4·81%).

The methiodide **13** was obtained by adding MeI to the ethereal soln of **10**; m.p. 235° (dec) (from Me_2CO–Et_2O). (Found: C, 52·12; H, 6·44; N, 4·02. $C_{15}H_{22}IN$ requires: C, 52·48; H, 6·46; N, 4·07%).

1-*Cyano*-4-(α-*hydroxyethyl*)-4-*phenylpiperidine*. BrCN (2·75 g, 26 mmoles) in $CHCl_3$ was added dropwise to a stirred soln of **4** (4 g, 18 mmoles) in $CHCl_3$ (10 ml) at 5°. The resulting soln was stirred for 3 hr at room temp, and then 10 ml of 0·1N HCl added. The organic layer was separated, washed with water and dried (Na_2SO_4). Evaporation of solvent afforded 3·2 g (77%) of title compound as a yellow oil; ν_{max}^{film} 2200 cm^{-1} (C≡N). The analytical sample was obtained as a viscous colorless oil; b.p. 170–173°/0·05 mm. (Found: C, 72·74; H, 7·96; N, 12·26. $C_{14}H_{18}N_2O$ requires: C, 73·01; H, 7·88; N, 12·17%).

1-*Carbamyl*-4-(α-*phenethyl*)-1,2,5,6-*tetrahydropyridine* (**11**). To the above crude cyano derivative (2 g, 8·6 mmoles) 18% HCl (10 ml) was added and the mixture heated under reflux for 5 hr. After cooling the mixture was basified with conc. NH_4OH and extracted with $CHCl_3$. Evaporation of dried solvent gave crude **11** (1·3 g, 65%) crystallized from Me_2CO; m.p. 154–155°. (Found: C, 73·02; H, 7·96; N, 12·47. $C_{14}H_{18}N_2O$ requires: C, 73·01; H, 7·88; N, 12·17%). **11** on hydrolysis under milder conditions (1N HCl, 6 hr reflux) gave **9** after the usual treatment.

4-*Benzhydrylidenepiperidine* (**14**) was prepared from **5** by method B. The base was distilled; b.p. 120–125°/0·05 mm; m.p. 83° (lit.[3] 86–88°). (Found: C, 86·54; H, 7·81; N, 5·82. Calc. for $C_{18}H_{19}N$: C, 86·70; H, 7·68; N, 5·68%); hydrochloride, m.p. 286° (from EtOH). (Found: C, 75·83; H, 7·06; N, 4·73. Calc. for $C_{18}H_{20}ClN$: C, 75·65; H, 7·05; N, 4·89%).

1-*Methyl*-4-*benzhydrylidenepiperidine* (**15**) was prepared by method B. The base[4] was distilled; b.p. 110–112/0·05 mm; yield 65%; hydrobromide, m.p. 270–272° (from EtOH). (Found: C, 66·16; H, 6·39; N, 3·86. $C_{19}H_{22}BrN$ requires: C, 66·28; H, 6·43; N, 4·06%).

REFERENCES

[1] M. Ōki and H. Iwamura, *Bull. Chem. Soc. Japan* **33**, 681 (1960)

[2] J. Diamond, W. F. Bruce and F. T. Tyson, *J. Org. Chem.* **30**, 1840 (1965)

[3] K. W. Wheeler, J. K. Seyler, F. P. Palopoli and F. J. McCarty, *US Patent* 2,898,339 Aug. 4 (1959); *Chem. Abstr.* **54**, 581f (1960)

[4] N. Sperber, F. J. Villani, M. Sherlock and D. Papa, *J. Am. Chem. Soc.* **73**, 5010 (1951)

[5] J. Diamond, W. F. Bruce and F. T. Tyson, *J. Org. Chem.* **26**, 2058 (1961)
[6] A. F. Casy and H. Birnbaum, *J. Chem. Soc.* 5130 (1964)
[7] A. H. Beckett, A. F. Casy, R. G. Lingard, M. A. Iorio and K. Hewitson, *Tetrahedron* **22**, 2735 (1966)
[8] H. Booth and J. H. Little, *Ibid.* **23**, 291 (1967)
[9] C. M. Lee, A. H. Beckett and J. K. Sugden, *Ibid,* **22**, 2721 (1966)
[10] B. Elpern, *J. Am. Chem. Soc.* **76**, 281 (1954)
[11] M. A. Iorio and S. Chiavarelli, *Tetrahedron* **25**, 5235 (1969)
[12] J. M. McManus, J. W. McFarland, C. F. Gerber, W. M. McLamore and G. D. Laubach, *J. Med. Chem.* **8**, 766 (1965)
[13] A. F. Casy, A. H. Beckett, M. A. Iorio and H. Z. Youssef, *Tetrahedron* **21**, 3387 (1965)
[14] O. Eisleb, *US Patent* 2,248,018 July 1 (1941)