of the bridgehead methyl. Furthermore, if substituents influence the longest-wavelength *Cotton* effect in the way *Burgstahler & Naik* suggest, they would tend to reinforce the observed positive value, making a distinction between the different origins of the optical activity in that case difficult.

In conclusion we feel that the twisted glyoxal model ist still the best starting point for discussing the optical activity of asymmetric α-diketones. As previously reported [2] [10], calculations on twisted glyoxal also interpret very satisfactorily the electronic absorption spectra of α-diones for different angles of twist between the two carbonyl groups, in particular the characteristic variation of the wavelength of the first (longest-wavelength) transition, as well as changes in the relative intensity of absorption of the first and second transition. The evidence furnished against the twisted glyoxal model, as a means of interpreting CD. spectra, does not seem to us sufficient to question its basic applicability. But we agree with *Burgstahler & Naik* that the question of substituent effects should be further pursued, and that additional spectroscopic evidence would be most highly welcome[3]).

We thank Prof. *A. W. Burgstahler* for stimulating discussions and an interesting exchange of information.

BIBLIOGRAPHY

[1] *A. W. Burgstahler & N. C. Naik*, Helv. *54*, 2920 (1971).
[2] *W. Hug & G. Wagnière*, Helv. *54*, 633 (1971).
[3] *J. Levisalles & H. Rudler*, Bull. Soc. chim. France *1967*, 2059.
[4] *P. Witz*, doctoral thesis, University of Strasbourg, 1964.
[5] *E. L. Eliel*, 'Stereochemistry of Carbon Compounds', p. 239–247, McGraw Hill, New York 1962.
[6] *K. M. Wellman, E. Bunnenberg & C. Djerassi*, J. Amer. chem. Soc. *85*, 1870 (1963); see also *W. Klyne*, Tetrahedron *13*, 29 (1961); *G. Snatzke & D. Becker, ibid. 20*, 1921 (1964).
[7] *A. W. Burgstahler & R. C. Barkhurst*, J. Amer. chem. Soc. *92*, 7601 (1970).
[8] *W. Hug, J. Kuhn, K. J. Seibold, H. Labhart & G. Wagnière*, Helv. *54*, 1451 (1971).
[9] *W. B. Whalley*, Chemistry & Ind. *1962*, 1024; *G. Snatzke*, Tetrahedron *21*, 413, 421, 439 (1965).
[10] *W. Hug & G. Wagnière*, Theoret. chim. Acta *18*, 57 (1970).

[3]) The Publication Committee hereby declares that this reply terminates the discussion of this object in the Helvetica chimica acta.

69. Stereochemical Assignment of the Two Isomeric Tropine N-Oxides by Proton Magnetic Resonance at 220 MHz

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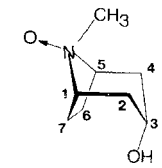
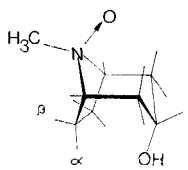
(11. II. 72)

Summary. Proton magnetic resonance spectra of tropine and the two isomeric tropine N-oxides have been analysed at 220 MHz. Chemical shifts in the N-oxides are expressed relative to tropine ($\Delta\nu^{N}_{NO}$) and permit unequivocal structural assignments of the predominant isomer (**1**, equatorial N-oxide) and the minor isomer (**2**).

Oxidation of tropine (**3**) by hydrogen peroxide leads to two isomeric N-oxides which have recently been separated and described by means of IR.-, ^{1}H-NMR.- and mass spectra [1]. Based on an inspection of proton spectra obtained in aqueous solution at 100 MHz the main product had been tentatively assigned structure **2**. The preferred axial attack of the oxidizing reagent appeared in line with previous studies of the stereochemistry of the ring nitrogen in a series of tropane oxides [2]. Here the arguments were based mainly upon a comparison of the proton chemical shifts (60 MHz) of N-methyl groups in N-oxides and N-quaternary compounds. At 60 and 100 MHz the chemical shifts of the individual ring protons which should allow an unequivocal assignment of the stereochemistry of the tropane oxides cannot be obtained. In the case of the oxidation product of scopolamine (**4b**) it has been proved by X-ray crystallography [3] that the oxygen atom at nitrogen is in the equatorial



1



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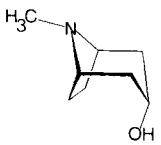

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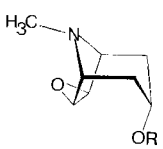

4

a) R = H
b) R = COCHC$_6$H$_5$ (CH$_2$OH)

position. In view of the previous NMR. results and of the somewhat different stereochemical conditions in scopolamine as compared with the other tropane bases, the latter result however may not necessarily be generalized.

In connection with our calculations of proton chemical shifts in N-oxides [4] we have been interested in a detailed analysis of the proton spectra of the two tropine N-oxides and a definite assignment of their stereochemistry.

We have carried out the oxidation of tropine according to *Werner & Schickfluss* [1] and obtained the two isomers in a ratio of approximately 2:1. Crystallization from ethanol-ether afforded the predominant component (first isomer), m.p. 252°. From the mother liquor a second crystalline product was obtained by further crystallization (same solvent mixture) in which the ratio of the two isomers was now 1:2.

The proton magnetic resonance spectra of the two products were measured in 0.5 M CD_3OD solutions on a *Varian* HR-220 (MHz) spectrometer with tetramethylsilane as an internal lock-signal. The spectrum of the first isomer, m.p. 252°, is illustrated in Fig. 1. The proton at C(3) gives rise to a triplet at 3,96 ppm, the N-

methyl group to a singlet at 3,18 ppm and the broad non-resolved signal at 3.51 ppm can be assigned to the two enantiotopic bridgehead protons at C(1) and C(5). The doublet at highest field (1.98 ppm) shows a splitting of 16 Hz (J_{gem}). By comparison

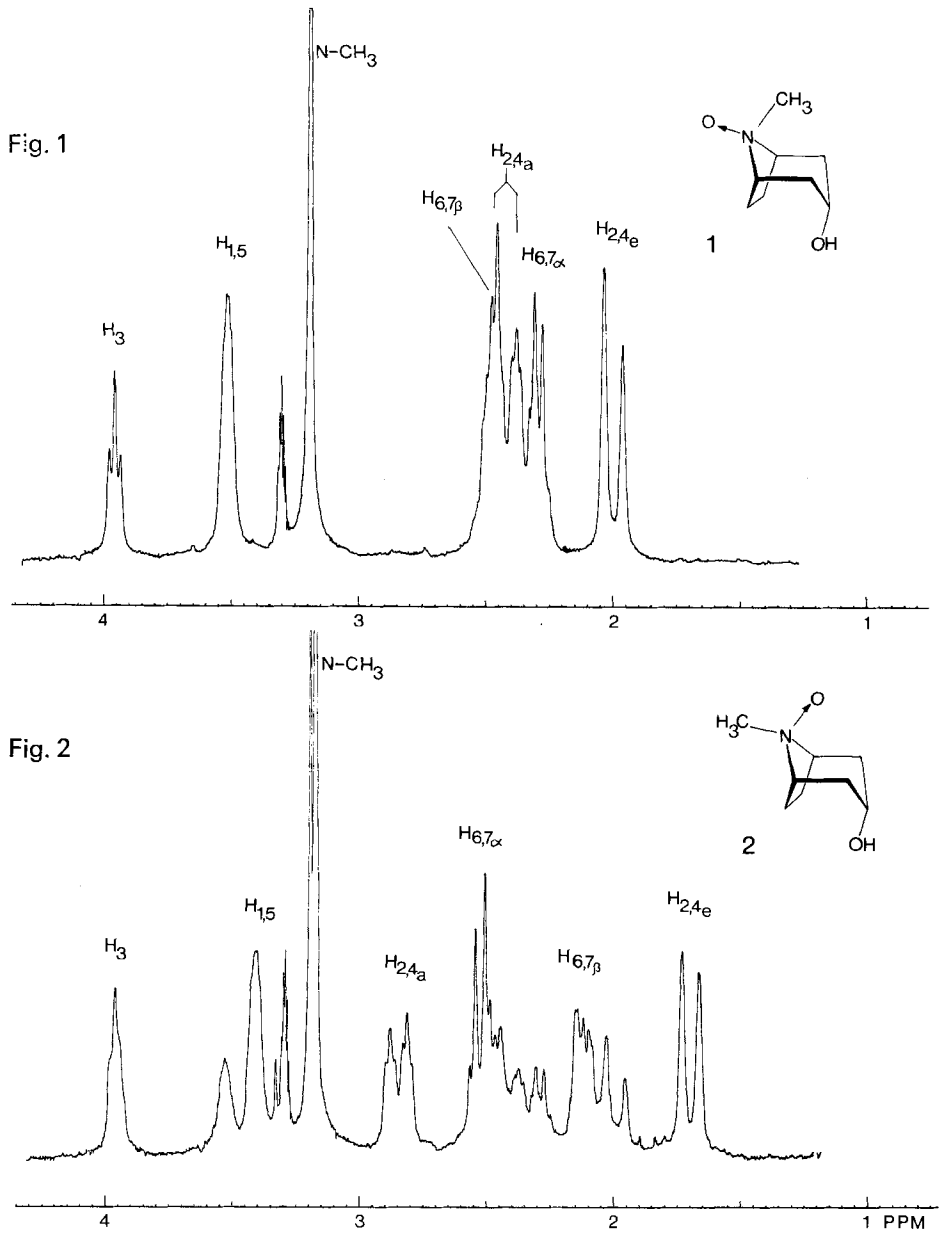

Fig. 1. *220 MHz ^{1}H-NMR. spectrum of tropine N-oxide* **1** *in CD_3OD*

Fig. 2. *220 MHz ^{1}H-NMR. spectrum of enriched tropine N-oxide* **2** *(2:1 mixture with tropine N-oxide* **1***) in CD_3OD. The signals of* **2** *only are labelled*

with the spectrum of scopine (6,7-β-epoxy-tropine, **4a**) this doublet must be assigned to one of the pairs of enantiotopic methylene protons at C(2) and C(4) of the piperidine ring. The methylene region of the scopine spectrum (Fig. 3) allows

Fig. 3

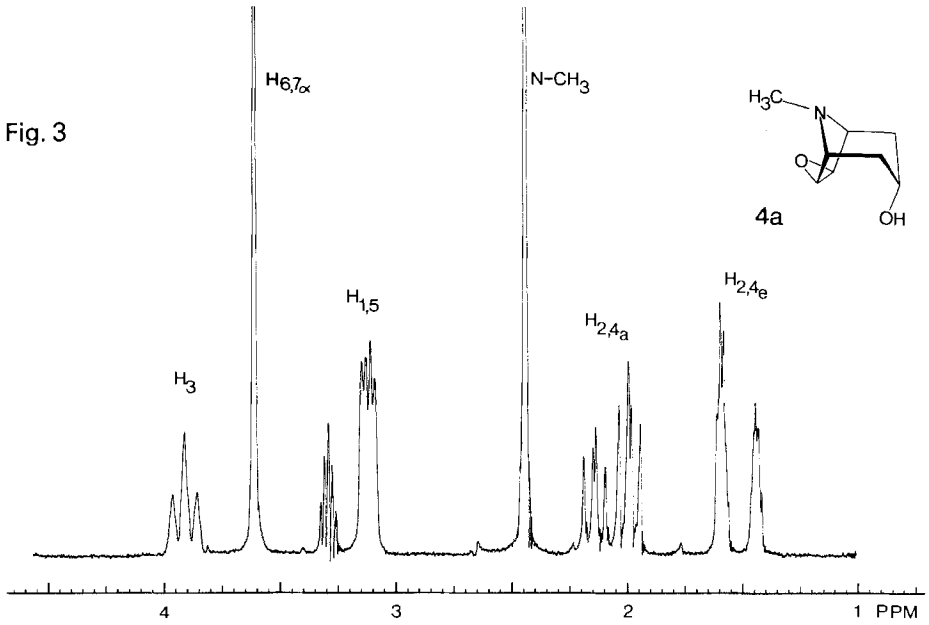

Fig. 3. *100 MHz ^{1}H-NMR. spectrum of scopine* (**4a**) *in CD_3OD*

the assignment of the high-field doublet to the pair of equatorial protons at C(2) and C(4). These protons show only weak coupling with the proton at C(3) and the bridgehead protons at C(1) and C(5). The signal of the pair of axial protons shows two additional well resolved splittings due to interaction of these protons with H-C(3) ($J_{2e,3} = J_{4e,3} = 4.8$ Hz) and with H-C(1) and H-C(5) ($J_{2e,1} = J_{4e,5} = 4.0$ Hz), respectively [2]. The resonance of the axial protons (2.40 ppm) in tropine N-oxide, m.p. 252°, is partly hidden by a signal of the methylene protons of the pyrrolidine ring, but is clearly resolved in the other isomer (Fig. 2) as the doublet with triplet fine structure at 2.84 ppm. The signal of the pair of α-methylene protons at C(6) and C(7) appears as a doublet at 2.27 ppm and the β-methylene protons give a multiplet at 2.45 ppm. The assignment of the signal at 2.27 ppm to the α-methylene protons is supported by the resonance of the α-protons in scopine appearing as a singlet and indicating no spin coupling between these protons and the bridgehead protons at C(1) and C(5) (torsional angle $\sim$90°).

The assignment of the high-field doublet in the spectrum of tropine N-oxide, m.p. 252°, to the equatorial protons at C(2) and C(4) is in contrast to the analysis of *Werner & Schickfluss*. These authors assumed, probably by analogy with cyclohexane, that the high-field doublet arises from the axial methylene protons. It will be seen that the correct analysis of the methylene resonances in the piperidine ring is crucial in the assignment of the stereochemistry of the two N-oxide isomers.

The spectrum of the crystalline product containing the second isomer in enriched form is illustrated in Fig. 2. This spectrum clearly shows equivalent signals from two isomeric species with distinctly different chemical shifts. In the second isomer the two pairs of enantiotopic protons of the piperidine ring appear as two widely separated doublets at 1.69 ppm (equatorial H-C(2) and H-C(4), $J_{e,a} = 15$ Hz) and 2.84 ppm (axial H-C(2) and H-C(4)), the latter showing the characteristic fine-structure already discussed in the spectrum of scopine. The two pairs of methylene protons in the pyrrolidine ring give rise to a doublet at 2,52 ppm (H_α-C(6) and H_α-C(7)) and a multiplet at 2.11 ppm (H_β-C(6) and H_β-C(7)). The other signals of the second isomer are found at 3.17 ppm (N–CH_3), 3.42 ppm (bridgehead H-C(1) and H-C(5)) and 3.97 ppm (H-C(3)), the last coinciding with the corresponding signal of the first isomer.

On the basis of the chemical shifts of all protons in the two isomeric tropine N-oxides (Table 1) an unequivocal assignment of their stereochemistry is possible.

Table 1

Chemical shifts, δ [ppm] [a])

	$H_{1,5}$	$H_{2e,4e}$	$H_{2a,4a}$	H_3	$H_{6\alpha,7\alpha}$	$H_{6\beta,7\beta}$	N–CH_3
N-oxide **1**	3.51	1.98	2.40	3.96	2.27	2.45	3.18
N-oxide **2**	3.42	1.69	2.84	3.97	2.52	2.11	3.17
tropine (**3**)	3.08	1.70	2.06 [b])	3.93	2.14	2.00	2.25

For this purpose we express the observed chemical shifts in the isomeric N-oxides relative to the shifts of the corresponding protons in tropine as $\Delta\nu_{NO}^{N}$ ($= \nu_N - \nu_{NO}$) values [Hz at 220 MHz] (Table 2).

Table 2

Relative chemical shifts $\Delta\nu_{NO}^{N}$ [Hz at 220 MHz]

	$H_{1,5}$	$H_{2e,4e}$	$H_{2a,4a}$	H_3	$H_{6\alpha,7\alpha}$	$H_{6\beta,7\beta}$	N–CH_3
tropine/N-oxide **1**	–94	–61	–74	–6	–28.5	–101	–205
tropine/N-oxide **2**	–74	+3	–171	–10	–83.5	–26	–202

[a]) Measured in 0.5 M CD_3OD solution, $\pm$0,01 ppm.

[b]) Calculated from an AB analysis based on the signal of the equatorial protons.

From a number of experimental arguments it has been concluded that the N-methyl group in tropine prefers the equatorial position [5]. The chemical shifts of the ring protons in tropine and both N-oxides will be influenced by the orientation of the N-methyl group. However, for an explanation of the large $\Delta\nu_{NO}^{N}$ values observed for the methylene protons we assume that these shifts are caused mainly by field effects originating from the electric dipole and to a smaller extent from the induced magnetic dipole of the N–O bond [4]. The $\Delta\nu$ values for the bridgehead and N-methyl protons are determined both by inductive and field effects.

On inspection of *Dreiding* models of structure **1** it must be expected that the $\Delta\nu_{NO}^{N}$ value of the β-protons at C(6) and C(7) is larger than the corresponding value of the axial protons at C(2) and C(4). This follows from the near coplanarity of the C–H and N–O bonds in the first case. In structure **2** the axial protons

at C(2) and C(4) should show an even larger $\Delta\nu_{NO}^{N}$ value due to the smaller distance between the proton and the centre of the N–O dipole. Therefore, from the observed $\Delta\nu_{NO}^{N}$ values in Table 2 one has to conclude that the first isomer (m.p. 252°; $H_{6\beta,7\beta}$: $\Delta\nu_{NO}^{N} = -101$ Hz; $H_{2a,4a}$:$\Delta\nu_{NO}^{N} = -74$ Hz) must be assigned structure **1** and the second isomer ($H_{2a,4a}$:$\Delta\nu_{NO}^{N} = -171$ Hz; $H_{6\beta,7\beta}$:$\Delta\nu_{NO}^{N} = -26$ Hz) structure **2**. This assignment is supported by the relative magnitudes of the $\Delta\nu_{NO}^{N}$ values for the β-protons (−101 Hz) and the α-protons (−28.5 Hz) at C(6) and C(7) in isomer **1** and the corresponding values for the axial (−171 Hz) and equatorial protons (+3 Hz) at C(2) and C(4) in isomer **2**. Different deshielding effects of the N–O bond in the two isomers are also experienced by the bridgehead protons at C(1) and C(5). Since the torsional angle of the N–O and C–H bonds in **1** is smaller than in **2** the bridgehead protons in **1** are more deshielded.

For a quantitative and more detailed analysis of the chemical shifts caused by field effects of the N–O bond in the two isomeric tropine N-oxides and other aliphatic N-oxides calculations using specific parameters for the electric and induced magnetic dipoles of the N–O bond are in progress.

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BIBLIOGRAPHY

[1] *G. Werner & R. Schickfluss*, Liebigs Ann. Chem. *746*, 65 (1971).
[2] *N. Mandava & G. Fodor*, Can. J. Chem. *46*, 2761 (1968).
[3] *C. S. Huber, G. Fodor & N. Mandava*, Can. J. Chem. *49*, 3258 (1971).
[4] *P. Hamm & W. v. Philipsborn*, Helv. *54*, 2363 (1971).
[5] *R. J. Bishop, G. Fodor, A. R. Katritzky, F. Soti, L. E. Sutton & F. J. Swinbourne*, J. chem. Soc. (C) *1966*, 74.

70. On the Mechanism of Decarboxylation of Betanidine. A Contribution to the Interpretation of the Biosynthesis of Betalaines

by **E. Dunkelblum**[1]), **H. E. Miller**[2]) and **André S. Dreiding**

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(3. X. 70)

Zusammenfassung. Bei der Biogenese des Betanins (**2**) aus Dopa (**1**) wird die Carboxylgruppe der Aminosäure in die Carboxylgruppe-C(19) umgewandelt. Dieser Schluss beruht auf einem Deuterierungsversuch, bei dem gezeigt wird, dass die Monodecarboxylierung von Betanidin (**3**) zu einem Verlust von C(19) führt und dass dabei die Doppelbindung C(17)=C(18) nach C(14)=C(15) wandert. Wenn radioaktives Betanidin (**3**), erhalten aus Einbauexperimenten mit DL-Dopa-[1-^{14}C], in Äthanol decarboxyliert wird, erhält der danach isolierte Dimethylester **7** des Decarboxybetanidin (**6**)-hydrochlorids nur noch 14% des ^{14}C.

Bei der alkali-katalysierten Äquilibrierung von Betanidin (**3**) $\rightleftarrows$ Isobetanidin (**9**) tritt im Gegensatz zur Decarboxylierung keine Wanderung der Doppelbindung ein.

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