Stereospecific Synthesis of Chiral *N*-(*p*-Methoxyphenylalkyl)pyridinium Salts

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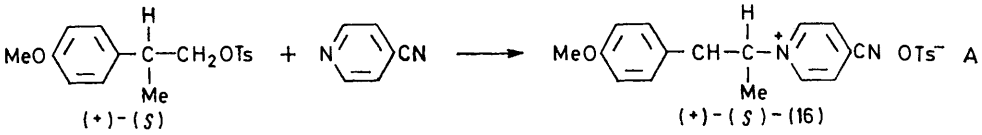
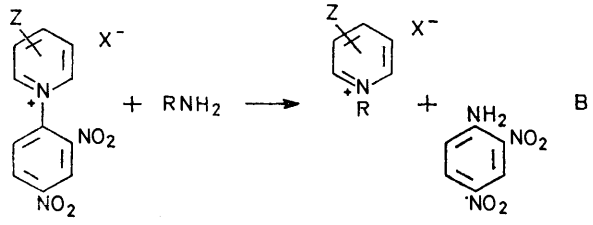
A series of chiral *N*-(*p*-methoxyphenylalkyl)pyridinium salts (1)—(15) were prepared from their parent chiral (*p*-methoxyphenylalkyl)amines with retention of configuration by the Zincke reaction.

FOR our study on the optical activity of intramolecular charge-transfer transitions [1] we needed optically active *N*-(*p*-methoxyphenylalkyl)pyridinium ions containing strongly electronegative substituents in the pyridinium group and one or more chiral centres in the alkyl group. Unfortunately, the so-called Menschutkin reaction [2,3] of an optically active halide or toluene-*p*-sulphonate, RY (Y = Cl, Br, I, or OTs) with (substituted) pyridines leads to extensive racemization when Y is attached directly to an asymmetric (*i.e.* secondary or tertiary) centre and furthermore the quaternization is often accompanied by side reactions such as elimination and rearrangement.[4] As an exceptional case we described earlier [1] the stereospecific synthesis of compound (16) by direct quaternization of 4-cyanopyridine with a primary toluene-*p*-sulphonate to give the 'secondary' pyridinium salt (16) with anchimeric assistance *via* a phenonium ion (equation A). Naturally the application



(+)-(*S*) (+)-(*S*)-(16)

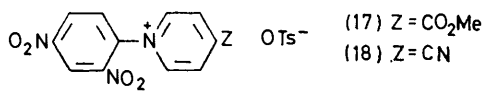
of this mechanistic principle for stereospecific syntheses is limited, and we therefore searched for a more general method: we considered the widely applicable synthesis of *N*-aryl and *N*-(arylalkyl)pyridinium ions from amines,



discovered by Zincke.[5-7] This method involves reaction of a primary amine with an *N*-(2,4-dinitrophenyl)-pyridinium ion (equation B). In this way pyridinium chlorides have been synthesized both unsubstituted [6-8] and with 3-$CONH_2$,[9-13] 4-$CONH_2$,[13] and 3-$CSNH_2$ [11] as ring substituents. According to the mechanism proposed [8,14] the C–N bond in the amine is not broken during the reaction, but (as far as we know) the stereospecificity has never been proved experimentally.

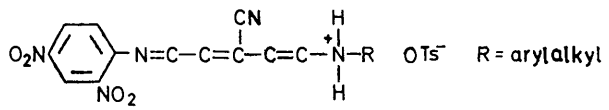
RESULTS AND DISCUSSION

Reaction of 2,4-dinitrophenyltoluene-*p*-sulphonate with 4-methoxycarbonyl- and 4-cyano-pyridine yielded the Zincke salts (17) and (18) respectively, which cannot be obtained [15,16] from reaction of these pyridines with the less reactive [17] 1-chloro-2,4-dinitrobenzene. Both (17) and (18) react smoothly with aniline to yield the corresponding *N*-phenylpyridinium salts. With (arylalkyl)amines, only (17) reacts normally in the Zincke reaction to yield the desired *N*-(arylalkyl)pyridinium salts. On the other hand the cyano-derivative (18) gives with (arylalkyl)amines mixtures from which a dark red solid often precipitated. This presumably contains a highly conjugated system, as indicated in (19),



(17) Z = CO_2Me
(18) Z = CN

unstable in solution and reacting with an excess of amine to give non-identified products with evolution of hydrogen cyanide. Reaction of (17) with optically



(19)

active forms of the appropriate amines yielded the 4-methoxycarbonylpyridinium salts (1)—(15) (see the Table) with retention of configuration (as shown below).

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[2] J. Menschutkin, *J. Russ. Phys. Chem. Soc.*, 1902, **34**, 411; cited in *Chem. Central-Blatt*, 1902, **73**, *II*, 86.
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[7] Th. Zincke, *Annalen*, 1905, **341**, 369.
[8] E. N. Marvell and I. Shahidi, *J. Amer. Chem. Soc.*, 1970, **92**, 5646.
[9] S. Shifrin, *Biochim. Biophys. Acta*, 1965, **96**, 173.
[10] J. A. Secrist and N. J. Leonard, *J. Amer. Chem. Soc.*, 1972, **94**, 1702.
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[13] H. E. Bosshard, Dissertation, Eidgenössische Technische Hochschule Zürich, Zürich, 1970.
[14] E. van den Dunghen, J. Nasielski, and P. van Laer, *Bull. Soc. chim. belges*, 1957, **66**, 661.
[15] A. F. Vompe and N. F. Turitsyne, *Doklady Akad. Nauk. S.S.S.R.*, 1949, **64**, 341.
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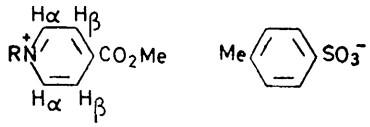
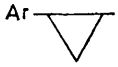
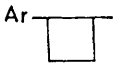
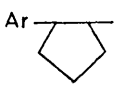
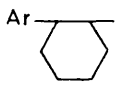
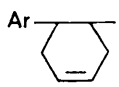
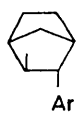
[17] 'The Chemistry of Functional Groups,' ed. H. Feuer, vol. I, Interscience, New York, 1969, p. 487.

The optical activity of the new pyridinium salts was found to be independent of the reaction temperature (20—60°), time (0·5—2 h), and solvent (methanol or dimethylformamide), even when the amino-group was attached directly to the asymmetric centre. Reagent tamination with diastereoisomeric pyridinium salts was never encountered, and even in the reaction products from (17) with *cis*-amines no trace of the thermodynamically more favourable *trans*-pyridinium salts could be detected. This strongly suggests that the

Structure and some physical parameters of the pyridinium salts synthesized



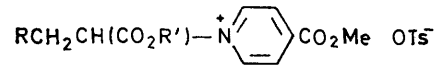
Compound	R [a]	Optical purity/% (± 1%) [b]	$[\Phi]_{400}^{25}$/° [d]	¹H N.m.r. shifts [δ/p.p.m. (±0·02 p.p.m.)] and coupling constants [J/Hz (±0·3 Hz)] in CD_3OD H-α	H-β	$J_{1,2}$	$J_{2,3}$
(1)	Ar(Me)CH	95	−390	9·28	8·42		
(2)	Ar(Bu)^{t}CH	96	−260	9·42	8·48		
(3)	Ar(Me)$CHCH_2$	(*ca.* 30)	*e*	8·90	8·25		
(4)	Ar(Bu^t)$CHCH_2$	>99	−2630	8·97	8·23		
(5)	$ArCH_2$(Me)CH	76	+3550	9·12	8·35		
(6)	$ArCH_2$(Bu^t)CH	95	+2950	9·27	8·37		
(7) *cis*		91	+1030	8·96	8·19	(10)	
(7) *trans*		>99	+4120	9·23	8·46	4·8	
(8) *trans*		>99	+4450	9·01	8·40	9·1	
(9) *trans*		>99	−6020	9·11	8·38	9·7	
(10) *cis*		>99	+3140	8·77	8·21	5·3	
(10) *trans*		>99	−2260	9·10	8·31	11·0	
(11) *cis*		95	−920	8·53	8·29	3·3	
(11) *trans*		0		9·32	8·36	11·2	
(12)	 (Ar-*exo*)	84	+2540	9·19	8·43	3·6	5·6
(13)	 (Ar-*endo*)	>99	−2970	9·05	8·34	~0	5·7
(14)	 (Ar-*exo*)	84	+5900	9·20	8·41	3·4	4·6
(15)	 (Ar-*endo*)	*c*		9·01	(8·43)	~0	4·7

[a] Ar = *p*-methoxyphenyl in all cases. [b] Considered to equal that of the starting amines (*cf.* ref. 22). [c] Only obtained as a mixture (14) : (15) = 3 : 1 from a similar mixture of the parent amines. [d] Molecular rotations (in 96% EtOH) were corrected to 100% optical purity. [e] $[\Phi]_{400}^{25}$ +90°, not corrected to 100% optical purity.

(17) was treated with several amines containing more than one asymmetric carbon atom, yielding the salts (7)—(15) (see the Table).

By means of ¹H n.m.r. spectroscopy (see below) it was proved that in all cases retention of configuration at the carbon atom carrying the amino-group occurs. Con- Zincke reaction proceeds with complete retention of configuration and that by analogy the same is true for the pyridinium salts derived from the amines with only one chiral centre (1)—(6). Moreover our results show that there is no racemization afterwards under the reaction conditions. This latter conclusion is not

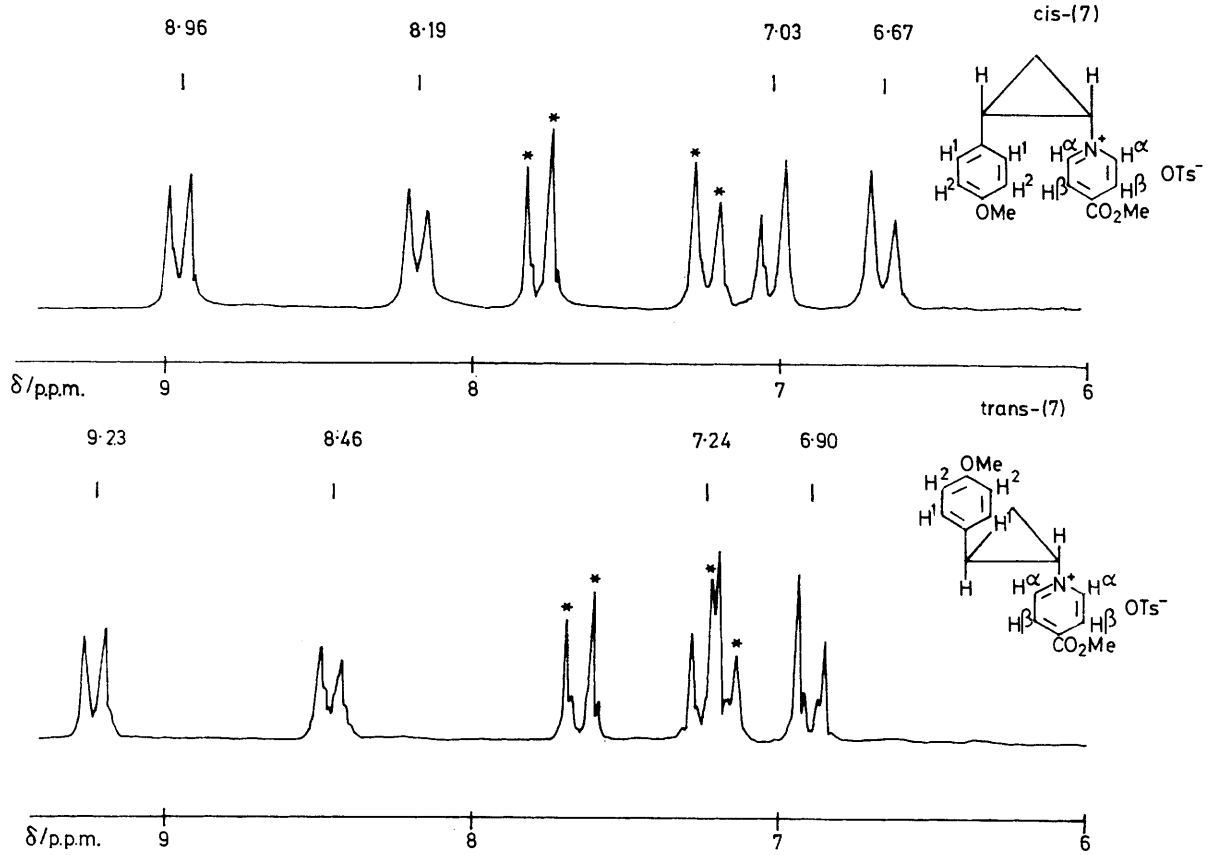
justified in reactions with amino-acid derivatives. Amino-acid esters, for example, react smoothly with our standard Zincke reagent (17) to give (20). However,



(20)

the optical activity of products (20) depends strongly on the reaction time and complete racemization occurs within 5 min under the reaction conditions (methanol pounds relative to the corresponding *trans*-isomers (Table), thus making it very easy to distinguish between such isomers [*cf.* the spectra of *cis*- and *trans*-(7) in the Figure].

For the *trans*-norbornene and *trans*-norbornane derivatives there exists the additional possibility of *exo–endo* isomerism. The position of the pyridinium group in these compounds can be determined from the vicinal coupling constant $J_{1,2}$ between the bridgehead proton H-1 and the proton H-2 on the C-atom carrying



Partial ^{1}H n.m.r. spectra (at 100 MHz) for *cis*- and *trans*-(7), showing the large upfield shift of the aromatic protons in the *cis*-isomer (signals due to the toluene-*p*-sulphonate ion are marked by an asterisk)

solution at room temperature), under which the starting amino-acid esters are optically stable. The racemization is undoubtedly due to the lability of the tertiary proton in (20). Under the influence of the two adjacent electronegative groups it readily exchanges with deuterium in D_2O even under neutral conditions. Similar observations have been made by Bosshard.[13]

The structural determination of the pyridinium salts depended mostly on ^{1}H n.m.r. spectroscopy. The chemical shift of the aromatic protons in the *p*-methoxyphenyl and the 4-methoxycarbonylpyridinium groups is strongly influenced by the relative orientation of these aromatic systems. Mutual shielding causes a distinct upfield shift of the signals of H-1 and H-α in *cis*-com-

the pyridinium group. The torsion angle between H-1 and H-2 can be either 80° (H-2 *endo*) or *ca.* 45° (H-2 *exo*). This leads to calculated values [18] of approximately 0 and 3·5 Hz respectively for $J_{1,2}$, which means that the signal for H-2 (which lies in a region not obscured by other signals) will either appear as a doublet (by coupling with H-3 only) or as a distorted triplet ($J_{2,3}$ *ca.* 5 Hz). This agrees with observations made by others [19-21] for a large number of norbornene and norbornane derivatives.

EXPERIMENTAL

^{1}H N.m.r. spectra were recorded on a Varian HA-100 instrument with $CDCl_3$ or CD_3OD as solvents and with Me_4Si as internal reference. Molecular and specific

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rotations were calculated from the rotation measured on a Fica Spectropol-1 spectropolarimeter and a Zeiss LEP polarimeter, and are compiled in the Table. O.r.d. and c.d. spectra will be discussed in a forthcoming publication. All pyridinium salts gave satisfactory elemental analyses. The preparation of the amines and their optical resolution is reported elsewhere.[22]

4-*Cyano*-N-(2,4-*dinitrophenyl*)*pyridinium Toluene*-p-*sulphonate* (18).—2,4-Dinitrophenyl toluene-*p*-sulphonate (27 g, 0·11 mol) and 4-cyanopyridine (40·0 g, 0·38 mol; three fold excess) were heated on an oil-bath at 90°. A homogeneous melt was obtained, which solidified after 1 h, and heating was continued for an additional 4 h. The red solid was dissolved in MeOH, precipitated with ether, and recrystallized from MeOH twice, with the addition of decolourizing charcoal and a drop of concentrated HCl, to give the salt (18) (29·7 g, 61%), m.p. 215—217°.

N-(2,4-*Dinitrophenyl*)-4-*methoxycarbonylpyridinium Toluene*-p-*sulphonate* (17).—In the same way 2,4-dinitrophenyltoluene-*p*-sulphonate (27·0 g, 0·11 mol) was converted with a three-fold excess of 4-methoxycarbonylpyridine into (17) (30·8 g, 59%), m.p. 213—215°.

The Pyridinium Salts (1)—(15).—All the pyridinium salts (1)—(15) were formed by addition over 2—30 min of the reagent (17) (*ca.* 0·8 mol. equiv.) in methanol or dimethylformamide to a stirred solution of the appropriate amine (*ca.* 1·0 mol. equiv.) in methanol or dimethylformamide at room temperature [for (1), (3), (5), and *trans*-(7) and -(14)] or at 60° [for (2), (4), (6), and *cis*-(7), -(10), and -(11)]. In this way an excess of amine can be maintained throughout the reaction period, an essential condition for successful reaction. The course of the reaction can be followed by the changes in colour: after addition of (17) the colour immediately becomes dark red (ring opening) and turns rapidly within minutes into the yellow colour of the pyridinium salt and the expelled 2,4-dinitroaniline. For the sterically unhindered cases [*e.g.* (3) and (5)] in particular, prolonged reaction times must be avoided to exclude the formation of products resulting from aminolysis of the 4-methoxycarbonyl group by excess of amine. A typical example of a Zincke reaction is given below for the formation of *trans*-(10).

N-(trans-2-p-*Methoxyphenylcyclohexyl*)-4-*methoxycarbonylpyridinium Toluene*-p-*sulphonate* [trans-(10)].—To a magnetically stirred solution of (−)-(*trans*-(2-p-methoxyphenylcyclohexyl)amine (200 mg, 1·0 mmol) in MeOH (1 ml), *N*-(2,4-dinitrophenyl)-4-methoxycarbonylpyridinium toluene-*p*-sulphonate (17) (380 mg, 0·8 mmol) in MeOH (7 ml) was added dropwise at room temperature. After the dark red colour of the reaction mixture had turned yellow, the reaction was considered complete and the MeOH was partly removed under reduced pressure. The concentrated mixture was then poured into a large excess of ether, and the oily precipitate isolated by centrifugation and dissolved in a minimum amount of water. The aqueous solution was continuously extracted with ether overnight to remove traces of 2,4-dinitroaniline. Then the water layer was extracted with chloroform several times, the combined extracts dried, and the chloroform removed under reduced pressure. The resulting yellow oil was dissolved in methanol, ether was added, and the precipitate separated by centrifugation. This procedure was repeated three times. Finally the oil was stored under vacuum (0·01 mmHg) to induce crystallization (yield 250 mg, 50%).

We acknowledge the assistance of Mrs. M. Sep, the late Mr. D. J. H. Staalman, and Mr. S. Q. J. Zonneveld in the synthetic work, and we thank Mrs. M. Steeneken and Mr. C. Kruk for the ^{1}H n.m.r. spectra and Mr. H. Pieters for determination of the elemental analyses.

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[22] A. J. de Gee, Dissertation, University of Amsterdam, 1973.