Substituent Effects in Saturated Systems. Preparation, Stereochemistry, and Acidity of Pipecolic (Piperidine-2-carboxylic) Acid Derivatives

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The preparation and properties of *cis*- and *trans*-4-substituted pipecolic (piperidine-2-carboxylic) acids are described, the substituents being methyl and t-butyl. Their stereochemistry has been assigned according to the method of preparation and confirmed by ^{1}H n.m.r. spectroscopy and epimerisation experiments. The epimerisation experiments show that in the corresponding isomeric ethyl pipecolates the conformational preference of the ethoxycarbonyl group is less than would be expected from comparison with cyclohexanecarboxylates. The difference is attributed to dipolar repulsions involving the axial ethoxycarbonyl group and the nitrogen lone pair. Using the hydrochlorides of the substituted pipecolic acids, measurements of the acidity of the ammonium group (pK_a^2) and the carboxy-group (pK_a^1) reveal a significant dependence upon conformation which may be rationalised in terms of hindrance to internal hydrogen bonding (' hydrogen chelation ').

FOR the *cis*- and *trans*-isomers of compounds such as the conjugate bases of the 4-substituted pipecolic (piperidine-2-carboxylic) acids (1) different relative conformational arrangements are available to the nitrogen lone pair and the carboxy-group. This implies that the acidity of pairs of isomers might differ and that they might also differ in chelating ability towards metal ions. The magnitude of these effects cannot easily be predicted and we have accordingly prepared compounds (1) and characterised the *cis*- and *trans*-isomers. As a prelude to a comparison of the chelating ability of the pipecolic acid derivatives we have measured the pK_a values associated with the ammonium ion of the conjugate acid (pK_a^2) and the carboxy-group of the neutral molecule (pK_a^1).

RESULTS AND DISCUSSION

Preparative Methods and Stereochemistry.—The substituted pipecolic acids and esters were prepared according to Scheme 1. Further details are given in the Experimental section.

For the compounds with R = Me and t-Bu hydrogenation of the acid over Adams catalyst at low temperature and atmospheric pressure gave, according to g.l.c. analysis of the ethyl esters on two columns, two isomeric ethyl pipecolates one of which predominated to the extent of 98%. Under these mild conditions a *cis*-configuration would be expected with both the alkyl and ethoxycarbonyl groups equatorial. At high temperatures and pressures, and in alkaline solution, hydrogenation over Raney nickel afforded a mixture of the isomeric ethyl pipecolates which was rich (*ca.* 70—75%) in the isomer predominating from low pressure hydrogenation. Under these alkaline, high temperature conditions epimerisation of the product would be expected and *trans*-stereochemistry can be assigned to the minor product.

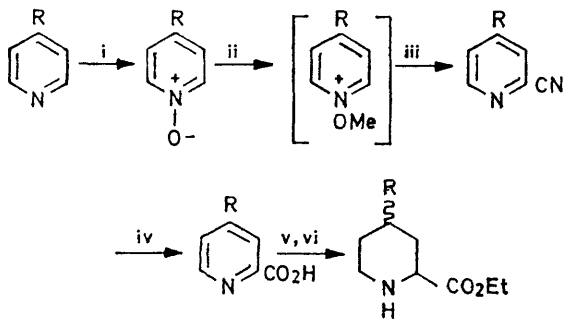
The n.m.r. spectra of the conformationally biassed

ethyl *cis*- and *trans*-4-t-butylpipecolates have features which confirm the conclusions concerning stereochemistry [Figure 1(a)]. The low field quartet (δ 3·78) is attributed to 2-H, and the absence of a large, diaxial coupling is consistent with the suggested *trans*-stereochemistry. First-order analysis of the splitting of this AMX quartet gives $J_{AX} = (J_{e,a}) = 5$ Hz and $J_{AM} = (J_{e,e}) = 2·5$ Hz. The two-proton multiplet (δ 2·95—2·65) is assigned to axial and equatorial 6-H. Using a computer of average transients (c.a.t.) (25 scans) the pair of quartets centred at δ 2·13, and attributed to 3eq-H, may be analysed in terms of a geminal coupling (13 Hz) and three fortuitously but plausibly equal couplings (2·5 Hz) involving 2eq-H, 4ax-H, and 5eq-H (which is in a planar W relationship with 3-H). Alternatively the pair of quartets may be attributed to 5eq-H with couplings of 2·5 Hz to the adjacent 4- and 6-H. The consistency of the above analysis strongly suggests that the stereochemistry of the isomer concerned is indeed *trans* and that the molecule is in the rigid chair conformation with the ethoxycarbonyl group axial.

An intriguing feature of the spectrum is the multiplicity of the signal due to the methylene protons of the ethoxycarbonyl group [δ 4·15, 16 lines using a c.a.t. (14 scans)]. The non-equivalence of the methylene protons may be the result of their proximity to the chiral centre at C-2 although this relationship is also present in the *cis*-isomer in which the methylene protons are equivalent according to the ^{1}H n.m.r. spectrum. An

a; $R^1 = R^2 = R^3 = H$
b; $R^1 = R^2 = H, R^3 = Me$
c; $R^1 = R^2 = H, R^3 = Bu^t$
d; $R^1 = R^3 = H, R^2 = Et$
e; $R^1 = R^2 = Et, R^3 = H$

(I)



i *cis*; ii *cis* and *trans*

SCHEME 1 Reagents: i, CH_3CO_3H; ii, Me_2SO_4; iii, KCN–H_2O, −5°; iv, 6N-HCl; v, H_2 (1 atm.)–PtO_2, 20° or H_2(150 atm.)–Ni–NaOH, 160°; vi, EtOH–H^+.

alternative suggestion, consistent with the ethoxycarbonyl group being in the hindered axial position, is that the rotation of the ester group is restricted by 1,3-diaxial interactions.

The ^{1}H n.m.r. spectrum [Figure 1(b)] of the *cis*-compound is not so amenable to first-order analysis.

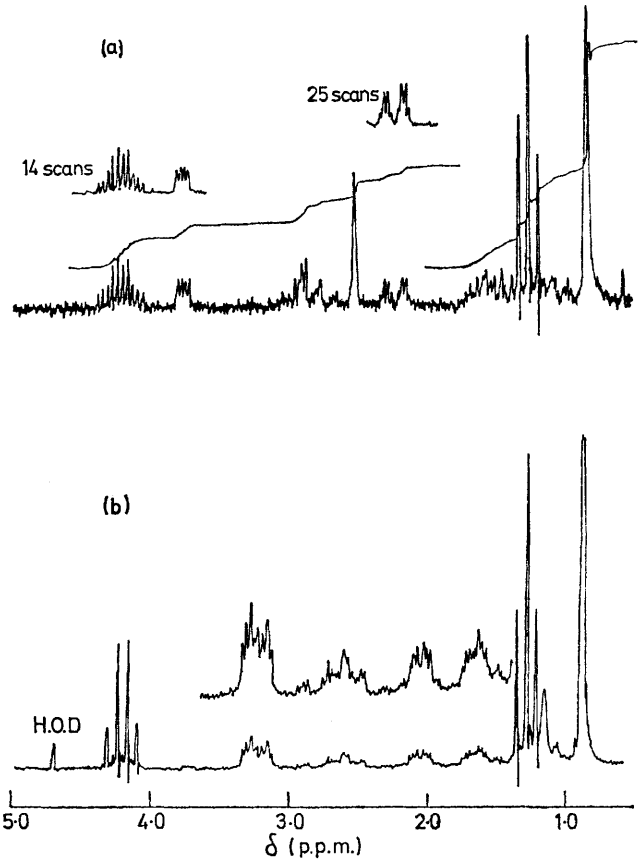


FIGURE 1 ^{1}H N.m.r. spectra (100 MHz) of (a) ethyl *trans*-4-t-butylpipecolate ($CDCl_3$) and (b) ethyl *cis*-4-t-butylpipecolate ($CDCl_3$–D_2O)

Signals attributable to 2ax- and 6eq-H overlap (δ 3·36—3·12). A multiplet (δ 2·78—2·45) may be assigned to 6ax-H.

Comparison of the ^{1}H n.m.r. spectra of the ethyl *cis*- and *trans*-4-methylpipecolates (Experimental section) is consistent with the less stable product, formed by epimerisation of the product of low pressure hydrogenation, being the *trans*-isomer, *i.e.* a flexible molecule giving rise at room temperature to a time-averaged spectrum.

Epimerisation Experiments.—Table 1 displays the results of g.l.c. analysis of isomeric mixtures following

TABLE 1

Epimerisation of substituted ethyl pipecolates

Compound	*cis* (%)	*trans* (%)	K_{351K}	$-\Delta G_{351K}$/ kJ mol^{-1}
Ethyl 4-methyl-pipecolate	68 ± 2	32 ± 2	0·47 ± 0·04	2·1 ± 0·4
Ethyl 4-t-butyl-pipecolate	75 ± 2	25 ± 2	0·33 ± 0·04	3·3 ± 0·4

epimerisation using sodium ethoxide in boiling ethanol. The equilibrium composition was independent of the configuration of the starting material.

An interesting feature of this system is that the conformational preference of the ethoxycarbonyl group is significantly lower than the value [1] (5·0 kJ mol^{-1}) most appropriate for the cyclohexane system. It is unlikely that the magnitude of 1,3-diaxial interactions would differ greatly between the piperidine and cyclohexane systems but consideration of the relevant conformations of the pipecolates (Figure 2) reveals an additional factor.

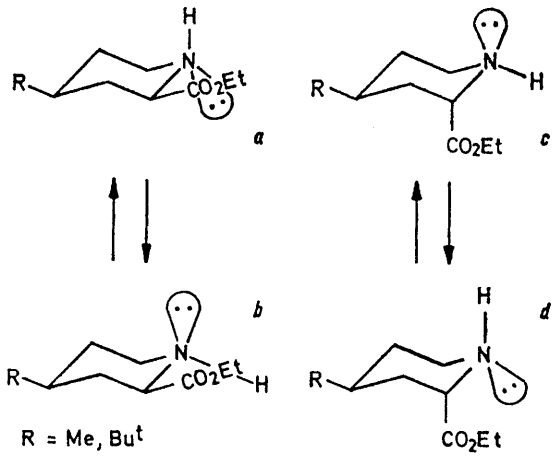
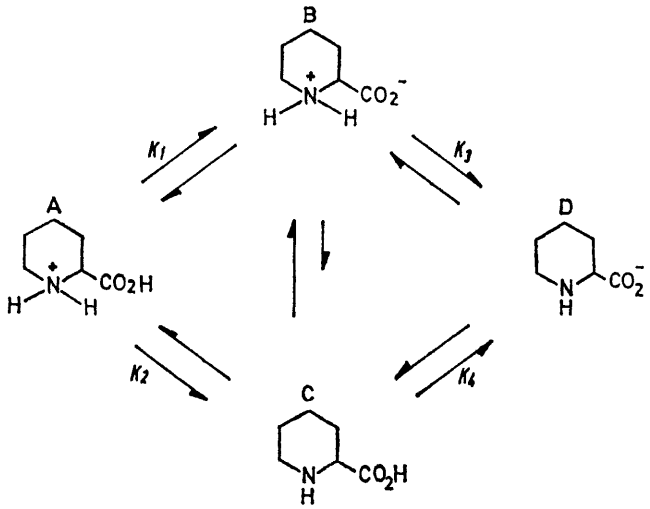


FIGURE 2



SCHEME 2

It is likely that the lone pairs associated with the ethoxycarbonyl group and the nitrogen atom are capable of a significant repulsive interaction of the sort responsible for the anomeric effect in nitrogen and oxygen heterocycles.[2] Consequently the conformation *c*, in which such repulsion is minimised, would be favoured and would explain the low conformational preference observed.

Acidity Measurements.—The substituted pipecolic acids will be involved in the ionisation process depicted in Scheme 2. The dissociation constants K_1—K_4 must be distinguished from the overall dissociation constants K_a^1 and K_a^2 which have been determined potentiometrically.

It is well established that for simple amino-acids [3] the neutral molecule is largely zwitterionic with [B] ≫ [C] by a factor of *ca.* 10^5. Consequently $K_1 \gg K_2$ and $K_4 \gg K_3$ resulting in $K_a^1 = K_1$ and $K_a^2 = K_3$ and in the ensuing discussion pK_a^1 refers to the ionisation of the carboxy-group and pK_a^2 refers to the ionisation of the ammonium ion. The measured pK_a values for the substituted pipecolic acids are given in Table 2.

TABLE 2

pK_a Values for substituted pipecolic acid hydrochlorides [a]

Acid	10^3 Concn. (mM)	pK_a^1	pK_a^2
Pipecolic	3·96	2·29	10·77
cis-4-Methylpipecolic	3·92	2·27	10·74
trans-4-Methylpipecolic	3·96	2·28	10·74
cis-4-t-Butylpipecolic	3·88	2·40	10·87
trans-4-t-Butylpipecolic	2·76	2·59	10·74
N-Ethylpipecolic	4·00	2·04	
NN-Diethylpipecolic	4·00	2·08	

[a] Measurements conducted in water at 20 ± 0·2° and judged accurate to ±0·02 pK units.

For the conformationally biassed 4-t-butyl acids there is a clear dependence on conformation of the acidity of both the carboxy and ammonium groups. In the *trans*-4-t-butyl compound (CO_2H axial), and relative to other members of the series, the acidity of the carboxy-function is diminished whereas that of the ammonium group is comparable. For the corresponding *cis*-isomer (CO_2H equatorial) the acidity of the carboxy-group is diminished somewhat but is still comparable with that of other members in the series whereas the ammonium group is less acidic.

The conformational dependence of proton ionisation constants is often rationalised in terms of steric hindrance to solvation of the ions, *i.e.* diminished solvation of a carboxylate anion causing the carboxy-function to be less acidic [4] and decreased solvation of the ammonium ion enhancing its acidity.[4a,5] This would explain the conformational dependence of pK_a^1 but the pK_a^2 values suggest for the *cis*-4-t-butyl derivative an unreasonable enhancement of solvation of the ammonium ion.

Intramolecular hydrogen bonding, which for the pipecolic acids may be viewed [6] as 'hydrogen chelation,' provides a satisfactory rationalisation of the effects on pK_a^1 and pK_a^2. The zwitterionic forms of the *cis*- and *trans*-4-t-butyl derivatives may be viewed as shown in Figure 3. In both cases internal hydrogen bonding results in the formation of five-membered, 'hydrogen chelate' rings but because of 1,3-diaxial interactions the conformation involving an axial carboxylate group will

[1] J. A. Hirsch 'Topics in Stereochemistry' eds. N. L. Allinger and E. L. Eliel, Wiley, New York, vol. 1, 1967.
[2] E. L. Eliel, *Accounts Chem. Res.*, 1970, **3**, 1.
[3] J. T. Edsall and M. H. Blanchard, *J. Amer. Chem. Soc.*, 1933, **55**, 2337.
[4] (*a*) M. Tichý, J. Jonás, and J. Sicher, *Coll. Czech. Chem. Comm.*, 1959, **24**, 3434; (*b*) R. D. Stolow, *J. Amer. Chem. Soc.*, 1959, **81**, 5806.
[5] C. W. Bird and R. C. Cookson, *J. Chem. Soc.*, 1960, 2343.
[6] Z. Foldi, R. Foldi, and S. Foldi, *Acta Chim. Acad. Sci. Hung.*, 1957, **11**, 339; *Chem. and Ind.*, 1957, 465.

be the less stable. This favouring of the equatorial ring therefore rationalises the enhanced ionisation of the equatorial carboxylic acid group and the stabilised ammonium ion in the *cis*-isomer. Apparently the rigidity imposed by t-butyl substitution enhances this effect.

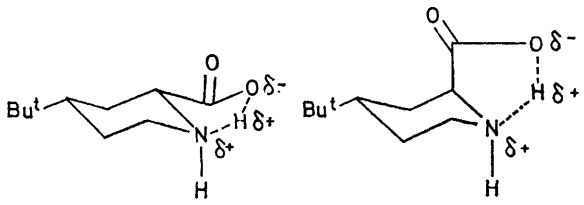


FIGURE 3

The similarity of both pK_a^1 and pK_a^2 for the other members of the pipecolic acid series suggests that in all the acidity of the carboxylic acid group (lower pK_a^1). This is contrary to the expected inductive effect of alkyl groups and possibly a result of decreased dispersal of positive charge through hydrogen bonding to solvent molecules.[8] A similar effect can be observed following *N*-ethyl substitution in pipecolic acid although the addition of a second ethyl group does not cause a further decrease in pK_a^1.

EXPERIMENTAL

Materials.—The 4-alkylpyridines, 4-alkylpyridine 1-oxides, and 3-cyano-4-alkylpyridines were made according to Scheme 1 using minor adaptations of reported methods.[9] The yields obtained, and data supporting the characterisation of new compounds are contained in Table 3.

Recrystallisation of the acids from alcoholic solvents proved to be very difficult and in consequence the ethyl esters were used for purposes of characterisation. The acids were subsequently obtained by hydrolysis of the esters and handled as their hydrochlorides which were recrystallised to constant m.p. from ethanol or methanol. Accurate titrimetric determination of the equivalent weight of the hydrochlorides proved to be a suitable check of purity (Table 4).

TABLE 3

Characterisation of intermediates prepared according to Scheme 1

Compound	Method of preparation (see Scheme 1)	Yield (%)	M.p. or (b.p.) (°C)	^{1}H N.m.r. data [a]	Mass of molecular ion
4-Methylpyridine-1-oxide	i	87	183—184 (lit.,[9b] 185)		
4-t-Butylpyridine-1-oxide	i	93	104—105	δ($CDCl_3$) 8·14 (2H, d, *J* 7·5 Hz), 7·26 (2H, d, *J* 7·5 Hz), 1·34 (9H, s)	151·0997 ($C_9H_{13}NO$ requires 151·0990)
2-Cyano-4-methylpyridine	iii	60	88—89 (lit.,[9d] 89)		
2-Cyano-4-t-butylpyridine	iii	46	(94 at 0·3 mmHg)	δ($CDCl_3$) 8·63 (1H, d, *J* 5 Hz), 7·74 (1H, q, *J* 0·9 Hz), 7·57 (1H, d, *J* 5 Hz), 1·34 (9H s)	160·0998 ($C_{10}H_{12}N_2$ requires 160·1000)
4-Methylpicolinic acid	iv	70	134—135 (lit.,[9d] 136)		
4-t-Butylpicolinic acid acid	iv	73	78—79	δ(CF_3CO_2D) 8·60 (1H, d, *J* 6·5 Hz), 8·49 (1H, d, *J* 1·5 Hz), 8·08 (1H, m), 1·29 (9H, s)	179·0944 ($C_{10}H_{18}NO_2$ requires 179·0946)
Ethyl *cis*-4-methylpipecolate	v, Raney nickel	38 [b]	(88 at 4 mmHg)	δ($CDCl_3$) 4·18 (2H, q, *J* 7 Hz), 3·45—3·18 (1H, m), 3·18—2·99 (1H, q, *J* 1·2 Hz), 2·88—2·37 (1H, m), 2·2—1·1 (6H, m), 1·28 (3H, t, 7 Hz), 0·95 (3H, d, *J* 5·5 Hz)	171·1260 ($C_9H_{17}NO_2$ requires 171·1259)
Ethyl *trans*-4-methylpipecolate	v, Raney nickel	38 [b]	(125 at 5 mmHg)	δ($CDCl_3$) [d] 4·19 (2H, d, *J* 7 Hz), 3·73—3·51 (1H, m), 2·29—2·74 (2H, q, *J* 1·3 Hz), 2·28—1·98 (2H, m), 1·8—1·0 (4H, m), 1·28 (3H, t, *J* 7 Hz), 0·94 (3H, d, *J* 5·5 Hz)	171·1255
Ethyl *cis*-4-t-butylpipecolate	v, Raney nickel	45 [b]	(104 at 1·3 mmHg)	δ($CDCl_3$) [d] 4·14 (2H, q, *J* 7 Hz), 3·39—3·14 (2H, m), 2·28—2·45 (1H, m), 2·22—1·82 (2H, m), 1·82—1·48 (1H, m), 1·42—1·02 (6H, m), 0·95 (9H, s)	213·1725 ($C_{12}H_{23}NO_2$ requires 213·1729)
Ethyl *trans*-4-t-butylpipecolate	v, Raney nickel	45 [b]	(140 at 1·0 mmHg)	δ($CDCl_3$) [d] 4·38—4·08 (2H, m), 3·82—3·73 (1H, q), 3·02—2·60 (2H, m), 2·53 (1H, m), 2·37—2·13 (1H, m), 1·79—0·95 (7H, m), 0·91 (9H, s)	213·1724

[a] Measured at 60 MHz unless stated otherwise. [b] Yield of mixture of isomers. [c] Hot-box temperature for short-path distillation. [d] At 100 MHz.

three compounds the carboxylate function is predominantly equatorial. An implication is that both the hydrochloride and zwitterion of *trans*-4-methylpipecolic acid, exist as mixtures of conformations in which those with an axial methyl group predominate.

Alkyl group substitution at the nitrogen atom of amino-acids is known [7] from the glycine series to enhance

[7] F. Basolo and Y. T. Chen, *J. Amer. Chem. Soc.*, 1954, **76**, 953.

[8] M. Brickman, J. H. P. Utley, and J. H. Ridd, *J. Chem. Soc.*, 1965, 6851.

[9] (*a*) H. C. Brown and J. Murphy, *J. Amer. Chem. Soc.*, 1951, **73**, 2308; (*b*) *Org. Synth.*, 1953, **33**, 79; (*c*) *ibid.*, 1962, **42**, 30; (*d*) F. R. Case and T. J. Kasper, *J. Amer. Chem. Soc.*, 1956, **78**, 5842.

Epimerisation Experiments.—Potassium metal (*ca.* 0·05 g) was dissolved in dry ethanol (15 ml). The ester (0·1 mM) was added to the mixture which was heated under reflux.

TABLE 4

Substituted pipecolic acid hydrochlorides

Acid hydrochloride	M.p. (°C with decomp.)	Purity by titration (%)
Pipecolic	260—262 (lit., 263) [a]	99
cis-4-Methylpipecolic	252—253	98
trans-4-Methylpipecolic	233—236	99
cis-4-t-Butylpipecolic	308—311	97
trans-4-t-Butylpipecolic	296—299	96
N-Ethylpipecolic	205—207	98
NN-Diethylpipecolic	203—205	99

[a] E. B. Maxted and A. P. Walker, *J. Chem. Soc.*, 1948, 1093.

Small samples (2 ml) were withdrawn after 1, 3, and 21 days and worked-up separately as follows.

Ethanol was evaporated carefully at reduced pressure and the residue was dissolved in diethyl ether (50 ml), then washed with water (2 ml), and dried (K_2CO_3). G.l.c. analysis of the samples was carried out using a Perkin-Elmer F.11 instrument (column, 20% Carbowax on Chromosorb W).

The experiments were conducted starting with pure *cis*-esters and also mixtures of the isomers. Each experiment was carried out in duplicate.

Acidity Measurements.—The standard [10] potentiometric titration method was used in the following manner.

A small sample of the amino-acid hydrochloride was dried over phosphorus pentoxide in a desiccator for 18 h. A quantity (0·25 mmol) was weighed out accurately into a pre-calibrated volumetric flask. This was made up to 10·0 ml with water which had previously been distilled from alkaline permanganate under nitrogen. An aliquot portion of the stock solution was transferred in a pre-calibrated pipette to a titration vessel. Pure water (3·00 or 4·00 ml) was added. The vessel was thermostatically controlled, using a water jacket, to $\pm 0{\cdot}2$ °C of the required temperature and was equipped with a small magnetic stirrer and a nitrogen inlet and outlet. The nitrogen had previously been bubbled through a purification train to remove oxygen and carbon dioxide and then saturated with water. The vessel also contained a combination glass–calomel electrode and a polystyrene delivery tube from an 'Agla' micrometer syringe which contained aqueous carbonate-free sodium hydroxide (0·200N).

The titrant was added in equal portions (0·200 ml) and the pH was recorded after each delivery using a Beckmann Research pH meter (model 101900).

Standardisation against the potassium hydrogen tartrate buffer solution was checked immediately after titration. If the pH differed by more than 0·01 from the start to finish of a titration the result was rejected. Also rejected were experiments which did not give eight or more pK_a values falling within a range of 0·06.

We gratefully acknowledge the receipt of a grant from the United Kingdom Atomic Energy Authority both for maintenance (D. E. C.) and running costs. We are also grateful to Mr. K. T. B. Scott, Mr. J. Grimes, and Dr. P. Ball of the U.K.A.E.A. for helpful discussions.

[2/2831 *Received*, 18*th December*, 1972]

[10] A. Albert and E. P. Serjeant, 'Ionisation Constants of Acids and Bases,' Methuen, London, 1962.