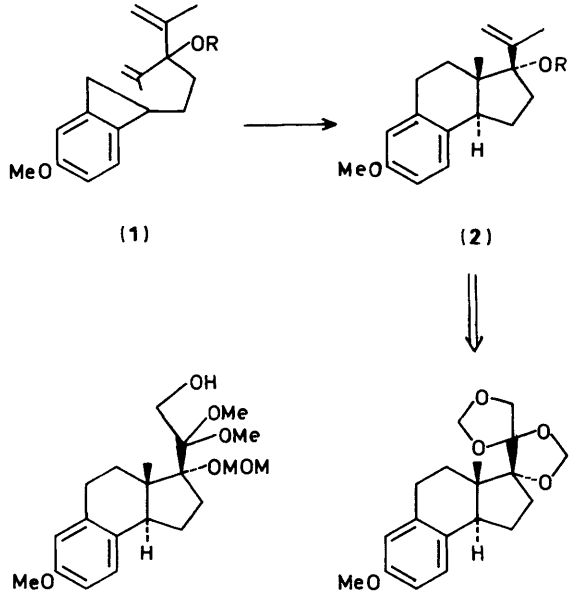
A Novel Route to the Des-*A* Corticosteroids

Hideo Nemoto, Mari Moizumi, Mitsuo Nagai, and Keiichiro Fukumoto *
Pharmaceutical Institute, Tohoku University, Aobayama, Sendai 980, Japan
Tetsuji Kametani
Institute of Medicinal Chemistry, Hoshi University, Ebara 2-4-41, Shinagawa-ku, Tokyo 142, Japan

A novel and efficient synthesis of *trans*-2,3,3a,4,5,9b-hexahydro-3α-hydroxy-3β-(2-hydroxyacetyl)-7-methoxy-3aβ-methyl-1*H*-benz[*e*]indene (**10**) starting from *trans*-2,3,3a,4,5,9b-hexahydro-3β-isopropenyl-7-methoxy-3α-methoxymethoxy-3aβ-methyl-1*H*-benz[*e*]indene (**5**) and its conversion into 2′,2′,3a-trimethyl-7-oxo-2,3,3a,4,5,6,7,8,9,9b-decahydro-1*H*-benz[*e*]indene-3-spiro-4′-(1,3-dioxan)-5′-yl acetate (**14**) are described.

Many studies [1] have sought to introduce dihydroxyacetone and oxygen substituents at the C-17 and C-11 positions of steroids because of their important physiological activity.[2] Further, systems lacking the usual tetracyclic steroid structure (*e.g.*, 16,17-secosteroids or compounds without either ring D or A of the steroid nucleus) have recently attracted much attention because of their hormonal or antihormonal activities.[3]

During synthetic studies of des-*A* *B*-trienic steroids *via* intramolecular cycloadditions, we have focussed on the stereoselective synthesis of des-*A* *B*-aromatic steroids with suitable masking of the dihydroxyacetone side-chain at C-17 position [1a] (steroid numbering), because of its synthetic flexibility in constructing ring A and introducing functional groups at C-9 and C-11 positions. Earlier,[1a] we developed an efficient route to the tricyclic isopropenyl alcohol (**2**) by thermolysis of the di-isopropenylbenzocyclobutenes (**1**), and converted it into the des-*A* *B*-trienic steroids (**3**) and (**4**) with masked dihydroxyacetone side-chains; the latter transformation was, however, less than satisfactory (Scheme 1). Here we report



Scheme 1.

an efficient way for converting the tricyclic methoxymethyl ether (**5**) into the dioxanone derivative (**11**) and also into the oxo acetate (**14**).

Epoxidation of the tricyclic methoxymethyl ether (**5**) [1a,†] was effected by treatment with *m*-chloroperbenzoic acid (MCPBA) in the presence of potassium fluoride and sodium fluoride in CH_2Cl_2 under modified Camps' conditions [5] to give the epoxide (**6**) [*m/z* 332 (M^+)] (69% yield), which was then subjected to base-catalysed epoxide ring-opening by lithium diethylamide in ether to afford the allyl alcohol (**7**) [*m/z* 332 (M^+)] (99% yield). The acetate (**8**) [*m/z* 374 (M^+)] (82% yield) formed by acetylation of the allyl alcohol (**7**) was then converted into the ketone (**9**) [*m/z* 376 (M^+)] (56% overall yield) by successive treatment with *N*-methylmorphorine *N*-oxide (NMO) in the presence of a catalytic amount of osmium tetraoxide in aqueous tetrahydrofuran (THF)–t-butyl alcohol followed by periodic acid in THF–ether. Direct deprotection of both hydroxy groups in compound (**9**) was achieved by treatment with camphorsulphonic acid (CSA) in boiling aqueous THF to give the dihydroxy ketone (**10**) (75% yield) which was identical with an authentic sample [1a] (i.r., n.m.r., and mixed m.p.).

Next, the dioxanone (**11**) (73% yield), prepared by a standard method using 2-methoxypropene in the presence of a catalytic amount of CSA in CH_2Cl_2, was reduced with sodium borohydride to give the alcohol (**12**) [*m/z* 332 (M^+)] (94% yield) as a diastereoisomeric mixture at C-20 (steroid numbering) position. Successive treatment of the alcohol (**12**) with lithium in liquid ammonia and acetic anhydride in pyridine afforded the acetate (**13**) (60% overall yield). Finally, the acetate (**13**) was converted into the oxo acetate (**14**) [*m/z* 362 (M^+)] (40% yield) by the selective hydrolysis of the enol ether group using pyridinium toluene-*p*-sulphonate as a catalyst in wet acetone (Scheme 2).

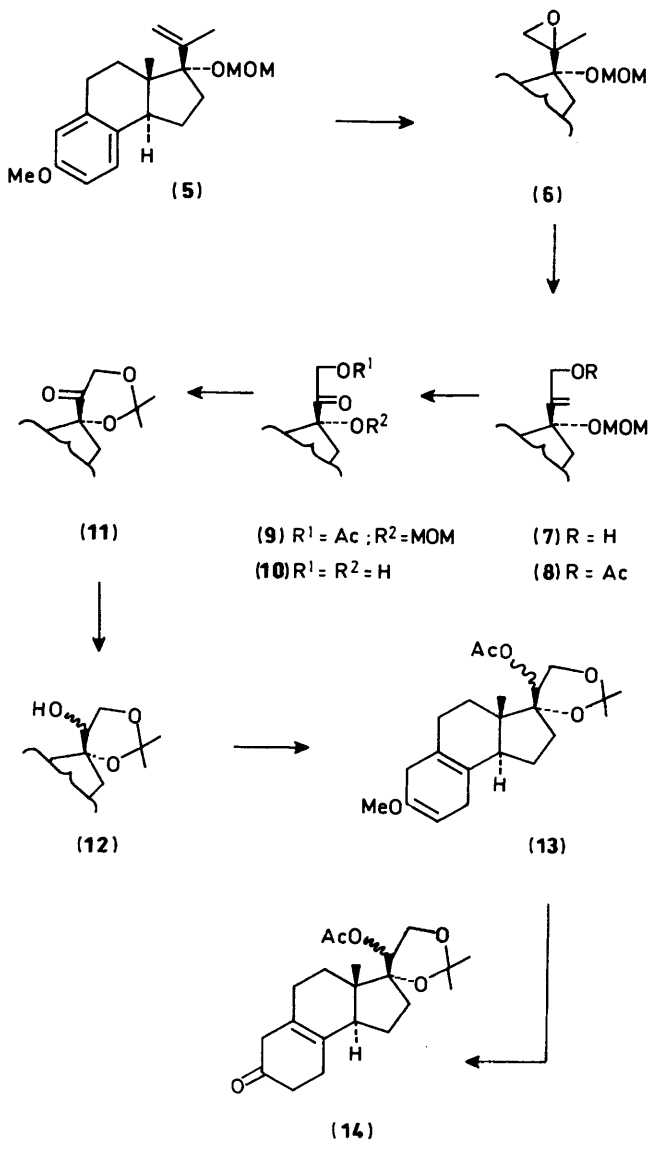
Thus, we have achieved an efficient route to the des-*A* steroids (with a masked dihydroxyacetone side-chain) which could be potential intermediates in the synthesis of corticosteroids.

Experimental

General Methods.—All m.p.s were uncorrected. I.r. spectra were recorded on a Hitachi 260-10 spectrophotometer. N.m.r. spectra were measured on JEOL-PMX-60 and JEOL-PS-100 spectrometer. Chemical shifts were reported as δ values relative to internal tetramethylsilane (Me_4Si). Mass spectra were taken on Hitachi M-52G and JEOL-JMX-01SG-2 spectrometers.

trans-3β-(1,2-*Epoxy*-2-*methylpropyl*)-2,3,3a,4,5,9b-*hexahydro*-7-*methoxy*-3α-*methoxymethoxy*-3aβ-*methyl*-1H-*benz*[e]*indene* (**6**).—KF (400 mg, 6.88 mmol) and NaF (1.2 g, 25.58 mmol) were added to a stirred solution of MCPBA (800 mg,

† All compounds reported in this paper are racemic. For convenience only one enantiomer is shown.



Scheme 2.

3.16 mmol) in CH_2Cl_2 (10 ml) at room temperature. After 1 h, a solution of the tricyclic methoxymethyl ether (**5**)[1a] (79 mg, 0.25 mmol) in CH_2Cl_2 (10 ml) was added to this stirred solution and the reaction mixture was stirred for 12 h at the same temperature. After addition of KF (1.2 g, 28.58 mmol), stirring was continued for 20 h after which the reaction mixture was filtered through Celite (1 g). The filtrate was evaporated to yield a residue which was chromatographed on silica gel (1 g) using hexane–ethyl acetate (94:6 v/v) as eluant to afford the *epoxide* (**6**) (57 mg, 69%) as an oil (Found: C, 71.95; H, 8.4. $C_{20}H_{28}O_4$ requires C, 72.25; H, 8.5%); δ(CCl_4) 0.50 (3 H, s, 7a-Me), 1.33 (3 H, s, CH_2OCMe), 2.66—2.83 (2 H, m, CH_2OC), 3.33 (3 H, s, OCH_2OMe), 3.70 (3 H, s, ArO*Me*), 4.63 and 5.05 (2 H, each d, *J* 7 Hz, OCH_2O), and 6.60—7.00 (3 H, m, ArH); *m/z* 332 (M^+).

trans-3β-(1-*Hydroxymethylvinyl*)-2,3,3a,4,5,9b-*hexahydro*-7-*methoxy*-3α-*methoxymethoxy*-3aβ-*methyl*-1H-*benz*[e]*indene* (**7**).—A solution of the epoxide (**6**) (457 mg, 1.4 mmol) in ether (26 ml) was added dropwise to a stirred solution of $LiNEt_2$ [prepared from butyl-lithium (1.56M in hexane; 2.84 ml) and diethylamine (0.5 ml, 5 mmol) in ether (26 ml)] at 0 °C. After refluxing for 5 h, the reaction mixture was diluted with water (50 ml) and extracted with ether. The extract was washed with saturated brine, dried ($MgSO_4$), and evaporated to yield a residue which was chromatographed on silica gel (10 g) using hexane–ethyl acetate (1:1 v/v) as eluant to afford the *allyl alcohol* (**7**) (452 mg, 99%) as colourless needles, m.p. 100.5—101.5 °C (from ether) (Found: C, 72.0; H, 8.55. $C_{20}H_{28}O_4$ requires C, 72.25; H, 8.5%); $\nu_{max.}$($CHCl_3$) 3 400 (OH) cm^{-1}; δ($CDCl_3$) 0.42 (3 H, s, 7a-Me), 3.36 (3 H, s, CH_2OMe), 3.76 (3 H, s, ArO*Me*), 4.08 and 4.28 (2 H, each d, *J* 13 Hz, CH_2OH), 4.60 and 5.55 (2 H, each br s, $=CH_2$), and 6.60—7.00 (3 H, m, ArH); *m/z* 332 (M^+).

trans-3β-(1-*Acetoxymethylvinyl*)-2,3,3a,4,5,9b-*hexahydro*-7-*methoxy*-3α-*methoxymethoxy*-3aβ-*methyl*-1H-*benz*[e]*indene* (**8**).—Acetic anhydride (0.3 ml, 2.6 mmol) was added to a stirred solution of the allyl alcohol (**7**) (175 mg, 0.5 mmol) in pyridine (0.5 ml) at 0 °C and the resulting mixture was stirred for 1 h at room temperature. The reaction mixture was then diluted with ether (10 ml) and washed successively with water, 10% hydrochloric acid, saturated aqueous sodium hydrogen carbonate, and saturated brine. The organic layer was dried (Na_2SO_4) and evaporated to yield the residue which was chromatographed on silica gel (5 g) using hexane–ethyl acetate (4:1 v/v) as eluant to give the *acetate* (**8**) (65 mg, 82%) as an oil (Found: C, 70.45; H, 8.15. $C_{22}H_{30}O_5$ requires C, 70.55; H, 8.1%); $\nu_{max.}$($CHCl_3$) 1 730 (C=O) cm^{-1}; δ($CDCl_3$) 0.48 (3 H, s, 7a-Me), 2.10 (3 H, s, MeCO), 3.36 (3 H, s, CH_2OMe), 3.76 (3 H, s, ArO*Me*), 4.53 and 4.73 (2 H, each d, *J* 13 Hz, OCH_2O), 4.62 (2 H, br s, CH_2OAc), and 6.60—7.00 (3 H, m, ArH); *m/z* 374 (M^+).

trans-3β-(2-*Acetoxyacetyl*)-2,3,3a,4,5,9b-*hexahydro*-7-*methoxy*-3α-*methoxymethoxy*-3aβ-*methyl*-1H-*benz*[e]*indene* (**9**).—A catalytic amount of OsO_4 and NMO (603 mg, 4.5 mmol) were added to a stirred solution of the acetate (**8**) (441 mg, 1.2 mmol) in a mixture of water (1 ml), THF (3 ml), and Bu^{t}OH (10 ml) at room temperature. After 12 h, NMO (603 mg, 4.5 mmol) was added and stirring was continued for 60 h at the same temperature. The reaction mixture was then diluted with water and sodium hydrogen sulphite, filtered through Celite (1 g), and the filtrate was extracted with ethyl acetate. The extract was washed with saturated brine, dried ($MgSO_4$), and evaporated to yield a residue which was dissolved in THF–ether (2:1; 30 ml) and treated with $HIO_4 \cdot 2H_2O$ (1.02 g, 4.5 mmol). After being stirred for 1 h at room temperature, the reaction mixture was diluted with water (30 ml) and extracted with ether. The extract was washed successively with saturated aqueous sodium hydrogen carbonate, water, and saturated brine, dried ($MgSO_4$), and evaporated to yield a residue which was chromatographed on silica gel (10 g) using hexane–ethyl acetate (95:5 v/v) as eluant to give the *ketone* (**9**) (247 mg, 56%) as colourless needles, m.p. 121—122 °C (from ether) (Found: C, 66.95; H, 7.35. $C_{21}H_{28}O_6$ requires C, 67.0; H, 7.5%); $\nu_{max.}$($CHCl_3$) 1 730 (C=O) cm^{-1}; δ($CDCl_3$) 0.50 (3 H, s, 7a-Me), 2.15 (3 H, s, MeCO), 3.38 (3 H, s, CH_2OMe), 3.75 (3 H, s, ArO*Me*), 4.72 (2 H, br s, OCH_2O), 4.82 and 5.05 (2 H, each d, *J* 16.8 Hz, CH_2OAc), and 6.60—7.00 (3 H, m, ArH); *m/z* 376 (M^+).

trans-2,3,3a,4,5,9b-*Hexahydro*-3α-*hydroxy*-3β-(2-*hydroxyacetyl*)-7-*methoxy*-3aβ-*methyl*-1H-*benz*[e]*indene* (**10**).—A stirred solution of the ketone (**9**) (307 mg, 0.8 mmol) and CSA (207 mg, 0.89 mmol) in a mixture of THF (10 ml) and water (10 ml) was refluxed for 72 h. The reaction mixture was then diluted with water (20 ml) and extracted with ether. The extract was washed with saturated sodium hydrogen carbonate, water, and saturated brine, dried (Na_2SO_4), and evaporated to yield a residue which was chromatographed on silica gel (5 g) using

hexane–ethyl acetate (4:1 v/v) as eluant to give the ketone (**10**) (177 mg, 75%) as needles (from ether), m.p. 139—140 °C. This was identical with the authentic sample[1a] in its i.r. ($CHCl_3$), and n.m.r. ($CDCl_3$), and mixed m.p.

7-*Methoxy*-2′,2′,3a-*trimethyl*-2,3,3a,4,5,9b-*hexahydro*-1H-*benz*[e]*indene*-3-*spiro*-4′-(1,3-*dioxan*)-5′-*one* (**11**).—A catalytic amount of CSA was added to a stirred solution of the ketone (**10**) (249 mg, 0.86 mmol) and 2-methoxypropene (0.13 ml, 1.29 mmol) in CH_2Cl_2 (25 ml) at 0 °C and stirring was continued for 20 min at the same temperature. The reaction mixture was then diluted with chloroform (30 ml), washed with saturated aqueous sodium hydrogen carbonate, dried (Na_2SO_4), and evaporated to yield a residue which was chromatographed on silica gel (5 g) using hexane–ethyl acetate (9:1 v/v) as eluant to give the *dioxanone* (**11**) (206 mg, 73%) as a glass; $\nu_{max.}$($CHCl_3$) 1 715 (C=O) cm^{-1}; δ($CDCl_3$) 0.50 (3 H, s, 7a-Me), 1.50 and 1.55 (6 H, each s, CMe_2), 3.73 (3 H, s, ArO*Me*), 4.08 and 4.36 (2 H, each d, *J* 19.6 Hz, OCH_2CO), and 6.50—7.00 (3 H, m, ArH); *m/z* 330 (M^+) (Found: M^+, 330.1826. $C_{20}H_{26}O_4$ requires *M*, 330.1830).

7-*Methoxy*-2′,2′,3a-*trimethyl*-2,3,3a,4,5,9b-*hexahydro*-1H-*benz*[e]*indene*-3-*spiro*-4′-(1,3-*dioxan*)-5′-*ol* (**12**).—$NaBH_4$ (47.2 mg, 1.25 mmol) was added portionwise to a stirred solution of the dioxanone (**11**) (206 mg, 0.62 mmol) in a mixture of MeOH (15 ml) and THF (8 ml) at 0 °C and stirring was continued for 1 h at the same temperature. After evaporation of the solvent, the residue was diluted with ethyl acetate (50 ml), washed with water, dried ($MgSO_4$), and evaporated to yield a residue which was chromatographed on silica gel (5 g) using hexane–ethyl acetate (8:1 v/v) as eluant to give the *alcohol* (**12**) (196 mg, 94%) as an oil (Found: C, 72.75; H, 8.75. $C_{20}H_{28}O_4$ requires C, 72.25; H, 8.5%); $\nu_{max.}$($CHCl_3$) 3 550 (OH) cm^{-1}; δ($CDCl_3$) 0.64 and 0.69 (3 H, each s, 7a-Me), 1.25 and 1.31 (3 H, each s, CMe), 1.46 and 1.52 (3 H, each s, CMe), 3.76 (3 H, s, ArO*Me*), and 7.00—6.50 (3 H, m, ArH); *m/z* 332 (M^+).

2′,2′,3a-*Trimethyl*-7-*oxo*-2,3,3a,4,5,6,7,8,9,9b-*decahydro*-1H-*benz*[e]*indene*-3-*spiro*-4′-(1,3-*dioxan*)-5′-*yl Acetate* (**14**).—Li (4.5 mg, 0.65 mmol) was added to a stirred solution of the alcohol (**12**) (43 mg, 0.13 mmol) in a mixture of THF (4 ml), EtOH (0.6 ml), and liquid ammonia (30 ml) at −78 °C and stirring was continued for 30 min at the same temperature. After addition of EtOH (2 ml), liquid ammonia was evaporated off to yield a residue which was diluted with water (10 ml) and extracted with ether. The extract was washed with saturated brine, dried (Na_2SO_4), and evaporated to yield a residue which was dissolved in pyridine (0.5 ml). Acetic anhydride (0.06 ml, 0.65 mmol) was then added to this solution at room temperature. After being stirred for 3 h at the same temperature, the reaction mixture was diluted with water (5 ml) and extracted with ether. The extract was washed successively with saturated aqueous sodium hydrogen carbonate, saturated aqueous copper(II) sulphate, water, and saturated brine, dried (Na_2SO_4), and evaporated to yield a residue which was chromatographed on silica gel (1 g) using hexane–ethyl acetate (95:5 v/v) as eluant to afford the acetate (**13**) (29.2 mg, 60%) as an oil; $\nu_{max.}$($CHCl_3$) 1 730 (C=O) cm^{-1}; δ(CCl_4) 0.63 (3 H, s, 3a-Me), 1.27 and 1.47 (6 H, s, each s, CMe_2), 2.00 (3 H, s, COMe), 3.50 (3 H, s, OMe), 4.50 (1 H, m, C*H*OAc), and 4.90 (1 H, t, *J* 1.5 Hz, =CH).

A solution of the acetate (**13**) (16 mg, 0.04 mmol) and a catalytic amount of pyridinium toluene-*p*-sulphonate in wet acetone (2 ml) was stirred for 9 h at room temperature. The reaction mixture was then treated with sodium hydrogen carbonate (30 mg) and evaporated to yield a residue. This was diluted with ether, washed with water, dried (Na_2SO_4), and evaporated, and the residue chromatographed on silica gel (0.5 g) using hexane–ethyl acetate (9:1 v/v) as eluant to give the *oxo acetate* (**14**) (4.8 mg, 40%) as an oil; $\nu_{max.}$($CHCl_3$) 1 730 (C=O) and 1 710 (C=O) cm^{-1}; δ($CDCl_3$) 0.63 (3 H, s, 3a-Me), 1.31 and 1.52 (6 H, each s, CMe_2), 2.07 (3 H, s, MeCO), 2.72 (2 H, br s, C_6H_2), 3.59 (1 H, dd, *J* 11.3 and 5.8 Hz, CH*H*O) 3.95 (1 H, dd, *J* 11.3 and 4.9 Hz, CH*H*O), and 5.02 (1 H, dd, *J* 5.8 and 4.9 Hz, C*H*OAc); *m/z* 362 (M^+) (Found: M^+, 362.2096. $C_{21}H_{30}O_5$ requires *M*, 362.2092).

Acknowledgements

We thank Miss K. Mushiake, Miss K. Koike, Mrs. E. Niwa, and Mrs. H. Nagai of this Institute for microanalyses and spectral measurements.

References

1 (*a*) H. Nemoto, M. Nagai, Y. Abe, M. Moizumi, K. Fukumoto, and T. Kametani, *J. Chem. Soc., Perkin Trans. 1*, 1987, 1727 and references cited herein; see also (*b*) M. A. Khalil, J. C. Lay, and H. J. Lee, *J. Pharm. Sci.*, 1985, **74**, 180; (*c*) R. M. Moriarty, O. Prakash, and M. P. Duncan, *Synthesis*, 1985, 943; (*d*) A. M. Turuta, A. V. Kamernitzky, T. M. Fadeeva, and A. V. Zhulin, *ibid.*, 1985, 1229; (*e*) Y. Tamura, T. Yakura, J. Haruta, and Y. Kita, *Tetrahedron Lett.*, 1985, **26**, 3837; (*f*) M. Fetizon, P. Goulaouic, and I. Hanna, *ibid.*, 1985, **26**, 4925; (*g*) I. Nitta, S. Fujimori, and H. Ueno, *Bull. Chem. Soc. Jpn.*, 1985, **58**, 978; (*h*) I. Nitta, S. Fujimori, T. Haruyama, S. Inoue, and H. Ueno, *ibid.*, 1985, **58**, 981; (*i*) I. Nitta, T. Haruyama, S. Fujimori, S. Inoue, and H. Ueno, *ibid.*, 1985, **58**, 1081; (*j*) Y. Horiguchi, E. Nakamura, and I. Kuwajima, *J. Org. Chem.*, 1986, **51**, 4323.

2 M. H. Griggs and J. Brotherton, 'Steroid Biochemistry and Pharmacology,' Academic Press, New York, 1970.

3 (*a*) L. O. Randall and J. J. Selitto, *Endocrinology*, 1958, **62**, 693; (*b*) A. Boris and R. H. Stevens, *ibid.*, 1966, **78**, 549; (*c*) G. Znati and M. E. Wolff, *J. Med. Chem.*, 1973, **16**, 90; (*d*) H. Morales-Alanis, M.-J. Brienne, J. Jacques, M.-M. Bouton, L. Nédélec, V. Torelli, and C. Tournemine, *ibid.*, 1985, **28**, 1796.

5 F. Camps, J. Coll, A. Messeguer, and F. Pujol, *Chem. Lett.*, 1983, 971.

Received 21*st April* 1987; *Paper* 7/703