Steroid Analogues. Part 5.[1] Synthesis of Δ^9-6,7-Dinor-5,8-seco-steroids *via* Δ^3-1,3,4-Thiadiazolines †

By **David J. Humphreys,* Christopher E. Newall, Gordon H. Phillipps,** and **Gerald A. Smith,** Organic Chemistry Department, Glaxo Research Ltd., Greenford, Middlesex UB6 0HE

A general synthesis of symmetrical bi(cycloalkylidene)s is reported, involving successive reaction of an azine with hydrogen sulphide to give a 1,3,4-thiadiazolidine, oxidation to a Δ^3-1,3,4-thiadiazoline, pyrolysis to a thiiran, and desulphurisation. The stereochemistry of the products and intermediates was elucidated by ^{1}H n.m.r. spectroscopy with reference to the Woodward–Hoffmann rules and to conformation theory. The intermediate thiadiazolidines may also be prepared by direct condensation of a cycloalkanone with hydrazine and hydrogen sulphide, with different stereochemical consequences.

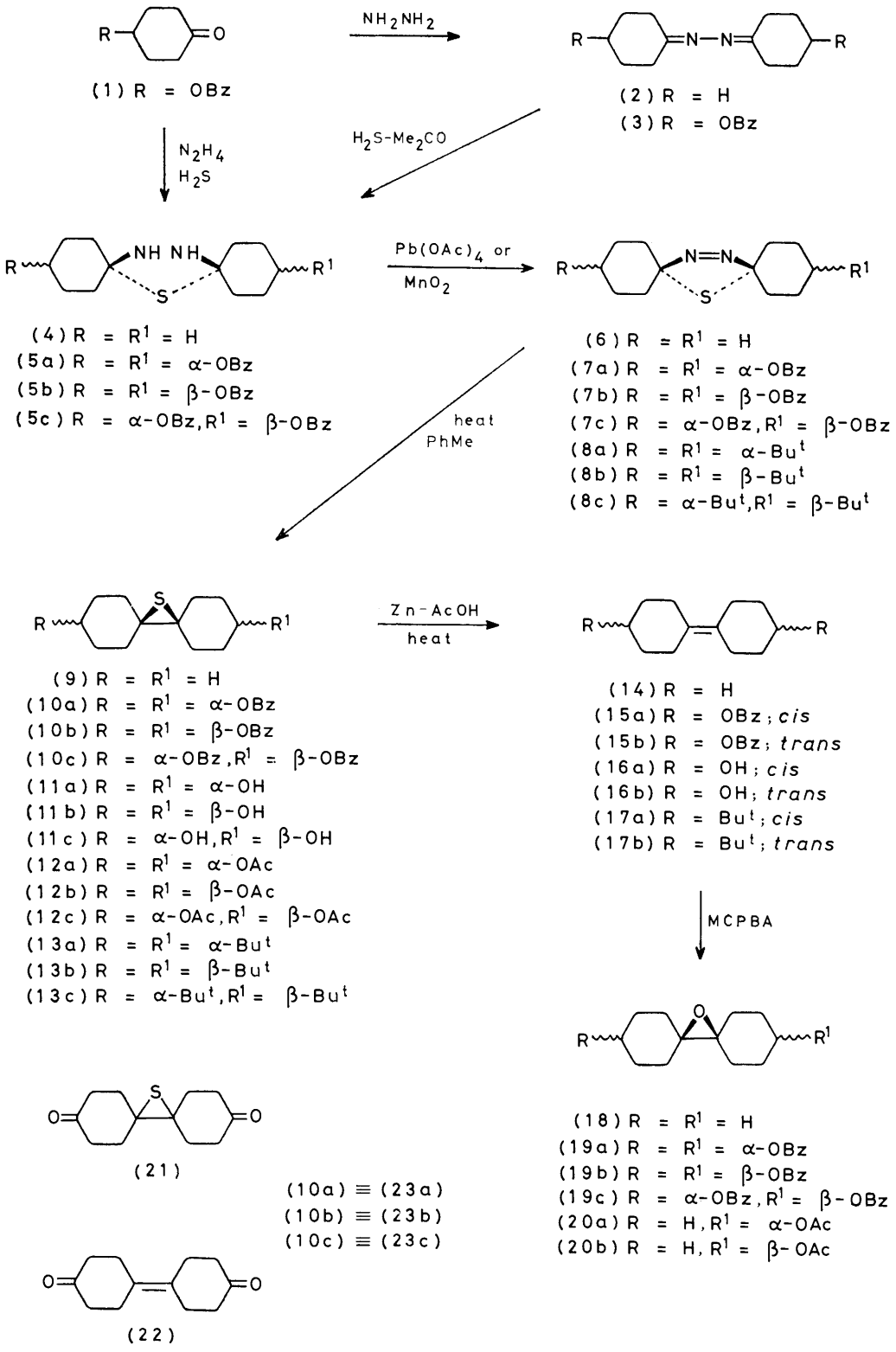
A novel synthesis of mixed azines by oxidation of carboxyhydrazones with lead dioxide is described. Combined with the above process, this constitutes a general synthesis of unsymmetrical bicycloalkylidenes. This method has been used to prepare 3,17-disubstituted Δ^9-6,7-dinor-5,8-secoestrenes. The stereochemistry at C-3 in these olefins and in the intermediate episulphides was assigned by correlation with known compounds, and the orientation of the sulphur atom in the episulphides was elucidated by ^{1}H n.m.r. spectroscopy with reference to conformation theory and the Woodward–Hoffmann rules. Unexplained differences in the ^{1}H n.m.r. spectra of secosteroidal epoxides and episulphides are described.

In the preceding paper [1] we described the synthesis of some Δ^9-6,7-dinor-5,8-seco-estrenes and -pregnenes *via* β-lactones. In this paper we report the preparation of similar compounds by a 'two-fold extrusion process',[2] *i.e.* the removal of the elements of nitrogen and sulphur

† Part of the material contained in this and the preceding paper was presented at the 4th International Symposium on Synthesis in Organic Chemistry, Cambridge, July 1975.

[1] Part 4, D. J. Humphreys and C. E. Newall, preceding paper.

[2] (*a*) D. H. R. Barton and B. J. Willis, *J. C. S. Perkin I*, 1972, 305; (*b*) D. H. R. Barton, F. S. Guziec, and I. Shahak, *ibid.*, 1974, 1794.



(1) R = OBz

(2) R = H
(3) R = OBz

(4) R = R¹ = H
(5a) R = R¹ = α-OBz
(5b) R = R¹ = β-OBz
(5c) R = α-OBz, R¹ = β-OBz

(6) R = R¹ = H
(7a) R = R¹ = α-OBz
(7b) R = R¹ = β-OBz
(7c) R = α-OBz, R¹ = β-OBz
(8a) R = R¹ = α-Bu^t
(8b) R = R¹ = β-Bu^t
(8c) R = α-Bu^t, R¹ = β-Bu^t

(9) R = R¹ = H
(10a) R = R¹ = α-OBz
(10b) R = R¹ = β-OBz
(10c) R = α-OBz, R¹ = β-OBz
(11a) R = R¹ = α-OH
(11b) R = R¹ = β-OH
(11c) R = α-OH, R¹ = β-OH
(12a) R = R¹ = α-OAc
(12b) R = R¹ = β-OAc
(12c) R = α-OAc, R¹ = β-OAc
(13a) R = R¹ = α-Bu^t
(13b) R = R¹ = β-Bu^t
(13c) R = α-Bu^t, R¹ = β-Bu^t

(14) R = H
(15a) R = OBz; *cis*
(15b) R = OBz; *trans*
(16a) R = OH; *cis*
(16b) R = OH; *trans*
(17a) R = Bu^t; *cis*
(17b) R = Bu^t; *trans*

(18) R = R¹ = H
(19a) R = R¹ = α-OBz
(19b) R = R¹ = β-OBz
(19c) R = α-OBz, R¹ = β-OBz
(20a) R = H, R¹ = α-OAc
(20b) R = H, R¹ = β-OAc

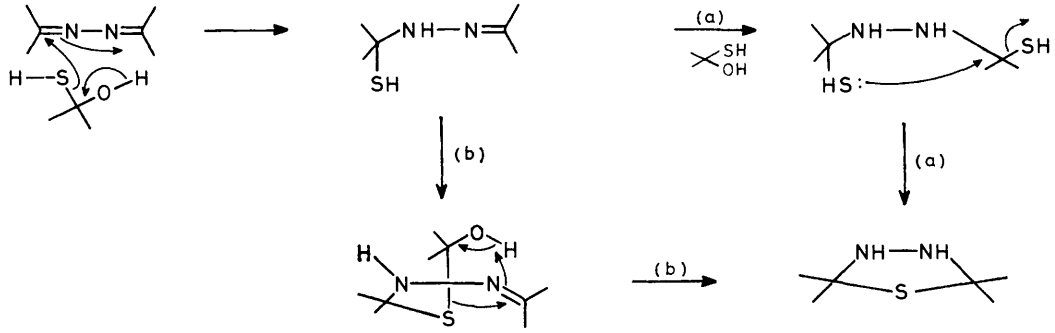
(21)

(22)

(10a) ≡ (23a)
(10b) ≡ (23b)
(10c) ≡ (23c)

SCHEME 1

from a Δ^3-1,3,4-thiadiazoline to give an olefin. Our interest in this route followed the publication of two syntheses of 1,1'-bi(cyclohexylidene) (14) from the thiadiazoline (6), prepared by oxidation [2a,3] of the known [4] thiadiazolidine (4). Thus, pyrolysis of the thiadiazoline (6) gave quantitatively the thiiran (9), which was desulphurised with butyl-lithium to give the olefin (14) in 77% yield.[3] Alternatively, pyrolysis of (6) in the presence of triphenylphosphine gave the olefin (14) in one step, in 77% yield.[2a]



SCHEME 2

Thiadiazolidines may be prepared either by condensation of a ketone with hydrazine and hydrogen sulphide in ethanol,[4] or by reaction of an azine with hydrogen sulphide.[2a,3] It seems that, owing to their instability relative to azines and hydrogen sulphide,[3] the use of thiadiazolidines as intermediates in the preparation of thiadiazolines is applicable only to special cases which include, fortuitously, the present work. For this reason, Kellogg and his co-workers [3] have devised a synthesis of thiadiazolines from azines by 1,4-addition of chlorine followed by reaction with hydrogen sulphide.

We decided to test the general applicability of this two-fold extrusion process by attempting the preparation of a number of symmetrically and unsymmetrically substituted bi(cyclohexylidene)s before embarking on the synthesis of the tricyclic compounds which were our ultimate objective.

General Methods.—Barton and Willis [2a] used acetone–benzene (1 : 1) as the solvent for addition of hydrogen sulphide to the azine (2). We found that the solvent of choice for addition of hydrogen sulphide to more complicated azines was acetone–dichloromethane (1 : 2). The reaction did not proceed in the absence of acetone, and we therefore postulate that the ketone mediates *via* a six-membered cyclic transition state, in one of the ways shown in Scheme 2. It seems that there is no direct interaction between ketone and azine, since there is no evidence for the incorporation of acetone into the products. This is surprising in view of the ease with which mixtures of azines undergo 'scrambling' (see later).

The unsubstituted thiadiazolidine (4) is preferably prepared by condensation of cyclohexanone with hydrazine and hydrogen sulphide in ethanol,[4] as the product crystallises from the reaction mixture pure and in high yield. Symmetrical disubstituted thiadiazolidines may be prepared in the same way or by addition of hydrogen sulphide to the corresponding azine; the method of preparation used affects the stereochemistry of the product (see later). Unsymmetrical thiadiazolidines can, of course, only be prepared *via* mixed azines.

Owing to their instability the thiadiazolidines are best oxidised immediately to the corresponding thiadiazolines. Dichlorodicyanobenzoquinone,[2a] diethyl azodiformate,[3] and lead tetra-acetate [2a] have been used for this purpose. While we have found the use of lead tetra-acetate in dichloromethane to be satisfactory, giving essentially quantitative yields of thiadiazolines, the oxidation was more conveniently accomplished by manganese dioxide [5] in acetone–dichloromethane (1 : 2). Thus, addition of hydrogen sulphide to the azine and the subsequent oxidation can be carried out in one vessel and in the same solvent system.

The pyrolysis of thiadiazolines with triphenylphosphine, although efficient in the case of (6), gave poor results with more complex systems, so that the two-stage process *via* a thiiran seemed more promising. Desulphurisation of the thiiran (9) was attempted using various reagents, *viz.* Grignard reagents, alkyllithiums,[6] methyl iodide,[7] and iodine,[8] but none was satisfactory, and none was compatible with the presence of sensitive functional groups. We found that excellent yields of olefins were obtained when thiirans were heated under reflux with zinc in acetic acid; the only side-reaction observed was acetylation of free hydroxy-groups, which could be avoided by addition of water to the reaction mixture.

Symmetrical Olefins.—Synthesis. The olefin chosen for investigation was the 4,4'-disubstituted bi(cyclohexylidene) (15) which can exist as *cis*- and *trans*-

[3] J. Buter, S. Wassenaar, and R. M. Kellogg, *J. Org. Chem.*, 1972, **37**, 4045.
[4] K. Ruhlmann, *J. prakt. Chem.*, 1959, **8**, 285
[5] U. K. Pat. 871 487.
[6] (*a*) B. M. Trost and S. D. Ziman, *J. Org. Chem.*, 1973, **38**, 932; (*b*) N. P. Neureiter and F. G. Bordwell, *J. Amer. Chem. Soc.*, 1959, **81**, 578; (*c*) R. D. Schuetz and R. L. Jacobs, *J. Org. Chem.*, 1961, **26**, 3467.
[7] G. K. Helmkamp and D. J. Pettit, *J. Org. Chem.*, 1960, **25**, 1754.
[8] G. K. Helmkamp and D. J. Pettit, *J. Org. Chem.*, 1962, **27**, 2942.

isomers. The method used to prepare the thiadiazolidine (5) had a profound effect on the stereochemistry of the product. When 4-benzoyloxycyclohexanone (1) was treated in ethanol with hydrazine hydrate and hydrogen sulphide at 10 °C for 3 days a single thiadiazolidine (5c) was isolated. This was oxidised with lead tetra-acetate or manganese dioxide to the corresponding thiadiazoline (7c) which, on pyrolysis in toluene, gave a mixture of the two *cis*-substituted thiiranes (10a and b), in the ratio 1 : 2. (Stereochemical assignments for all these compounds are discussed in the next section.)

In contrast, addition of hydrogen sulphide to the azine (3) in acetone–dichloromethane (1 : 2) for 5 h at 10 °C gave a mixture of all three possible isomers (by t.l.c.); attack on each C=N bond evidently occurs about 60% *anti* and 40% *syn* to the benzoyloxy-groups, since the isomer ratio (by t.l.c.) was initially *ca.* 1 : 2 : 3, the *trans*-isomer (5c) predominating. When a portion of the mixture was kept for 3 days, some equilibration occurred, and the ratio became 3 : 3 : 4 approximately, the *trans*-isomer (5c) still being slightly favoured. Oxidation of the 1 : 2 : 3 mixture with manganese dioxide and pyrolysis of the product gave a mixture of the thiiranes (10a—c); chromatography gave the *trans*-isomer (10c) (41%) and a mixture of the *cis*-isomers (10a and b) (47%). Since (10a and b) originated from the *trans*-thiadiazoline (7c), it is clear that pyrolysis of the *cis*-isomers (7a and b) gave rise to the *trans*-thiiran (10c), in accord with the theoretical prediction (see later).

Reduction of the thiiranes (10) with zinc and acetic acid gave high yields of the olefins (15) with retention of configuration, *i.e.* (10a and b) gave (15a), while (10c) gave (15b). Pyrolysis of the isomeric mixture (7) in the presence of triphenylphosphine gave only a 20% yield of the olefins (15).

The *cis*-dibenzoyloxythiiranes (10a and b) were hydrolysed with some difficulty to the corresponding diols (11a and b), respectively. The latter were slowly oxidised by Jones reagent to give mixtures of the dione (21) and partially oxidised material, but on prolonged reaction the product (21) was destroyed by secondary oxidation. Oxidation of the diols (11) by the Moffatt procedure [9] appeared to proceed cleanly, but difficulties in separating the product from dicyclohexylurea resulted in a low yield of the dione (21).

The bisbenzoyloxy-olefins (15a and b) were hydrolysed under standard conditions to the corresponding diols (16a and b). Oxidation of these diols using Jones reagent was unsuccessful; since every hydrogen atom in the dione (22) is either allylic or adjacent to a carbonyl group, the product was probably lost through over-oxidation. However, Moffatt oxidation gave the desired dione (22), which was freed from dicyclohexylurea *via* its hydrogen sulphite complex.

[9] K. E. Pfitzner and J. G. Moffatt, *J. Amer. Chem. Soc.*, 1965, **87**, 5661, 5670.
[10] R. B. Woodward and R. Hoffmann, 'The Conservation of Orbital Symmetry,' Academic Press, 1970.
[11] J. J. Uebel, *Tetrahedron Letters*, 1967, 4751.

Stereochemistry.—The stereochemistry of the compounds in this series follows from the fact that inversion of configuration occurs during conversion of a thiadiazolidine into a thiiran. According to the Woodward–Hoffmann rules,[10] pyrolysis of a thiadiazoline should result in suprafacial disrotatory extrusion of nitrogen leading to retention of configuration in the resulting sulphonium ylide; conrotatory cyclisation of the ylide would then give a thiiran of configuration opposite to that of the thiadiazoline. This prediction has been confirmed experimentally by the pyrolysis of alkyl-substituted thiadiazolines.[3] Thus, in this series, pyrolysis of the two *cis*-substituted thiadiazolines (7a and b) would give the same *trans*-substituted thiiran (10c), while the *trans*-thiadiazoline (7c) could, by conrotatory cyclisation of the ylide in different directions, lead to the two *cis*-thiirans (10a and b). Condensation of 4-benzoyloxycyclohexanone with hydrazine and hydrogen sulphide gave a single thiadiazolidine which was converted by successive oxidation and pyrolysis into a mixture of two thiiranes. It follows that the latter are the *cis*-isomers (10a and b) and that they arose from the thiadiazoline (7c).

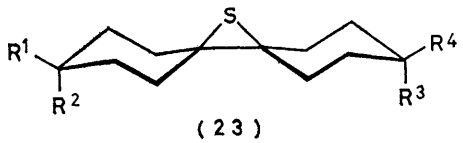
The n.m.r. spectrum of one of these isomeric thiiranes shows a signal at τ 5.15 ($W_{\frac{1}{2}}$ 22 Hz) corresponding to two axial protons adjacent to the benzoyloxy-groups, and that of the other shows a signal at τ 4.95 ($W_{\frac{1}{2}}$ 11 Hz) corresponding to two equatorial protons, indicating that the cyclohexane rings exist in a rigid chair conformation. Some control is evidently exerted by the benzoyloxy-groups on the direction of conrotatory cyclisation of the ylide, since the isomer ratio is 2 : 1 in favour of the diequatorially substituted isomer. It is clear, too, that the sulphur atom in a thiiran prefers to adopt a fixed conformation relative to a cyclohexane ring, and consideration of steric interactions indicates that this is a pseudoaxial (23) rather than a pseudoequatorial (24) position (Scheme 3).

It has been established by kinetic,[11] low temperature ^{1}H n.m.r.,[12] and dipole moment [13] studies that in cyclohexanespiro-oxiran there is a preference of *ca.* 0.27 kcal mol^{-1} for the conformation in which the oxygen is pseudoaxial; in a 4-substituted cyclohexanespiro-oxiran this preference is largely over-ridden [11] so that the 4-substituent occupies mainly an equatorial position, whether *cis*- or *trans*- to the heteroatom. ^{13}C N.m.r. studies [14] have shown a similar preference (0.16 kcal mol^{-1}) for the pseudoaxial conformation in cyclohexanespiroaziridine; a stronger preference (0.42 kcal mol^{-1}) for the pseudoaxial conformation has been demonstrated for cyclohexanespirothiiran by dipole moment measurements.[13] No measurements have yet been made on 4-substituted cyclohexanespirothiirans, but it is clear from our results that, where each carbon

[12] R. G. Carlson and N. S. Behn, *Chem. Comm.*, 1968, 339; *J. Org. Chem.*, 1967, **32**, 1363.
[13] R. A. Y. Jones, A. R. Katritzky, P. G. Lehmann, A. C. Richards, and R. Scattergood, *J.C.S. Perkin II*, 1972, 41.
[14] G. W. Buchanan and R. Kohler, *J. Org. Chem.*, 1974, **39**, 1011.

atom of the thiiran ring forms part of a cyclohexane ring, the interactions between the two rings result in an enhancement of the normal preference of the sulphur atom so that it predominates over the normal conformational preferences of the 4-substituents. This effect is evidently strong, since groups such as the benzoyloxy-group, which would normally adopt an equatorial position, are thereby constrained to take up an axial orientation, as shown by the n.m.r. spectra of the isomeric thiiran dibenzoates (10). On this basis, we assign the structures (10a and b), respectively, to the diaxially and diequatorially substituted thiirans.

Similarly, pyrolysis of the *cis*-substituted thiadiazolines (7a and b) gave rise to the *trans*-substituted thiiran (10c), which showed n.m.r. signals attributable to one axial and one equatorial proton adjacent to the ester groups.



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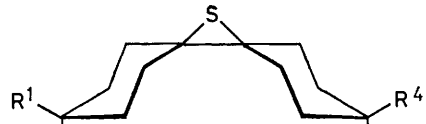

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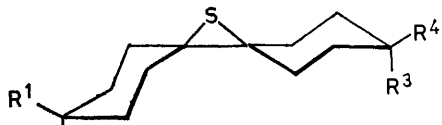


(25)

a; $R^1 = R^4 = H$
b; $R^2 = R^3 = H$
c; $R^1 = R^3 = H$

SCHEME 3

Cheletropic removal of sulphur from a thiiran is predicted [10] to occur with retention of configuration in the resulting olefin. Desulphurisation of thiirans by phosphine sulphides [15] and by butyl-lithium [6a] has been show to occur by a cheletropic mechanism with the predicted stereochemistry; it is likely that desulphurisation with zinc occurs by a similar mechanism. The mechanism of desulphurisation by iodine [7] and by methyl iodide [8] is less clear but here, too, the same stereochemical results are observed. Thus, we may with some confidence conclude that the *trans*-substituted thiiran (10c) gave the *trans*-olefin (15b), and similarly (10a and b) gave (15a). The i.r. and n.m.r. spectra of the olefins (15a and b) were virtually identical, so that it seems likely that these compounds exist in all-chair conformations, such that both substituents lie equatorially in each isomer (*cf.* ref. 16*b*). The stereochemistry of the olefins was confirmed by epoxidation with *m*-chloroperbenzoic acid: the *trans*-olefin (15b) gave only one epoxide (19c) while the *cis*-isomer (15a) gave two epoxides, in the ratio 2 : 3. It is probable that the major isomer is (19a), resulting from attack from the less hindered side of the molecule, and that the minor isomer is (19b).

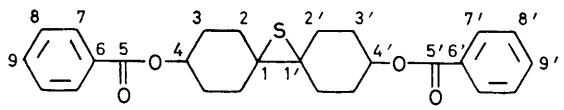
While this paper was in preparation, we were interested to note the parallel results reported by Kellogg: [16] treatment of 4-t-butylcyclohexanone azine with hydrogen sulphide under pressure, followed by oxidation, gave the thiadiazolines (8a—c) in the ratio *ca.* 2 : 3 : 4.[16a] Pyrolysis of (8a or b) gave the expected *trans*-thiiran (13c), but pyrolysis of (8c) is reported to have given only one *cis*-thiiran. The structure (13a) was assigned to this product on theoretical grounds based on the assumption that each cyclohexane ring in such a thiiran would adopt the chair conformation in which the substituent was equatorial. Thus, it was assumed that, since the *trans*-thiiran (13c) showed non-equivalent t-butyl groups in the ^1H n.m.r. spectrum, and non-equivalent rings in the ^{13}C n.m.r. spectrum, it had the structure (25c). The product of the pyrolysis of (8c) had a symmetrical structure (by ^1H and ^{13}C n.m.r.), which was assigned as (13a) [*i.e.* (24a)] rather than (13b) [*i.e.* (23b)] since its rate of desulphurisation with tri-n-butylphosphine was 120 times that of (13c). The difference in rate was ascribed to the existence of 1,3-diaxial interactions in the transition state derived from (25c) which would be lacking in (24a), and enhanced in (23b).

That the isomers (10a—c) have the same fixed conformation was demonstrated by ^1H n.m.r. spectroscopy (see above). ^{13}C N.m.r. spectroscopy (see Table) confirmed that the *cis*-isomers (10a and b) had symmetrical structures [*i.e.* (23a and b), respectively] and demonstrated that if, as in the *trans*-isomer (10c), the rings bore differently oriented substituents, they were non-equivalent. From these results, Kellogg's *trans*-thiiran (13c) clearly has the structure (23c), and the *cis*-thiiran produced by pyrolysis of (8c) is either (13a), with structure (23a), or (13b), with structure (23b). If the t-butyl group exerts a greater effect than the benzoyloxy-group

[15] D. B. Denny and M. J. Boskin, *J. Amer. Chem. Soc.*, 1960, **82**, 4736.

[16] (*a*) R. M. Kellogg, M. Noteboom, and J. K. Kaiser, *J. Org. Chem.*, 1975, **40**, 2573; (*b*) R. M. Kellogg and J. K. Kaiser, *ibid.*, p. 2575; (*c*) R. M. Kellogg, M. Noteboom, and J. K. Kaiser, *Tetrahedron*, 1976, **32**, 164.

during cyclisation of the ylide, this may lead to sole formation of the diequatorial isomer (13b). On the other hand, the relative rates of desulphurisation of



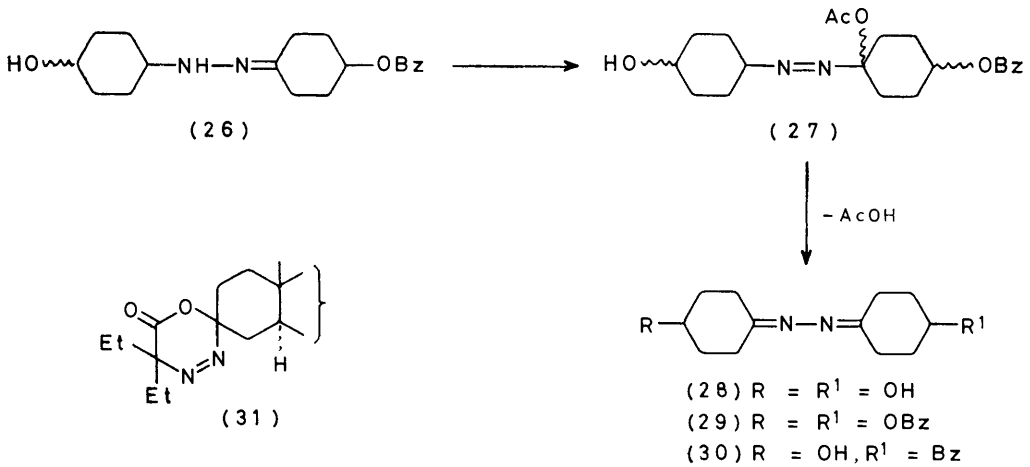
Proton-decoupled ^{13}C n.m.r. spectra of thiirans (10a—c) [δ ($CDCl_3$) relative to internal Me_4Si]

Compound	(10a)	(10b)	(10c)
Structure	(23a)	(23b)	(23c)
C-1, -1′		58.6	58.8
	59.8		59.3
C-2, -2′, -3, -3′	28.9		29.3
	30.3		30.4
		31.0	31.1
		31.5	31.4
C-4, -4′	70.0		70.0
		72.1	72.3
C-5, 5′	165.8		Not
		166.0	measured
C-6, -6′	130.9	130.6	130.7
C-7, -7′, -8, -8′	128.4	128.3	128.4
	129.6	129.6	129.6
C-9, -9′	132.9	132.9	132.9

(13c) and (13a/b) may reflect different degrees of steric hindrance to attack on the sulphur atom by a bulky phosphine; if so, this would indicate that the isomer formed was (13a).

upon an efficient synthesis of mixed azines. Various attempts to prepare mixed azines directly, *e.g.* by condensation of a hydrazone with a ketone, led to mixtures of azines. Another approach involved oxidation of an alkylhydrazone to the corresponding azo-acetate [17] followed by pyrolytic elimination of acetic acid (Scheme 4). Condensation of 4-benzoyloxycyclohexanone with 4-hydroxycyclohexylhydrazine gave the hydrazone (26), which was efficiently oxidised using lead tetra-acetate to the azo-acetate (27). However, pyrolysis of the latter in boiling dimethylformamide resulted in a mixture of all three possible azines (28)—(30). We therefore concluded that mixed azines could only be prepared under mild conditions, *i.e.* at low temperatures in the absence of acids and bases.

Barton and Willis,[2a] in their investigation of olefin synthesis by two-fold extrusion processes, prepared the spirocyclic azolactone (31) by condensation of chlolestan-3-one with 2-ethyl-2-hydrazinobutyric acid and oxidation of the resulting carboxy-hydrazone with lead tetra-acetate. Photolysis of the azolactone in cyclohexane brought about expulsion of carbon dioxide to give, in excellent yield, the mixed azine derived from cholestanone and pentan-3-one. This route looked promising, and we therefore embarked on a synthesis of 1-hydrazinocyclohexanecarboxylic acid (35) (Scheme 5). Reaction of 1-bromocyclohexanecarboxylic acid with an excess of hydrazine in ethanol [18] gave the required hydrazino-acid (35), but in only 21% yield after recrystallisation; the reaction was accompanied by considerable



SCHEME 4

^1H N.m.r. and i.r. spectra of the olefins (17a) and (17b) obtained by desulphurisation of (13a or b) and (13c), respectively, were essentially identical.[16b]

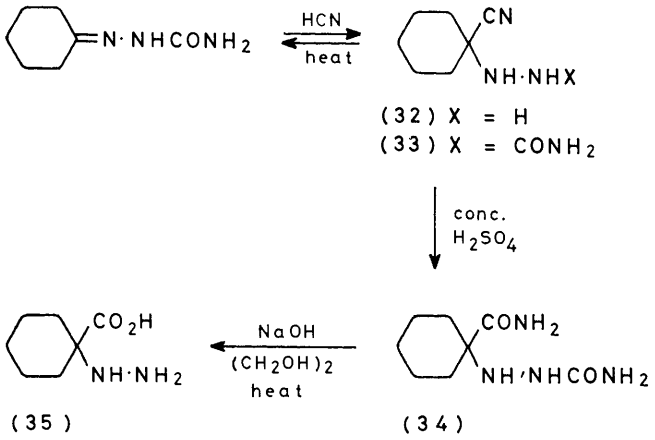
Unsymmetrical Olefins.—Synthesis of mixed azines. The extension of the ' two-fold extrusion process ' to the preparation of unsymmetrical olefins was dependent elimination of hydrogen bromide. An alternative approach used the hydrazine analogue [19] of the Strecker synthesis, *viz.* reaction of hydrazine hydrochloride and potassium cyanide with cyclohexanone. The expected 1-cyanocyclohexylhydrazine (32) was obtained as the hydrochloride, together with the corresponding cyclohexanone hydrazone; however, the nitrile (32) was not

[17] D. C. Iffland, L. Salisbury, and W. R. Schafer, *J. Amer. Chem. Soc.*, 1961, **83**, 747; D. C. Iffland and T. M. Davies, *ibid.*, 1963, **85**, 2182; B. T. Gillis and M. P. LaMontagne, *J. Org. Chem.*, 1967, **32**, 3318; R. W. Hoffman and H. J. Luthardt, *Chem. Ber.*, 1968, **101**, 3851, 3861.

[18] A. Carmi, G. Pollak, and H. Yellin, *J. Org. Chem.*, 1960, **25**, 44.

[19] Von W. Knobloch and G. Subert, *J. prakt. Chem.*, 1967, **36**, 29.

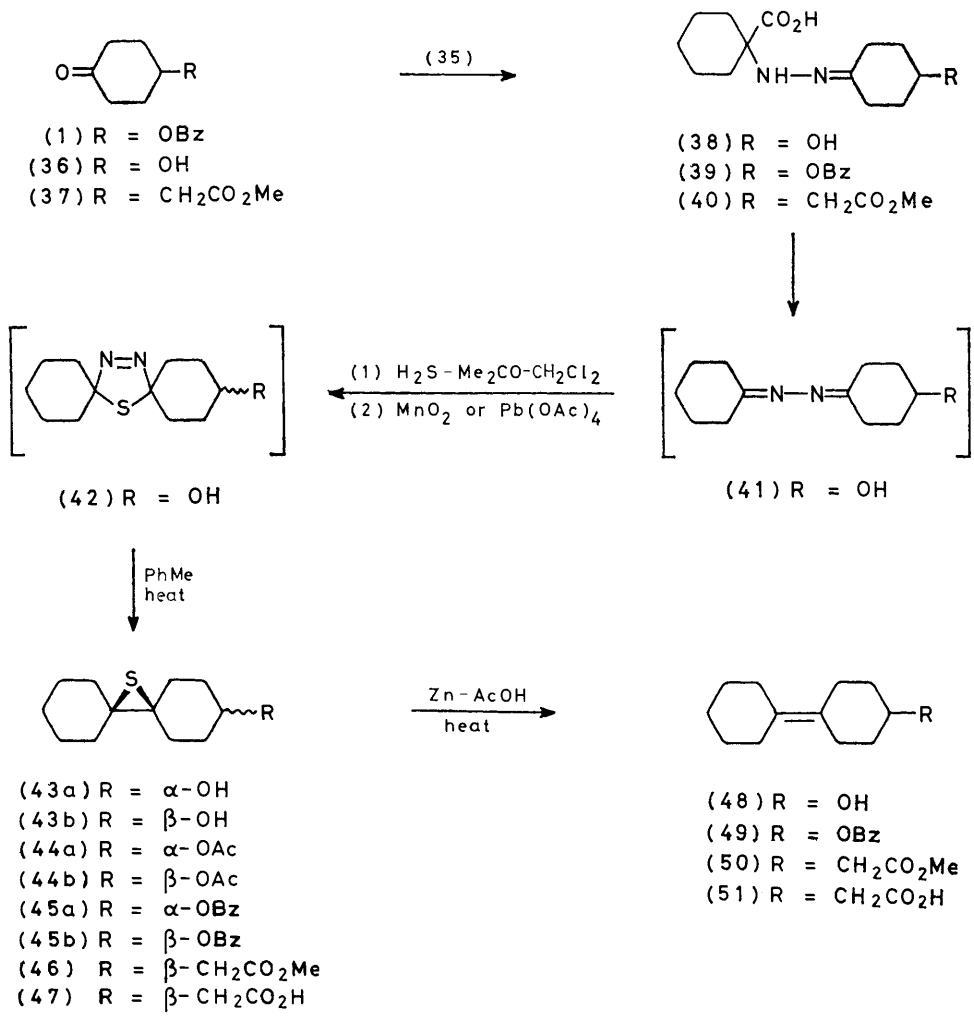
hydrolysed by hot hydrochloric acid, but reverted to cyclohexanone. In order to avoid hydrazone formation,



SCHEME 5

hydrogen cyanide was added to cyclohexanone semicarbazone, the adduct (33) being formed quantitatively. The latter was inert to cold concentrated hydrochloric acid and lost hydrogen cyanide on heating; strongly basic conditions also caused elimination of hydrogen cyanide. It was reasoned that protonation of the nitrogen atom nearest the nitrile might hinder the elimination of hydrogen cyanide. Indeed, hydrolysis of (33) with concentrated sulphuric acid, followed by basification, gave the corresponding amide (34) in 68% yield. Complete hydrolysis of (34) was achieved by treatment with sodium hydroxide in boiling ethylene glycol to give the hydrazino-acid (35) in an overall yield of 61% after recrystallisation.

We decided to test the efficiency of Barton's synthesis [2a] of mixed azines by condensing the hydrazino-acid (35) with 4-hydroxycyclohexanone (36), since any scrambling of the product (41) would be readily detected by t.l.c. (Scheme 6). The hydrazone–acid (38) was obtained in high yield and was oxidised with lead tetra-acetate to a mixture of two products. The minor product was identified as the expected azolactone (52) by its u.v. absorbance and conversion on irradiation into the mixed azine (41); the major component proved to be the mixed azine (41). There was no evidence for



SCHEME 6

scrambling. As the normal products of oxidation of simple hydrazones by lead tetra-acetate are azo-acetates it was thought that the azine (41) might have been formed *via* the azo-acetate (53), as shown. To test this hypothesis the concentration of acetate present during the reaction was varied: a higher concentration was obtained by addition of acetic acid, while an acetate-free oxidation was achieved by use of lead dioxide. In the event, the effect was the opposite of that expected; the former reaction gave a complex mixture, while in the latter a solution of the pure mixed azine (41) was obtained. Thus, the oxidation of a carboxy-hydrazone by lead dioxide constitutes a mild and novel method for the preparation of a solution of a mixed azine. The solvent used had little effect on the reaction, nor did the presence of small quantities of organic bases, although high concentrations of triethylamine inhibited the reaction almost completely.

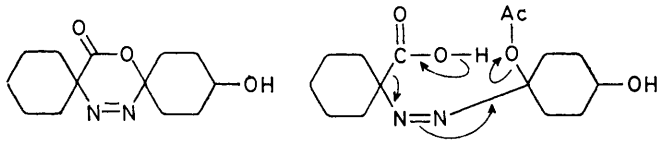
Synthesis of Olefins from Mixed Azines.—This procedure, coupled with the two-fold extrusion process outlined above, provides an efficient synthetic route to unsymme rical bi(cycloalkylidene)s. The high solubility of hydrogen sulphide in dichloromethane made this the solvent of choice for oxidations with lead dioxide. After filtration, the azine solution was treated with acetone and hydrogen sulphide; the subsequent oxidation, pyrolysis, and desulphurisation were carried out as already described.

Addition of hydrogen sulphide to the azine (41) occurred even in the absence of an added ketone, but only when acetone was present could the excess of hydrogen sulphide be removed without reversion of the thiadiazolidine to the azine (41). If acetone does indeed mediate in the ring closure of a monosulphide adduct [Scheme 2, route (b)] a high concentration of acetone would stabilise the thiadiazolidine by ensuring that ring opening was immediately followed by reclosure.

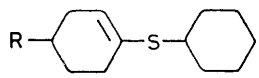
Reaction mixtures in which hydrazones of hydroxy-ketones were used as the starting material always contained some of the parent hydroxy-ketone, and it would appear that hydrazones or azines derived from these compounds may be especially prone to hydrolysis. Another drawback associated with the presence of free hydroxy-groups was discovered following pyrolysis of the thiadiazoline (42). Chromatography of the product gave, in addition to the thiirans (43), a compound whose spectral characteristics and elemental analysis were consistent with the structure (54); acidic hydrolysis of this compound was accompanied by a strong smell of thiol. This by-product may have arisen by abstraction of a proton from the ylide by the hydroxy-group. The problem could be overcome by esterification, which rendered the system aprotic and reduced the basicity of the oxygen atom.

The thiirans (43a and b) were obtained in the ratio 3 : 7, the equatorially substituted isomer predominating. Desulphurisation of a mixture of (43a and b) gave the olefin (48) in 37% overall yield from the hydrazone (38). The hydrazone (39) was similarly converted into the thiirans (45a and b) (49% yield, ratio 2 : 5) and thence into the olefin (49) (45% overall yield). Hydrolysis of (45a and b) gave (43a and b). The stereochemistry of the products was determined as for the symmetrical compounds.

Condensation of the ester (37) with the hydrazino-acid (35) gave, in excellent yield, the hydrazone (40) which was converted in the usual manner into the thiiran (46) and thence into the olefin (50). N.m.r. spectroscopy of (46) in the presence of the lanthanoid shift reagent $Eu(fod)_3$ showed that it was entirely the equatorially substituted isomer; there was no evidence for the axial isomer. This is not readily explained, although it is possible that there is a similar interaction between the ylide and the axial 4-substituent as is thought to occur with the hydroxy-compound (42), to give a thio-enol ether (55). Indeed, acidic treatment of the mother



(52) (53)



(54) R = OH
(55) R = CH_2CO_2Me

SCHEME 7

liquors from crystallisation of (46) gave rise to a very strong odour of thiol, and a compound chromatographically identical with the oxo-ester (37) was produced. Hydrolysis of the esters (46) and (50) gave the acids (47) and (51), respectively.

Δ^9-6,7-*Dinor*-5,8-*secoestrenes.*—*Preparation of the hydrazino-acid* (59). Having shown that unsymmetrical bi(cyclohexylidene)s could be prepared efficiently *via* mixed azines, we approached our main objective, the synthesis of Δ^9-6,7-dinor-5,8-seco-steroids. Since most biologically active steroids possess an oxygen function at C-3, the preparation of 1-hydrazino-4-hydroxycyclohexanecarboxylic acid (59) was attempted. The reaction of the corresponding 1-bromo-acid or an *O*-protected derivative with hydrazine was not practicable owing to the likelihood of concomitant loss of the oxygen function.[20] Thus, an analogue of the Strecker synthesis seemed to be the most promising approach. The semicarbazone of 4-benzoyloxycyclohexanone was unreactive towards hydrogen cyanide. However, the more soluble propionylhydrazone (57) reacted slowly but efficiently with hydrogen cyanide to give the adduct (56). The two isomers of (56) were readily separated by column chromatography; the isomer with an axial benzoate predominated. It was subsequently found

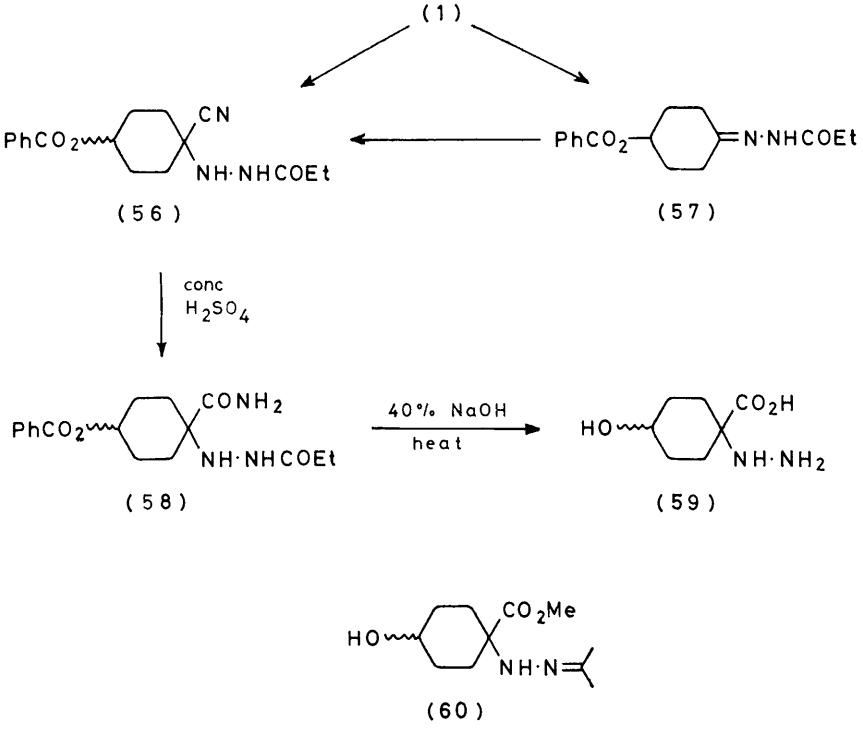
[20] D. S. Noyce and H. I. Weingarten, *J. Amer. Chem. Soc.*, 1957, **79**, 3093.

that the hydrazone (57) could be formed and treated *in situ* with hydrogen cyanide.

The separate isomers of the nitrile (56) were hydrolysed by concentrated sulphuric acid to the corresponding amides (58), the nitrile with an axial benzoate giving the amide with an equatorial benzoate, and *vice versa*. On a large scale, the mixed isomers of (56) were hydrolysed; the amides (58) could be efficiently separated by crystallisation if desired. Hydrolysis of the mixed amides (58) to the desired hydrazino-acid (59) was is discussed below. The thiirans were converted into the desired olefins by treatment with zinc and acetic acid.

The sequence was first proved by condensation of (35) with the acetoxy-ketone (62) and conversion of the crude hydrazone (65) into the olefin (77) in an overall yield of 22% from (62). The acetate (77) was hydrolysed to the corresponding alcohol (78), identical with a sample prepared by the pyrolysis of a β-lactone.[1]

An attempt to carry a sample of the hydroxy-ketone (61) [21] through the above sequence was unsuccessful



SCHEME 8

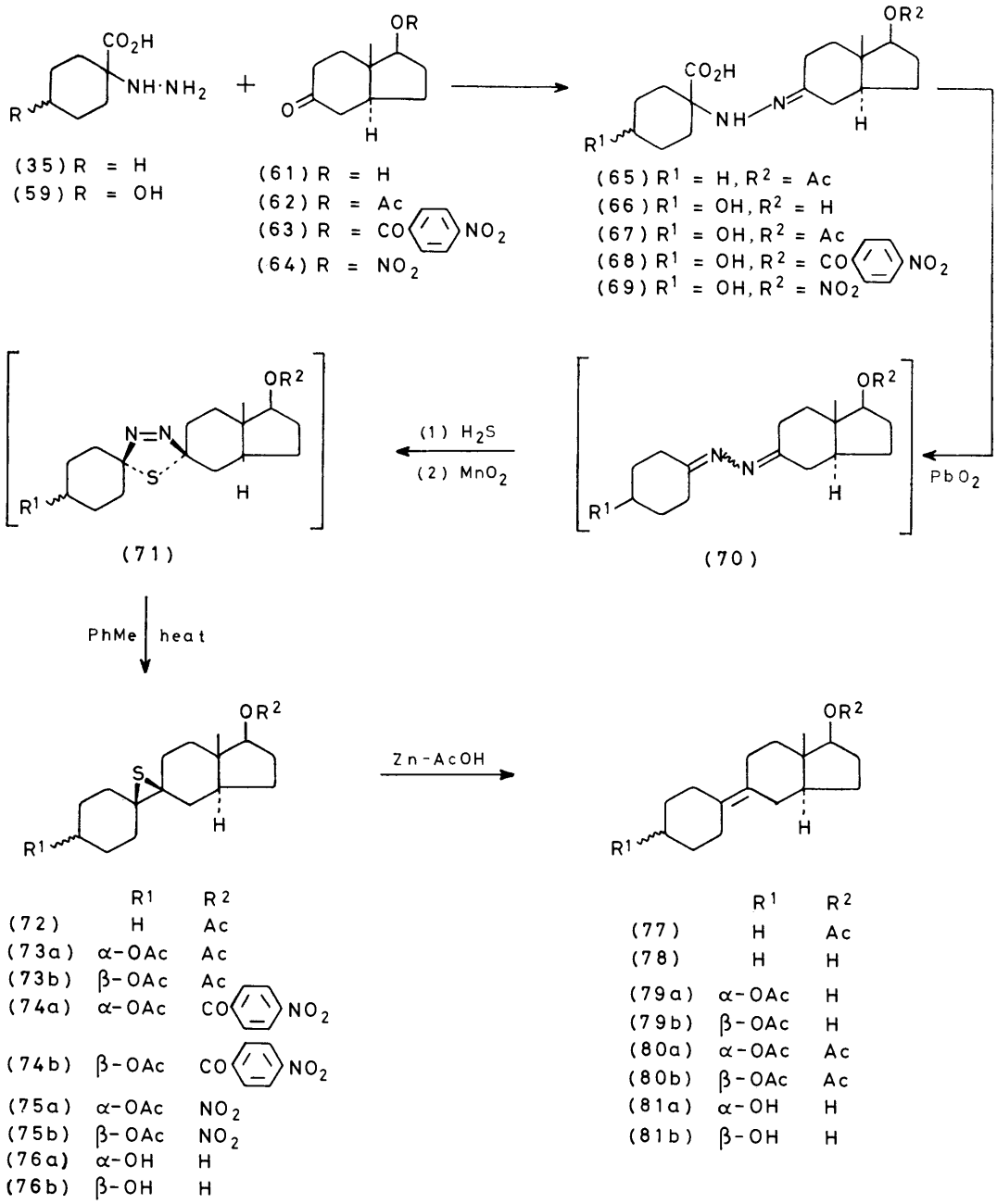
achieved in 40% yield using boiling aqueous 40% sodium hydroxide. The separated isomers of the amide (58) were hydrolysed similarly and the total products were converted into the derivatives (60). These derivatives were distinguishable by g.l.c. and n.m.r. and were not contaminated with each other. There had therefore been no equilibration of isomers during the hydrolysis.

Preparation of seco-steroids. Condensation of the hydrazino-acid (35) or its 4-hydroxy-derivative (59) with the bicyclic ketones (61)—(64) gave hydrazones which, after purification, were oxidised with lead dioxide to give solutions of chromatographically pure azines (70). The latter were converted, without isolation of the intermediates, into the corresponding thiirans by the general method described above. Where the hydroxy-hydrazino-acid (59) was used, the product was a mixture of two thiirans isomeric at the 3-position. These isomers could generally be separated by chromatography and/or crystallisation. The sulphur atom had the same orientation relative to rings C and D in each isomer of a pair (see later); the stereochemistry of the sulphur bridge owing to extensive decomposition, mainly during pyrolysis of the thiadiazoline (71; $R^1 = R^2 = H$), attributable to the presence of the hydroxy-group (see above).

Condensation of the ketol (61) with the hydroxy-hydrazino-acid (59) gave the hydrazone (66), which was converted in the usual way into a thiadiazoline. Potential problems associated with the hydroxy-groups were avoided by acetylation of the thiadiazoline, and appropriate precautions were taken to ensure an aprotic medium during the ensuing pyrolysis. The thiiran diacetates (73a and b) were obtained in 41% overall yield, in the ratio *ca.* 1 : 2. The latter (73b) crystallised preferentially from methanol; chromatography of the liquors provided a sample of the 3α-acetoxy-isomer (73a). Also isolated was the dimethyl acetal of the acetoxy-ketone (62), which presumably arose by hydrolysis of the mixed azine (70; $R^1 = OH$, $R^2 = H$), as was expected in view of our experience with simple hydroxy-substituted azines.

[21] D. J. Humphreys, C. E. Newall, H. A. Paskins, and G. H. Phillipps, *J.C.S. Perkin I*, 1978, 15.

Similarly, the thiiran diacetates (73a and b) were obtained from the hydrazino-acid (59) and the oxo-acetate (62), and were separated by chromatography. The yield of (73) was 59% based on the ketone (62); again, starting material (62) (16%) was recovered.



	R1	R2
(72)	H	Ac
(73a)	α-OAc	Ac
(73b)	β-OAc	Ac
(74a)	α-OAc	CO
(74b)	β-OAc	CO
(75a)	α-OAc	NO2
(75b)	β-OAc	NO2
(76a)	α-OH	H
(76b)	β-OH	H

	R1	R2
(77)	H	Ac
(78)	H	H
(79a)	α-OAc	H
(79b)	β-OAc	H
(80a)	α-OAc	Ac
(80b)	β-OAc	Ac
(81a)	α-OH	H
(81b)	β-OH	H

SCHEME 9

Desulphurisation of the mixed thiirans (73a and b) gave the olefin diacetates (80a and b) which were not separated; the separate isomers were obtained as by-products of desulphurisation of the nitro-oxythiirans (75) (see later).

To facilitate the detection of any side-products other than those formed by hydrolysis of the azine (70) the u.v.-absorbing *p*-nitrobenzoyl ester (63) was prepared and converted by standard procedures into a mixture of the isomeric thiirans (74), in 38% overall yield; the 3β-isomer (74b) crystallised preferentially from ethyl acetate. There was no evidence for by-products other than the starting material (63) (31%).

Later work was directed towards the synthesis of the seco-steroidal 3-hydroxy-17-ketones (84).[1] This was best achieved by the use of a protecting group for the hydroxy-ketone (61) which could be removed selectively

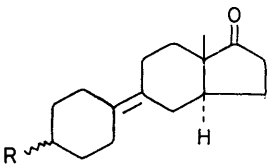
in the presence of a 3-acetate. The nitrate ester was chosen as being stable to all the reaction conditions and conveniently removable during desulphurisation of the thiiran with zinc and acetic acid. The nitrate ester (64) was prepared by the action of fuming nitric acid and acetic anhydride on the hydroxy-ketone (61); isolation of (64) *via* its hydrogen sulphite complex gave material sufficiently pure for condensation with the hydrazino-acid (59). The resulting hydrazone was converted in the usual way into the corresponding mixed azine and thence into the thiadiazoline (71; $R^1 = OH$, $R^2 = NO_2$), which was acetylated before pyrolysis. The isomeric thiirans (75) were isolated in up to 39% overall yield, and were readily separated by chromatography. By-products isolated from this reaction included the starting material (64) (12%) and the isomeric thiirans (12b and c) (3.4 and 4.2%, respectively) derived by 'scrambling' of the mixed azine (70; $R^1 = HO$, $R^2 = NO_2$). Our failure to isolate the third isomer (12a) is surprising in view of the fact that all three isomers of the corresponding dibenzoate were isolated (see before). Reduction of the thiirans (75) to the olefins (79) was quite violent, and was not easily controlled by slow addition of zinc powder to a solution of the thiiran nitrates in acetic acid. It was accompanied by partial acetylation of the product to give the diacetates (80). The two isomers of (80) were readily separable by chromatography, but the separate isomers of the 17-hydroxy-3-acetate (79) were only accessible from pure isomers of the nitro-oxythiiran (75).

The 17-alcohols (79a and b) were oxidised by the Moffat procedure [9] to give the 17-ketones (83a and b), respectively, in high yield. The relative chromatographic polarity of these oxo-acetates was reversed on hydrolysis to the hydroxy-ketones (84a and b). The latter were identical with samples prepared by the pyrolysis of β-lactones,[1] a correlation which enabled the assignment of stereochemistry at the 3-position in all the secosteroidal olefins and thiirans described herein. The separated isomers of the oxo-acetate (83) reacted rapidly with sodium acetylide to give the corresponding 17α-ethynyl derivatives (87) in good yield.

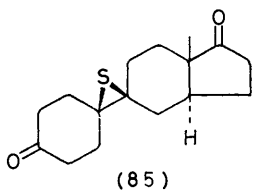
Hydrolysis of an isomeric mixture of the diacetates (80) gave the corresponding diols (81) which were oxidised by the Moffatt procedure to the dione (86). This compound formed a very strong hydrogen sulphite complex, from which it could be freed only by treatment with strong acid; this led to decomposition, presumably involving migration of the double bond. In subsequent work, therefore, the dione (86) was purified by chromatography. It was selectively reduced by the hexachloroiridic acid reagent (*cf.* ref. 21) to give, after acetylation, a mixture of the 3α- and 3β-acetoxy-17-ketones (83a and b) in the ratio 3 : 2, respectively.

The thiiran diacetates (73) were similarly converted by hydrolysis and subsequent oxidation with dimethyl sulphoxide–dicyclohexylcarbodi-imide into the dione (85).

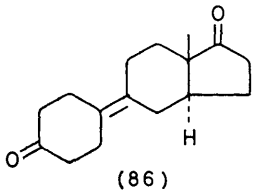
Stereochemistry.—The assignment of stereochemistry at the 3-position in the compounds described in this paper followed from the hydrolysis of the separated isomers of the oxo-acetate (83) to the alcohols (84a and b), of known [1] stereochemistry, produced by the pyrolysis of β-lactones. The more polar acetate yielded the less



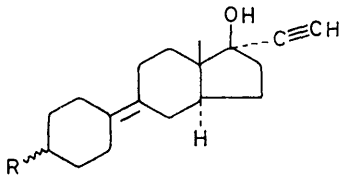
(82) R = H
(83a) R = α-OAc
(83b) R = β-OAc
(84a) R = α-OH
(84b) R = β-OH



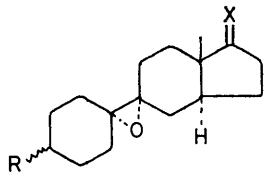
(85)



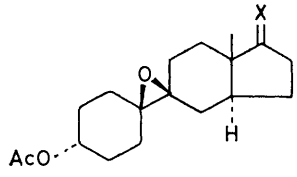
(86)



(87a) R = α-OH
(87b) R = β-OH



(88) R = H, X = O
(89a) R = α-OAc, X = O
(89b) R = β-OAc, X = O
(90a) R = α-OAc, X = α-H, β-OAc
(90b) R = β-OAc, X = α-H, β-OAc



(91) X = O
(92) X = α-H, β-OAc

SCHEME 10

polar (3α-) alcohol (84a), and *vice versa*. Consequently, the stereochemistry at C-3 in those olefins made by the sulphur extrusion process which are derivatives or precursors of the acetates (83a and b) could be established. The more polar (3α-) acetate (83a) gave the less polar 17α-ethynyl-3α,17β-diol (87a) and *vice versa*. The less

polar oxo-acetate (83b) arose from the less polar 17-alcohol (79b), which was accordingly assigned the 3β-configuration. The latter (79b) and the less polar of the diacetates (80) arose from the same isomer of the thiiran (75); the less polar diacetate was therefore the 3β-isomer (80b). The 3α-isomer (80a) was hydrolysed to the 3α,17β-diol (81a).

Furthermore, the stereochemistry at C-3 in the thiirans (75), from which the acetates (79) and (80) were derived, could now be elucidated. The cheletropic removal of sulphur from an episulphide proceeds with retention of configuration in the resulting olefin.[10] Thus, whatever the orientation of the sulphur atom, a 3β-substituted thiiran must lead to a 3β-substituted olefin, and so forth. The less polar isomer of the 3-acetoxy-17β-nitro-oxythiiran (75) gave rise to the 3β-acetates (79b) and (80b) and was therefore the 3β-isomer (75b). The n.m.r. spectra of the less polar (3β-) and more polar (3α-) isomers (75b) and (75a) show signals attributable to an axial 3-H and an equatorial 3-H, respectively. The less polar isomers of the thiirans (73) and (74) each possess an axial 3-H, and the more polar isomer of (73) possesses an equatorial 3-H, as shown by their n.m.r. spectra; by analogy with the nitrates (75), these compounds were assigned the stereochemistry shown in (73b), (74b), and (73a), respectively.

It is evident that some degree of selectivity occurs during the synthesis of the seco-steroidal episulphides since, of the four possible isomers, *viz.* 9α,10α-epithio- and 9β,10β-epithio-compounds each isomeric at the 3-position, only two are isolated. There is little evidence to suggest that the other isomers are formed other than in trace amounts. Those isomers isolated differ only in the orientation of the 3-substituent, since the separate isomers of the diacetate (73) were each converted to the same dione (85).

It is possible that some stereoselectivity occurs during the processes leading to the formation of the thiadiazoline (71) so that only one of the two possible structures (*viz.* 9α,10α-epithio- and 9β,10β-epithio-) is formed. However, this is not sufficient to explain the results, since it is evident that the ylide derived from either of these isomeric structures could theoretically undergo conrotatory cyclisation in one direction to give a β-thiiran, while rotation in the opposite direction would lead to an α-thiiran. The observed stereoselectivity implies that conrotatory cyclisation of the ylide must occur in one direction only, irrespective of whether there is any selectivity in the production of the thiadiazoline. Such a predisposition might exist for thermodynamic reasons if, as suggested by Kellogg,[3] the ylide was ' tilted ', and not planar; if this was so, a different ylide might be produced from each isomeric thiadiazoline (71) and cyclisation of these might lead to different products, so that some stereoselectivity in the formation of (71) is not precluded. Some evidence to suggest that one direction of cyclisation may be favoured was obtained from pyrolysis of the *trans*-thiadiazoline (7c); a mixture of the diequatorially (10b) and diaxially (10a) substituted thiirans was obtained in the ratio 2 : 1. This behaviour is paralleled in the case of the monobenzoates (45). It is possible that, where one component of the ylide is a bicyclononane, this tendency is enhanced, so that the cyclisation occurs exclusively in one direction.

Our results in the bicyclic series showed that the sulphur atom has a strong preference for the pseudoaxial position with respect to a cyclohexane ring. If one assumes that this relationship holds where one component is a bicyclonane (and there is no obvious reason why it should not), it follows that a 3α-substituent in a seco-steroidal episulphide will be axial if the sulphur atom is β-oriented and equatorial if the sulphur atom is α-oriented. Since the thiirans (75a) and (75b) have been shown to possess an axial 3α-acetate and an equatorial 3β-acetate, respectively, we postulate that in these compounds and, by analogy, in all the other seco-steroidal thiirans, the sulphur atom has the β-orientation.

We naturally sought some experimental evidence, chemical or otherwise, to support this hypothesis. Epoxidation with a bulky reagent of a seco-steroidal olefin of known configuration at C-3 should give the corresponding 9α,10α-epoxide, attack occurring from the less hindered side of the molecule. If the same sort of conformational preferences were to exist with epoxides as with episulphides, and our assignments for the latter are correct, the orientation of the 3-substituent in a given epoxide should be opposite to that in the thiiran from which the olefin was derived.

Epoxidation of the 3β-acetoxy-17-ketone (83b) with *m*-chloroperbenzoic acid gave only one product, presumed to be the α-epoxide (89b). This assumption was confirmed when epoxidation of the slightly more hindered 3α-acetate (83a) gave, besides the α-epoxide (89a), a small amount of what was presumed to be the isomeric β-epoxide (91). Similarly, epoxidation of the 3-deoxy-17-ketone (82) gave, besides the α-epoxide (88), a little of the corresponding β-epoxide. Similarly the 3β,17β-diacetate (80b) gave the α-epoxide (90b), while its 3α-isomer (80a) gave the α-epoxide (90a) together with some of the β-epoxide (92).

An examination of the n.m.r. spectra of these epoxides did not support our theory. Whereas pairs of 3-acetoxy-episulphides isomeric at the 3-position show in the one case a signal at τ 5.15 ($W_{\frac{1}{2}}$ 22 Hz) attributable to an axial proton, and in the other case a signal at τ 4.95 ($W_{\frac{1}{2}}$ 11 Hz) attributable to an equatorial proton, the corresponding epoxides show signals at τ 5.16 ($W_{\frac{1}{2}}$ 16 Hz) and 5.07 ($W_{\frac{1}{2}}$ 12 Hz). This effect is unexplained, but it is possible that ring A of the epoxides exists in a twist conformation rather than a chair. The *cis*- and *trans*-thiiran acetates (44) and the corresponding epoxides (20), prepared for comparison, showed a precisely analogous effect, as did the benzoyloxy-epoxides (19a and b).

In view of these inconclusive results, we sought some chemical proof of structure. However, we were unable to convert the α-epoxide (90b) into the corresponding β-episulphide by reaction with triphenylphosphine

sulphide [22] or potassium thiocyanate.[23] Attempted oxidation of (73b) and (74) to the corresponding episulphoxides [24] for the purpose of n.m.r. studies (*cf.* refs. 3, 24, and refs. cited therein) led only to decomposition (*cf.* ref. 24).

EXPERIMENTAL

For preamble see Part 1.[21]

General Methods.—Condensation of hydrazino-acids with cycloalkanones. The hydrazino-acid (10 mmol) and the ketone (10 mmol) were heated under reflux in ethanol (20—100 ml) in a nitrogen atmosphere for 1—4 h. The mixture was cooled, filtered to remove any unchanged hydrazino-acid, and evaporated. If necessary, the residual hydrazone–acid was purified by crystallisation or trituration with ether.

Oxidation of carboxy-hydrazones to azines. The hydrazone–acid (25 mmol) in dichloromethane (500 ml) was stirred for 1 h with lead dioxide (100 g). The mixture was filtered through kieselguhr and the residue was washed with dichloromethane to give a chromatographically pure solution of the azine.

Addition of hydrogen sulphide to azines. A solution of the azine (25 mmol) in dichloromethane (600 ml) was treated with acetone (300 ml) and saturated with hydrogen sulphide at 15 °C. The mixture was stirred at 15 °C under reflux for 1—8 h, until reaction was complete (t.l.c.). Any lead sulphide present was removed by filtration through kieselguhr, and the hydrogen sulphide was evaporated off under reduced pressure below room temperature.

The resulting solution of thiadiazolidine in dichloromethane was oxidised in one of two ways:

(*a*) By addition of lead tetra-acetate (15 g, 34 mmol) in dichloromethane; the reaction was quenched after 15 min by addition of aqueous sodium hydrogencarbonate and the mixture was filtered through kieselguhr. The organic phase was separated, dried, and evaporated.

(*b*) By stirring with manganese dioxide [5] (50 g) for 30 min, filtration, and evaporation.

At this stage thiadiazolines containing hydroxy-groups were generally acetylated (acetic anhydride–pyridine); the product was washed well with sodium hydrogen carbonate to ensure a non-acidic medium in the ensuing pyrolysis.

The crude thiadiazoline was then heated under reflux in toluene for 1 h, and the solution was evaporated. The residue was partitioned between ether and aqueous sodium hydrogensulphite to remove the parent ketone. The ethereal solution was dried and evaporated to give the thiiran, which was purified by chromatography and/or crystallisation.

Desulphurisation of thiirans. The thiiran (10 mmol) was heated under reflux for about 1 h in acetic acid (50 ml) containing zinc dust (10 g). The mixture was filtered and the product was isolated either by evaporation or by pouring into water and extraction or collection of the precipitated olefin.

Condensation of 4-Benzoyloxycyclohexanone with Hydrazine and Hydrogen Sulphide.—4-Benzoyloxycyclohexanone [25] (1) (5 g, 23 mmol) was suspended in ethanol (25 ml) and the mixture was saturated with hydrogen sulphide under reflux at 10 °C. Hydrazine hydrate (545 mg, 11 mmol) in water (5 ml) was added over 45 min to the stirred mixture, which was then stirred under reflux for 5 h, and kept in a stoppered flask at room temperature for 3 days. The product was collected to give **3,11-trans-*bisbenzoyloxy*-7-*thia*-14,15-*diaza*-*dispiro*[5.1.5.2]*pentadecane*** (5c) as a white solid (4.9 g, 85%), m.p. 145—147°, $\nu_{max.}$ 3 340 (NH) and 1 712 cm^{-1} (ester), τ 5.88 (2 H, m, NH·NH) and 4.75 (2 H, m, C*H*OBz) (Found: C, 66.7; H, 6.2; N, 5.6; S. 7.0. $C_{26}H_{30}N_2O_4S$ requires C, 66.9; H, 6.5; N, 6.0; S, 6.9%).

3,11-trans-*Bisbenzoyloxy*-7-*thia*-14,15-*diazadispiro*[5.1.-5.2]*pentadec*-14-*ene* (7c).—The thiadiazolidine (5c) (4.48 g, 9 mmol) was stirred with manganese dioxide (9 g) in dichloromethane (50 ml) and acetone (22 ml) for 5 min. The mixture was filtered through Celite and the filtrate was evaporated under reduced pressure at room temperature. The residual solid (4.05 g, 88%) crystallised from methanol–dichloromethane to give the *thiadiazoline* (7c), m.p. 210°, $\nu_{max.}$ 1 718 cm^{-1} (ester), τ 4.71 (2 H, m, C*H*OBz) (Found: C, 66.9; H, 6.1; N, 6.0; S, 6.9. $C_{26}H_{28}N_2O_4S$ requires C, 67.2; H, 6.1; N, 6.0; S, 6.9%).

3,10-cis-*Bisbenzoyloxy*-13-*thiadispiro*[5.0.5.1]*tridecane* (10a *and* b).—The thiadiazolidine (5c) (51 g, 109 mmol) and lead tetra-acetate (54.3 g, 123 mmol) were stirred together at 0 °C in dichloromethane (700 ml) for 15 min. The resulting suspension was treated with an excess of aqueous sodium hydrogencarbonate and filtered through kieselguhr. The organic phase was separated, dried, and evaporated. The residual thiadiazoline (7c) was heated under reflux in toluene (500 ml) for 1 h, then cooled. Filtration gave the *diequatorial thiiran dibenzoate* (10b) (15.7 g, 33%) as crystals, m.p. 216—218°, $\nu_{max.}$ 1 700 cm^{-1} (ester), τ 4.87 (2 H, m, $W_{\frac{1}{2}}$ *ca.* 19 Hz, axial C*H*OBz) (Found: C, 71.8; H, 6.4; S, 7.2. $C_{26}H_{28}O_4S$ requires C, 71.5; H, 6.4; S, 7.3%).

The liquors were evaporated and crystallised from chloroform–petrol to give a mixture of the diaxial (10a) and diequatorial (10b) isomers (5.47 g, 11.5%). The remaining liquors were chromatographed on silica gel. Elution with dichloromethane gave (i) the *trans*-isomer (10c) (1.0 g, 2%); (ii) a mixture of the *cis*-isomers (10a and b) (4.6 g, 10%). Further elution with dichloromethane–ether (50 : 1) gave the crude *diaxial isomer* (10a) (11.3 g, 24%) which, after successive recrystallisations from ethanol and ethyl acetate, gave crystals, m.p. 133—134°, $\nu_{max.}$ 1 700 cm^{-1} (ester), τ 4.60 (2 H, m, $W_{\frac{1}{2}}$ *ca.* 9 Hz, *eq* C*H*OBz) (Found: C, 71.6; H, 6.6; S, 7.4. $C_{26}H_{28}O_4S$ requires C, 71.5; H, 6.4; S, 7.3%). The total yield of thiiran was 38 g (80%).

4-Benzoyloxycyclohexanone Azine (3).—4-Benzoyloxycyclohexanone (1) (4.4 g, 20 mmol), ethanol (15 ml), and hydrazine hydrate (0.5 ml, 10 mmol) were mixed at room temperature to give a homogeneous solution which was kept at 0 °C for 4 h. The resulting crystals were collected and dried to give the *azine* (3) (3.0 g, 70%), m.p. 112—113°, $\nu_{max.}$ (Nujol) 1 705 cm^{-1} (ester), τ 4.63 (2 H, m, C*H*OBz) (Found: C, 72.0; H, 6.6; N, 6.5. $C_{26}H_{28}N_2O_4$ requires C, 72.2; H, 6.5; N, 6.5%).

3,10-*Bisbenzoyloxy*-13-*thiadispiro*[5.0.5.1]*tridecane* (10) ***from* 4-*Benzoyloxycyclohexanone Azine*.**—The azine (3) (3.6 g, 8.3 mmol) was treated with hydrogen sulphide by the general method described above to give a solution of the thiadiazolidines (7a—c) in the ratios *ca.* 4 : 9 : 12 (by t.l.c.). After evaporation of hydrogen sulphide this mixture was oxidised with manganese dioxide and the product was pyrolysed in toluene. On cooling, the solution deposited

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the diequatorial thiiran dibenzoate (10b) (700 mg, 19%). P.l.c. (CH_2Cl_2) of the liquors gave (i) a white solid (1.5 g, 41%) which gave, from ethyl acetate, the trans-*thiiran dibenzoate* (10c), m.p. 192—194°, $\nu_{max.}$ 1 710 cm^{-1} (ester), τ 4.60 (1 H, m, $W_{\frac{1}{2}}$ 11 Hz, *eq* C*H*OBz) and 4.83 (1 H, m, $W_{\frac{1}{2}}$ 22 Hz, *ax* C*H*OBz) (Found: C, 71.2; H, 6.4; S, 7.5. $C_{26}H_{28}O_4S$ requires C, 71.5; H, 6.4; S, 7.3%); (ii) a mixture of the *cis*-isomers (10a and b) (1.7 g, 47%).

3,10-cis-*Dihydroxy*-13-*thiadispiro*[5.0.5.1]*tridecane, Diequatorial Isomer* (11b).—The diequatorial thiiran dibenzoate (10b), (7 g, 16 mmol) and potassium hydroxide (5.4 g, 96 mmol) were heated under reflux in methanol (100 ml), dimethyl sulphoxide (70 ml), and water (15 ml) until a clear solution was obtained. The mixture was poured into water and extracted with chloroform. The organic phase was dried and evaporated (finally at 1 mmHg) and the residue was recrystallised from methanol to give the diol (11b) as a methanol solvate (2.5 g, 68%) from which the solvent could not be removed. Recrystallisation from tetrahydrofuran gave the pure *diol* (11b), m.p. 188.5—189.5°, $\nu_{max.}$ 3 610 cm^{-1} (OH), τ(C_5D_5N) 6.00 (2 H, m, $W_{\frac{1}{2}}$ *ca.* 19 Hz, *ax* C*H*OH) (Found: C, 62.9; H, 8.8; S, 14.1. $C_{12}H_{20}O_2S$ requires C, 63.2; H, 8.8; S, 14.0%). A further quantity of the diol (11b) (760 mg, 21%), m.p. 189—190°, separated from the aqueous phase.

3,10-cis-*Dihydroxy*-13-*thiadispiro*[5.0.5.1]*tridecane, Diaxial Isomer* (11a).—The diaxial thiiran dibenzoate (10a) (4.34 g, 10 mmol) was hydrolysed as in the previous experiment. The mixture was poured into water and the product (1.85 g, 82%) was collected and dried. It gave (from methanol) white crystals of the *diol* (11a), m.p. 197—199°, $\nu_{max.}$ (Nujol) 3 430, 3 360, and 3 185 cm^{-1} (OH), τ(C_5D_5N) 5.75 (2 H, m, $W_{\frac{1}{2}}$ *ca.* 10 Hz, *eq* C*H*OH) (Found: C, 62.9; H, 8.8; S, 14.1. $C_{12}H_{20}O_2S$ requires C, 63.2; H. 8.8; S, 14.0%).

cis-4,4′-*Bisbenzoyloxy*-1,1′-*bi*(*cyclohexylidene*) (15a).—The thiadiazoline (7c) (2.0 g, 4.3 mmol) was pyrolysed in toluene to give a mixture of the *cis*-thiirans (10a and b) which was desulphurised as described above to give a white solid (1.59 g, 91%). Recrystallisation from methanol gave the *olefin* (15a), m.p. 96.5—97.5°, $\nu_{max.}$ 1 703 cm^{-1} (ester), τ 4.75 (2 H, m, C*H*OBz) (Found: C, 76.5; H, 7.1. $C_{26}H_{28}O_4$,0.25H_2O requires C, 76.3; H, 7.0%).

cis-3,10-*Bisbenzoyloxy*-13-*oxadispiro*[5.0.5.1]*tridecane* (19a *and* b).—The *cis*-olefin (15a) (1.01 g, 2.5 mmol) in dichloromethane (40 ml) was treated with *m*-chloroperbenzoic acid (85%; 508 mg, 2.5 mmol). After 15 min the mixture was washed with 5% sodium hydrogen carbonate, dried, and evaporated. P.l.c. (CH_2Cl_2) of the residue (1.05 g) yielded (i) the *less polar epoxide* (440 mg), presumed to be (19b), which gave (from ether–petrol–dichloromethane) crystals, m.p. 200—201°, $\nu_{max.}$ 1 708 cm^{-1} (ester), τ 4.84 (2 H, m, $W_{\frac{1}{2}}$ *ca.* 14 Hz, C*H*OBz) (Found: C, 74.0; H, 6.7. $C_{26}H_{28}O_5$ requires C, 74.3; H, 6.7%); (ii) the *more polar epoxide* (666 mg), presumed to be (19a), which gave (from ether) crystals, m.p. 149—150°, $\nu_{max.}$ 1 708 cm^{-1} (ester), τ 4.72 (2 H, m, $W_{\frac{1}{2}}$ *ca.* 12 Hz, C*H*OBz) (Found: C, 74.2; H, 6.7. $C_{26}H_{28}O_5$ requires C, 74.3; H, 6.7%).

trans-4,4′-*Bisbenzoyloxy*-1,1′-*bi*(*cyclohexylidene*) (15b).—A mixture of the thiirans (10a—c) (12.6 g, 28.9 mmol) was desulphurised as above. The product was crystallised from methanol to give (i) a mixture of the *cis*- and *trans*-olefins (15a and b) (5.56 g) in which the latter predominated; further recrystallisation gave the trans-*olefin* (15b), m.p. 175—176°, $\nu_{max.}$ 1 703 cm^{-1} (ester), τ 4.75 (2 H, m, C*H*OBz) (Found: C, 76.9; H, 7.0. $C_{26}H_{28}O_4$ requires C, 77.2; H, 7.0%); (ii) the *cis*-olefin (15a) (1.335 g), m.p. 94.5—95.5°. The mother liquors contained a mixture of the two olefins (3.78 g).

trans-4,4′-*Dihydroxy*-1,1′-*bi*(*cyclohexylidene*) (16b).—The *trans*-dibenzoate (15b) (1.87 g, 4.6 mmol) was heated under reflux for 45 min in methanol (100 ml) and water (7 ml) containing potassium hydroxide (2.59 g, 46 mmol). The solution was evaporated to *ca.* 20 ml and diluted with water (120 ml). The precipitate was collected and dried to give the trans-*diol* (16b) (750 mg, 83%), m.p. 201—204°, $\nu_{max.}$ (Nujol) 3 300 and 3 220 cm^{-1} (OH), τ[$(CD_3)_2SO$] 6.40 (2 H, m, C*H*OH) (Found: C, 72.6; H, 10.0. $C_{12}H_{20}O_2$,0.125H_2O requires C, 72.5; H, 10.3%).

cis-4,4′-*Dihydroxy*-1,1′-*bi*(*cyclohexylidene*) (16a).—The *cis*-dibenzoate (15a) (4.6 g, 11.4 mmol) was hydrolysed as above to give the cis-*diol* (16a) (1.97 g, 88%), m.p. 192—193°, $\nu_{max.}$ (Nujol) 3 254 cm^{-1} (OH), τ[$(CD_3)_2SO$] 6.40 (2 H, m, C*H*OH) (Found: C, 73.2; H, 10.1. $C_{12}H_{20}O_2$ requires C, 73.5; H, 10.2%).

13-*Thiadispiro*[5.0.5.1]*tridecane*-3,12-*dione* (21).—A mixture of the *cis*-diols (11a and b) (2.598 g, 11.4 mmol) was oxidised by the Moffatt procedure [9] to give a solid (3.09 g). Chromatography on silica gel in dichloromethane–ether (24 : 1) gave the *dione* (21) (500 mg, 20%), which gave (from methanol) crystals, m.p. 181—183°, $\nu_{max.}$ 1 720 cm^{-1} (C=O), τ 7.40 (8 H, m, CH_2), 7.56 (4 H, m, CH_2), and 7.77 (4 H, m, CH_2) (Found: C, 63.3; H, 7.25; S, 13.5. $C_{12}H_{16}O_2S$,-0.25H_2O requires C, 63.0; H, 7.15; S, 14.0%).

1,1′-*Bi*(*cyclohexylidene*)-4,4′-*dione* (22).—The diol (16a) (3.92 g, 20 mmol) was oxidised as above and the crude product was partitioned between ether and 10% sodium hydrogen sulphite. The aqueous phase was acidified to pH 1 with hydrochloric acid and extracted with chloroform. The extract was washed with aqueous sodium hydrogencarbonate, dried, and evaporated. The residue was crystallised from di-isopropyl ether to give the *dione* (22) (1.29 g, 34%), m.p. 121—122°, $\nu_{max.}$ (Nujol) 1 710 cm^{-1} (C=O) (Found: C, 74.6; H, 8.45. $C_{12}H_{16}O_2$ requires C, 75.0; H, 8.4%).

4-(*Ethoxycarbonylhydrazono*)*cyclohexyl Benzoate*.—4-Benzoyloxycyclohexanone (20 g, 92 mmol) in ethanol (100 ml) was treated with ethyl carbazate (10 g) and triethylamine (0.5 ml) and the mixture was kept at 0 °C for 3 days. The product was collected, washed with 50% aqueous ethanol, and dried to give the *title compound* (23 g, 82%), m.p. 106—107°, $\lambda_{max.}$ (EtOH) 228.5 nm (ε 24 600), $\nu_{max.}$ 3 370 (NH), 1 738 and 1 709 cm^{-1} (esters), τ 8.70 (3 H, t, *J* 7 Hz, OCH_2CH_3), 5.71 (2 H, q, *J* 7 Hz, OCH_2CH_3), and 4.68 (1 H, m, C*H*OBz) (Found: C, 63.2; H, 6.8; N, 9.3. $C_{16}H_{20}N_2O_4$ requires C, 63.1; H, 6.6; N, 9.2%).

4-(2-*Ethoxycarbonylhydrazino*)*cyclohexyl Benzoate*.—The above hydrazone (3 g) was hydrogenated over Adams catalyst (200 mg) in ethyl acetate (100 ml) and acetic acid (5 ml). After filtration, the solution was washed with aqueous sodium hydrogencarbonate, dried, and evaporated to give the title compound as an oil (2.5 g, 75%), $\nu_{max.}$ 3 430 and 3 295 (NH), and 1 709 cm^{-1} (esters), τ 8.74 (3 H, t, *J* 7 Hz, OCH_2CH_3), 5.81 (2 H, q, *J* 7 Hz, OCH_2CH_3), and 4.80 (1 H, m, C*H*OBz).

4-*Hydroxycyclohexylhydrazine*.—The above disubstituted hydrazine (20 g) was stirred under reflux for 2 h with aqueous 40% sodium hydroxide (40 ml). The resulting suspension was diluted with propan-2-ol (250 ml), neutralised with solid carbon dioxide, and filtered through kieselguhr. The filter pad was washed with propan-2-ol and the

combined filtrates were evaporated with the aid of benzene. The residue was triturated with ether–methanol (5 : 1, 120 ml) and the solution was filtered and evaporated to give the crude title compound (9.0 g, 105%), $\nu_{max.}$ 3 600—2 500 cm^{-1} (OH, NH, NH_2).

4-(4-*Hydroxycyclohexylhydrazono*)*cyclohexyl Benzoate* (26).—4-Benzoyloxycyclohexanone (1 g, 4.6 mmol) and 4-hydroxycyclohexylhydrazine (1 g, 7.7 mmol) were dissolved in methanol (5 ml) under nitrogen and the solution was kept overnight, then partitioned between water and ether. The organic phase was washed with water, dried, and evaporated, and the residue was crystallised from ether to give the hydrazone (26) (400 mg, 26%), $\nu_{max.}$ 3 600 (OH) and 1 709 cm^{-1} (ester), τ 6.10 (1 H, m, C*H*OH) and 4.72 (1 H, m, C*H*OBz).

4-*Acetoxy*-4-(4-*hydroxycyclohexylazo*)*cyclohexyl Benzoate* (27).—The hydrazone (26) (2.3 g, 7 mmol) was treated with lead tetra-acetate (3.6 g, 8.1 mmol) in dichloromethane (150 ml) at 5 °C. The mixture was washed with aqueous sodium thiosulphate, dried, and evaporated, and the residual oil was chromatographed on alumina. Ethyl acetate–petrol (1 : 4) eluted 4-benzoyloxycyclohexanone; ethyl acetate eluted the *azo-acetate* (27) (1.9 g, 70%) as an oil, $\nu_{max.}$ 3 615, 3 490 (OH), 1 730 (OAc), and 1 710 cm^{-1} (OBz), τ 7.89 and 7.90 (3 H, both s, $OCOCH_3$), 6.48 (1 H, m, CH–N=), 6.04 (1 H, m, C*H*OH), and 4.69 and 4.90 (1 H, both m, $W_{\frac{1}{2}}$ 8 and 22 Hz, respectively, *eq* and *ax* C*H*OBz) (Found: C, 64.5; H, 7.4; N, 6.7. $C_{21}H_{28}N_2O_5$ requires C, 64.9; H, 7.3; N, 7.2%).

Reaction of Cyclohexanone with Potassium Cyanide and Hydrazine Hydrochloride.—A mixture of potassium cyanide (6.5 g, 0.1 mol), hydrazine hydrate (10 ml, 0.2 mol), water (60 ml), and hydrazine hydrochloride (5.2 g, 50 mmol) was treated with cyclohexanone (10 ml, 0.1 mol) and stirred at room temperature for 2 h. The crystalline product (2.1 g, 10%) was collected and identified as (1-*cyanocyclohexyl-hydrazono*)*cyclohexane*, m.p. 85°, $\nu_{max.}$ 2 230 cm^{-1} (C≡N), τ 5.30br (1 H, s, NH) (Found: C, 70.5; H, 9.6; N, 20.5. $C_{13}H_{21}N_3,0.125H_2O$ requires C, 70.5; H, 9.7; N, 19.0%).

The filtrate was extracted with dichloromethane and the extract was washed with 5N-hydrochloric acid (50 ml). A crystalline solid separated from the aqueous phase and was collected and dried to give 1-*cyanocyclohexylhydrazine hydrochloride*, m.p. 140—142°, $\nu_{max.}$ (KBr) 3 190 (NH), 2 800—2 600 (NH_3^+), and 2 228 cm^{-1} (C≡N) (Found: C, 47.5; H, 8.2; Cl. 20.4; N, 24.4. $C_7H_{14}ClN_3$ requires C, 47.9; H, 8.0; Cl, 20.2; N, 24.0%).

1-*Semicarbazidocyclohexanecarbonitrile* (33).—50% Sulphuric acid (29 g) was added with cooling to a stirred solution of potassium cyanide (19.3 g, 0.34 mol) in water (60 ml). Cyclohexanone semicarbazone (23 g, 0.15 mol) and ethanol (150 ml) were added and the mixture was stirred at 0 °C for 1 h. A slow stream of nitrogen was passed through the solution overnight at room temperature, the effluent gas being bubbled through hypochlorite solution to destroy hydrogen cyanide. The solution was evaporated to low volume, water was added, and the product (27.2 g, 96%) was collected, dried, and recrystallised from ethanol to give *compound* (33), m.p. 169°, $\nu_{max.}$ 3 510, 3 380, and 3 330 (NH, NH_2), and 1 690, 1 600, and 1 565 cm^{-1} (CONH), τ[$(CD_3)_2SO$] 4.53 (1 H, d, *J* 2.5 Hz, N*H*NHCONH$_2$), 3.97br (2 H, s, $CONH_2$), and 2.80 (1 H, d, *J* 2.5 Hz, NHN*H*-$CONH_2$) (Found: C, 52.5; H, 7.6; N, 31.1. $C_8H_{14}N_4O$ requires C, 52.7; H, 7.7; N, 30.8%).

1-*Semicarbazidocyclohexanecarboxamide* (34).—1-Cyanocyclohexylsemicarbazide (33) (1 g, 5 mmol) was dissolved with stirring in concentrated sulphuric acid (5 ml) at room temperature. After 5 min the solution was poured onto ice (25 g), neutralised with 40% sodium hydroxide, and cooled. The resulting solid was collected, washed with water, and dried to give the *amide* (34) (600 mg, 55%), m.p. 197—198°, $\nu_{max.}$ (Nujol) 3 458—3 190 (NH), 1 660, 1 635, 1 574, and 1 530 cm^{-1} (CONH), τ[$(CD_3)_2SO$] 2.38br (s) and 3.05br (s) ($NHCON\mathit{H}_2$), 3.43br (1 H, s, NH·N*H*CONH$_2$), 4.01br (2 H, s, $CONH_2$), and 5.20br (1 H, s, N*H*·NHCONH$_2$) (Found: C, 47.7; H, 8.1; N, 27.7. $C_8H_{16}N_4O_2$ requires C, 48.0; H, 8.0; H, 28.0%).

1-*Hydrazinocyclohexanecarboxylic Acid* (35).—(a) *From* 1-*bromocyclohexanecarboxylic acid*. The bromo-acid [26] (20 g, 96 mmol) in ethanol (50 ml) was treated with hydrazine hydrate (90%; 100 ml). After 1 h, the mixture was evaporated to dryness with the aid of toluene. The residue was adsorbed onto Zeocarb 225 ion-exchange resin (H^+ form) which was then washed well with ethanol. Elution of the resin with 4% ammonia (s.g. 0.880) in 50% aqueous ethanol and evaporation of the eluate gave a solid which was triturated with methanol. The undissolved solid (5.4 g, 35%) was recrystallised from water to give the *hydrazino-acid* (35), m.p. 242—243°, $\nu_{max.}$ (Nujol) 3 360 and 3 273 (NH), 3 100—2 100 (OH, NH_3^+), and 1 550 cm^{-1} (CO_2^-) (Found: C, 53.0; H, 8.9; N, 17.9. $C_7H_{14}N_2O_2$ requires C, 53.1; H, 8.9; N, 17.7%).

(b) *From* 1-*semicarbazidocyclohexanecarboxamide*. The amide (34) (270 g, 1.35 mol) and sodium hydroxide (270 g, 6.8 mol) were stirred under reflux in ethylene glycol (1.45 l) for 8 h in a stainless steel vessel. (Care is required as evolution of ammonia is initially rapid and causes much frothing.) The mixture was cooled, poured onto ice (1.5 kg), and neutralised with acetic acid (750 ml) (again severe frothing). The hydrazino-acid (35) (170 g, 80%) was collected, washed with water, and dried. Recrystallisation from water gave material (130 g, 61%), m.p. 235—240°.

4-(1-*Carboxycyclohexylhydrazono*)*cyclohexanol* (38).—Condensation of the hydrazino-acid (35) (3.75 g, 24 mmol) with 4-hydroxycyclohexanone [25] (36) (2.72 g, 24 mmol) and crystallisation of the product (5.03 g, 83%) from water gave the *hydrazone* (38), m.p. 158—159°, $\nu_{max.}$ 3 610 (OH), 3 600—2 300 (OH, NH), and 1 735 and 1 700 cm^{-1} (CO_2H), τ[$(CD_3)_2SO$] 6.25 (1 H, m, C*H*OH) (Found: C, 60.4; H, 8.8; N, 10.9. $C_{13}H_{22}N_2O_3,0.25H_2O$ requires C, 60.3; H, 8.8; N, 10.8%).

13-*Thiadispiro*[5.0.5.1]*tridecan*-3-*ol* (43).—The hydrazone (38) (9.5 g, 37 mmol) was converted into the mixed azine (41) and thence into the corresponding thiirans (43). The product was chromatographed on alumina (500 g): (i) elution with dichloromethane–ether (19 : 1) gave a solid (550 mg, 7%) which was crystallised twice from petrol–dichloromethane to give the *axial alcohol* (43a), m.p. 130—131°, $\nu_{max.}$ 3 605 cm^{-1} (OH), τ 5.96 (1 H, m, $W_{\frac{1}{2}}$ 12 Hz, *eq* C*H*OH) (Found: C, 67.95; H, 9.4; S, 15.2. $C_{12}H_{20}OS$ requires C, 67.9; H, 9.5; S, 15.1%); (ii) further elution with the same solvent gave an oil (1.3 g) which was further chromatographed on alumina in ether–petrol (1 : 2) to give a compound (200 mg) whose spectral characteristics [$\nu_{max.}$ 3 602 and 3 460 cm^{-1} (OH), τ 6.20 (1 H, m, C*H*OH) and 4.18 (1 H, m, =CH–)] were consistent with (4-hydroxycyclohex-1-enyl)cyclohexyl sulphide (54); (iii) further elution with dichloromethane–ether (9 : 1) gave a solid (1.3 g, 17%) which was recrystallised twice from petrol–dichloromethane

[26] J. von Braun, *Ber.*, 1934, **67**, 218.

to give the *equatorial alcohol* (43b), m.p. 135—136°, $\nu_{max.}$ 3 600 cm^{-1} (OH), τ 6.20 (1 H, m, $W_{\frac{1}{2}}$ 22 Hz, *ax* C*H*OH) (Found: C, 67.9; H, 9.6; S, 14.95. $C_{12}H_{20}OS$ requires C, 67.9; H, 9.5; S, 15.1%).

4-*Hydroxy*-1,1′-*bi*(*cyclohexylidene*) (48).—The hydrazone (38) (1.0 g, 3.9 mmol) was converted as above into the thiiran (43) and the crude product was heated under reflux for 45 min with zinc in acetic acid; a strong smell of thiol was noted. The crude product contained some acetate ($\nu_{max.}$ 1 750 cm^{-1}) and was therefore heated under reflux for 30 min in a mixture of ethanol (25 ml) and 2N-sodium hydroxide (10 ml). The mixture was partitioned between ether and water, and the organic phase was dried and evaporated to give the olefin [27] (48) (260 mg, 37%).

4-(1-*Carboxycyclohexylhydrazono*)*cyclohexyl Benzoate* (39).—Condensation of 4-benzoyloxycyclohexanone (1) [25] (24.3 g, 0.11 mol) with the hydrazino-acid (35) (16.75 g, 0.106 mol) and recrystallisation of the product (36.2 g, 95%) from ethanol gave the *hydrazone* (39), m.p. 184—186°, $\nu_{max.}$ (Nujol) 2 700 and 2 500—2 000 (=$\overset{+}{N}H$, $\overset{+}{N}H_2$), 1 720 (ester), and 1 605 cm^{-1} (CO_2^-), τ[$(CD_3)_2SO$] 4.70 (1 H, m, C*H*OBz) (Found: C, 66.8; H, 7.4; N, 7.7. $C_{20}H_{26}N_2O_4$ requires C, 67.1; H, 7.3; N, 7.9%).

3-*Benzoyloxy*-13-*thiadispiro*[5.0.5.1]*tridecane* (45).—The hydrazone (39) (20 g, 56 mmol) was converted in the usual way into the thiiran (45). The crude product was crystallised from methanol to give the *equatorial isomer* (45b) (4.0 g, 23%) as crystals, m.p. 135—136°, $\nu_{max.}$ 1 702 cm^{-1} (ester), τ 4.82 (1 H, m, $W_{\frac{1}{2}}$ *ca.* 20 Hz, *ax* C*H*OBz) (Found: C, 72.1; H, 7.5; S, 10.0. $C_{19}H_{24}O_2S$ requires C, 72.1; H, 7.6; S, 10.1%). The liquors were chromatographed on alumina in petrol–dichloromethane (1 : 1) to give (i) the equatorial isomer (45b) (1.6 g, 9%); (ii) a mixture of axial and equatorial isomers (1.0 g, 6%); (iii) the *axial isomer* (45a) (2.1 g, 12%) which gave (from methanol) crystals, m.p. 91°, $\nu_{max.}$ 1 701 cm^{-1} (ester), τ 4.62 (1 H, m, $W_{\frac{1}{2}}$ *ca.* 10 Hz, *eq* C*H*OBz) (Found: C, 72.2; H, 7.6; S, 10.2. $C_{19}H_{24}O_2S$ requires C, 72.1; H, 7.6; S, 10.1%).

4-*Benzoyloxy*-1,1′-*bi*(*cyclohexylidene*) (49).—The hydrazone (39) (1.0 g, 2.8 mmol) was converted as above into the thiiran (45) and the crude product was reduced with zinc and acetic acid. P.l.c. (C_6H_6–EtOAc, 9 : 1) of the product yielded the olefin (49) (275 mg, 35%), m.p. 70—71° (lit.,[27] 75—76°).

Methyl 4-(1-*Carboxycyclohexylhydrazono*)*cyclohexylacetate* (40).—4-Oxocyclohexylacetic acid [28] (20 g, 128 mmol) was esterified with hydrogen chloride in methanol (175 ml) for 1 h at room temperature. The mixture was then evaporated to dryness with the aid of toluene. Condensation of the residue with the hydrazino-acid (35) (20 g, 127 mmol) gave the *hydrazone* (40), (34.5 g, 87%), m.p. 165°, $\nu_{max.}$ (Nujol) 2 800—2 600 (NH_2^+), 1 738 (ester), and 1 605 cm^{-1} (CO_2^-), τ[$(CD_3)_2SO$] 6.38 (3 H, s, OCH_3) (Found: C, 61.7; H, 8.4; N, 9.0. $C_{16}H_{26}N_2O_4$ requires C, 61.9; H, 8.4; N, 9.0%).

3-*Methoxycarbonylmethyl*-13-*thiadispiro*[5.0.5.1]*tridecane* (46).—The hydrazone (40) (8 g, 26 mmol) was converted in the usual way into the thiiran (46). The crude product was chromatographed on alumina (500 g) in petrol–dichloromethane (1 : 1) to give (i) the thiiran (9) (200 mg, 3.8%); (ii) the *equatorial ester* (46) (1.6 g, 24%) which gave (from methanol) crystals, m.p. 97—98°, $\nu_{max.}$ 1 722 cm^{-1} (ester), τ($CDCl_3$) 6.30 (3 H, s, OCH_3), τ[$CDCl_3$ + Eu(fod)$_3$] 3.71 (3 H, s, OCH_3), 4.87 and 4.99 (2 H, both s, $CH_2CO_2CH_3$), and 5.9br (1 H, m, $CHCH_2CO_2CH_3$) (Found: C, 67.2; H, 9.0; S, 12.05. $C_{15}H_{24}O_2S$ requires C, 67.1; H, 9.0; S, 11.9%).

3-*Carboxymethyl*-13-*thiadispiro*[5.0.5.1]*tridecane* (47).—The methyl ester (46) (1.1 g, 4.1 mmol) was heated under reflux for 1 h in methanol (30 ml) containing 2N-sodium hydroxide (5 ml). Water was added, followed by hydrochloric acid, and the precipitated solid was collected and washed with water. Recrystallisation from ethanol gave the *acid* (47) (960 mg, 92%), m.p. 201°, $\nu_{max.}$ (Nujol) 3 400—2 200 (OH) and 1 690 cm^{-1} (CO_2H) (Found: C, 65.9; H, 8.7; S, 12.4. $C_{14}H_{22}O_2S$ requires C, 66.1; H, 8.7; S, 12.6%).

4-*Methoxycarbonylmethyl*-1,1′-*bi*(*cyclohexylidene*) (50).—The thiiran (46) (3 g, 11 mmol) was desulphurised in the usual way to give the *olefin* (50) (2.3 g, 87%), m.p. 56—57°, $\nu_{max.}$ (Nujol) 1 732 cm^{-1} (ester), τ 6.30 (3 H, s, OCH_3) (Found: C, 76.1; H, 10.3. $C_{15}H_{24}O_2$ requires C, 76.2; H, 10.2%).

4-*Carboxymethyl*-1,1′-*bi*(*cyclohexylidene*) (51).—The ester (50) (1.8 g, 7.5 mmol) was heated under reflux for 1 h in methanol (60 ml) containing 2N-sodium hydroxide (10 ml). The solution was acidified with hydrochloric acid and diluted with water. The resulting solid was collected and recrystallised from ethanol to give the *acid* (51) (1.3 g, 77%), m.p. 135—136°, $\nu_{max.}$ (Nujol) 3 500—2 200 (OH) and 1 681 cm^{-1} (CO_2H), τ −0.68br (1 H, s, CO_2H) (Found: C, 75.4; H, 9.9. $C_{14}H_{22}O_2$ requires C, 75.6; H, 10.0%).

4-*Benzoyloxycyclohexanone Propionylhydrazone* (57).—4-Benzoyloxycyclohexanone [25] (4.36 g, 20 mmol) and propionylhydrazine (1.76 g, 20 mmol) were heated under reflux in ethanol (10 ml) for 1 h, then cooled at 0 °C. The product was collected and dried to give the *hydrazone* (57) (2.7 g, 45%), m.p. 106—107°, $\nu_{max.}$ (Nujol) 3 210 (NH), 1 710 (ester), and 1 664 and 1 460 cm^{-1} (CONH), τ 8.81 (3 H, t, *J* 7 Hz, $COCH_2CH_3$), 7.44 (2 H, q, *J* 7 Hz, $COCH_2CH_3$), 6.67 (1 H, m, C*H*OBz), and 0.75br (1 H, s, NH) (Found: C, 66.6; H, 7.0; N, 9.5. $C_{16}H_{20}N_2O_3$ requires C, 66.7; H, 7.0; N, 9.7%).

4-*Benzoyloxy*-1-(2-*propionylhydrazino*)*cyclohexanecarbonitrile* (56).—(*a*) The hydrazone (57) (1.4 g, 4.9 mmol) and potassium cyanide (1.3 g, 20 mmol) in ethanol (20 ml) were treated with cooling with concentrated sulphuric acid (1 g, 10 mmol) in water (2 ml). After 3 days, the mixture was partitioned between water and ether, and the organic phase was dried and evaporated to give the nitrile (56) (1.5 g, 98%) as a mixture of isomers. This material (300 mg) was subjected to p.l.c. ($CHCl_3$–MeOH, 19 : 1) to give (i) the *less polar isomer* which gave (from methanol) white crystals (190 mg, 62%), m.p. 86—89°, $\nu_{max.}$ (Nujol) 3 500—3 100 (NH), 2 230 (C≡N), 1 708 (ester), 1 650 and 1 535 cm^{-1} (CONH), τ[$(CD_3)_2SO$] 8.91 (3 H, t, *J* 7 Hz, $COCH_2CH_3$), 7.81 (2 H, q, *J* 7 Hz, $COCH_2CH_3$), 6.80 (1.5 H, d, *J* 5 Hz, CH_3OH), 4.82 (1 H, m, $W_{\frac{1}{2}}$ 9 Hz, *eq* C*H*OBz), and 4.20 and 0.45 (2 H, each d, *J* 7 Hz, N*H*·N*H*) (Found: C, 63.1; H, 7.0; N, 12.4. $C_{17}H_{21}N_3O_3$,0.5CH_3OH requires C, 63.4; H, 7.0; N, 12.7%); (ii) the *more polar isomer* which gave (from methanol) white crystals (60 mg, 20%), m.p. 126°, $\nu_{max.}$ (Nujol) 3 410 and 3 300 (NH), 2 252 (C≡N), 1 718 (ester), 1 670 and 1 545 cm^{-1} (CONH), τ[$(CD_3)_2SO$] 8.93 (3 H, t, *J* 7 Hz, $COCH_2CH_3$), 7.83 (2 H, q, *J* 7 Hz, $COCH_2CH_3$), 4.97 (1 H, m, $W_{\frac{1}{2}}$ 15 Hz, *ax* C*H*OBz), and 4.27 and 0.54 (2 H, each d, *J* 7 Hz, NH·NH) (Found: C, 64.5; H, 6.8; N, 13.2. $C_{17}H_{21}N_3O_3$ requires C, 64.8; H, 6.7; N, 13.3%).

[27] D. J. Humphreys, P. M. Lawrence and C. E. Newall, *J.C.S. Perkin I*, 1978, 19.

[28] D. D. Phillips and D. N. Chatterjee, *J. Amer. Chem. Soc.*, 1958, **80**, 1360.

(*b*) On a larger scale, 4-benzoyloxycyclohexanone (21.8 g, 0.1 mol) and propionylhydrazine (8.8 g, 0.1 mol) were heated under reflux for 1 h in ethanol (400 ml). The cooled and stirred mixture was treated successively with potassium cyanide (13 g, 0.2 mol) and a solution of concentrated sulphuric acid (10 g, 0.1 mol) in water (20 ml). After 2 days, water was added to give the mixed isomers of the nitrile (56) (26 g, 83%). The isomers can be separated by column chromatography over silica gel: the less polar isomer is eluted with dichloromethane, and the more polar isomer with methanol–dichloromethane (1 : 4).

4-*Benzoyloxy*-1-(2-*propionylhydrazino*)*cyclohexanecarboxamide* (58).—The nitrile (56) (mixed isomers; 292 g, 927 mmol) was dissolved in concentrated sulphuric acid (1 500 ml) below 10 °C with efficient stirring and the solution was poured slowly onto ice (12 kg). The mixture was neutralised with ammonia (s.g. 0.880; 4.5 l) below 30 °C and the supernatant liquors were decanted. The residual gum was triturated with ethyl acetate (2 l) and the resulting solid was collected and dried to give the *equatorial benzoyloxy-isomer* (108 g, 35%), m.p. 122—125°, $\nu_{max.}$ 3 550, 3 440, 3 360 (NH), 1 709 (ester), and 1 680 and 1 560 cm^{-1} (CONH), τ[$(CD_3)_2SO$] 8.98 (3 H, t, *J* 7 Hz, $COCH_2CH_3$), 7.85 (2 H, q, *J* 7 Hz, $COCH_2CH_3$), 5.05 (1 H, m, $W_{\frac{1}{2}}$ 17 Hz, *ax* *CH*OBz), and 4.75 and 1.05 (2 H, each d, *J* 7 Hz, NH·NH) (Found: C, 58.1; H, 7.2; N, 11.9. $C_{17}H_{23}N_3O_4,H_2O$ requires C, 58.2; H, 7.2; N, 12.0%). The ethyl acetate solution was evaporated and the residue was triturated with ether and water. The resulting solid was collected and dried to give the *axial benzoyloxy-isomer* which gave (from aqueous methanol) white crystals, m.p. 85—90°, $\nu_{max.}$ (Nujol) 3 470, 3 365, 3 320, 3 270, and 3 155 (NH), 1 714 (ester), and 1 660 and 1 560 cm^{-1} (CONH), τ[$(CD_3)_2SO$] 8.98 (3 H, t, *J* 7 Hz, $COCH_2CH_3$), 7.88 (2 H, q, *J* 7 Hz, $COCH_2CH_3$), 4.92 (1 H, m, $W_{\frac{1}{2}}$ 8 Hz, *eq* *CH*OBz), and 4.79br(s) and 1.16br (s) (2 H, NH·NH) (Found: C, 58.0; H, 7.3; N, 11.8. $C_{17}H_{23}N_3O_4,H_2O$ requires C, 58.2; H, 7.2; N, 12.0%).

Hydrolysis of the separated isomers of the nitrile (56) showed that the nitrile with an axial benzoyloxy-group gave the amide (58) with an equatorial benzoyloxy-group, and *vice versa*.

1-*Hydrazino*-4-*hydroxycyclohexanecarboxylic Acid* (59).—The amide (58) (equatorial benzoyloxy-isomer; 108 g, 325 mmol) was heated under reflux for 1 h in aqueous 40% sodium hydroxide (250 ml) under nitrogen in a stainless steel flask. Water (50 ml) was added to dissolve the precipitate and heating was continued for a further 4 h. Acetic acid (200 ml) was added and the solution was cooled to 5 °C. The resulting solid (20 g) was collected, washed with methanol, and dried.

Benzaldehyde (20 ml) was added to the liquors, which were kept for 3 days, then extracted with dichloromethane. The extract was evaporated and the residue was steam distilled until there was very little smell of benzaldehyde. The aqueous solution was decanted and evaporated, and the residue was crystallised from methanol to give a second solid (5 g). The two solids were combined and crystallised from water to give the *hydrazino-acid* (59) (22.4 g, 40%), m.p. 243°, $\nu_{max.}$ (Nujol) 3 465, 3 372, 3 280, and 3 150—2 300 (OH, NH), and 1 660 cm^{-1} (CO_2H), τ(D_2O) 6.20 (1 H, m, *CH*OH) (Found: C, 45.8; H, 7.9; N, 15.2. $C_7H_{14}N_2O_3,0.5H_2O$ requires C, 45.9; H, 8.2; N, 15.3%).

(±)-7β-*Acetoxy*-6β-*methyl*-trans-*bicyclo*[4.3.0]*nonan*-3-*one* (62).—The hydroxy-ketone [21] (61) (500 mg, 3 mmol) was kept for 24 h with acetic anhydride (3 ml) and pyridine (6 ml) and the mixture was partitioned between ether and water. The organic phase was washed successively with 2N-hydrochloric acid, water, and saturated sodium hydrogen carbonate, dried, and evaporated to give the acetate (62) (600 mg, 95%) as a gum, $\nu_{max.}$ 1 720 (ester) and 1 710 cm^{-1} (C=O), τ 8.95 (3 H, s, CH_3), 7.92 (3 H, s, $OCOCH_3$), and 5.20 (1 H, m, *CH*OAc).

(±)-17β-*Acetoxy*-6,7-*dinor*-5,8-*secoestr*-9-*ene* (77).—The oxo-acetate (62) (570 mg, 2.7 mmol) and the hydrazino-acid (35) (430 mg, 2.7 mmol) were condensed to give the corresponding hydrazone (65), which was treated by the general method described above. P.l.c. (CH_2Cl_2) of the crude product yielded the *olefin* (77) (130 mg, 18%), $\nu_{max.}$ 1 722 cm^{-1} (ester), τ 9.15 (3 H, s, CH_3), 7.99 (3 H, s, $OCOCH_3$), and 5.40 (1 H, m, 17α-H), g.l.c. purity 94% (Found: C, 70.2; H, 9.15. $C_{18}H_{28}O_2,0.5CH_2Cl_2$ requires C, 69.7; H, 9.1%). Hydrolysis gave the corresponding 17-alcohol, identical with an authentic specimen.[1]

(±)-3α (*and* β),17β-*Diacetoxy*-9β,10β-*epithio*-6,7-*dinor*-5,8-*secoestrane* (73a *and* b).—(a) *From the hydroxy-ketone* (61). Condensation of the hydroxy-ketone (61) (1.0 g, 6 mmol) and the hydrazino-acid (59) (1.0 g, 5.9 mmol) gave the corresponding hydrazone (66), which, because of its low solubility, was oxidised with lead dioxide in dichloromethane (100 ml) containing methanol (20 ml). The solvents were removed *in vacuo* below 5 °C after addition of hydrogen sulphide to the azine, and the thiadiazolidine was oxidised with manganese dioxide in acetone–dichloromethane (1 : 3). The crude thiadiazoline was acetylated before pyrolysis in toluene. The crude thiiran (1.6 g) was crystallised from ether to give a solid (225 mg, 11%), which was recrystallised from methanol to give the 3β,17β-*diacetate* (73b), m.p. 178—179°, $\nu_{max.}$ 1 725 cm^{-1} (esters), τ 9.12 (3 H, s, CH_3), 7.96 (6 H, s, 2 × $OCOCH_3$), 5.30 (1 H, dd, *J* 7 and 8.5 Hz, 17α-H), and 5.18 (1 H, m, $W_{\frac{1}{2}}$ 24 Hz, *ax*-3-H) (Found: C, 65.3; H, 8.3; S, 8.7. $C_{20}H_{30}O_4S$ requires C, 65.5; H, 8.3; S, 8.8%). The combined liquors were chromatographed on alumina (500 g) in dichloromethane to give (i) the 3β,17β-diacetate (73b) (230 mg, 11.5%); (ii) a mixture of (73b) and the 3α,17β-diacetate (73a) (190 mg, 9.5%); (iii) an oil (545 mg) which crystallised from methanol to give the 3α,-17β-*diacetate* (73a) (190 mg, 9.5%), m.p. 137—140°, $\nu_{max.}$ 1 720 cm^{-1} (esters), τ 9.13 (3 H, s, CH_3), 7.95 and 7.97 (6 H, both s, 2 × $OCOCH_3$), 5.29 (1 H, dd, *J* 7 and 8.5 Hz, 17α-H), and 4.94 (1 H, m, $W_{\frac{1}{2}}$ 11 Hz, *eq*-3-H) (Found: C, 65.4; H, 8.2; S, 8.75. $C_{20}H_{30}O_4S$ requires C, 65.5; H, 8.3; S, 8.8%). The total yield of thiiran was 41.5%. The remaining liquors consisted mainly of the dimethyl acetal of the oxo-acetate (62).

(b) *From the oxo-acetate* (62). Condensation of the oxo-acetate (62) (12.0 g, 57 mmol) with the hydrazino-acid (59) (10.7 g, 62 mmol) afforded the *hydrazone* (67), $\nu_{max.}$ 3 600 (OH), 3 600—2 200 (OH, NH), and 1 712 cm^{-1} (CO_2H, ester), τ[$(CD_3)_2SO$] 9.11 (3 H, s, CH_3), 7.98 (3 H, s, $OCOCH_3$), 6.50 (1 H, m, *CH*OH), and 5.30 (1 H, m, *CH*OAc) (Found: C, 57.8; H, 8.2; N, 6.8. $C_{19}H_{30}N_2O_5,1.5H_2O$ requires C, 58.0; H, 8.4; N, 7.1%). Successive oxidation, addition of hydrogen sulphide, oxidation, and pyrolysis gave a gum which was partitioned between ether and aqueous 10% sodium hydrogensulphite. Basification of the aqueous phase and extraction with dichloromethane yielded the oxo-ester (62) (2.2 g, 16%). Evaporation of the ethereal solution and chromatography of the residue on alumina [petrol–dichloromethane (1 : 4), then dichloromethane as

eluant] gave (i) the 3β,17β-diacetate (73b) (4.72 g, 28%); (ii) a mixture of (73b) and (73a) (1.0 g, 6%); (iii) the 3α,-17β-diacetate (73a) (4.22 g, 25%).

(±)-7β-(p-*Nitrobenzoyloxy*)-6β-*methyl*-trans-*bicyclo*[4.3.0]-*nonan*-3-*one* (63).—The hydroxy-ketone (61) (2 g, 12 mmol) was treated with *p*-nitrobenzoyl chloride (2.44 g, 13 mmol) in pyridine (20 ml) at 25 °C for 1 h. The mixture was partitioned between dichloromethane and aqueous sodium hydrogen carbonate, and the organic phase was washed successively with 2N-hydrochloric acid, water, and aqueous sodium hydrogencarbonate, dried, and evaporated. The residue was crystallised from ether to give the p-*nitrobenzoate* (63) (1.36 g, 36%), m.p. 135—137°, $\lambda_{max.}$ (EtOH) 258 nm (ε 13 700), $\nu_{max.}$ 1 720 (ester) and 1 709 cm^{-1} (C=O), τ 8.82 (3 H, s, CH_3), 5.01 (1 H, m, C*H*OCOAr), and 1.78 (4 H, s, aromatic) (Found: C, 64.6; H, 6.2; N, 4.2. $C_{17}H_{19}NO_5$ requires C, 64.4; H, 6.0; N, 4.4%).

(±)-3α-(*and* β-)*Acetoxy*-9β,10β-*epithio*-17β-(p-*nitrobenzoyloxy*)-6,7-*dinor*-5,8-*secoestrane* (74a *and* b).—Condensation of the oxo-ester (63) (1.16 g, 3.6 mmol) and the hydrazinoacid (59) (1.0 g, 5.7 mmol) gave the hydrazone (68), which was converted in the usual way into a thiadiazoline. Acetylation and pyrolysis of the latter gave a gummy solid (1.2 g) which was subjected to p.l.c. (CH_2Cl_2) to give (i) the oxo-ester (63) (400 mg, 31%); (ii) the thiirans (74a and b) (640 mg, 38%). Crystallisation of this mixture from ethyl acetate gave the 3β-*acetate* (74b) (130 mg, 8%), m.p. 191—192°, $\lambda_{max.}$ (EtOH) 258 nm (ε 14 900), $\nu_{max.}$ 1 730 cm^{-1} (esters), τ 8.98 (3 H, s, CH_3), 7.92 (3 H, s, $OCOCH_3$), 5.05 (1 H, m, 3-H), and 4.95 (1 H, m, 17α-H) (Found: C, 63.6; H, 6.6; N, 3.1; S, 6.5. $C_{25}H_{31}NO_6S$ requires C, 63.4; H, 6.6; N, 3.0; S, 6.8%).

(±)-6β-*Methyl*-7β-*nitro-oxy*-trans-*bicyclo*[4.3.0]*nonan*-3-*one* (64).—The hydroxy-ketone (61) (15 g, 90 mmol) in dichloromethane (150 ml) was added at −10 °C to a mixture of fuming nitric acid (77.5 ml) and acetic anhydride (295 ml). The mixture was stirred at −10 °C for 1 h, then poured into a mixture of ice (3 kg) and 2N-sodium hydroxide (3 l) with efficient stirring. After 10 min, sodium carbonate (150 g) was added slowly and the mixture was stirred for 1 h, then extracted with dichloromethane. Evaporation of the dried extract left a brown oil, which was partitioned between ether and aqueous sodium hydrogensulphite. The aqueous phase was treated with potassium hydrogen carbonate (200 g) and then 2N-sodium hydroxide (to pH 9.5), and extracted with dichloromethane. The extract was dried and evaporated to give the *nitrate ester* (64) as a pale yellow solid (11.7 g, 61%), m.p. 55—56°, $\nu_{max.}$ 1 725sh and 1 709 (C=O) and 1 635 cm^{-1} (O–NO_2), τ 8.91 (3 H, s, CH_3) and 5.10 (1 H, m, $CHONO_2$) (Found: C, 56.1; H, 7.0; N, 6.6. $C_{10}H_{15}NO_4$ requires C, 56.3; H, 7.1; N, 6.6%).

(±)-3α-(*and* β-)*Acetoxy*-9β,10β-*epithio*-17β-*nitro-oxy*-6,7-*dinor*-5,8-*secoestrane* (75a *and* b).—Condensation of the nitrate ester (64) (11.07 g, 52 mmol) with the hydrazinoacid (59) (10 g, 57 mmol) afforded the *hydrazone* (69) (20 g) $\nu_{max.}$ 3 610 (OH), 3 600—2 300 (OH, NH), and 1 745 and 1 720 cm^{-1} (CO_2H), τ[$(CD_3)_2SO$] 9.11 (3 H, s, CH_3), 6.50 (1 H, m, C*H*OH), and 4.95 (1 H, m, C*H*ONO_2) (Found: C, 53.7; H, 7.6; N, 10.8. $C_{17}H_{27}N_3O_6,0.5H_2O$ requires C, 53.9; H, 7.5; N, 11.1%). The latter (4.77 g, 12.5 mmol) was converted in the usual way into a thiadiazoline, which was acetylated before pyrolysis in toluene. The residue (2.6 g) in ether was extracted thoroughly with 10% sodium hydrogensulphite to give the nitro-oxy-ketone (64) (320 mg, 12%). The ethereal solution was evaporated and the residue was chromatographed on alumina (500 g) in dichloromethane to give (i) a mixture of the thiirans (75a and b) (1.5 g, 31%); (ii) 3,10-trans-*diacetoxy*-13-*thiadispiro*-[5.0.5.1]*tridecane* (12c) (160 mg, 4.1%) which gave (from aqueous methanol) crystals, m.p. 87—93°, $\nu_{max.}$ 1 730 cm^{-1} (ester), τ 7.95 (6 H, s, 2 × $OCOCH_3$), 5.15 (1 H, m, $W_{\frac{1}{2}}$ *ca.* 22 Hz, *ax* C*H*OAc), and 4.92 (1 H, m, $W_{\frac{1}{2}}$ *ca.* 11 Hz, *eq* C*H*OAc) (Found: C, 61.0; H, 7.6; S, 9.8. $C_{16}H_{24}O_4S,0.125H_2O$ requires C, 61.1; H, 7.8; S, 10.2%); (iii) 3,10-*cis*-diequatorial *diacetoxy*-13-*thiadispiro*[5.0.5.1]*tridecane* (12b) (130 mg, 3.3%) which gave (from methanol) crystals, m.p. 176—177°, $\nu_{max.}$ 1 730 cm^{-1} (ester), τ 7.95 (6 H, s, 2 × $OCOCH_3$), and 5.15 (2 H, m, $W_{\frac{1}{2}}$ *ca.* 20 Hz, 2 × *ax* C*H*OAc) (Found: C, 61.4; H, 7.8; S, 10.1. $C_{16}H_{24}O_4S$ requires C, 61.5; H, 7.7; S, 10.3%).

Fraction (i) (400 mg) was subjected to p.l.c. (alumina; CH_2Cl_2) and the two bands obtained were crystallised from methanol to give (i) the 3β-*acetate* (75b) (60 mg), m.p. 157—158°, $\nu_{max.}$ 1 729 (ester) and 1 635 cm^{-1} (O–NO_2), τ 9.09 (3 H, s, CH_3), 7.95 (3 H, s, $OCOCH_3$), 5.13 (1 H, m, $W_{\frac{1}{2}}$ *ca.* 22 Hz, *ax*-3-H), and 5.65 (1 H, dd, *J* 7 and 9 Hz, 17α-H) (Found: C, 58.4; H, 7.4; N, 3.7; S, 8.6. $C_{18}H_{27}NO_5S$ requires C, 58.5; H, 7.4; N, 3.8; S, 8.7%); (ii) the 3α-*acetate* (75a) (45 mg), m.p. 145—146°, $\nu_{max.}$ 1 729 (ester) and 1 635 cm^{-1} (O–NO_2), τ 9.08 (3 H, s, CH_3), 7.95 (3 H, s, $OCOCH_3$), 5.02 (1 H, dd, *J* 7 and 9 Hz, 17α-H), and 4.91 (1 H, m, $W_{\frac{1}{2}}$ 11 Hz, *eq*-3-*H*) (Found: C, 58.0; H, 7.3; N, 3.6; S, 8.2. $C_{18}H_{27}NO_5S,0.25H_2O$ requires C, 57.8; H, 7.4; N, 3.7; S, 8.6%).

(±)-3β-*Acetoxy*-17β-*hydroxy*-6,7-*dinor*-5,8-*secoestr*-9-*ene* (79b) *and the* 3β,17β-*Diacetate* (80b).—The 3β-acetoxy-17-nitrate (75b) (1.5 g, 4.1 mmol) was desulphurised with zinc and acetic acid; the initial reaction was vigorous at room temperature, but the mixture was heated under reflux for 30 min to ensure complete reduction. The product was chromatographed on alumina in dichloromethane to give (i) a solid (185 mg, 13%) which was crystallised from aqueous methanol to give the 3β,17β-*diacetate* (80b), m.p. 87—88°, $\nu_{max.}$ 1 722 cm^{-1} (esters), τ 9.11 (3 H, s, CH_3), 7.98 (6 H, s, 2 × $OCOCH_3$), 5.40 (1 H, m, 17α-H), and 5.15 (1 H, m, 3-H) (Found: C, 71.6; H, 8.9. $C_{20}H_{30}O_4$ requires C, 71.8; H, 9.0%); (ii) the 17β-*hydroxy*-3β-*acetate* (79b) as a gum (800 mg, 68%), $\nu_{max.}$ 3 605 (OH), 1 720 cm^{-1} (ester), τ 9.18 (3 H, s, CH_3), 8.00 (3 H, s, $OCOCH_3$), 6.36 (1 H, m, 17α-H), and 5.10 (1 H, m, 3-H) (Found: C, 74.0; H, 9.7. $C_{18}H_{28}O_3$ requires C, 73.9; H, 9.65%).

(±)-3α-(*and* β-)*Acetoxy*-17β-*hydroxy*-6,7-*dinor*-5,8-*seco*-*estr*-9-*ene* (79) (*Isomeric Mixture*) *and the* (±)-3α(*and* β),-17β-*Diacetates* (80a *and* b). The 3-acetoxy-17-nitrate (75) (mixed isomers) (7.0 g, 18.9 mmol) was desulphurised as above and the product was chromatographed on alumina to give (i) the 3β,17β-diacetate (80b) (360 mg, 6.5%), (ii) the 3α,17β-*diacetate* (80 a) as an oil (320 mg, 6%), $\nu_{max.}$ 1 722 cm^{-1} (esters), τ 9.13 (3 H, s, CH_3), 7.98 (6 H, s, 2 × $OCOCH_3$), 5.40 (1 H, m, 17α-H), and 5.14 (1 H, m, 3-H) (Found: C, 70.9; H, 8.8. $C_{20}H_{30}O_4,0.25H_2O$ requires C, 70.9; H, 9.1%); (iii) a mixture of the 3α- and 3β-*acetoxy*-17-*alcohols* (79a and b) (4.25 g, 75%) as an oil, $\nu_{max.}$ 3 605 (OH) and 1 720 cm^{-1} (ester), τ 9.18 (3 H, s, CH_3), 8.00 (3 H, s, $OCOCH_3$), 6.36 (1 H, m, 17α-H), and 5.10 (1 H, m, 3-H) (Found: C, 72.3; H, 9.3. $C_{18}H_{28}O_3,0.5\ H_2O$ requires C, 72.2; H, 9.1%).

(±)-9β,10β-*Epithio*-6,7-*dinor*-5,8-*secoestrane*-3,17-*dione* (85).—(*a*) The 3β,17β-diacetate (73b) (1 g, 2.7 mmol) was heated under reflux for 4 h in aqueous methanol containing

sodium carbonate (1 g). The mixture was partitioned between water and dichloromethane, and the organic phase was dried and evaporated. The residual diol (76b) was oxidised with dimethyl sulphoxide–dicyclohexylcarbodi-imide [9] to give the crude dione (85).

(*b*) The 3α,17β-diacetate (73a) (1 g) was treated similarly to give the crude dione (85), which was identical (i.r.) with the material described in (*a*). The two products were combined and subjected to p.l.c. (acetone–petrol, 1 : 3) to give a solid (800 mg, 50%). Recrystallisation from ethyl acetate gave the *dione* (85) (650 mg, 41%), m.p. 189°, $\nu_{max.}$ 1 732 [C(17)=O] and 1 713 cm^{-1} [C(3)=O], τ 9.01 (3 H, s, CH_3) (Found: C, 68.7; H, 8.2; S, 10.5. $C_{16}H_{22}O_2S$ requires C, 69.0; H, 8.0; S, 11.5%).

(±) 3α,17β-*Dihydroxy*-6,7-*dinor*-5,8-*secoestr*-9-*ene* (81a).—The 3α,17β-diacetate (80a) (270 mg) was warmed with 2N-sodium hydroxide (5 ml) in ethanol (20 ml) for 30 min. The mixture was acidified with 2N-hydrochloric acid and concentrated *in vacuo*. The product was collected and dried to give the *diol* (81a) (140 mg, 69%), m.p. 159—167°, $\nu_{max.}$ (Nujol) 3 650—2 300 cm^{-1} (OH), τ[$(CD_3)_2SO$] 9.25 (3 H, s, CH_3) and 6.50 (2 H, m, 3- and 17α-H) (Found: C, 75.4; H, 10.2. $C_{16}H_{26}O_2$,0.25H_2O requires C, 75.4; H, 10.4%).

(±)-6,7-*Dinor*-5,8-*secoestr*-9-*ene*-3,17-*dione* (86).—The thiiran diacetate (73) (mixed isomers) (6 g, 16.5 mmol) was desulphurised with zinc and acetic acid, and the product was hydrolysed as above to give the diols (81) (3.7 g, 90%). The latter were oxidised with dimethyl sulphoxide–dicyclohexylcarbodi-imide [9] and the product was purified by p.l.c. (acetone–petrol, 1 : 4), followed by crystallisation from ether, to give the *dione* (86) (1.75 g, 44%), m.p. 76—78°, $\nu_{max.}$ 1 730 [C(17)=O] and 1 710 cm^{-1} [C(3)=O], τ 9.07 (3 H, s, CH_3) (Found: C, 78.1; H, 9.1. $C_{16}H_{22}O_2$ requires C, 78.0; H, 9.0%).

(±)-3α(*and* β)-*Acetoxy*-6,7-*dinor*-5,8-*secoestr*-9-*en*-17-*one* (83a *and* b).—The 17β-hydroxy-3-acetate (79) (mixed isomers) was oxidised with dimethyl sulphoxide–dicyclohexylcarbodi-imide [9] and the crude product was chromatographed over alumina in petrol–dichloromethane (4 : 1 to 3 : 7) to give (i) the less polar 17-ketone (1.2 g, 25%), which was crystallised from petrol to give the 3β-*acetate* (83b), m.p. 72—73°, $\nu_{max.}$ 1 730 cm^{-1} (C=O, ester), τ 9.05 (3 H, s, CH_3), 7.98 (3 H, s, $OCOCH_3$), and 5.12 (1 H, m, 3-H) (Found: C, 74.6; H, 9.0. $C_{18}H_{26}O_3$ requires C, 74.4; H, 9.0%); (ii) a mixture of (83a and b) (0.83 g, 18%); (iii) the more polar 17-ketone (1.38 g, 28%), which crystallised from methanol to give the 3α-*acetate* (83a), m.p. 89—91°, $\nu_{max.}$ 1 733 cm^{-1} (C=O, ester), τ 9.05 (3 H, s, CH_3), 7.98 (3 H, s, $OCOCH_3$), and 5.10 (1 H, m, 3-H) (Found: C, 74.1; H, 9.1. $C_{18}H_{26}O_3$ requires C, 74.4; H, 9.0%).

(±)-3β-*Acetoxy*-6,7-*dinor*-5,8-*secoestr*-9-*en*-17-*one* (83b).—The 17β-hydroxy-3β-acetate (79b) (600 mg, 2.05 mmol) was oxidised as above, and the crude product was chromatographed on alumina, to give the 3β-acetate (83b) (455 mg, 76%), m.p. 72—73°.

(±)-17α-*Ethynyl*-6,7-*dinor*-5,8-*secoestr*-9-*ene*-3β,17β-*diol* (87b).—Sodium (1.8 g, 78 mmol) was dissolved in ammonia (300 ml) containing iron(III) nitrate (35 mg) and the mixture was stirred until the blue colour faded (1 h). Purified acetylene was passed into the suspension for 1 h, after which the 3β-acetoxy-17-ketone (83b) (450 mg, 1.5 mmol) was added in tetrahydrofuran (25 ml). Acetylene was passed through the stirred mixture for 3 h, then ammonium chloride (5 g) was added, the ammonia was evaporated off, and the residue was partitioned between water and dichloromethane. The organic phase was dried and evaporated and the residual gum was chromatographed on silica gel [eluant ether–dichloromethane (1 : 4 to 3 : 2)]. The product (350 mg, 82%) was recrystallised from aqueous acetone to give *compound* (87b), m.p. 148—149°, $\nu_{max.}$ 3 605 (OH) and 3 300 cm^{-1} (≡CH), τ 9.06 (3 H, s, CH_3), 7.45 (1 H, s, ≡CH), and 6.18 (1 H, m, 3-H) (Found: C, 77.8; H, 9.4. $C_{18}H_{26}O_2$,0.25H_2O requires C, 77.5; H, 9.6%).

(±)-17α-*Ethynyl*-6,7-*dinor*-5,8-*secoestr*-9-*ene*-3α,17β-*diol* (87a).—The 3α-acetoxy-17-ketone (83a) (390 mg, 1.3 mmol) was treated as above and the crude product was chromatographed on silica gel. Crystallisation from aqueous methanol gave *compound* (87a) (310 mg, 85%), m.p. 168—169°, $\nu_{max.}$ 3 605 (OH) and 3 300 cm^{-1} (≡CH), τ 9.05 (3 H, s, CH_3), 7.46 (1 H, s, ≡CH), and 6.17 (1 H, m, 3-H) (Found: C, 76.2; H, 9.3. $C_{18}H_{26}O_2$,0.5H_2O requires C, 76.3; H, 9.6%).

(±)-3β-*Hydroxy*-6,7-*dinor*-5,8-*secoestr*-9-*en*-17-*one* (84b).—The less polar (3β) acetoxy-ketone (83b) (400 mg, 1.3 mmol) was heated under reflux with potassium carbonate (400 mg) in 50% aqueous methanol for 2 h. The mixture was concentrated and extracted with dichloromethane, and the extract was dried and evaporated. The residual gum was crystallised from ether–petrol to give the *hydroxy-ketone* (84b) (290 mg, 85%), m.p. 90—91°, $\nu_{max.}$ 3 620 (OH) and 1 722 cm^{-1} (C=O), τ 9.02 (3 H, s, CH_3) and 6.18 (1 H, m, 3-H) (Found: C, 76.65; H, 9.6. $C_{16}H_{24}O_2$,0.125H_2O requires C, 76.7; H, 9.75%), identical with a sample prepared by pyrolysis of a β-lactone [1] (but not fully characterised).

(±)-3α-*Hydroxy*-6,7-*dinor*-5,8-*secoestr*-9-*en*-17-*one* (84a).—The more polar (3α) acetoxy-ketone (83a) (50 mg) was hydrolysed as above, and the product was crystallised from ether–petrol to give the *hydroxy-ketone* (84a) (20 mg, 50%), m.p. 108°, $\nu_{max.}$ 3 620 (OH) and 1 722 cm^{-1} (C=O), τ 9.05 (3 H, s, CH_3) and 6.20 (1 H, m, 3-H) (Found: C, 77.4; H, 9.6. $C_{16}H_{24}O_2$ requires C, 77.4; H, 9.7%), identical with a sample prepared by the pyrolysis of a β-lactone.[1] This material (84a) was less polar than the product (84b) from the previous experiment.

Reduction of the Dione (86) *by the Hexachloroiridic Acid Reagent*.—The dione (86) (1.1 g, 4.5 mmol) was heated under reflux for 5 h with a stock solution of hexachloroiridic acid (*cf.* ref. 21), adjusted to pH 5 with triethylamine immediately before use. The mixture was partitioned between water and ether, and the organic phase was washed with 2N-hydrochloric acid, then 2N-sodium carbonate, dried, and evaporated. The residue was kept for 5 h at room temperature in pyridine (10 ml) and acetic anhydride (5 ml). The mixture was evaporated to dryness and the residue was chromatographed over alumina in dichloromethane to give (i) the 3β-acetate (83b) which gave (from petrol) crystals (365 mg, 33%), m.p. 71—72°; (ii) the 3α-acetate (83a) which gave (from methanol) crystals (530 mg, 48%), m.p. 89—90°.

(±)-9α,10α-*Epoxy*-6,7-*dinor*-5,8-*secoestran*-17-*one* (88).—The olefin [1] (82) (697 mg, 3 mmol) was treated with *m*-chloroperbenzoic acid (85%; 610 mg, 3 mmol) in dichloromethane (40 ml). After 15 min, the mixture was shaken with 5% sodium hydrogen carbonate, dried, and evaporated. P.l.c. (CH_2Cl_2) of the residue yielded (i) a gum (128 mg), $\nu_{max.}$ 1 725 cm^{-1} (C=O), τ 8.90 and 8.98 (3 H, both s, CH_3), probably containing the 9β,10β-epoxide as the major component; (ii) a solid (590 mg, 79%) which was crystallised

from petrol to give the 9α,10α-*epoxide* (88) as pale yellow rosettes, m.p. 71—73°, $\nu_{max.}$ 1 725 cm^{-1} (C=O), τ 9.10 (3 H, s, CH_3) (Found: C, 77.4; H, 9.4. $C_{16}H_{24}O_2$ requires C, 77.4; H, 9.7%).

(±)-3β,17β-*Diacetoxy*-9α,10α-*epoxy*-6,7-*dinor*-5,8-*seco-estrane* (90b).—The olefin (80b) (100 mg) was epoxidised as above, and the product (110 mg) was crystallised from petrol to give the α-*epoxide* (90b), m.p. 116—117°, $\nu_{max.}$ 1 724 cm^{-1} (esters), τ 9.16 (3 H, s, CH_3), 8.96 and 8.99 (6 H, both s, 2 × $OCOCH_3$), 5.36 (1 H, t, *J* 7 Hz, 17α-H), and 5.16 (1 H, m, $W_{\frac{1}{2}}$ 16 Hz, 3-H) (Found: C, 68.45; H, 8.65. $C_{20}H_{30}O_5$ requires C, 68.5; H, 8.6%).

(±)-3α,17β-*Diacetoxy*-9α,10α-*epoxy*-6,7-*dinor*-5,8-*seco-estrane* (90a).—The olefin (81a) (70 mg) was acetylated with acetic anhydride and pyridine and the product (80a) was epoxidised as above. P.l.c. ($CHCl_3$) of the product (108 mg) yielded (i) a gum (16 mg), τ 9.03 (3 H, s, CH_3), 7.93 and 7.96 (6 H, each s, 2 × $OCOCH_3$), 5.30 (1 H, m, 17α-H), and 4.90 (1 H, m, $W_{\frac{1}{2}}$ 12 Hz, 3-H) which was probably the β-epoxide (92); (iii) the α-*epoxide* (90a) (80 mg) which gave (from petrol) crystals, m.p. 113—114°, $\nu_{max.}$ 1 725 cm^{-1} (esters), τ 9.15 (3 H, s, CH_3), 7.95 (6 H, s, 2 × $OCOCH_3$), 5.35 (1 H, m, 17α-H), and 5.07 (1 H, m, $W_{\frac{1}{2}}$ 12 Hz, 3-H) (Found: C, 68.3; H, 8.65. $C_{20}H_{30}O_5$ requires C, 68.5; H, 8.6%).

(±)-3β-*Acetoxy*-9α,10α-*epoxy*-6,7-*dinor*-5,8-*secoestran*-17-*one* (89b).—The 3β-hydroxy-ketone (84b) (43 mg) was acetylated with acetic anhydride and pyridine, and the product was epoxidised as above. The product (61 mg) was crystallised from ether–petrol to give the α-*epoxide* (89b), m.p. 105—107°, $\nu_{max.}$ 1 725 cm^{-1} (C=O, ester), τ 9.08 (3 H, s, CH_3), 7.96 (3 H, s, $OCOCH_3$), and 5.17 (1 H, m, $W_{\frac{1}{2}}$ 15 Hz, 3-H) (Found: C, 70.4; H, 8.4. $C_{18}H_{26}O_4$ requires C, 70.6; H, 8.55%).

(±)-3α-*Acetoxy*-9α,10α-*epoxy*-6,7-*dinor*-5,8-*secoestran*-17-*one* (89a).—The 3α-hydroxy-ketone (84a) (25 mg) was acetylated and epoxidised as above. P.l.c. ($CHCl_3$) of the product (37 mg) gave (i) a gum (4 mg), τ 8.98 (3 H, s, CH_3), 7.96 (3 H, s, $OCOCH_3$), and 5.13 (1 H, m, $W_{\frac{1}{2}}$ 14 Hz, 3-H), which was probably the β-epoxide (91); (ii) a white solid (19 mg) which gave (from ether–petrol) crystals of the α-*epoxide* (89a), m.p. 106—106.5°, $\nu_{max.}$ 1 722 cm^{-1} (C=O, ester), τ 9.08 (3 H, s, CH_3), 7.96 (3 H, s, $OCOCH_3$), and 5.02 (1 H, m, $W_{\frac{1}{2}}$ 12 Hz, 3-H) (Found: C, 69.4; H, 8.6. $C_{18}H_{26}O_4 \cdot \frac{1}{4}H_2O$ requires C, 69.5; H, 8.6%).

4-*Acetoxy*-1,1′-*bi*(*cyclohexylidene*).—The alcohol (48) (270 mg, 1.5 mmol) was acetylated with acetic anhydride and pyridine, and the product was crystallised from ether–petrol to give the *acetate*, m.p. 55—57°, $\nu_{max.}$ 1 720 cm^{-1} (ester), τ 7.97 (3 H, s, $OCOCH_3$) and 5.09 (1 H, m, C*H*OAc) (Found: C, 75.6; H, 10.0. $C_{14}H_{22}O_2$ requires C, 75.6; H, 10.0%).

cis- *and* trans-3-*Acetoxy*-13-*oxadispiro*[5.0.5.1]*tridecane* (20b *and* a).—The above acetoxy-olefin (235 mg, 1.06 mmol) was epoxidised as described, and the product was subjected to p.l.c. ($CHCl_3$) to give (i) the less polar epoxide (115 mg, 46%) which was recrystallised from ether–petrol to give the cis-*isomer* (20b) as needles, m.p. 72—73°, $\nu_{max.}$ 1 722 cm^{-1} (ester), τ 7.96 (3 H, s, $OCOCH_3$) and 5.15 (1 H, m, $W_{\frac{1}{2}}$ 16 Hz, C*H*OAc) (Found: C, 70.2; H, 9.3. $C_{14}H_{22}O_3$ requires C, 70.55; H, 9.3%); (ii) the more polar trans-*isomer* (20a) (99 mg, 39%) as a gum, $\nu_{max.}$ 1 725 cm^{-1} (ester), τ 7.96 (3 H, s, $OCOCH_3$) and 5.05 (1 H, m, $W_{\frac{1}{2}}$ 12 Hz, C*H*OAc) (Found: C, 70.6; H, 9.4%).

cis-3-*Acetoxy*-13-*thiadispiro*[5.0.5.1]*tridecane* (44b).—The 3*eq*-hydroxy-thiiran (43b) (106 mg) was acetylated with acetic anhydride and pyridine and the product (135 mg) was crystallised from petrol to give the *acetate* (44b), m.p. 75—76°, $\nu_{max.}$ 1 722 cm^{-1} (ester), τ 7.97 (3 H, s, $OCOCH_3$) and 5.19 (1 H, m, $W_{\frac{1}{2}}$ 22 Hz, *ax* C*H*OAc) (Found: S, 12.4. $C_{14}H_{22}O_2S$ requires S, 12.6%).

trans-3-*Acetoxy*-13-*thiadispiro*[5.0.5.1]*tridecane* (44a).—The 3*ax*-hydroxy-thiiran (43a) (64 mg) was acetylated as above and the product (75 mg) was crystallised from petrol to give needles of the *acetate* (44a), m.p. 52—54°, $\nu_{max.}$ 1 718 cm^{-1} (ester), τ 7.94 (3 H, s, $OCOCH_3$) and 4.94 (1 H, m, $W_{\frac{1}{2}}$ 11 Hz, *eq* C*H*OAc) (Found: C, 65.95; H, 8.6; S, 12.5. $C_{14}H_{22}O_2S$ requires C, 66.1; H, 8.7; S, 12.6%).

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