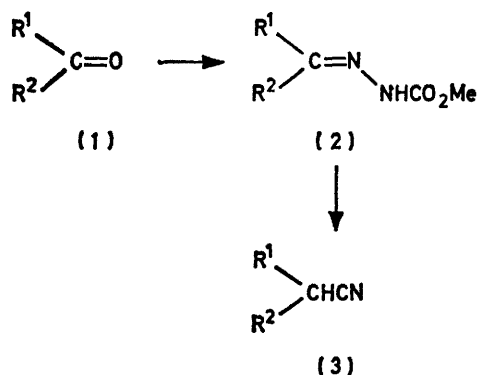


## The Conversion of Aldehydes and Ketones *via* their 2,4,6-Tri-isopropylbenzenesulphonyl Hydrazones into Nitriles containing One Additional Carbon Atom

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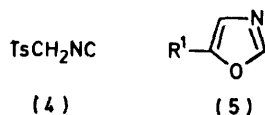
2,4,6-Tri-isopropylbenzenesulphonyl hydrazones of aliphatic and alicyclic aldehydes and ketones react readily with potassium cyanide in boiling methanol solution to give the corresponding nitriles (containing one more carbon atom than the original aldehyde or ketone) in satisfactory yields. Under the same conditions, benzaldehyde 2,4,6-tri-isopropylbenzenesulphonyl hydrazone gives phenylacetone nitrile in very low yield. In some cases, the arenosulphonyl hydrazones may be generated *in situ*, in methanol solution, from the carbonyl compounds and 2,4,6-tri-isopropylbenzenesulphonylhydrazide (11a), thereby constituting a one-pot preparation of the nitriles.

No completely general procedure for the direct conversion of both aldehydes and ketones into nitriles containing an additional carbon atom has been reported. The most obvious procedure involves the initial formation of cyanohydrins. However, the conversion of cyanohydrins into the corresponding nitriles, for example by dehydration followed by catalytic hydrogenation, is feasible only in the absence of certain other functions.



SCHEME 1

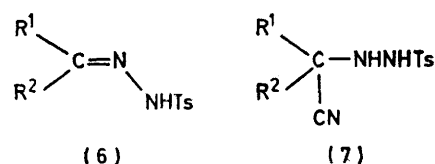
In 1971, Ziegler and Wendler showed<sup>1a</sup> that the ketones (1) could be converted (Scheme 1) into the corresponding nitriles (3) containing an additional carbon atom *via* their methoxycarbonyl hydrazones (2). As acetone, cyclohexanone, and two derivatives of cyclohexanone were the only substrates examined, this method has not been shown to be general. Although the overall yields reported were quite satisfactory, the procedure consists of four steps one of which involved the use of liquid hydrogen cyanide.



In 1972, Oldenzil and van Leusen found<sup>2</sup> that when adamantanone was treated with toluene-*p*-sulphonylmethyl isocyanide (4) and sodium ethoxide in 1,2-dimethoxyethane-ethanol solution at 0 °C, 2-cyanoadamantane was obtained in 85% yield. On the basis of this observation, these workers subsequently developed<sup>3</sup> a general method for the transformation of ketones into

nitriles containing an additional carbon atom. Aliphatic, alicyclic, and aromatic ketones may be used as substrates in this reaction<sup>3</sup> and the isolated yields of nitriles (3) are usually *ca.* 70–80%. It is less clear whether or not aldehydes may be converted into nitriles by this procedure. Thus the same Dutch group reported<sup>4</sup> that when aromatic aldehydes (1; R<sup>1</sup> = aryl, R<sup>2</sup> = H) are heated with toluene-*p*-sulphonylmethyl isocyanide (4) in the presence of potassium carbonate in methanol solution, good yields of the corresponding 5-substituted oxazoles (5) are obtained. However, Schöllkopf and Schröder showed<sup>5</sup> that both benzaldehyde and pivaldehyde (1; R<sup>1</sup> = Bu<sup>t</sup>, R<sup>2</sup> = H) could be converted into the corresponding nitriles (3; R<sup>2</sup> = H, R<sup>1</sup> = Ph and Bu<sup>t</sup>, respectively) by a related procedure.

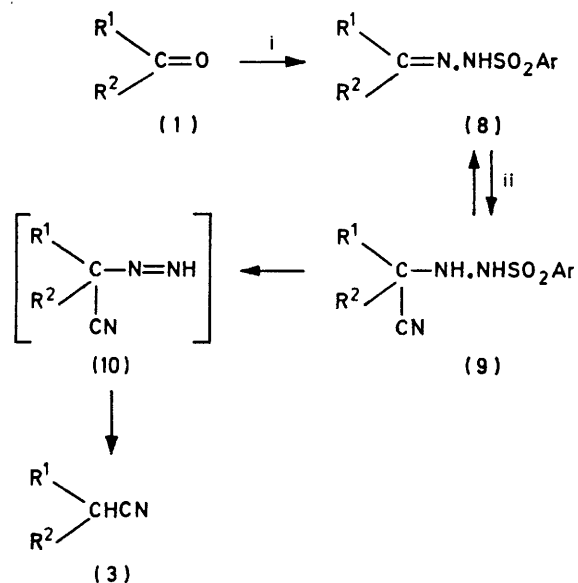
In 1972, Cacchi *et al.* reported<sup>6</sup> a procedure related to the above methoxycarbonyl hydrazone method<sup>1</sup> (Scheme 1), for the conversion of ketones into nitriles. These workers showed<sup>6</sup> that the toluene-*p*-sulphonyl hydr-



azones (6) of cyclohexanone and heptan-4-one react with hydrogen cyanide (generated *in situ* from potassium cyanide and acetic acid) to give the corresponding adducts [7; R<sup>1</sup> = R<sup>2</sup> = Pr and R<sup>1</sup>, R<sup>2</sup> = -(CH<sub>2</sub>)<sub>5</sub>-, respectively], which may be isolated crystalline in good yields. When the latter compounds are heated in decalin at 180 °C, the desired nitriles (3) are obtained.<sup>6</sup> However, in a later publication, the same workers reported<sup>7</sup> that the thermally promoted conversion of (7) into (3) is accompanied by the competitive elimination of hydrogen cyanide, thus limiting the yields of nitriles (3) obtained. Such loss of product by elimination was overcome<sup>7</sup> by the introduction of two additional steps, thereby leading to mixtures of the corresponding *S*-ethyl carbothioates and carboxylic acids.

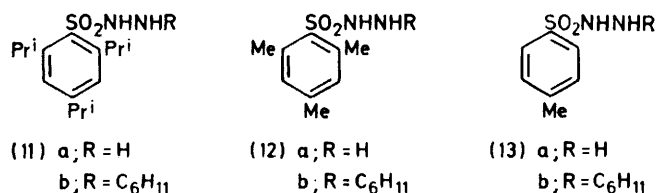
The present approach (Scheme 2) to the conversion of aldehydes and ketones into nitriles containing an additional carbon atom is related to the procedure of Cacchi *et al.*<sup>6</sup> but differs from it in two very important

respects. First, as the thermally promoted decomposition of the hydrogen cyanide adduct (9) of an arenosulphonyl hydrazone will almost inevitably lead to some arenosulphonyl hydrazone (8) regeneration, the adduct (9) is generated *in situ* and the reaction is allowed to proceed in the presence of an excess of potassium



SCHEME 2 Reagents: i, TPSH (13) in MeOH or tetrahydrofuran, room temp.; ii, KCN in boiling MeOH (Ar = 2,4,6-Pr<sub>3</sub>C<sub>6</sub>H<sub>2</sub>)

cyanide in methanol solution. It is then expected that (8) and (9) will be in equilibrium and that the equilibrium will be shifted to the right as (9) is converted into (3). The presence of an excess of cyanide ion is additionally advantageous in that the latter conversion almost certainly involves the base-catalysed elimination of the elements of arenosulphonic acid (ArSO<sub>2</sub>H) to give the di-imide derivative (10) which then readily fragments to give nitrogen and the desired nitrile. In practice, the present approach involves only two steps (Scheme 2): (i) the conversion of the carbonyl compound into its arenosulphonyl hydrazone (8) and (ii) heating the latter compound with an excess (usually threefold) of potassium



cyanide in methanol solution. As it is usually unnecessary to isolate the intermediate arenosulphonyl hydrazone (8), both steps of the conversion of (1) into (3) may generally be carried out in the same flask (see below).

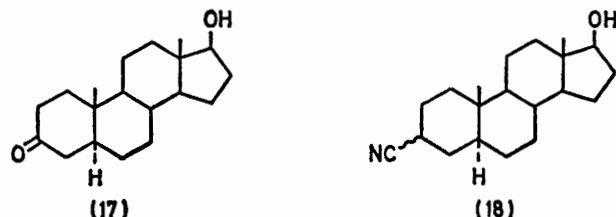
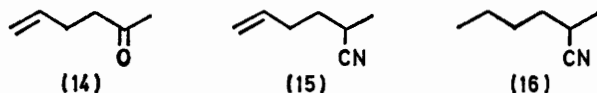
The second important respect in which the present approach differs from that of Cacchi *et al.*<sup>6</sup> is that 2,4,6-tri-isopropylbenzenesulphonyl hydrazones<sup>8</sup> (8; Ar = 2,4,6-Pr<sub>3</sub>C<sub>6</sub>H<sub>2</sub>) are used instead of the corresponding toluene-*p*-sulphonyl hydrazones (6). Several years ago,

we found<sup>8</sup> that 2,4,6-tri-isopropylbenzenesulphonyl hydrazone (TPSH; 11a) decomposed at *ca.* 380 times the rate of toluene-*p*-sulphonyl hydrazone (13a) and at *ca.* 16 times the rate of mesitylene-2-sulphonyl hydrazone (MSH; 12a) in the presence of one molecular equivalent of triethylamine in methanol solution. We have since found<sup>9</sup> that the cyclohexyl derivative of MSH (12a) undergoes decomposition, under the same conditions, at a rate of more than two orders of magnitude faster than that of MSH (12a) itself and that (13b) is similarly much more labile than toluene-*p*-sulphonyl hydrazone (13a). Thus the half-times of decomposition of (12b) and (13b), in the presence of one molecular equivalent of triethylamine in [2H<sub>4</sub>]methanol solution at 35 °C, were found<sup>9</sup> to be 1.1 and 12.4 min, respectively. By extrapolation, the half-time of decomposition of the corresponding cyclohexyl derivative (11b) of TPSH (11a) would be expected to be a few seconds under the latter conditions. It therefore seems likely that the hydrogen cyanide adducts (9; Ar = 2,4,6-Pr<sub>3</sub>C<sub>6</sub>H<sub>2</sub>) of 2,4,6-tri-isopropylbenzenesulphonyl hydrazones (8; Ar = 2,4,6-Pr<sub>3</sub>C<sub>6</sub>H<sub>2</sub>), once formed, would be rapidly converted into the corresponding nitriles (3) in the presence of an excess of potassium cyanide in boiling methanol solution.

TPSH (11a), which may readily be prepared<sup>8</sup> in two steps from technical grade 1,3,5-tri-isopropylbenzene, reacts rapidly with many aldehydes and ketones, even in the absence of an acidic catalyst, at room temperature to give the corresponding 2,4,6-tri-isopropylbenzenesulphonyl hydrazones (8; Ar = 2,4,6-Pr<sub>3</sub>C<sub>6</sub>H<sub>2</sub>) in high yields. Indeed, the simplest experimental procedure [Table, experiments nos. (1)–(3)] for the present reaction<sup>10</sup> involves first allowing the substrate carbonyl compound (1) to react with a small excess (1.25 molecular equivalents) of TPSH (11a) in methanol solution for 1 h at room temperature, then adding a three-fold excess of potassium cyanide and finally heating the reaction mixture, under gentle reflux, for 2 h. No attempt is made to isolate the intermediate arenosulphonyl hydrazones (8; Ar = 2,4,6-Pr<sub>3</sub>C<sub>6</sub>H<sub>2</sub>). The product nitriles (3) are then isolated as relatively pure (>95%, by g.l.c.) liquids by distillation. In view of the fact that most of the reactions were carried out on only a 0.02 molar scale (see Experimental section), the isolated yields of nitriles (see Table) may be regarded as quite satisfactory.

A slight modification of the above procedure is more suitable for substrates which do not react so rapidly with TPSH (11a). As the latter compound (11a) decomposes much more slowly in tetrahydrofuran than in methanol solution,<sup>8</sup> it is sometimes advisable to form the 2,4,6-tri-isopropylbenzenesulphonyl hydrazones (8; Ar = 2,4,6-Pr<sub>3</sub>C<sub>6</sub>H<sub>2</sub>) in tetrahydrofuran solution. The products are then concentrated under reduced pressure and allowed to react, as above, with potassium cyanide in boiling methanol solution. This modified and more generally applicable procedure was used advantageously in the reactions involving heptan-4-one (1; R<sup>1</sup> = R<sup>2</sup> = Pr), pinacolone (1; R<sup>1</sup> = Bu<sup>t</sup>, R<sup>2</sup> = Me), and cyclododecanone [1; R<sup>1</sup>, R<sup>2</sup> = -(CH<sub>2</sub>)<sub>11</sub>-] [experiments nos. (6), (7),

and (9)]; it was also used in the conversion of *n*-heptaldehyde and *n*-octaldehyde [ $R^1 = H$ ,  $R^2 = (CH_2)_5-CH_3$  and  $(CH_2)_6CH_3$ , respectively] into the corresponding nitriles [experiments nos. (4) and (5)]. Very satisfactory yields were obtained except in the case of the nitrile (3;  $R^1 = Bu^t$ ,  $R^2 = Me$ ) derived from pinacolone [experiment no. (7)].



As TPSH (11a) is a ready source<sup>8</sup> of di-imide, especially in methanol solution, care has to be taken in the derivatization of aldehydes and ketones containing carbon-carbon multiple bonds. Thus hex-1-en-5-one (14) was allowed to react [experiment no. (8)] with only a very slight excess (1.05 molecular equivalents) of TPSH (11a) in tetrahydrofuran solution and its 2,4,6-tri-isopropylbenzenesulphonyl hydrazone was isolated as a

occurred very rapidly in methanol solution and the derivative crystallized spontaneously from the reaction medium in high yield. Following reaction of the latter compound with potassium cyanide in boiling methanol solution, compound (18) was isolated as a colourless solid in 67% overall yield. On the basis of melting point [see Table, footnote *g*] and n.m.r. spectroscopic data, it seems clear that a mixture of the 3 $\alpha$ - and 3 $\beta$ -epimers of (18) was obtained.

The present method for the conversion of aldehydes and ketones into nitriles is clearly superior to any procedure involving the deoxygenation of initially formed cyanohydrins. Indeed, it is unlikely that hex-1-en-5-one (14) and 17 $\beta$ -hydroxy-5 $\alpha$ -androstan-3-one (17) could readily be converted into the corresponding nitriles [(15) and (18), respectively] *via* their cyanohydrins. In the case of (14), it would be difficult to avoid concomitant reduction of the carbon-carbon double-bond [to give (16)] and in the case of (17), the 17-hydroxy-function may well be removed during the conversion. The present method is also much more convenient than the related four-step procedure<sup>1</sup> involving the addition of hydrogen cyanide to methoxycarbonyl hydrazones (2) [Scheme 1]. It is perhaps more appropriate to compare it with the procedure<sup>3</sup> involving toluene-*p*-sulphonylmethyl isocyanide (4).

The latter procedure appears to be experimentally convenient and is suitable<sup>3</sup> for the synthesis of nitriles from aliphatic and alicyclic ketones. However, there is

Conversion of aldehydes and ketones *via* their 2,4,6-tri-isopropylbenzenesulphonyl hydrazones into nitriles

Expt. no.	Substrate	TPSH (13a) (mol. equiv.)	Solvent	Time <sup>a</sup> (h)	KCN (mol. equiv.)	Time <sup>b</sup> (h)	Product	Isolated yield <sup>c</sup> (%)	B.p. (°C) [mmHg]
(1)	Cyclopentanone	1.25	MeOH	1	3	2	C <sub>5</sub> H <sub>9</sub> CN	67	101 [100]
(2)	Cyclohexanone	1.25	MeOH	1	3	2	C <sub>6</sub> H <sub>11</sub> CN	72	61 [11]
(3)	Cyclohexane-carbaldehyde	1.25	MeOH	1	3	2	C <sub>6</sub> H <sub>11</sub> CH <sub>2</sub> CN	71	82 [11]
(4)	<i>n</i> -Heptaldehyde	1.25	THF <sup>d</sup>	3	3	2	Me(CH <sub>2</sub> ) <sub>6</sub> CN	70	80 [11]
(5)	<i>n</i> -Octaldehyde	1.25	THF <sup>d</sup>	3	3	2	Me(CH <sub>2</sub> ) <sub>7</sub> CN	68	102 [11]
(6)	Heptan-4-one	1.5	THF <sup>d</sup>	2	3	3	Pr <sub>2</sub> CHCN	73	63 [11]
(7)	Pinacolone	1.57	THF <sup>d</sup>	3	3	3	Bu <sup>t</sup> CH(Me)CN	60	148–150
(8)	Hex-1-en-5-one (14)	1.05	THF	2 <sup>e</sup>	3	5	CH <sub>2</sub> =CH(CH <sub>2</sub> ) <sub>2</sub> CH(Me)CN (15)	75	98 [100]
(9)	Cyclododecanone	1.25	THF <sup>d</sup>	16	3	4	C <sub>12</sub> H <sub>22</sub> CN	77	147 [11]
(10)	17 $\beta$ -Hydroxy-5 $\alpha$ -androstan-3-one (17)	1.16	MeOH	<i>f</i>	2.9	2	(18)	67	<i>g</i>

<sup>a</sup> This is the time required for 2,4,6-tri-isopropylbenzenesulphonyl hydrazone formation at 20 °C. <sup>b</sup> This is the time required for the completion of the reaction between the 2,4,6-tri-isopropylbenzenesulphonyl hydrazone and potassium cyanide in boiling methanol.

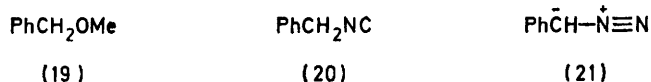
<sup>c</sup> This is the overall isolated yield for the two steps. <sup>d</sup> The tetrahydrofuran is removed under reduced pressure and the residue is redissolved in methanol (see Experimental section). <sup>e</sup> After this time, the crystalline 2,4,6-tri-isopropylbenzenesulphonyl hydrazone, m.p. 107–109 °C, was isolated in 98% yield (see Experimental section). <sup>f</sup> The 2,4,6-tri-isopropylbenzenesulphonyl hydrazone precipitated from the reaction mixture almost immediately and was isolated crystalline, m.p. 168–170 °C (decomp.), in 94% yield.

<sup>g</sup> Crystallization of this product from methanol gave colourless crystals (39.5%), m.p. 187–190 °C. A second crop (28%), m.p. 148–151 °C, was obtained by adding water to the mother-liquors. Material with m.p. 216–217 °C was obtained after two further recrystallizations of the higher-melting material from methanol.

crystalline solid in 98% yield. The latter compound was then heated with potassium cyanide in boiling methanol solution and the corresponding nitrile (15), free from its dihydro-derivative (16), was isolated from the products in good yield. Finally, 17 $\beta$ -hydroxy-5 $\alpha$ -androstan-3-one (17) was converted [experiment no. (10)] into compound (18) in satisfactory yield. In this experiment, 2,4,6-tri-isopropylbenzenesulphonyl hydrazone formation

no evidence that it can be used, even under Schöllkopf and Schröder's conditions,<sup>5</sup> to convert simple aliphatic and alicyclic aldehydes into nitriles rather than into the corresponding 5-substituted oxazoles<sup>4</sup> (5). The present method is experimentally very straightforward and has the advantage that it may be used to convert both aliphatic (alicyclic) aldehydes [experiments nos. (3)–(5)] and ketones into nitriles.

Aromatic ketones may be converted into nitriles by Oldenzel and van Leusen's procedure<sup>3</sup> and benzaldehyde may be converted into phenylacetonitrile under Schöllkopf and Schröder's conditions.<sup>5</sup> However, preliminary results suggest that the present method is unsuitable for the preparation of aromatic nitriles. Thus, when benzaldehyde 2,4,6-tri-isopropylbenzenesulphonyl hydrazone (8; R<sup>1</sup> = Ph, R<sup>2</sup> = H, Ar = 2,4,6-Pr<sup>i</sup><sub>3</sub>C<sub>6</sub>H<sub>2</sub>) was treated with an excess of potassium cyanide in methanol at room temperature, a bright orange colour developed immediately. When the reactants were heated, under reflux, for 15 min, the colour disappeared and phenylacetonitrile (3; R<sup>1</sup> = Ph, R<sup>2</sup> = H) (ca. 7%) and benzyl methyl ether (19) (ca. 35%) were obtained as the major products. It is interesting to note that benzyl isocyanide (20) was also obtained, albeit in very



low yield (ca. 1%). It seems likely that benzyl methyl ether (19) and perhaps also phenylacetonitrile were the products of a Bamford-Stevens reaction,<sup>11</sup> that is, that the substrate (8; R<sup>1</sup> = Ph, R<sup>2</sup> = H, Ar = 2,4,6-Pr<sup>i</sup><sub>3</sub>C<sub>6</sub>H<sub>2</sub>) was first converted into phenyldiazomethane (21). Fortunately, the conditions of the present nitrile synthesis (*i.e.* potassium cyanide in methanol) are insufficiently basic for the Bamford-Stevens reaction<sup>11</sup> to compete to a significant extent except when an aryl or possibly other electron-accepting substituent is present to facilitate the formation of an intermediate diazoalkane.

2,4,6-Tri-isopropylbenzenesulphonyl hydrazones (8; Ar = 2,4,6-Pr<sup>i</sup><sub>3</sub>C<sub>6</sub>H<sub>2</sub>) are the most suitable substrates for the present purpose in that their use leads to relatively fast reactions and usually to good yields of nitriles. However, toluene-*p*-sulphonyl- and mesitylene-2-sulphonyl hydrazones (6 and 8; Ar = 2,4,6-Me<sub>3</sub>C<sub>6</sub>H<sub>2</sub>, respectively) may also be used. Thus when cyclohexanone toluene-*p*-sulphonyl hydrazone [6; R<sup>1</sup>, R<sup>2</sup> = -(CH<sub>2</sub>)<sub>5</sub>-] was heated, under reflux, with a three-fold excess of potassium cyanide in methanol for 36 h, cyclohexanecarbonitrile [3; R<sup>1</sup> = R<sup>2</sup> = -(CH<sub>2</sub>)<sub>5</sub>-] was obtained in 56% yield. The latter compound [3; R<sup>1</sup> = R<sup>2</sup> = -(CH<sub>2</sub>)<sub>5</sub>-] was obtained in 63% yield when cyclohexanone mesitylene-2-sulphonyl hydrazone<sup>10</sup> [8; R<sup>1</sup>, R<sup>2</sup> = -(CH<sub>2</sub>)<sub>5</sub>-, Ar = 2,4,6-Me<sub>3</sub>C<sub>6</sub>H<sub>2</sub>] was heated with potassium cyanide in methanol, under the same conditions, for 8 h.

#### EXPERIMENTAL

Unless otherwise stated, <sup>1</sup>H and <sup>13</sup>C n.m.r. spectra were measured with a Bruker HFX 90 FT spectrometer. I.r. spectra of liquids (as films) and solids (in CHCl<sub>3</sub> solution) were measured with a Perkin-Elmer 257 grating spectrometer. Mass spectra were obtained with A.E.I. MS 9 and MS 30 spectrometers. G.l.c. was carried out with a Perkin-Elmer F11 gas chromatograph on a 100 cm Carbowax C 20M column at 120 °C. T.l.c. was carried out on plates

coated with Merck Kieselgel GF<sub>254</sub>. Technical grade 1,3,5-tri-isopropylbenzene was purchased from Koch-Light Ltd.

2,4,6-Tri-isopropylbenzenesulphonohydrazide (TPSH; 11a) (with PETER GRICE).—This compound was prepared as described previously<sup>8b</sup> except that the final step, involving trituration with ice-cold water, was omitted. TPSH, so obtained, may be further purified by dissolving it in the minimum quantity of dry ether (*ca.* 10 ml g<sup>-1</sup>) at 0 °C and then adding ice-cold light petroleum (b.p. 30–40 °C; *ca.* 16 ml g<sup>-1</sup>).

Cyclopentanecarbonitrile [3; R<sup>1</sup>, R<sup>2</sup> = -(CH<sub>2</sub>)<sub>4</sub>-]. Cyclopentanone (1.7 g, 20 mmol) and TPSH (7.5 g, 25 mmol) were stirred together in methanol (30 ml) solution at room temperature for 1 h. Potassium cyanide (3.9 g, 60 mmol) was then added and the reaction mixture was heated, under gentle reflux, for 2 h. After water (20 ml) had been added, the products were extracted with dichloromethane (60 ml) and the extract washed with saturated aqueous sodium hydrogen carbonate (100 ml) and water (50 ml). The dried (MgSO<sub>4</sub>) organic layer was evaporated carefully under reduced pressure and the residue distilled to give cyclopentanecarbonitrile, b.p. 101 °C at 100 mmHg; yield 1.28 g (67%);  $\nu_{\text{max}}^{\text{film}}$  2 240 cm<sup>-1</sup>; R<sub>T</sub> 2.5 min; (M-1)<sup>+</sup> at *m/e* 94.065 9 (calc. 94.065 7); <sup>1</sup>H n.m.r. (CDCl<sub>3</sub>):  $\delta$  1.45–2.2 (8 H, m) and 2.72 (1 H, m); <sup>13</sup>C n.m.r. (CDCl<sub>3</sub>):  $\delta$  25.0, 27.9, 31.3, and 123.5.

Cyclohexanecarbonitrile [3; R<sup>1</sup>, R<sup>2</sup> = -(CH<sub>2</sub>)<sub>5</sub>-].—(a) Cyclohexanone (1.97 g, 20 mmol) and TPSH (7.5 g, 25 mmol) were stirred together in methanol (30 ml) solution at room temperature for 1 h. Potassium cyanide (3.9 g, 60 mmol) was then added and the procedure described above in the preparation of cyclopentanecarbonitrile was followed to give cyclohexanecarbonitrile, b.p. 61 °C at 11 mmHg; yield 1.58 g (72%);  $\nu_{\text{max}}^{\text{film}}$  2 250 cm<sup>-1</sup>; R<sub>T</sub> 4.4 min; M<sup>+</sup> at *m/e* 109.088 6 (calc. 109.089 1); <sup>1</sup>H n.m.r. (CDCl<sub>3</sub>):  $\delta$  1.3–2.2 (10 H, m) and 2.66 (1 H, m); <sup>13</sup>C n.m.r. (CDCl<sub>3</sub>):  $\delta$  24.1, 25.3, 28.0, 29.6, and 122.6.

(b) Potassium cyanide (3.9 g, 60 mmol) was added to a solution of cyclohexanone toluene-*p*-sulphonyl hydrazone (5.32 g, 20 mmol) in methanol (30 ml) solution and the mixture was heated under reflux. After 36 h, when t.l.c. indicated that no substrate remained, the products were worked up as above to give cyclohexanecarbonitrile, b.p. 68 °C at 12 mmHg; yield 1.2 g (56%).

(c) Potassium cyanide (3.9 g, 60 mmol) was added to a solution of cyclohexanone mesitylene-2-sulphonyl hydrazone<sup>10</sup> (5.9 g, 20 mmol) in methanol (30 ml) solution and the mixture was heated under reflux. After 8 h, when t.l.c. indicated that no substrate remained, the products were worked up as above to give cyclohexanecarbonitrile, b.p. 68 °C at 12 mmHg; yield 1.4 g (63%).

Cyclohexylacetonitrile (3; R<sup>1</sup> = C<sub>6</sub>H<sub>11</sub>, R<sup>2</sup> = H).—Freshly distilled cyclohexanecarbaldehyde (2.25 g, 20 mmol) and TPSH (7.5 g, 25 mmol) were stirred together in methanol (30 ml) solution at room temperature for 1 h. Potassium cyanide (3.9 g, 60 mmol) was then added and the procedure described above in the preparation of cyclopentanecarbonitrile was followed to give cyclohexylacetonitrile, b.p. 82 °C at 11 mmHg; yield 1.75 g (71%);  $\nu_{\text{max}}^{\text{film}}$  2 250 cm<sup>-1</sup>; R<sub>T</sub> 8.7 min; M<sup>+</sup> at *m/e* 123.103 4 (calc. 123.103 5); <sup>1</sup>H n.m.r. (CDCl<sub>3</sub>):  $\delta$  1.0–2.0 (11 H, m) and 2.25 (2 H, d, *J* = 5.9 Hz); <sup>13</sup>C n.m.r. (CDCl<sub>3</sub>):  $\delta$  24.7, 25.8, 32.4, 34.9, and 118.8.

Octanenitrile (3; R<sup>1</sup> = C<sub>6</sub>H<sub>13</sub>, R<sup>2</sup> = H).—A solution of freshly distilled n-heptaldehyde (2.28 g, 20 mmol) and TPSH (7.5 g, 25 mmol) in tetrahydrofuran (30 ml) was stirred at

room temperature for 3 h and the products were then evaporated under reduced pressure. The residue was dissolved in methanol (30 ml) and the solution obtained was heated with potassium cyanide (3.9 g, 60 mmol), under gentle reflux, for 2 h. The products were then worked up, according to the procedure described above in the preparation of cyclopentanecarbonitrile, to give octanenitrile, b.p. 80 °C at 11 mmHg; yield 1.81 g (70%);  $\nu_{\text{max}}^{\text{film}}$  2 240  $\text{cm}^{-1}$ ;  $R_T$  5.0 min;  $M^+$  at  $m/e$  125.120 9 (calc. 125.120 5);  $^1\text{H}$  n.m.r. ( $\text{CDCl}_3$ ):  $\delta$  0.89 (3 H, m), 1.1—1.9 (10 H, m), and 2.34 (2 H, t,  $J = 6.6$  Hz);  $^{13}\text{C}$  n.m.r. ( $\text{CDCl}_3$ ):  $\delta$  14.1, 17.2, 22.6, 25.5, 28.5, 28.7, 31.6, and 119.9

**Nonanenitrile** (3;  $\text{R}^1 = \text{C}_7\text{H}_{15}$ ,  $\text{R}^2 = \text{H}$ ).—The procedure used was identical to that described above in the preparation of octanenitrile except that freshly distilled n-octaldehyde (2.56 g, 20 mmol) was used instead of an equivalent amount of n-heptaldehyde. Nonanenitrile (1.89 g, 68%) had b.p. 102 °C at 11 mmHg;  $\nu_{\text{max}}^{\text{film}}$  2 250  $\text{cm}^{-1}$ ;  $R_T$  8.7 min;  $M^+$  at  $m/e$  139.135 8 (calc. 139.136 1);  $^1\text{H}$  n.m.r. ( $\text{CDCl}_3$ ):  $\delta$  0.89 (3 H, m), 1.1—1.9 (12 H, m), and 2.34 (2 H, t,  $J = 6.6$  Hz);  $^{13}\text{C}$  n.m.r. ( $\text{CDCl}_3$ ):  $\delta$  14.1, 17.2, 22.7, 25.4, 28.7, 29.0, 31.8, and 119.9.

**2-n-Propylvaleronitrile** [3;  $\text{R}^1 = \text{R}^2 = \text{CH}_2(\text{CH}_2)_2$ ].—A solution of heptan-4-one (2.28 g, 20 mmol) and TPSH (8.9 g, 30 mmol) in THF (20 ml) was stirred at room temperature for 2 h and the products then evaporated under reduced pressure. The residue was dissolved in methanol (30 ml) and the solution obtained was heated with potassium cyanide (3.9 g, 60 mmol), under gentle reflux, for 3 h. The products were then worked up, according to the procedure described above in the preparation of cyclopentanecarbonitrile, to give 2-n-propylvaleronitrile, b.p. 63 °C at 11 mmHg; yield 1.84 g (73%);  $\nu_{\text{max}}^{\text{film}}$  2 240  $\text{cm}^{-1}$ ;  $R_T$  2.4 min;  $(M + 1)^+$  at  $m/e$  126.128 2 (calc. 126.128 2);  $^1\text{H}$  n.m.r. ( $\text{CDCl}_3$ ):  $\delta$  0.96 (6 H, m), 1.55 (8 H, m), and 2.3—2.65 (1 H, m);  $^{13}\text{C}$  n.m.r. ( $\text{CDCl}_3$ ):  $\delta$  13.6, 20.5, 31.2, 34.4, and 122.3.

**2,2,3-Trimethylbutyronitrile** (3;  $\text{R}^1 = \text{Me}$ ,  $\text{R}^2 = \text{Bu}^t$ ).—A solution of pinacolone (3.0 g, 30 mmol) and TPSH (13.9 g, 47 mmol) in tetrahydrofuran (20 ml) was stirred at room temperature for 3 h and the products then evaporated under reduced pressure. The residue was dissolved in methanol (30 ml) and the solution obtained was heated with potassium cyanide (3.9 g, 60 mmol), under gentle reflux, for 3 h. The products were then worked up, according to the procedure described above in the preparation of cyclopentanecarbonitrile, to give 2,2,3-trimethylbutyronitrile, b.p. 148—150 °C; yield 2.0 g (60%);  $\nu_{\text{max}}^{\text{film}}$  2 240  $\text{cm}^{-1}$ ;  $R_T$  1.2 min;  $(M - 15)^+$  at  $m/e$  96.078 5 (calc. 96.081 3);  $^1\text{H}$  n.m.r. ( $\text{CDCl}_3$ ):  $\delta$  1.05 (9 H, s), 1.26 (3 H, d,  $J = 7.3$  Hz), and 2.43 (1 H, quart,  $J = 7.3$  Hz);  $^{13}\text{C}$  n.m.r. ( $\text{CDCl}_3$ ):  $\delta$  13.3, 26.9, 32.8, 37.3, and 122.3.

**2-Methylhex-5-enenitrile** (15).—A solution of hex-1-en-5-one (1.97 g, 20 mmol) and TPSH (6.26 g, 21 mmol) in tetrahydrofuran (30 ml) was stirred at room temperature. After 2 h, the reaction solution was concentrated (to ca. 15 ml) and water (30 ml) was added and the crystalline 2,4,6-triisopropylbenzenesulphonyl hydrazone (7.4 g, 98%), m.p. 107—109 °C, was collected by filtration. The latter material and potassium cyanide (3.9 g, 60 mmol) were heated together, under gentle reflux in methanol (30 ml) for 5 h. The products were then worked up, according to the procedure described above in the preparation of cyclopentanecarbonitrile, to give 2-methylhex-5-enenitrile, b.p. 98 °C at 100 mmHg; yield 1.62 g (75%);  $\nu_{\text{max}}^{\text{film}}$  2 240  $\text{cm}^{-1}$ ;  $R_T$  2.1 min;  $M^+$  at  $m/e$  109.085 6 (calc. 109.086 0);  $^1\text{H}$  n.m.r.

( $\text{CDCl}_3$ ):  $\delta$  1.32 (3 H, d,  $J = 7.0$  Hz), 1.5—1.8 (2 H, m), 2.1—2.3 (2 H, m), 2.64 (1 H, m), 4.95—5.2 (2 H, m), and 5.6—6.0 (1 H, m);  $^{13}\text{C}$  n.m.r. ( $\text{CDCl}_3$ ):  $\delta$  17.9, 24.9, 31.1, 33.2, 116.3, 122.8, and 136.4.

**Cyclododecanecarbonitrile** [3;  $\text{R}^1, \text{R}^2 = -(\text{CH}_2)_{11}-$ ].—A solution of cyclododecanone (3.65 g, 20 mmol) and TPSH (7.5 g, 25 mmol) in tetrahydrofuran (30 ml) was stirred at room temperature for 16 h and the products then evaporated under reduced pressure. The residue was dissolved in methanol (30 ml) and the solution obtained was heated with potassium cyanide (3.9 g, 60 mmol), under gentle reflux, for 4 h. The products were then worked up, according to the procedure described above in the preparation of cyclopentanecarbonitrile, to give cyclododecanecarbonitrile, b.p. 147 °C at 11 mmHg; yield 2.97 g (77%);  $\nu_{\text{max}}^{\text{film}}$  2 240  $\text{cm}^{-1}$ ;  $R_T$  6.2 min (100 cm Carbowax C 20M column, 200 °C);  $(M - 1)^+$  at  $m/e$  192.174 2 (calc. 192.174 3);  $^1\text{H}$  n.m.r. ( $\text{CDCl}_3$ ):  $\delta$  1.2—2.0 (22 H, m) and 2.45—2.8 (1 H, m);  $^{13}\text{C}$  n.m.r. ( $\text{CDCl}_3$ ):  $\delta$  21.9, 23.2, 23.3, 23.6, 23.8, 26.6, 27.3, and 123.0.

**3-Cyano-5 $\alpha$ -androstan-17- $\beta$ -ol** (18).—A solution of 17 $\beta$ -hydroxy-5 $\alpha$ -androstan-3-one (1.0 g, 3.45 mmol) in methanol (5 ml) was added to a solution of TPSH (1.2 g, 4.0 mmol) in methanol at 20 °C. The crystalline 2,4,6-triisopropylbenzenesulphonyl hydrazone (1.85 g, 94%), m.p. 168—170 °C (decomp.) which precipitated almost instantaneously was collected by filtration, washed with a little cold methanol, and dried. The latter material and potassium cyanide (0.67 g, 10 mmol) were heated together in methanol (15 ml), under gentle reflux, for 2 h and the products then allowed to cool. After water (20 ml) had been added, the products were extracted with dichloromethane (50 ml) and the extract washed with saturated aqueous sodium hydrogen carbonate (20 ml) and water (20 ml). The dried ( $\text{MgSO}_4$ ) organic layer was evaporated under reduced pressure and the residue purified by chromatography on silica gel. Concentration of the fractions eluted by  $\text{CHCl}_3$ - $\text{EtOH}$  (98:2 v/v) were evaporated under reduced pressure to give 3-cyano-5 $\alpha$ -androstan-17- $\beta$ -ol; yield 0.70 g (67% overall yield). Recrystallization of this material from methanol gave colourless crystals (0.41 g, 39.5%), m.p. 187—190 °C (m.p. 216—217 °C after two further recrystallizations from methanol) (Found, in material dried over  $\text{P}_2\text{O}_5$  at 50 °C: C, 79.8; H, 10.5; N, 4.6.  $\text{C}_{20}\text{H}_{31}\text{NO}$  requires C, 79.7; H, 10.4; N, 4.65%);  $\nu_{\text{max}}^{\text{CHCl}_3}$  2 220  $\text{cm}^{-1}$ ;  $M^+$  at  $m/e = 301$  (18%);  $^1\text{H}$  n.m.r. of recrystallized material ( $\text{CDCl}_3$ ):  $\delta$  0.73 (3 H, s), 0.79 (3 H, s), 0.80—1.85 (22 H, m), 2.05 (1 H, m), 2.94br (1 H, s), and 3.63 (1 H, t,  $J \sim 7.5$  Hz).

**Reaction between Potassium Cyanide and Benzaldehyde 2,4,6-Triisopropylbenzenesulphonyl hydrazone** (8;  $\text{R}^1 = \text{Ph}$ ,  $\text{R}^2 = \text{H}$ ,  $\text{Ar} = 2,4,6\text{-Pr}_3\text{C}_6\text{H}_2$ ). Potassium cyanide (4.7 g, 72 mmol) was added to a solution of (10;  $\text{R}^1 = \text{Ph}$ ,  $\text{R}^2 = \text{H}$ ,  $\text{Ar} = 2,4,6\text{-Pr}_3\text{C}_6\text{H}_2$ ) (10.0 g, 26 mmol) in methanol (50 ml). The resulting deep orange coloured reaction mixture was heated under reflux. After 15 min, when t.l.c. indicated that no starting material remained, the products were worked up according to the procedures described above in the preparation of cyclopentanecarbonitrile to give a colourless oil, b.p. 95 °C at 11 mmHg; yield 1.5 g. G.l.c. (100 cm Carbowax C 20M column at 150 °C), revealed at least six components with  $R_T$  values 1.2 (ca. 75%), 2.0 (ca. 2%), 2.7 (ca. 5%), 5.9 (ca. 2%), 7.3 (ca. 2%), and 9.1 min (ca. 15%).

The most abundant component ( $R_T$  1.2 min) was identified as benzyl methyl ether on the basis of its mass ( $M^+$  at  $m/e$

122.072 1) and  $^1\text{H}$  n.m.r. [ $\text{CDCl}_3$ ]:  $\delta$  3.29 (3 H, s), 4.36 (2 H, s), and 7.26 (5 H, m)] spectra. The second most abundant component ( $R_T$  9.1 min) was identified as phenylacetonitrile on the basis of its g.l.c. retention time and its mass ( $M^+$  at  $m/e = 117$ ), i.r. ( $\nu_{\text{max}}^{\text{film}}$  2 255  $\text{cm}^{-1}$ ) and  $^1\text{H}$  n.m.r. [90 MHz, in  $\text{CDCl}_3$ :  $\delta$  3.74 (2 H, s) and 7.35 (5 H, m)] spectra. The product with  $R_T$  5.9 min was identified as benzyl isocyanide by comparison [g.l.c. and i.r. spectrum ( $\nu_{\text{max}}^{\text{film}}$  2 160  $\text{cm}^{-1}$ )] with an authentic sample.

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