The Conversion of Gibberellic Acid into Steroid Analogues

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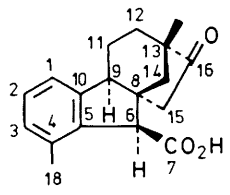
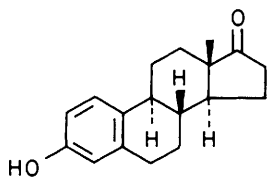
The expansion of ring B of the gibberellins by formolysis of the toluene-*p*-sulphonate of the 7-hydroxymethyl analogue of gibberic acid affords the steroid analogue, 4-methyl-15(14→8α)-*abeo*-16-noroestra-1,3,5(10)-trien-17-one.

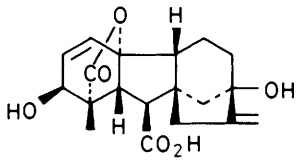
There is a formal resemblance between some degradation products of the gibberellins [*e.g.* gibberic acid (**1**)] and the steroid hormones [*e.g.* oestrone (**2**)]. This similarity is enhanced by expansion of the five-membered ring B of the gibberellins to a six-membered ring. The availability of gibberellic acid (**3**) which is produced in tonne quantities annually by commercial fermentations, has led us to investigate the expansion of ring B in the context of the preparation of steroid analogues.



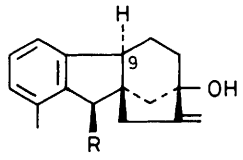
(**1**)



(**2**)



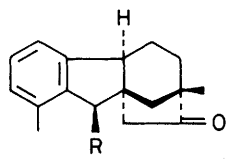
(**3**)



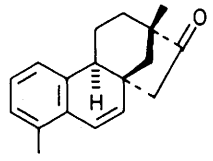
(**4**) R = CO_2H
(**5**) R = CO_2Me
(**6**) R = CH_2OH

Treatment of gibberellic acid (**3**) with dilute hydrochloric acid at room temperature gave allogibberic acid (**4**)[1] in which the C-9 hydrogen atom now has the steroidal 9α-configuration.[2] The methyl ester (**5**),[1] prepared with diazomethane, was reduced directly with lithium aluminium hydride in ether to afford the alcohol (**6**) [δ 4.18 (2 H m, 7-H); $\nu_{max.}$ 3 340 cm^{-1}] in 83% yield. Wagner-Meerwein rearrangement of the C/D ring junction[3] using refluxing methanolic hydrochloric acid, proceeded in 85% yield to afford the 8:13-isogibberellin (**7**). This compound lacked the ^1H n.m.r. signals at δ 4.78 and 5.0 assigned to the 17-methylene but possessed a new C–CH_3 signal at δ 1.04. In the 8:13-isogibberellin series C-13 has a configuration comparable to that of the steroids.

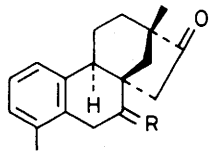
The solvolysis of the toluene-*p*-sulphonates of 9-hydroxymethylfluorenes in formic acid[4] affords phenanthran-9-ols whilst similar conditions lead[5] to the ring expansion of indanylmethanol toluene-*p*-sulphonates. These conditions were therefore explored in the gibberic acid series. Reaction of the alcohol (**7**) with toluene-*p*-sulphonyl chloride in pyridine gave an 81% yield of the toluene-*p*-sulphonate (**8**) [$\nu_{max.}$ 1 580 and 1 180 cm^{-1}; δ 2.45 (Ar-Me), 7.36 and 7.79 (each 2 H, *J* 8.4 Hz)]. The hindered rotation of the primary alcohol was revealed by the non-equivalent proton resonances [δ 3.56 (dd, *J* 3.4 and 8.7 Hz, 6α-H), 4.32 (dd, *J* 8.7 and 10.3 Hz) and 4.77 (dd, *J* 3.4 and 10.3 Hz, 7-H)], relationships which were established by spin-decoupling experiments. Treatment of the toluene-*p*-sulphonate (**8**) with refluxing formic acid for 15 min (t.l.c. control), gave a



(**7**) R = CH_2OH
(**8**) R = $CH_2OSO_2 \cdot C_6H_4 \cdot Me$
(**10**) R = $=CH_2$



(**9**)



(**11**) R = α-H,β-OCHO
(**12**) R = α-H,β-OH
(**13**) R = α-OH,β-H
(**14**) R = =O
(**15**) R = H_2

mixture of four products which were separated by flash chromatography on silica. The first compound to be eluted (**9**) (7%) had i.r. and u.v. spectra characteristic of a styrene [$\nu_{max.}$ 1 680 and 1 560 cm^{-1}; $\lambda_{max.}$ 223 (ε 23 700) and 278 (10 230)]. It showed *cisoid* double bond proton resonances [δ 5.98 and 6.72 (*J* 9.7 Hz)] in the ^1H n.m.r. spectrum and hence it was formulated as the cyclohexene (**9**) rather than the isomeric methylenecyclopentane (**10**). The absence of an additional secondary methyl ^1H n.m.r. signal in its hydrogenation product (*vide infra*) supported this. The major product (76%) was the formate ester (**11**) [$\nu_{max.}$ 1 736 and 1 710 cm^{-1}; δ 8.20 (s, OCHO) and 5.36 (*J* 10.3 and 6.9 Hz, CHOR)]. This was hydrolysed by treatment with 5% methanolic sodium methoxide to a secondary alcohol (**12**) which was also obtained in the solvolysis reaction in 5% yield. The alcohol showed i.r. absorption at $\nu_{max.}$ 3 530, 3 220br, and 1 760 cm^{-1} and a ^1H n.m.r. signal at δ 4.07 (1 H, dd, *J* 6.9 and 10.8 Hz, C*H*OH). The

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Table 1. ^{13}C N.m.r. resonances of 4-methyl-15(14→8α)-*abeo*-16-noroestratrien-17-ones (determined at 90.55 MHz in $CDCl_3$)

	Compound		
Carbon atom	(15)	(12)	(14)
1	123.2	123.3	122.9
2	125.8	126.3	126.9
3	127.7	128.0	128.9
4	135.1	134.0	129.2
5	136.8	136.8	131.4
6	24.8	35.8	42.8
7	34.5	69.6	210.7
8	38.5	44.2	51.5
9	43.2	43.2	40.9
10	137.8	136.9	137.3
11	22.9	23.0	21.1
12	34.5	35.0	34.0
13	49.5	49.1	50.0
14	42.6	35.1	41.3
15	52.6	45.7[a]	46.1
17	221.8	221.5	219.0
18	20.1	20.0	19.8
13-Me	19.8	19.8	19.6

[a] Signal decreases and becomes a triplet in ^2H material.

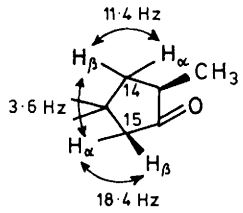
(ε 9 170) and 264 nm (430); $\nu_{max.}$ 1 780 and 1 720 cm $^{-1}$]. Secondly comparison of the ^{13}C n.m.r. spectra (see Table 1) of the alcohol (**12**) and the ketone (**14**) with their desoxy counterpart (**15**) showed that the oxygen functions produced a major downfield shift (Δδ 5.7 and 13 p.p.m. respectively) in the position of a singlet resonance assigned to C-8. The resonances were assigned by comparison with 4-methyloestratrien-17-one.[6]

The position of the oxygen functions at C-7 having been established, the stereochemistry of the alcohols followed from two pieces of evidence; firstly the magnitude of the 6-H,7-H coupling constants and secondly the effect of the hydroxy groups on the ring C/D and C-9 proton resonances particularly the aromatic solvent-induced shifts. The C*H*OH ^1H n.m.r. resonance in the major alcohol (**12**) appeared at δ 4.07 (dd, *J* 6.9 and 10.8 Hz). Spin-decoupling experiments showed that it was coupled to signals at δ 2.57 (dd, *J* 10.8 and 16.8 Hz) and δ 3.18 (dd, *J* 6.9 and 16.8 Hz). On the other hand irradiation of the C*H*OH resonance (δ 3.95) in the minor alcohol (**13**) removed a coupling (*J* 4.6 Hz) from a double doublet at δ 3.00 (*J* 4.6 and 18.4 Hz) and sharpened a doublet (*J* 18.4 Hz) at δ 2.83. These coupling constants led to the dihedral angles shown in the Newman projections (**16**) and (**17**). The ring D proton resonances (see Table 2) were identified in the following manner. Monodeuteriation (*M*$^+$, *m/z* 271.168. $C_{18}H_{21}{}^2HO_2$ requires *M*$^+$, *m/z* 271.170) of the ring D ketone (**12**) by treatment with sodium deuterioxide at room temperature for 2

Table 2. ^1H N.m.r. signals of 4-methyl-15(14→8α)-*abeo*-16-noroestratrien-17-ones (determined at 360 MHz in $CDCl_3$ except where stated)

	Compound							
Proton	(15)	(9)	(12)	(12)[c]	(13)	(13)[c]	(11)[d]	(14)
1-H	7.05	7.05	7.07	N.a.	7.08	N.a.	7.08	N.a.
2-H	7.12	7.21	7.15	N.a.	7.16	N.a.	7.16	7.16
3-H	7.25	7.15	7.23	N.a.	7.30	N.a.	7.23	N.a.
6-Hα	N.a.	6.72	3.18	3.28	3.00	3.05	3.30	3.82
β			2.57	2.88	2.83	2.97	2.64	3.48
7-H	N.a.	5.98	4.07	4.20	3.95	4.20	5.36	
9-H	2.80	2.99	2.90	2.88	3.22	3.63	2.97	3.23
14-Hα	1.43	1.29	1.74	2.04	1.41	1.47	1.80	1.46
β	1.78	1.80	1.49	1.49	1.57	1.32	1.64	1.62
15-Hα	2.37	2.48	2.12[a]	2.26	2.57	2.84	2.18	2.32
β	2.18	2.34	2.90[b]	3.38	2.22	2.46	2.53	3.12
13-Me	0.94	0.93	0.96	1.02	0.94	0.98	0.97	0.96
18-H	2.25	2.35	2.27	2.27	2.25	2.20	2.24	2.31

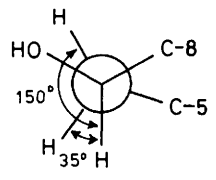
N.a. = not assigned; [a] = resonance becomes a singlet in ^2H material; [b] = resonance disappears in ^2H material; [c] = spectrum determined in $C_5{}^2H_5N$; [d] = OCHO resonance δ 8.20. Coupling constants on ring D shown in (**A**).



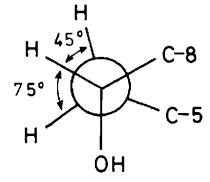
(**A**)

final product (**13**) obtained from the chromatography, in 0.5% yield, was an isomeric secondary alcohol [$\nu_{max.}$ 3 570, 3 480, and 1 770 cm^{-1}; δ 3.95 (br s, *w*/2 10 Hz, C*H*·OH)]. Oxidation of both alcohols with pyridinium chlorochromate in methylene chloride gave the same ketone (**14**). Hydrolysis of the crude formolysis product gave the isomeric alcohols in the ratio 9:1 suggesting that some of the epimeric formate was also formed.

The position of an oxygen function in the formate (**11**) and the alcohols (**12**) and (**13**) at C-7 was established as follows. The ketone (**14**) did not show the u.v. or i.r. characteristics of an acetophenone but rather those of a saturated ketone [$\lambda_{max.}$ 215



(**16**)



(**17**)

h led to the exchange of the 15-*exo* proton.[7] Comparison of the ^{1}H n.m.r. spectrum of the product with that of the undeuteriated compound showed that a resonance at δ 2.90 (*J* 18.4 Hz) had disappeared whilst a signal at δ 2.12 (*J* 3.6 and 18.4 Hz) had collapsed to a doublet (*J* 3.6 Hz) which represented a long-range coupling to a signal at δ 1.49. The 15-*endo* protons on the bicyclo[3.2.1]octane moiety of the 8,13-isogibberellins can be distinguished from their 15-*exo*-counterparts by the long-range 'W' type coupling that they show to a proton on the methylene bridge.[8] These assignments (see Table 2) were then confirmed by a series of spin-decoupling experiments on both the alcohols (**12**) and (**13**), the ketone (**14**) and the alkene (**9**). The pyridine-induced ^{1}H n.m.r. shifts were then examined. In the 7β-alcohol (**12**) the resonance assigned to the 14-*exo* proton shows a downfield shift of 0.3 p.p.m. whilst the 15-*exo* proton shows a downfield shift of 0.48 p.p.m. On the other hand in the 7α-alcohol (**13**) only the C-15 protons show a downfield shift (0.27 and 0.24 p.p.m.). Molecular models show that only a 7α-hydroxy group can influence both C-15 protons. However the most informative solvent-shift difference came from the 9α-proton signal which only showed a significant downfield shift in the 7α-alcohol (0.41 p.p.m.). The major alcohol produced in the solvolysis reaction is thus the 7β-alcohol which possesses a pseudo-equatorial conformation.

Elimination of the hydroxy group in (**12**) using phosphorus oxychloride in pyridine gave the alkene (**9**) in 86% yield. Hydrogenation of the latter over 10% palladium on charcoal gave the saturated compound (**15**) in 94% yield. This compound lacked olefinic resonances in its ^{1}H n.m.r. spectrum. In conclusion this rearrangement reaction has established an efficient route to a novel series of steroids in which ring D has been modified to form 4-methyl-15(14→8α)-*abeo*-16-noroestra-1,3,5(10)-trien-17-one. Molecular models indicate that this system is significantly bent compared with the relatively flat oestratrienes. Steroids with this structural variation would not be readily available by modification of normal steroids.

Experimental

Throughout ether refers to diethyl ether. Allogibberic acid, prepared from gibberellic acid, had m.p. 199—203 °C (lit.,[1] 200—203 °C).

Reduction of Methyl Allogibberate.—Allogibberic acid (2.72 g) in dry methanol (25 ml) and anhydrous ether (25 ml) was treated with ethereal diazomethane until the yellow colour persisted. The solvents were evaporated under reduced pressure and the residual oil (2.8 g) was then dissolved in anhydrous ether (50 ml) and heated with lithium aluminium hydride (1 g) under reflux under nitrogen for 3 h. Ethyl acetate (20 ml) and water were then added, the solution was filtered, and the ethyl acetate extract was washed with brine and dried. The solvent was evaporated to give ent-7,13-*dihydroxy*-19,20-*bisnorgibberella*-1,3,5(10),16-*tetraene* (**6**) (2.2 g) which crystallized from benzene as plates, m.p. 148—150 °C (Found: C, 79.6; H, 8.0. $C_{18}H_{22}O_2$ requires C, 79.9, H, 8.2%); $\nu_{max.}$ 3 340br, 1 660, 1 570, 1 215, 1 070, 1 045, and 900 cm^{-1}; δ 6.95 (3 H, br, Ar), 5.00 and 4.78 (2 H, m, 17-H), 4.18 (2 H, m, 7-H), 3.22 (1 H, m, 6-H), 2.81 (1 H, 9α-H), and 2.16 (3 H, s, 4-Me).

Rearrangement of Rings C *and* D *in* (**6**).—The above alcohol (**6**) (2.2 g) in methanol (200 ml) was heated with a mixture of concentrated hydrochloric acid (67 ml) and water (67 ml) under reflux for 1 h. The solvent was evaporated under reduced pressure to afford ent-7-*hydroxy*-13-*methyl*-16-*oxo*-17,19,20-*trisnor*-8,13-*isogebberella*-1,3,5(10)-*triene* (1.88 g) (**7**) which crystallized from aqueous methanol as needles, m.p. 92—93 °C (Found: C, 75.3; H, 8.2. $C_{18}H_{22}O_2{\cdot}H_2O$ requires C, 75.0; H, 8.4%); $\nu_{max.}$ 3 460, 3 400, 3 220, 1 715, 1 560, 1 225, and 1 025 cm^{-1}; δ 7.02 (3 H, m, ArH), 4.3 (2 H, m, 7-H), 3.4 (1 H, m, 6α-H), 2.90 (1 H, m, 9α-H), 1.78 (3 H, s, Ar-Me), and 1.04 (3 H, s, 13-Me). The *toluene*-p-*sulphonate*, prepared with toluene-*p*-sulphonyl chloride in anhydrous pyridine at room temperature for 20 h, crystallized from methanol as needles, m.p. 148.5—150 °C (Found: C, 70.7; H, 6.65. $C_{25}H_{28}O_4S$ requires C, 70.75; H, 6.6%); $\nu_{max.}$ 1 735, 1 595, 1 305, 1 180, and 1 170 cm^{-1}; δ (determined at 360 MHz), 0.96 (3 H, s, 13-Me), 1.35 (1 H, d, *J* 11.8 Hz, 14-H), 1.66 (1 H, dd, *J* 3.6 and 11.8 Hz, 14-H), 2.25 (3 H, s, 4-Me), 2.32 (1 H, dd, *J* 3.6 and 17.8 Hz, 15-H), 2.45 (3 H, s, Ar-Me), 2.57 (1 H, d, *H* 17.8 Hz, 15-H), 2.83 (1 H, t, *J* 7 Hz, 9-H), 3.56 (1 H, dd, *J* 3.4 and 8.7 Hz, 6α-H), 4.32 (1 H, dd, *J* 8.7 and 10.3 Hz, 7-H), 4.77 (1 H, dd, *J* 3.4 and 10.3 Hz, 7-H), 6.96 (2 H, d, *J* 7.3 Hz, 1- and 3-H), 7.14 (1 H, t, *J* 7.3 Hz, 2-H), and 7.36 and 7.79 (each 2 H, d, *J* 8.4 Hz, Ar-H).

Formolysis of Toluene-p-*sulphonate* (**8**).—The above toluene-*p*-sulphonate (**8**) (1 g) was heated under reflux in 90% formic acid (20 ml) for 15 min. (After 10 min, t.l.c. showed the disappearance of starting material and the appearance of four new spots.) The cold solution was poured into ice–water (200 ml) and the white precipitate (0.623 g) collected and chromatographed on silica. Elution with 5% ethyl acetate–light petroleum gave 4-*methyl*-15(14→8α)-abeo-16-*noroestra*-1,3,5(10),6-*tetraen*-17-*one* (**9**) (43 mg) which crystallized from acetone–light petroleum as needles, m.p. 168—170 °C (Found: C, 85.1; H, 7.9. $C_{18}H_{20}O$ requires C, 85.7; H, 7.9%); $\nu_{max.}$ 1 770, 1 680, 1 560, 1 080, and 780 cm^{-1}; n.m.r. data see Table 2. Further elution with 10% ethyl acetate–light petroleum gave 7β-*formyloxy*-4-*methyl*-15(14→8α)-abeo-16-*noroestra*-1,3,5(10)-*trien*-17-*one* (**11**) (533 mg) which crystallized from acetone–light petroleum as needles, m.p. 71—72 °C (Found: C, 76.3; H, 7.8. $C_{19}H_{22}O_3$ requires C, 76.5; H, 7.4%); $\nu_{max.}$ 1 736, 1 710, 1 585, 1 180br, 970, and 790 cm^{-1}; for n.m.r. data see Table 2. Elution with 30% ethyl acetate–light petroleum gave 7β-*hydroxy*-4-*methyl*-15(14→8α)-abeo-16-*noroestra*-1,3,5(10)-*trien*-17-*one* (**12**) (31 mg) which crystallized from ether as plates, m.p. 161—163 °C (Found: C, 79.6; H, 8.0. $C_{18}H_{22}O_2$ requires C, 79.95; H, 8.2%); $\nu_{max.}$ 3 530, 3 220br, 1 760, 1 655, 1 590, 1 260, and 1 070 cm^{-1}; for n.m.r. data see Table 2. Further elution gave 7α-*hydroxy*-4-*methyl*-15(14→8α)-abeo-16-*noroestra*-1,3,5(10)-*trien*-17-*one* (**13**) (3.5 mg) which crystallized from ether as plates, m.p. 99—101 °C or in a polymorphic form from acetone–light petroleum as needles, m.p. 158—160 °C (Found: C, 79.8; H, 8.1. $C_{18}H_{22}O_2$ requires C, 79.95; H, 8.2%); $\nu_{max.}$ 3 570, 3 480, 1 770, 1 650, 1 570, 1 240, and 1 060 cm^{-1}; for n.m.r. data see Table 2. The experiment was repeated and the precipitate (676 mg) was dissolved in 5% sodium methoxide in methanol (20 ml) and stirred at room temperature for 1 h (t.l.c. control). The solution was poured into a large volume of water and the precipitate (547 mg) was collected and chromatographed on silica to afford the alkene (**9**) (46.5 mg, 7.8%), the alcohol (**12**) (429 mg, 67.4%), a mixture of (**12**) and (**13**) (13.4 mg), and the alcohol (**13**) (45.1 mg, 7.1%). Further analysis of the hydrolysate by h.p.l.c. on Suspherisil in ethyl acetate–hexane (3:7) gave a ratio of 9:1 between (**12**) and (**13**).

Hydrogenation of the Alkene (**9**).—The above alkene (**9**) (32 mg) and 10% palladium on charcoal (30 mg) in ethyl acetate (5 ml) were stirred under an atmosphere of hydrogen for 4 h until uptake ceased. The solvent was evaporated and the product recovered to afford 4-*methyl*-15(14→8α)-abeo-16-*noroestra*-1,3,5(10)-*trien*-17-*one* (30 mg) which crystallized from acetone–light petroleum as needles, m.p. 144—146 °C (Found, C, 85.0; H, 8.7. $C_{18}H_{22}O$ requires C, 85.6; H, 9.0%); $\nu_{max.}$ 1 750, 1 690, and 1 582 cm^{-1}; $\lambda_{max.}$(MeOH) 230 (ε 608), 267 (162), and 272 nm (135); for n.m.r. data see Table 2.

Oxidation of the Alcohols (**12**) *and* (**13**).—(*a*) Pyridinium chlorochromate (388 mg) was suspended in methylene chloride (5 ml) and the alcohol (**12**) (160 mg) was rapidly added. The mixture was stirred at room temperature for 1.5 h when t.l.c. showed that some starting material remained. A further batch of pyridinium chlorochromate (100 mg) was added and the mixture was stirred for a further 30 min after which t.l.c. showed that the reaction was complete. The mixture was diluted with ether (10 ml) and filtered through Florisil which was then rinsed with further ether. Evaporation of the solvent gave 4-*methyl*-7-*oxo*-15(14→8α)-abeo-16-*noroestra*-1,3,5(10)-*trien*-17-*one* (**14**) (110 mg) which crystallized from acetone as prisms, m.p. 214–217 °C (Found C, 80.3; H, 7.5. $C_{18}H_{20}O_2$ requires C, 80.6; H, 7.5%); $\nu_{max.}$ 1 780, 1 720, 1 580, and 1 280 cm^{-1}; $\lambda_{max.}$(MeOH) 215 (ε 9 170) and 264 nm (429); for n.m.r. data see Table 2.

(*b*) The alcohol (**13**) (54 mg) was oxidized with pyridinium chlorochromate (200 mg) as above to afford the ketone (**14**) (26 mg), m.p. 214—217 °C identified by its i.r. spectrum. There was no depression of mixed m.p.

Deuteriation of the Alcohol (**12**).—The alcohol (**12**) (30 mg) in dioxane (2 ml) was treated with sodium deuterioxide (prepared from sodium, 350 mg in deuterium oxide 5 ml) (2.5 ml) at room temperature for 3 h. The solution was neutralized with hydrochloric acid (3 ml), water (2 ml) was added and the product filtered and recrystallized from ether. [15-^{2}H]-4-Methyl-7β-hydroxy-15(14→8α)-*abeo*-16-noroestra-1,3,5-(10)-trien-17-one (22 mg) crystallized from ether as needles, m.p. 162—165 °C (Found: *M*, *m/z* 271.168. $C_{18}H_{21}{}^2HO_2$ requires M^+, *m/z* 271.170); for ^{1}H and ^{13}C n.m.r. data see Tables 1 and 2.

Dehydration of the Alcohol (**12**).—The alcohol (**12**) (50 mg) in pyridine (1 ml) was cooled to 5 °C in an ice-bath, phosphorus oxychloride (100 mg) was added and the solution was left at room temperature for 22 h. It was then refluxed for 2 h and cooled and poured into ice–water (15 ml). The solution was acidified with dilute hydrochloric acid and the product filtered off and chromatographed on silica. Elution with 5% ethyl acetate–light petroleum gave 4-methyl-15(14→8α)-*abeo*-16-noroestra-1,3,5(10),6-tetraen-17-one (40 mg) which crystallized as needles, m.p. 167—169 °C, identical (i.r. and mixed m.p.) with the material described above.

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