Depsidone Synthesis. Part 18.[1] Dihydronidulin

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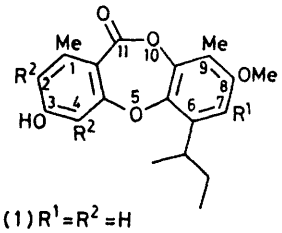
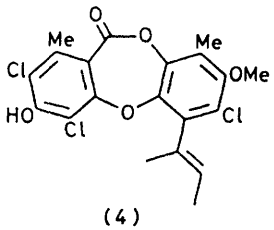
The synthesis of 3,4,7-trichloro-3-hydroxy-8-methoxy-1,9-dimethyl-6-s-butyldibenzo[*b,e*][1,4]dioxepin-11-one (dihydronidulin) (2), a derivative of the fungal depsiodone nidulin (4), by benzophenone–grisadienedione–keten–depsidone interconversion is described.

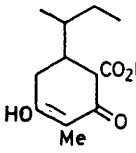
In Part 11 [2] we described the synthesis of tridechlorodihydronidulin (1), a degradation product of the fungal depsidone nidulin (4).[3] Attempts were made, by chlorination under various conditions, to convert tridechlorodihydronidulin (1) into dihydronidulin (2). Although it was possible to introduce chlorine at the 2- and 4-positions of compound (1) it was not possible to introduce chlorine into the sterically hindered 7-position.[4]



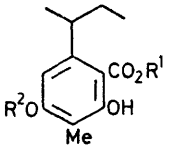
(1) $R^1=R^2=H$
(2) $R^1=R^2=Cl$
(3) $R^1=Cl, R^2=H$



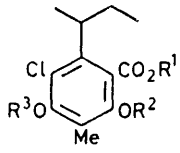
(4)



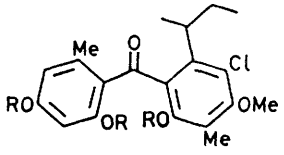
(5)



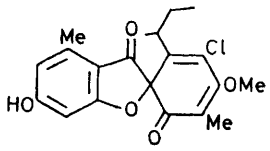
(6) $R^1=Et, R^2=H$
(7) $R^1=H, R^2=Me$



(8) $R^1=Et, R^2=R^3=H$
(9) $R^1=Et, R^2=R^3=Me$
(10) $R^1=Et, R^2=H, R^3=Me$
(11) $R^1=Et, R^2=CH_2Ph, R^3=Me$
(12) $R^1=H, R^2=CH_2Ph, R^3=Me$



(13) $R=CH_2Ph$
(14) $R=H$



(15)

We now describe a synthesis of dihydronidulin (2) in which the chlorine at the 7-position was introduced at an early stage of the synthesis.

Racemic (*E*)-ethyl 4-methylhex-2-enoate was obtained by esterification of the known acid.[5] Condensation of the ester with ethyl 3-oxopentanoate [6] in presence of sodium ethoxide gave the dihydro-compound (5). Marmor has reported that similar condensations between ethyl acetoacetate and αβ-unsaturated esters give markedly reduced yields when there is chain branching at the γ-carbon of the unsaturated ester.[7] We find, on the contrary, that the yield of the dihydro-compound (5) is only slightly lower than that obtained in the condensation of methyl crotonate and methyl 3-oxopentanoate.[8] A number of methods were investigated for the conversion of the dihydro-compound (5) into the aromatic compound (6). In the event, this conversion was best accomplished by treatment of the dihydro-compound (5) with 1 mol equiv. of bromine. The structure of the product (6) followed from spectroscopic and elementary analytical data, and by its conversion into the acid (7), which had been synthesized previously.[2]

Chlorination of compound (6) was achieved with sulphuryl chloride and the product (8) was converted into its di-*O*-methyl ether (9). This was selectively demethylated by treatment with boron trichloride, and the product (10) on benzylation furnished compound (11). Hydrolysis of compound (11) gave the acid (12) which on Friedel–Crafts reaction with 3,5-bisbenzyloxytoluene [9] in presence of trifluoroacetic anhydride afforded the benzophenone (13). Hydrogenolytic debenzylation of compound (13) gave the trihydroxybenzophenone (14).

Oxidative coupling of the trihydroxybenzophenone (14) gave directly the depsidone (3). The initial product of this reaction is the grisadienedione (15), since homolytic aromatic substitution occurs preferentially in the chloro-substituted ring.[10] The grisadienedione (15) then suffers rearrangement [10] *via* a keten intermediate to the depsidone (3). Chlorination of the depsidone (3) with *N*-chlorosuccinimide in boiling dioxan in presence of toluene-*p*-sulphonic acid gave synthetic dihydronidulin (2) identical with the specimen obtained by reduction of the double bond of nidulin (4).

EXPERIMENTAL

General directions have been given before.[11]

(E)-*Ethyl* 4-*Methylhex*-2-*enoate*.—(±)-2-Methylbutan-1-ol was oxidized by the method of Badin and Pascu [12] to 2-methylbutanal which was condensed with malonic acid in pyridine by the method of Linstead and Mann,[5] and furnished (*E*)-4-methylhex-2-enoic acid. The acid (112.0 g), dry ethanol (1 l), and concentrated sulphuric acid (10 ml) were boiled under reflux for 20 h. The usual work-up gave the ester as an oil (95.5 g), b.p. 93—95 °C at 13 mmHg (lit.,[13] 183—185°) (Found: C, 69.3; H, 10.1. Calc. for $C_9H_{16}O_2$: C, 69.2; H, 10.3%).

Ethyl 4-Hydroxy-3-methyl-2-oxo-6-s-butylcyclohex-3-enecarboxylate (5).—The foregoing ester (21.4 g) was added dropwise with stirring to sodium ethoxide [from sodium (3.0 g)] in absolute ethanol (40 ml) and ethyl 3-oxopentanoate [6] (20.0 g). After the addition the mixture was stirred and heated under reflux for 24 h and then most of the ethanol was removed by distillation. The residue was diluted with water and extracted with ether; these extracts were discarded. The aqueous layer was cooled in ice and acidified with ice-cold concentrated hydrochloric acid. The crystalline precipitate (17.1 g) was separated by filtration, washed with a little water, and dried *in vacuo*. A sample formed needles of the *ester* (5) (from ether–light petroleum), m.p. 108—110 °C (Found: C, 66.2; H, 8.5%; M^+, 254. $C_{14}H_{22}O_4$ requires C, 66.1; H, 8.7%; M, 254).

Ethyl 2,4-Dihydroxy-3-methyl-6-s-butylbenzoate (6).—Bromine (4.62 g) in acetic acid (25 ml) was added over 5 min to a solution of the dihydro-ester (5) (7.35 g) in acetic acid (25 ml) with stirring and exclusion of light. The mixture was then diluted with ice and water and extracted with ethyl acetate. The extract was washed in turn with saturated aqueous sodium hydrogencarbonate, water, and finally with saturated brine. The crude product was chromatographed over silica gel with 0—2.5% ethyl acetate–light petroleum as eluant. This gave the ester (6) (3.7 g) as a viscous oil, b.p. 150 °C (bath) at 0.05 mmHg (Found: C, 66.65; H, 8.1%; M^+, 252. $C_{14}H_{20}O_4$ requires C, 66.65; H, 8.0%; M, 252); δ($CDCl_3$, 90 MHz) 0.83 (3 H, t, 4′-Me), 1.15 (3 H, d, 1′-Me), 1.40 (3 H, t, ester Me), 1.55 (2 H, d of quintets, $J_{3',2'} = J_{3',4'} = 7.0$ Hz, $J_{3',3'}$ 2.0 Hz, diastereotopic CH_2), 2.11 (3 H, s, 3-Me), 3.56 (1 H, sextet, CH), 4.41 (2 H, q, ester CH_2), 5.92br (1 H, s, D_2O exchangeable OH), 6.32 (1 H, s, 5-H), and 11.74 (1 H, s, OH). A small sample of this material was converted, by methylation, partial demethylation, and hydrolysis [as for the conversion of (8) into (10)], into 2-hydroxy-4-methoxy-3-methyl-6-s-butylbenzoic acid (7),[2] needles (from aqueous methanol), m.p. and mixed m.p. 123—125 °C.

Ethyl 5-Chloro-2,4-dihydroxy-3-methyl-6-s-butylbenzoate (8).—Freshly distilled sulphuryl chloride (5.65 g) in dichloromethane (30 ml) was added dropwise with stirring and exclusion of light to the phenol (6) (10.5 g) in dichloromethane (60 ml). After 1 h the solution was diluted with ethyl acetate and washed with water and with saturated brine. The crude product was chromatographed over silica gel with 1—2.5% ethyl acetate–light petroleum as eluant. This gave the *ester* (8) (8.55 g) as an oil (Found: M^+, 286.097 7. $^{12}C_{14}{}^{1}H_{19}{}^{35}Cl^{16}O_4$ requires M, 286.097 2); δ($CDCl_3$, 90 MHz) 0.82 (3 H, t, 4′-Me), 1.38 (3 H, d, 1′-Me), 1.39 (3 H, t, ester Me), 1.87 (2 H, d of quintets $J_{3'3'} = J_{3',4'} = 7.0$ Hz, $J_{3',3'}$ 2.0 Hz, diastereotopic CH_2), 2.16 (3 H, s, 3-Me), 3.48 (1 H, sextet, CH), 4.32 (2 H, q, ester CH_2), and 6.29 and 10.07 (each 1 H, s, D_2O exchangeable OH).

Ethyl 5-Chloro-2,4-dimethoxy-3-methyl-6-s-butylbenzoate (9).—Prepared by methylation of the phenol (8) with methyl sulphate and potassium carbonate in boiling acetone, the ester (9) was obtained as an *oil* (Found: M^+, 314.128 9. $^{12}C_{16}{}^{1}H_{23}{}^{35}Cl^{16}O_4$ requires M, 314.128 5); δ($CDCl_3$, 90 MHz) 0.84 (3 H, t, 4′-Me), 1.34 (3 H, d, 1′-Me), 1.37 (3 H, t, ester Me), 1.74br (2 H, quintet, diastereotopic CH_2), 2.22 (3 H, s, 3-Me), 2.94vbr (1 H, CH), 3.74 and 3.79 (each 3 H, s, OMe), and 3.81 (2 H, q, ester CH_2).

Ethyl 5-Chloro-2-hydroxy-4-methoxy-3-methyl-6-s-butylbenzoate (10).—Boron trichloride (8.0 g) in dichloromethane (25 ml) was added with stirring at 0 °C to a solution of the ester (9) (5.4 g) in dichloromethane (50 ml). The solution was stirred at 0 °C for 0.5 h and at room temperature for 1 h and then worked up in the usual way. The ester (10) (4.8 g) was obtained as an *oil* (Found: M^+, 300.112 5. $^{12}C_{15}{}^{1}H_{21}{}^{35}Cl^{16}O_4$ requires M, 300.112 8); δ($CDCl_3$, 90 MHz) 0.82 (3 H, t, 4′-Me), 1.39 (3 H, d, 1′-Me), 1.39 (3 H, t, ester Me), 1.87 (2 H, d of quintets, $J_{3',2'}$ $J_{3',4'} = 7.0$ Hz, $J_{3',3'}$ 2.9 Hz, diastereotopic CH_2), 2.18 (3 H, s, 3-Me), 3.38 (1 H, sextet, CH), 3.79 (3 H, s, OMe), 4.40 (2 H, q, ester CH_2), and 9.40br (1 H, D_2O exchangeable OH).

2-Benzyloxy-5-chloro-4-methoxy-3-methyl-6-s-butylbenzoic Acid (12).—The phenol (10) (4.8 g), benzyl bromide (4 ml), and potassium carbonate (6.0 g) were stirred in *NN*-dimethylformamide (30 ml) under dry nitrogen for 24 h. The excess of benzyl bromide was removed from the crude benzyl ether (11) by steam distillation. The benzyl ether and potassium hydroxide (7.0 g) in dimethyl sulphoxide (75 ml) and water (10 ml) were heated and stirred on a steam-bath for 23 h, when more potassium hydroxide (1.0 g) was added and heating was continued for a further 4.5 h. The cooled solution was diluted with water and extracted with ether; the extracts were discarded. The aqueous layer was acidified and extracted with ethyl acetate. The *acid* (12) (4.8 g) formed prisms (from ether–light petroleum), m.p. 147—148 °C (Found: C, 66.0; H, 6.3; Cl, 9.85%; M^+, 362, 364. $C_{20}H_{23}ClO_4$ requires C, 66.2; H, 6.4; Cl, 9.75%; M, 362, 364); δ($CDCl_3$, 90 MHz) 0.84 (3 H, t, 4′-Me), 1.39 (3 H, d, 1′-Me), 1.77 (2 H, br quintet, diastereotopic CH_2), 2.25 (3 H, s, 3-Me), 3.05vbr (1 H, CH), 3.82 (3 H, s, OMe), 4.92 (2 H, s, CH_2), and 8.96br (1 H, OH).

2,2′,4′-Tribenzyloxy-5-chloro-4-methoxy-3,6′-dimethyl-6-s-butylbenzophenone (13).—3,5-Bisbenzyloxytoluene [9] (12.0 g) in dichloromethane (50 ml) was added dropwise over 0.5 h at 0 °C to a stirred solution of the acid (12) (4.8 g) and trifluoroacetic anhydride (15 ml) in dichloromethane (100 ml). The cooling-bath was removed and the solution was stirred for a further 2.5 h and then diluted with ether and washed in turn with water, dilute ammonium hydroxide, water, and saturated brine. The crude product was chromatographed over silica gel with 0—2.5% ethyl acetate–light petroleum as eluant. This gave the *benzophenone* (13) (6.1 g) as prisms (from dichloromethane–light petroleum), m.p. 99—100 °C (Found: C, 75.7; H, 6.3; Cl, 5.5. $C_{41}H_{41}ClO_5$ requires C, 75.85; H, 6.35; Cl, 5.45%).

5-Chloro-2,2,4′-trihydroxy-4-methoxy-3,6′-dimethyl-6-s-butylbenzophenone (14).—The benzophenone (13) (6.0 g) and 10% palladium–charcoal (1.0 g) were stirred under hydrogen in ethyl acetate (200 ml) containing concentrated hydrochloric acid (10 drops). The usual work-up gave the *benzophenone* (14) (3.3 g) as clusters of needles (from dichloromethane), m.p. 177—179 °C (Found: C, 62.95; H, 5.85; Cl, 9.4%; M^+, 378, 380. $C_{20}H_{23}ClO_5$ requires C, 63.4; H, 6.1; Cl, 9.35%; M, 378, 380); δ($CDCl_3$, 80 MHz) 0.70 (3 H, t, 4″-Me), 1.19 (3 H, d, 1″-Me), 1.64 (2 H, br quintet, diastereotopic CH_2), 1.83 and 2.20 (each 3 H, s, 6′-Me and 3-Me), 2.57 (1 H, sextet, CH), 3.82 (3 H, s, OMe), 5.44 and 5.46 (total 2 H, each br s, D_2O exchangeable OH), 6.16 and 6.32 (2 H, AB, $J_{3',5'}$ 2.4 Hz, 3′- and 5′-H), 12.52 and 12.74 (total 1 H, each s, D_2O exchangeable OH).

7-Chloro-3-hydroxy-8-methoxy-1,9-dimethyl-6-s-butyldibenzo[b,e][1,4]*dioxepin-11-one* (3).—Potassium hexacyanoferrate(III) (4.4 g) in water (275 ml) was added dropwise to a stirred solution of the benzophenone (14) (2.2 g) and potassium carbonate (16.5 g) in water (550 ml). The solution was stirred for 2 h and then acidified with dilute hydrochloric

acid and extracted with ethyl acetate. The crude product was chromatographed over silica gel with 5—15% ethyl acetate–light petroleum as eluant. The *depsidone* (3) (2.0 g) formed clusters of prisms (from ether–light petroleum), m.p. 165—166 °C (Found: C, 63.8; H, 5.9; Cl, 9.6%; M^+, 376, 378. $C_{20}H_{21}ClO_5$ requires C, 63.75; H, 5.6; Cl, 9.4%; *M*, 376, 378); δ($CDCl_3$, 90 MHz) 0.84 (3 H, t, 4′-Me), 1.38 (3 H, d, 1′-Me), 1.85 (2 H, quintet, CH_2), 2.28 (3 H, s, 9-Me), 2.48 (3 H, s, $W_{\frac{1}{2}}$ 1.9 Hz, 1-Me), 3.68 (1 H, sextet CH), 3.76 (3 H, s, OMe), 6.64 and 6.69 (2 H, AB, *J* 2.2 Hz, 2- and 4-H), and 7.37 (1 H, s, D_2O exchangeable OH); irradiation at δ 2.48 sharpened the AB system.

3,4,7-*Trichloro*-3-*hydroxy*-8-*methoxy*-1,9-*dimethyl*-6-*s*-*butyldibenzo*[b,e][1,4]*dioxepin*-11-*one* (*Dihydronidulin*) (2).—(a) *From the depsidone* (3). The depsidone (3) (253 mg) was heated under reflux in dioxan (25 ml) for 96 h and at intervals of 24 h four additions of *N*-chlorosuccinimide (510 mg) and a few crystals of toluene-*p*-sulphonic acid were made. The cooled solution was diluted with water and extracted with ethyl acetate. The crude product was purified by preparative t.l.c. (10% ethyl acetate–light petroleum) and formed prisms (from ether–hexane) of *dihydronidulin* (2) (216 mg), m.p. 148—149 °C (lit.,[14] 147—150 °C) (Found: C, 53.9; H, 4.4; Cl, 23.9. $C_{20}H_{19}Cl_3O_5$ requires C, 54.0; H, 4.3; Cl, 23.85%), identical (mixed m.p.; R_F values in three solvent systems; mass and n.m.r. spectra) with the sample described in (b); δ($CDCl_3$, 90 MHz) 0.81 (3 H, t, 4′-Me), 1.38 (3 H, d, 1′-Me), 1.92 (2 H, d of quintets, $J_{3',2'} = J_{3',4'} = 7.0$ Hz, $J_{3,'3'}$ 3.2 Hz, diastereotopic CH_2), 2.31 and 2.53 (each 3 H, s, Me), 3.75 (3 H, s, OMe), 4.25 (1 H, sextet, CH), and 5.24vbr (1 H, D_2O exchangeable OH); *m/e* 446 (7%), 444 (7, M^+), 418 (7), 417 (8), 416 (8), 415 (6), 413 (12), 412 (13), 411 (72), 410 (21), 409 (100), 383 (8), 381 (11), 375 (6), 362 (10), 360 (11), 221 (5), 219 (6), and 201 (5).

(b) *From nidulin* (4). Nidulin (4) (71.4 mg) and platinum oxide (40 mg) were stirred in acetic acid (10 ml) under hydrogen until absorption ceased. The crude product, obtained in the usual way, was purified by preparative t.l.c. (10% ethyl acetate–light petroleum) and formed prisms (65 mg) of dihydronidulin (2) (from ether–pentane), m.p. 148—149 °C.

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