Synthesis of (±)-Versimide [Methyl α-(Methylsuccinimido)acrylate] and Related Compounds

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Racemic versimide, pencolide methyl ester (methyl α-*cis*-citraconimidocrotonate), and a number of analogous substituted α-imido-acrylates, -crotonates, and -dimethylacrylates have been synthesised.

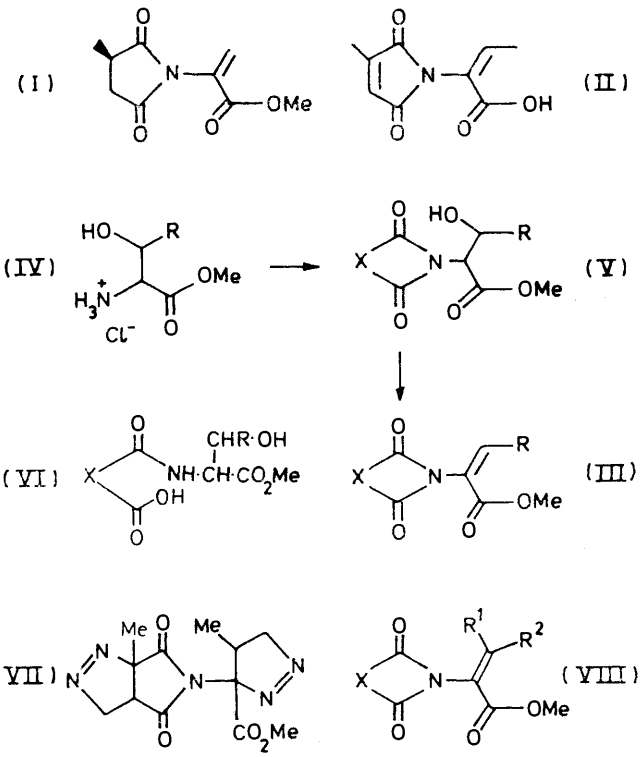
VERSIMIDE, a metabolite of *Aspergillus versicolor*, has been formulated [1,2] as methyl (+)-(*R*)-α-(methylsuccinimido)acrylate (I), and a closely related compound, pencolide,[3] from *Penicillium multicolor*, as α-*cis*-citraconimidocrotonic acid (II). We report a synthesis of (±)-versimide. Since versimide was of interest as an insecticide, the synthesis of a number of related substituted methyl α-imido-acrylates, -crotonates, and -dimethylacrylates was undertaken, including methyl α-*cis*-citraconimidocrotonate (III; R = Me, X = CMe:CH) (pencolide methyl ester). These syntheses were first outlined by us in a Patent.[4] Subsequently a different synthesis of versimide has been published.[5]

The synthesis of the acrylates (III; R = H) and the crotonates (III; R = Me) involved the condensation of serine or threonine methyl ester hydrochloride (IV) with a variety of substituted succinic and maleic anhydrides at 100° in anhydrous dioxan containing triethylamine. The methyl β-hydroxy-α-(succinimido)propionates (V; R = H), or the butyrates (V; R = Me), or the corresponding α-maleimido-esters were formed, and these were separated from any amic acid (VI), also formed during the reaction, by treatment with ethyl acetate–sodium hydrogen carbonate. The crude β-hydroxy-α-imido-esters formed were characterised by i.r. and n.m.r. spectroscopy. These hydroxy-esters were dehydrated to the required α-imido-acrylates or -crotonates by use of anhydrous potassium hydrogen sulphate in boiling dimethylformamide. This acidic reagent was used because the α-imido-acrylates and -crotonates are readily cleaved by alkali.

Methyl α-(methylsuccinimido)acrylate, prepared by the foregoing method from methylsuccinic anhydride and serine ester, was identical in all respects (other than optical rotation) with versimide. The analogous product from citraconic anhydride and threonine ester, methyl α-*cis*-citraconimidocrotonate (III; R = Me, X = CMe:CH) corresponded to pencolide methyl ester. It has been reported [3] that treatment of pencolide with diazomethane results in methylation of the carboxy-group followed by formation of a 1 : 1 adduct, $C_{11}H_{13}N_3O_4$, m.p. 119—120°.[3] We have treated pencolide methyl ester with diazomethane under the same conditions and have obtained a 2 : 1 adduct, $C_{12}H_{15}N_5O_4$, m.p. 118—119°. The n.m.r. spectrum showed signals for four protons at τ *ca.* 5 ($-CH_2-N{=}N$) and for two further protons at τ *ca.* 7, in agreement with structure (VII).

[1] B.P. 1,187,070/1970.
[2] A. G. Brown, *J. Chem. Soc.* (*C*), 1970, 2572.
[3] J. H. Birkinshaw, M. G. Kalyanhur, and C. E. Stickings, *Biochem. J.*, 1963, **86**, 237.
[4] Belg. Pat., BE 758,473.
[5] P. R. Atkins and I. T. Kay, *Chem. Comm.*, 1971, 430.

α-Imido-ββ-dimethylacrylates were synthesised by condensation of methyl α-amino-ββ-dimethylacrylate with the appropriate anhydride at 180—200°.



The structures of the various imides listed in Tables 1—3 were confirmed by n.m.r. spectroscopy, the chemical shifts of the protons in the imide ring being typical of those expected for the substituent X. The α-(succinimido)- and α-(maleimido)-crotonates were ascribed the *cis*-structure as outlined in an earlier communication.[6] For the α-imido-acrylates (VIII; $R^1 = R^2 = H$) (Table 1) the signal for proton R^1 varied between τ 3·26 and 3·48, and that for R^2 between τ 3·93 and 4·20. With the α-imidocrotonates (VIII; $R^1 = H$, $R^2 = Me$) (Table 2) the signal for R^1 was a quartet (J 7 Hz) in the range τ 2·71—2·72 and that for the methyl group R^2 was a doublet (J 7 Hz) at τ 8·22—8·27; for the ββ-dimethylacrylates (VIII; $R^1 = R^2 = Me$) (Table 3) the methyl signals were in the ranges τ 7·57—7·65 and 8·14—8·22, respectively

EXPERIMENTAL

N.m.r. spectra were obtained with a Varian A60A spectrometer (tetramethylsilane as internal reference) for solutions in deuteriochloroform. I.r. spectra were recorded for either liquid films or Nujol mulls with a Perkin-Elmer 137 spectrophotometer and m.p.s were obtained with a Kofler hot-stage apparatus. The serine, threonine, and anhydrides used were all racemic.

Methyl α-(Methylsuccinimido)acrylate (I) [(±)-*Versimide*] (III; R = H, X = CHMe·CH_2).—A suspension of serine methyl ester hydrochloride (9·50 g, 0·061 mol) in dry dioxan (50 ml) was treated with triethylamine (6·16 g, 0·061 mol). After 2 h, methylsucinnic anhydride (6·96 g, 0·061 mol) was added and the mixture was heated under reflux for 12 h. The resulting mixture was cooled and the triethylamine hydrochloride was filtered off and washed with anhydrous dioxan. The combined filtrates were evaporated to dryness under reduced pressure to give a brown gum which dissolved in ethyl acetate (200 ml). The amic acid was removed from this by washing with aqueous sodium hydrogen carbonate until effervescence ceased. The ethyl acetate solution was then washed with brine, dried ($MgSO_4$), and evaporated to leave a brown gum which was crude *methyl β-hydroxy-α-(methylsuccinimido)-propionate* (3·43 g, 26%); $\nu_{max.}$ 3500, 1750, and 1710 cm^{-1}; τ 8·61 (3H, d, J 6·5 Hz, imide Me), 6·8—7·7 (3H, m, imide ring), 6·97br (1H, s, exchangeable, OH), 6·20 (3H, s, OMe), 5·88 (2H, d, J 5·5 Hz, CH_2·O), and 5·12 (1H, t, J 5·5 Hz, N–CH).

Crude methyl β-hydroxy-α-(methylsuccinimido)propionate (3·40 g, 0·016 mol) was dissolved in anhydrous dimethylformamide (25 ml), and powdered, freshly fused potassium hydrogen sulphate (2·5 g) was added. The mixture was heated under reflux for 3 h and then cooled and filtered, and the filtrate was concentrated to a brown oil under reduced pressure. This was chromatographed on a column of silica gel, with benzene–acetone (9 : 1) as eluant; the first major component eluted was *methyl α-(methylsuccinimido)acrylate*, identical (i.r. and n.m.r. spectra, t.l.c.) with versimide. It was obtained as a yellow oil (0·65 g, 21%); $\nu_{max.}$ 1780, 1720, and 1645 cm^{-1}; τ 8·59 (3H, d, J 6·5 Hz, imide Me), 6·8—7·7 (3H, m, imide ring), 6·19 (3H, s, OMe), and 4·09 (1H, s) and 3·36 (1H, s) (=CH_2).

The compounds in Tables 1 and 2 were prepared in the same manner. The yield quoted is that from the anhydride. The esters were not further purified by distillation owing to the occurrence of extensive decomposition and polymerisation on heating at elevated temperatures.

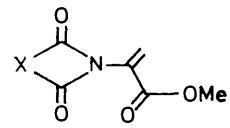
Methyl α-(cis-Dimethylsuccinimido)acrylate (III; R = H, X = CHMe·CHMe) was prepared by the catalytic (10% Pd–C) reduction of *methyl β-hydroxy-α-(dimethylmaleimido)-propionate* (V; R = H, X = CMe·CMe) in ethyl acetate, followed by dehydration in the usual manner. *Methyl α-phthalimidocrotonate* (III; R = Me, X = *o*-C_6H_4) was obtained as a 4 : 1 mixture of *cis*- and *trans*-isomers, as determined by n.m.r. spectroscopy. The *trans*-isomer (VIII; R^1 = Me, R^2 = H, X = *o*-C_6H_4) showed τ 3·49 (1H, q, J 7·5 Hz, =C*H*Me) and 7·68 (3H, d, J 7·5 Hz, =CH·CH_3).

Methyl ββ-Dimethyl-α-nitroacrylate.—Nitrogen was passed through a solution of fuming nitric acid (100 ml) and water (15 ml) until the colour disappeared. The temperature of the stirred solution was maintained at 16—18°, and methyl ββ-dimethylacrylate (39 g) was added during 45 min. After a further 2 h at room temperature the mixture was poured into ice–water (400 ml) and extracted with methylene dichloride (2 × 100 ml). The organic phase was washed with water, aqueous sodium hydrogen carbonate, and water, and dried ($MgSO_4$). The solvent was distilled off at atmospheric pressure and the residual oil was distilled under reduced pressure to give methyl ββ-dimethyl-α-nitroacrylate (32 g, 59%), b.p. 88—94°/1·8 mmHg, n_D^{21} 1·4658.

Methyl α-Amino-ββ-dimethylacrylate.—Aluminium amalgam [from aluminium turnings (5·0 g)] was stirred under ether (150 ml) and one quarter of a solution of methyl ββ-dimethyl-α-nitroacrylate (10·0 g) in ether (40 ml) was added. The mixture was warmed until a reaction began,

[6] A. G. Brown and T. C. Smale, *Chem. Comm.*, 1969, 1489.

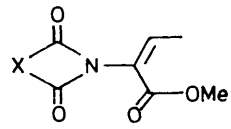
TABLE 1



X	Yield (%)	Found (%) C	H	N	Formula	Required (%) C	H	N
$CH_2{\cdot}CH_2$	4	52·5	5·1	7·3	$C_8H_9NO_4$	52·5	5·0	7·7
$CHMe{\cdot}CH_2$	5	54·5	5·7	7·1	$C_9H_{11}NO_4$	54·8	5·6	7·1
$CMe_2{\cdot}CH_2$	13	57·0	6·4	6·6	$C_{10}H_{13}NO_4$	56·9	6·2	6·6
cis-$CHMe{\cdot}CHMe$	54	56·5	6·1	6·5	$C_{10}H_{13}NO_4$	56·9	6·2	6·6
$CHPr^i{\cdot}CH_2$	12	59·0	6·9	6·1	$C_{11}H_{15}NO_4$	58·7	6·7	6·2
$CHPh{\cdot}CH_2$	17	63·9	5·2	4·9	$C_{14}H_{13}NO_4$	64·7	5·1	5·4
CH—CH | | CH_2–CH_2	13	57·1	5·4	6·6	$C_{10}H_{11}NO_4$	57·4	5·3	6·7
CH——CH * | | $[CH_2]_4$	37	61·1	6·5	5·0	$C_{13}H_{15}NO_4$	60·8	6·4	5·9
CH=CMe	6	No analyses, but satisfactory n.m.r. obtained.						
CMe=CMe	63	58·0	5·5	6·6	$C_{10}H_{11}NO_4$	57·4	5·3	6·7
CPh=CH	13	65·3	4·5	5·2	$C_{14}H_{11}NO_4$	65·4	4·3	5·4
C═══C | $[CH_2]_4$	63	62·1	5·7	5·7	$C_{12}H_{13}NO_4$	61·3	5·6	6·0
o-C_6H_4 †	49	62·2	3·9	5·9	$C_{12}H_9NO_4$	62·3	3·9	6·1
2,3-C_5H_3N	3	56·9	3·7	11·9	$C_{11}H_8N_2O_4$	56·9	3·5	12·1

* M.p. 50—51° (from ethanol). † M.p. 107—108° (from ethanol).

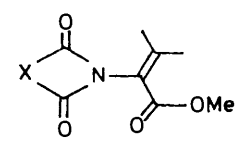
TABLE 2



X	Yield (%)	Found (%) C	H	N	Formula	Required (%) C	H	N
$CHMe{\cdot}CH_2$	14	57·0	6·4	6·6	$C_{10}H_{13}NO_4$	56·9	6·2	6·6
$CMe_2{\cdot}CH_2$	24	58·9	6·8	6·0	$C_{11}H_{15}NO_4$	58·7	6·7	6·2
$CHPr^i{\cdot}CH_2$	19	60·4	7·2	5·8	$C_{12}H_{17}NO_4$	60·2	7·2	5·9
CMe=CH	39	57·4	5·6	6·3	$C_{10}H_{11}NO_4$	57·4	5·3	6·7
CMe=CMe *	70	59·2	6·0	6·1	$C_{11}H_{13}NO_4$	59·2	5·9	6·3
C═══C | $[CH_2]_4$	84	65·5	6·2	4·7	$C_{13}H_{15}NO_4$	62·6	6·1	5·6 ‡
o-C_6H_4 †	38	63·5	4·6	5·7	$C_{13}H_{11}NO_4$	63·7	4·5	5·7

* M.p. 92—94° (from ethanol). † *cis–trans*-Mixture. ‡ Satisfactory C, H, and N values could not be obtained for this compound, though the n.m.r. spectrum justified the ascribed structure.

TABLE 3



X	Yield (%)	Found (%) C	H	N	Formula	Required (%) C	H	N
$CH_2{\cdot}CH_2$ *	16	56·8	6·1	6·6	$C_{10}H_{13}NO_4$	56·9	6·2	6·6
$CHMe{\cdot}CH_2$	24	57·1	6·9	6·0	$C_{11}H_{15}NO_4$	58·7	6·7	6·2
CH=CH †	12	57·3	5·4	6·6	$C_{10}H_{11}NO_4$	57·4	5·3	6·7
CMe=CH	16	59·2	6·0	6·2	$C_{11}H_{13}NO_4$	59·2	5·9	6·3
$CHPh{\cdot}CH_2$	29	65·6	6·1	4·8	$C_{16}H_{17}NO_4$	66·9	6·0	4·9
o-C_6H_4 ‡	20	64·4	5·0	5·0	$C_{14}H_{13}NO_4$	64·9	5·1	5·4

* M.p. 127—128° (from ethanol). † M.p. 67—70° (from ethanol). ‡ M.p. 66—72° (from ethanol).

and the remaining nitro-compound was added during 15 min, at the same time as water (5 ml). The mixture was stirred at room temperature for 2 h and then filtered. The solids were washed with ether and the combined filtrates were dried ($MgSO_4$). The ether was distilled off to leave the crude amine (5·2 g, 64%); $\nu_{max.}$ 3400, 3300, 1740, 1700, 1640, and 1600 cm^{-1}; τ 8·25 (3H, s, vinylic Me), 7·93 (3H, s, vinylic Me), 6·91br (2H, s, NH_2), and 6·22 (3H, s, OMe). T.l.c. of the crude product indicated that it was 80% pure and it was used without further purification.

Methyl ββ-Dimethyl-α-succinimidoacrylate (VIII; R^1 = R^2 = Me, X = $CH_2{\cdot}CH_2$).—Methyl α-amino-ββ-dimethylacrylate (2·5 g, 0·02 mol) and succinic anhydride (2·0 g, 0·02 mol) were fused together at 180° for 15 min. The resulting dark red syrup was chromatographed on silica gel, with benzene–acetone (17 : 3) as eluant; the first compound eluted was *methyl ββ-dimethyl-α-succinimidoacrylate* (0·65 g, 16%), which crystallised as needles, m.p. 127—128° (from ethanol); $\nu_{max.}$ (Nujol) 1780, 1720, and 1640 cm^{-1}; τ 8·22 (3H, s, vinylic Me), 7·64 (3H, s, vinylic Me), 7·18 (4H, s, $CH_2{\cdot}CH_2$), and 6·29 (3H, s, OMe).

The compounds listed in Table 3 were prepared in a similar way.

Reaction of Pencolide Methyl Ester with Diazomethane.—Methyl α-*cis*-citraconimidocrotonate (1·0 g) in ether (20 ml) was treated with ethereal diazomethane [prepared from *N*-methyl-*N*-nitrosourea (1·5 g)]. After 18 h the solution was concentrated under reduced pressure and the residual gum was crystallised from ether (400 ml) to give *methyl 4-methyl-3-(1-methyl-6,8-dioxo-2,3,7-triazabicyclo*[3,3,0]*oct-2-en-7-yl)-Δ¹-pyrazoline-3-carboxylate* (VII) (260 mg, 19%), m.p. 118—119° (decomp.); $\nu_{max.}$ (Nujol) 1790, 1750, 1720, and 1550 cm^{-1} (Found: C, 49·3; H, 5·2; N, 23·5. $C_{12}H_{15}N_5O_4$ requires C, 49·1; H, 5·2; N, 23·9%).

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