3,7-Bis(hydroxymethyl)-1-benzoxepin-5(2*H*)-one, a Novel Oxygen Heterocyclic Metabolite from Cultures of the Fungus *Marasmiellus ramealis* (Bull. *ex* Fr.) Singer [1]

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3,7-Bis(hydroxymethyl)benzoxepin-5(2*H*)-one (2) has been isolated from *Marasmiellus ramealis* cultures. Its structure was established by (a) spectrometry and (b) the synthesis of the corresponding 3,7-bis(methoxycarbonyl) compound (5), itself the product of mild oxidation of (2). The synthesis of (5) represents a new route to the benzoxepinone ring system.

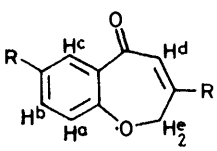
In the course of biosynthetic studies aimed at the elucidation of the biogenesis of marasin (1), the metabolites present in the ether extract of the culture fluid of the Tricholomataceae species *Marasmiellus ramealis*

$$HC{\equiv}C{\cdot}C{\equiv}C{\cdot}CH{=}C{=}CH{\cdot}CH_2{\cdot}CH_2OH \qquad (1)$$

(Bull. *ex* Fr.) Singer, tribus *Collybieae*, were re-examined. The metabolites of this fungus, previously called *Marasmius ramealis* (Bull. *ex* Fr.) Fr.,[2] were studied by Bendz [3] who isolated from its cultures both marasin (1) and 3-methyl-8-hydroxyisocoumarin. We have now isolated from surface cultures of *M. ramealis* substantial amounts (5.6 mg l^{-1} culture fluid) of a further metabolite to which we have assigned structure (2). This assignment was made on the basis of (a) spectroscopic and analytical data obtained on the metabolite (2) and on its simple transformation products (3)—(5), and (b) the unambiguous synthesis of the diester (5). The new metabolite (2) appears to be the first 1-benzoxepin-5(2*H*)-one of natural origin; examples of tricyclic chromans containing the benzoxepin ring system have been reported.[4,†] Synthetic 1-benzoxepin-5(2*H*)-ones have only recently been reported [5] and our synthesis of (5) represents a new preparative method for these compounds.

Isolation of the diol (2) involved extraction of the ether extract of the *M. ramealis* culture fluid with water, re-extraction of the aqueous phase with ethyl acetate (or ether), and chromatography of the final organic extract followed by crystallisation. The metabolite (2) melted at 100—100.5 °C and was optically inactive. It gave a positive Fehling and a negative ferric chloride test. The i.r. spectrum established the presence of hydroxy (3 350 cm^{-1}) and unsaturated carbonyl, possibly cross conjugated ketone (1 660 cm^{-1}), groupings.

Treatment of the metabolite (2) with acetic anhydride–pyridine gave a diacetate (3) while mild oxidation (MnO_2, CH_2Cl_2) afforded an unstable dialdehyde (4) which, in turn, was further converted (MnO_2–KCN–MeOH) into the diester (5). These transformations imply the presence of two allylic and/or benzylic hydroxymethyl groups. The elemental analyses and mass spectra of the compounds involved [(2) had M^+ at *m/e* 220, (3) at 304, (4) at 216, and (5) at 276] showed the constitution of (2) to be $C_{12}H_{12}O_4$.



(2) R = $CH_2^fOH^g$
(3) R = $CH_2^fOCOCH_3^h$
(4) R = CH^iO
(5) R = $CO_2CH_3^i$

τ Values and coupling constants (*J*/Hz) for compounds (2)—(5) *

	a (1 H)	b (1 H)	c (1 H)	d (1 H)	e (2 H)	f (2 + 2 H)	g (2 H)	h (3 + 3 H)	i (1 + 1 H)	j (3 + 3 H
(2)	2.96 (d, 8)	2.47 (dd, 8 and 2)	2.09 (d, 2)	3.53br (s)	5.30 (s)	5.35 (s) 5.65 (s)	5.30—5.80			
(3)	3.04 (d, 9)	2.60 (dd, 9 and 2)	2.11 (d, 2)	3.66br (s)	5.00 (s)	5.30 (s) 5.39 (s)		7.91 (s) 7.99 (s)		
(4)	2.75 (d, 8)	1.92 (dd, 8 and 2)	1.43 (d, 2)	2.92 (s)	4.94 (s)				−0.01 (s) 0.21 (s)	
(5)	2.95 (d, 9)	1.96 (dd, 9 and 2)	1.46 (d, 2)	2.83 (s)	5.00 (s)					6.13 (s) 6.15 (s)

* Spectra were recorded at 90 MHz in CCl_4 except for compound (2) which was examined in acetone.

† We thank Dr. F. M. Dean of Liverpool University for bringing this to our attention after the preliminary report of this work appeared.

[1] Preliminary communication, J. K. Holroyde, A. F. Orr, and V. Thaller, *J.C.S. Chem. Comm.*, 1976, 242.

[2] *cf.* R. Singer, 'The Agaricales in Modern Taxonomy', J. Cramer, Weinheim, 1962.

[3] G. Bendz, *Arkiv Kemi*, 1959, **14**, 305, 511.

[4] F. M. Dean and D. A. H. Taylor, *J. Chem. Soc.* (*C*), 1966, 114, 144; F. M. Dean, B. Parton, N. Somvichien, and D. A. H. Taylor, *Tetrahedron Letters*, 1967, 3459.

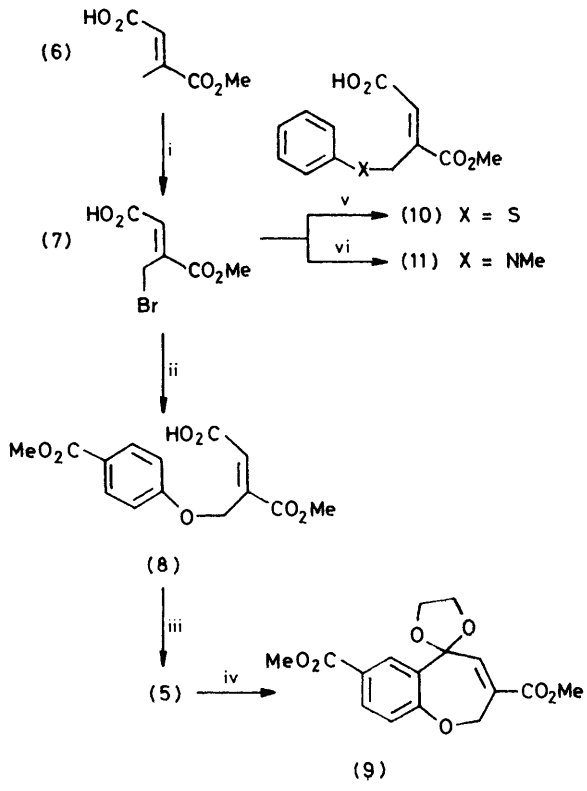
[5] H. Hofmann and P. Hofmann, *Chem. Ber.*, 1973, **106**, 3571; *Annalen*, 1974, 1301; H. Hofmann and J. H. Haberstroh, *ibid.*, 1973, 2032.

^{1}H N.m.r. data for compounds (2)—(5) are recorded in the Table. These, along with the information mentioned above, made the structural assignment of (2) possible. The resonances of the hydroxylic protons (H^g) and of the hydroxy-bearing methylene groups (H^f) of (2) were readily assigned by their disappearance on deuterium oxide exchange and oxidation to (4) respectively. The proton spectra of all four compounds (2)—(5) clearly indicate a 1,2,4-arrangement of the three aromatic protons, while the position of the doublet for H^c in (2) suggests that one of the substituents flanking this proton is a carbonyl group. In the dialdehyde (4), both H^c and H^b resonate at even lower fields, establishing that the aryl hydroxymethyl group of (2) occupies the position shown. The relative chemical shifts of the remaining aromatic proton H^a in compounds (2)—(5) indicate the proximity of an ether oxygen. The only structure consistent with the molecular formula ($C_{12}H_{12}O_4$), the presence of a vinylic hydroxymethyl group, and the lack of coupling between the remaining protons H^d and H^e requires the fused ring system as well as the allyl aryl ether arrangement shown.

The ^{13}C n.m.r. spectrum of (2) was recorded in deuterium oxide–deuterioacetone. The proton decoupled spectrum shows distinct resonances for each of the 12 carbon atoms and some qualitative allocations were made which are in agreement with the proposed structure. The three resonances in the δ 62—70 region are thought to arise from the three oxygen-bearing methylene groups: the broadening of these signals on off-resonance decoupling indicated that they arose from non-quaternary carbon atoms. The group of eight signals at δ 120—160 is considered to belong to aromatic and olefinic carbons, while the resonance at δ 189.6 is consistent with that of a carbonyl carbon. Of the last nine signals only those at δ 121.1, 126.9, 128.9, and 134.0 were broadened on off-resonance decoupling; thus the signals at δ 128.0, 137.0, 158.2, 158.5, and 189.6 represent the quaternary carbon atoms.

The assignment of structure (2) to the new metabolite was confirmed by synthesising the diester (5) in a three-step sequence (Scheme). The known [6] acid-ester (6) was converted into the crystalline bromide (7) and this, in turn, to the *p*-methoxycarbonylphenyl ester (8). The latter was separated from excess of phenol with potassium monohydrogen phosphate. The cyclisation of (8) to the diester (5) was carried out *via* the acid chloride with aluminium trichloride. It was hoped that by protecting the oxo-grouping as the ethylene acetal, reduction of the diester would be possible and hydrolysis of the acetal would yield the diol (2). Although the oxo-diester (5) was readily converted into the ethylene acetal (9), this and a variety of hydride reducing agents [7] led only to the breakdown of the ring system.

The bromo-acid (7) comprises a multifunctional isoprene unit and may have future potential in natural product synthesis. The easy conversion of (7) into the ether (8) suggested reactivity of the halogen towards nucleophilic displacement which was proved by synthesising the sulphide (10) and the amine (11). Although the properties of benzothiepins [8] made successful cyclisation of (10) under conditions analogous to those used for preparing (5) rather unlikely, it was tried: not unexpectedly only tars were obtained. Attempts at cyclising the amine (11) resulted in complex mixtures.



SCHEME

Reagents: i, *N*-bromosuccinimide; ii, *p*-$MeO_2C{\cdot}C_6H_4OH$, KOH, H_2O; iii, a, $SOCl_2$, b, $AlCl_3$, CH_2Cl_2; iv, $HOCH_2{\cdot}CH_2OH$, $MeC_6H_4SO_3H$, C_6H_6; v, KSC_6H_5, H_2O; vi, $MeNHC_6H_5$

EXPERIMENTAL

Instruments used: u.v., Unicam SP 800; i.r., Unicam SP 200 and SP 100; ^{1}H n.m.r., Perkin-Elmer R10 and R14; mass spectra (direct insertion), Varian-MAT CH7 and VGMM70–70; ^{13}C n.m.r., Bruker HFX; m.p.s (corr.), Kofler hot-stage apparatus.

Chromatography: SiO_2 H.B.L. M60 in columns and Merck HF_{254} in 0.3 mm (t.l.c.) and $PF_{254+366}$ in 1 mm layers, respectively.

Petrol refers to light petroleum of b.p. 30—40 °C.

Growth of Marasmiellus ramealis (*Bull.* ex *Fr.*) *Singer and Isolation of* 3,7-*Bis*(*hydroxymethyl*)-1-*benzoxepin*-5(2H)-*one* (2).—The fungus was grown as a surface culture on 3% malt extract for 35 days. The culture fluid (90 l from 120 flasks) was decanted and continuously extracted with Et_2O for 48 h. The Et_2O extract was concentrated to 500 ml and extracted with H_2O (4 × 200 ml). The combined

[6] R. Anschütz, *Annalen*, 1907, **353**, 144.
[7] E. R. H. Walker, *Chem. Soc. Rev.*, 1976, **5**, 23.
[8] W. E. Parham and D. G. Weetman, *J. Org. Chem.*, 1969., **34**, 56; H. Hofmann, B. Meyer, and P. Hofmann, *Angew. Chem. Internat. Edn.*, 1972, **11**, 423.

H_2O extracts were saturated with NaCl and extracted with EtOAc (5 × 200 ml). The EtOAc extract was dried, concentrated, and chromatographed on a SiO_2 column from EtOAc. The fractions absorbing at $\lambda_{max.}$ 327 and 266 nm were combined, concentrated, and afforded the *diol* (2) (503 mg, 5.6 mg l^{-1} culture fluid) which was crystallised from EtOAc–petrol, m.p. 100—100.5 °C (Found: C, 65.65; H, 5.4. $C_{12}H_{12}O_4$ requires C, 65.45; H, 5.45%), $\lambda_{max.}$ (EtOH) 327 (ε 1 700), 266 (11 200), and 218 nm (20 600) [this changed on dilute NaOH addition to $\lambda_{max.}$ 327 (rel. *E* 1.0), 250infl. (3.08), 234 infl. (3.75), and 206 nm (16.3) and reverted on acidification to the original absorption pattern], $\nu_{max.}$ (KBr) 3 280 (OH bonded), 1 670 (CO), 1 635 and 1 610 (CH=CH), 1 575, 1 490, 1 155, 1 075, 1 040, 1 015, and 840 cm^{-1} (aromatic); *m/e* 220 (M^+, 46%), 191 (34), 161 (30), 151 (100), and 105 (32) (for ^1H n.m.r. spectrum see Table); δ(^{13}C) [$(CD_3)_2CO$–D_2O] 62.2, 62.7, 69.3, 121.1, 126.9, 128.0, 128.9, 134.0, 137.0, 158.2, 158.5, and 189.6.

3,7-*Bis*(*acetoxymethyl*)*benzoxepin*-5(2H)-*one* (3).—The diol (2) (30 mg) was stirred in pyridine (0.5 ml) and Ac_2O (0.3 ml) at 20 °C for 18 h. The reaction mixture was poured into H_2O and extracted with Et_2O. The Et_2O extract was washed with HCl (2N) and brine, dried, concentrated, and separated by p.l.c. (Et_2O). The band with R_F 0.5 gave the liquid *diacetate* (3) (30 mg, 72%) (M^+, 304.095 5. $C_{16}H_{16}O_6$ requires *M*, 304.094 7), $\lambda_{max.}$ (EtOH) 325 (ε 2 000), 263 (11 300), and 218 nm (23 000); $\nu_{max.}$ (CCl_4) 1 760 (AcOC), 1 675 (CO), and 1 645 and 1 620 cm^{-1} (CH=CH); *m/e* 304 (M^+, 11%), 244 (54), 216 (28), 202 (32), 185 (35), and 43 (100); for ^1H n.m.r. spectrum see Table.

3,7-*Bisformylbenzoxepin*-5(2H)-*one* (4).—The diol (2) (25 mg) and MnO_2 (200 mg) were stirred in CH_2Cl_2 (5 ml) for 0.5 h. Filtration (Celite), concentration of the filtrate, and p.l.c. (Et_2O) gave the unstable *dialdehyde* (4) (18 mg, 73%), (M^+, 216.041 9. $C_{12}H_8O_4$ requires *M*, 216.042 2), $\lambda_{max.}$ (EtOH) 325 (rel. *E* 0.09), 253 (1.0), and 213 (0.42) nm; $\nu_{max.}$ (CCl_4) 2 820, 2 710, 1 695, 1 653, 1 635, 1 415, 1 365, 1 290, 1 142, and 1 115 cm^{-1}; *m/e* 216 (M^+, 100%), 188 (26), 187 (31), 159 (51), and 149 (33); for n.m.r. results see Table.

3,7-*Bis*(*methoxycarbonyl*)-1-*benzoxepin*-5(2H)-*one* (5).—The dialdehyde (4) (18 mg), MnO_2 (50 mg), KCN (10 mg), and AcOH (0.1 ml) were stirred in MeOH (5 ml) for 12 h. The mixture was filtered (Celite) and the filtrate mixed with Et_2O (20 ml); this was then washed (brine), dried, and concentrated to yield the diester (5) (12 mg, 51%) which was identical in all respects with the specimen obtained by total synthesis.

(E)-3-*Methoxycarbonylbut*-2-*enoic Acid* (6).—This compound was prepared by a modification of the synthesis described by Anschütz.[6] Bromine (2 ml, 5.85 g) was added to methyl 2-methylacetoacetate (5 g) vigorously stirred in HBr (49%, 2 ml) at a rate which kept the temperature of the reaction mixture in the range 35—40 °C. Stirring was continued for 10 min, after which the reaction mixture was taken up in Et_2O; the latter was then washed with brine till neutral and then dried and concentrated. The residue, H_2O (25 ml), and $BaCO_3$ (12.5 g) were heated to 100 °C (steam-bath) for 45 min after which the mixture was cooled, and filtered; the residue was washed with a little EtOH. The filtrate was washed twice with Et_2O, acidified (dil. HCl), and extracted with Et_2O. The Et_2O extract was washed, dried, and concentrated. The brown residue and petrol (50 ml) were heated to boiling with vigorous swirling for 1 min. The petrol was decanted and the extraction was repeated four times. The combined petrol extracts were concentrated (vacuum) to colourless prisms which on crystallisation (petrol) gave the pure half-ester (6) (0.915 g, 16.5%), m.p. 83—84 °C (lit.,[6] 84 °C); τ(CCl_4) 7.70 (3 H, d, *J* 1 Hz, CH_3·C=CH), 6.20 (3 H, s, CH_3O_2C), 3.20 (1 H, d, *J* 1 H, CH_3·C=C*H*), and −1.5 br (1 H, CO_2H). (The whole synthesis should be carried out in a fume cupboard since the halogenated by-products are powerful lachrymators.)

(Z)-3-*Methoxycarbonyl*-4-*bromobut*-2-*enoic Acid* (7).—The half-ester (6) (3 g), *N*-bromosuccinimide (3.71 g), and dibenzoyl peroxide (50 mg) were refluxed in CCl_4 (100 ml) for 2 h. The reaction mixture was cooled (0 °C), filtered (removal of succinimide), and the filtrate concentrated to 20 ml, and kept at −5 °C for several hours. The separated crystals were collected and the mother liquor was further concentrated to yield an additional crop of crystals. The combined crops were recrystallised (CCl_4) to yield the *bromo-half ester* (7) (3 g, 65%), m.p. 89—91 °C (Found: C, 32.4; H, 3.2. $C_6H_7BrO_4$ requires C, 32.3; H, 3.15%), $\lambda_{max.}$ (EtOH) 215 nm (ε 13 100), $\nu_{max.}$ (CCl_4) 3 000, 1 740, 1 705, and 1 650 cm^{-1}; τ($CDCl_3$) 6.10 (3 H, s, CO_2CH_3), 5.30 (2 H, s, CH_2Br), 3.15 (1 H, s, C=CH), and −1.05 (1 H, s, CO_2H); *m/e* 206 [M^+ − 18 (for ^{81}Br), 39%], 204 [M^+ − 18 (for ^{79}Br), 40], 192 (26), 190 (26), 125 (46), 111 (51), 84 (29), 59 (37), 45 (27), and 39 (100).

(E)-3-*Methoxycarbonyl*-4-(4-*methoxycarbonylphenoxy*)*but*-2-*enoic Acid* (8).—The acid (7) (0.5 g) was added with stirring to a saturated solution (5 ml) of methyl *p*-hydroxybenzoate in aqueous KOH (10%) at 20 °C and stirring was continued for 2 h. The reaction mixture was acidified (dil. HCl) and extracted with Et_2O. The Et_2O-layer was washed with brine and then extracted twice with K_2HPO_4 (5% in H_2O). The phosphate-extract was washed with Et_2O, acidified, and extracted with Et_2O. The Et_2O extract was washed, dried, and concentrated. The oily residue crystallised (Et_2O–petrol) to the *aryl ether* (8) (0.4 g, 60%), m.p. 120—122 °C (Found: C, 57.25; H, 4.95. $C_{14}H_{14}O_7$ requires C, 57.15; H, 4.8%), $\lambda_{max.}$ (EtOH) 256 nm (ε 23 300); $\nu_{max.}$ (KBr) 3 210, 1 725, 1 700, and 1 655 cm^{-1}; τ($CDCl_3$) 6.17 (3 H, s, OCH_3), 6.14 (3 H, s, OCH_3), 4.78 (2 H, s, $ArOCH_2$), 3.05 (1 H, s, C=CH), 3.06 (2 H, d, *J* 9 Hz, aryl-H), 2.04 (2 H, d, *J* 9 Hz, aryl-H), and −0.22 (1 H, s, CO_2H); *m/e* 294 (M^+, 12%), 276 (17), 152 (40), 143 (20), 141 (100), and 59 (41).

3,7-*Bis*(*methoxycarbonyl*)-1-*benzoxepin*-5(2H)-*one* (5).—The acid (8) (1 g) was heated under reflux in $SOCl_2$ (25 ml) for 2 h. The reaction mixture was concentrated (vacuum) and the residue was dissolved in CH_2Cl_2 (50 ml). To this, vigorously stirred at 20 °C, $AlCl_3$ (powdered, 0.51 g) was added in portions during 0.25 h and stirring was continued for 2 h more. The reaction mixture was poured into H_2O, the CH_2Cl_2 layer was separated, washed with brine, $NaHCO_3$–H_2O, and brine, dried, and concentrated. The residue crystallised (EtOH); the mother liquor was chromatographed on a SiO_2 column and the corresponding fraction and the crystals were combined and recrystallised (EtOH) to yield the *diester* (5) (0.5 g, 52%), m.p. and mixed m.p. 97—98 °C (Found: C, 60.85; H, 4.4. $C_{14}H_{12}O_6$ requires C, 60.85; H, 4.4%), $\lambda_{max.}$ (EtOH) 237 nm (ε 27 600); $\nu_{max.}$ (CCl_4) 1 728, 1 655, and 1 640 cm^{-1}; for ^1H n.m.r. see Table; *m/e* 276 (M^+, 100%), 245 (43), 244 (45), 233 (40), 217 (40), 216 (68), 189 (48), and 185 (35).

3,7-*Bis*(*methoxycarbonyl*)-5,5(2H)-*ethylenedioxy*-1-*benzoxepin* (9).—The oxo-diester (5) (485 mg), $MeC_6H_4SO_3H$ (25 mg), and ethylene glycol (3 ml) were refluxed (24 h) in benzene (25 ml) in an apparatus equipped with a Dean–Stark

reflux head. The mixture was poured into $NaHCO_3$–H_2O, the benzene layer was washed with brine, dried, and concentrated. On column chromatography (SiO_2), starting material (5) (160 mg, 33%) was recovered and the required *acetal* (9) (232 mg, 41%) was obtained; it crystallised from MeOH, m.p. 148—149 °C (Found: C, 59.9; H, 4.95. $C_{16}H_{16}O_7$ requires C, 60.0; H, 5.05%), $\lambda_{max.}$ (EtOH) 265 (ε 6 200) and 229 nm (16 500); $\nu_{max.}$ (CCl_4) 1 724 cm^{-1}; τ($CDCl_3$) 6.22 (3 H, s, OCH_3), 6.09 (3 H, s, OCH_3), 5.89 (4 H, m, OCH_2·CH_2O), 5.05 (2 H, s, H^e), 2.90 (1 H, s, H^d), 2.78 (1 H, d, *J* 9 Hz, H^a), 1.99 (1 H, dd, *J* 9 and 2 Hz, H^b), and 1.80 (1 H, s, H^c); *m/e* 320 (M^+, 15%), 289 (10), 261 (100), 233 (20), 217 (19), and 189 (31).

(Z)-3-*Methoxycarbonyl*-4-*phenylthiobut*-2-*enoic Acid* (10).—The bromo-acid (7) (5.0 g) was added in one portion to vigorously stirred potassium thiophenoxide–H_2O [100 ml; prepared from KOH (5.61 g) and thiophenol (10 g)] and stirring was continued for 1 h. Excess of dil. HCl was added, the reaction mixture was extracted with Et_2O, the Et_2O extract was washed twice with brine, and then extracted with K_2HPO_4–H_2O. The phosphate extract was washed with Et_2O, acidified (dil. HCl), and extracted with Et_2O. The Et_2O-extract was washed, dried, concentrated, and the residue crystallised (Et_2O–petrol) to yield the *acid* (10) (3.65 g, 64.5%), m.p. 110—111 °C (Found: C, 57.0; H, 4.95. $C_{12}H_{12}O_4S$ requires C, 57.15; H, 4.8%), $\lambda_{max.}$ (EtOH) 250 (rel. *E* 1.0) and 212 nm (1.8); $\nu_{max.}$ ($CHCl_3$) 3 000, 1 722, and 1 640 cm^{-1}; τ($CDCl_3$) 6.2 (3 H, s, OCH_3), 5.73 (2 H, s, CH_2S), 3.36 (1 H, s, C=CH), 2.70 (5 H, m, aromatic H), and −0.32br (1 H, s, CO_2H); *m/e* 252 (M^+, 26%), 234 (68), 220 (17), 205 (12), 202 (13), 191 (24), 174 (29), 147 (100), and 109 (53).

(E)-3-*Methoxycarbonyl*-4-(N-*methyl*-N-*phenylamino*)*but*-2-*enoic Acid* (11).—The bromo-acid (7) (200 mg) was stirred for 2 h in freshly distilled $MeNHC_6H_5$ (5 ml) at 20 °C. On dilution with Et_2O the reaction mixture was extracted with $NaHCO_3$–H_2O. The $NaHCO_3$ layer was acidified (dil. HCl) and washed with Et_2O. The pH of the H_2O solution was adjusted to 7 (with $NaHCO_3$) and the solution was saturated with NaCl. The precipitated oil was taken up in Et_2O and the H_2O solution was extracted with Et_2O (×2). The combined Et_2O extracts were dried, concentrated, and the residue was chromatographed (SiO_2 column) to give the liquid acid (11) (58 mg, 26%), $\lambda_{max.}$ (EtOH) 295 (rel. *E* 1.0) and 252 nm (7.0); $\nu_{max.}$ ($CHCl_3$) 3 000, 1 710, and 1 640 cm^{-1}; τ($CDCl_3$) 7.12 (3 H, s, NCH_2), 6.26 (3 H, s, OCH_3), 5.63 2 H, s, CH_2N), 2.83 (6 H, m, aromatic H and C=CH), and −2.02br (1 H, s, CO_2H); *m/e* 249 (M^+, 18%), 231 (17), 188 (34), 144 (100), 120 (44), 107 (29), 106 (37), 105 (17), 104 (18), and 77 (46).

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