aminoindan is present as a racemic mixture, so that it is conceivable that the active component in this compound could be twice the measured agonistic potency. Sufficient quantities of the separated racemate still must be obtained for isomeric assignments. The α-methyl amino acid, aminobutyric acid (Aib), has been substituted successively into both the second and third residues of the 1-aminoindan analogue. Tyr-Aib-Gly-1-aminoindan is approximately 6% as active as the D-Ala²-1-aminoindan analogue, while Tyr-Gly-Aib-1-aminoindan is almost entirely without biological activity (Table III, compounds **10** and 11).

The aminoindan analogues of enkephalin almost completely eliminate the torsional freedom of both $\chi_1$ and $\chi_2$ corresponding to the side chain torsional bonds of Phe⁴ in enkephalin. Thus, there are a total of eight torsional bonds for Tyr-D-Ala-Gly-aminoindan instead of the ten rotational parameters required for the tetrapeptide fragment Tyr-D-Ala-Gly-Phe.[37] The aminoindan analogues of enkephalin containing α-methyl amino acids should also prove to be useful conformation probes of the opiate–enkephalin receptors. Marshall et al.[38] have shown that the α-methyl substituent severely restricts local peeptide backbone flexibility in a quantifiable fashion. The predicted torsional values are consistent with experimental $\phi_i$, $\psi_i$ torsional values obtained from the crystallographic determinations of peptides containing α-methyl amino acids.[39] The analogues of aminoindan containing Aib therefore have only six freely rotatable torsional bonds because of the severe conformational constraints imposed by the α-methyl amino acid. Conformational analyses of these conformationally hindered and yet biologically active 1-aminoindan analogues of enkephalin using analytical as well as the more traditional, iterative algorithms should aid in the characterization of the μ receptor found in the guinea pig ileal and rat brain binding assays.

## Conclusion

These novel analogues of enkephalin, in conjunction with earlier structure–activity data, confirm that chemical substituents present in the first and fourth residues of enkephalin fulfill a three-site requirement for biological activity. These substituents correspond to the phenolic ring and amino terminus of tyrosine-1 and substituents present in phenylalanine-4 which fulfill the requirements of a required hydrophobic third site. Our earlier three-site model[31,37] resulted in a proposed conformation for receptor-bound enkephalin, which is consistent with structure–activity data obtained from the guinea pig ileal and rat brain binding assays for pentapeptide analogues of enkephalin containing *N*-methyl amino acids, D-amino acids, and α-methyl amino acids. However, a class of derivatized tripeptides, of which Tyr-D-Ala-Gly-benzylamine is representative, must adopt a receptor-bound conformation different from that of the native enkephalins and their pentapeptide analogues in order to fit the three-site model. Interestingly, some of the flexible classes of opiates such as the meperidine family do not have a readily identifiable tyramine[40] moiety like that of morphine, and it has been proposed by Portoghese[40] and more recently by Galt[41] that these compounds bind in a different fashion than the rigid opiates. Further synthesis and conformational analysis of the 1-aminoindan family of peptide analogues should aid in characterizing the chemical and conformational in vitro requirements of these derivatized tripeptides with opioid-like activity.

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# β-Adrenergic Blocking Agents. 20.[1] (3-Hydroxyprop-1-enyl)-Substituted 1-(Aryloxy)-3-(alkylamino)propan-2-ols

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The synthesis of a series of (3-hydroxyprop-1-enyl)-substituted 1-(aryloxy)-3-(alkylamino)propan-2-ols is described. These compounds were investigated for their β-adrenoreceptor blocking properties and their selectivity of action. Among the *o*-(hydroxypropenyl)-substituted derivatives we have found some potent noncardioselective β-adrenoreceptor blocking agents which have a greater blocking action on the $\beta_2$ receptor, thus resembling propranolol. The *p*-(hydroxypropenyl)-substituted analogues were generally less potent and tended to be cardioselective. The structure–activity relationships are discussed in the light of the hypothesis that the cardioselectivity of *p*-amido-substituted (aryloxy)propanolamines is attributable, in part, to binding of the amide group to some additional site on the β receptor; our findings argue against a similar interaction for the allylic hydroxyl group.

The factors which influence the potency and the cardioselectivity of the β-adrenoreceptor blocking actions of substituted (aryloxy)propanolamines have been extensively studied. There is evidence that various substituents in the aryl ring para to the oxypropanolamine side chain tend to give compounds which are relatively more cardioselective than the corresponding ortho isomers, although the potency is also markedly reduced.[2,3] It has also been stated that para amidic substituents in the aryl ring confer both potency and cardioselectivity and that this is possibly due to binding between the para-amidic group and some ad-

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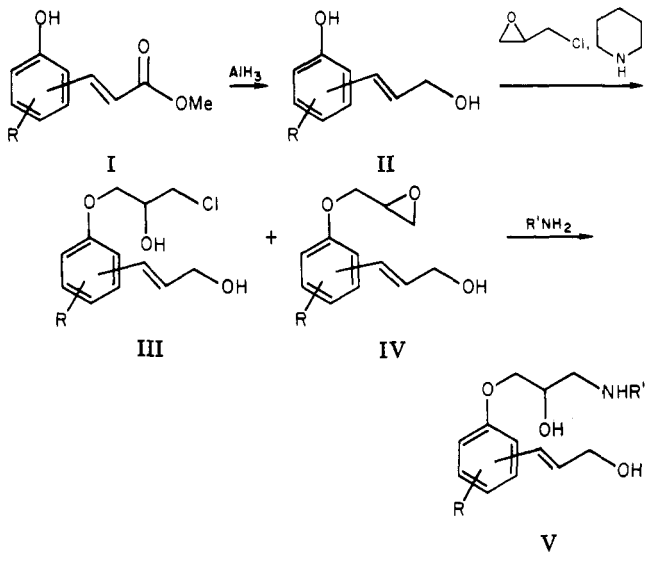
Scheme I



ditional site on the cardiac $\beta$-receptor.[2] It was therefore of interest to study a series of compounds which possessed groupings capable of binding to this putative additional site, and to this end we prepared a series of hydroxypropenyl-substituted (aryloxy)propanolamines. In general, we found some extremely potent nonselective compounds in the ortho series, while compounds of the para series showed some degree of cardioselectivity but, with the exception of compound **19**, also showed a marked drop in potency which is what one would have expected for a general para substituent.

**Chemistry.** The starting substituted hydroxycinnamyl alcohols were prepared by reduction of the corresponding $\alpha,\beta$-unsaturated esters I (Scheme I). We found that lithium aluminium hydride reduction of the $\alpha,\beta$-unsaturated esters gave mixtures of the required cinnamyl alcohols and the fully reduced alcohols, but satisfactory yields of the substituted cinnamyl alcohols were obtained using aluminium hydride.[4] In contrast, Wigfield and Taymaz[5] have reported that aluminium hydride reduction of ethyl 4-methoxycinnamate did not give any of the expected cinnamyl alcohol but gave instead a quantitative yield of 4-allylanisole and its isomer 4-propenylanisole. In our own work, hydrocarbons were only occasionally obtained as minor products (e.g., some 2-chloro-4-propenylphenol was produced during reduction of methyl 3-chloro-4-hydroxycinnamate) and we were unable to reproduce Wigfield and Taymaz's reduction of ethyl 4-methoxycinnamate, obtaining instead a good yield of 4-methoxycinnamyl alcohol with only minor quantities (ca. 3%) of 4-propenylanisole and 4-allylanisole detectable by GLC. The *o-cis*-hydroxycinnamyl alcohols were prepared by the previously reported $LiAlH_4$ reduction of coumarins.[6] The substituted hydroxycinnamyl alcohols II were reacted with excess epichlorohydrin using piperidine as catalyst to give the chlorohydrin III, sometimes mixed with the epoxide IV. The chlorohydrin or chlorohydrin–epoxide mixture was converted into the substituted (aryloxy)propanolamine V by heating with excess amine in 2-propanol. These methods have been reported fully elsewhere,[7] but a typical preparation is given under Experimental Section.

**Pharmacology.** $\beta$-Adrenoceptor blocking potency was estimated in vivo using the previously described cat preparation.[8] The results given in the tables are expressed as the total dose, infused over a period of 30 min, causing a 50% inhibition of the tachycardia produced by a submaximal dose of isoproterenol (0.2 $\mu$g/kg, iv). The degree (percent) of blockade of the vasodepressor response at that dose level is also given. The relative potencies of these two systems give some indication of selectivity for $\beta_1$ (cardiac) as opposed to $\beta_2$ (vascular) receptors. Mean log $ED_{50}$ values were calculated for each compound on the basis of two or three tests, and the standard errors of the means were computed. On average, these mean values had an error of 30%.

## Discussion

As previously reported for other series of substituted 1-(aryloxy)-3-(alkylamino)propan-2-ols,[9,10] *tert*-butylamino substituted analogues are more potent than the corresponding isopropylamino derivatives (compare **4** and **5**; **7** and **8**; **18** and **19**).

For the *o*-(hydroxypropenyl) derivatives (Table I) it was found that the cis isomers **1** and **3** were less potent than the corresponding trans isomers **2** and **4**. Compounds which had no substituent para to the oxypropanolamine side chain (i.e., $R_1$ = H) were extremely potent (compounds **1**, **2**, and **10**), and the introduction of a para substituent lead to a marked reduction in potency (compounds **3–9**) which roughly correlated with the size of the substituent, although compound **9** is anomalous. Alkyl substituents on the $\alpha$-carbon atom of the double bond also conferred high potency (**10** and **12**) (Table II); however, potency decreased as the size of the alkyl substituent increased (compare **12** and **13** with **10**). Compound **11**, which is substituted on the $\beta$-carbon atom, is approximately 20 times less potent than **10**. The hydroxypropenyl compounds **1** and **2** are more potent than hydroxymethyl compound **24** and are also more potent than the isomeric compound oxprenolol (**26**). With the exception of the 4-methoxy analogue **6**, these substituted *o*-(hydroxypropenyl) derivatives are not cardioselective, which agrees with some observations on cardioselectivity made by Smith[2] in which he showed that in a series of para-substituted 1-(aryloxy)-3-(isopropylamino)propan-2-ols the 4-methoxy analogue showed a greater degree of cardioselectivity than the 4-methyl and 4-chloro analogues. Indeed, it is clear from Tables I and II that the ortho-substituted derivatives **1–5** and **7–13** show a degree of $\beta_2$ selectivity and thus resemble propranolol, **27**.

In the meta series (Table IV), **21** was intermediate in potency between the ortho isomer **2** and the para isomer **14**. Introduction of a substituent ortho to the oxypropanolamine side chain led to a complete loss of activity (**22** and **23**).

In the para series (Table III), compound **14** was barely active, but the potency was improved by ortho substitution (**15** and **17–19**), although overall the potency was considerably less than that found for the ortho series (except for **19**).

The most interesting feature of the para series is that most of the active compounds showed some degree of cardioselectivity (**15**, **18**, and **19**); cf. practolol (**28**). The cardioselectivity and drop in potency found in the para series agree with the observations of Smith[2] and also those

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(6) D. Kumari, S. K. Mukerjee, and T. R. Seshardi, *Tetrahedron*, **22**, 3491, (1966).
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(8) J. D. Fitzgerald and S. R. O'Donnell, *Br. J. Pharmacol.*, **43**, 222 (1971).
(9) L. H. Smith, *J. Med. Chem.*, **20**, 705 (1977).
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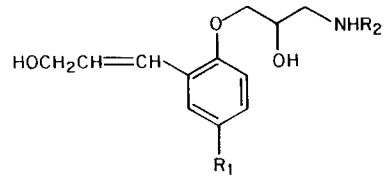
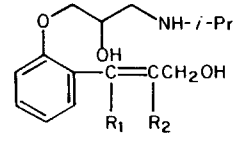
Table I




| no. | $R_1$ | $R_2$ | salt | isomer | mp, °C | crystn solvent | yield,[a] % | emp formula | anal. | dose, μg/kg, giving 50% inhibn of tachycardia | inhibn, %, of depressor response |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | H | *i*-Pr | $(COOH)_2$ | cis | 136–138 | EtOH–$Et_2O$ | 7.5[b] | $C_{17}H_{25}NO_7 \cdot 0.25H_2O$ | C, H, N | 23 | 51 |
| 2 | H | *i*-Pr | base | trans | 105–107 | benzene–pet. ether (60–80 °C) | 26[b] | $C_{15}H_{23}NO_3$ | C, H, N | 8 | 69 |
| 3 | $CH_3$ | *i*-Pr | $(COOH)_2 \cdot 0.5H_2O$ | cis | 140–142 | EtOH–$Et_2O$ | 5[b] | $C_{17}H_{26}NO_5 \cdot 0.5H_2O$ | C, H, N | 226 | 97 |
| 4 | $CH_3$ | *i*-Pr | $0.5(COOH)_2$ | trans | 133–136 | EtOH–$Et_2O$ | 16 | $C_{17}H_{26}NO_5$ | C, H, N | 189 | 63 |
| 5 | $CH_3$ | *t*-Bu | $(COOH)_2$ | trans | 162–163 | EtOH–$Et_2O$ | 72 | $C_{19}H_{29}NO_7$ | C, H, N | 100 | 98 |
| 6 | $OCH_3$ | *i*-Pr | $0.5(COOH)_2$ | trans | 165–167 | EtOH–$H_2O$–$Et_2O$ | 46 | $C_{17}H_{26}NO_6$ | C, H, N | 146 | 20 |
| 7 | Cl | *i*-Pr | base | trans | oil | | 9 | $C_{15}H_{22}ClNO_3 \cdot H_2O$ | C, H, N | 860 | 94 |
| 8 | Cl | *t*-Bu | $0.5(COOH)_2$ | trans | 199–201 | MeOH–$H_2O$–$Et_2O$ | 22 | $C_{17}H_{25}ClNO_5$ | C, H, N, Cl | 400 | 132 |
| 9 | Br | *i*-Pr | base | trans | 74–80 | toluene–pet. ether (60–80 °C) | 5 | $C_{15}H_{22}BrNO_3$ | C, H, N | 543 | 94 |

[a] Yield based on chlorohydrin. [b] Yield based on phenol.

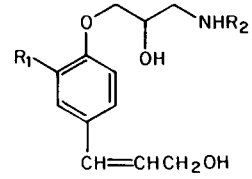
Table II




| no. | $R_1$ | $R_2$ | salt | mp, °C | crystn solvent | yield,[a] % | emp formula | anal. | dose, μg/kg, giving 50% inhibn of tachycardia | inhibn, %, of depressor response |
|---|---|---|---|---|---|---|---|---|---|---|
| 10 | H | $CH_3$ | $(COOH)_2 \cdot 0.5H_2O$ | 90–100 | *i*-PrOH–EtOAc | 5 | $C_{18}H_{27}NO_7 \cdot 0.5H_2O$ | C, H, N | 12 | 85 |
| 11 | $CH_3$ | H | base | oil | | 4 | $C_{16}H_{25}NO_3 \cdot 0.5H_2O$ | C, H, N | 257 | 98 |
| 12 | H | $CH_2CH_3$ | base | oil | | 25 | $C_{17}H_{27}NO_3 \cdot 0.5H_2O$ | C, H, N | 43 | 191 |
| 13 | H | $CH_2CH_2CH_3$ | base | oil | | 16 | $C_{18}H_{29}NO_3 \cdot H_2O$ | C, H, N | 188 | 100 |

[a] Yield based on chlorohydrin. Mixtures of cis and trans isomers.

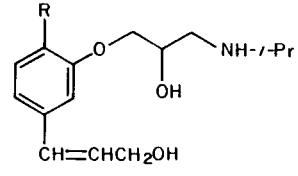
Table III




| no. | $R_1$ | $R_2$ | isomer | mp, °C | salt | crystn solvent | yield,[a] % | emp formula | anal. | dose, μg/kg, giving 50% inhibn of tachycardia | inhibn, %, of depressor response |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 14 | H | *i*-Pr | trans | 194–196 | 0.5(COOH)$_2$ | MeOH-Et$_2$O | 7[b] | $C_{16}H_{25}NO_5$ | C, H, N | 1818 | 58 |
| 15 | $OCH_3$ | *i*-Pr | trans | 141–142 | 0.5(COOH)$_2$ | EtOH-Et$_2$O | 25 | $C_{17}H_{26}NO_6$ | C, H, N | 980 | 20 |
| 16 | $OCH_2CH_3$ | *i*-Pr | trans | 67–70 | base | toluene-pet. ether (60–80 °C) | 14 | $C_{17}H_{27}NO_4 \cdot 0.5H_2O$ | C, H, N | NA | |
| 17 | Cl | *t*-Bu | trans | 186–190 | (COOH)$_2$ | EtOAc-EtOH | 18[c] | $C_{17}H_{25}ClNO_5 \cdot 0.5H_2O$ | C, H, N | 753 | 76 |
| 18 | Br | *i*-Pr | trans | 91–93 | base | toluene-pet. ether (60–80 °C) | 38 | $C_{15}H_{22}BrNO_3$ | C, H, N, Br | 390 | 40 |
| 19 | Br | *t*-Bu | trans | 133–135 | base | toluene | 69 | $C_{16}H_{24}BrNO_3$ | C, H, N, Br | 71 | 31 |
| 20 | $CH_2CH{=}CH_2$ | *t*-Bu | trans | 95 | (COOH)$_2$ | EtOH-EtOAc | 17 | $C_{19}H_{29}NO_3$ | C, H, N | NA | |

[a] Yield based on chlorohydrin. [b] Yield based on phenol. [c] Yield based on epoxide.

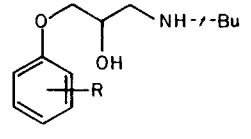
Table IV




| no. | R | salt | isomer | mp, °C | crystn solvent | yield, % | emp formula | anal. | dose, μg/kg giving 50% inhibn of tachycardia | inhibn, %, of depressor response |
|---|---|---|---|---|---|---|---|---|---|---|
| 21 | H | base | trans | 93–100 | benzene | 31[a] | $C_{15}H_{23}NO_3$ | C, H, N | 1020 | not measured |
| 22 | $OCH_3$ | (COOH)$_2 \cdot H_2O$ | trans | 105–107 | EtOAc-EtOH | 70[a] | $C_{18}H_{27}NO_8 \cdot H_2O$ | C, H, N | NA | |
| 23 | Br | base | trans | 118–120 | toluene | 49[a] | $C_{15}H_{22}BrNO_3$ | C, H, N, Br | NA | |

[a] Yield based on epoxide.

Table V




| no. | R | salt | mp, °C | crystn solvent | yield,[a] % | emp formula | anal. | dose, μg/kg giving 50% inhibn of tachycardia | inhibn, %, of depressor response |
|---|---|---|---|---|---|---|---|---|---|
| 24[b] | 2-$CH_2OH$ | 0.5(COOH)$_2$ | 188–190 | EtOH | 40 | $C_{15}H_{24}NO_5 \cdot 0.75H_2O$ | C, H, N | 35 | 99 |
| 25[b] | 4-$CH_2OH$ | 0.5(COOH)$_2$ | 203–205 | EtOH | 21 | $C_{15}H_{24}NO_5 \cdot 0.25H_2O$ | C, H, N | 956 | 84 |
| 26 (oxprenolol) | | | | | | | | 30[c] | 58[c] |
| 27 (propranolol) | | | | | | | | 62 | 85 |
| 28 (practolol) | | | | | | | | 167 | 8 |

[a] Prepared by $NaBH_4$ reduction of the corresponding aldehyde. [b] Kindly provided by Dr. J. Ashby. [c] Data taken from ref 2.

of Åblad and co-workers,[3] who showed that the para isomer of alprenolol [4′-allylphenoxy-3-(isopropylamino)propan-2-ol] was cardioselective, while the ortho and meta isomers were not. Åblad also mentioned similar findings for the isomers of oxprenolol, which were later confirmed by Vaughan-Williams and co-workers.[11] However, what is particularly interesting in this series is that the 2-bromo derivative **19** is as potent as propranolol and shows some degree of cardioselectivity.

In conclusion, we have found some very potent nonselective compounds in the ortho series (**1**, **2**, and **10**) and identified a potent cardioselective compound (**19**) in the para series. In general, cardioselectivity was only found in compounds of the para series, and this was coupled with a reduced $\beta$-blocking potency which is what we would have expected for a general para substituent and indicates that the hydroxyl moiety of the hydroxypropenyl group is probably not participating in binding to any extra site on the $\beta$ receptor.

## Experimental Section

All melting points were obtained using an Electrothermal capillary melting point apparatus and are uncorrected. Where analyses are indicated only by symbols of the elements, analytical results obtained for these elements are within ±0.4% of theoretical values. NMR and IR data were consistent with the structures. NMR spectra were recorded either on a Varian HA-100 or a Varian A-60 using tetramethylsilane as the internal standard. IR spectra were recorded on a Perkin-Elmer 157 infrared spectrophotometer.

**Reduction of Ethyl 4-Methoxycinnamate.** A solution of aluminium chloride (0.86 g, 0.0064 mol) in ether (10 mL) was added to a cooled stirred suspension of lithium aluminium hydride (0.75 g, 0.20 mol) in ether (15 mL) under nitrogen. The mixture was stirred at room temperature for 15 min and a solution of ethyl 4-methoxycinnamate (1.5 g, 0.0073 mol) in ether (25 mL) was added dropwise over 10 min. The reaction mixture was stirred for 30 min and quenched with water (2 mL), dilute NaOH (2 mL), and water (2 mL). The resulting mixture was acidified with dilute HCl. The ether layer was collected and dried over anhydrous magnesium sulfate. The ether was evaporated to give a solid residue: yield 960 mg (81%). A GLC analysis (5% OV17 at 250 °C) showed ca. 3% of a 1:1 mixture of 4-propenylanisole and *p*-allylanisole and ~97% 4-methoxycinnamyl alcohol. The residue was crystallized from benzene to give 4-methoxycinnamyl alcohol: yield 560 mg (47%); mp 78.5–79.5 °C (lit.[12] mp 79–79.5 °C). Anal. ($C_{10}H_{12}O_2$) C, H.

***trans*-2-Bromo-4-(3-hydroxypropen-1-yl)phenol.** A solution of aluminium chloride (4.46 g, 0.033 mol) in ether (50 mL) was added dropwise to a stirred suspension of lithium aluminium hydride (3.63, 0.095 mol) in ether (50 mL) maintained at 0 °C and was stirred at this temperature for 15 min. A solution of *trans*-methyl 3-bromo-4-hydroxycinnamate (9.3 g, 0.036 mol) in ether (200 mL) was added dropwise to the cooled $AlH_3$ suspension, and the mixture was stirred at room temperature for 1 h. Excess aluminium hydride was decomposed by the cautious sequential addition of water (4 mL), 2 N NaOH (4 mL), and water (4 mL). The precipitated solids were filtered and the ethereal filtrate was retained. The precipitated solids were digested with dilute HCl and the acid solution obtained was extracted with chloroform (3 × 25 mL). The combined chloroform–ether extracts were dried over anhydrous magnesium sulfate and evaporated to dryness under vacuum. The residue was crystallized from chloroform to give *trans*-2-bromo-4-(3-hydroxypropen-1-yl)phenol: yield 4.0 g (48%); mp 102–105 °C. Anal. ($C_9H_9BrO_2$) C, H, N, Br.

**1-[*trans*-2-Bromo-4-(3-hydroxyprop-1-enyl)phenoxy]-3-(*tert*-butylamino)-2-propanol (19).** A mixture of *trans*-2-bromo-4-(3-hydroxypropen-1-yl)phenol (1.3 g, 0.0057 mol), epichlorohydrin (15 mL), and piperidine (4 drops) was heated on the steam bath for 4 h. The excess epichlorohydrin was evaporated off under vacuum, and the residue was chromatographed on Florisil eluted with chloroform. The oily chlorohydrin was collected, yield 1.4 g (76%), and used directly for the next stage.

A mixture of chlorohydrin (0.7 g, 0.002 mol), 2-propanol (20 mL), and *tert*-butylamine (25 mL) was heated under reflux for 12 h. The reaction mixture was evaporated to dryness, and the residue was partitioned between chloroform (25 mL) and dilute HCl (50 mL). The acid layer was basified with NaOH and extracted with chloroform (3 × 25 mL). The chloroform extracts were dried over anhydrous magnesium sulfate and the solvent was removed under vacuum. The residue was crystallized from toluene to give **19**: yield 540 mg (69%); mp 133–135 °C. Anal. ($C_{16}H_{24}BrNO_3$) C, H, N, Br.

**Acknowledgment.** The author thanks J. F. Coope and G. W. Golding for their expert technical assistance, Dr. J. D. Fitzgerald and J. Carter for providing the biological data, and C. J. Howarth for providing the analytical data.

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