products arising from 1 (V_R 0.10, 0.53).

The column fractions containing 1 were passed through a Dowex 50 (H^+) column, and the resulting acidic solution of 1 was freeze-dried to give the product as a yellow solid without significant decomposition. In contrast, freeze-drying the ammonium formate buffer solutions of 1, any increase in pH, or the addition of nucleophiles (acetate, thiols, or alkylammonium compounds such as Tris) above a pH of 6 decomposed 1 to give products with retention times (V_R) of 0.10 and 0.53.

Reduction of an aqueous solution of either 1 or **5a**, with a 4-equiv excess of sodium borohydride gave products presumed from UV and liquid chromatography (V_R 0.53 from 1) to be the hydroquinone derivatives **7** and 8: UV for the nucleoside 8 (0.1 M ammonium formate, pH 4.4) λ_{max} 265 nm (ϵ 9000), λ_{min} 245 nm (8000).

Treatment of an aqueous solution of the hydroquinone nucleotide **7** with a slight excess of 3% aqueous hydrogen peroxide gave a product with the same ultraviolet spectra and liquid chromatography retention time as the quinone 1.

Enzyme Assay. The enzyme was assayed by modification of the radioisotope assays described by Roberts[32] and Lomax and Greenberg.[33] The solution (0.1 mL) contained 25 mM mercaptoethanol, 0.22 mM *dl*-tetrahydrofolic acid, 6.75 mM formaldehyde, 5 mM sodium bicarbonate, 3 mM magnesium chloride, 0.12 mM EDTA, 6 mM potassium phosphate buffer, pH 6.8, 10 μL of the diluted enzyme solution, substrate, and, when indicated, inhibitor. Control reactions lacked the cofactor, tetrahydrofolic acid. The substrate 2′-deoxy[5-^{3}H]uridine 5′-phosphate was used at a specific activity of 500 μCi/μmol. For maximum velocity studies for active enzyme determination the substrate concentration was 50 μM. The assays were started by the addition of the enzyme to the complete mixture and then incubated at 30 °C. Incubation was stopped at 30 s by the addition of 50 μL of 20% trichloroacetic acid. A 20% aqueous suspension of charcoal (0.25 mL) was added, and the solution was vortexed and allowed to stand for 15 min. The suspension was filtered through a cotton-plugged Pasteur pipet, and 0.1 mL of the filtrate was counted in Beckman Ready Solve HP scintillation fluid. Counting efficiency was 33%; control samples lacking the cofactor were found to have less than 5% of the respective sample counts. Velocity is reported in the adjusted value of picomoles of ^3H_3O formed per minute in the assay.

Preincubation Studies. The enzyme concentration was determined by absorbance at 278 nm by using an extinction coefficient of 1.05×10^5 and a dimer molecular weight of 70000. Passage of a concentrated solution of the activated enzyme through a 1 × 20 cm column of Sephadex G-25 with 0.05 M phosphate buffer at pH 6.8 gave the pure enzyme free of 2-mercaptoethanol. This enzyme preparation was reasonably stable for several days at 2 °C; the specific activity of the enzyme used in the preincubation studies ranged from 2.6 to 3.2 μmol of product formed min^{-1} (mg of protein)$^{-1}$. The enzyme in concentrations ranging from 0.1 to 0.4 μM was preincubated at 30 °C in 50 μL of solution containing 6 mM potassium phosphate buffer, pH 6.8, 3 mM magnesium chloride, 0.12 mM ethylenediaminetetracetic acid, and varying concentrations of the compounds tested for inactivation of the enzyme. Substrate protection was evaluated by including the indicated concentration of substrate at a specific activity of 500 μCi/μmol. After incubation for the indicated time period, the assay for remaining active enzyme was started by the addition of 50 μL of a solution containing buffer and other components of the assay to give the same concentrations as noted in the enzyme assay. A high substrate concentration (50 μM) was used in these assays to afford reasonably high velocity and to competitively reduce the enzyme inactivation by the inhibitor during the assay. The assay was run for 60 s and treated as described in the enzyme assay section. Inactivation of the enzyme was measured by comparing the velocity at time zero to that at the indicated incubation times. Under the conditions of the assay, the uninhibited enzyme retained 96% of the initial activity after 4 min of incubation.

Dialysis Studies. The enzyme was preincubated with varying concentrations of inhibitor for 5 min. Control and inhibited enzyme preparations were then dialyzed in two changes of a 4000-fold volume of a solution containing 0.01 M potassium phosphate buffer, pH 6.8. Dialysis was performed with and without 50 mM 2-mercaptoethanol.

Acknowledgment. This work was supported by a grant (CA 7522) from the National Cancer Institute of the National Institutes of Health. The authors acknowledge the reviewers and Professor Robert Hanzlik of the University of Kansas for suggestions and Mrs. Leman Al-Razzak for the preparation of compound **4a**.

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Synthesis and Monoamine Oxidase Inhibitory Activities of α-Allenic Amines in Vivo and in Vitro. Different Activities of Two Enantiomeric Allenes[1]

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A series of 15 α-allenic amines, including primary, secondary, and tertiary ones, was synthesized, partly by organocopper chemistry. Their ability to inhibit mouse and rat brain mitochondrial monoamine oxidase (MAO) in vivo and in vitro, respectively, was evaluated. Almost all compounds were quite potent inhibitors of MAO, some as potent as deprenyl. Like deprenyl, most of the compounds were selective inhibitors of the B form of MAO. The two enantiomeric forms of *N*-methyl-*N*-(2,3-pentadienyl)benzylamine (**2**) were prepared and the *R*-(−) form was found to be 2.7 times as active as the (+) form in vivo and 25 times as active in vitro. Most of the compounds were tested for their ability to potentiate the phenylethylamine (PEA) response in mice, and a good correlation between the potency of MAO inhibition and PEA potentiation was found. Compound **5**, as the only compound tested, did not potentiate the blood pressure response to tyramine.

Mitochondrial monoamine oxidase (MAO) is an enzyme that is involved in the oxidative deamination of transmitter amines.[2] The existence of two forms of MAO was first reported by Johnston,[3] who found that one form, which he named MAO-A, was inactivated by the acetylene inhibitor clorgyline, while the other form, which he named

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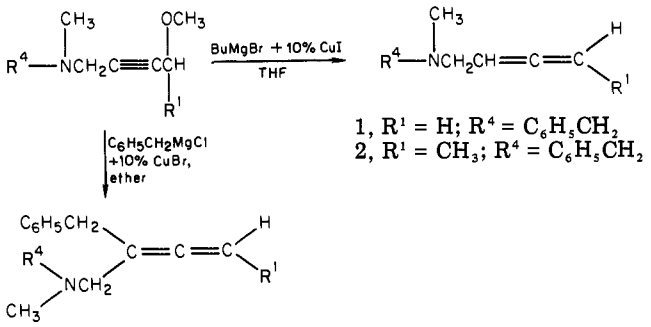
Scheme I. Organocuprate Reactions of Acetylenic Amino Ethers. Method A



1, R^1 = H; R^4 = $C_6H_5CH_2$
2, R^1 = CH_3; R^4 = $C_6H_5CH_2$

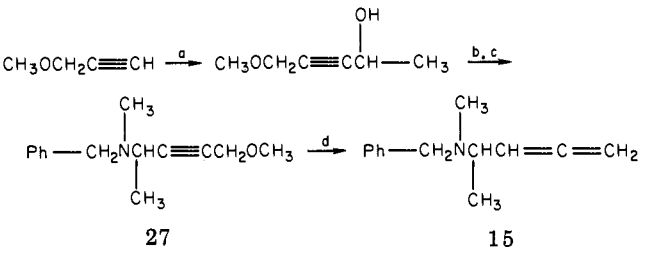
3, R^1 = H; R^4 = CH_3

MAO-B, was not. Later, Knoll and Magyar introduced deprenyl as a selective inhibitor of MAO-B.[4] Furthermore, there is some substrate specificity;[5,6] for example, serotonin (5-HT) and noradrenaline (NA) are preferentially deaminated by MAO-A, and β-phenylethylamine (PEA) by MAO-B, and amines such as tyramine, tryptamine, and dopamine are oxidized by both forms of MAO. Also, there is a difference in selectivity between different species and tissues;[6] for instance, dopamine is a B substrate in man (brain and platelet) but an A substrate in the rat.[7] The existence of multiple forms of MAO has, however, been questioned, and several authors have suggested that MAO is an enzyme with multiple binding sites but only one molecular unit.[6] Thus, a model for human brain MAO with two binding sites has recently been described.[8] Several types of compounds are inhibitors of MAO,[9] and some of them can be used clinically, mainly in the treatment of depression.[10] Another clinical application of MAO inhibitors is in the pharmacological treatment of Parkinson's disease; such inhibitors are only of the MAO-B type. MAO inhibitors affecting mood, i.e., antidepressant agents, on the other hand, should preferentially act on MAO-A.[11]

Deprenyl and clorgyline are acetylenic (propargylic) amines. Another example of a MAO inhibitor belonging to this class is pargyline. These acetylenic amines are oxidized by MAO to form an unknown reactive intermediate, which then reacts covalently with the flavin coenzyme of MAO; i.e., the amines are enzyme-activated, irreversible inhibitors (cf. ref 12). In the case of pargyline, the structure of the adduct has been determined.[13] The structure of the adduct formed between the allenic amine 1, a known inhibitor of MAO,[14] and MAO is fundamentally different from the acetylene adducts.[15] It is currently under investigation.[16] In connection with this work, we have developed new synthetic methods for α-allenic amines, which are generally useful and are particularly suited for the preparation of labeled allenic amines needed in the above studies.[17,18]

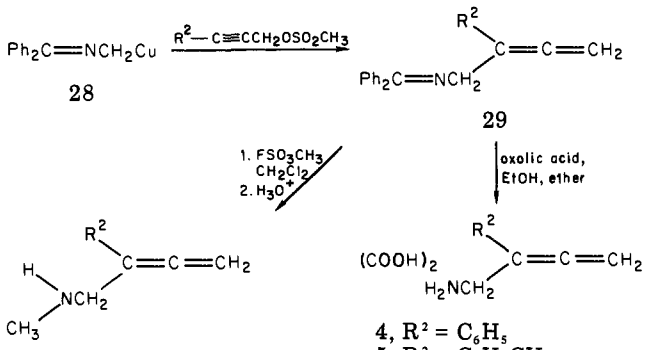
The present paper describes the synthesis, partly by use of the methods mentioned, of 17 α-allenic amines and their MAO inhibitory activities.

Scheme II[a]



[a] Reagents: a = BuLi, CH_3CHO; b = CH_3SO_2Cl, Et_3N; c = $PhCH_2NHCH_3$; d = BuMgBr + 10% CuI.

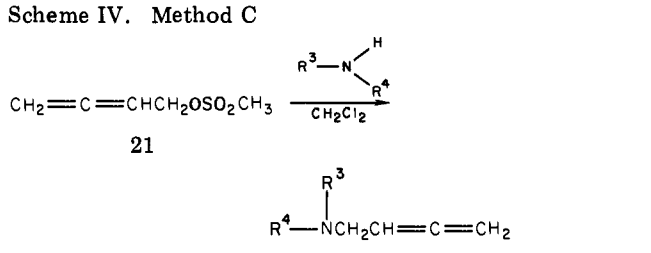
Scheme III. Allenic Amines via Allenic Imines. Method B



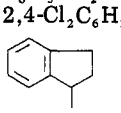
9, R^2 = $C_6H_5CH_2$

4, R^2 = C_6H_5
5, R^2 = $C_6H_5CH_2$
6, R^2 = 4-$ClC_6H_4CH_2$
7, R^2 = 4-$CH_3C_6H_4CH_2$
8, R^2 = 4-$CH_3OC_6H_4CH_2$

Scheme IV. Method C



10, R^3 = H; R^4 = $C_6H_5CH_2$
11, R^3 = CH_3; R^4 = $C_6H_5CH_2CH(CH_3)$
12, R^3 = CH_3; R^4 = 2,4-$Cl_2C_6H_3OCH_2CH_2CH_2$

13, R^3 = CH_3; R^4 = 

14, R^3, R^4 = 

Chemistry. Three different methods, A–C, were used for preparing the allenic amines listed in Table I.

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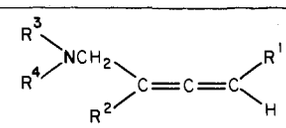
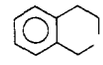
Table I. α-Allenic Amines



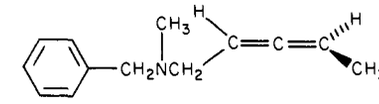
compd	R^1	R^2	R^3	R^4	method	formula[a]	mp, °C	anal.
1	H	H	CH_3	$C_6H_5CH_2$	A	$C_{12}H_{15}N\cdot HCl$[b,c]	117–119	
2	CH_3	H	CH_3	$C_6H_5CH_2$	A	$C_{13}H_{17}N\cdot C_2H_2O_4$[d]	135–136	
(*R*)-(−)-2	CH_3	H	CH_3	$C_6H_5CH_2$	C	$C_{13}H_{17}N\cdot C_2H_2O_4$[e]	137–138	C, H, N
(*S*)-(+)-2	CH_3	H	CH_3	$C_6H_5CH_2$	C	$C_{13}H_{17}N\cdot C_2H_2O_4$[f]	137–138	C, H, N
3	H	$C_6H_5CH_2$	CH_3	CH_3	A	$C_{13}H_{17}N\cdot HCl$[g]	125–127	
4	H	C_6H_5	H	H	B	$C_{10}H_{11}N\cdot C_2H_2O_4\cdot H_2O$	160[h]	C, H, N
5	H	$C_6H_5CH_2$	H	H	B	$C_{11}H_{13}N\cdot HCl$[c]	143–145	C, H, N
6	H	4-$ClC_6H_4CH_2$	H	H	B	$C_{11}H_{12}ClN\cdot C_2H_2O_4$	158–160	H, N; C[i]
7	H	4-$CH_3C_6H_4CH_2$	H	H	B	$C_{12}H_{15}N\cdot C_2H_2O_4$	158–160	H, N; C[j]
8	H	4-$CH_3OC_6H_4CH_2$	H	H	B	$C_{12}H_{15}NO\cdot C_2H_2O_4$	154–157	C, H, N
9	H	$C_6H_5CH_2$	H	CH_3	B	$C_{12}H_{15}N\cdot C_2H_2O_4$[k]	174–176	
10	H	H	H	$C_6H_5CH_2$	C	$C_{11}H_{13}N\cdot HCl$	142–143	C, H, N
11	H	H	CH_3	$C_6H_5CH_2CH(CH_3)$	C	$C_{14}H_{19}N\cdot C_2H_2O_4$	123–124	C, H, N
12	H	H	CH_3	2,4-$Cl_2C_6H_3OCH_2$-CH_2CH_2	C	$C_{14}H_{17}Cl_2NO\cdot HCl$	105–106	C, H, N
13	H	H	CH_3		C	$C_{14}H_{17}N\cdot C_2H_2O_4$	165–167	C, H, N
14	H	H			C	$C_{13}H_{15}N\cdot HCl$	171–173	C, H, N

[a] Recrystallization solvent, EtOH–ether, unless otherwise indicated. [b] Literature[14] mp 118–120 °C. [c] Recrystallization solvent, EtOAc. [d] Literature[18] mp 135–136 °C. [e] $[\alpha]^{22}_D$ −46.8° (*c* 0.87, CH_3OH). [f] $[\alpha]^{22}_D$ +44.8° (*c* 0.91, CH_3OH). [g] Literature[18] mp 125–127 °C. [h] Decomposes. [i] C: calcd, 55.0; found, 55.9. [j] C: calcd, 63.9; found, 62.9. [k] Literature[17] mp 174–176 °C.

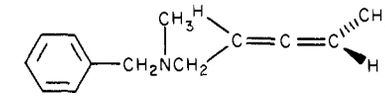
Method A, by which compounds **1–3** and **15** were prepared, is depicted in Scheme I. The complete synthesis of compound **15** is shown in Scheme II. This reaction, in which acetylenic amino ethers react with organocuprates to give allenic amines, has recently been described.[18] The choice of solvent determines the nature of the formed allene. Tetrahydrofuran (THF) or THF–ether (3:1) gives "reduced" allenes (cf. the formation of **1** and **2** in Scheme I), while ether as the solvent mainly gives alkylated allenes (cf. compound **3** in Scheme I).

The second method, method B, is illustrated in Scheme III. This recently described method[17] is a general synthetic method for primary and *N*-methyl-substituted α-allenic amines. In this reaction, an organocopper reagent (**28**), derived from metalated *N*-methyldiphenylmethanimine and $Me_2S\cdot CuBr$, reacts with propargylic sulfonates, in a 1,3-substitution reaction, to give allenic imines. Hydrolysis, or rather alcoholysis, of these imines (general formula **29** in Scheme III) directly gave the oxalic acid salt of the allenic amines **4–8**. Alkylation of the allenic imine **29** (R^2 = benzyl) with methylfluorosulfonate prior to hydrolysis gave the *N*-methyl-substituted allenic amine **9** (Scheme III).

Method C, which we have used in the preparation of primary, secondary, and tertiary allenic amines, is a simple S_N2 reaction between a methanesulfonate (mesylate) of an allenic alcohol and an amine (Scheme IV). The most suitable solvent seems to be dichloromethane, and the reaction temperature for an optimal yield should be below zero (ca. −5 °C) when the mesylate is added to the amine. The yields for compounds **10–14** varied from 36 to 56%. The enantiomeric forms of **2** were obtained from (*R*)-(−)-2,3-pentadien-1-ol and (*S*)-(+)-2,3-pentadien-1-ol by the method depicted in Scheme IV. The synthesis of (*R*)-(−)-2,3-pentadien-1-ol has been described, and its absolute configuration and enantiomeric purity have been discussed.[19] The (*S*)-(+)-2,3-pentadien-1-ol was obtained in the same way, starting from resolved (*R*)-(+)-3-butyn-2-ol. The optical purities of the amines (*R*)- and (*S*)-**2** were estimated to be about 90% ee, based on the reported optical purity of (*R*)-2,3-pentadien-1-ol.[19]



(*R*)-(−)-**2**



(*S*)-(+)-**2**

Results and Discussion

MAO Inhibition. Table II shows the in vitro and in vivo MAO inhibiting activities, i.e., IC_{50} and ED_{50} values, respectively, for the compounds in Table I. The acetylenic, MAO-A and MAO-B selective inhibitors clorgyline and (−)-deprenyl were tested under the same conditions, and the results are presented in Table II. Also included in this table are the in vitro data for compound **15**.

All the allenic compounds, except the clorgyline analogue **12**, were more active inhibitors of the deamination of PEA than of 5-HT in vivo; i.e., they were more or less selective MAO-B inhibitors. In vitro, however, reversed selectivity was surprisingly observed for compounds **3** and **11**.

In general, the potency in vivo and in vitro were in fair agreement. One exception was the relatively low potency in vivo of the tetrahydroisoquinoline derivative **14**, as compared with its fairly high activity in vitro. This was most likely due to extensive metabolism in vivo. The

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Table II. Pharmacological Data of the Compounds Studied

compd	MAO inhibition: in vitro IC_{50},[a] μM: 5-HT	in vitro IC_{50},[a] μM: PEA	in vivo ED_{50},[b] μmol/kg ip: 5-HT	in vivo ED_{50},[b] μmol/kg ip: PEA	potentiation of PEA,[c] μmol/kg ip
1	8.2	0.17	>48 (12%)	17	NT[d]
2	29	15	>72 (18%)	36	NT
(*R*)-(−)-2	17	2.3	>36 (0%)	20	72
(*S*)-(+)-2	51	50	>72 (14%)	54	>72
3	25	>100	>72 (19%)	54	>72
4	7.2	0.24	>39 (17%)	8	>79
5	20	0.14	>26 (14%)	12	51
6	0.26	0.04	18	7	35
7	1.1	0.36	>38 (7%)	23	>38
8	0.7	0.58	39	16	36
9	6.2	0.44	>38 (7%)	11	76
10	1.8	0.15	>51 (17%)	6	26
11	0.8	4.7	>69 (18%)	52	34
12	0.004	4.6	6	33	60
13	1.8	0.36	35	1.7	9
14	7.0	4.3	>90 (14%)	>90 (24%)	>90
15	43	>100	NT	NT	NT
(−)-deprenyl	0.65	0.013	>89 (25%)	2.0	5
clorgyline	0.0007	0.68	2.6	>65 (17%)	>65

[a] Rat hypothalamic mitochondria; 2.5 μM of [^{14}C]5-HT or [^{14}C]PEA. [b] Mouse forebrain homogenates. The animals were sacrificed 1 h after the ip injections of the test compounds. [c] The lowest dose potentiating the awakening effect of phenethylamine (10 mg/kg sc) in mice pretreated with reserpine (5 mg/kg sc 18 h prior to the experiment). [d] Not tested.

tertiary amine **3**, in contrast to compound **14**, exhibited relatively higher activity in vivo than in vitro. A most reasonable explanation for this is enzymatic N-demethylation to the corresponding secondary amine **9**, which belongs to the more active compounds in the whole series.

The allenic inhibitors can be divided into two gross structural classes, namely, (i) an arylalkylamine class with a 2,3-butadienyl substituent on the nitrogen (compounds **1**, **2**, and **10**–**14**) and (ii) a class comprising compounds **3**–**9**, which are 2-phenyl- or 2-benzyl-substituted 2,3-butadienylamines. The structural unit, $NCH_2C{=}C{=}C$, was kept intact in the two series, since an α-methyl substituent, as in compound **15**, most likely interferes with the oxidation by MAO, resulting in a poor inhibitor (cf. in vitro data for **15** in Table II). A similar result was obtained in the pargyline series, where *N*-(1-methyl-2-propynyl)-*N*-methylbenzylamine was more than a thousand times less active than pargyline.[20] No difference in the profile of activity between these two series, both of which comprise a very limited number of compounds, is apparent from the data in Table II. On a molecular level, however, it has recently been shown that compounds **1** and **5**, which are typical representatives of the two series, differ essentially in their mode of inactivation of MAO.[16] The allene **1** gives rise to a reaction product that, mainly through its typical UV spectrum, has been characterized as a 4a,5-adduct with the flavin. Compound **5**, in contrast, reacts with MAO to give an unknown type of adduct, as seen from its unique UV spectrum. However, the weak in vitro inhibitor **3**, which is the *N*,*N*-dimethyl derivative of **5**, gives an adduct with a spectrum different from those of compounds **1** and **5**.[16] Moreover, the structures of the adducts derived from the MAO-A and MAO-B inhibitors **12** and **13**, respectively, are not known.

Compound **1** reacts covalently with the active site of MAO and is, consequently, an irreversible inhibitor.[16] Several of the compounds were examined regarding their in vivo inhibitory activities after 24 h. From these results, which are given in Table III, it is evident that the compounds are irreversible MAO inhibitors. Interestingly, there is a marked difference in irreversibility between compounds **1** and **5**, supporting the hypothesis that their reactions with MAO involve two different pathways (see above).

Table III. MAO-B Inhibition 24 h after the Injection into Mice

compd	dose, μmol/kg ip	*n*	MAO inhibn,[a] %: PEA
1	150	4	70 ± 1
2	150	4	61 ± 3
3	150	4	50 ± 2
5	150	4	39 ± 2
10	150	4	67 ± 2
(−)-deprenyl	24	4	65 ± 3

[a] Mean plus or minus SEM.

In the first series of compounds, the structure was varied almost exclusively in the arylalkylamine part (compounds **10**–**14**). The secondary amine **10** was somewhat more active in vivo than the tertiary analogue **1** reported previously. On the other hand, its selectivity in hindering deamination of 5-HT and PEA in vitro was somewhat lower than that of compound **1**. The deprenyl analogue **11** (racemate) was unexpectedly much less potent in inhibiting MAO-B, both in vivo and in vitro, than (−)-deprenyl. In addition it showed less selectivity between MAO-A and MAO-B.

The clorgyline analogue **12** was approximately ten times less active than clorgyline in vitro but had a very similar selectivity factor for MAO-A inhibition (1150 compared with 971 for clorgyline). In contrast to clorgyline, the selectivity of compound **12** was not maintained in vivo (selectivity factor 5.5).

The most active of all tested allenes in vivo was the indanyl derivative **13**. Its propargylic analogue is a known potent inhibitor.[21] Compound **13** is as active as (−)-deprenyl. The allene **13** is, however, less B selective than deprenyl, with a selectivity factor of 20 in vivo and of 5 in vitro.

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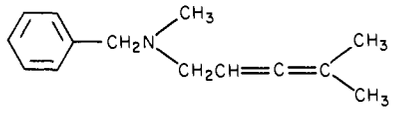
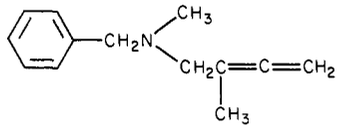
Compound **2** is a homologue of compound **1** where the modifications were made in the reactive part of the molecule. Not unexpectedly, the activity declined, most notably in vitro. Another methyl group in the terminal allene position, as in compound **16**, gives a very poor inhibitor.[16]



16



17

Compound **17**, with a 2-methyl group in the butadienyl chain, had an IC_{50} value 440 times as high as compound **1** (bovine liver MAO, substrate benzylamine).[22] Since the activity of compound **2** was still clearly measurable, we decided to test its separately prepared enantiomers. In these tests, some enantioselective inhibition of MAO-B was established, with the (−) form 2.7 times as active as the (+) form in vivo and 25 times as active in vitro. The difference in vitro is surprisingly large; the (−) form of 2,3-pentadienylamine was 3–5 times as active as the (+) form in inhibiting bovine liver MAO in vitro, using the B substrate benzylamine.[22]

The second series of allenic amines (**3–9**) consisted of compounds with a new basic structure unique among MAO inhibitors. Our exploration of structure–activity relationships in this class unfortunately had to be very restricted, owing to difficulties in the syntheses.

In this series, the 2,3-butadienyl chain was kept intact, and the variation of the structure was achieved by altering the substituents at the nitrogen and/or at position 2 in the butadienyl chain. Compounds **4–8** are primary amines, and they were all quite active both in vivo and in vitro. One compound (**4**) has a phenyl substituent in the allene chain, and the potency and selectivity of this compound were comparable to those of its benzylic analogue **5**.

The chloro, methyl, and methoxy para-substituted analogues of compound **5**, namely **6**, **7**, and **8**, respectively, had increased activity with 5-HT as substrate in vivo and in vitro. This shows that the MAO selectivity is partly determined by the substituents on the aromatic ring. Thus, polar substituents on the ring make the compounds more active on MAO-A. The MAO-A selectivity is also influenced by the distance between the aromatic ring and the reactive part of the molecule.[23] Only the chloro derivative **6** was more active on MAO-B than compound **5**, and, in fact, this derivative was the most potent MAO-B inhibitor tested in vitro.

Two methyl groups on the nitrogen atom, as in compound **3**, drastically decreased the activity, especially in vitro (cf. above), whereas the secondary methylamine **9** was just as potent as the primary amine **5**.

Potentiation of PEA and 5-HTP. Most of the compounds were tested for their ability to potentiate the PEA response in reserpinized mice (Table II), and it was found that the most potent MAO inhibitors, (−)-deprenyl, **13**, **10**, **8**, and **6**, were also the most potent compounds in the potentiation test. Some of the active MAO inhibitors, however, displayed only a slight effect in this test, e.g., compound **4**, which may have been due to additional pharmacological effects obscuring the PEA response.

Table IV. Potentiation by Compound 12 of the 5-Hydroxytryptophan (5-HTP) Syndrome in Mice[a]

compd	ED_{50}, μmol/kg ip		
	head twitches	tremor	abduction
12	1.7	5.1	5.4
clorgyline[b]	1.4	4.5	5.6

[a] The compounds were injected ip 1 h prior to 90 mg/kg iv of 5-HTP. [b] Data from ref 30.

The 5-hydroxytryptophan (5-HTP) syndrome in mice was potentiated by the MAO-A inhibitor **12**, which was equipotent with clorgyline in this respect (Table IV).

Blood Pressure Response to Tyramine. Like deprenyl, but unlike most other MAO inhibitors, compound **5**, in the dose range 20 to 160 μmol/kg, did not potentiate the blood pressure response to orally administered tyramine.

In conclusion, we have shown, by extending the observations of Halliday et al.,[14] that several different types of amines bearing a 2,3-butadienyl chain are quite potent inhibitors of MAO. From our work it can be concluded that, depending on the substitution pattern, these inhibitors can be of either A or B type.

Experimental Section

Chemistry. Melting points were determined in open capillary tubes and are uncorrected. Elemental analyses were carried out by the Microanalytical Laboratory, Royal Agricultural College, Uppsala. IR spectra were recorded on a Perkin-Elmer Infracord 157 G spectrometer, ^1H NMR spectra on a Perkin-Elmer R 12 spectrophotometer (60 MHz) or on a JEOL FX 100 spectrometer (100 MHz), and mass spectra (at 70 eV) on an LKB 9000 instrument. These spectra were routinely recorded and are in full accordance with the proposed structures. Optical rotations were obtained on a Perkin-Elmer 141 spectropolarimeter. Merck silica gel F_{254} (0.2 mm) sheets were used for TLC analyses. Preparative column chromatography was performed on Merck silica gel 60 (230–400 mesh). All organocopper reactions were carried out in an atomosphere of argon or nitrogen.

4-(4-Chlorophenyl)-, 4-(4-Methylphenyl)-, and 4-(4-Methoxyphenyl)-2-butyn-1-ol (18–20). These compounds were all prepared according to a method given in ref 17 by reaction of an appropriate benzylcopper reagent with $BrC{\equiv}CCH_2OTHP$. **18**: yield 17%; NMR ($CDCl_3$) δ 3.25 (br s, 1 H), 3.51 (t, 3 H), 4.25 (t, 3 H), 7.21 (br s, 4 H). **19**: yield 33%; NMR ($CDCl_3$) δ 2.30 (s, 3 H), 2.9 (br s, 1 H), 3.52 (t, 2 H), 4.22 (t, 2 H), 7.15 (br s, 4 H). **20**: yield 32%; NMR ($CDCl_3$) δ 2.65 (br s, 1 H), 3.52 (t, 2 H), 3.72 (s, 3 H), 4.21 (t, 3 H), 6.7–7.35 (m, 4 H).

Methanesulfonate Ester (Mesylate) of 2,3-Butadienol (21). To a stirred solution of 2,3-butadienol[24] (3.3 g, 0.047 mol), triethylamine (5.6 g, 0.055 mol), and dichloromethane (50 mL) at −20 °C was added 5.8 g (0.050 mol) of methanesulfonyl chloride over a period of 10 min. The solution was stirred at −20 °C for another 30 min. after addition of dichloromethane (50 mL), the organic phase was washed with water (4 × 15 mL), dried over $MgSO_4$, and concentrated in vacuo to give 5.8 g (83%) of **21**. Compound **21** was used without further purification: IR (film) 1950 cm^{-1}; NMR ($CDCl_3$) δ 3.00 (s, 3 H), 4.55–5.0 (m, 4 H), 5.1–5.5 (m, 1 H).

Mesylates of 4-(4-Chlorophenyl)-, 4-(4-Methylphenyl)-, and 4-(4-Methoxyphenyl)-2-butyn-1-ol (22–24). These mesylates were prepared similarly to compound **21**, with compounds **18**, **19**, and **20**, respectively. They were purified on silica gel (eluent ether–light petroleum 1:1). **22**: yield 80%; NMR ($CDCl_3$) δ 3.00 (s, 3 H), 3.61 (t, 3 H), 4.84 (t, 3 H), 7.2 (br s, 4 H). **23**: yield 82%; NMR ($CDCl_3$) δ 2.30 (s, 3 H), 3.00 (s, 3 H), 3.58 (t, 3 H), 4.82 (t,

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3 H), 7.1 (br s, 4 H). **24**: yield 69%; NMR ($CDCl_3$) δ 3.00 (s, 3 H), 3.59 (t, 3 H), 3.74 (s, 3 H), 4.81 (t, 3 H), 6.7–7.4 (m, 4 H).

Mesylate of (*R*)-(−)-2,3-Pentadien-1-ol (25). By following the standard procedure with (*R*)-(−)-2,3-pentadien-1-ol,[19] $[\alpha]^{22}_D$ −89.6° (*c* 4.38, CH_3OH), 90% of crude **25** was obtained: $[\alpha]^{22}_D$ −51.9° (*c* 4.54, CH_2Cl_2); IR (film) 1960 cm^{-1}; NMR ($CDCl_3$) δ 1.72 (dd, 3 H), 3.00 (s, 3 H), 4.55–4.85 (m, 2 H), 5.05–5.55 (m, 2 H).

Mesylate of (*S*)-(+)-2,3-Pentadien-1-ol (26). This mesylate was prepared similarly to **21** with (*S*)-(+)-2,3-pentadien-1-ol:[25] $[\alpha]^{22}_D$ +89.7° (*c* 5.60, CH_3OH). The yield of crude **26** was 96%: $[\alpha]^{22}_D$ +50.7° (*c* 4.96, CH_2Cl_2). For spectroscopic data, see preceding paragraph on compound **25**.

***N*-(4-Methoxy-1-methyl-2-butynyl)-*N*-methylbenzylamine (27).** A mesylate of 5-methoxy-3-pentyn-2-ol[26] was prepared similarly to compound **21**. The mesylate was not isolated and was allowed to react with *N*-methylbenzylamine in CH_2Cl_2 according to the standard procedure in method C: yield 25%; NMR ($CDCl_3$) δ 1.35 (d, 3 H), 2.22 (s, 3 H), 3.42 (s, 2 + 3 H), 3.4–3.6 (m, 1 H), 4.18 (d, 2 H), 7.30 (s, 5 H); MS (70 eV), *m/e* 217 (M^+).

Allenic Amines from Organocuprate Reactions of Acetylenic Amino Ethers (Scheme I, Method A). The preparation of compounds **1–3** by this method, as well as the method itself, has been reported previously.[18]

***N*-(1-Methyl-2,3-butadienyl)-*N*-methylbenzylamine (15).** This was prepared similarly to compounds **1** and **2** according to the described procedure,[18] starting from compound **27**: yield 40% (GLC). Compound **15** was separated from a simultaneously formed acetylenic amine by the use of preparative GLC (20% SE 30, 200 °C): IR (film) 1950 cm^{-1}; NMR ($CDCl_3$) δ 1.21 (d, 3 H)e, 2.18 (s, 3 H), 3.3–3.6 (m, 3 H), 4.73 (dd, 2 H), 5.1–5.35 (m, 1 H), 7.30 (s, 5 H). The oxalate of **15** had a melting point of 134–135 °C after recrystallization from ethanol–ether. Anal. ($C_{15}H_{19}NO_4$) H, N; C: calcd, 64.95; found, 64.20.

Allenic Amines via Allenic Imines (Scheme III, Method B). Compounds **4–9** were all prepared according to a method described elsewhere.[17] The synthesis and characterization of compounds **4**, **5**, and **9** have been reported previously.[17]

2-(4-Chlorobenzyl)-2,3-butadienylaminium Hydrogen Oxalate (6). The standard procedure was followed, using **22**, and **6** was obtained in a yield of 23%: NMR (liberated amine, $CDCl_3$) δ 1.50 (br s, 2 H), 2.95–3.3 (m, 4 H), 4.6–4.9 (m, 2 H), 7.10 (br s, 4 H).

2-(4-Methylbenzyl)-2,3-butadienylaminium Hydrogen Oxalate (7). The standard procedure was followed, using **23**, which gave **7** in a yield of 17%: NMR (liberated amine, $CDCl_3$) δ 1.33 (br s, 2 H), 2.28 (s, 3 H), 3.0–3.35 (m, 4 H), 4.65–4.9 (m, 2 H), 7.0 (br s, 4 H).

2-(4-Methoxybenzyl)-2,3-butadienylaminium Hydrogen Oxalate (8). Following the standard procedure, with **24**, **8** was obtained in a yield of 27%: NMR (D_2O) δ 3.38 (t, 3 H), 3.44 (t, 3 H), 3.80 (s, 3 H), 5.00–5.11 (m, 2 H), 6.90–7.29 (m, 4 H).

Allenic Amines from Reactions of Amines with Mesylates of Allenic Alcohols (Scheme IV, Method C). To a stirred mixture of an appropriate amine (2.0 equiv) in dichloromethane at −5 °C was added the mesylate (1.0 equiv) dropwise over a 15-min period. The temperature was allowed to slowly reach room temperature, and the mixture was stirred overnight. The mixture was then poured into saturated K_2CO_3 solution and extracted three times with dichloromethane. Drying over K_2CO_3 + Na_2SO_4 and evaporation of the solvent gave a crude allenic amine, which was purified by silica gel chromatography (eluent ether) or by distillation.

(*R*)-(−)-*N*-2,3-Pentadienyl-*N*-methylbenzylamine [(*R*)-(−)-2]. Application of the standard procedure, using *N*-methylbenzylamine and **25**, gave the above compound in a yield of 56% after purification on silica gel: $[\alpha]^{22}_D$ −62.4° (*c* 2.56, CH_3OH). For spectroscopic data, see ref 18.

(*S*)-(+)-*N*-2,3-Pentadienyl-*N*-methylbenzylamine [(*S*)-(+)-2]. The standard procedure was followed, using *N*-methylbenzylamine and **26**, and the above compound was obtained in a yield of 70% after purification on silica gel: $[\alpha]^{22}_D$ +61.7° (*c* 3.49, CH_3OH). For spectroscopic data, see ref 18.

***N*-2,3-Butadienylbenzylamine (10).** This was prepared from **21** and benzylamine according to the standard procedure, except that benzylamine was used in a large excess and as solvent: yield after distillation 50%; bp 70–72 °C (0.4 mm); IR (film) 1950 cm^{-1}; NMR ($CDCl_3$) δ 1.38 (s, 1 H), 3.1–3.35 (m, 2 H), 3.80 (s, 2 H), 4.6–4.85 (m, 2 H), 5.05–5.4 (m, 1 H), 7.35 (s, 5 H).

***N*-2,3-Butadienyl-α,*N*-dimethylphenethylamine (11).** This was prepared from α,*N*-dimethylphenethylamine and **21** according to the standard procedure. After distillation under reduced pressure, compound **11** was obtained in a yield of 36%: bp 87–91 °C (0.3 mm); IR (film) 1950 cm^{-1}; NMR ($CDCl_3$) δ 0.90 (d, 3 H), 2.28 (s, 3 H), 2.25–2.9 (m, 5 H), 2.95–3.3 (m, 2 H), 4.5–4.8 (m, 2 H), 4.9–5.3 (m, 1 H), 7.2 (s, 5 H).

***N*-2,3-Butadienyl-*N*-methyl-2-(2,4-dichlorophenoxy)-propylamine (12).** The standard procedure was followed, using *N*-methyl-3-(2,4-dichlorophenoxy)propylamine[27] and **21**. After purification on silica gel, **12** was obtained in a yield of 52%: IR (film) 1950 cm^{-1}; NMR ($CDCl_3$) δ 1.85–2.2 (m, 2 H), 2.30 (s, 3 H), 2.40 (t, 2 H), 3.0–3.2 (m, 2 H), 4.05 (t, 2 H), 4.6–4.8 (m, 2 H), 4.95–5.3 (m, 1 H), 6.8–7.4 (m, 3 H).

***N*-2,3-Butadienyl-*N*-methyl-1-indanamine (13).** The standard procedure, using *N*-methylindanamine[21] and **21**, followed by column chromatography, gave **13** in a yield of 47%: IR (film) 1950 cm^{-1}; NMR ($CDCl_3$) δ 1.85–2.1 (m, 2 H), 2.20 (s, 3 H), 2.75–3.2 (m, 4 H), 4.35–4.85 (m, 3 H), 4.95–5.35 (m, 1 H), 7.1–7.35 (m, 4 H).

2-(2,3-Butadienyl)-1,2,3,4-tetrahydroisoquinoline (14). This was prepared from 1,2,3,4-tetrahydroisoquinoline and **21** according to the standard procedure. After column chromatography, **14** was obtained in a yield of 56%: IR (film) 1950 cm^{-1}; NMR ($CDCl_3$) δ 2.6–2.95 (m, 4 H), 3.05–3.25 (m, 2 H), 3.62 (s, 2 H), 4.6–4.85 (m, 2 H), 5.05–5.4 (m, 1 H), 7.0–7.2 (m, 4 H).

Pharmacology. MAO Inhibition in Vitro. Mitochondria from pooled rat hypothalami were used as the enzyme source. The tissue was homogenized in 10 vol of ice-chilled 0.32 M sucrose with an all-glass homogenizer. The homogenate was centrifuged at 800*g* for 10 min at 2 °C. The supernatant was centrifuged at 10000*g* for 20 min. The pellet was rehomogenized in 0.32 M sucrose, and the centrifugation was repeated. The mitochondria were suspended in the initial volume of 0.32 M sucrose and stored at −18 °C.

The inhibitor at various concentrations was preincubated with the enzyme in 0.1 M sodium phosphate buffer, pH 7.4, at 37 °C for 10 min. The radioactive substrate [^{14}C]PEA or [^{14}C]5-HT at a final concentration of 2.5 μM was then added to the incubation mixture (final volume 1.0 mL). The incubation was continued for 30 min, and the reaction was stopped by the addition of 1.0 mL of 1 M HCl. The radioactive acid metabolite ([^{14}C]phenylacetic acid or 5-hydroxy[^{14}C]indoleacetic acid) was extracted into 6.0 mL of ethyl acetate by vigorous mixing for 15 s. The radioactivity in 4.0 mL of the organic extract was measured in a liquid scintillation spectrometer after addition of 1.0 mL of ethanol and 10 mL of Econofluor. The IC_{50} values were determined from semilogarithmic plots of five to eight different concentrations of the test compounds.

MAO Inhibition in Vivo. Male albino mice (NMRI) weighing 18–22 g were injected intraperitoneally with the test compound (0.2 mL/20 g of body weight). The forebrains (approximately 100 mg) were homogenized in 10 vol of ice-chilled 0.1 M sodium phosphate buffer, pH 7.4. The incubation mixture in glass-stoppered centrifuge tubes contained 10 μM [^{14}C]PEA, 10 μM [^{3}H]5-HT, 100 μL of the homogenate, and phosphate buffer to a final volume of 1.0 mL. The incubation was performed for 10 min at 37 °C. The radioactive acid metabolites were extracted as described above. ^{3}H and ^{14}C were measured in separate channels in a liquid scintillation spectrometer. The two substrates did not interfere with each other under the conditions used. Five animals per dose of the test compound were examined. ED_{50} values (i.e., 50% decrease of the enzyme activity) were determined from semilogarithmic plots.

(25) The detailed synthesis of this alcohol will be reported elsewhere.

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Potentiation of Phenethylamine in Mice. PEA hydrochloride (10 mg/kg sc) was given to mice pretreated 18 h beforehand with reserpine, 5 mg/kg sc. In combination with inhibitors of the B form of MAO (but not with those of the A form), PEA caused an awakening effect and tremor in these mice. The test compounds were injected intraperitoneally 1 h prior to the injection of phenethylamine, and the mice were observed in the 30-min period thereafter. The lowest dose producing potentiation of the phenethylamine effect was determined.

Potentiation of the 5-HTP Syndrome in mice was determined as described by Ross et al.[28] The test compound was injected 1 h prior to intravenous injection of *dl*-5-HTP, 90 mg/kg.

Blood pressure response to tyramine was studied in conscious rats via a permanent catheter introduced into the abdominal aorta, by a method to be described elsewhere.[29] Tyramine was given orally in a dose of 10 mg/kg 2 h before oral administration of the test compound in various doses and also 1 h after the test compound. The arterial blood pressure was monitored for 1 h after administration of tyramine, with a Statham P23 Db transducer, and recorded on a polygraph.

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Registry No. 1, 16719-32-7; 1 (base), 16719-33-8; 2, 85506-92-9; (*R*)-2, 85506-94-1; (*R*)-2 (base), 85506-93-0; (*S*)-2, 85506-96-3; (*S*)-2 (base), 85506-95-2; 3, 82086-61-1; 3 (base), 73586-40-0; 4, 85507-19-3; 5, 75166-24-4; 5 (base), 73586-38-6; 6, 85506-98-5; 7, 85507-00-2; 8, 85507-02-4; 9, 85507-03-5; 10, 85507-04-6; 10 (base), 70882-08-5; 11, 85507-05-7; 11 (base), 73586-41-1; 12, 85507-06-8; 12 (base), 73586-42-2; 13, 85507-08-0; 13 (base), 85507-07-9; 14, 85507-09-1; 14 (base), 85507-20-6; 15, 85507-10-4; 15 oxalate, 85507-23-9; 18, 34905-12-9; 19, 34905-11-8; 20, 85507-11-5; 21, 85507-12-6; 22, 85507-13-7; 23, 85507-14-8; 24, 85507-15-9; 25, 85507-16-0; 26, 85507-17-1; 27, 85507-18-2; (*S*)-(+)-2,3-pentadien-1-ol, 85507-21-7; 5-methoxy-3-pentyn-2-ol mesylate, 85507-22-8; α,*N*-dimethylphenethylamine, 7632-10-2; *N*-methyl-3-(2,4-dichlorophenoxy)propylamine, 85507-24-0; *N*-methylindanamine, 2084-72-2; 2,3-butadienol, 18913-31-0; (*R*)-(−)-2,3-pentadien-1-ol, 65032-23-7; *N*-methylbenzylamine, 103-67-3; benzylamine, 100-46-9; 1,2,3,4-tetrahydroisoquinoline, 91-21-4; MAO, 9001-66-5.

Synthesis and Antiviral Activity of Distamycin A Analogues: Substitutions on the Different Pyrrole Nitrogens and in the Amidine Function

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Several new analogues of the antiviral antibiotic distamycin A were synthesized and assayed for their effects on influenza and herpes simplex virus. The new compounds **5b–j** (R_{1-3} = H, CH_3, and C_2H_5, $R_{4,5}$ = H and CH_3) were obtained via stepwise prepared formylated trimeric benzyl 4-aminopyrrole-2-carboxylates **3a–h**, which after catalytic hydrogenolysis were coupled as *N*-succinimidyl esters directly with the proper β-aminopropionamidine, unsubstituted or substituted with one or two methyl groups in the amidine function. Most of the new analogues did not exhibit significant effects on the viruses studied, but three compounds (**5f–h**) displayed activity on herpes virus as demonstrated in plaque formation and virus yield assays. Elevated cytotoxicity was simultaneously observed for **5g** and **5h**. For compound **5f**, a partial separation of antiherpes activity and cytotoxicity was accomplished. The differences in antiherpes activity did not correspond to the differences in the inhibition of herpes virus DNA polymerase.

The antiviral antibiotic distamycin A continues to be of interest both from chemical and biological points of view, and the present standpoint in regards to its mechanism of action has recently been briefly outlined.[1] Shortly before we submitted our paper dealing with a novel synthesis of distamycin A,[2] two other papers, unnoticed by us, describing new analogues appeared.[3,4] Of all the numerous distamycin derivatives hitherto synthesized, only very few seem to have higher antiviral activity than the parent compound.

Chemistry. The present paper describes the preparation of several new distamycin analogues utilizing our previous general synthetic approach[2] (Scheme I). The new analogues were either substituted on the amidine nitrogen with one or two methyl groups, as in **5i** and **5j**, or modified on the pyrrole nitrogen. In **5b–e**, one or all methyl groups were replaced by ethyl, whereas **5f–h** possessed one unsubstituted pyrrole nitrogen. The introduction of the protecting *tert*-butyloxycarbonyl (Boc) group on the intermediate unstable aminopyrrolecarboxylic acids with Boc-F afforded **1a–c** in acceptable yields and offered no special problems. Compounds **1a–c** were conveniently esterified via their cesium salts with benzyl bromide in DMF and provided benzyl (Bzl) esters **1d–f** in excellent yields. After conventional deprotection, the resulting amino analogues were acylated with the appropriate acid **1a–c** by using 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide (EDC) as dehydrating agent to give the corresponding dimers **2a–f**. In this connection it was observed that the otherwise good yield in this condensation was significantly

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