The Synthesis of Some Analogs of the Hallucinogen 1-(2,5-Dimethoxy-4-methylphenyl)-2-aminopropane (DOM). III.[1] Some Derivatives of 3-phenylalanine

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Received June 18, 1973

Syntheses of the hydrochlorides of 3-(2,5-dimethoxyphenyl)alanine, 3-(2,5-dimethoxy-4-methylphenyl)alanine, and 3-(4-bromo-2,5-dimethoxyphenyl)alanine are described. A phenol, $C_{10}H_{14}ClNO_4$, related to the second of these three compounds was also prepared and is concluded to be a monohydrate of the lactone, 3-amino-6-hydroxy-7-methylhydrocoumarin hydrochloride.

On décrit les synthèses des chlorhydrates de (diméthoxy-2,5 phényl)-3 alanine, de (diméthoxy-2,5 méthyl-4 phényl)-3 alanine et de (bromo-4 diméthoxy-2,5 phényl)-3 alanine. On a aussi préparé un dérivé du type phénol, $C_{10}H_{14}ClNO_4$, relié au second de ces trois composés, qui s'est révélé être un monohydrate de la lactone, chlorhydrate d'amino-3 hydroxy-6 méthyl-7 hydrocoumarin.

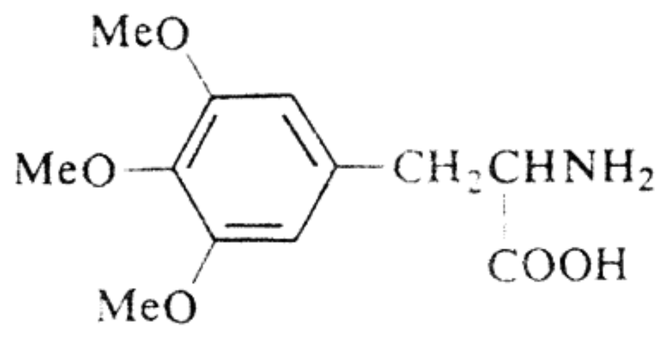
[Traduit par le journal]

Can. J. Chem., **52**, 390 (1974)

When mescaline is administered to animals, the amount which reaches the brain is very low (1, 2). In an attempt to obtain higher brain levels, the amino acid analog, 3-(3,4,5-trimethoxyphenyl)alanine (**1**), was prepared, it being rationalized that this compound would be actively transported across the blood–brain barrier and might be decarboxylated in the brain to yield mescaline (3, 4). When evaluated pharmacologically, however, the amino acid **1** failed to demonstrate any psychotomimetic activity. Mescaline, itself, is a weak psychotomimetic drug and so we decided to prepare for pharmacological evaluation, amino acid analogs of the more potent psychotomimetic drugs, 1-(2,5-dimethoxyphenyl) 2-aminopropane (5), 1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane (5) (DOM), and 1-(4-bromo-2,5-dimethoxyphenyl)-2-aminopropane (6, 7). The envisaged compounds were not expected to act as substrates for brain decarboxylase enzymes (*cf.* 8); activity *per se* was being investigated. The compounds were interesting for other reasons. Since they were amino acids, they would be expected to be capable of entering the CNS system and might possibly evoke pharmacological effects other than psychotomimetic ones.

For the reasons given, syntheses of 3-(2,5-dimethoxy-4-methylphenyl)alanine (**2***a*), 3-(2,5-dimethoxyphenyl)alanine (**2***b*), and 3-(4-bromo-2,5-dimethoxyphenyl)alanine (**2***c*) were undertaken.

Phenylalanines have been prepared by a variety of methods including one which employed an azlactone as a suitable intermediate (9). This was the method employed in the present investigation and is summarized in Scheme 1. Thus, when 2,5-dimethoxy-4-methylbenzaldehyde was reacted with acetylglycine in the presence of acetic anhydride and sodium acetate, the bright orange azlactone, 4-(2,5-dimethoxy-4-methylbenzylidene)-2-methyl-2-oxazolin-5-one (**3***a*), was formed. Hydrolysis of **3***a* in aqueous acetone gave α-acetamido-2,5-dimethoxy-4-methylcinnamic acid (**4***a*), which was reduced catalytically to *N*-acetyl-3-(2,5-dimethoxy-4-methylphenyl)alanine (**5***a*). Treatment of the latter with hydrochloric acid caused hydrolysis of the amide group and gave the required 3-(2,5-dimethoxy-4-methylphenyl)alanine hydrochloride (**2***a*). In the



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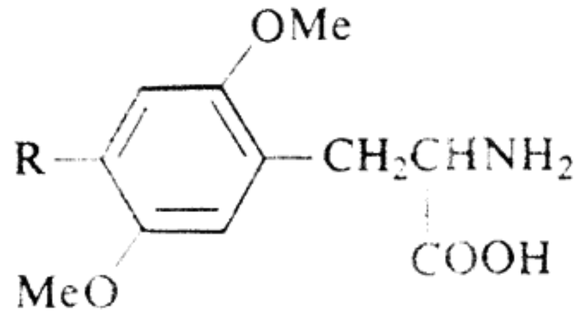

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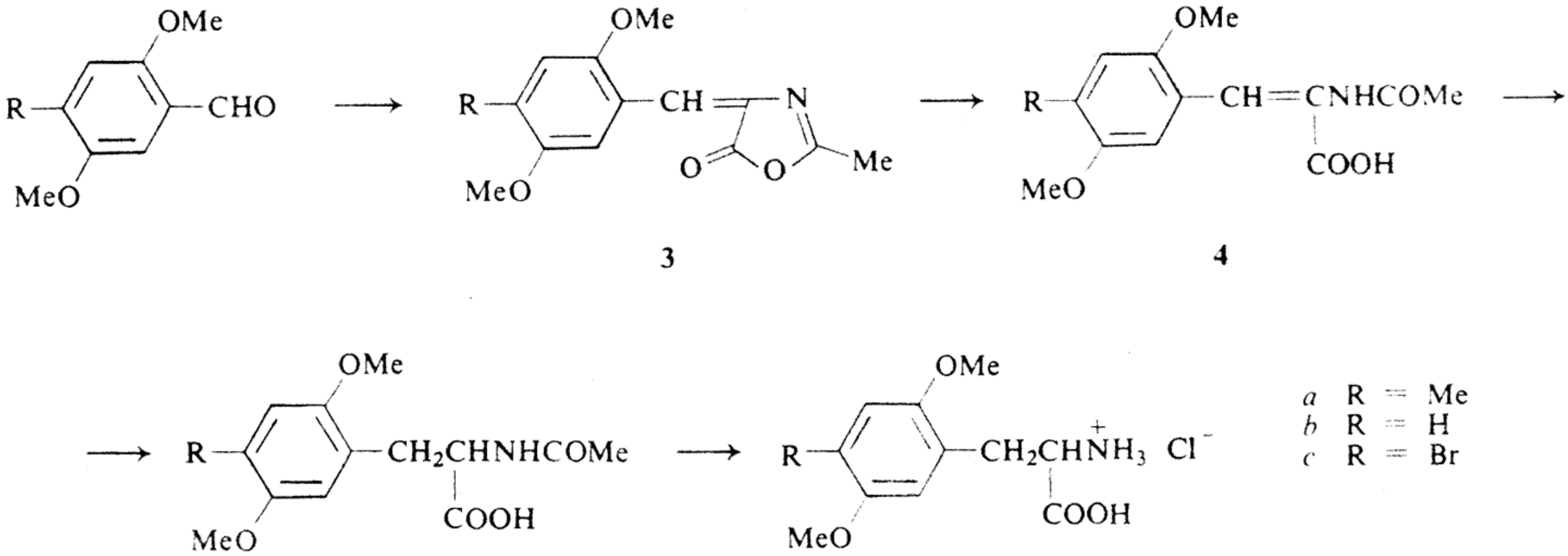
a R = Me
b R = H
c R = Br

[1]Part II see ref. 15.



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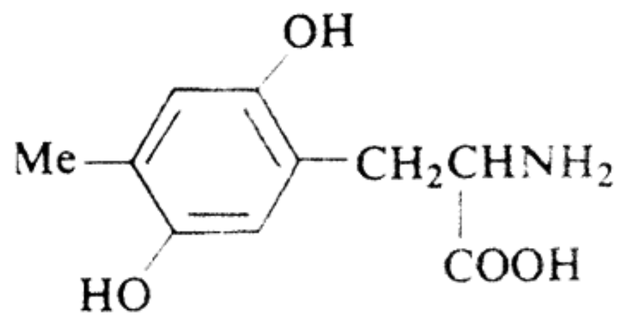
SCHEME I

same way, 2,5-dimethoxybenzaldehyde was converted to 3-(2,5-dimethoxyphenyl)alanine hydrochloride (**2***b*) via intermediates **3***b*, **4***b*, and **5***b*.

The action of bromine water on *N*-acetyl-3-(2,5-dimethoxyphenyl)alanine (**5***b*) gave a monobromo derivative. A 60 MHz n.m.r. spectrum of this product showed two one-proton singlet signals (δ 7.03 and 7.18) which indicated that these aromatic protons were *para* to each other, and enabled identification of the bromo compound as *N*-acetyl-3-(4-bromo-2,5-dimethoxyphenyl)alanine (**5***c*). This amide was then hydrolyzed with hydrochloric acid to 3-(4-bromo-2,5-dimethoxyphenyl)alanine hydrochloride (**2***c*).

In view of the study by Ferrini and Glässer (8), it is possible that, in contrast with the dimethyl ether (**2***a*), 3-(2,5-dihydroxy-4-methylphenyl)alanine (**6**) might be a substrate for a brain decarboxylase system and, if so, would produce *in vivo* 2-(2,5-dihydroxy-4-methylphenyl) ethylamine (**7**), a compound with possible psychotomimetic activity. The feasibility of preparing **6** was considered remote since spontaneous lactonization would be expected to occur in an acidic medium and yield the lactone **8**. However, a synthesis of **6** was attempted with the thought in mind that if the lactone **8** did form, it might itself possess pharmacological activity, or alternatively might hydrolyze *in vivo* to the more interesting amino acid **6**.



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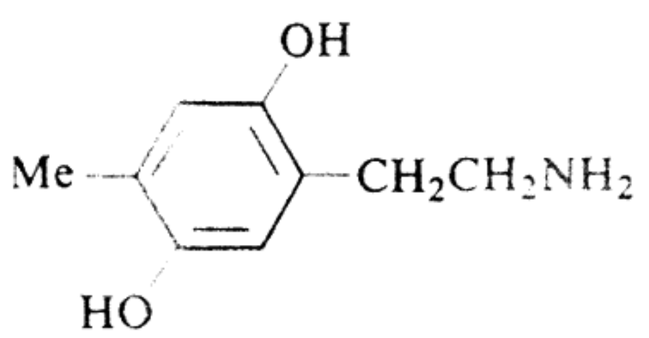

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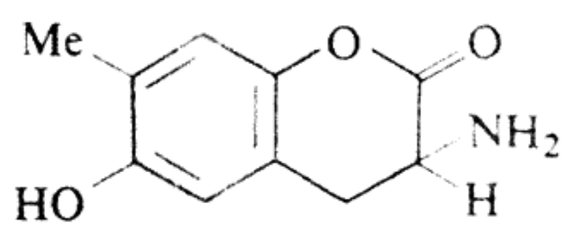

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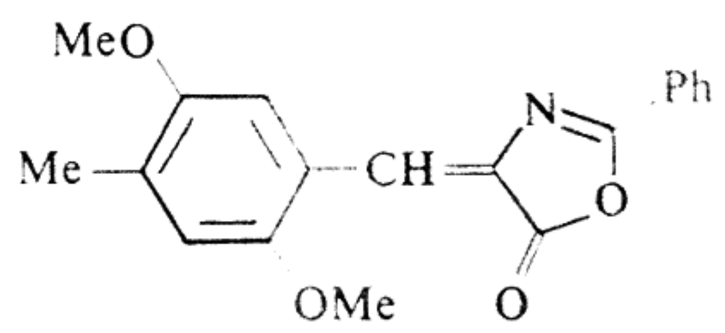

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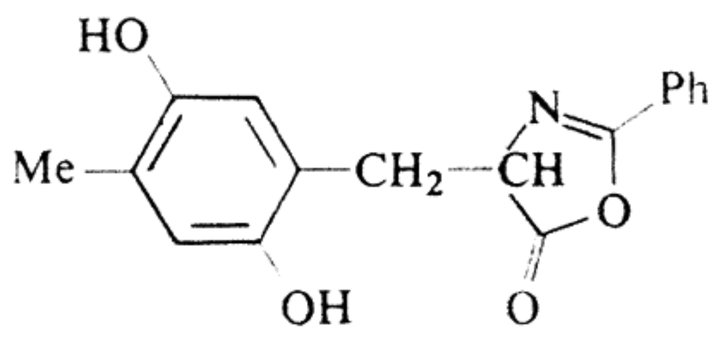

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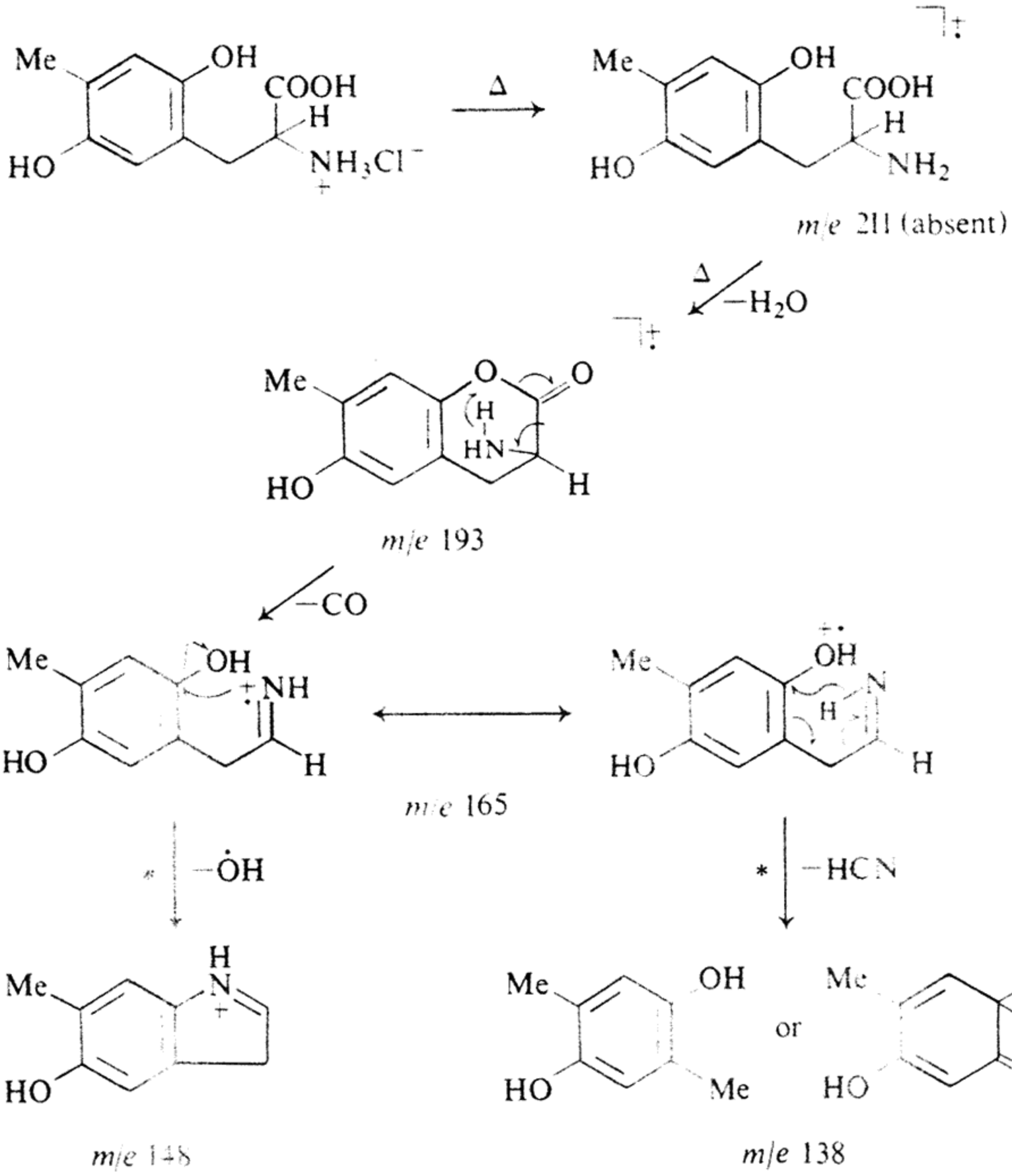
When 3-(2,5-dimethoxy-4-methylphenyl)alanine (**2***a*) was reacted with phosphorus and hydriodic acid, a small quantity of a product was isolated but could not be purified. 4-(2,5-Dimethoxy-4-methylbenzylidene)-2-phenyl-2-oxazolin-5-one (**9**), prepared for another study (10), was then heated under reflux with phosphorus and hydriodic acid and was converted in low yield to a colorless product, $C_{17}H_{15}NO_4$. The i.r. spectrum of this material displayed bands at 1765 (lactone), 1642 (C=N), and 3440 and 3300 cm^{-1} (free and bonded OH), enabling identification as 4-(2,5-dihydroxy-4-methylbenzyl)-2-



SCHEME 2

phenyl-2-oxazolin-5-one (**10**). The mother liquor remaining after removal of **10** gave a blue color when treated with ninhydrin reagent, suggesting the presence of an α-amino acid (11), but attempts to find the isoelectric point and isolate this product proved unsuccessful.

Treatment of the azlactone **9** with phosphorus and hydriodic acid was repeated but for a longer time. When the p*H* of the reaction mixture was adjusted to 4.5 a solid, which gave a positive ninhydrin reaction, precipitated from solution in modest yield. The compound was amphoteric; it formed a hydrochloride, and an aqueous solution when treated with ferric chloride turned blue, indicative of a phenol. A correct analysis for $C_{10}H_{14}ClNO_4$ was consistent with the product being a monohydrate of the expected lactone **8** hydrochloride, or alternatively, the hydrochloride of amino acid **6**. The carbonyl stretching band in the i.r. spectrum was located at 1765 cm^{-1} which was more indicative (12) of the lactone. However, this stretching frequency is not far removed from the range quoted (13) for α-amino acid hydrochlorides (1730–1755 cm^{-1}) and is reasonably close to the carbonyl stretching frequencies of amino acids **2***a* and *b*. The mass spectrum displayed diagnostic ions of *m/e* 193, 165, 148, and 138 but no ions of greater mass. This, also, suggested the lactone (mass of anhydrous base, 193), but the mass spectrum may be explained in terms of the phenylalanine (**6**) structure if thermal decomposition of the hydrochloride of **6** to the base is followed by dehydration to the lactone **8** prior to fragmentation. The fragment ions of *m/e* 165, 148, and 138 were identified as $C_9H_{11}NO_2$, $C_9H_{10}NO$, and $C_8H_{10}O$, respectively, by accurate mass measurements, and their formation from the lactone molecular ion can be rationalized as illustrated in Scheme 2; the *ortho* effect involved in the *m/e* 165 → *m/e* 148 fragmentation is reminiscent of the expulsion of $\cdot OCH_3$ from *o*-methoxybenzylketoximes (14).

To help distinguish between the two possibilities **6** and **8**, an n.m.r. spectrum of the compound was recorded in DMSO. Since the methylene and methine signals of both structures **6** and **8** would

be expected to display ABX coupling patterns, an interpretation of these signals would not permit a choice between the two possibilities. However, when the downfield deuterium-exchangeable signals were examined, it was revealed that signals ascribable to only four protons (*i.e.* $\overset{+}{N}H_3$ and O*H*) were present. This evidence is consistent with the product of the action of phosphorus and hydriodic acid on the azlactone **9** being the hydrochloride of lactone **8** and not of the amino acid **6**, which would give signals for six downfield deuterium-exchangeable protons.

Compounds **2***a* and **8** were subjected to a preliminary pharmacology screening in the rat. Both lacked symptoms characteristic of DOM intoxication. Compound **8** appeared to possess some stimulant properties. Compounds **2***b* and **2***c* await pharmacological evaluation.

Experimental

Melting points (capillary tube) are uncorrected. Infrared spectra were recorded on a Beckman IR-10 spectrophotometer as Nujol mulls, and n.m.r. spectra were taken on a varian A-60D spectrometer with tetramethylsilane as internal standard. Dr. A. M. Hogg and his associates, Department of Chemistry, University of Alberta, recorded the mass spectra on an A.E.I. MS-9 or MS-12 mass spectrometer at an ionizing potential of 70 eV using the direct probe technique. Elemental analysis were determined at the Faculty of Pharmacy and Pharmaceutical Sciences by Mr. W. Dylke.

*4-(2,5-Dimethoxy-4-methylbenzylidene)-2-methyl-2-oxazolin-5-one (**3a**)*

A mixture of 2,5-dimethoxy-4-methylbenzaldehyde (22.0 g), acetylglycine (11.8 g), sodium acetate (6.0 g), and acetic anhydride (24 ml) was heated under reflux for 2 h, then cooled to 5°. The orange precipitate was thoroughly washed with water in which the title compound (17.9 g) was insoluble. Recrystallization from benzene gave m.p. 128–130°; i.r. ν_{max} 1650 (C=N), 1795 (C=O) cm^{-1}.

Anal. Calcd. for $C_{14}H_{15}NO$: C, 64.35; H, 5.79; N, 5.36. Found: C, 64.46; H, 5.78; N, 5.29.

*4-(2,5-Dimethoxybenzylidene)-2-methyl-2-oxazolin-5-one (**3b**)*

This product (18.2 g), m.p. 129–131° (from benzene), was prepared in the same manner from 2,5-dimethoxybenzaldehyde (22.0 g).

Anal. Calcd. for $C_{13}H_{13}NO$: C, 62.89; H, 5.68; N, 5.64. Found: C, 63.16; H, 5.68; N, 5.40.

*α-Acetamido-2,5-dimethoxy-4-methylcinnamic Acid (**4a**)*

A solution of the azlactone **3***a* (15 g) in water (80 ml) and acetone (200 ml) was heated under reflux for 4 h. The acetone was distilled off and insoluble starting material removed by filtration. The title compound (3.2 g) crystallized from the filtrate on cooling. Repeating the procedure with the recovered starting material gave a further 2.1 g of **4***a*. Crystallization from ethanol–water gave m.p. 206–208°; i.r. ν_{max} 1648, 1690 (C=O), 2500–2750 (OH), 3230 (NH) cm^{-1}; n.m.r. (DMSO-d_6) δ 2.00 (s, 3H, $COCH_3$), 2.21 (s, 3H, CH_3), 3.73 (s, 3H) and 3.80 (s, 3H) (OCH_3 groups), 6.81 (s, 1H), 7.26 (s, 1H), and 7.60 (s, 1H) (aromatic protons and CH), 9.17 (s, br, 1H, exchanges with D_2O, OH).

Anal. Calcd. for $C_{14}H_{17}NO_5$: C, 60.20; H, 6.14; N, 5.02. Found: C, 60.45; H, 6.60; N, 5.36.

*α-Acetamido-2,5-dimethoxycinnamic Acid (**4b**)*

This product (9.5 g), m.p. 208–209° (from ethanol) was prepared in the same manner from azlactone **3***b* (15.0 g); i.r. ν_{max} 1655, 1695 (C=O), 2400–2600 (OH), 3250 (NH) cm^{-1}.

Anal. Calcd. for $C_{13}H_{15}NO_5$: C, 58.86; H, 5.70; N, 5.28. Found: C, 59.14; H, 6.20; N, 4.91.

*N-Acetyl-3-(2,5-dimethoxy-4-methylphenyl)alanine (**5a**)*

A solution of α-acetamido-2,5-dimethoxy-4-methylcinnamic acid (5.0 g) in ethanol (100 ml) containing 10% palladium–charcoal (0.5 g) was hydrogenated at room temperature and 50 p.s.i. until uptake of hydrogen ceased. Evaporation of the filtrate gave a quantitative yield of the title compound, m.p. 159–160° (from ethanol); i.r. ν_{max} 1655 (amide C=O), 1720 (acid C=O), 3310 (NH) cm^{-1}.

Anal. Calcd. for $C_{14}H_{19}NO_5$: C, 59.77; H, 6.81; N, 4.98. Found: C, 59.54; H, 6.73; N, 4.89.

*N-Acetyl-3-(2,5-dimethoxyphenyl)alanine (**5b**)*

This product m.p. 160–162° (from ethanol) was similarly prepared in quantitative yield from α-acetamido-2,5-dimethoxycinnamic acid (7.0 g); i.r. ν_{max} 1630 br, 1730 (C=O), 3310 (NH) cm^{-1}.

Anal. Calcd. for $C_{13}H_{17}NO_5$: C, 58.41; H, 6.41; N, 5.24. Found: C, 58.38; H, 6.60; N, 5.21.

*N-Acetyl-3-(4-bromo-2,5-dimethoxyphenyl)alanine (**5c**)*

Bromine water was added dropwise to a stirred solution of *N*-acetyl-3-(2,5-dimethoxyphenyl)alanine (1.0 g) in ethanol (100 ml) until a pale orange color persisted. Stirring was continued for a further 0.5 h, then the solution was basified (5% $NaHCO_3$) and evaporated. The mixture was suspended in 5% HCl solution (50 ml) and extracted with chloroform (2 × 30 ml). Evaporation of the chloroform gave an oil which was dissolved in 5% $NaHCO_3$ solution and the solution filtered. Acidification of the filtrate (dilute HCl) gave the title compound (0.62 g), m.p. 178–180° (from ethanol); i.r. ν_{max} 1650, 1730 (C=O), 3310 (NH) cm^{-1}; n.m.r. (DMSO-d_6) δ 1.79 (s, 3H, $COCH_3$) 3.06 (m, 2H, CH_2), 3.78 (s, 6H, OCH_3 groups), 4.15–4.80 (m, 1H, CH), 7.03 (s, 1H), and 7.18 (s, 1H) (aromatic protons), 8.20 (d, 1H, J = 8 Hz, NH).

Anal. Calcd. for $C_{13}H_{16}BrNO_5$: C, 45.10; H, 4.66; N, 4.05. Found: C, 45.04; H, 4.73; N, 3.81.

*3-(2,5-Dimethoxy-4-methylphenyl)alanine Hydrochloride (**2a**)*

A suspension of *N*-acetyl-3-(2,5-dimethoxy-4-methylphenyl)alanine (4.0 g) in concentrated HCl (60 ml) was heated under reflux for 4 h, then evaporated to dryness. The residue was suspended in acetone in which the title compound (2.8 g) was insoluble. Crystallization from ethanol gave m.p. 241–242°; i.r. ν_{max} 1580, 1950, 2410–2670 ($\overset{+}{N}$—H), 1745 (C=O) cm^{-1}; n.m.r. (DMSO-d_6)

δ 2.18 (s, 3H, CH_3), 3.18 (d, 2H, J = 6 Hz, CH_2), 3.65–4.23 (m, 7H, overlapping CH and OCH_3 signals), 6.84 (s, 1H) and 7.00 (s, 1H) (aromatic protons), 8.66 (s, br, 4H, exchange with D_2O, $\overset{+}{N}H_3$ and OH).

Anal. Calcd. for $C_{12}H_{17}ClNO_4$: C, 52.46; H, 6.24; N, 5.10. Found: C, 52.40; H, 6.55; N, 4.86.

3-(2,5-Dimethoxyphenyl)alanine Hydrochloride (2b)

This product (1.52 g), m.p. 225° (from ethanol–ether (lit. (8) no m.p. reported)) was obtained similarly by hydrolysis of *N*-acetyl-3-(2,5-dimethoxyphenyl)alanine (2.0 g); i.r. ν_{max} 1585, 2420–2680 ($\overset{+}{N}$—H), 1750 (C=O) cm^{-1}.

Anal. Calcd. for $C_{11}H_{16}ClNO_4$: C, 50.48; H, 6.16; N, 5.35. Found: C, 50.12; H, 6.29; N, 5.35.

3-(4-Bromo-2,5-dimethoxyphenyl)alanine Hydrochloride (2c)

This product (0.41 g), m.p. 252–253° (from ethanol–acetone) was prepared in a similar manner from *N*-acetyl-3-(4-bromo-2,5-dimethoxyphenyl)alanine (0.5 g); i.r. ν_{max} 1590, 2420–2680 ($\overset{+}{N}$—H), 1735 (C=O) cm^{-1}.

Anal. Calcd. for $C_{11}H_{15}BrClNO_4$: C, 38.79; H, 4.44; N, 4.11. Found: C, 39.07; H, 4.62; N, 4.11.

Treatment of 4-(2,5-Dimethoxy-4-methylbenzylidene)-2-phenyl-2-oxazolin-5-one (9) with Phosphorus and Hydriodic Acid

(*i*) To a solution of the title compound (10) (21.0 g) in acetic anhydride (60 ml) containing red phosphorus (18.0 g) was added 50% HI (60 ml) over 1 h. The red reaction mixture was heated under reflux for 3 h, cooled, filtered, and evaporated to a semisolid residue. Water (100 ml) was added and the resulting suspension was shaken several times with ether. This treatment caused the separation of a solid at the interface. The ether extracts were discarded. The aqueous solution remaining gave a positive ninhydrin reaction but attempts to cause precipitation of any product by slowly altering the p*H* of the cooled solution with dilute NH_4OH and dilute HCl were unsuccessful.

The interfacial material (3.1 g), m.p. 262–264° (from ethanol) was 4-(2,5-dihydroxy-4-methylbenzyl)-3-phenyl-2-oxazolin-5-one (**10**); i.r. ν_{max} 1642 (C=N), 1765 (C=O), 3300 br, 3440 (OH) cm^{-1}; mass spectrum *m/e* (% relative abundance) 297 (8) ($C_{17}H_{15}NO_4$).

Anal. Calcd. for $C_{17}H_{15}NO_4$: C, 68.67; H, 5.09; N, 4.71. Found: C, 68.41; H, 5.51; N, 4.48.

(*ii*) The reaction described immediately above was repeated on the title compound (13.0 g) except that heating under reflux was continued for 5 h. The filtrate this time was extracted with ether prior to being evaporated to give a brown oil. To a filtered solution of this oil in water (100 ml), dilute NH_4OH solution was added slowly. At p*H* 4.5, a solid (3.2 g) precipitated, m.p. 250–300° (dec.). An aqueous solution of this material turned blue when treated with ninhydrin reagent. A portion of the solid (1.5 g) was dissolved in concentrated HCl and evaporated. The product (1.1 g, m.p. 245–250°) when crystallized from ethanol–ether, gave 3-amino-6-hydroxy-7-methylhydrocoumarin hydrochloride monohydrate (**8**, 0.44 g), m.p. 255–257°; i.r. ν_{max} 1765 (C=O), 2450–2650 ($\overset{+}{N}$—H), 3120 br, 3300 (OH) cm^{-1}; n.m.r. (DMSO-d_6) δ 2.13 (s, 3H, CH_3), 3.27 (d, 2H, J = 10 Hz, CH_2), 4.57 (t, 1H, J = 10 Hz, CH), 6.85 (s, 1H) and 6.93 (s, 1H) (aromatic protons), 8.10–10.10 (m, br, ~4H, exchanges with D_2O, $\overset{+}{N}$—H and OH protons); mass spectrum *m/e* (% relative abundance) 193 (11) ($C_{10}H_{11}NO_3$), 165 (80) ($C_9H_{11}NO_2$), 148 (18) ($C_9H_{10}NO$), 138 (22) ($C_8H_{10}O_2$) (formula confirmed by accurate mass measurements).

Anal. Calcd. for $C_{10}H_{14}ClNO_4$: C, 48.49; H, 5.70; N, 5.66. Found: C, 48.81; H, 5.96; N, 5.44.

The authors wish to thank the Medical Research Council of Canada for operating grant MA-2993 (to R.T.C.) and a studentship (to J.L.M.), and Dr. D. F. Biggs for assistance in pharmacological evaluations.

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