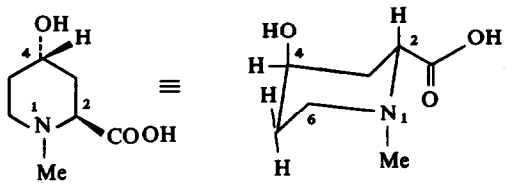
bours. The C-6 protons and four methylene protons appeared as multiplets at 3.2–3.6 (2H) and 1.9–2.4 (4H), respectively. A singlet at 3.0 (3H) was attributed to the =N—Me protons.

Ovalin formed a methyl ester with ethereal CH_2N_2 as a gummy mass, R_f 0.58 (PC *n*-BuOH–HCO_2H–H_2O, 15:3:2); IR (KBr) cm^{-1}: 3400 (OH) and 1730 (C=O of ester). ^1H NMR (60 MHz, solvent D_2O): δ 4.1–4.6 (2H, *m*), 3.55–3.85 (2H, *m*), 3.35 (3H, *s*), 3.3 (3H, *s*) and 2.0–2.5 (4H, *br m*). On acetylation with Ac_2O–$HClO_4$, ovalin formed a monoacetate as an oil; R_f 0.57 (PC *n*-BuOH–HCO_2H–H_2O; 15:3:2). IR (Nujol) cm^{-1}: 1750 and NMR (solvent D_2O); δ 4.2 (2H, *br m*), 3.5 (2H, *m*), 3.0 (3H, *s*, =N—Me), 2.3 (3H, *s*, —OAc) and 1.9–2.3 (4H, *m*). Formation of a monoacetate and methyl ester supported the presence of a hydroxyl and carboxyl group. Based on the above data, structure (1) is proposed for ovalin which is supported by MS fragmentations *m/e* 114 (99.5) ($M^+ - 45$), 96 (100) ($M^+ - 45 - 18$) and 70 (99.9%).

Ovalin showed a positive Cotton effect at 205 nm ($\Delta\varepsilon$ +0.00453) in the circular dichroism spectrum recorded in H_2O similar to (−)-*trans*-4-hydroxypipecolic acid which has a positive Cotton effect at 204 nm ($\Delta\varepsilon$ +0.0061) in H_2O [6]. The above data suggest that ovalin is (2*S*,4*R*)-4-hydroxy-*N*-methylpipecolic acid.



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N-METHYLTYRAMINE, A BIOLOGICALLY ACTIVE AMINE IN *ACACIA* SEEDS

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Key Word Index—*Acacia*; Leguminosae; chemotaxonomy; *N*-methyltyramine; migraine.

Abstract—The seeds of *Acacia* species belonging to the 'pennata' group characteristically contain *N*-methyltyramine (approximately 0.5% dry weight). Like tyramine, *N*-methyltyramine increases blood pressure in the anaesthetized rat, relaxes guinea pig ileum and increases both the force and rate of contraction of guinea-pig right atrium by inducing the release of noradrenaline.

INTRODUCTION

Seven *Acacia* species, *A. bonariensis* Gill. ex Hook & Arn., *A. brevispica* Harms., *A. caesia* W. & A., *A. kraussiana* Meisn. ex Benth., *A. schweinfurthii* Brenan & Exell, *A. pennata* (L.) Willd., *A. pentagona* (Schumach & Thonn.) Hook f., belonging to the 'pennata' group of Bentham's series Vulgares were reported recently to accumulate an unidentified ninhydrin-reacting compound in their seeds [1]. We have now isolated this compound from seeds of *A. schweinfurthii* Brenan & Exell, and identified it as *N*-methyltyramine (NMT).

This is, as far as we are aware, the first report of NMT in *Acacia* seeds but it is known to occur in leaves of *A. rigidula*, *A. roemeriana* and *A. berlandieri* [2, 3]. The leaves of *A. berlandieri* (Guajillo) also contain tyramine, and when eaten by sheep and goats in the Pecos region of Texas they cause a neurological disease known as 'guajillo wobbles' or 'limerleg' which affects the animal's gait [3].

While isolating NMT from *A. schweinfurthii*, one of us (C.S.E.) developed acute migraine-type headaches, which

recurred during the preparation of an authentic sample of NMT from *N*-methyltyrosine. This led us to suppose that NMT might have similar pharmacological properties to tyramine (a recognized cause of dietary migraine [4] in experimental animals and man). This possibility has been investigated.

RESULTS AND DISCUSSION

The basic ninhydrin-positive compound isolated from seeds of *A. schweinfurthii* proved to be indistinguishable from authentic *N*-methyltyramine on the basis of NMR, IR, and MS, ionic mobility and colour reactions. NMT provides a clear taxonomic 'marker' for species of the 'pennata' group as seeds of no other species of *Acacia* (130 analysed to date) accumulate this compound.

The pharmacological actions of NMT evaluated on rat blood pressure, isolated guinea pig trachealis muscle, atrium and ileum were identical with those of tyramine. Tyramine and NMT were equipotent in all tissues. These findings are consistent with those of Camp [5] who described a pressor response to NMT in the goat which was inhibited by reserpine pretreatment. Camp also showed that NMT decreased the noradrenaline content of the rat heart, a known action of tyramine.

EXPERIMENTAL

Isolation of N-*methyltyramine.* Finely ground seed (500 g) of *Acacia schweinfurthii* Brenan and Exell was stirred with 75% EtOH (4 l.) in which was suspended a 'sausage' of cation exchange resin 'Amberlite IR-120 in the H^+ form) contained in 5 cm dia Visking tubing sealed at the ends. After 48 hr the 'sausage' was removed and absorbed amino acids and amines displaced from the resin by washing successively with Py (1 N) and NH_4OH (2 N). The 'unknown' was displaced by NH_4OH and after evaporating the ammoniacal soln to dryness under red. pres. the residue was redissolved in H_2O and applied to a column (65 × 2 cm) of Amberlite IR-120 in the NH_4^+ form. The column was washed with H_2O and the 'unknown' displaced by itself with 0.2 N NH_4OH. The fractions containing the unknown were concd to a syrup under red. pres. and on cooling crystals separated (220 mg). (Found: C, 71.28; H, 8.57; N, 9.21. $C_9H_{13}NO$ requires: C, 72.08; H, 8.67; N, 9.26%.) The MS showed abundant ions at *m/e* 151 and 107 (molar ion $-CH_2 \cdot NHCH_3$). The NMR spectrum showed a quartet at δ 7.05 consistent with a *para*-substituted aromatic nucleus, a singlet at δ 2.69 consistent with the presence of a methyl group, a triplet at δ 2.93 expected of a methylene group adjacent to the nitrogen and a triplet at δ 3.27 corresponding to a methylene group adjacent to the aromatic nucleus. The integrals of the singlet, triplet, triplet and quartet were in the ratio of 3:2:2:4. The 'unknown' moved with authentic NMT when subjected to HVE on paper at pH 1.9 and 3.6. The NMR, IR and MS of the isolated compound and synthetic NMT were identical. Authentic NMT and the isolate gave identical colour reactions with ninhydrin (grey-green) and Pauli's reagent (red).

Synthesis of N-*methyltyramine.* L-*N*-Methyltyrosine (isolated from seeds of *Combretum zeyheri* [6]) was dry-distilled at 250° [7] and the product (NMT) recrystallized from H_2O.

Pharmacological actions of N-*methyltyramine.* In common with noradrenaline and tyramine, NMT increased both systolic and diastolic blood pressures of the pentobarbitone-anaesthetized rat, relaxed acetylcholine-induced tone of the guinea pig isolated trachealis muscle, and increased the rate and force of contraction of the spontaneously beating guinea pig isolated right atrium. NMT also inhibited electrically evoked contractions of the guinea pig ileum. Tyramine and NMT were equipotent on all tissues.

Inhibitors of noradrenaline uptake by sympathetic neurones, e.g. desmethylimipramine, are known to prevent the access of tyramine to its neuronal site of action and therefore prevent tyramine from releasing noradrenaline from vesicles. On the guinea pig isolated atria, desipramine (10^{-6} g/ml) inhibited the actions of both tyramine and NMT on both rate and force of contraction to an identical extent, but caused a slight potentiation of the responses to noradrenaline.

Adrenergic neurone blockers, e.g. guanethidine, prevent tyramine's action by inhibiting the release of noradrenaline from sympathetic neurones. Guanethidine (1 mg/kg) displaced the log dose–response curves elicited with tyramine and NMT on the rat blood pressure to the right in a parallel manner. The dose–response curve to noradrenaline was displaced to the left indicating potentiation.

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