A note on the chloroform-soluble alkaloids of *Fagara macrophylla*

A preliminary chromatographic screening of the stem and root barks of *Fagara macrophylla* (Oliv.) Engl. indicated the presence of at least six chloroform-soluble bases of which skimmianine, angoline, and angolinine were named and fagaramide was tentatively proposed (Calderwood & Fish, 1966). Further work has resulted in the isolation and characterization of fagaramide and skimmianine together with chelerythrine, nitidine, and trace amounts of a weakly basic acridone alkaloid which on silica gel (tlc, 3 solvent systems) corresponds to 1-hydroxy-2,3-dimethoxy-10-methyl-acridan-9-one. The latter compound has been found in *Fagara leprieurii* Engl. (Fonzes & Winternitz, 1968a).

The previously reported angoline is now known (Fonzes & Winternitz, 1968b) to be 9-methoxychelerythrine and occurs as an artifact following extraction. Our isolation of chelerythrine from *F. macrophylla* confirms the report of this alkaloid by Torto Sefcovic & others (1969). Likewise our report of nitidine confirms that of Torto & Mensah (1970) from the root bark but we have also proved the presence, in smaller concentrations, of the above-named bases (except the acridone alkaloid) in the stem bark. From tlc characteristics and ultraviolet spectrum, nitidine appears to be identical with the previously reported angolinine and from our present work it seems that it is the predominant alkaloid in this species giving yields of about 0·025 % from root bark and only 0·002 % from stem bark.

Fagaramide ($C_{14}H_{17}O_3N$), white crystals m.p. 119–120° (softening at 104°) (EtOH) (m.p., tlc, i.r.), u.v. $\lambda_{max.}^{EtOH}$ 219, 236, 282, 290, 323 nm (log ϵ 3·23, 3·18, 3·14, 3·15, 3·19): fagaramide hydrochloride m.p. 136° (EtOH).

Skimmianine ($C_{14}H_{13}O_4N$), white crystals m.p. 175–6° ($CHCl_3$–light petroleum 40–60°) (m.p., tlc, i.r.), u.v. $\lambda_{max.}^{EtOH}$ 249, 320, 332 nm (log ϵ 4·90, 3·90, 3·90).

Chelerythrine isolated as the chloride ($C_{21}H_{18}O_4N^+Cl^-$), yellow needles m.p. 198–9° ($EtOH/Et_2O$) (m.p., tlc, i.r.), u.v. $\lambda_{max.}^{EtOH}$ 227, 273, 281(sh), 320, 343 nm (log ϵ 4·26, 4·53, 4·46, 4·34, 4·16): Chelerythrine nitrate m.p. 235–7° (EtOH/2N HNO_3).

Nitidine isolated as the chloride and purified as the nitrate ($C_{21}H_{18}O_4N^+NO_3^-$) green prisms m.p. 275–7° (EtOH–2N HNO_3) (m.p., tlc, i.r.), u.v. $\lambda_{max.}^{EtOH}$ 231, 273, 281, 304(sh), 329 nm (log ϵ 4·37, 4·50, 4·49, 4·39, 4·36).

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Division of Pharmacognosy & Forensic Science,
Department of Pharmaceutical Chemistry,
University of Strathclyde,
*Glasgow, C.*1, *U.K.*

F. FISH
P. G. WATERMAN

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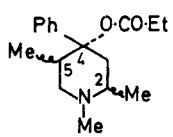
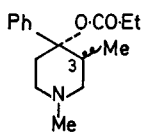
Analgesic potency and stereochemistry of trimeperidine and its isomers and analogues

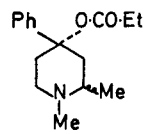
Reports on the analgesic trimeperidine (γ-promedol) and its isomers that have appeared since 1956 (Prostakov & Mikheeva, 1962) have failed to provide either pharmacological detail or firm evidence of stereochemistry. A generous gift of the precursor 4-piperidone by Dr. N. S. Prostakov has enabled us to investigate these compounds and to apply modern physical techniques to solving their stereochemistry that were not available when the work was originally done. We isolated three 1,2,5-trimethyl-4-propionyloxy-4-phenylpiperidines (I) which corresponded



I



II



III

with the isomeric γ-, β- and α-forms of the Russian workers. The compounds were assayed for their analgesic properties in mice by the hot-plate test along with analogues lacking 2-methyl (α- and β-prodine, II) or 5-methyl substituents (III). We thank Dr. E. L. May of the National Institutes of Health for these data. Hot-plate ED50 values and stereochemical findings, given in Table 1, enable the following points to be made:

(1) The high activities of the promedol isomers and the fact that replacement of *N*-methyl by *N*-phenethyl in γ-promedol has a potency enhancing effect (Portoghese, 1965), provide good evidence of these esters having a morphine-like action at the analgesic receptor.

(2) The fact that the most active promedol isomer (β-) is equipotent with β-prodine (β-II) further demonstrates the superiority of *cis* 3-Me/4-Ph geometry over the *trans* arrangement in 4-phenylpiperidine analgesics (Casy, 1968; Casy, Chatten & Khullar, 1969).

Table 1. *Stereochemical findings and hot-plate ED50 values*

Compound	Configuration*	Hot-plate ED50 in mice mg/kg, subcutaneous inj.
γ-I	*cis* 2Me/4Ph, *trans* 5Me/4Ph	1·6
γ-I†		0·91
β-I	*cis* 2Me/4Ph/5Me	0·18
α-I	*trans* 2Me/4Ph, *cis* 5Me/4Ph	0·58
α-II	*trans* 3Me/4Ph	0·92
β-II	*cis* 3Me/4Ph	0·18
α-III	*trans* 2Me/4Ph	1·32
β-III	*cis* 2Me/4Ph	1·37
Pethidine	—	4·7

* The preferred conformation of γ-I is a chair with 4-phenyl equatorial; there is evidence that significant skew-boat populations (with 4-phenyl pseudo-equatorial) arise in the case of β- and α-I.
† *N*-Methyl replaced by *N*-phenethyl.