657. *The Local Anæsthetic in* Fagara xanthoxyloides.

By K. BOWDEN and W. J. ROSS.

The substance in *Fagara xanthoxyloides* which produces formication and local anæsthesia of the mucous membranes has been shown to be *N*-isobutyldeca-*trans*-2,*trans*-4-dienamide (I).

IN 1947 Paris and Moyse-Mignon [1] reported the presence in root-bark of *Fagara xanthoxyloides* (*Zanthoxylum Senegalense* D.C.) of a substance which, when applied to the tongue, caused intense formication followed by local anæsthesia. The authors, however, were unable to obtain the substance pure or report on its constitution.

We found that light-petroleum extracts of the root-bark, on distillation in a high vacuum, gave a series of fractions, b. p. 135—150°/10^{-2} mm. (~0·55% based on root-bark), from which the active principle was obtained as shiny needles (~0·17% calculated on root-bark). Analysis and molecular weight determination indicated the molecular formula $C_{14}H_{25}NO$. The infrared spectrum had absorption bands at 3304 and 3083 cm.$^{-1}$, suggesting a secondary amide group; this agreed with the found figure of nearly one active hydrogen per molecule. The ultraviolet absorption, ($\lambda_{max.}$ 259 mμ, ε 32,860) indicated a conjugated system, possibly related to sorbamide ($\lambda_{max.}$ 257 mμ, ε 27,200).[2]

Hydrogenation in the presence of Adams catalyst showed the presence of two double bonds. The formation of an adduct with maleic anhydride indicated their conjugated nature in a *trans,trans*-configuration, a view supported by the intensity of absorption in the ultraviolet. We were unable, however, to prepare an adduct with tetracyanoethylene.[3] Acid or alkaline hydrolysis of the hydrogenated material gave decanoic acid and isobutylamine. Furthermore, the hydrogenation product was identical with *N*-isobutyldecanamide.

The structure of the di-unsaturated acyl group was indicated by the formation of hexanoic acid and oxalic acid on oxidation with permanganate.[4] The remaining part of the molecule was revealed by the isolation of *N*-isobutyloxamic acid from the oxidation mixture. The structure of the active principle is therefore (I).

$CH_3{\cdot}[CH_2]_4{\cdot}[CH{:}CH]_2{\cdot}CO{\cdot}NH{\cdot}CH_2{\cdot}CHMe_2$ (I)

During investigations on the active principles of *Anacyclus pyrethrum* D.C., Crombie [5] synthesised a compound of structure (I), with m. p. 90° and $\lambda_{max.}$ 251, 258, 264 mμ (ε 26,800, 29,700, and 26,800). In a later paper [6] he quoted the infrared spectrum of the substance and it is essentially the same as that of the compound we have isolated from *Fagara xanthoxyloides*.

---

[1] Paris and Moyse-Mignon, *Ann. pharm. franç.*, 1947, **5**, 410.
[2] Eisner, Elvidge, and Linstead, *J.*, 1953, 1372.
[3] Ozolins and Schenk, *Analyt. Chem.*, 1961, **33**, 1035.
[4] Jacobson, *J. Amer. Chem. Soc.*, 1953, **75**, 2584.
[5] Crombie, *Chem. and Ind.*, 1952, 1034.
[6] Crombie, *J.*, 1955, 1007.

EXPERIMENTAL

All melting points are uncorrected. Infrared spectra were recorded for Nujol mulls, using a Unicam S.P. 100 spectrophotometer with an S.P. 130 grating attachment. Ultraviolet spectra were recorded in 95% ethanol with a Unicam S.P. 500 instrument.

Examination of Fagara xanthoxyloides *root-bark.*—Ground root-bark (900 g.) was continuously extracted with light petroleum (b. p. 40—60°) in a Soxhlet apparatus for 48 hr. The extract was reduced in volume to 100 ml. and set aside at 0° overnight; a small amount of insoluble material which had separated was filtered off and discarded. The filtrate was evaporated to dryness and a dark brown oil remained. This was distilled at 10^{-2} mm. to give fraction 1, b. p. 136° (0·54 g.), which did not solidify or crystallise from petroleum (b. p. 40—60°) at 0°. Fraction 2, b. p. 138—144° (3·45 g.), and fraction 3, b. p. 146—154° (1·62 g.), solidified to pale yellow waxy masses, and, after several recrystallisations from light petroleum (b. p. 40—60°) at 0°, afforded the *active principle* (1·4 g.) as shiny needles, m. p. 90—90·5°, $\lambda_{\max.}$ 259 mμ (ε 32,860), $\nu_{\max.}$ 3304s, 3083m, 1659s, 1630s, 1620s, 1552s cm.$^{-1}$ (Found: C, 75·0; H, 11·2; N, 6·5; O, 7·3; active hydrogen, 0·42%; *M* (Rast), 204. $C_{14}H_{25}NO$ requires C, 75·3; H, 11·3; N, 6·3; O, 7·2; active hydrogen, 0·45%. *M*, 223).

Hydrogenation of the Active Principle.—The above material (0·51 g.) in ethanol (15 ml.) containing Adams catalyst (from 0·06 g. of platinum oxide) was shaken in hydrogen until absorption ceased (111 ml. absorbed. Calc. for two double bonds: 110·4 ml. at 22°/762·5 mm.). The catalyst was filtered off and the filtrate evaporated to dryness *in vacuo* to give the product as a pale yellow oil which rapidly solidified, b. p. 140°/0·3 mm., m. p. 34—36° undepressed by an authentic specimen of *N*-isobutyldecanamide, m. p. 37—38°, $\nu_{\max.}$ 3302s, 3090m, 1649s, 1560s cm.$^{-1}$ (Found: C, 74·1; H, 13·0; N, 6·2. Calc. for $C_{14}H_{29}NO$: C, 73·95; H, 12·9; N, 6·2%).

Hydrolysis of Hydrogenation Product.—(*a*) The above product (0·5 g.) in aqueous methanol (10 ml., 1 : 1) containing potassium hydroxide (1 g.) was heated under reflux for 26 hr. The mixture was diluted with water (10 ml.) and extracted with ether (3 × 20 ml.) (Soln. *A*). The aqueous solution was acidified with dilute hydrochloric acid and the product isolated in ether (3 × 15 ml.) and dried ($MgSO_4$). Removal of the solvent gave an oil which solidified to a waxy solid (0·068 g.), m. p. 28—31°, undepressed on admixture with authentic decanoic acid, m. p. 31°, and gave an *S*-benzylthiouronium salt, m. p. 145—147°, $\nu_{\max.}$ 3150s, 3040s, 1690m, 1568s, 1530s cm.$^{-1}$ (Found: C, 64·1; H, 8·9; N, 8·4. Calc. for $C_{18}H_{30}N_2O_2S$: C, 63·9; H, 8·9; N, 8·3%). The *S*-benzylthiouronium salt of decanoic acid had m. p. and mixed m. p. with the above sample, 145—147° (Found: C, 64·0; H, 9·1; N, 8·5%). Soln. *A* was extracted with dilute hydrochloric acid and the aqueous phase evaporated to dryness to yield, after two recrystallisations from ethyl acetate–methanol, isobutylamine hydrochloride (0·03 g.), m. p. and mixed m. p., 173—175°. The ethereal solution was washed with water (2 × 10 ml.), dried ($MgSO_4$), and the solvent removed to yield the starting material (0·3 g.) as crystals, m. p. and mixed m. p. 34—36°.

(*b*) The hydrogenated material (0·15 g.), ethanol (1 ml.), and concentrated hydrochloric acid (1 ml.) were heated together at 100° in a sealed tube for 2 days. The mixture was diluted with water (10 ml.) and extracted with ether (3 × 10 ml.). Evaporation of the aqueous phase and two recrystallisations of the residue from ethyl acetate–methanol gave isobutylamine hydrochloride, m. p. and mixed m. p. 173—175°. The ethereal extract was dried ($MgSO_4$) and evaporated to dryness to yield a pale yellow oil which slowly solidified and gave an *S*-benzylthiouronium salt, m. p. 145—147°, undepressed on admixture with authentic *S*-benzylthiouronium decanoate. Rapid heating of the *S*-benzylthiouronium salts resulted in a higher melting-point (153°) being obtained. This is commented upon by Crombie.[7]

Maleic Anhydride Adduct of the Active Principle.—The active principle (0·108 g.) in benzene (1 ml.) containing maleic anhydride (0·06 g.) was heated at 100° in a sealed tube for 24 hr. On cooling to room temperature a crystalline mass of the adduct separated; it recrystallised from benzene as shiny needles, m. p. 198° (rapid heating); $\nu_{\max.}$ 3100w, 3044w, 1765m, 1730s, 1716s, 1680s cm.$^{-1}$ (Found: C, 67·6; H, 8·6; N, 4·5. Calc. for $C_{18}H_{27}NO_4$: C, 67·25; H, 8·45; N, 4·35%). Crombie[6] records m. p. 193° (variable) for the maleic anhydride adduct of *N*-isobutyldeca-*trans*-2,*trans*-4-dienamide.

Oxidation of the Active Principle.—The active principle (1·0 g.), suspended in water (100 ml.)

---

[7] Crombie, *J.*, 1955, 999.

at 75°, was mechanically stirred whilst finely powdered potassium permanganate (3·8 g.) was added during 3 hr., after which heating and stirring was continued for a further 30 min. The manganese dioxide was filtered off and washed with boiling water (2 × 15 ml.). The combined filtrates were reduced in volume to 20 ml., acidified with dilute sulphuric acid, and steam-distilled. The distillate (100 ml.) was extracted with ether (4 × 25 ml.), the ethereal solution dried ($MgSO_4$), and the solvent removed to yield an oil (0·34 g.) which gave an anilide, prepared *via* the acid chloride, m. p. 94—95°, undepressed on admixture with an authentic specimen of n-hexanilide, m. p. 94—95° (Found: C, 75·6; H, 8·8; N, 7·4. Calc. for $C_{12}H_{17}NO$: C, 75·35; H, 9·0; N, 7·3%). The steam-volatile acid also gave a *p*-bromophenacyl ester, m. p. 73°, undepressed by an authentic specimen of *p*-bromophenacyl hexanoate.

The solution of non-steam volatile products (50 ml.) was continuously extracted with ether for 2 days. The ether was evaporated, leaving a gum which was extracted with boiling light petroleum (4 × 25 ml., b. p. 60—80°). Evaporation of the extract and recrystallisation from the same solvent gave *N*-isobutyloxamic acid (0·3 g.), m. p. and mixed m. p. 105—107°; $\nu_{max.}$ 3302s, 3108mw, 1766s, 1684s cm.$^{-1}$ (Found: C, 49·8; H, 7·9; N, 9·4. Calc. for $C_6H_{11}NO_3$: C, 49·6; H, 7·6; N, 9·65%). The residue which remained was sublimed at 0·5 mm., yielding anhydrous oxalic acid (0·120 g.), m. p. and mixed m. p. 181—183°.

The authors wish to record with thanks the technical assistance of Miss A. L. Gayler, and are indebted to Dr. J. K. Morton, University College, Legon, Ghana, for a specimen of *Fagara xanthoxyloides*. We thank Dr. W. A. Bain for permission to publish the work.

SMITH KLINE AND FRENCH RESEARCH INSTITUTE,
WELWYN GARDEN CITY, HERTFORDSHIRE.

[*Received, January* 15*th*, 1963.]