

*Amides of Vegetable Origin. Part VI.\* Synthesis of Capsaicin.*

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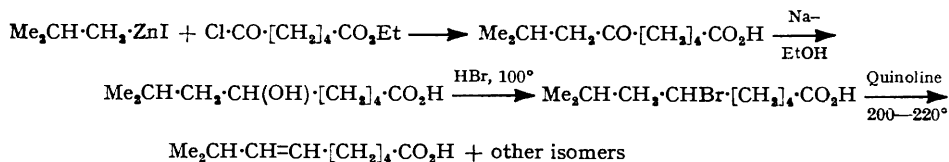
An unambiguous synthesis of capsaicin, *N*-(4-hydroxy-3-methoxybenzyl)-8-methylnon-*trans*-6-enamide, the active principle of red pepper, is described.

VARIOUS species of the genus *Capsicum* (for recent taxonomic information see Heiser and Smith, *Economic Botany*, 1953, **7**, 214) contain in their fruits (red peppers) an intensely sharp and pungent substance, capsaicin, which was first isolated by Thresh (*Pharm. J. and Trans.*, 1876—7, [iii], **7**, 21, 259, 473; 1877—8, **8**, 187). Miko (*Z. Nahr. Genussm.*, 1898, **1**, 818; 1899, **2**, 411) obtained it pure and crystalline (m. p. 63.5°) and recognised a phenolic hydroxyl and a methoxyl grouping. Its formulation as *N*-(4-hydroxy-3-methoxybenzyl)-8-methylnon-6-enamide is due to Nelson (*J. Amer. Chem. Soc.*, 1919, **41**, 1115, 1472; 1920, **42**, 597; 1923, **45**, 2179; contrast Lapworth and Royle *J.*, 1919, 1109). Its synthesis was claimed by Späth and Darling (*Ber.*, 1930, **63**, 737), the essential steps in the preparation of the intermediate 8-methylnon-6-enoic acid being as shown. As would be expected from this type of synthesis, a mixture of acids (presumably containing structural and geometrical isomers) was obtained from the quinoline dehydrohalogenation. The mixture could not be resolved by distillation or crystallisation but by a tedious

\* Part V, preceding paper.

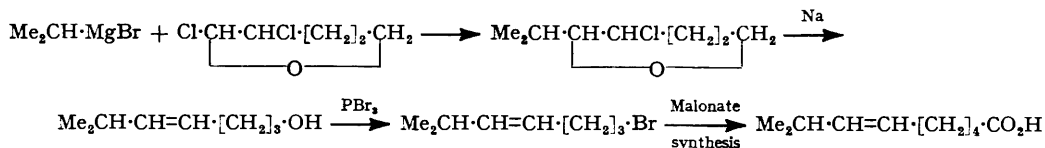
purification through the *N*-(3:4-dimethoxybenzyl)amide the acid was obtained sufficiently pure to establish identity of its *N*-(4-hydroxy-3-methoxybenzyl)amide with capsaicin.

The aims of the present work were, first, diagnosis of the configuration of capsaicin and then synthesis by an unambiguous stereospecific method. Capsaicin was isolated from capsicin oleoresin by a method similar to that of Lapworth and Royle (*loc. cit.*),



though final purification was effected by chromatography. Its infra-red spectrum showed a medium-strong band at  $968.5\text{ cm}^{-1}$ , indicative of a *trans*-double bond in a molecule of this type (cf. Part V), and a synthetical method was chosen for this isomer.

2:3-Dichlorotetrahydropyran was treated with *isopropylmagnesium bromide*. The 3-chlorotetrahydro-2-*isopropylpyran* thus produced reacted with powdered sodium giving,



after fractionation from a contaminant of low b. p., 6-methylhept-*trans*-4-en-1-ol, the configuration being based on previous experience of this reaction (Crombie and Harper, *J.*, 1950, 1707; Crombie, *J.*, 1952, 2997) and on the infra-red spectrum; the alcohol has not shown any indications of heterogeneity. On ozonolysis it gave *isobutyraldehyde*.

Conversion of 6-methylhept-*trans*-4-en-1-ol into its bromide, followed by a malonate reaction, completed the synthesis of 8-methylnon-*trans*-6-enoic acid, the carbon skeleton of which was proved by hydrogenation to the known 8-methylnonanoic acid. 8-Methylnon-*trans*-6-enoic acid was converted into its acid chloride and thence into the desired amide, which was identical with natural capsaicin. It had the characteristic intensely sharp taste, detectable in extreme dilution, and gave a positive test with vanadium oxychloride in carbon tetrachloride (Fodor, *Kiserlet Kozlemenyek*, 1930, 33, 155; cf. *Chem. Abs.*, 1931, 25, 2780). Dihydrocapsaicin was also prepared from the 8-methyl nonanoic acid described above.

#### EXPERIMENTAL

Analyses were carried out in the microanalytical laboratories of Imperial College (Mr. F. H. Oliver). Ultra-violet light absorptions were measured in ethanol with a Hilger medium quartz instrument (Mrs. I. Boston).

*Natural Capsaicin*.—This was isolated from capsicin oleoresin by a modification of Lapworth and Royle's procedure (*loc. cit.*): after chromatography on alumina and recrystallisation, it formed leaflets, m. p.  $64^\circ$ , from 9:1 light petroleum (b. p.  $40-60^\circ$ )—ether. Light absorption: max. at  $227, 281\text{ m}\mu$  ( $\epsilon$  7000, 2500). The infra-red spectrum (paraffin mull) showed bands (*inter alia*) at 3320 (NH broadened as it overlies the OH), 3090, 1650 (C=C), 1629 (amide A, C=O), 1598 ( $\text{Ph}_I$ ), 1553 (amide B), 1511 ( $\text{Ph}_{II}$ ), 1454, 1429, 1372, 1349, 1282, 1241, 1201, 1172, 1155, 1121, 1032, 968.5, 937.5, 843, 809, 718  $\text{cm}^{-1}$ . Assignments are tentative.

6-Methylhept-*trans*-4-en-1-ol.—*iso*Propylmagnesium bromide was prepared from magnesium (96 g.) and *isopropyl bromide* (480 g.) in ether (1 l.). The reagent was cooled in ice-water, and 2:3-dichlorotetrahydropyran solution [prepared by addition, during 12 hr., of the theoretical amount of chlorine to dihydropyran (252 g.) in ether (600 ml.) at  $0-7^\circ$ ] was slowly added with stirring. Towards the end of the addition, solid may separate and stirring become difficult. Excess of Grignard reagent was destroyed with ammonium chloride solution, and as much of the ether layer as possible decanted. The residue was decomposed with dilute hydrochloric acid (this caused some formation of tar). This solution was extracted with ether, and the united ethereal extracts were washed with sodium hydrogen carbonate solution

and dried ( $K_2CO_3$ ). Evaporation and distillation yielded crude 3-chlorotetrahydro-2-isopropylpyran (mixture of stereoisomers) which was collected between 65° and 110°/12 mm. ( $n_D^{21}$  1.4592). In 4 experiments the yields were 31, 33, 36, and 38%.

The crude product (165 g.) was added slowly to powdered sodium (65 g.) covered by anhydrous ether (cf. Crombie and Harper, *J.*, *loc. cit.*). The product was treated with methanol and then water, and the ether layer separated. The aqueous phase was extracted with ether, and the united extracts were evaporated and distilled. A small fore-run was rejected and the main product (86.5 g.) had b. p. 53—58°/12 mm.,  $n_D^{20}$  1.4429. This was united with a batch of similar material (56.6 g.) obtained from 3-chlorotetrahydro-2-isopropylpyran (148 g.) and fractionated through a gauze-packed Stedman column (3 ft.). After elimination of low-boiling material (48.6 g.; b. p. 37—38°/14 mm.,  $n_D^{23}$  1.4354) (Found: C, 73.9, 74.3; H, 12.1, 12.3%), 6-methylhept-trans-4-en-1-ol (63.2 g.), b. p. 87°/14 mm.,  $n_D^{21}$  1.4430 (Found: C, 74.65; H, 12.55.  $C_8H_{16}O$  requires C, 75.0; H, 12.6%), was obtained. Ozonolysis of the latter yielded isobutyraldehyde, isolated as the 2:4-dinitrophenylhydrazone, m. p. and mixed m. p. 181°. The *p*-diphenylurethane, crystallised from light petroleum (b. p. 40—60°), had m. p. 99° (Found: C, 77.3; H, 7.75.  $C_{21}H_{25}O_2N$  requires C, 78.0; H, 7.8%).

**6-Methylhept-trans-4-enyl Bromide.**—Phosphorus tribromide (12.0 g.) was added slowly to the *trans*-alcohol (16.0 g.) and pyridine (3.5 ml.), with stirring at 0° which was maintained for 30 min., and the crude bromide was distilled directly. It was dissolved in light petroleum (b. p. 40—60°), washed with dilute sodium hydroxide solution and then water, dried, and redistilled (12.3 g.). It had b. p. 68—73°/13 mm.,  $n_D^{25}$  1.4690 (Found: C, 49.9; H, 8.1; Br, 40.7.  $C_8H_{15}Br$  requires C, 50.45; H, 7.9; Br, 41.5%).

**8-Methylnon-trans-6-enoic Acid.**—A solution of ethyl sodiomalonate was prepared from sodium (2.7 g.), ethanol (80 ml.), and ethyl malonate (19.0 g.). 6-Methylhept-trans-4-enyl bromide (23 g.) was added dropwise with stirring and the mixture refluxed for 2 hr.; as much alcohol as possible was then removed on a steam-bath. The residual crude alkenylmalonic ester was refluxed with aqueous potassium hydroxide for 3 hr., then cooled and acidified (Congo-red). Extraction with ether gave the alkenylmalonic acid which was decarboxylated at 160—180° (2 hr.). The resulting acid was dissolved in dilute aqueous sodium hydroxide, and the solution extracted with ether. After acidification of the aqueous phase the pure acid was collected with ether, dried ( $Na_2SO_4$ ), and distilled. 8-Methylnon-trans-6-enoic acid (10.7 g., 52%), b. p. 130—132°/12 mm.,  $n_D^{25}$  1.4460, was obtained (Found: C, 70.25; H, 10.55.  $C_{10}H_{18}O_2$  requires C, 70.55; H, 10.65%). The *p*-bromophenacyl ester crystallised from ethanol in needles, m. p. 64° (Found: C, 58.85; H, 6.5.  $C_{18}H_{23}O_3Br$  requires C, 58.85; H, 6.3%).

**8-Methylnonanoic Acid.**—The above acid (800 mg.) was hydrogenated in dioxan, with Adams platinum catalyst, until absorption of gas ceased (110 ml. of  $H_2$  at 20°/750 mm.: Calc., 114 ml.). The catalyst was removed, the solvent evaporated, and the acid distilled (b. p. 100—102°/3 mm.,  $n_D^{24}$  1.4352) (Found: C, 69.35; H, 11.7. Calc. for  $C_{10}H_{20}O_2$ : C, 69.7; H, 11.7%). Its amide had m. p. 103—104°. Levene and Allen (*J. Biol. Chem.*, 1916, 27, 462) give m. p. 103°.

**N-(4-Hydroxy-3-methoxybenzyl)-8-methylnon-trans-6-enamide.**—4-Hydroxy-3-methoxybenzylamine hydrochloride, prepared by Nelson's method (*J. Amer. Chem. Soc.*, 1919, 41, 1115) in 51% yield, had m. p. 214° (from ethanol). The free base was dried at 100° before use and had m. p. 132°.

8-Methylnon-trans-6-enoic acid (1.04 g.) was treated with thionyl chloride (1.3 mol.) and set aside for 18 hr. at 20°. It was then heated at 100° for 30 min. and excess of reagent removed under reduced pressure. The residual acid chloride, in ether (10 ml.), was added to the freshly prepared amine (1.8 g.; finely divided) suspended in ether (50 ml.). This mixture was shaken for 3 days and then poured into water and extracted. The extracts were dried and evaporated to yield the crude amide (1.49 g.) which crystallised from light petroleum (b. p. 40—60°)—ether in colourless leaflets, m. p. 65°, undepressed on admixture with natural capsaicin (Found: N, 4.45.  $C_{18}H_{27}O_3N$  requires N, 4.6%). Crystallisation is made difficult by a tendency to form oils. Light absorption: max. at 227, 280  $m\mu$  ( $\epsilon$  8200, 2700). The infra-red spectrum (700—1300  $cm^{-1}$ ) was identical with that of natural capsaicin reported above.

The *N*-(4-hydroxy-3-methoxybenzyl)amide of 8-methylnonanoic acid (0.45 g.) was prepared similarly from the acid (0.37 g.) and amine (0.33 g.). It had m. p. 64—65°. Nelson (*J. Amer. Chem. Soc.*, 1923, 45, 2179) gives m. p. 65° for the product of hydrogenation of natural capsaicin.