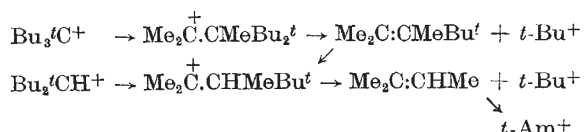In the reactions of di- and tri-*tert.*-butylcarbinols with hydrogen halides (the solvolysis of related alkyl halides is being examined similarly) fission of the carbon framework occurs, so that, in addition to the normal and Wagner re-arranged halides, lower halides, notably *tert.*-butyl and *tert.*-amyl halides, are produced. Such fission is particularly facile with the tri-*tert.*-butyl compound. These are essentially unimolecular eliminations (E1), in which the ion t-Bu$^+$ separates from where a proton usually does[5], such separation probably attaining observed rates partly on account of steric factors[2d]. The stages between initial heterolysis and final chloride-ion uptake may be written thus :

$$\text{Bu}_3{}^t\text{C}^+ \rightarrow \text{Me}_2\overset{+}{\text{C}}.\text{CMeBu}_2{}^t \rightarrow \text{Me}_2\text{C:CMeBu}^t + t\text{-Bu}^+$$

$$\text{Bu}_2{}^t\text{CH}^+ \rightarrow \text{Me}_2\overset{+}{\text{C}}.\text{CHMeBu}^t \rightarrow \text{Me}_2\text{C:CHMe} + t\text{-Bu}^+$$
$$\searrow$$
$$t\text{-Am}^+$$

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[1] Dostrovsky, Hughes and Ingold, *J. Chem. Soc.*, 173 (1946).

[2] (a) Hughes, *J. Chem. Soc.*, 255 (1935). Cooper, Hughes, Ingold and MacNulty, *ibid.*, 1183, 1280, 1283 (1937). (b) Hughes, Ingold, Martin and Meigh, *Nature*, **166**, 679 (1950), and unpublished results. (c) Shorter and Hinshelwood, *J. Chem. Soc.*, 2412 (1949). (d) Brown and Fletcher, *J. Amer. Chem. Soc.*, **71**, 1845 (1949).

[3] (a) Results of present authors. (b) Prof. P. D. Bartlett and co-workers reported similarly large factors at an International Colloquium in Montpellier, France (April 1950), where our results and conclusions were also communicated.

[4] Dostrovsky and Hughes, *J. Chem. Soc.*, 171 (1946).

[5] Hughes and Ingold, *J. Chem. Soc.*, 2038 *et seq.* (1948). cf. Whitmore and Stahly *J. Amer. Chem. Soc.*, **55**, 4153 (1933).

Synergistic Effect of a Third Active Glycoside of Senna

STOLL *et al.*[1,2] have isolated from senna (leaf and fruit of *Cassia acutifolia* Delile and *C. angustifolia* Vahl.) the active glycosides, sennosides *A* and *B*, which, they state, represent about 90 per cent of the total glycosidal content. No evidence is given, however, that the entire activity of the crude drug is due to these glycosides.

As part of a general investigation on this group of anthraquinone drugs, we have compared the biological activities of the pure sennosides with that of samples of the leaf and fruit, and in no instance does the activity of these glycosides account for the total activity of the crude drug. Furthermore, samples of leaf containing much less sennosides than samples of fruit had similar biological activities. We have investigated the likely theories which would explain these discrepancies and have found that there is a third glycoside (or glycosides ?) present in small amounts which is as active as the sennosides and, more important, exerts a marked synergistic effect when present in a proportion of about 15 per cent of the total glycosidal content. Proportions of about 5 per cent exerted practically no synergistic action.

In the samples of leaf referred to above, this third glycoside represented about 12–15 per cent of the total glycosides, whereas in the samples of fruit it represented only 2–4 per cent. These facts would therefore explain why a sample of leaf is as active as

a sample of pod even though it contained much less sennosides, and also may go a long way to accounting for the total activity of the crude drug.

Further details will be published elsewhere.

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[2] Stoll, A., Kussmaul, W., and Becker, B., *Helv. Chim. Acta*, 32, 1892 (1949).

Tissue Metabolism and Peripheral Circulation

THE regulation of blood flow in the peripheral tissues is still an unsolved problem in the physiology of the circulation. The cause of reactive hyperæmia following the release of a previously clamped artery has been attributed to an accumulation of specific vasodilator substances (as acetylcholine, histamine, etc.), or to metabolites with vasodilator effects (especially lactate and pH changes). Rein[1] regards the co-operation of both factors as the clue to a proper blood supply.

In our experiments, the carbohydrate metabolism of muscles was inhibited at various levels. The metabolic rate of the poisoned area, the response of its vessels to some vasodilator substances, adrenaline, and the development of reactive hyperæmia were investigated. Experiments were performed *in vivo* on anæsthetized dogs. The blood-flow of the area (comprising 95 per cent muscle) was measured, the blood of which was channelled through the vena profunda femoris[2]. Arterio-venous oxygen difference was measured colorimetrically[3]; lactate was determined by the method of Elgart and Harris[4].

The infusion of 1–2 per cent iodoacetic acid into the arteria profunda femoris (0·8 c.c./min. for 20 min.) caused a marked increase of blood flow and lactate production, accompanied by a smaller increase of oxygen uptake. Later, all three values decreased, and, 3–4 hr. after the infusion, lactate production was below its starting level and a gradually ensuing contracture of the vessels set in.

The Pasteur reaction due to the intra-arterial infusion of potassium cyanide (0·8 mgm./min.), which is normally accompanied by a very marked vasodilatation, is abolished after 1–2 hr. following iodoacetate infusion. At this stage of the experiment both potassium cyanide and acetylcholine cause vasoconstriction, instead of vasodilatation. Reactive hyperæmia is either completely abolished or appears only in a very reduced form. Nitroglycerine and perparine (a tetraethoxy derivative of papaverine) are without effect. The sensitivity to epinephrine is unchanged, but vasoconstriction is not followed by consecutive vasodilatation.

Iodoacetate, as an inhibitor of —SH, inhibits the synthesis of acetylcholine, which, according to Burn's investigations[5], offers a possible explanation of the inverse action of acetylcholine. It is also known[6] that during iodoacetate poisoning the adenosinetriphosphate content of the muscles decreases, and finally with the ensuing contracture adenosinetriphosphate disappears from the muscle.