independent measurements were made on methylcellulose solutions having essentially constant densities but varying viscosities up to 200 cps. The delivery rates of all of the methylcellulose solutions were nearly identical, indicating that viscosity is not a determining factor under the study conditions. Based on these observations, the differences in delivery rates can be attributed to the effect of density. The data in Fig. 3 illustrate this dependency on density. Here the inverse square-root relationship predicted by Eq. 1 seems to hold well for all test conditions.

The experimental data appear to be in good agreement with theoretical predictions. Using airless spray equipment, the delivery rate was found to be: *(a)* directly proportional to the square root of pressure, *(b)* directly proportional to the area of the nozzle orifice, and *(c)* inversely proportional to the square root of density.

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Metabolism of Δ^1-Tetrahydrocannabinol by Mouse Hepatic Microsomes: Identification of 6α-Hydroxytetrahydrocannabinol

Keyphrases □ Tetrahydrocannabinol—metabolism by mouse hepatic microsomes, identification of 6α-hydroxytetrahydrocannabinol □ 6α-Hydroxytetrahydrocannabinol—identification, metabolism of tetrahydrocannabinol by mouse hepatic microsomes □ Marijuana—metabolism of tetrahydrocannabinol by mouse hepatic microsomes, identification of 6α-hydroxytetrahydrocannabinol

To the Editor:

The body of knowledge concerning the biotransformations of Δ^1-tetrahydrocannabinol has grown considerably in the past few years (1). However, the nature of the transformations in the mouse has not been firmly established, even though it has been used in studying the pharmacology of tetrahydrocannabinol. Several reports on distribution (2–5) suggested that the principal metabolites in this species are hydroxytetrahydrocannabinols, in analogy with those isolated from rats, rabbits, monkeys, and humans. The purpose of this study was to identify the major metabolites of ^{14}C-Δ^1-tetrahydrocannabinol produced by the microsomal fraction of mouse liver.

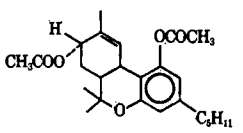
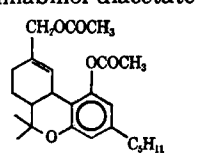
Table I—Metabolism of Δ^1-Tetrahydrocannabinol by Liver Microsomes

TLC Zone	R_f	Assignment[b]	Percent Recovered Products[a] Mouse[c]	Rat[d]
1	0.67	Δ^1-Tetrahydrocannabinol acetate	9.42	19.2
2	0.40	6α-Hydroxy-Δ^1-tetrahydrocannabinol diacetate	26.3	10.0
3	0.30	7-Hydroxy-Δ^1-tetrahydrocannabinol diacetate	34.1	53.3
4	0.13	6α,7-Dihydroxy-Δ^1-tetrahydrocannabinol triacetate (?)	30.2	17.6

[a] Recoveries of added radioactivity were approximately 50%. [b] All materials were acetylated prior to TLC with a mixture of acetic anhydride and pyridine. [c] Adult male CD-1 mice (30–33 g). [d] Adult male Sprague–Dawley rats (190–230 g).

The preparation of the microsomes, the incubation conditions, and the extraction procedure were identical to those previously reported for the rat (6). The residue obtained after extraction of the incubation mixture and evaporation of the solvent was acetylated to minimize decomposition of the products during isolation. The mixtures of acetates were separated by silica gel TLC (30% ether in hexane, developed twice), and the locations of the radioactive zones were determined by autoradiography. The four major zones were eluted and chromatographed a second time in the same manner to obtain materials pure enough for GLC–mass spectrometry. Comparison of

Table II—GLC–Mass Spectrometry[a]

Metabolite	Retention Time, min	Principal Ions[b]
 6α-Hydroxy-Δ^1-tetrahydrocannabinol diacetate	7.0	372 (3.4), 354 (100), 339 (21), 312 (82), 297 (65), 295 (18)
 7-Hydroxy-Δ^1-tetrahydrocannabinol diacetate	7.5	372 (3.8), 354 (43), 312 (100), 297 (28), 259 (31)

[a] The spectra were obtained on a Finnegan 1015 at 70 ev. The conditions were: column, 0.6 m (2 ft) 2% OV-1; column temperature, 180–240° (8°/min); carrier gas, helium; and injector temperature, 255°. [b] The expected molecular ion at 414 could not be obtained at ionizing voltages of 70 or 20 ev. Using a different instrument, Dr. C. E. Hignite was able to observe a molecular ion at 414 for TLC zone 3. Numbers in parentheses refer to relative intensities.

the products with authentic standards[1] by TLC, GLC, and GLC–mass spectrometry led to the identification of three of the four zones. A parallel study was done with rat liver microsomes for comparison purposes (Tables I and II). The identification of zone four rests mainly on its TLC mobility, because it was not possible to isolate sufficient pure material for GLC–mass spectrometry analysis. A possible metabolite, 6β-Δ^1-tetrahydrocannabinol, can be excluded on the basis of its markedly different TLC mobility from that reported (8).

It can be seen from the results that mouse liver microsomes metabolize Δ^1-tetrahydrocannabinol even more extensively than the analogous rat system. The most notable difference is the greater proportion of 6α-hydroxy-Δ^1-tetrahydrocannabinol *versus* 7-hydroxy-Δ^1-tetrahydrocannabinol. Concurrent results from another laboratory have also shown that 6α- and 7-hydroxy-Δ^1-tetrahydrocannabinols are major products when Δ^1-tetrahydrocannabinol is incubated with mouse liver microsomes[2]. Since both metabolites are psychoactive (7), evidence for their presence in a particular species is of importance in interpreting pharmacological studies with Δ^1-tetrahydrocannabinol. The production of 6α-hydroxy-Δ^1-tetrahydrocannabinol becomes of equal interest to that of 7-hydroxy-Δ^1-tetrahydrocannabinol since the former has been tentatively identified in human plasma (8).

Our results may also help to establish the nature of one unknown metabolite from rat lung and liver reported by Nakazawa and Costa (9). While we have not been able to make a direct comparison, it seems likely that their R_f 0.48 metabolite is 6α-hydroxy-Δ^1-tetrahydrocannabinol, since both our and their rat liver experiments produced only one substance intermediate in mobility between Δ^1-tetrahydrocannabinol and 7-hydroxy-Δ^1-tetrahydrocannabinol.

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[1] Labeled and unlabeled Δ^1-tetrahydrocannabinol as well as samples of the metabolites were obtained from the National Institute of Mental Health.

[2] Professor S. Agurell, Faculty of Pharmacy, Stockholm S-113 86, Sweden, personal communication.

BOOKS

REVIEWS

Selective Toxicity, Fifth Edition. By ADRIEN ALBERT. Chapman and Hall, London, England, 1973. 597 pp. 15 × 23 cm. Price £7.

"Selective toxicity" is defined by Adrien Albert as "the injury of living matter without harming another kind with which the first is in intimate contact." Those organisms (including humans) that are not injured are referred to as "economic species," while those which are harmed are classified as "uneconomical species." Examples can be given where chemical agents that are toxic to one type of plant have little effect upon other plants growing on the same plot of land. In the animal world, insecticides are so chosen to bring death to insects and pest without harming useful animals and plant life. Selective toxicity as interpreted by Albert is applicable to all drugs since they will alter one or more physiological or biochemical processess to help bring about a state of normalcy. For a large number of drugs the toxic effect is reversible, for example, the general anesthetics, sedatives, and drugs used to relieve pain. Other drugs such as the antibiotics bring about a nonreversible toxic effect, in this case to the noneconomic species, the bacteria, without harm to the host (economic species).

In an oversimplification, selective toxicity may be considered a general approach of helping rid the world of undesirable organisms through chemical agents while permitting useful ones to flourish. Even though the mechanisms by which one chemical agent can harm one species while having relatively little effect upon another are complex and often unknown, Albert approaches the subject in a very methodical and deliberate manner and bases his thesis, as in the past, upon the chemical structure and physical properties of the agents.

The present edition is the fifth and when compared to the first (1951) and second editions (1960) monumental growth of the book is apparent. For example, the 1960 issue was a mere 233 pages *versus* the present 597 pages. While the 1960 edition was a relatively breezy approach to the subject which could be read with