

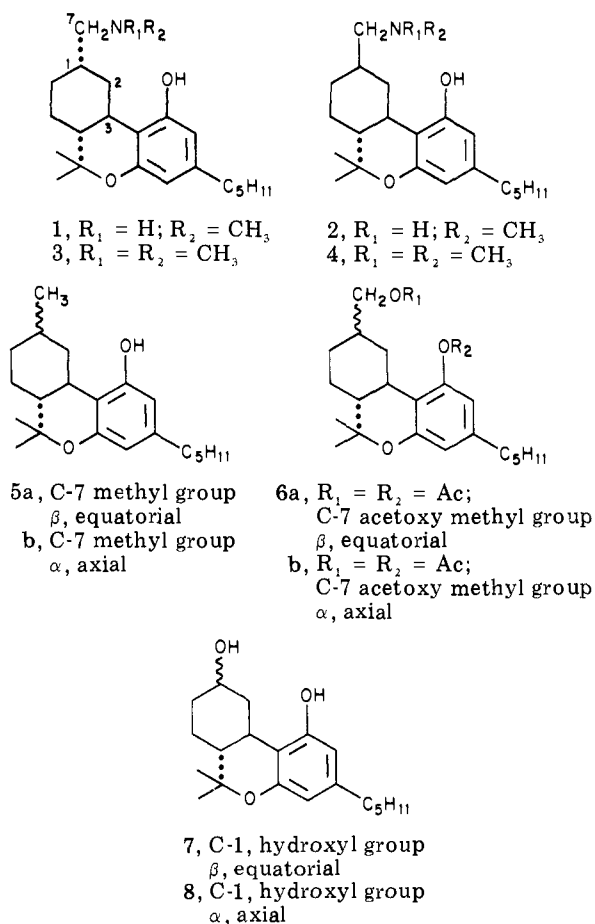
Activity of Novel Aminocannabinoids in Baboons

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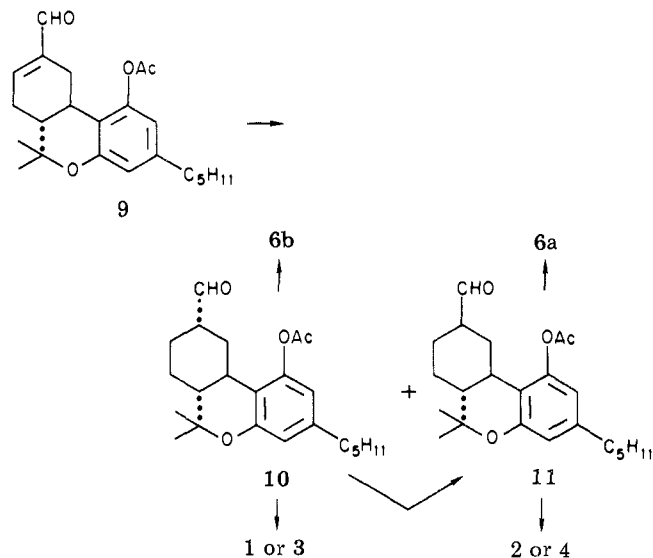
The axial and equatorial isomers of 7-(methylamino)hexahydrocannabinol (1 and 2) and 7-(dimethylamino)hexahydrocannabinol (3 and 4) were prepared by reductive amination of the corresponding cannabinoid aldehydes. The amines caused some tranquility in baboons but did not evoke the typical cannabimimetic syndrome caused by psychoactive cannabinoids. However the axial amines (1 and 3) but not the equatorial ones (2 and 4) caused bouts of scratching and yawning. The latter is a rare pharmacological effect hitherto not observed with other cannabinoids.

The stereochemistry at the C-1 position affects activity in some cannabinoids. We have reported¹ that the equatorial isomer of hexahydrocannabinol (5a) is nearly 20 times more psychoactive than the axial isomer (5b) when tested in rhesus monkeys. The same regularity was observed with the 7-hydroxyhexahydrocannabinol diacetates (6a and 6b):² the equatorial 6a caused the typical psychotropic reactions in rhesus monkeys at doses at least 10 times lower than those of the axial 6b. 7-Nor-1-hydroxyhexahydrocannabinol (7) in which the hydroxyl group is equatorial is a potent analgetic in rodents; the axial isomer 8 is inactive.³

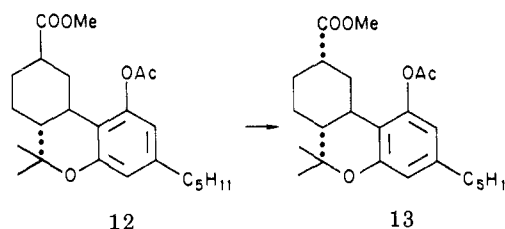


It seemed of interest to test further this regularity. We chose to prepare the two unknown cannabinoid pairs, the 7-(methylamino)hexahydrocannabinols 1 and 2 and the 7-(dimethylamino)hexahydrocannabinols 3 and 4. In addition to obtaining new data on the stereochemical requirements for cannabinoid activity, we hoped to observe novel pharmacological effects as alkylamino moieties are ubiquitous in medicinally active compounds.

Chemistry. The known 7-oxo- Δ^6 -tetrahydrocannabinol acetate (9)⁴ was reduced by catalytic hydrogenation over palladium. The mixture of 7 α -oxohexahydrocannabinol acetate (10) and 7 β -oxohexahydrocannabinol acetate (11) thus obtained was separated by silicic acid chromatography to give the isomeric aldehydes in 34.6% and 20.8% yields, respectively. The stereochemistry was determined by treatment of 10 with mild base followed by acetylation. The axial 10 was converted into the equatorial 11. Under the same conditions 11 gave only unchanged starting material. These reactions demonstrate that the carbonyl group on C-1 in 10 is equatorial.



We have previously observed⁵ that in the related pair of isomers, 12 and 13, the equatorial carbomethoxyl group in 12 is isomerized to an axial one (leading to 13) on treatment with sodium methoxide followed by acetylation.



- (1) Edery, H.; Grunfeld, Y.; Ben-Zvi, Z.; Mechoulam, R. *Ann. N.Y. Acad. Sci.* 1971, 191, 40.
- (2) Mechoulam, R.; Lander, N.; Varkony, T. H.; Kimmel, I.; Becker, O.; Ben-Zvi, Z.; Edery, H.; Porath, G. *J. Med. Chem.* 1980, 23, 1068.
- (3) Wilson, R. S.; May, E. L. *J. Med. Chem.* 1975, 18, 700. Wilson, R. S.; May, E. L.; Martin, B. R.; Dewey, W. L. *Ibid.* 1976, 19, 1165.
- (4) Mechoulam, R.; Ben-Zvi, Z.; Agurell, S.; Nilsson, I. M.; Nilsson, J. L. G.; Edery, H.; Grunfeld, Y. *Experientia* 1973, 29, 1193.
- (5) Mechoulam, R.; Lander, N.; Tamir, I.; Ben-Zvi, Z.; Kimmel, Y. *Angew. Chem., Int. Ed. Engl.* 1980, 19, 543.

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Table I. Psychotropic Effects, Yawning, and Scratching Caused by Aminocannabinoids in Baboons

compd	stereochem of C-1 alkyl or substituted alkyl	dose, ^a mg/kg	psychotropic ^b activity	yawning and scratching
7 α -(methylamino)hexahydrocannabinol (1)	axial	2.0	–	present
		5.0	–	present
		10.0	±	present
7 β -(methylamino)hexahydrocannabinol (2)	equatorial	2.0	–	absent
		5.0	±	absent
		10.0	±	absent
7 α -(dimethylamino)hexahydrocannabinol (3)	axial	2.0	–	present
		5.0	–	present
		10.0	–	present
7 β -(dimethylamino)hexahydrocannabinol (4)	equatorial	2.0	–	absent
		4.0	–	absent
Δ^1 -tetrahydrocannabinol ^c	not applicable	0.05	+	absent
		0.1	++	absent
		0.5	+++	absent
7 β -hexahydrocannabinol (5a) ^c	equatorial	0.1	±	absent
		0.5	++	absent
		1.0	+++	absent
7 α -hexahydrocannabinol (5b) ^c	axial	1.0	–	absent
		2.0	+	absent

^a Two animals per dose used. ^b For test method and notation, see text and Experimental Section. ^c Tabulated for comparison purposes.

Hence in order to eliminate the possibility that such an unusual isomerization had taken place in the above-described base equilibrations of the aldehydes **10** and **11** and in order to confirm our stereochemical assignments, **10** and **11** were reduced with sodium borohydride and were then acetylated. The diacetates **6b** and **6a** thus obtained, respectively, were identical with compounds previously described whose stereochemistry had been unequivocally determined.⁵

The aldehyde **10** was treated with methylamine hydrochloride. The intermediate Schiff base presumably obtained was not isolated but was directly reduced with sodium cyanoborohydride⁶ to give the required 7 α -(methylamino)hexahydrocannabinol (**1**) in a 56% yield. 7 β -(Methylamino)hexahydrocannabinol (**2**) was obtained in the same manner from the aldehyde **11** in a 70% yield.

The dimethyl derivatives **3** and **4** were obtained by the procedure followed for the monomethyl derivatives except that dimethylamine was used in the condensation reaction and the reduction with the sodium cyanoborohydride was considerably prolonged.

The IR spectra of **3** and **4** differ substantially in their fingerprint region. In the NMR spectra the most conspicuous difference is in the shifts of the aromatic protons: in the equatorial isomer **4** the two aromatic protons (at δ 5.79 and 6.06) are considerably more separated than in the axial isomer (δ 6.22 and 6.27). The nonidentity of the products of the reductive amination reactions of the two isomeric aldehydes with dimethylamine indicates that these reactions do not proceed through a common (enamine?) intermediate (cf. ref 6).

Pharmacology. In our cannabinoid research until recently we used solely the rhesus monkey as a model most closely comparable to the human.^{2,7} However the present study was undertaken with baboons (*Papio papio*) of ei-

ther sex, 4.2–6.8-kg body weight. These monkeys show sensitivity and pattern of behavior response to cannabinoids very similar to that of rhesus,⁸ and hence to humans.^{9,10}

The estimation of the psychotropic effects in rhesus is semiquantitative and has been described in some detail.^{9,10} The behavior disturbances and its scoring in baboons are the same as in rhesus: (–) no change; (±) tranquility; (+) drowsiness, decreased motor activity, occasional partial ptosis, occasional head drop; (++) stupor, ataxia, suppression of motor activity, full ptosis, typical crouched posture (thinker position) kept for up to 3 h (the animal may, however, regain normal behavior for short periods of time if external sensorial stimuli are applied); (+++) severe stupor and ataxia, full ptosis, immobility, crouched posture lasting for more than 3 h, and absence of reaction to external stimuli. We consider a compound not “cannabimimetic”⁹ if at 5 mg/kg iv it fails to induce the characteristic syndrome (score +) induced by psychoactive cannabinoids. None of the amines tested in the present series showed more than (±) activity.

Results and Discussion

The results are tabulated in Table I. Neither the (methylamino)cannabinoids **1** and **2** nor the (dimethylamino)cannabinoids **3** and **4** elicited any of the major effects typical of the psychoactive cannabinoids. With the monomethylamino derivatives **1** and **2** tranquility and decreased motor activities were observed at doses of many orders of magnitude higher than those of Δ^1 -THC. In all cases the animals recovered normal motor activity within 2.5 h of injection.

The most salient effect observed was that the axial derivatives **1** and **3** evoked bouts of yawning. Either male or female baboons started yawning 5–20 min after administration of the drug. They yawned every 12–15 s for periods of 25–40 min, and the yawning was accompanied by vigorous body scratching, which, however, disappeared

- (6) House, H. O. “Modern Synthetic Reactions”; W. A. Benjamin: Menlo Park, CA, 1972; p 18. Borch, R. F. *Synthesis* 1972, 52, 124. Borch, R. F.; Bernstein, M. D.; Durst, H. D. *J. Am. Chem. Soc.* 1971, 93, 2897. Le Bris, A.; Lefebvre, G.; Coussemont, F. *Bull. Soc. Chim. Fr.* 1964, 1366, 1374, 1584, 1594.
- (7) Mechoulam, R.; Ederly, H. “Marijuana. Chemistry, Pharmacology, Metabolism and Clinical Effects”; Mechoulam, R., Ed.; Academic Press: New York, 1973; p 101.

- (8) Giono-Barber, P.; Paris, M.; Bertuletti, G.; Giono-Barber, H. *J. Pharmacol. (Paris)* 1974, 5, 591. Ederly, H.; Porath, G., unpublished observations.

- (9) Ederly, H. *Arch. Toxicol.* 1983, Suppl. 6, 91.

- (10) Grunfeld, Y.; Ederly, H. *Psychopharmacology* 1969, 14, 200.

before the end of the bouts of yawning. The effects were considered genuinely drug elicited as in no case were they noted either after injection of the solvent 1 week later or during the control observation period (1 h in midmorning prior to the injection of compounds). The relatively long control period was considered imperative for accurate observations as caged nonhuman primates occasionally do yawn and scratch themselves. Moreover, these features occur at high frequency (1/2.5 s) when monkeys are subjected to visual stimuli leading to emotional stress.¹¹ At this stage it could not be established whether the crisis of scratching and yawning elicited by the axial analogues expressed some kind of "inner emotional turmoil" of baboons.

As mentioned above and discussed previously in considerable detail,^{1,2} the stereochemistry at the C-1 position affects cannabimimetic activity; the C-7 methyl or acetoxymethyl groups (cf. compounds **5a** and **6a**) have to be in the near plane of the cannabinoid for significant activity to be noted. The axial isomers **5b** and **6b** are considerably less active. The amines described now do not possess cannabimimetic activity. However the noncannabimimetic activity that is observed, namely, yawning and scratching, shows stereochemical requirements opposite to those for cannabimimetic activity: the axial rather than the equatorial isomers are active. Hence it seems plausible that the biochemical basis of the two activities is dissimilar. At present the biochemical basis of either cannabimimetic activity or yawning and scratching (in this series) remains to be elucidated. The observation that compounds of the same chemical family cause unrelated pharmacological effects is a general phenomenon in medicinal chemistry and is presumably due to chemical similarities at the site of action.

Induction of yawning by drugs is relatively rare. It has been produced by a number of chemically unrelated substances such as α -melanocyte-stimulating hormone, cholinomimetic drugs, apomorphine, and others.¹² As the phenomenon is more selectively elicited in males, it has been proposed to be under control of androgenic hormones¹³ with intervention of serotonergic-dopaminergic-cholinergic neural pathways.¹² Some psychoactive cannabinoids have been reported to cause scratching in dogs,¹⁴ but little is known on the nature of this effect. Δ^1 -THC, however, does not cause conspicuous scratching in monkeys.

Concerning the present axial cannabinoids, two main mechanisms for the scratching effect could be envisaged: (a) a peripheral one involving stimulation of cutaneous sensory nerve terminals by a pruritogenic released substance such as histamine or (b) direct activation of central pathways, particularly in the spinal cord.¹⁵ We favor this latter possibility as so far there is no evidence of histamine-releasing capacity of cannabinoids.¹⁴

Experimental Section

Pharmacology. The solvent used was propylene glycol except for compound **1**, which was dissolved in 0.1 N HCl and the solution made isotonic with NaCl. The compounds were administered into

the left or right antecubital vein. The volume injected was 0.05–0.1 mL/kg for propylene glycol and 0.2 mL/kg for the acid solution. As the quantities of compounds available were limited, only two animals per dose level were employed. The magnitude of the psychotropic effect was compared with that of Δ^1 -THC (see Table I).

Chemistry. The instrumentation and techniques used were described in a previous publication.²

Hydrogenation of 7-Oxo- Δ^6 -tetrahydrocannabinol Acetate (9). A solution of 7-oxo- Δ^6 -tetrahydrocannabinol acetate (**9**)⁴ (2.9 g, 7.84 mmol) in EtOH (50 mL) was hydrogenated with 10% palladium on carbon (290 mg) at 40 psi for 24 h. Fresh catalyst was added and the hydrogenation was continued for another 24 h. The solution was filtered and the EtOH was evaporated. The residue was chromatographed on silica gel (450 g). Elution with 20% ether in light petroleum ether gave two main products. The less polar one was shown to be 7 α -oxohexahydrocannabinol acetate (**10**; 1.0 g, 34.6%): mp 66–67 °C; MS, *m/e* 372 (M^+ , 33), 330 (100); $[\alpha]_D -127^\circ$ (EtOH); UV λ_{max} 276 nm (sh, ϵ 2145), 282 (2320); IR (neat) 2810, 2710, 1770 (OAc), 1730 (CHO) cm^{-1} ; 1H NMR ($CDCl_3$) δ 0.88 (t, 3, w- CH_3), 1.01, 1.36 (2 s, 3 each, CH_3), 2.45 (s, 3, OAc), 2.51 (t, 2, benzylic), 3.23 (br d, 1, $C_{2\alpha}$), 6.42, 6.56 (2 s, each, aromatic), 9.79 (s, 1, aldehyde proton). Anal. ($C_{23}H_{32}O_4$) C, H. The more polar product was 7 β -oxohexahydrocannabinol acetate (**11**; 0.6 g, 20.8%) as a colorless oil: MS, *m/e* 372 (M^+ , 29%), 330 (100%); $[\alpha]_D -172^\circ$ (EtOH); UV λ_{max} 278 nm (sh, ϵ 2355), 283 (2496); IR (neat) 2805, 2705 1765 (OAc), 1720 (CHO) cm^{-1} ; 1H NMR ($CDCl_3$) δ 0.90 (t, 3, w- CH_3), 1.09, 1.30 (2 s, 3 each, CH_3), 2.29 (s, 3 H, OAc), 2.49 (t, 2 H, benzylic), 2.86 (br d, 1, $C_{2\alpha}$), 6.40, 6.55 (2 s, 1 each, aromatic), 9.64 (s, 1, aldehyde proton).

Equilibration of Aldehydes 10 and 11. Aldehyde **10** (58 mg, 0.16 mmol) was dissolved in MeOH (5 mL) and sodium bicarbonate (13 mg) was added. The reaction mixture was stirred overnight and was then filtered, diluted with water, extracted with ether, and the extract was dried and evaporated. The oily residue was acetylated with acetic anhydride–pyridine and the acetylated product was analyzed by thin-layer chromatography (TLC) (50% ether in petroleum ether) by comparison to compounds **10** and **11**. The TLC showed that the axial **10** had converted almost entirely into the equatorial **11**.

When the equatorial aldehyde **11** was subjected to the above reaction conditions, the only product observed was unchanged starting material.

Reduction of Aldehydes 10 and 11. The axial aldehyde **10** (100 mg) was dissolved in MeOH (10 mL) and sodium borohydride (100 mg) was added in portions. After 10 min the reaction mixture was diluted with a 10% aqueous solution of KOH (10 mL) and extracted with ether. The extract was dried over magnesium sulfate and evaporated. The oily residue was acetylated with acetic anhydride (1 mL) and pyridine (2 mL), left overnight, and then evaporated to dryness. The residue was chromatographed on silica gel. Elution with 3% ethyl acetate in petroleum ether gave the known⁵ diacetate **6b** (TLC, IR, and NMR comparisons).

Following the same procedure the aldehyde **11** gave the known⁵ diacetate **6a**.

7 α -(Methylamino)hexahydrocannabinol (1). Methylamine hydrochloride (408 mg, 6 mmol) was added to a solution of the above described aldehyde **10** (250 mg, 0.67 mmol) in absolute MeOH (10 mL). The solution was stirred for 30 min at room temperature and then $NaBH_3CN$ (31 mg, 0.5 mmol) was added. The solution was stirred at room temperature for 1.5 h, KOH (1.0 g) was added, and stirring was continued until the pellets were dissolved. The MeOH was removed under vacuum. The residue was dissolved in water (10 mL) and the resulting solution was extracted with ether (3 \times 20 mL). The combined ether extracts were dried over magnesium sulfate and evaporated to give a colorless oil, which on crystallization from diethyl ether/pentane gave **1** (130 mg, 56%): mp 198–199 °C dec; MS, *m/e* 345 (M^+ , 100); $[\alpha]_D -91^\circ$ (EtOH) UV λ_{max} 276 nm (ϵ 1084), 282 (1104); IR (neat) 2940, 1620, 1580, 1430 cm^{-1} ; 1H NMR ($CDCl_3$) δ 0.86 (t, 3, w- CH_3), 1.06, 1.35 (2 s, 3 each CH_3), 2.41 (t, 2, benzylic), 2.56 (s, 3, NCH_3), 2.69 (m, 2, CH_2N), 6.11 (d, 1, aromatic), 6.16 (d, 1, aromatic). Anal. ($C_{23}H_{35}NO_2$) C, H, N.

7 β -(Methylamino)hexahydrocannabinol (2). The preparation of this compound follows exactly the procedure described above for the synthesis of **1**, except that the equatorial aldehyde

- (11) Hall, K. R. L. *Nature (London)* 1962, 192, 1258.
- (12) Yamada, K. K.; Furukawa, T. *Arch. Pharmacol.* 1981, 316, 155.
- (13) Berendsen, H. E.; Nickolson, V. J. *Behav. Neur. Biol.* 1981, 33, 123.
- (14) Paton, W. D. M.; Pertwee, R. G. "Marijuana. Chemistry, Pharmacology, Metabolism and Clinical Effects"; Mechoulam, R., Ed.; Academic Press: New York, 1973; p 225.
- (15) Feldberg, W. "A pharmacological approach to the brain from its inner and outer surface"; E. Arnold (Publishers) Ltd.: London, 1963; p 55.

11 is used as starting material. The reaction product was an oil, which was purified by chromatography on Florisil. Elution with 10% MeOH in CHCl_3 gave compound 2 as an oil (70%): MS, m/e 345 (M^+ , 100); $[\alpha]_D -99^\circ$; UV λ_{max} 278 nm (ϵ 569), 285 (586); IR (CHCl_3) 2920, 1620, 1580, 1425 cm^{-1} ; $^1\text{H NMR}$ (CDCl_3) δ 0.87 (t, 3, w- CH_3), 1.02, 1.33 (2 s, 3 each, CH_3), 2.41 (t, 2, benzylic), 2.51 (s, 3, NCH_3), 2.59 (m, 2, CH_2N), 6.01 (d, 1, aromatic), 6.14 (aromatic).

7 α -(Dimethylamino)hexahydrocannabinol (3). The preparation of this compound follows the procedure described above for the synthesis of 1, except that dimethylamine hydrochloride instead of methylamine hydrochloride is used as one of the starting materials. The reduction with NaBH_3CN is continued for 72 h rather than just 1.5 h. The reaction product was an oil, which was purified by chromatography on aluminum oxide "for dry column". Elution with 2% MeOH in CHCl_3 gave compound 3 (66% yield) as an oil: MS, m/e 359 (M^+); $[\alpha]_D -99^\circ$ (EtOH); IR (CHCl_3) 1625, 1570, 1030 cm^{-1} ; $^1\text{H NMR}$ (CDCl_3) δ 0.87 (t, 3, w- CH_3), 1.04, 1.36 (2 s, 3 each, CH_3), 2.34 (s, 6, CH_3NCH_3), 6.22 (1, aromatic), 6.27 (1, aromatic).

7 β -(Dimethylamino)hexahydrocannabinol (4). The preparation of this compound follows the procedure described above for the synthesis of 1, except that dimethylamine hydrochloride

instead of methylamine hydrochloride and the equatorial aldehyde 11 instead of 10 are used as starting materials. The reduction with NaBH_3CN takes 24 h rather than 1.5 h needed for compound 1. The reaction product was an oil, which was purified by chromatography on aluminum oxide "for dry column". Elution with 2% MeOH in CHCl_3 gave compound 4 (55%) as an oil: MS, m/e 359 (M^+); $[\alpha]_D -126^\circ$ (EtOH); UV λ_{max} 275 nm (ϵ 1325), 282 (1380); IR (CHCl_3) 1625, 1585, 1430 cm^{-1} ; $^1\text{H NMR}$ δ 0.86 (t, 3, w- CH_3), 1.04, 1.32 (2 s, 3 each, CH_3), 2.30 (s, 6, CH_3NCH_3), 5.79 (1, aromatic), 6.06 (1, aromatic).

Acknowledgment. N. Lewis¹⁶ was a recipient of a Lady Davis award during his stay as visiting professor from Ohio State University. We thank the Israel Institute for Psychobiology for partial support.

Registry No. 1, 91385-16-9; 2, 91385-17-0; 3, 91385-18-1; 4, 91385-19-2; 9, 51263-83-3; 10, 91385-20-5; 11, 91385-21-6; methylamine hydrochloride, 593-51-1; dimethylamine hydrochloride, 506-59-2.

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Book Reviews

Bioactive Carbohydrates: In Chemistry, Biochemistry, and Biology. By John F. Kennedy and Charles A. White. Halsted Press, New York. 1983. 331 pp. 16 × 23.5 cm. ISBN 0-470-27527-8. \$79.95.

A major obstacle to anyone learning carbohydrate chemistry is the seemingly unrelated nomenclature and diverse structural types for this class of natural products. Appropriately, therefore, the first two chapters of this book, which is designed primarily as an introductory textbook, begins with a detailed, systematic presentation of the names for monosaccharides, oligosaccharides, and polysaccharides and carefully analyzes their stereochemical differences. The manner in which monosaccharides are bound together to yield oligosaccharides is well presented and the authors provide many structures in three-dimensional conformational drawings which is very helpful.

Chapter 3 discusses the primary, secondary, tertiary, and quaternary structures of polysaccharides and relates them to proteins. Reactions of carbohydrates are presented. Included is the oxidation of monosaccharides to aldonic and alduronic acids, which are carefully distinguished, reduction to alditols, and treatment with acid to produce furans and base to cause epimerization and aldose/ketose isomerizations. A discussion of the derivatization of monosaccharides begins with an indication that, due to the polyfunctional nature of carbohydrates, selective protection of various sites is necessary to affect an appropriate change selectively at another center. With this in mind, the formation of glycosides, ethers, esters, and cyclic acetals is described.

In Chapter 4 a good discussion of the isolation and purification of carbohydrates is given along with the use of hydrolysis, periodate oxidation (the Smith degradation), alkaline degradation, mass spectra, NMR spectra, electrophoresis, and chromatographic techniques for identifying carbohydrates. The use of enzymes in the structural analysis of polysaccharides is given together with an exhaustive table of the enzymes capable of performing these tasks.

The chemical and biochemical synthesis of monosaccharides forms the major portion of Chapter 5. In describing chain lengthening as a synthetic approach to monosaccharides, the Nef reaction (using nitromethane) and the Fischer-Killani reaction (via cyanohydrins) are presented. In degrading monosaccharides to other monosaccharides, the Wohl and Ruff degradations are

discussed. Epimerization of monosaccharides introduces another means of preparing these simple carbohydrates. The Fischer glycosidation and Koenigs-Knorr preparation of oligosaccharides are given, and a description of the biosynthesis of carbohydrates is extensive and well done.

A detailed presentation of monosaccharides appears in Chapter 6. In this chapter, acidic sugars (aldonic, uronic, and aldaric acids), sugar alcohols (alditols and inositols), aminosugars (including 2-amino-2-deoxy-D-glucose), deoxysugars, nitrosugars (which do not exist widely in nature but are useful in preparing aminosugars), halogenosugars, thiosugars, and unsaturated sugars are discussed.

Chapter 7 deals with naturally occurring disaccharides (sucrose, lactose, and the trehaloses) and trisaccharides (raffinose and melezitose). Also discussed are maltose and cellobiose, which are disaccharides resulting from the hydrolysis of the polysaccharides starch and cellulose, respectively. The breadth of the book is illustrated here with a mention of the use of cyclomaltooligosaccharides (i.e., cycloamyloses, cyclodextrins, etc.) to form inclusion compounds with small molecules and the use of these compounds in biochemical studies. An interesting immunological explanation is also given for the conversion of D-glucose to D-galactose in mammary glands for incorporation into lactose. The infant receiving the milk then converts the D-galactose back to D-glucose during digestion.

This is followed by an extensive presentation of polysaccharides (Chapter 8), beginning with the plant polysaccharides (starch, which is well described, and cellulose as homopolysaccharides and gums, mucilages, pectins, and hemicelluloses as heteropolysaccharides), algal polysaccharides, microbial polysaccharides (teichoic acids, cell wall peptidoglycans, extracellular polysaccharides, and Gram-positive and Gram-negative bacterial capsular polysaccharides), lipopolysaccharides, fungal polysaccharides, and animal polysaccharides (glycogen and chitin). Timely, from a medicinal chemistry point of view, is the discussion of the antigenic nature of the Gram-positive bacterial capsular polysaccharides and the lipopolysaccharides. Also contained in this chapter is a compilation of the less common monosaccharides found in bacterial polysaccharides.

In Chapter 9 the authors devote a great deal of attention, perhaps justifiably so, to glycoproteins and proteoglycans. An easily retained definition of each with an accompanying distinction between them is provided. Even though plant and algal glyco-