Summary

The influence of anaerobiose and of varied oxygen tensions upon respiration and histamine release during anaphylactic reaction in guineapig lung slices *in vitro* was studied.

No histamine was liberated in the absence of oxygen. With increasing oxygen tensions, increasing histamine quantities were released; these quantities reached the control values when the atmosphere contained 10% oxygen.

These results indicate that the mechanism of histamine release in the anaphylactic reaction is linked with the aerobic metabolism of the cell.

Effect of Reserpine Analogues on Tissue Serotonin

In a recent note, it was reported that a differential effect was exerted on brain serotonin by reserpine and its analogues: carbethoxysyringoyl methyl reserpate (SU 3118 or syrosingopine) and methyl-18-O(3-N, N-dimethylaminobenzoyl) reserpate (SU 5171). Reserpine and SU 5171 release brain serotonin and induce sedation, while SU 3118, an hypotensive agent without sedative effect, is unable to release brain serotonin[1–3].

Since a poor penetration of SU 3118 into the brain might account for the lack of brain serotonin depletion, the effect of SU 3118, in comparison with SU 5171 and reserpine, on serotonin content of other organs has been investigated.

The method used was the following: Sprague-Dawley rats of the average weight of 200 g were injected intraperitoneally with different concentrations of reserpine (kindly supplied by Dr. V. Ghetti, CIBA, S.p.A., Milano) or SU 3118, or SU 5171 (received through the courtesy of Dr. A. J. PLUMMER, CIBA Labs., Summit, N. J.). 4 h after the administration, the animals were killed by decapitation and the serotonin content of brain, intestine, kidney, lung, and spleen was determined by the method of BOGDANSKI *et al.*[4] employing a Farrand spectrophotofluorimeter.

The results obtained are reported in a Table.

[1] R. A. MAXWELL, H. POVALSKI, and A. J. PLUMMER, J. Pharmacol. exper. Therap. *125*, 178 (1959).

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[3] S. GARATTINI, A. MORTARI, A. VALSECCHI, and L. VALZELLI, Nature *183*, 1273 (1959).

[4] D. F. BOGDANSKI, A. PLETSCHER, B. B. BRODIE and S. UDENFRIEND, J. Pharmacol. exper. Theap. *117*, 82 (1956).

While reserpine and SU 5171 deplete serotonin in all the organs tested (except kidney in the case of SU 5171) SU 3118, at a concentration of 20 mg/kg lowers only lung and spleen serotonin. 20 mg/kg of SU3118 are less effective than 5 mg/kg of reserpine in releasing intestinal serotonin.

These results suggest that lung and spleen are more sensitive than other organs to the action of SU 3118. Under the action of SU 3118, the cerebral, intestinal, and renal serotonin behave similarly. Therefore, the hypothesis of a resistance of the blood-brain barrier to SU 3118 seems unlikely.

S. GARATTINI, R. KATO, and L. VALZELLI

Istituto di Farmacologia e di Terapia, Università degli Studi, Via A. Del Sarto 21, Milano, July 11, 1959.

Riassunto

La differenza di comportamento dimostrata, nel ridurre il tasso di serotonina di diversi organi, da due derivati reserpinici (SU 3118–SU 5171) non sembra potersi ricondurre solo ad una differente capacità di attraversamento della barriera ematoencefalica da parte delle due molecole in istudio.

Treatment	Dose mg/kg i. p.	Serotonin content (γ/g ± S. E.)				
		Brain	Intestine	Kidney	Lung	Spleen
Controls	—	0·43 ± 0·08	4·76 ± 0·24	0·34 ± 0·03	2·86 ± 0·16	3·51 ± 0·24
Reserpine . . .	2·5	0·17 ± 0·005	2·95 ± 0·15	0·19 ± 0·02	1,6 ± 0·23	1·09 ± 0·24
Reserpine . . .	5	0·12 ± 0·006	2,04 ± 0·12	—	—	—
SU 3118	20	0·46 ± 0·005	3·37 ± 0·36	0·29 ± 0·03	1·64 ± 0·27	1·04 ± 0·09
SU 3118	50	0·13 ± 0·011	2·64 ± 0·05	—	—	—
SU 5171	5	0·25 ± 0·009	3·98 ± 0·24	0·49 ± 0·07	1·84 ± 0·28	2·23 ± 0·73
SU 5171	7·5	0·12 ± 0·005	2·73 ± 0·21	0·28 ± 0·02	1·21 ± 0·07	0·59 ± 0·03

Each value represents the average of at least 8 determinations.

The Stereochemistry of some Naturally Occurring Guaianolides and Isophotosantonic Lactone

Recent work on the stereochemistry of cycloheptanes[1,2] has pointed out the general similarity of these systems to the more widely studied cyclohexane compounds. The application of the principles discussed by these workers, namely that a substituent group in a cycloheptane prefers the *quasi*-equatorial conformation, and that elimination reactions proceed *via* the same *trans-anti*-parallel route as in cyclohexanes, coupled with the logical extension from the cyclohexane field that a *cis* fused γ-lactone is more stable than the corresponding *trans* isomer, permits the deduction of provisional stereochemical relationships in several sesquiterpenic lactones. BARTON[3] has already assigned structure I to geigerin on the basis of rotatory dispersion data[4], and an assumption regarding the nature of the lactone ring similar to that which we have made.

[1] J. W. HUFFMAN and J. E. ENGLE, J. org. Chem., in press.

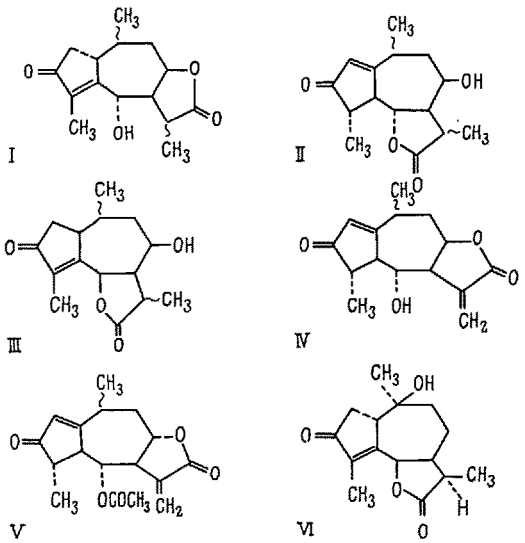
[2] N. L. ALLINGER, J. Amer. chem. Soc. *81*, 231 (1959).

[3] D. H. R. BARTON and J. E. D. LEVISALLES, J. chem. Soc., *1958*, 4518.

[4] C. DJERASSI, J. OSIECKI, and W. HERZ, J. org. chem. *22*, 1361 (1957).

The conformation of I is fixed by the ring fusion, and demands that the carbon-carbon bond at C_1 be *quasi*-equatorial to the seven-membered ring. Consequently the substituents at C_6, C_7, and C_8 will be *e'*, *e'*, and *a'*, respectively.

The assignment of stereochemistry to the remaining substances, desacetylisotenulin (II), helenalin (IV), balduilin (V, or the equivalent structure with the lactone and acetoxyl interchanged), and isophotosantonic lactone (VI), rests on the following arguments. All of these substances have been shown to have the configuration indicated at C_1, C_4 and C_5 by rotatory dispersion studies[4]. In addition tenulin, helenalin, and balduilin have the same configuration at C_7 and C_{10}[5]. These compounds, as well as geigerin (I), and isophotosantonic lactone (VI) are all readily hydrogenated to saturated ketones under mild conditions[3,4]. On the other hand, desacetylneotenulin (III) which has unnatural stereochemistry at C_1 and is formed under conditions which should not disturb the configuration at C_7, is not readily hydrogenated[4,6]. During this interconversion, in order to maintain the *e'* conformation at the ring fusion it is necessary for the seven membered ring to flip to an alternate conformation, causing all the other substituent groups to undergo corresponding conformational changes. The differences in ease of hydrogenation may then be explained by the presence of a bulky *e'* group at C_7 in tenulin, being changed to *a'* in desacetylneotenulin. This group then shields the double bond from hydrogenation. On this basis the stereochemistry at C_7 is assigned as shown in desacetylisotenulin, helenalin, balduilin, and isophotosantonic lactone.



The assignment of configuration to the hydroxyl groups rests upon the following observations. Dihydroisotenulin on basic hydrolysis and subsequent reacidification affords desacetyldihydroisotenulin and an isomeric lactone resulting from lactonization at C_8. On this basis the oxygens at C_6 and C_8 must be equivalent (*cis*), and on the basis of our assumptions regarding the stereochemistry of these lactones, *vide supra*, they must also be *cis* to the carbon chain at C_7. This gives rise to the partial stereochemistry for desacetylisotenulin as illustrated (II).

[5] W. Herz, R. B. Mitra, and P. Jayaraman, Abstr. Papers 136th National Meeting of the American Chemical Society, Sept. 13-18 (1959), p. 50 P.

[6] B. H. Braun, W. Herz, and K. Rabindran, J. Amer. chem. Soc. *78*, 4423 (1956).

Helenalin (IV), and its derivatives, on hydrolysis and reacidification are recovered unchanged[7,8] indicating that the groups at C_7 and C_8 are *cis*, and that the C_6 hydroxyl is probably *trans* to the side chain. Herz has recently shown that balduilin (V) is epimeric with tenulin at C_6, and helenalin at C_8[5], giving balduilin the structure shown.

The stereochemistry at C_{10} in isophotosantonic lactone (VI) rests upon the following argument. Dehydration of (VI) with thionyl chloride in pyridine affords an exocyclic, non-conjugated olefin[8], while acid catalyzed dehydration gives the doubly unsaturated, conjugated ketone. On this basis we propose that the C_{10} hydroxyl group is *cis* to the hydrogen at C_1, otherwise dehydration with thionyl chloride should have afforded the conjugated isomer *via* a *trans* elimination involving the activated hydrogen at C_1. The configuration at C_6 is assigned as shown, with inversion taking place during the formation of VI from santonin by analogy with the santonin-desmotroposantonin conversion[9]. The stereochemistry of the methyl group in the side chain is considered to be unchanged from that in santonin[10], in view of the fact that the conditions for the formation of VI from santonin do not appear vigorous enough to cause epimerization of a group adjacent to a saturated carbonyl. A similar argument may be used in support of the proposed configuration at C_7, which is the same as that in santonin.

J. W. Huffman

School of Chemistry, Georgia Institute of Technology, Atlanta (Georgia), August 17, 1959.

Zusammenfassung

Die Stereochemie der Sesquiterpene Tenulin, Balduilin und Helanilin sowie isophotosantonisches Lakton wird behandelt und provisorische Strukturformeln für diese Substanzen vorgeschlagen.

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[8] D. H. R. Barton, P. de Mayo, and M. Shafiq, J. chem. Soc. *1957*, 929.

[9] Huang-Minlon, J. Amer. chem. Soc. *70*, 611 (1948).

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The Effect of Insulin on Production of Granulation Tissue in Rats[1]

The effect of hormones on connective tissue has been extensively studied. The formation of granulation tissue – one of the basic reactions of the mesenchyme – is influenced by several hormones. The stimulation of this process by STH, thyroxine, and aldosterone and the inhibition by cortisone and sexual steroids is well known[2–9].

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[3] M. Taubenhaus and G. D. Amromin, Endocrinol. *44*, 359 (1949).

[4] P. Desaulles, Z. ges. exp. Med. *124*, 30 (1954).

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[6] T. H. Rindani, Arch. int. Pharmacodyn. *99*, 467 (1954).

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[9] G. Dombrádi and S. Karády, Acta physiol. Acad. hung., Suppl. *5*, 92 (1954).