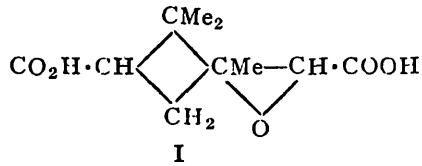
PROFESSOR L. RUZICKA

THE work of Ruzicka can be broadly divided into three distinct groups: (*a*) his earlier work on quinatoxins, (*b*) his researches on the higher carbon ring compounds, and (*c*) his extensive researches on the chemistry of terpenes and allied bodies, including the sterols and resin acids. In this short article an attempt will be made to present an account of his work in a connected manner so that a proper perspective could be formed of his brilliant achievements.

Researches on terpenes and allies.—Ruzicka's first published paper[1] was with Staudinger in 1911, when he published some work on the ketenes. After this, there is a long gap and his next paper[2] was published in 1918 in which he described a complete synthesis of fenchone. The conversion of borneol into camphene has been explained hitherto in two ways by the assumption, on the one hand of a tricyclene and on the other, of a substance containing bivalent carbon. From the first, camphene would result by the fission of the trimethylene ring. Whilst in the case of a secondary alcohol such as borneol the above two explanations are possible, the Wagner rearrangement of a tertiary alcohol is possible only through a tricyclene. Methyl borneol and methyl fenchyl alcohol both give on dehydration the same mixture of hydrocarbons from which both camphor and fenchone are obtained on ozonisation. The reaction can be explained only if a common tricyclene be assumed to be formed from both tertiary alcohols.[3]

In 1919, a synthesis of linalool[4] was effected by treating the sodio derivative of methyl heptenone (formed with sodamide) with acetylene in dry ether. The dehydro linalool formed was ingeneously reduced with sodium and traces of water to linalool. In 1921, considerable progress[5] was made towards the total synthesis of pinene. Ethyl



I

γ-pinonate was condensed with ethyl chloroacetate to a glycidic ester from which the acid (I) was prepared. The latter was converted by heating *in vacuo* to the semi-aldehyde of homopinocamphoric acid. The Dickemann reaction on the ester gave γ-pinocamphone. Since α-pinene has already been obtained from the corresponding alcohol pinocampheol, therefore a partial synthesis of pinene was claimed.

In 1922 began a series of investigations on the dehydrogenation of terpenes with sulphur which paved the way for the final elucidation of structure of many members of this group and the related substances. A substantial advance in our knowledge of the sesqui-terpenes[6] resulted from the investigation of the nature of aromatic substances produced by heating them with sulphur. The dehydrogenation of cadinene, calamenol, zingiberene and the sesqui-terpene from Javanese citronella oil gave one and the same hydrocarbon, $C_{15}H_{18}$, termed cadalene which was proved by synthesis to be 1 : 6-dimethyl-4-isopropyl naphthalene.

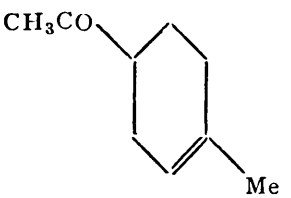
A complete synthesis of nerolidol and farnesol[7] was occomplished by condensing αβ-dihydro-ψ-ionone, $Me_2C : CH.CH_2.CH_2.CMe : CH.CH_2.CH_2.COCH_3$, with acetylene, as in the case of the synthesis of linalool, and dehydro dl-nerolidol was obtained. The reduction of the latter with sodium in moist ether gave dl-nerolidol [$Me_2C = CH.CH_2.CH_2CMe = CH.CH_2 - CH_2 - CMe(OH) - CH = CH_2$] which passed into farnesol with acetic anhydride. The formation of eudalene from eudesmol and selinene, established that in the biogenesis of the terpenes the three isoprene residues joined end to end (as in farnesol) can be coiled up to produce the cadinene frame work and also may coil up in two other alternative manners, of which eudalene represents one type. When farnesene is treated with acetic acid containing a little sulphuric acid,[8] it is converted into the acetate of α-bisabolol; the alcohol on treatment with hydrogen chloride gives a trihydrochloride identical with natural bisabolene from oil of opopanax. Since farnesene[7] had been synthesised from geranyl chloride *via* dihydro-ψ-ionone and nerolidol, hence a complete synthesis of bisabolene was accomplished.

The structure of zingiberene was investigated and the carbon skeleton of zingiberene was proved to be the same as that of bisabolene.

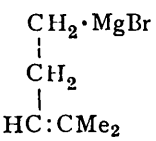
The constitution of santonin was investigated by Clemo and Haworth who synthesised desmotroposantonin and more or less

settled its constitution but proof was still needed for the position of the methyl group. Ruzicka dehydrogenated with selenium the Clemmensen reduction product of tetrahydro-santonin and isolated 1-methyl-7-ethyl-naphthalene[10] which thus placed it in the eudesmol (selinene) group of terpenes.

The synthesis[12] of bisabolol and bosabolene was accomplished as follows: The ketone II, obtained by ozonolysis of β-terpeneol was condensed with the Grignard reagent from ε-bromo-β-methyl Δ^2-pentene



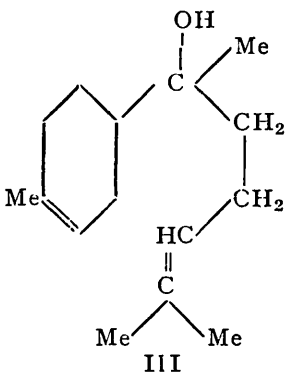
II



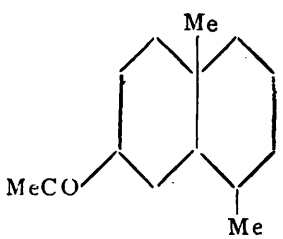
giving bisabolol III. This synthesis removed all doubts as to the position of the double bond. The conversion of the dehydration product of dihydro-eudesmol by ozonolysis into acetyl dimethyl decalin of the structure IV proved the position of the hydroxy group in eudesmol.

The oxidation of abietic acid with excess of permanganate gives two acids,[13] $C_{11}H_{16}O_6$ and $C_{12}H_{18}O_6$. The former is dehydrogenated by selenium to *m*-xylene and the latter to 1 : 2 : 3 trimethyl benzene. From this the conclusion was drawn that the methyl group which is lost in the dehydrogenation of abietic acid to retene occupies the 12 and not the 11 position as hitherto supposed. The position of the carboxyl group in abietic acid was determined by the researches of Ruzicka and Haworth and the fact that the acid and its ester combine with maleic anhydride[14] proved the presence of a system of conjugated double bonds and thus the skeleton of abietic acid was conjectured. The suggested formula of abietic acid, however, is only derivable from irregular isoprene chains. It has now been shown by Wienhaus[22] *et al* that abietic acid and maleic anhydride do not react below 130° to an appreciable extent. The primary acids of pinus sylvestris react at ordinary temperature both with maleic anhydride and benzoquinone. Therefore the conjugated double bonded system in abietic acid is unproved and the spectroscopic and refractometric measurements also do not indicate it.

The stereochemical problems arising out of the *cis*- and *trans*-locking of the polycyclic hydroaromatic compounds present an almost insurmountable obstacle in the determination of structure of these bodies. Refractometric measurements[15] and a comparison of m.ps. of different derivatives with those in the decalin series indicate that cholestane has a trans-trans-cis or trans-trans-trans configuration. It has been pointed out



III



IV

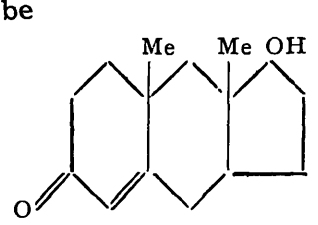
that the trans fusion of the rings II and III may well account for the non-formation of ketones from 1 : 6 dicarboxylic acids obtained by the opening of ring II or III. Much of the work on the stereochemistry of the sterols is due to Ruzicka[28] who has dealt with the assignment of the configurations. Practically all the known steroids belong to one of two ring systems: (*a*) the cholestane type or (*b*) coprostane type. These differ in the orientation of the hydrogen on C_5 relative to 10-methyl group which is *trans* in type (*a*) and *cis* in type (*b*). Ruzicka's view is that cholestanol has the locking trans, trans-antitrans-antitrans configuration. The hydrolysis of acetates and benzoates of epimeric pairs (*a*) cholestanol and epicholestanol, (*b*) coprostanol and epicoprostanol, (*c*) cholesterol and epicholesterol showed that all compounds denoted as *trans* were more readily hydrolysed than the *cis*-epimerides.

The original Rosenheim-King formula was based on the formation of chrysene by the dehydrogenation of cholic acid. Ruzicka reinvestigated the problem but could not find any chrysin. Ergosterol gave a hydrocarbon $C_{26}H_{26}$, the next higher homologue of the hydrocarbon $C_{25}H_{24}$ produced from cholesterol. The synthesis of Diel's hydrocarbon by Bergmann and Hillemann showed that during selenium dehydrogenation the migration of a methyl group occurs and the value

of this method becomes thus questioned. However, subsequent researches from many countries have now proved the conditions under which an angular methyl group may migrate and therefore the method is still a valuable one for determining structure.

Androsterone.—The male sexual hormone $C_{19}H_{30}O_2$ isolated in minute quantities was proved to be a hydroxy ketone. Its sterol-like structure was merely surmised. Ruzicka[17] found that β-cholestanyl chloride and cholestanyl acetate could be oxidised by chromic acid to ketones in which the side chain is completely removed. In a later paper the oxidation[18] of three remaining isomerides of cholestanyl acetate was described. The substance derived from epi-dihydrocholesterol had an activity equal to that of the natural hormone and was identical with it. Ruzicka has suggested that androsterone arises in nature by a process similar to that by which it is prepared *in vitro*—epimerisation of the hydroxy group of dihydrocholesterol followed by the oxidation of the side chain.

The question of the activity of these hormones has been studied and it has been found that androstane diol[10] is four or five times more active in promoting growth of comb but only slightly more active in promoting vesicular growth than androsterone. The most active of all is testosterones, a substance isolated from tests by Laquer,[20] which is five times as active as androsterone in promoting growth of comb and twenty times more active in promoting vesicular growth. The structure of testesterone[21] was shown to be



David[23] confirmed this view by oxidising it to androstene 3 : 17 dione.

It seems that testesterone is the true hormone and that androsterone and related substances are products of its metabolism.

It was shown by Laquer that testesterone displays its maximum biological activity only in presence of an 'X-substance' present in testicular extracts. It was shown that by esterification of testesterone, its activity is much enhanced. The most active ester was found to be the propionate[24] which is now used clinically under the name 'perandren'.

The Triterpenes.—The determination of m.w. of triterpenes presents many difficulties. Recent investigations have shown that many of these compounds may have as many as 30 C atoms.[25] The functional groups are difficult to detect. The CO group in $\alpha\beta$-unsaturated ketones could only be detected spectroscopically and the acid groups would not esterify under ordinary conditions. The action of ozone is unreliable and perbenzoic acid gives unsatisfactory results.

The results of dehydrogenation of the triterpenes are now available and much of the information has been supplied by Ruzicka and his collaborators. As a result of these investigations the structure of oleanolic acid and hederagenin are now fairly clear.

The isoprene rule is now so firmly established that more than usual interest attaches to the problem of the structure of artemesia ketone which violates the isoprene rule. The structural position has been consolidated by the synthesis[26] of its tetrahydro derivative from $\alpha\alpha$-dimethyl butyryl chloride and *iso*-butyl zinc iodide $CHMe_2.CH_2ZnI + ClCO.CMe_2Et = CHMe_2.CH_2.CO.CMe_2Et$.

Large carbon rings.—The preparation of the ring ketones by the distillation of the calcium salts of normal $\alpha\omega$ fatty dicarboxylic acids has been restricted to the preparation of C_5, C_6 and C_7 cyclic ketones which can be obtained in about 30% yield. The cyclo octanone prepared by this method was found to be a mixture. Ruzicka[29] showed that 5% pure cyclo-octanone could be prepared from calcium azelate and 10% from cerium azelate. By the use of thorium salts the yield could be increased to 25%. The identification of by-products (cyclohexanone and nonanone-2) proved that the azelaic acid underwent fission to a pimelate and an acetate. Cyclononanone was also prepared in poor yield, due no doubt to the fission of the dicarboxylic acid. The higher ketones C_{10} to C_{18} were obtained by the vacuum distillation of the corresponding thorium salts. The yield of the ketones passed through a minimum (0·1–0·2%) at C_{10} and thereafter rose. The odour of the ketones resembled civet from C_{16} to C_{18}. According to the classical theory of Baeyer, the strain in a cycloheptadecane is $-24°41'$ whilst a cyclopropane has $+24°44'$. But the cyclic ketones from C_7 to C_{18} underwent no change when heated with concentrated hydrochloric acid

at 180–200°. Cycloheptadecanone was passed over thoria at 400–420° and was recovered unchanged. Therefore, it became clear that the larger rings relieved their strain by throwing up some of the carbon atoms in space. This was evident from the consideration of volume contribution of CH_2 in an alkane and a cycloalkane. The volume contribution of CH_2 in an alkane is 16·1, whilst the following values were obtained for cycloparaffins:

No. of CH_2 groups	4	5	6	7	15	17
V/n	20·4	18·8	18·0	17·3	16·1	16·1

The values for the smaller rings represent the volume occupied by CH_2 groups *plus* a share of the internal space. From C_{15} onwards the carbon atoms completely fill up the internal space and hence the value becomes equal to the CH_2 of an alkane. The value for heat of combustion of the methylene group has been found[30] in large rings to be 156 to 157 Kg-Cals. This corresponds to 157 Kg-Cals. for the methylene group in a paraffin and thus there can be no doubt as to their multiplanar configuration.

The structure of muscone (the ketone of musk) was found to be a methyl cyclopentadecanone and civetone, the ketone from civet cat was proved to be a heptadecanone. The synthesis[31] of *dl* muscone was effected in 1934 and in 1935 members of the C_{33} group were described as also the preparation of 7 to 18 membered saturated and unsaturated cyclic imines.[32] Civetone was converted into *iso*-oxime by ammonia and hydrochloric acid in benzene, the *iso*-oxime was converted into thio-oxime and then reduced with sodium and acetic acid in ethanol and heptadecamethyleneimine isolated. The polymethylenes (16 membered) attached to a benzene ring in *meta* and *para* position[33] were also prepared.

The modified quinatoxins.—Ruzicka[34] prepared a series of quinatoxine like compounds, *e.g.*, 4-quinolyl-(ε-aminopentyl) ketone, 4-(6-methoxyquinolyl ε-aminopentyl ketone, 4-pyridyl δ-methylaminobutyl ketone, 4-(6-methoxyquinolyl)-(δ-aminobutyl)ketone, etc. These compounds were tested by Giemsa but found to have no curative value. These experiments are significant in view of the later discovery of plasmoquin.

The above summary gives a very imperfect idea as to the versatility of Ruzicka's mind. The recognition of his work by the award of a Nobel Prize is an encouragement to all workers in organic chemistry as unlike other branches of science, work in organic chemistry involves considerable spade work and the results have little appeal to the lay public.

J. N. RAY.

University Chemical Laboratory,
Lahore.

---

1 *Annalen*, 1911, **380**, 278–303.
2 *Ber.*, 1917, **50**, 1362–74.
3 *Helv. Chim. Acta.*, 1918, **1**, 110.
4 *Ibid.*, 1919, **2**, 182–88.
5 *Ibid.*, 1921, **4**, 666.
6 *Ibid.*, 1922, **5**, 345, 562, 710.
7 *Ibid.*, 1923, **6**, 483–502.
8 *Ibid.*, 1925, **8**, 259.
9 *Ibid.*, 1924, **7**, 379.
10 *Ibid.*, 1930, **13**, 1117.
11 *Ibid.*, 1930, **13**, 1402.
12 *Ibid.*, 1932, **15**, 3.
13 *Ibid.*, 1925, **8**, 637.
14 *Ibid.*, 1932, **15**, 1289.
15 *Ibid.*, 1933, **16**, 327.
16 *Ibid.*, 1933, **16**, 216, 812.
17 *Ibid.*, 1934, **17**, 1387.
18 *Ibid.*, 1934, **17**, 3519.
19 *Ibid.*, 1935, **18**, 210.
20 *Z. Physiol. Chem.*, 1935, **233**, 281.
21 *Helv. Chim. Acta*, 1935, **18**, 1264.
22 *Ber.*, 1936, **69**, 2198.
23 *Acta. Brev. Neerl*, 1935, **5**, 85.
24 *Helv. Chim. Acta.*, 1936, **19**, 1141.
25 *Ibid.*, 1932, **15**, 472; 1936, **19**, 1136, 1402; 1937, **20**, 312.
26 *Ibid.*, 1936, **19**, 646.
27 *J. Soc. Chem. Ind.*, 1935, **54**, 509.
28 *Helv. Chim. Acta.*, 1936, **19**, 842; 1937, **20**, 1557.
29 *Ibid.*, 1926, **9**, 389.
30 *Ibid.*, 1933, **16**, 162.
31 *Ibid.*, 1934, **17**, 1308.
32 *Ibid.*, 1935, **18**, 659.
33 *Ibid.*, 1932, **15**, 1220.
34 *Ibid.*, 1924, **7**, 995.