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SCHIZANDRIN - LIGNAN OF UNUSUAL STRUCTURE

N.K. Kochetkov, A. Khorlin, O.S. Chizhov and V.I. Sheichenko

Institute for Chemistry of Natural Products,

Academy of Sciences, Moscow

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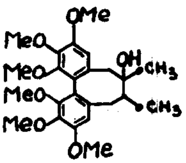
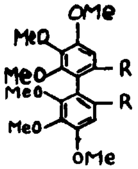
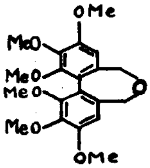
WE have recently described[1] the isolation and some properties of schizandrin, schizandrol and γ-schizandrin - Schizandra chinensis Baill. seed oil components. The present communication contains data, which may serve as basis for suggesting structure (I) for schizandrin.



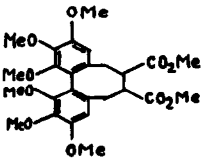
I



IIa R = COOH
IIb R = COOCH3
IIc R = CH_2Br



III



IV

Schizandrin has the molecular formula $C_{24}H_{32}O_7$ * (Found C, 66.44, 66.52; H, 7.20, 7.39; OCH_3 41.75, 41.50; C-CH_3 5.54, 5.56. Calc. C, 66.65; H, 7.46; 6O CH_3 43.05; 2 C-CH_3 6.95). Schizandrin I.R.-spectrum contains a sharp hydroxyl band (3495 cm^{-1}). This hydroxyl is inert towards CrO_3 in CH_3COOH and acetic anhydride in pyridine which is an indication of its tertiary character. $KMnO_4$-oxidation of schizandrin in 2% KOH for 48 hours at 50° gave an aromatic dicarboxylic acid $C_{20}H_{22}O_{10}$, m.p. 240-242°, R_f 0.10

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* The previously published analytical data were not exact.[1]

[1] N.K. Kochetkov, A. Khorlin and O.S. Chizhov, J.Gen.Chem. (U.S.S.R.) 31, 3454 (1961).

(butanol - 1.5 N ammonia 1:1), dimethyl ester m.p. 93-95°. Hathway[2] gives m.p. 243° for 4,5,6,4',5',6'-hexamethoxydiphenic acid (IIa) and for the dimethyl ester (IIb) m.p. 95-97°. Mixed melting point, I.R.- and U.V.-spectra, paper chromatography (R_f-value and colour of spots by detection with Male reagent) and thin non-fixed layer chromatography on alumina of the dimethyl ester showed our products to be completely identical with specially prepared samples of IIa and IIb.

The 2,2'-hydrogens of the diphenyl nucleus in the schizandrin molecule could have been substituted either by short side chains or by a two-, three- or four-membered bridge. The choice between these structures was made on the basis of the U.V.-spectrum of schizandrin. Turner et al.[3] showed, that the U.V.-spectra of the biphenyl derivatives, containing a bridge between the 2,2'-positions, depend upon the number of members in the cycle. Absorption peaks, arising from the aromatic rings conjugation, shift in the direction of smaller wavelengths and become flatter on passing from an eight-membered to a six-membered cycle. There is also a concurrent narrowing of the longer-wave peak. Furthermore, unbridged biphenyl derivatives, substituted in the 2,2'- and 6,6'-positions are known to have no conjugation peaks.[4]

Schizandrin U.V.-spectrum was similar to that of dimethyl-1,2,3,4-dibenzocycloöcta-1,3-dien-6,7-dicarboxylate. In order to exclude any violation of the above mentioned regularities, which could have been caused by the presence of six methoxyls, we synthesized a number of more suitable model compounds, namely, 1,2,3,8,9,10-hexamethoxy-5,6-dihydrophenantrene

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[2] D.E. Hathway, J.Chem.Soc. 519 (1957).

[3] G.H. Beaven, G.R. Bird, D.M. Hall, E.A. Johnson, J.E. Ladbury, M. Leslie and E.E. Turner, J.Chem.Soc. 2708 (1957) and other parts of the series.

[4] B Williamson and W.H. Rodebush, J.Amer.Chem.Soc. 63, 3018 (1941).

(V), hexamethoxydihydrodibenzoxepin (III) and dimethylhexamethoxydibenzocyclooöctadien-6,7-dicarboxylate (IV).*

The U.V.-spectra of these compounds as well as of schizandrin are shown in Figs. 1 and 2. There is a close similarity between the U.V.-spectra of schizandrin and compound IV, whereas all the other substances differ from the former.

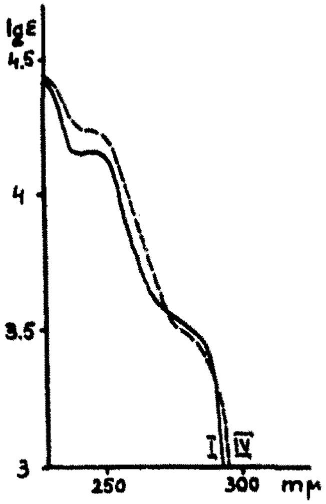


Fig. 1.

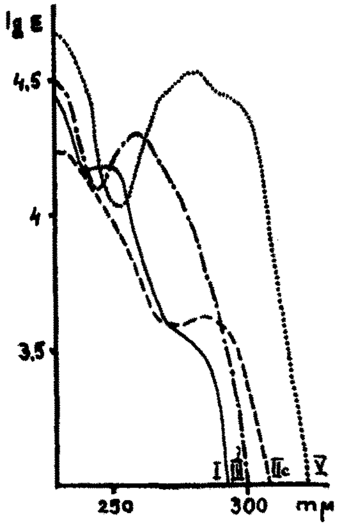
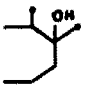
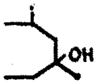


Fig. 2.

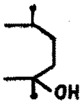
Schizandrin is thus a dibenzocyclooöctadiene derivative. It follows, that besides structure I five other structures are possible. As the hydroxyl is not affected by hydrogenolysis, formulae VIII-X seem less probable.



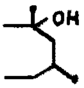
VI



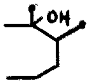
VII



VIII



IX



X

Structure I was confirmed by the NMR-spectrum of schizandrin**, which

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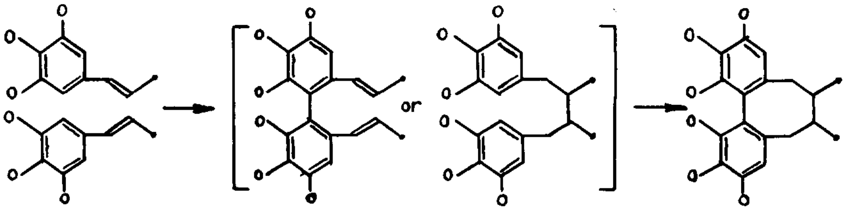
[*] The synthesis will be described elsewhere.

[**] The NMR-spectrum was observed at 40 Mc in carbon tetrachloride solution vs. benzene as an external etalon.

exhibited peaks, characteristic of aromatic hydrogens(16.4 and 18.8 cps), methoxyl (129 and 140 cps), methyl (235, 249 and 255 cps), hydroxyl (214 cps) and methylene (182 and 187 cps). The most essential information for the choice between the structures VI-X and I was obtained from the analysis of the width and position of the methylene peaks. The area of this wide doublet corresponds to four protons. The chemical shift corresponds to alkylbenzene CH_2-groups. The considerable width of the doublet is due to difference in the position of protons at the hydroxyl, as well as to axial equatorial hydrogens shift and spin-spin splitting. By no means does this doublet correspond to chemical shift between the methylene groups of structures VI, VII, IX and X, which should have led to a distance of 35-40 cps between the peaks[5].

Though the structure of I is rather uncommon, its biosynthesis can be well imagined to proceed through dimerization of a precurser of the isoelemicyne type:



Structures VI-X, on the other hand, cannot be explained from the biogenetic viewpoint without additional assumptions.

Schizandrin is the first representative of the new type of lignans, characterized by an aryl-aryl bond and an eight-membered ring.

γ-Schizandrin and schizandrol, isolated from Schizandra chinensis, have U.V.-spectra, quite similar to that of schizandrin, and presumably contain the same 1,2,3,4-dibenzocycloöcta-1,3-diene system. It is known,

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[5] N.F. Chamberlin, Analyt.Chem. **31**, 56 (1959).

that seven-membered cycles are sometimes formed by oxidative coupling of phenols, but we believe this to be the first case of such a pathway for an eight-membered cycle.

Acknowledgements - Our grateful thanks are due to M. Grachev translating this article.