troleum ether, yielded 1.5 g. (79%) of colorless crystals, m.p. 230°. The second fraction, eluted with a mixture of benzene and petroleum ether (1:4), gave 0.10 g. of unidentified yellow material. The third fraction, eluted with benzene, gave 0.25 g. of an unidentified, deeply red material.

Anal. Calcd. for $C_{26}H_{20}$: C, 93.94; H, 6.06. Found: C, 93.69; H, 6.07.

The other hydrocarbons were prepared in a similar way.

BLACKSBURG, VIRGINIA

[CONTRIBUTION FROM THE UNITED STATES DEPARTMENT OF AGRICULTURE, AGRICULTURAL RESEARCH SERVICE, ENTOMOLOGY RESEARCH BRANCH]

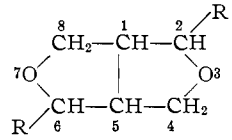
The Synthesis of *dl*-Sesamin and *dl*-Asarinin[1]

BY MORTON BEROZA AND MILTON S. SCHECHTER

RECEIVED SEPTEMBER 29, 1955

dl-Sesamin—2,6-bis-(3,4-methylenedioxyphenyl)-*cis*-3,7-dioxabicyclo[3.3.0]octane—and its diastereoisomer, *dl*-asarinin, have been synthesized. Separate reductions of the oily and crystalline forms of the diethyl ester of 2,3-bis-(3,4-methylenedioxybenzoyl)-succinate (X) with lithium aluminum hydride gave different tetrahydroxy compounds XIa, XIb. Compound XIa, from the reduction of the oily form of X upon heating with ethanolic hydrochloric acid, lost two molecules of water to give *dl*-sesamin. *dl*-Sesamin has been epimerized in part to *dl*-asarinin. The tetrahydroxy compound XIb, from the reduction of the crystalline form of X upon heating with ethanolic hydrochloric acid, lost only one molecule of water to give as the main product a tetrahydrofuran compound XII. The stereochemistry of the synthesis is discussed and an explanation for the course of the synthesis is presented. Stereochemical considerations indicate that a third racemic isomer of *dl*-sesamin and *dl*-asarinin should be possible.

Although the chemical structure of sesamin and asarinin shown in formula I was proved in 1939 by Bruchhausen and Gerhard,[2] a synthesis of these compounds has not been reported. This paper describes the synthesis of the racemic forms of these compounds.



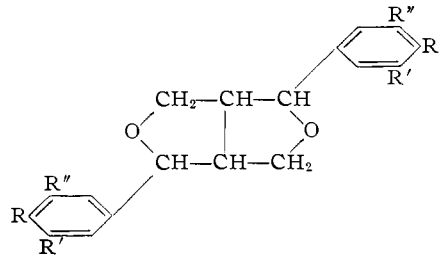
I, R = 3,4-methylenedioxyphenyl

The known optically active stereoisomers having the sesamin formula (I) are *d*- and *l*-sesamin (rotations +68° and −68°), isosesamin and asarinin (rotations +122° and −122°). *d*-Sesamin is a constituent of the unsaponifiable fraction of sesame oil. Each of the other isomers has been found naturally.[3-6]

Sesamin, asarinin and isosesamin became important when they were found[7,8] to increase markedly the insecticidal potency of pyrethrins without themselves being insecticidal. Haller, *et al.*,[7] demonstrated that the 3,4-methylenedioxyphenyl group was essential for sesamin's synergistic activity with pyrethrins. This discovery led to the commercial development of such excellent synergists as piperonyl butoxide,[9] sulfoxide,[10] *n*-propyl isomer,[11] and piperonyl cyclonene.[9]

Treatment of *d*-sesamin with ethanolic hydrochloric acid results in an equilibrium mixture of it and its diastereoisomer isosesamin.[3,4] Similar treatment of asarinin gives an equilibrium mixture of it and *l*-sesamin. These changes result from the reversible epimerization of the groups on carbon atoms 2 and 6.

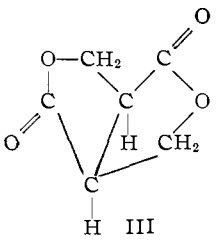
Paralleling the structural studies on sesamin and its isomers were the investigations on pinoresinol (IIa) and eudesmin (IIb). The relationship of these compounds to asarinin and sesamin was established by the conversion of asarinin and *d*-sesamin to eudesmin and pinoresinol dimethyl ether,[12] the epimeric forms of which are also known.[13]



IIa, R = OH, R′ = OCH_3, R″ = H for pinoresinol
IIb, R = R′ = OCH_3, R″ = H for eudesmin and pinoresinol dimethyl ether
IIc, R = OH, R′ = R″ = OCH_3 for syringaresinol

Each of the aforementioned compounds contains a 3,7-dioxabicyclo[3.3.0]octane nucleus with 3,4-substituted aryl groups in the 2- and 6-positions. Further confirmation of the correctness of this structure was supplied by Erdtman and Gripenberg[14] and Beroza,[15] who isolated the *di*-γ-lactone of α,β-bis-(hydroxymethyl)-succinic acid (III) as an oxidation product from pinoresinol and from *d*-sesamin and asarinin. Because dilactone III was optically active, they concluded that the hydrogen atoms at positions 1 and 5 must be in the *cis* configuration. A *trans* configuration would give a symmetrical molecule which could not exhibit optical activity.

(1) Presented at the 128th Meeting of the American Chemical Society, Minneapolis, Minn., September 15, 1955.
(2) F. von Bruchhausen and H. Gerhard, *Ber.*, **72**, 830 (1939).
(3) T. Kaku, N. Kutani and J. Takahashi, *J. Pharm. Soc. Japan*, **56**, 80 (1936).
(4) Huang-Minlon, *Ber.*, **70**, 951 (1937).
(5) T. Kaku and H. Ri, *J. Pharm. Soc. Japan*, **57**, 184 (1937).
(6) J. B. Davenport and M. D. Sutherland, *Australian J. Chem.*, **7**, 384 (1954).
(7) H. L. Haller, F. B. La Forge and W. N. Sullivan, *J. Econ. Entomol.*, **35**, 247 (1942).
(8) C. Eagleson, U. S. Patent 2,202,145 (May 28, 1940).
(9) H. Wachs, *Science*, **105**, 530 (1947).
(10) M. E. Synerholm, A. Hartzell and V. Cullmann, *Contrib. Boyce Thompson Inst.*, **15**, 35 (1947).
(11) M. E. Synerholm and A. Hartzell, *ibid.*, **14**, 79 (1945).
(12) T. Kaku and H. Ri, *J. Pharm. Soc. Japan*, **57**, 1015 (1937).
(13) T. Kaku and H. Ri, *Keizyo J. Med.*, **9**, 5 (1938).
(14) H. Erdtman and J. Gripenberg, *Acta Chem. Scand.*, **1**, 71 (1947).
(15) M. Beroza, THIS JOURNAL, **77**, 3332 (1955).



III

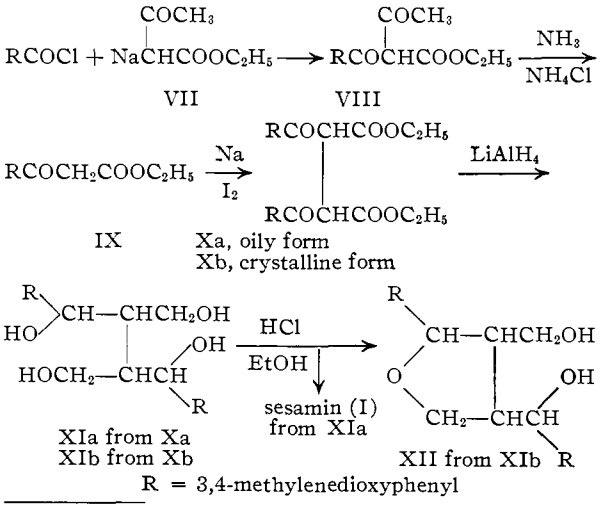
Because of the high strain involved, the *trans* structure for the nucleus was considered by Erdtman and Gripenberg[14] and Beroza[15] to be sterically improbable. Rolla and Marinangeli[16] denied the possibility of a centrosymmetrical formula for sesamin on the basis of the high value of the dipole moment which they found for sesamin.

Shortly after we started the present synthesis, Freudenberg and Dietrich[17] reported a chemical synthesis of pinoresinol. A solution of ferulic acid (IV) and ferric chloride upon aeration with oxygen reacted to give dehydrodiferulic acid (V). Reduction with lithium aluminum hydride gave 1,4-bis-(3-methoxy-4-hydroxyphenyl)-2,3-bis-(hydroxymethyl)-1,4-butanediol (VI). Closure by dehydration during distillation in high vacuum, chromatography of the product on paper and treatment with dinitrofluorobenzene led to the isolation of a small amount of the dinitrophenyl ether of *dl*-pinoresinol. In a similar manner Freudenberg and Schraube[18] were able to synthesize syringaresinol (IIc).

Our attempts to synthesize sesamin by Freudenberg's route starting with 3-(3,4-methylenedioxyphenyl)-acrylic acid were unsuccessful, probably because this compound contained no phenolic-hydroxyl groups.

Bruchhausen and Gerhard[2] attempted the synthesis of sesamin but did not attain their goal. We employed one of their intermediates, the diethyl ester of α,α'-dipiperonoylsuccinic acid (X), as a starting point in our synthesis.

The synthesis of sesamin, 2,6-bis-(3,4-methylenedioxyphenyl) - *cis* - 3,7 - dioxabicyclo[3.3.0]octane, which was finally devised, utilizes the steps



(16) M. Rolla and A. M. Marinangeli, *Boll. sci. facolta chim. ind. Bologna*, **7**, 48 (1949).

(17) K. Freudenberg and H. Dietrich, *Chem. Ber.*, **86**, 1157 (1953).

(18) K. Freudenberg and H. Schraube, *ibid.*, **88**, 16 (1955).

The oily Xa and crystalline Xb forms of compound X were reduced separately with lithium aluminum hydride. In both cases the keto and ester groups were reduced to give as the main crystalline products the tetrahydroxy compounds XIa and XIb, respectively. Each of these melted at about 180°; however, a mixture melting point of the two gave a large depression, showing that the compounds were different.

Ring closure of the tetrahydroxy compound XIa, derived from the oil, was effected by heating with 1% ethanolic hydrochloric acid. The main product of the reaction, *dl*-sesamin, was obtained in 75% yield and melted at 125–126°. The melting point was undepressed in admixture with *dl*-sesamin prepared from equal parts of natural *d*- and *l*-sesamin.[3,4] The synthetic and natural *d*-sesamin had identical infrared[19] and ultraviolet[20] absorption spectra. Likewise, tests against house flies showed no significant differences in the synergistic activity of these compounds with pyrethrins.[21]

Synthetic *dl*-sesamin was partially converted to *dl*-asarinin by refluxing in ethanolic hydrochloric acid. The *dl*-asarinin and *dl*-sesamin were separated by chromatography in 47 and 32% yield, respectively. The melting point of this synthetic *dl*-asarinin was undepressed in admixture with *dl*-asarinin prepared from natural materials.[3,4]

From the mother liquors of compound XIa, there were obtained in very small yields two additional tetrahydroxy compounds, XIc and XId, having the same empirical formula as XIa. XIc melted at 189–190°, XId at 199–200°. Upon ring closure with ethanolic hydrochloric acid, both these compounds gave *dl*-sesamin plus a very small amount of *dl*-asarinin. XIc and XId are apparently polymorphic forms of XIa. Melting points of material from cross-seeding experiments seemed to confirm this conclusion, although studies on the infrared spectra of their solutions were inconclusive on this point.

The main product obtained by ring closure of XIb upon heating with 1% ethanolic hydrochloric acid was a compound melting at 119.5–120° and believed to have structure XII. Its elementary analysis showed that only one molecule of water had been eliminated. The compound contained two active hydrogen atoms (Zerewitinoff), thus eliminating the possibility that it was a tetrahydronaphthalene type structure (as in formula XIV). The weakly acidic conditions of closure precluded the formation of a tetrahydrofuran ring by etherification of the two primary carbinol groups. Oxidation of compound XII with potassium permanganate in acetone gave a 22% yield of piperonylic acid, indicating the presence of a methylenedioxyphenylcarbinol group. Similar oxidation of sesamin gave a negligible yield of piperonylic acid. These results make it unlikely that XII has a tetrahydrofuran ring containing both methylenedioxyphenyl groups. The failure of this compound to lose another molecule of water and close completely is discussed later.

(19) M. Beroza, *J. Am. Oil Chemists' Soc.*, **31**, 302 (1954).

(20) P. Budowski, R. T. O'Connor and E. T. Field, *ibid.*, **28**, 51 (1951).

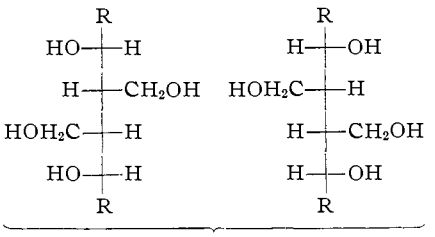
(21) Acknowledgment is gratefully made to W. A. Gersdorff and P. G. Piquett of the Entomology Research Branch for the entomological tests.

In addition to the crystalline tetrahydroxy compounds XIa, XIb, XIc and XId, a more soluble, gum-like product was obtained by evaporation of the mother liquors in each lithium aluminum hydride reduction of compounds Xa and Xb. These gum-like materials were heated with ethanolic hydrochloric acid, and the products were subjected to chromatography, but no crystalline or otherwise characterizable compounds could be isolated in appreciable quantity except small amounts of sesamin from the former and some compound XII from the latter reduction product (probably due to the presence of some XIa and XIb in the respective mother liquors).

Stereoisomerism.—The stereoisomerism encountered in the compounds employed in this synthesis is of interest. Bruchhausen and Gerhard[2] stated that compound X existed in both an oily and a crystalline form, which were produced in almost equal quantities, without further discussion of the nature of the isomerism. As we will show later, there seems to be evidence that the crystalline form Xb is a *meso* compound and the oily form Xa contains as a major component the racemic isomer. Xa also contains some enolic forms (positive ferric chloride test) which are in equilibrium with the *meso* and racemic compounds.[22] Xb is a diketo compound since it gives a negative test for enols.

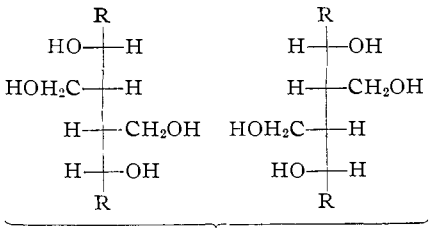
On prolonged standing of an ether solution of Xa, additional amounts of the crystalline compound Xb are obtained. This conversion is probably favored because the extreme insolubility of Xb in ether causes it to crystallize out of the solution, thus displacing the equilibrium in its favor.

Reduction of the racemic form of X by lithium aluminum hydride could theoretically produce three racemic forms of the tetrahydroxy compound XI



dl

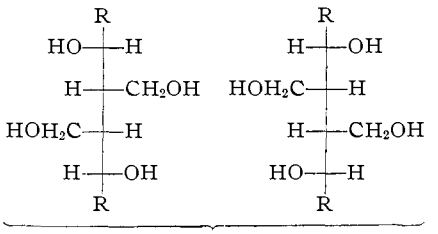
A



dl

B

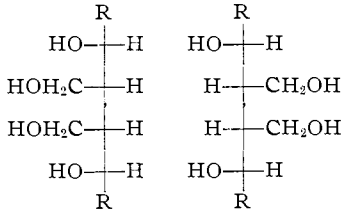
(22) Compare, for example, the diethyl ester of dibenzoylsuccinic acid, which can exist in seven inactive forms—two diketo (one *meso* and one racemic), two ketoenol, and three dienol forms—some of which may be interconvertible; see Beilstein's "Handbuch der Organischen Chemie," Vol. 10, 4th Ed., Julius Springer, Berlin, 1927, p. 913.



dl

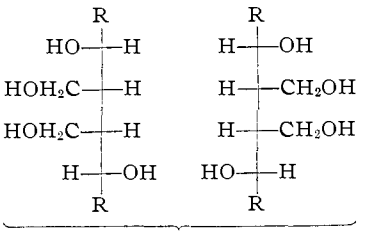
C

Reduction of the meso form of X could produce three forms of compound XI, two of which would be *meso* and the other a *dl*- or racemic form



meso D

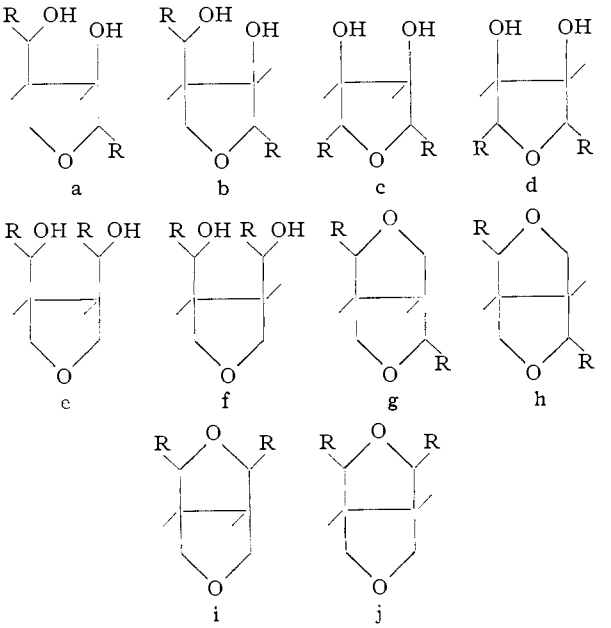
meso E



dl

F

Theoretically, the following ten compounds may be produced by dehydration of the various isomers (A, B, C, D, E or F) of compound XI



Theoretically the tetrahydroxy compounds A, B and C (formed by reduction of the racemic form of

X) could, on dehydration, yield compounds of the structure a, d or f by the loss of one molecule of water and structures g or j by the loss of two molecules (not counting the isomers due to the asymmetric carbon atoms to which the methylenedioxyphenyl groups are attached).

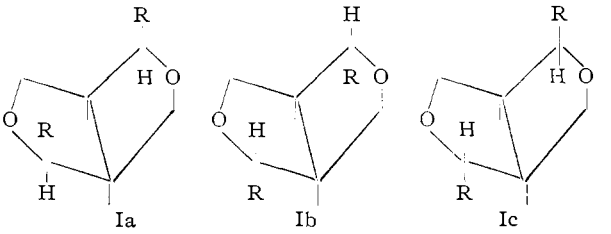
There are two important factors in the ring closures of the tetrahydroxy compounds XIa and XIb. Firstly, reaction rate studies[23] show that the rate of etherification and the yield of ether formed from a substituted benzyl alcohol decrease sharply as the alcohol with which it is etherified changes from primary to secondary to tertiary. Consequently, the methylenedioxyphenylcarbinol groups of the tetrahydroxy compounds XIa and XIb would be expected to react more readily with the primary carbinol groups than with each other, or more readily than the primary carbinol groups with each other. Secondly, steric considerations favor the formation of a *cis*-3,7-dioxabicyclo[3.3.0]octane structure, which is practically strainless, whereas the *trans* structure probably cannot be formed because of excessive strain.[24]

These considerations favor the formation of a rather than d or f. Furthermore, a would immediately close to the practically strainless structure g. It is not likely that any d or f, if formed, could close by loss of another molecule of water to j because of the great strain involved in the resulting *trans* structure.

It follows that the preferred route of ring closure of the tetrahydroxy compound from the racemic form of X should give g, a compound having the sesamin or asarinin type of structure. Indeed, sesamin and a very small amount of asarinin were the only compounds isolated from the closure of XIa (from the oily form of X). This shows that a major portion of the oily form of X (Xa) was the racemic rather than the *meso* form. We have been able to obtain only one of three possible tetrahydroxy compounds upon reduction of the oily form of X.

Theoretically the tetrahydroxy compounds D, E and F formed by the reduction of the *meso* form of X could, on dehydration, yield compounds of the structure b, c or e by the loss of one molecule of water and of structure h or i by the loss of two molecules of water (not counting isomers due to the asymmetric carbon atoms to which the methylenedioxyphenyl groups are attached). Again by application of the above-mentioned principles relating to etherification and *cis* and *trans* fused-ring structures, it follows that structure b should be formed in preference to c or e. If little or none of structures c or e were formed, i could not be formed in appreciable yield. Structure b could not close to h, since this closure would involve the formation of the sterically improbable *trans*-3,7-dioxabicyclo-[3.3.0]octane structure. Hence, b would be the most likely possibility in the dehydration of the tetrahydroxy compounds D, E or F. The fact that the only crystalline product XII isolated upon closure of XIb (from crystalline form of X) was half-closed shows that compound Xb (crystalline form) is the *meso* modification. We have been able to obtain only one of three possible tetrahydroxy compounds upon reduction of the crystalline form of X.

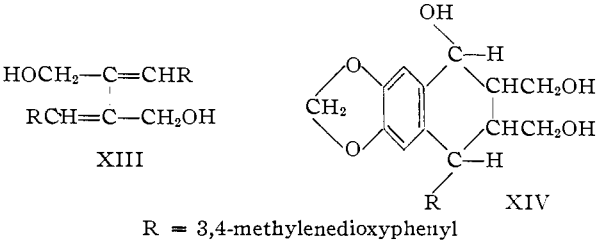
Consideration of the stereochemistry of structure g indicates three isomers to be possible,[25] one from each of the three compounds A, B and C. The structures are



Ia Ib Ic

Ic is asarinin.[26] Sesamin is either Ia or Ib. The third isomer is still unknown at present. In our synthesis we were able to obtain but one of the three possible tetrahydroxy compounds upon reduction of the oily form of X. Upon closure with dilute ethanolic hydrochloric acid, it yielded sesamin as the main product together with a very small amount of asarinin. We were unable to isolate any tetrahydroxy compounds which, on closure, yielded asarinin or the unknown sesamin isomer as the main product. It is possible that steric factors favor the formation of but one tetrahydroxy compound from the reduction of each form of X. By the chromatographic procedure *dl*-sesamin and *dl*-asarinin were readily separated, but evidence of a third sesamin-type isomer could not be found.

In this study we have attempted to explain the formation of those compounds that we were able to isolate in pure form. Other compounds, such as XIII and XIV, are possible products in the dehydration of the tetrahydroxy compounds. Intermolecular condensations to form polymers are also possible.



XIII XIV

R = 3,4-methylenedioxyphenyl

Experimental

Attempted Synthesis of Sesamin by Freudenberg's Method.[17]—3-(3,4-Methylenedioxyphenyl)-acrylic acid and ferric chloride in methanol were shaken in the presence of oxygen in a closed apparatus provided with a eudiometer. No oxygen uptake was observed, even though the solution was heated and various amounts of water and ferric chloride were added. The only product isolated after treatment was some of the methyl ester of the starting acid, 132–133°.

Ethyl Piperonoylacetate (IX).—The directions of Bruchhausen and Gerhard[2] on 20-fold quantities were followed, with employment of sodium acetoacetate prepared with sodium hydride. Upon completion of the reaction, 128 g. of the product was filtered off. The more volatile components of the mother liquor, such as acetoacetic ester, were removed

(23) E. F. Pratt and P. W. Erickson, THIS JOURNAL, **78**, 76 (1956).

(24) Compare the work of A. Michael and J. Ross, *ibid.*, **55**, 3684 (1933), who were unable to form the *trans* structure even under forcing conditions.

(25) Compare with the structures of epipinoresinol presented by J. Gripenberg, *Acta. Chem. Scand*, **2**, 82 (1948).

(26) H. Erdtman and Z. Pelcbowicz, *Chemistry and Industry*, 567 (1955).

at 3 mm. by heating in a 150° bath, and the residue was taken up in ether. An additional 61 g. of ester slowly came out when the ether solution was kept at −10°; total yield of IX, 189 g. (62%), m.p. 37–39°.

Diethyl 2,3-Bis-(3,4-methylenedioxybenzoyl)-succinate (Xa, Xb).—This compound (diethyl α,α′-dipiperonoylsuccinate) was prepared according to the directions of Bruchhausen and Gerhard.[2] These authors obtained an almost quantitative yield consisting of equal amounts of the oily Xa and crystalline Xb forms. Repetition of their procedure three times on preparations of various sizes likewise gave practically quantitative yields. In each case about 30% of the crystalline form was obtained, the remainder being an oil. However, in two cases the oily form was evaporated to dryness under reduced pressure. After it had stood for several weeks, the product was taken up in ether and allowed to remain overnight, whereupon additional material crystallized out, giving about a 45% total yield of Xb. Upon prolonged standing of the ether solution in a refrigerator, more Xb continued to come out slowly.

The crystalline compound Xb, m.p. 161–162°, gave no color with ethanolic ferric chloride, whereas the oily fraction Xa gave a red-brown color.

1,4-Bis-(3,4-methylenedioxyphenyl)-2,3-bis-(hydroxymethyl)-1,4-butanediol (XIa, XIc, XId) from Xa.—Into a dry, nitrogen-filled flask 20.3 g. of lithium aluminum hydride (large excess) was added while nitrogen was slowly passed into the flask followed by 1400 ml. of dry ether. Over a 1.5-hour period 42 g. of Xa in 400 ml. of dry ether was added with stirring, and the solution was refluxed overnight.

The flask was cooled in an ice-bath, and 90 ml. of water and 1700 ml. of 10% sulfuric acid solution were cautiously added. The reaction mixture was filtered to give 7.4 g. (21%) of crystalline product, m.p. 170–180°. The ether layer in the filtrate was separated and evaporated to give 18.2 g. of a gum-like material (G-1). By recrystallization of the crystalline fraction from pyridine–ether and methanol, 3.4 g. (10%) of a compound XIa melting at 180–181° was obtained.

Anal. Calcd. for $C_{20}H_{22}O_8$: C, 61.5; H, 5.69. Found: C, 61.9; H, 5.92.

From the mother liquors several less pure crops were obtained, which could be purified by recrystallization only with difficulty owing to the presence of higher melting compounds. One such compound (about 100 mg.) melted at 199–200° (XId). Because of the paucity of material it was not completely purified. However, its analysis checked with that of the other tetrahydroxy compounds, XIa and XIb.

Anal. Calcd. for $C_{20}H_{22}O_8$: C, 61.5; H, 5.69. Found: C, 62.17; H, 5.67.

Another compound (about 40 mg.) was obtained on slow crystallization of one of the mother liquors by picking out from the main batch crystals that were different in form. This compound (XIc) on recrystallization from pyridine–ether melted at 189–190°, and its analysis likewise checked that of the other tetrahydroxy compounds.

Anal. Calcd. for $C_{20}H_{22}O_8$: C, 61.5; H, 5.69. Found: C, 61.49; H, 5.66.

Attempts to obtain additional crystalline compounds from gum G-1 were unsuccessful even though it was allowed to stand in several solvents.

1,4-Bis-(3,4-methylenedioxyphenyl)-2,3-bis-(hydroxylmethyl)-1,4-butanediol (XIb) from Xb.—In a setup similar to the preceding one, 7.26 g. of lithium aluminum hydride (large excess) was added followed by 500 ml. of dry ether while nitrogen was being passed into the flask. A Butt extractor containing 15 g. of Xb was interposed between the flask and the condenser, and the ether was allowed to reflux for 6 hours, by which time the compound had been completely extracted into the flask. After the contents had been stirred overnight under reflux, the flask was cooled in an ice-bath, and 30 ml. of water followed by 600 ml. of 10% sulfuric acid solution were cautiously added. Some of the product crystallized out; hence the ether was evaporated. The insoluble material was filtered off and recrystallized by extraction in a Butt extractor with ethanol. The ethanol solution was concentrated to 150 ml. and left for several days in a refrigerator. The crystals were filtered off and washed with ether, yielding 2.45 g. (20%), m.p. 180–181° (XIb).

Anal. Calcd. for $C_{20}H_{22}O_8$: C, 61.5; H, 5.69. Found: C, 61.45; H, 5.79.

An additional 1.3 g. (10.5%), m.p. 179–180°, crystallized out from the mother liquor in a few days, and on addition of more ether more crystals slowly continued to come out (1.45 g., m.p. 176–179°); total yield 42%. The filtrate was evaporated to give 5.06 g. of a gum-like material (G-2). The additional crystalline crops appeared to be the same as the first crop since mixture melting points were not depressed. Further purification was effected by crystallization from pyridine–ether.

Acetates of Tetrahydroxy Compounds.—A solution of 23.2 mg. of XIb in 1.2 ml. of pyridine and 0.7 ml. of acetic anhydride was allowed to stand overnight. The pyridine and acetic anhydride were evaporated under reduced pressure. The residue was dissolved in ether and petroleum ether was added just to turbidity. After the solution had stood overnight, 28 mg. of crystals separated, m.p. 147–147.5°.

Anal. Calcd. for $C_{28}H_{30}O_{12}$: C, 60.20; H, 5.42. Found: C, 60.34; H, 5.34.

When prepared by this procedure, the acetate of XIa could not be made to crystallize and therefore could not be properly purified. Nevertheless, the values for saponification equivalent and acetyl determinations indicated 4 acetyl groups to be present. Calcd. for 4 acetyl groups: sapn. equiv., 139.5; acetyl, 43. Found: sapn. equiv., 134; acetyl, 46.8.

No crystalline acetate or benzoate could be obtained from the gums G-1 or G-2.

***dl*-Sesamin (I).**—Tetrahydroxy compound XIa (241 mg.) was heated under reflux in 2 ml. of about 1% ethanolic hydrochloric acid (1 drop of concentrated hydrochloric acid per ml. of absolute ethanol). The reaction mixture was shaken until the compound dissolved (5 minutes) and then allowed to reflux 40 minutes longer. On cooling to room temperature, *dl*-sesamin crystallized out. It was filtered off and washed with cold ethanol; weight 155 mg. (71%), m.p. 123–124.5°. Recrystallization from ethanol raised the melting point to 125–126°, undepressed in admixture with *dl*-sesamin prepared from natural materials.

Anal. Calcd. for $C_{20}H_{18}O_6$: C, 67.77; H, 5.12. Found: C, 67.73; H, 5.30.

The infrared and ultraviolet absorption spectra were identical with those of natural sesamin.

Chromatography of *dl*-Sesamin Mother Liquor.—The mother liquor was neutralized with concentrated ammonia and evaporated to dryness. The residue was taken up in chloroform and filtered from the insoluble ammonium chloride. The chloroform solution was placed on an 80-g. silicic acid (Merck) column (2.5 cm. in diameter) and washed into the gel with several ml. of 1:1 chloroform–isoöctane followed by 75 ml. of isoöctane. The column was developed with ethyl acetate in isoöctane (v./v.) as follows: 3% until the asarinin was removed, 7% until the sesamin was eluted and finally with 20%. The elution of the compounds was followed by measuring the ultraviolet absorption at 288 mμ. By this procedure 10 mg. (4%) more of *dl*-sesamin, 2 mg. of *dl*-asarinin and an unidentified oily fraction were obtained. The column was then sectioned and each section was extracted with 1:1 ethanol–chloroform to give several fractions which could not be made to crystallize or be otherwise characterized.

***dl*-Asarinin (I).**—To 2 ml. of 2 *N* ethanolic hydrochloric acid was added 59.1 mg. of synthetic *dl*-sesamin, and the mixture was refluxed overnight. The product was neutralized with ammonia, taken up in chloroform, washed with water, dried over sodium sulfate, and chromatographed as described above, 2.5% instead of 3% of ethyl acetate in isoöctane being used as the first eluting solvent. On the basis of total absorbance (at 288 mμ) of the respective fractions, 21.7 mg. of sesamin and 29.8 mg. of asarinin were recovered. By actual weight 19.5 mg. (32%) and 27.5 mg. (47%), respectively, were isolated.

Attempted Epimerization of *dl*-Sesamin with 1% Acid.—The persistent appearance of small amounts of *dl*-asarinin with the *dl*-sesamin product made us suspect that the latter was being epimerized partially to the former by the 45-minute heating in 1% ethanolic hydrochloric acid. After *dl*-sesamin was subjected to this treatment, no appreciable amount of *dl*-asarinin could be detected by chromatographing the product. However, some epimerization may take

place before closure of compound XIa upon heating with this acid. It is also possible that XIa contained a very small amount (about 1%) of a second tetrahydroxy compound which gives *dl*-asarinin.

Closure of Compounds XIc and XId.—Ring closure of XIc with the hydrochloric acid as described above, followed by chromatography of the product, yielded 68% of *dl*-sesamin and a minute amount of *dl*-asarinin. Similar treatment of XId gave a 61% yield of *dl*-sesamin and 11% of *dl*-asarinin. It is possible that XId, admittedly not pure, contained some of the tetrahydroxy compound which closes to *dl*-asarinin.

Because XIc and XId both gave mainly *dl*-sesamin upon closure, it is believed that they are polymorphic forms of XIa. Nujol mulls of XIc and XId gave infrared curves different from that of a mull of XIa. To determine whether these compounds are polymorphs, we determined their infrared absorption spectra in solution. The compounds were not soluble in non-polar solvents commonly employed in infrared work; hence spectra of their solutions in dimethylformamide between 9.5 and 15 μ were determined. In the curves of XIa, XIc and XId we could detect no differences; however, the curve for XIb in this solvent was also similar, so that the infrared studies did not conclusively prove or disprove that XIa, XIc and XId are polymorphic.[27]

Seeding experiments seemed to confirm that XId was polymorphic with XIa. For instance, XId (m.p. 199–200°) dissolved in pyridine–ether was seeded with XIa (m.p. 180–181°), but the crystals that deposited still melted at 199°. When XIa dissolved in pyridine–ether was seeded with XId, the crystalline product melted unsharply at about 195°. Not enough XIc remained to run similar experiments with it.

Closure of Compound XIb (from Xb).—Compound XIb (500 mg.) was treated with 5 ml. of 1% ethanolic hydrochloric acid as described for XIa. The product was chromatographed in the same manner with increasing concentrations of ethyl acetate in isoöctane. No substance was eluted until a zone (70 mg.) was removed with 10% ethyl acetate. Another zone (61 mg.) was eluted with 20% ethyl acetate. These fractions could not be crystallized or otherwise characterized. The column was then sectioned, and a fraction eluted from the center section crystallized after several weeks, m.p. 119.5–120° (XII) after recrystallization from benzene. In subsequent experiments it was possible to obtain the same compound directly after closure with the ethanolic hydrochloric acid as follows: The reaction mixture was neutralized with ammonia, water was added and the liquid was extracted several times with chloroform. The solution was dried over sodium sulfate, the chloroform evaporated and the residue taken up in hot benzene. On cooling, the solution was seeded and the compound crystallized out in 50% yield. Recrystallization from benzene gave the pure product XII. From its analysis only one molecule of water had been eliminated from XIb, therefore the compound probably has only one tetrahydrofuran ring.

Anal. Calcd. for $C_{20}H_{20}O_7$: C, 64.7; H, 5.40. Found: C, 64.65; H, 5.54; active hydrogen atoms (Zerewitinoff) per mole found, 2.03.

The acetate and benzoate of XII were not crystalline.

Oxidation of Compound XII.—To a solution of 20 mg. of compound XII in 4 ml. of acetone was added 120 mg. of potassium permanganate. After refluxing for two hours, water plus a few drops of 30% hydrogen peroxide were added to the cooled mixture. The manganese dioxide was filtered off and washed with hot water. The filtrate was made definitely alkaline with potassium hydroxide solution, washed three times with chloroform and the washings were discarded. The aqueous layer was acidified with hydrochloric acid and extracted three times with chloroform. The chloroform solution was dried and evaporated and the residue was crystallized from a hot water–alcohol solution. The product was filtered and dried, yield 4 mg. (22%), m.p. 226–228°, undepressed in admixture with an authentic sample of piperonylic acid.

Sesamin (20 mg.) was oxidized as described above and a negligible amount of impure product (0.2 mg.) was obtained.

Closure of Gums G-1 and G-2.—Similar closure of gum G-1 with 1% ethanolic hydrochloric acid followed by chromatography of the product gave a very small amount of sesamin along with gummy or oily fractions which we were unable to characterize. Similar treatment of gum G-2 likewise yielded compound XII (25%) plus small amounts of oily or gummy materials not readily characterized.

Acknowledgments.—We gratefully acknowledge the help of J. Carol and M. Dolinsky of the Food and Drug Administration in obtaining the infrared spectra. We are also indebted to E. F. Pratt of the University of Maryland and J. L. Hartwell of the National Institutes of Health for helpful discussions on this problem.

BELTSVILLE, MARYLAND

(27) Many of the infrared absorption peaks obtained in mulls or in non-polar solvents become weak or absent in dimethylformamide. (Communication from M. Dolinsky, U. S. Food and Drug Administration.)

[CONTRIBUTION FROM THE MOORE LABORATORY OF CHEMISTRY, AMHERST COLLEGE]

7-Azaindole. III. Syntheses of 7-Aza Analogs of Some Biologically Significant Indole Derivatives[1]

BY MICHAEL M. ROBISON AND BONNIE L. ROBISON

RECEIVED OCTOBER 4, 1955

A number of 3-substituted 7-azaindoles have been prepared for the purposes of testing their biological activities and comparing further the chemical reactivities of 7-azaindole and indole. Compounds synthesized include 7-azaindole-3-acetic acid, β-(7-aza-3-indolyl)-propionic acid, 7-azaindole-3-carboxylic acid and 7-azatryptamine, as well as certain of their derivatives. The bromination of 7-azaindole and its coupling reaction with benzenediazonium chloride also were studied.

7-Azagramine serves,[2] as does gramine itself,[3] to alkylate acetamidomalonic ester. Hydrolysis and decarboxylation of the resulting aza compound results in the formation of 7-azatryptophan[2] which has been found to be a fairly effective tryptophan inhibitor in *Tetrahymena pyriformis*.[4] It was therefore considered of interest to extend the transformations of 7-azaindole to other preparations of aza analogs of biologically significant indole compounds. A corollary aim of these endeavors was further to investigate the chemistry of the ring system, which is in many ways similar to that of in-

(1) This investigation was supported in part by a research grant, number C-2574, from the National Cancer Institute of the National Institutes of Health, Public Health Service.

(2) M. M. Robison and B. L. Robison, THIS JOURNAL, **77**, 457 (1955).

(3) E. E. Howe, A. J. Zambito, H. R. Snyder and M. Tisbler, *ibid.*, **67**, 38 (1945).

(4) G. W. Kidder and V. C. Dewey, *Biochim. et Biophys. Acta*, **17**, 288 (1955).