the same conditions. Absorption of hydrogen ceased after 2.5 hours of shaking. Dilution of the filtered solution with one liter of ether precipitated the product.

Preparation of Salts of the Basic Ethers. Hydrochlorides.—The basic ether was dissolved in cold ether and the solution saturated with dry hydrogen chloride.

Dihydrogen Citrates.—An ether solution of the basic ether was added to a solution of a 10% excess of anhydrous citric acid (Pfizer) in methanol or acetone.

Sulfate.—In one case (*cf.* Table III) a sulfate was prepared by adding the calculated amount of concentrated sulfuric acid to an acetone solution of the basic ether.

Quaternary Salt.—The methiodide of isobornyl β-dimethylaminoethyl ether was prepared by adding 2.1 ml. (0.033 mole) of methyl iodide to a solution of 6.7 g. (0.03 mole) of the basic ether in 30 ml. of isopropyl alcohol. The solution became noticeably warm, and on cooling deposited crystals of the quaternary iodide (8.1 g., 74% yield).

Acknowledgment.—The authors are indebted to Mr. Richard M. Downing for the microanalyses reported herein. Samples of a number of intermediates were kindly supplied by the Hercules Powder Company and Glidden Company.

Summary

A series of terpene basic ethers is reported. Preliminary pharmacological data indicate a low order of antihistaminic and antispasmodic activity.

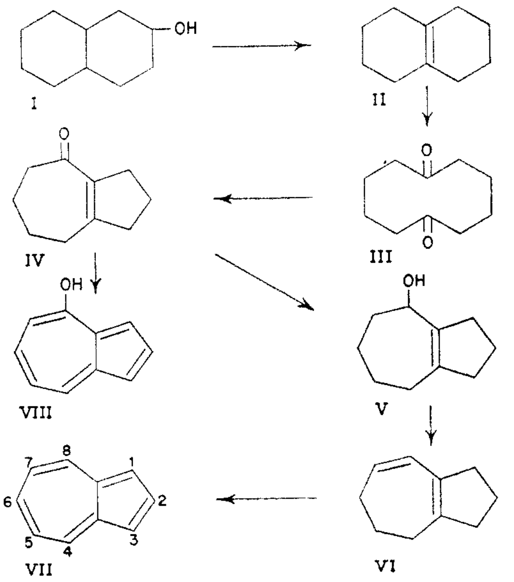
SYRACUSE 1, N. Y. RECEIVED MAY 3, 1950

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING, UNIVERSITY OF WASHINGTON]

Azulene. I. An Improved Synthesis[1a,b]

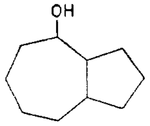
BY A. G. ANDERSON, JR., AND JERRY A. NELSON[1c]

A study of the chemistry of azulene (VII) in progress in this Laboratory required a synthetic method enabling continuous preparation of the pure material as a routine procedure. Consideration and some preliminary investigation of the methods reported in the literature[2] indicated that, while none was satisfactory for our needs, two of the syntheses appeared to be adaptable providing certain major difficulties could be overcome.



The synthesis of Plattner and St. Pfau[2a] from (9,10)-octalin (II) *via* 1,6-cyclodecanedione (III) and 4-keto-1,2,3,4,5,6,7,8-octahydroazulene (IV) was considered unsatisfactory in two respects. First, the route to II from decahydronaphthalene involved lengthy ozonization to decahydro-9-naphthol and dehydration of this decalol with zinc chloride to give mixed octahydronaphthalenes, from which the (9,10)-isomer was isolated in 14% overall yield. The direct dehydration of decahydro-2-naphthol with phosphorus pentoxide and phosphoric acid by Linstead[3] as later modified by Campbell and Harris[4] to give II in excellent yield seems to have been overlooked in connection with the preparation of azulene. We have found this procedure ideal for the preparation of the desired octalin in large quantities.

The second difficulty was the low yield (14%) of crude blue oil realized from the catalytic dehydrogenation of 4-hydroxydecahydroazulene (IX) and the lengthy purification of the crude product which gave only 1% (from the bicyclic alcohol) of crystalline azulene. As the formation of water in the dehydrogenation seemed undesirable, the preparation of a suitable oxygen-free intermediate was investigated. Reduction of IV with lithium aluminum hydride gave what is probably 4-hydroxy-1,2,3,4,5,6,7,8-octahydroazulene (V). This unsaturated alcohol was unstable, eliminating water spontaneously on standing, and could not be isolated in pure form. It was dehydrated directly by azeotropic removal of water from a refluxing benzene solution to give 1,2,3,4,5,6-hexahydroazulene (VI) in 97% yield from the ketone. The diene was dehydrogenated smoothly in the vapor phase under a nitrogen atmosphere at 320–340° over a 30% palladium-on-charcoal catalyst[5] suspended on asbestos in an electrically heated apparatus similar to that described by Nunn and Rapson[2g] to give azulene, with unreacted diene as the only major contaminant. Subsequent experimentation showed that better



IX

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[1] (a) Presented before the Division of Organic Chemistry at the 118th Meeting of the A.C.S., Chicago, Ill., September, 1950. (b) From the Ph.D. dissertation of Jerry A. Nelson. (c) Shell Oil Fellow, 1949–1950.

[2] (a) Pl. A. Plattner and A. St. Pfau, *Helv. Chim. Acta*, **19**, 858 (1936); **20**, 224 (1937); (b) **22**, 202 (1938); (c) H. Arnold, *Ber.*, **76**, 777 (1943); (d) Pl. A. Plattner, A. Furst and K. Jirasek, *Helv. Chim. Acta*, **29**, 730, 740 (1946); Pl. A. Plattner and G. Büchi, *ibid.*, **29**, 1608 (1946); (e) Pl. A. Plattner and A. Studer, *ibid.*, **29**, 1432 (1936); (f) Pl. A. Plattner, A. Furst and A. Studer, *ibid.*, **30**, 1091 (1947); (g) J. R. Nunn and W. S. Rapson, *J. Chem. Soc.*, 825 (1949).

[3] R. P. Linstead, A. B. Wang, J. H. Williams and K. D. Errington, *J. Chem. Soc.*, 1136 (1937).

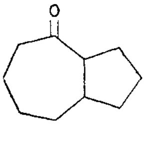
[4] W. P. Campbell and G. C. Harris, THIS JOURNAL, **63**, 2721 (1941).

[5] R. P. Linstead and S. L. S. Thomas, *J. Chem. Soc.*, 1130 (1940).

results could be obtained with the catalyst suspended on anhydrous alumina. The azulene so obtained and the unreacted diene were readily separated from each other and from small amounts of by-products by chromatography on an activated alumina column. The recovered diene could be recycled through the dehydrogenation apparatus without further purification. Crystalline azulene was obtained directly from the blue eluate fraction and further purified by sublimation *in vacuo* to give blue-violet plates in 18% net yield from the diene or 5.8% over-all yield from decahydro-2-naphthol. While the dehydrogenation apparatus as constructed is adaptable only to small amounts, it can be operated continuously and thus afford 250 mg. of pure azulene from an eight hour run. We have found the above route to azulene superior to direct dehydrogenation of IX in both yield and ease of purification of the crude dehydrogenation product.

Conversion of the intermediate cyclodecanedione (III), obtained readily by ozonolysis of II, to the bicyclic unsaturated ketone (IV) in the presence of sodium carbonate was first performed by Hückel and Schnitzspahn[6] and subsequently by Plattner, *et al.*[2a] Neither authors specified the reaction conditions nor reported yields obtained. In this investigation the condensation has been effected in 96% yield by refluxing the diketone in 5% aqueous sodium carbonate for one hour.

Catalytic dehydrogenation of IV yielded only traces of azulene. The major product obtained was a red oil which was soluble in aqueous sodium hydroxide, gave a positive ferric chloride test, coupled with diazotized aniline and reacted with benzoyl chloride. These properties plus the similarity of its ultraviolet absorption spectrum and that of its benzoate to characteristic azulene spectra (Fig. 1) indicate the compound may be the previously unreported 4-hydroxyazulene (VIII) for which we suggest the name 4-azulol. This same product was formed in lower yield from catalytic dehydrogenation of the corresponding saturated ketone (X). The substance was rather unstable and neither it nor the benzoate could be prepared analytically pure.



X

Neither the bicyclic unsaturated alcohol (V) nor the diene (VI) has been previously reported. Plattner, *et al.*,[2a] prepared the 4-methyl diene for which no absorption spectra data were given. The ultraviolet absorption spectrum of VI showed a single maximum at 254 mμ (log ε 3.70). The compound took up two molar equivalents of hydrogen in the presence of a reduced platinum oxide catalyst, was somewhat volatile, and polymerized on standing (rapidly in the presence of acids).

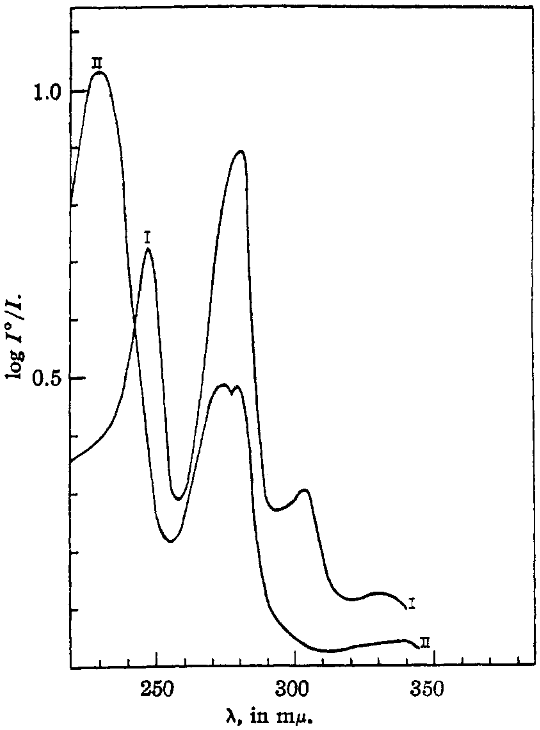
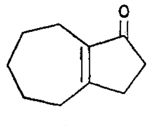


Fig. 1.—Absorption spectra in *n*-hexane of compounds thought to be: curve I, 4-hydroxyazulene (VIII); curve II, benzoate of 4-hydroxyazulene.

Because of the limitations with regard to quantity inherent in the vapor phase dehydrogenation as performed, various other methods were tried. Heating VI with sulfur from 200 to 240°[7] brought about vigorous evolution of hydrogen sulfide but the reaction mixture yielded only a minute amount of azulene. No azulene was obtained when a solution of VI and chloranil in xylene was refluxed for twelve hours.[8] Treatment of VI with three moles of N-bromosuccinimide in a reaction catalyzed by ultraviolet light and peroxides resulted in the evolution of hydrogen bromide. The reaction mixture, after removal of the succinimide and refluxing with 2,4,6-collidine, contained no azulene but yielded a green oil and three different green crystalline products each containing bromine. Ultraviolet absorption spectra (Fig. 2) indicated these substances to be bromoazulenes, possibly the 1-, 4- and 6-bromoazulenes which could arise from bromination at the four allylic positions of the diene and subsequent loss of three moles of hydrogen bromide. As no previous haloazulenes have been reported, this possibility could not be verified from the spectral data and the quantities obtained were insufficient for analysis or further chemical studies.

A second synthesis of Plattner, *et al.*,[2d,f] wherein 1-keto-1,2,3,4,5,6,7,8-octahydroazulene (XI) was obtained from cycloheptanone in 30% over-all yield, presented, in addition to the low yields in conversion of the product to azulene, the necessity for a satisfactory means of preparing cycloheptanone in large amounts.



XI

An improved synthesis of this ketone has recently

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[6] W. Hückel and L. Schnitzspahn, *Ann.*, **505**, 274 (1933).

[7] A. Vesterberg, *Ber.*, **36**, 4200 (1903)

[8] R. T. Arnold, THIS JOURNAL, **62**, 983 (1940).

been developed in This Laboratory[9] and, as the procedures given above for the conversion of IV to azulene should be adaptable to the analogous 1-keto compound, this method now affords a second possible convenient synthesis of azulene and investigation of this route is in progress.

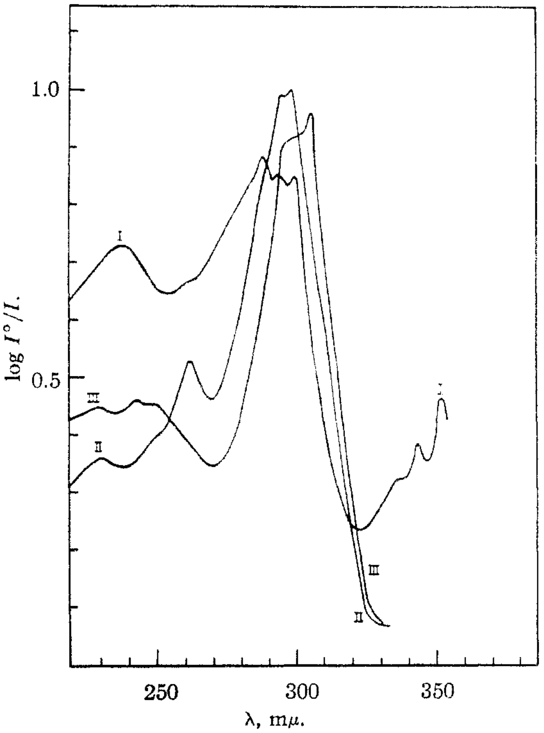

Fig. 2.—Absorption spectra in *n*-hexane of three compounds thought to be isomeric bromoazulenes.

Experimental

All melting points are uncorrected. A Beckman Model DU spectrophotometer was used for the absorption spectra determinations.

Decahydro-2-naphthol (I).[4]—A mixture of 1,2,3,4- and 5,6,7,8-tetrahydro-2-naphthols[10] was hydrogenated over a Raney nickel catalyst[11] at 150-170° and 2500 lb. pressure. After separation of the catalyst, the reaction mixture was distilled and the product obtained in 70% yield as the fraction boiling at 155-163° (53 mm.).

(9,10)-Octalin (II).—Treatment of the decahydro-2-naphthol with phosphoric acid anhydride and phosphoric acid as described by Campbell and Harris[4] afforded the desired octalin (b.p. 190-192°) in 78% yield.

1,6-Cyclodecanedione (III).—This cyclic diketone was obtained by ozonolysis[12] of (9,10)-octalin in 40% aqueous acetic acid as described by Plattner and Hulstkamp[13] except that the octalin was kept in suspension by vigorous mechanical stirring. As the yield (45%) was somewhat lower for large runs, possibly due to prolonged exposure of the diketone to ozone,[14] it was found undesirable to ozonize more than 40 g. at one time, each run requiring 10 to 12 hours. The diketone, after one recrystallization from ether, melted at 98-99°.

4-Keto-1,2,3,4,5,6,7,8-octahydroazulene (IV).[6]—1,6-Cyclodecanedione (50 g., 0.3 mole) was refluxed in 500 ml. of 5% sodium carbonate solution for one hour. The product was then steam distilled and the distillate simultaneously extracted with chloroform in an apparatus described by Vogel.[15] The chloroform was removed and the residue distilled. The fraction (43 g., 96%) boiling at 126-128° (15 mm.) was collected.

Reduction of 4-Keto-1,2,3,4,5,6,7,8-octahydroazulene (IV).—To a vigorously stirred mixture of lithium aluminum hydride (2 g.) and dry ether (100 ml.) under a nitrogen atmosphere was added dropwise 30 g. (0.2 mole) of 4-keto-1,2,3,4,5,6,7,8-octahydroazulene dissolved in 70 ml. of dry ether. After the addition of the ketone was complete, the reaction mixture was stirred for fifteen minutes, any excess lithium aluminum hydride cautiously decomposed with ice-water (5 ml.), and a solution of 10 g. of ammonium chloride and 25 ml. of 12 *N* hydrochloric acid in 100 ml. of water added. The resultant mixture was stirred vigorously until clear, the ethereal layer separated and the aqueous layer extracted twice with 50-ml. portions of ether. The combined ether extracts were washed twice with 100 ml. of water, dried over Drierite and the solvent removed *in vacuo* to give 30 g. of a colorless solid; m.p. 51-52° with loss of water. As this unsaturated alcohol, probably **4-hydroxy-1,2,3,4,5,6,7,8-octahydroazulene (V)**, spontaneously dehydrated on standing at room temperature and also during recrystallization, it was not obtained sufficiently pure for analysis.

1,2,3,4,5,6-Hexahydroazulene (VI).—The above unsaturated alcohol (30 g., 0.21 mole) was taken up in 100 ml. of anhydrous, thiophene-free benzene and the solution refluxed until no more benzene-water azeotrope distilled. A total of 3.6 ml. (0.2 mole) of water was collected. The benzene was then removed *in vacuo* leaving 26 g. (97%) of the diene. Distillation of a sample yielded, after a small forerun, a straw-colored liquid (b.p. 72° at 10 mm., $n^{21}\text{D}$ 1.5250) which had an absorption maximum at 254 mμ (log ε 3.70) in alkene free *n*-hexane.

Anal. Calcd. for $C_{10}H_{14}$: C, 89.5; H, 10.5. Found: C, 89.3; H, 10.3.

A solution of the distilled diene (0.1228 g., 0.00092 mole) in 25 ml. of 95% ethanol took up 1.96 molecular equivalents of hydrogen in the presence of a reduced platinum oxide catalyst.

Dehydrogenation of 1,2,3,4,5,6-Hexahydroazulene (VI). Method A. Catalytic Vapor Phase Dehydrogenation.—This was best accomplished in an apparatus similar to that described by Nunn and Rapson[2c] as follows: a freshly ignited asbestos plug 1 cm. in length was placed in the inlet end of the chamber, followed by 1 g. of 30% palladium-on-charcoal[9] suspended on 12 g. of ignited activated alumina (10 mesh), and finally by a second ignited asbestos plug. The filled chamber was then placed in an electrically heated combustion furnace equipped with a rheostat control and pyrometer and, after evacuation to a pressure of 15 mm. under a nitrogen atmosphere, was heated slowly to 320-340°. The diene (VI) was then admitted to the reaction chamber through the capillary at a rate of 1 g. per hour and the reaction products, consisting principally of unreacted diene and azulene, collected in a double Dry Ice-acetone trap. In a typical run 2 g. (0.015 mole) of the diene was allowed to pass through the chamber over a period of two hours, the resultant mixture taken up in 5 ml. of 20-40° C.P. petroleum ether and the solution chromatographed on an activated alumina column (25 × 100 mm.). The column was washed with petroleum ether to develop and elute the adsorbed substances. Removal of the solvent from the first eluate fraction left 1.64 g. of unreacted diene which could be recycled through the apparatus without further purification. Evaporation of the solvent from the second fraction yielded crystalline azulene which was purified by sublimation at room temperature and 1 mm. pressure to give 0.062 g. (18% net yield) of blue-violet plates; m.p. 98-99°. When fresh catalyst was used a small amount of naphthalene was sometimes formed during the initial period of the reaction.

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(9) H. J. Dauben, Jr., H. J. Ringold, R. H. Wade and A. G. Anderson, Jr., *ibid.*, accepted.

(10) This material was obtained from Dr. H. J. Dauben, Jr., and was prepared by a commercial hydrogenation company with a catalyst purported to be similar to copper chromite, *cf.* H. J. Dauben, Jr., B. C. McKusick and G. P. Mueller, THIS JOURNAL, **70**, 4179 (1948).

(11) A. A. Pavlic and Homer Adkins, *ibid.*, **68**, 1471 (1946).

(12) Ozone was prepared in an apparatus described by A. L. Henne and W. L. Perilstein, *ibid.*, **65**, 2183 (1943).

(13) Pl. A. Plattner and J. Hulstkamp, *Helv. Chim. Acta*, **27**, 211 (1944).

(14) W. Hückel, R. Danneel, A. Schwartz and R. Gercke, *Ann.*, **474**, 121 (1929), isolated δ-ketosebasic acid from the reaction mixture and any peracetic acid formed would be expected to react with the cyclic ketone. J. E. Leffler, *Chem. Revs.*, **45**, 403 (1949).

(15) A. I. Vogel, "A Textbook of Practical Organic Chemistry," Longmans, Green and Co., New York, N. Y., 1948, p. 223.

Method B. Dehydrogenation with Sulfur.[7]—The diene (1.34 g., 0.01 mole) was mixed with sulfur (1 g., 0.03 mole) in a two-bulb distillation flask and the flask placed in a Wood's metal-bath at 200°. The temperature was gradually raised over a period of fifteen minutes to 240° and maintained at this temperature for fifteen minutes. The receiver was then cooled in a Dry Ice-acetone-bath and the mixture distilled under slight vacuum. Approximately 5 mg. of impure azulene was obtained. The tarry residue indicated that extensive polymerization had occurred.

Method C. Catalytic Liquid Phase Dehydrogenation.—The diene (1.5 g., 0.011 mole) dissolved in 1 ml. of β-methylnaphthalene was mixed with 200 mg. of 10% palladium-on-charcoal and refluxed in a carbon dioxide atmosphere for 48 hours. At the end of this time the reaction mixture was taken up in 50 ml. of 20–40° petroleum ether, filtered, and extracted with 5 ml. of cold 85% phosphoric acid. The acid solution was washed twice with 25-ml. portions of petroleum ether, diluted with 25 ml. of ice-water and the diluted acid extracted with 10 ml. of petroleum ether. The amount of azulene obtained on evaporation of the solvent was too small to measure.

Reaction of 1,2,3,4,5,6-Hexahydroazulene (VI) with N-Bromosuccinimide.—A solution of the diene (1.34 g., 0.01 mole) in 50 ml. of carbon tetrachloride was added to N-bromosuccinimide (5.34 g., 0.03 mole) in a 100-ml. round-bottom flask fitted with a condenser and drying tube. The mixture was refluxed on a steam-bath for one hour with intermittent irradiation with ultraviolet light. At the end of this time a test for active bromine was negative. The reaction mixture, which had become dark green and evolved hydrogen bromide, was placed in an ice-bath for one hour, the succinimide removed by filtration, 11 ml. of 2,4,6-collidine added to the filtrate and the solution refluxed for two hours. Excess collidine was precipitated as the hydrochloride by titration of the cooled solution with ethereal hydrogen chloride to the end-point (pH 4) of Butter Yellow and the collidine hydrohalides removed by filtration. The solvent was removed by distillation *in vacuo* at room temperature and the residue dissolved in petroleum ether. Extraction of this solution with phosphoric acid yielded no azulene. Chromatography of the petroleum ether solution on activated alumina gave, in addition to an unstable green oil, three different green crystalline fractions, each of which contained bromine and showed absorption in the ultraviolet similar to that of azulene compounds (Fig. 2). The quantities obtained were insufficient for analysis or further chemical studies.

Catalytic Vapor Phase Dehydrogenation of 4-Keto-1,2,3-4,5,6,7,8-octahydroazulene (IV).—The dehydrogenation of 3.0 g. (0.02 mole) of 4-keto-1,2,3,4,5,6,7,8-octahydroazulene was performed as described above (Method A) for the dehydrogenation of 1,2,3,4,5,6-hexahydroazulene. The crude product obtained was taken up in petroleum ether and chromatographed on an activated alumina column. The column was washed with petroleum ether until unchanged starting material and a faint band of azulene were eluted. The remaining red band, more strongly adsorbed, was eluted with methanol. Evaporation of the solvent from the red methanol solution in a stream of nitrogen at room temperature left a red oil which was somewhat unstable and could not be obtained analytically pure. The substance decomposed on standing alone or when adsorbed on the alumina column and also in alkaline solution. It reacted immediately with 1% aqueous ferric chloride to give a dark greenish-brown solution. A solution of the oil in 5% aqueous sodium hydroxide gave an immediate red coloration and a slight orange precipitate when treated with a solution of benzenediazonium chloride. A solution of the red oil in *n*-hexane showed absorption maxima in the ultraviolet at 248, 282, 304 and 331 mμ (Fig. 1). These properties indicated the compound to be a phenolic derivative of azulene and thus probably **4-hydroxyazulene (VIII)**.

A sample of the red oil was dissolved in 10 ml. of petroleum ether and the solution extracted with 2 ml. of 10% sodium hydroxide. The brown alkaline solution was shaken immediately with 0.2 ml. of benzoyl chloride for 15 minutes and the oil which separated extracted with 5 ml. of petroleum ether. The separated organic layer was concentrated by evaporation in a stream of air to 0.2 ml. and chromatographed on a column (9 × 30 mm.) filled with Florosil[16] (60/100 mesh). The column was washed with petroleum ether to elute the deep blue band of the **benzoate**. Some decomposition of the benzoate occurred on the column (on activated alumina decomposition took place rapidly) and the derivative, obtained as a blue oil, could not be obtained sufficiently pure for analysis. A solution of the product in *n*-hexane showed absorption maxima in the ultraviolet at 231, 274, 280 and 340 mμ (Fig. 1).

Summary

An improved synthesis of azulene in six steps and 5.8% over-all yield from decahydro-2-naphthol *via* the new 1,2,3,5,6,7-hexahydroazulene, and the preparation of a new, unstable azulene derivative, probably 4-hydroxyazulene for which the name 4-azulol is suggested, are reported.

[16] An activated magnesium silicate sold by the Floridin Company, Warren, Pennsylvania.

SEATTLE, WASHINGTON RECEIVED JULY 5, 1950

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE OHIO STATE UNIVERSITY]

Osage Orange Pigments. XII.[1] Synthesis of Dihydro-iso-osajin and of Dihydroisopomiferin[2]

BY M. L. WOLFROM AND BERNARD S. WILDI[3]

The classical method for establishing the structure of an organic compound requires that, as a final step, the formula assigned by degradative methods be verified by a synthesis effected by controlled reactions from intermediates of known structure. The work herein reported is concerned with such a synthetic verification of the structures assigned[1] to osajin (XXV) and pomiferin (XXVI), the isoflavone pigments of the fruit of the osage orange (*Maclura pomifera* Raf.).

It is known that dihydro-iso-osajin (XXIII)[4] and dihydro-isopomiferin (XXIV)[4] may be obtained readily from osajin and pomiferin, respectively, by treatment of the pigments with hydriodic acid.[1] Furthermore, the nature of this change is well established.[1] Therefore, through the synthesis of dihydro-iso-osajin and dihydro-isopomiferin to be described, conclusive evidence is obtained in support of the structures assigned to osajin and pomiferin by degradative methods.

For the synthesis of the two pigment derivatives XXIII and XXIV, there was required dihydro-iso-osajinol (V), the basic structure from which they could be formed by introduction of the isoflavone

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[1] Preceding communication in this series: M. L. Wolfrom, W. D. Harris, G. F. Johnson, J. E. Mahan, S. M. Moffet and B. Wildi, THIS JOURNAL, **68**, 406 (1946).

[2] A preliminary notice of this work appeared in *Abstracts Papers Am. Chem. Soc.*, **113**, 60L (1948).

[3] Predoctoral Fellow of the American Chemical Society, 1946–1947.

[4] M. L. Wolfrom, F. L. Benton, A. S. Gregory, W. W. Hess, J. E. Mahan and P. W. Morgan, THIS JOURNAL, **63**, 422 (1941).