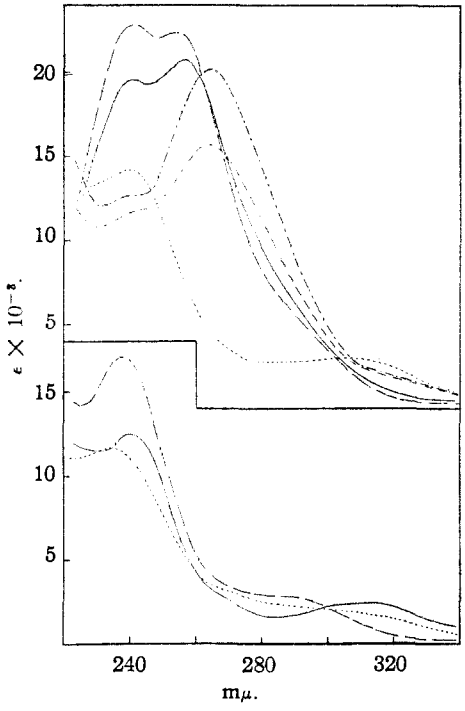


Fig. 6.—Top—sulfadiazine: —— ——, *p*H 11; ————, *p*H 7; —·—·—·—, *p*H 5.0; - - - -, *p*H 2.5; - - - - - - - -, *in 2 N* HCl. Bottom—2-benzenesulfonamidopyrimidine: —— ——, *p*H 11; ————, *p*H 5; - - - - - - -, in 2 *N* HCl.

6, bottom), it is evident that the 257 mμ band is again due to the *p*-aminobenzenesulfonamido absorption, while the 241 mμ band and the longer wave length weak absorption is due to the pyrimidine ring. There is a shift in wave length from 265 to 254 mμ of the sulfanilyl peak with change from acid to base coincident with acidic ionization. In strong acid, *i. e.*, with greatly decreased *p*-aminobenzenesulfonamido absorption, the curves for sulfadiazine and 2-benzenesulfonamidopyrimidine are almost identical.

As would be expected, 2-sulfanilamido-4-methylpyrimidine (sulfamerazine) and 2-sulfanilamido-4,6-dimethylpyrimidine (sulfamethazine) have absorption very similar to that of sulfadiazine.[4] There is a sulfanilyl peak near 260 mμ in neutral solution, a pyrimidyl peak at 241 mμ, and in strongly acid solution, also at 311 mμ.

Summary

1. The ultraviolet absorption spectra of several substituted benzenesulfonamide derivatives have been examined and characterized with respect to changes in *p*H.

2. By examination of the band changes with variation in *p*H, and by comparison with the action of the bands in simpler analogous compounds, the bands of the more complicated derivatives have been associated with the absorbing groups in the molecule.

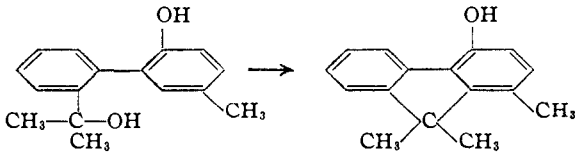
DETROIT, MICHIGAN RECEIVED MAY 25, 1944

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF ROCHESTER]

Syntheses Leading to Substituted Tetrahydrofluorenols

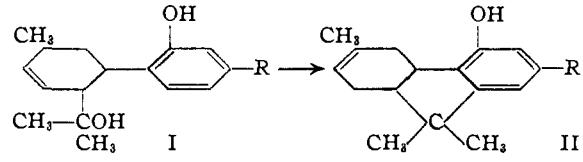
BY WARREN D. MCPHEE[1] AND FRANK J. BALL[2]

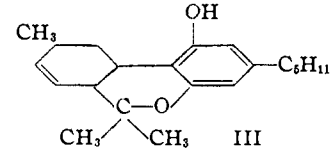
The interesting reaction reported by Anchel and Blatt[3] whereby dialkyl-*o*-xenylcarbinols may be dehydrated to 9,9-dialkylfluorenols by heating with acids, as shown in the example

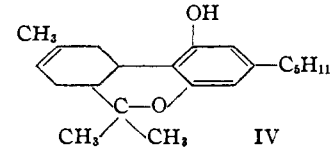


seemed to offer a new approach to the synthesis of tetrahydrofluorenols of type (II). A carbinol of structure (I) might be expected to cyclize to (II) under conditions similar to those used by Anchel and Blatt.

It was thought that these tetrahydrofluorenols might possess marihuana activity because of their structural relationship to the tetrahydrocannabinols (III and IV), differing only in the absence of the oxygen bridge of the pyran ring.







The tetrahydrocannabinols were demonstrated to have high physiological activity by Adams and

(1) Present address: Winthrop Chemical Company, Rensselaer, N. Y.

(2) Present address: West Virginia Pulp and Paper Company, Charleston, S. C.

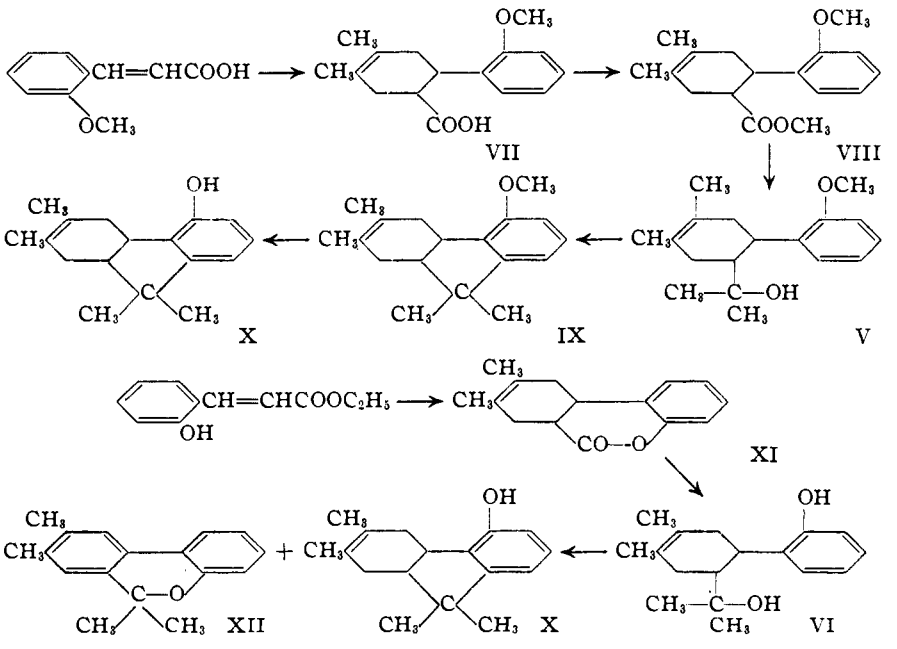
(3) Anchel and Blatt, THIS JOURNAL, 63, 1948 (1941).

his students.[4] Since then a large number of synthetics have been prepared, nearly all of which are active.[5] In general they have been of the tetrahydrodibenzopyran type, except for a few of low activity which are substituted benzopyrans.

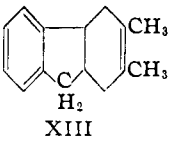
For use in preliminary experiments the two carbinols (V and VI) were prepared in order to study their dehydration. *cis-o*-Methoxycinnamic acid was condensed with 2,3-dimethyl-1,3-butadiene according to the method of Adams, McPhee, Carlin and Wicks.[6] The resulting acid (VII) was esterified and the ester (VIII) treated with methylmagnesium iodide, giving rise to the carbinol (V).

The second carbinol (VI) was prepared from ethyl *o*-hydroxycinnamate. Condensation of this ester with dimethylbutadiene resulted in the tetrahydrodibenzopyrone (XI), the loss of the elements of ethanol accompanying the diene reaction. Treatment of the pyrone with methylmagnesium iodide afforded the carbinol (VI).

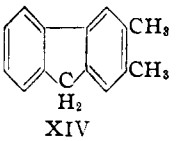
The treatment of (V) with glacial acetic and hydrochloric acids at 187° for twenty hours in a sealed tube yielded a non-crystalline substance, apparently homogeneous, which is no doubt the tetrahydrofluorene (IX). Cyclization by means of concentrated sulfuric acid, which was also used by Anchel and Blatt, was unsatisfactory and gave ether-insoluble material.



Heating (VI) with glacial acetic and hydrochloric acids at 215° for twenty-four hours resulted in the formation of a red oil, part of which is soluble in Claisen alkali and part of which is insoluble. The soluble portion afforded a viscous, high-boiling material which presumably is comprised mainly of the tetrahydrofluorenol (X). The insoluble material afforded a crystalline compound, the analytical values of which indicate that it is the dibenzopyran (XII). The formation of a pyran was not unexpected since this phenomenon had been observed by Anchel and Blatt, but the dehydrogenation of the alicyclic ring is unusual. However, somewhat similar dehydrogenations at high temperature have been noted. For example, Alder and Rickert[7] found that in the diene reaction of dimethylbutadiene and indene, both the expected dimethyltetrahydrofluorene (XIII) and the dimethylfluorene (XIV) were formed.



XIII



XIV

Demethylation of the methoxytetrahydrofluorene (IX) with hydrobromic and glacial acetic acids gave a light red oil which was crystallized as colorless plates. It was expected that this would be identical with the tetrahydrofluorenol (X) obtained by ring closure. However, inoculation of the latter, oily compound with these crystals did not induce crystallization, and the two compounds could not be shown to be identical. As indicated, the oil may not have been homogeneous, and this may explain the lack of success in its crystallization.

It is, of course, recognized that in the strongly acidic media used for the ring closure of the carbinols and for the demethylation of (IX), there is the possibility of migration of the double bonds in the alicyclic rings. However, the 2,3-position indicated in the formulas (IX and X) is the most favored, and isomerization to either the 1,2- or 3,4-positions is less likely. In this connection, see the discussion of Adams[8] concerning the rearrangement of the alicyclic double bonds of the tetrahydrocannabinols under the influence of acids.

(4) Adams, Loewe, Pease, Cain, Baker, Clark, McPhee, Wolff and Wearn, THIS JOURNAL, **62**, 2402, 2566 (1940); **63**, 2209 (1941).

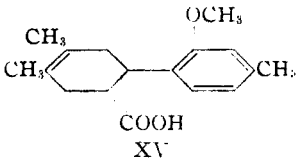
(5) Most recent papers: Adams, Loewe, Theobald and Smith, *ibid.*, **64**, 2653 (1942); Bergel, Morrison, Rinderknecht, Todd, Macdonald and Woolfe, *J. Chem. Soc.*, 286 (1943).

(6) Adams, McPhee, Carlin and Wicks, THIS JOURNAL, **65**, 356 (1943).

(7) Alder and Rickert, *Ber.*, **71**, 379 (1938).

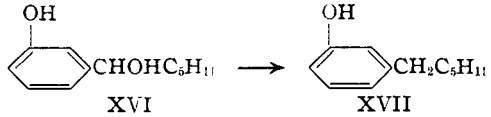
(8) Adams, Loewe, Pease, Cain, Wearn, Baker and Wolff, THIS JOURNAL, **62**, 2566 (1940).

Intermediates were prepared for the synthesis of higher homologous tetrahydrofluorenols. 2-Methoxy-4-methylcinnamic acid was prepared from 7-methylcoumarin, which was obtained from *m*-cresol by von Pechmann's malic acid method. The cinnamic acid added dimethylbutadiene, forming (XV).



XV

2-Methoxy-4-hexylcinnamic acid was also synthesized. The starting material was *m*-hydroxybenzaldehyde, which was treated with amylmagnesium iodide to give rise to the expected secondary alcohol (XVI). This was smoothly reduced at high temperature and pressure in the presence of copper chromite catalyst to *m*-hexylphenol (XVII). 7-Hexylcoumarin was prepared from *m*-hexylphenol and malic acid and was converted to 2-methoxy-4-hexylcinnamic acid by treatment with alkali and dimethyl sulfate.



XVI XVII

The synthesis of *m*-hexylphenol is a modification of that used by Alles, Icke and Feigen[9] for *m*-amylphenol. Theirs was a four-step process starting with *m*-methoxybenzaldehyde. By eliminating two reactions we have simplified the method and materially increased the over-all yield.

Experimental[10]

Methyl 4,5-Dimethyl-2-(*o*-methoxyphenyl)-4-cyclohexenecarboxylate (VIII).—*cis-o*-Methoxycinnamic acid was condensed with 2,3-dimethyl-1,3-butadiene to form the recently-reported acid adduct.[6] A mixture of 4.08 g. (0.015 mole) of this acid, 88 cc. of methyl alcohol and 8 drops of concentrated sulfuric acid was refluxed for seven hours. Half of the methyl alcohol was distilled off, and the remaining solution was poured into 150 cc. of water. The oil which separated was taken up in ether, washed three times with 5% sodium bicarbonate and dried. Acidification of the alkaline wash released 0.24 g. of the starting acid. Evaporation of the ether solution left 3.80 g. (85% yield) of needle-like crystals of m. p. 62.5–65.5°. Recrystallization from petroleum ether gave white crystals of the ester, m. p. 66.2–66.8°.

Anal. Calcd. for $C_{17}H_{22}O_3$: C, 74.42; H, 8.08. Found: C, 74.60; H, 8.13.

1,2-Dimethyl-4-(*o*-methoxyphenyl)-5-(α-hydroxyisopropyl)-1-cyclohexene (V).—To the Grignard reagent prepared from 12 cc. (0.193 mole) of methyl iodide and 3.53 g. (0.145 mole) of magnesium in 100 cc. of dry ether was added 4.04 g. (0.015 mole) of the ester (VIII) in small portions. The mixture was refluxed for four hours, then decomposed in cold dilute sulfuric acid, and extracted with ether. The ether was washed with 5% sodium bicarbonate, dried with calcium chloride, and evaporated, leaving 3.69 g. (91% yield) of the carbinol as slightly sticky crystals. One recrystallization from petroleum ether (b. p. 60–70°) yielded 3.12 g. (77%) of clear white prisms, m. p. 75–77°. On further recrystallization and after the solvent had been effectively removed (drying *in vacuo* at 54° for four days), the crystals melted at 75–75.8°.

Anal. Calcd. for $C_{18}H_{26}O_2$: C, 78.79; H, 9.55. Found: C, 78.96; H, 9.71.

Ring Closure of V.—According to the method of Anchel and Blatt,[3] a mixture of 2.29 g. (0.0083 mole) of the carbinol (V) and 25 cc. of hydrochloric–acetic acid mixture[11] was heated in a sealed tube for twenty hours at 187°. The dark red oil was poured into water and extracted with ether. The dull red ether solution was washed with water, dried over calcium chloride, desolvated and distilled. The product, 2,3,9,9-tetramethyl-5-methoxy-1,1a,-4,4a-tetrahydrofluorene (IX), distilled as a light yellow viscous oil, most of which came over between 160° and 165° (4 mm.); yield, 1.26 g. (59%).

Anal. Calcd. for $C_{18}H_{24}O$: C, 84.32; H, 9.44. Found: C, 84.30; H, 9.27.

Attempts to close the ring with concentrated sulfuric acid were unsuccessful. On adding the acid, the carbinol turned to a deep red oil. Dilution with water gave a green oil which was very insoluble in ether.

Demethylation of IX.—A solution of 0.57 g. (0.0022 mole) of the methoxytetrahydrofluorene (IX) in 5 cc. of 48% hydrobromic acid and 6 cc. of glacial acetic acid was refluxed. Soon a dark immiscible oil formed; the addition of 13 cc. more of acetic acid did not redissolve the material. After eight hours of refluxing the mixture was cooled, diluted with 400 cc. of water and extracted three times with ether. The combined ether extracts were washed extensively with 2 *N* sodium hydroxide, which failed to remove any noticeable material, as shown by acidification of the alkaline solutions. The ether was evaporated and the resulting oil was taken up in petroleum ether (b. p. 60–70°). This solution was extracted three times with Claisen alkali. The dark extract was acidified and extracted three times with ether. The combined ether solutions were washed with water, dried with calcium chloride, and then evaporated. The residue was distilled onto a "cold finger" condenser provided with a cup to retain the distillate. At a bath temperature of 185–220° and 1 mm. pressure, 0.25 g. (50%) of light yellow, highly viscous liquid was collected. Addition of petroleum ether (b. p. 40–60°) and subsequent evaporation transformed the oil to cream-colored plates, m. p. 148–153°. A portion of this material was recrystallized further from the same solvent, producing white plates, m. p. 155.5–156.5°. There was insufficient crystalline material for analysis (semi-micro) because of an accident.

8,9-Dimethyl-6a,7,10,10a-tetrahydrodibenzopyrone (XI).—A mixture of 13.2 g. (0.16 mole) of 2,3-dimethyl-1,3-butadiene and 20.5 g. (0.106 mole) of ethyl *o*-hydroxycinnamate[12] was heated in a glass liner in an autoclave for forty-seven hours at 150°. The cooled mixture contained long colorless crystals which were filtered; weight, 6.7 g.; m. p. 174–178.5°. The filtrate was heated to boil off the excess dimethylbutadiene. Cooling and the addition of ether resulted in the precipitation of further crystals; weight, 5.6 g.; m. p. 175–178°. The total yield of 12.3 g. represents 50% of the theoretical; it was of sufficient purity for the next reaction. Two recrystallizations from dilute alcohol produced long white needles, m. p. 178–180°. Adams, *et al.*,[6] prepared this compound in a state of purity in 5% yield from *trans-o*-hydroxycinnamic acid and in 22% yield from coumarin, and report m. p. 181–181.5° (cor.).

Anal. Calcd. for $C_{15}H_{16}O_2$: C, 78.91; H, 7.07. Found: C, 78.82; H, 7.01.

(9) Alles, Icke and Feigen, THIS JOURNAL, **64**, 2031 (1942).

(10) Analyses by Robert Bauman. All melting points are uncorrected.

(11) Three volumes of concentrated hydrochloric acid and one volume of glacial acetic acid, saturated at 0° with dry hydrogen chloride.

(12) Fries and Klostermann, *Ann.*, **362**, 11 (1908).

Another experiment at 170° for forty-two hours resulted in a 42% yield of the pyrone. Coumarin was also isolated in 18% yield.

1,2-Dimethyl-4-(*o*-hydroxyphenyl)-5-(α-hydroxyisopropyl)-cyclohexene (VI).—The Grignard reagent prepared from 55 cc. (0.89 mole) of methyl iodide, 10.9 g. (0.45 mole) of magnesium and 225 cc. of dry ether was treated with 13.6 g. (0.06 mole) of the solid pyrone (XI), added in small portions. The mixture was refluxed for two hours, cooled, poured into a mixture of 25 cc. of concentrated sulfuric acid and 100 cc. of ice. More ice was added as necessary during the decomposition of the reaction mixture, the total water being 800 cc. at the end. The ether layer was removed and the water layer extracted several times with ether. The combined ether extracts were washed with 5% bicarbonate solution and then evaporated. A colored crystalline product was formed; weight, 16 g. It was recrystallized from chloroform–petroleum ether (b. p. 60–70°); yield, 12.2 g. (85%); white micro crystals, m. p. 130–133°. Further recrystallization from alcohol produced fine white needles, m. p. 132–135°.

Anal. Calcd. for $C_{17}H_{24}O_2$: C, 78.42; H, 9.29. Found: C, 78.46; H, 9.23.

Cyclization of VI.—A solution of 2.62 g. (0.01 mole) of VI in 25 cc. of hydrochloric–acetic acid mixture[11] was heated in a sealed tube at 215° for twenty-four hours. On cooling, a thick red oil separated on the lighter colored acid layer. Two hundred and twenty-five cubic centimeters of water was added to the mixture, which was then extracted three times with ether. The ether extracts were washed thoroughly with 2 *N* sodium hydroxide; as before, the alkali removed no noticeable material. The ether was evaporated, the viscous residue was taken up in petroleum ether, and the solution was extracted five times with Claisen alkali. The alkaline extract was acidified with dilute hydrochloric acid, extracted with ether, and the ether dried over calcium chloride. The extract was desolvated and distilled as before onto the "cold finger" condenser. A colorless oil, b. p. 158–168° (1.5 mm.), came over at a bath temperature of 190°; weight, 0.68 g. (28% yield).

Anal. Calcd. for $C_{17}H_{22}O$: C, 84.25; H, 9.15. Found: C, 83.25; H, 8.97.

Several other experiments gave similar results, indicating that a pure compound is not obtained in this reaction. A mixture of the expected fluorenol (X) and the starting carbinol (VI) seems probable on the basis of analytical data.

6,6,8,9-Tetramethyl-6-dibenzopyran (XII).—The petroleum ether residue from the Claisen alkali extraction was desolvated and the resulting oil distilled. A slightly yellow, mobile oil was obtained at 120–130° (2 mm.); weight, 0.47 g. (21% yield). In a few hours the product crystallized; m. p. 89–97°. Two recrystallizations from dilute alcohol gave white needles, m. p. 100–100.5°.

Anal. Calcd. for $C_{17}H_{18}O$: C, 85.67; H, 7.61. Found: C, 85.62; H, 7.55.

2-Methoxy-4-methylcinnamic Acid.—On refluxing a solution of 24.24 g. (0.15 mole) of 7-methylcoumarin[13] in 150 cc. of water containing 13.4 g. (0.33 mole) of sodium hydroxide, all the coumarin went into solution in an hour. To the refluxing solution was added 57 cc. (0.61 mole) of dimethyl sulfate over a period of one and one-quarter hours, and refluxing was continued for two hours more. In order to saponify any methyl ester formed, 17.6 g. (0.44 mole) of sodium hydroxide in 34 cc. of water was added and the solution was boiled for another three hours. After cooling, the mixture was slowly poured into cracked ice into which 17.5 cc. of concentrated sulfuric acid had been stirred. The white precipitate weighed 28.12 g. (98%) after thorough washing to remove salts; m. p. 150–157°. On recrystallization from a alcohol, two crops of crystals were obtained. The first weighed 15.9 g. and had m. p. 159.5–160.7°; the second weighed 7.17 g. and melted at 158.5–160°. The acid is reported[14] to have m. p. 160–161°. The third and fourth crops contained a higher-melting impurity, probably the *trans* form of the acid which melts at 209–210°.[14] The two crops represent 80% yield.

4,5-Dimethyl-2-(*o*-methoxy-*p*-tolyl)-4-cyclohexenecarboxylic Acid (XV).—A mixture of 14.7 g. (0.076 mole) of 2-methoxy-4-methylcinnamic acid, 16 cc. (0.14 mole) of dimethylbutadiene, and 22.5 cc. of xylene was heated in a bomb for thirty-seven hours at 185°. The reaction mixture, which contained some granular crystals, was evaporated, filtered and the residue washed with petroleum ether (b. p. 40–60°). Recrystallization from benzene–petroleum ether (b. p. 90–100°) gave white crystals of m. p. 146–170°, which proved to be mainly the starting cinnamic acid. Recrystallization from benzene afforded white crystals, m. p. 182–189°; weight, 1.54 g. (7% yield). Three recrystallizations from benzene–petroleum ether (b. p. 40–60°) raised the m. p. to 195–197°.

Anal. Calcd. for $C_{17}H_{22}O_3$: C, 74.42; H, 8.08. Found: C, 74.62; H, 8.01.

3-Hydroxyphenyl-*n*-amylcarbinol (XVI).—Seventy-five grams of *n*-amyl iodide (0.38 mole), 8.9 g. (0.37 mole) of magnesium and 100 cc. of dry ether were converted to the Grignard reagent. On adding 15 g. (0.13 mole) of *m*-hydroxybenzaldehyde in 175 cc. of ether to the reagent, there was formed a gummy precipitate of the organometallic complex. To favor further reaction of the aldehyde, 100 cc. more ether was added and the mixture refluxed and stirred for seventeen hours. It was then poured into dilute sulfuric acid in ice. The ether layer was removed and the water layer extracted twice with ether. The ether extracts were washed with 5% sodium bicarbonate and dried with calcium chloride. Upon desolvation, 24.2 g. (97% yield) of the carbinol was obtained as cream colored crystals which melted at 90–95°. This was purified by recrystallization from alcohol to give 20.4 g. (82% yield) of white plates of m. p. 97.5–99°. Another recrystallization raised the m. p. to 100–100.5°.

Anal. Calcd. for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 74.58; H, 9.22.

***m*-Hexylphenol (XVII).**—A solution of 9.73 g. of the carbinol (XVI) in 30 cc. of absolute ethanol was hydrogenated in the presence of 2 g. of copper chromite on charcoal catalyst at 1750 lb. pressure and 185° for sixteen hours. The catalyst was filtered and the filtrate distilled. A colorless product, b. p. 111–113° (2–3 mm.), weighing 8.23 g. (92% yield) was obtained; $n^{22}D$ 1.5092; d^{22}_{22} 0.9486.

Anal. Calcd. for $C_{12}H_{18}O$: C, 80.85; H, 10.18. Found: C, 80.38; H, 10.21.

The **α-naphthylurethan of XVII** was prepared by the method of Tarbell, *et al.*[15] Upon recrystallization from petroleum ether it came down both as white needles and plates of m. p. 102.2–102.8°.

Anal. Calcd. for $C_{23}H_{25}NO_2$: C, 79.50; H, 7.25. Found: C, 79.54; H, 7.19.

7-Hexylcoumarin.—A thorough mixture of 3.71 g. (0.021 mole) of *m*-hexylphenol and 2.79 g. (0.021 mole) of malic acid was treated with 50 cc. of concentrated sulfuric acid. The mixture was heated in an oil-bath at 110–120° for one and one-half hours. The reaction was accompanied by the evolution of carbon monoxide, but the heat was removed before evolution ceased because the reaction mixture darkened considerably. On cooling, ice was added and a red oil separated. This was extracted with ether and the ether layer washed with sodium bicarbonate solution. On evaporation, 1.88 g. (39% yield) of brown crystals was obtained, m. p. 44–45°. Two recrystallizations from absolute alcohol gave white needles of m. p. 45.5–46°.

Anal. Calcd. for $C_{15}H_{18}O_2$: C, 78.23; H, 7.88. Found: C, 78.06; H, 7.88.

2-Methoxy-4-hexylcinnamic Acid.—7-Hexylcoumarin (0.40 g., 0.0017 mole) was refluxed with 5 cc. of 10% sodium hydroxide for one and one-half hours, in order to convert

(13) Fries and Klostermann, *Ber.*, **39**, 871 (1906).

(14) Rangaswami and Seshadri, *Proc. Indian Acad. Sci.*, **5A**, 249 (1936); *C. A.*, **31**, 5784 (1937).

(15) Tarbell, Mallatt and Wilson, THIS JOURNAL, **64**, 2229 (1942).

it to the hydroxycinnamic acid. Then 2 cc. (0.021 mole) of dimethyl sulfate was added dropwise and the mixture refluxed for forty minutes. An excess of 6 *N* sodium hydroxide was added and the resulting solution was refluxed for two hours. It was cooled and added to excess sulfuric acid in ice. The white precipitate that formed was taken up in ether and extracted with 2% sodium hydroxide. Acidification of the alkaline extract gave a colorless oil which was extracted with ether. The ether was dried with calcium chloride and evaporated, releasing 0.35 g. (76% yield) of well-formed white prisms of m. p. 73–76°. Two recrystallizations of the acid from petroleum ether (b. p. 60–70°) raised the m. p. to 77–77.8°.

Anal. Calcd. for $C_{16}H_{22}O_3$: C, 73.25; H, 8.45. Found: C, 73.56; H, 8.79.

Summary

The ring closure of two dialkyltetrahydroxenylcarbinols under the influence of mixed acetic and hydrochloric acids has been studied. 1,2-Dimethyl-4-(*o*-methoxyphenyl)-5-(α-hydroxyisopropyl)-cyclohexene forms a liquid product believed to be 2,3,9,9-tetramethyl-5-methoxy-1,1a,-4,4a-tetrahydrofluorene. The corresponding compound, 1,2-dimethyl-4-(*o*-hydroxyphenyl)-5-(α-hydroxyisopropyl)-cyclohexene, affords a mixture of two products, 2,3,9,9-tetramethyl-5-hydroxy-1,1a,4,4a-tetrahydrofluorene and 6,6,8,9-tetramethyl-6-dibenzopyran, the latter being the result of simultaneous dehydrogenation.

The diene synthesis of 8,9-dimethyl-6a,7,10,-10a-tetrahydrodibenzopyrone from dimethylbutadiene and ethyl *o*-hydroxycinnamate, and of 4,5-dimethyl-2-(*o*-methoxy-*p*-tolyl)-4-cyclohexenecarboxylic acid from dimethylbutadiene and 2-methoxy-4-methylcinnamic acid are described.

The preparation of 2-methoxy-4-hexylcinnamic acid from *m*-hydroxybenzaldehyde is reported.

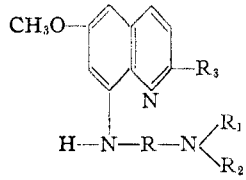
ROCHESTER, NEW YORK RECEIVED MAY 12, 1944

[CONTRIBUTION FROM THE LILLY RESEARCH LABORATORIES]

Derivatives of 6-Methoxy-8-aminoquinoline and 2-Methyl-6-methoxy-8-aminoquinoline. I

BY EWALD ROHRMANN AND H. A. SHONLE

While a very considerable number of 6-methoxy quinolines substituted in the 8 position by dialkylaminoalkylamino groups have been reported,[1,2,3] most of these have been of the type in which R_1 and R_2 were the same and limited to methyl, ethyl or isoamyl



In view of the reputed gametocidal action of some of the 6-methoxy-8-substituted aminoquinolines, it was thought desirable to investigate compounds in which R_1 and R_2 were different. One of the objects of the present program was to determine what effect variations in R_1 and R_2 (in regard to both weight and configuration) have upon the activity and toxicity of the products. Some 2-methyl-6-methoxy-8-substituted aminoquinolines are also reported in the present work.[4,5]

In the examples of substituted 8-aminoquinolines reported at this time R is either $-CH_2CH_2-$, $-CH(CH_3)CH_2-$ or $-CH_2CH_2CH_2-$; R_1 and R_2 are alkyl, cycloalkyl, aryl or alkaryl, and R_3 is H or CH_3.

The intermediate aminoalkanols were prepared from the appropriate secondary amines by reaction with ethylene oxide, propylene oxide or propylene chlorohydrin or the corresponding halohydrins, respectively.

The resulting disubstituted aminoalkanols were converted to the disubstituted aminoalkyl chloride hydrochlorides by treatment with thionyl chloride in chloroform or benzene solution.[6] In those cases in which a crystalline disubstituted aminoalkyl chloride hydrochloride was not obtained, the crude reaction product was treated with an excess of alkali and the liberated disubstituted aminoalkyl chloride purified by distillation. The disubstituted aminoalkylamino chlorides and their hydrochlorides were not analyzed. The details of the preparation and properties of the unsymmetrical secondary amines will be published at a later date in THIS JOURNAL.

Condensation to the substituted quinoline was carried out by refluxing in ethanol solution, either the disubstituted aminoalkyl chloride hydrochloride or the free disubstituted aminoalkyl chlorides, with 6-methoxy-8-aminoquinoline or 2-methyl-6-methoxy-8-aminoquinoline. The use of an alkaline condensing agent appears to be unnecessary.

The compounds prepared are listed in the accompanying tables. These compounds have been tested for antimalarial action against *Plasmodium lophurae* in ducklings by Mr. C. L. Rose of these laboratories. Complete details of their pharmacological properties will be published elsewhere.

(1) Magidson and Strukov, *Arch. Pharm.*, **271**, 569 (1933).

(2) Magidson, Madajerva and Rubzon, *ibid.*, **273**, 320 (1935).

(3) Fourneau, *et al.*, *Ann. Inst. Pasteur*, **46**, 514 (1931).

(4) Brahmachari and Bhattacharjee, *J. Indian Chem. Soc.*, **8**, 571 (1931).

(5) Brahmachari and Das-Gupta, *ibid.*, **9**, 37, 207 (1932).

(6) Magidson, *et al.*, *Arch. Pharm.*, **272**, 78 (1934).