

TABLE III
RESULTS OF BIOLOGICAL TESTS WITH COMPOUNDS IN
TABLES I AND II AGAINST VARIOUS ARTHROPODS^a

No.	Chigger ^b Toxicant	Body Louse ^c Toxicant	Mos- quito ^d Larvi- cide	Mos- quito ^e Re- pellent
I	1	1	1	1
II	1	1	4	1
III	1	1	4	1
IV	1	1	2	1
V	1	1	2	1
VI	1	1	3	1
VII	1	2	4	1
VIII	1	1	4	1
IX	1	1	4	1
X	1	1	4	1
XI	1	1	1	1
XII	1	1	1	1
XIII	2	1	1	1
XIV	1	2	1	1
XV	1	1	1	1
XVI	1	1	1	...
XVII	...	3	1	...
XVIII	1	1	1	...
XIX	3	1	1	2
XX	...	3	2	1
XXI	...	4	3	1
XXII	...	3	3	1
XXIII	...	4A	3	1
XXIV	...	3	3	1
XXV	...	4	3	1
XXVI	...	4	3	1
XXVII	...	1	1	1
XXVIII
XXIX	1	1	2	1
XXX	...	1	1	1
XXXI	...	1	1	1

^a Classification same as that given by King,^{5a} class 1 least and class 4 or 4A most effective. ^b *Trombicula splendens* Ewing. ^c *Pediculus humanus humanus* L. ^d *Anopheles quadrimaculatus* Say. ^e *Aedes aegypti* (L.).

Ethers and esters (Table II, XX-XXI, XXIII-XXXI) from phenols. The ethers were prepared from the phenol, alkyl bromide, potassium carbonate, and dry acetone according to published procedures.³ The ester was prepared in the usual way from a mixture of the phenol, benzene, pyridine, and the acid chloride.

1,2-Methylenedioxy-5-methoxy-4-propenylbenzene (Table II, XXVIII). XX (64 g.) was dissolved in 150 ml. of a saturated solution of potassium hydroxide in methanol.⁴ Methanol was removed by distillation until a liquid temperature of 110° was reached, and the solution was then refluxed for 6 hr. After cooling, the mixture was poured into cold water and extracted with ether. The ether layer was washed with a saturated salt solution and dried over anhydrous sodium sulfate. After filtering and evaporating the ether, the residue (XXVIII) crystallized.

5-Bromo-1,2-methylenedioxy-4-(2,3-dibromopropoxy)-benzene (XXIX). A mixture of 3,4-methylenedioxyphenyl allyl ether⁷ (47 g.) and glacial acetic acid (200 ml.) was cooled to 0°, and bromine (86 g.) was added with stirring at such a rate as to maintain the temperature below 15°. Stirring was continued for an additional hour at 15° and the mixture was allowed to stand at 25° overnight, after which it was poured into ice and water with stirring. After several hours the supernatant was decanted from the dark residue, and the latter was washed twice with cold water. Cold water was again added to the residue, and it was scratched to produce crystallization. The crystals were filtered, washed with cold water, and dried.

4-(2,3-Dibromopropyl)-5-methoxy-1,2-methylenedioxybenzene (XXX). This compound was prepared as above from XX (0.2 mole) and bromine (0.2 mole). The corresponding ethoxy compound (XXXI) was prepared from the ethoxy derivative in the same manner.

Acknowledgment. We are grateful to Shulton Inc., Clifton, N. J., for the sesamol used in this study, and to Dr. Carroll N. Smith and others of the staff of the Orlando, Fla., laboratory of the Entomology Research Division for conducting the biological tests.

BELTSVILLE, MD.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF FLORIDA]

Ocimene

J. ERSKINE HAWKINS AND WILLIAM A. BURRIS

Received April 20, 1959

This paper describes an improved apparatus for preparing ocimene from α -pinene. It also outlines the method of analysis of the product mixture. Infrared absorption curves of ocimene, alloocimene, dipentene, α -pinene, alloocimene dimer, and a synthetic mixture of the products are included. The values calculated for ocimene were n_D^{25} 1.4851, d_4^{25} 0.7926 g./cc.

In 1907, Enklaar¹ stated that he obtained some ocimene by the isomerization of alloocimene under the influence of a mixture of sulfuric and acetic acids. The known behavior of ocimene and alloocimene makes such an isomerization unlikely. Several attempts in this laboratory to verify Enklaar's statement were unsuccessful.

In 1940, Rice² reported the vapor phase formation

(1) C. J. Enklaar, *Rec. trav. chim.*, **26**, 157 (1907).

(2) F. O. Rice, U. S. Patent 2,190,369, Feb. 13, 1940.

of ocimene from α -pinene. In 1951, Hawkins and Hunt³ published a description and method of operating an apparatus for the production of ocimene from α -pinene in the vapor phase. More recently O'Connor and Goldblatt⁴ indicated that they have prepared ocimene by the isomerization

(3) J. E. Hawkins and H. G. Hunt, *J. Am. Chem. Soc.*, **73**, 5379 (1951).

(4) R. T. O'Connor and L. A. Goldblatt, *Anal. Chem.*, **26**, 1726 (1954).

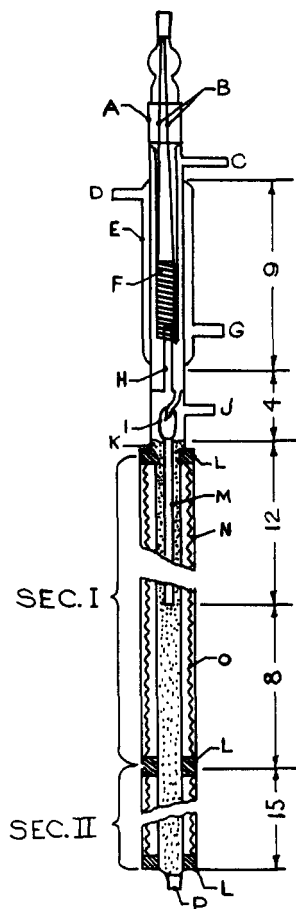
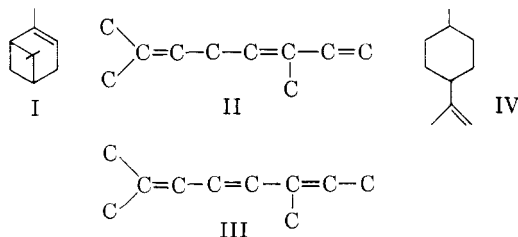


Fig. 1. Apparatus for production of ocimene by vapor phase pyrolysis of α -pinene

of α -pinene, but gave no description of the method used.

In view of the above it appeared profitable to construct a more efficient apparatus for the preparation of ocimene. This would then provide a more convenient source of ocimene for use in the determination of its physical and chemical properties.

When α -pinene is isomerized the principal components present in the product are α -pinene, I, ocimene, II, alloocimene, III, and dipentene, IV.



Apparatus. The glass apparatus used for the preparation is shown in Fig. 1. The design is for a continuous process and involves the principle of reverse take-off.

A is a standard-taper joint, 45/50, D and G are the condenser water outlet and inlet respectively, and L is asbestos packing.

Liquid α -pinene from a reservoir enters the apparatus at tube J and runs into the protruded packing K where it is vaporized by the column heater, N.

The α -pinene vapor then passes up through tube H and over the electrically heated nichrome spiral F. This spiral is supported by a cage of glass rods. One lead wire passes through the one hollow tube used in the cage and is sealed through glass at the bottom end of this tube. The other lead wire is sealed through glass just above the pyrolysis spiral. These two lead wires B are connected to a variable autotransformer. Tube C is connected to a vacuum system. The pyrolysed α -pinene vapor is condensed in E. The condensed pyrolysate drains into the column through the tube M. A drop counter I is provided above the packing so that the rate of liquid passing over the pyrolysis spiral can be observed. Tube M directs the pyrolysate into the column packing to a sufficient depth so that recycling of ocimene is prevented. The column heating jacket is divided into two separately controlled sections. These heating jackets consist of six nichrome wire spirals running the length of the heating section. Operation is improved by insulating the column with glass wool.

The primary purpose of Section I is to vaporize the α -pinene and prevent the recycling of the ocimene. The liquid α -pinene from the reservoir serves as reflux in Section I. Section II is for the purpose of returning the unreacted α -pinene to Section I and allowing only the higher boiling alloocimene, ocimene, and dipentene to pass down into the receiver connected at P. This receiver is cooled by passing cold water through its jacket. An outlet, attached to the water-cooled receiver, is connected to a three-way stopcock for evacuating a second receiver, which is detachable while the process is in operation.

The liquid pinene is delivered to tube J from a three-liter reservoir, connected to the vacuum line through a three-way stopcock. The vacuum lines from the reservoir, tube C, and the detachable receiver all lead to a cold finger dry ice trap. Any material trapped by the dry ice cold finger can be drained into the detachable receiver through its vacuum line. A drop counter is provided in the line from the reservoir to tube J for measuring the rate of introduction of α -pinene. This rate was regulated by a Hoke valve.

EXPERIMENTAL

Material used. The α -pinene used was obtained from the Glidden Company, Jacksonville, Fla., and was redistilled until $n_D^{25} = 1.4632 \pm 0.0001$.

Production of ocimene. The pyrolysis of α -pinene was usually carried out at about 5 mm. pressure to permit operation at lower temperatures. Once the proper vacuum had been established, the column heaters were turned on. The heaters were allowed to come to temperature at the operating voltage before α -pinene was introduced into the

TABLE I
COMPOSITIONS OF MIXTURES OBTAINED AT DIFFERENT VOLTAGES ACROSS THE PYROLYSIS SPIRAL

Volts	% Ocimene	% Alloöcimene	% α -Pinene	% Dipentene	Dipentene/ Ocimene	Alloöcimene + Ocimene/ Dipentene
27	14	0	62	15	1.1	0.9
28	29	9	40	27	0.9	1.4
30	29	19	16	29	1.0	1.7
33	19	25	14	35	1.8	1.3
35	29	28	10	35	1.2	1.6

column. The temperatures of the heating sections were indicated by thermocouples attached to an electronic recorder. After the introduction of liquid α -pinene, the column heating jacket temperatures quickly dropped to the operating level. The current in the pyrolysis spiral was not turned on until reflux appears at drop counter 1.

The four controllable variables of the apparatus are the power input to the pyrolysis spiral, the wattages developed in the two heating jackets, and the rate of introduction of the α -pinene. The power input to the pyrolysis spiral affects the heat transfer to the α -pinene vapor. A combination of this heat transfer rate and the rate of passage of α -pinene vapor over the spiral determines the temperature to which the vapor is heated. This temperature in turn determines the percentage of α -pinene which is isomerized in one pass over the spiral, the ratio of the dipentene to ocimene in the product, and the possible further isomerization of ocimene to alloöcimene before it is condensed. The α -pinene drop rate affects the column temperatures which in turn affect the efficiency of separating the α -pinene from the product.

The temperature of the upper column heater must be high enough to provide sufficient heat to vaporize the liquid α -pinene entering Section I and to vaporize the α -pinene in the liquid reflux from the pyrolysis spiral. The best indication of proper setting of the voltage across this heater is the ratio of the drop rate in the drop counter, 1, Figure 1, to the α -pinene drop rate from the reservoir. Under usual conditions this should be a minimum of 5 to 1. The amount of insulation on the outside of the heater must be kept constant after the proper setting is determined.

The temperature in the lower column must be high enough to strip practically all the α -pinene from the product before it enters the receiver. If either the percentage of α -pinene in the material coming into Section II or the rate of all material coming into Section II is too high, this section will be overloaded and the product will contain a substantial amount of α -pinene. If, on the other hand, the temperature of the lower heater is increased too much in order to compensate for this factor, the ocimene will be isomerized to alloöcimene. As long as this section is not overloaded, the proper voltage setting can be determined by the percentage of α -pinene in the product.

Low drop rate increases the percentage conversion on one pass over the spiral and the efficiency of α -pinene separation from the product, but may increase the proportion of alloöcimene found. The optimum drop rate, in the apparatus studied during this investigation, seemed to be between 5 and 30 drops a minute. Drop rates over 60 per minute tended to require excessive column temperatures to maintain reflux.

It is impossible to apply these optimum conditions to the operation of another apparatus; so, this information can be used only as a guide.

Experiments were run on the present column at various drop rates with 27, 28, 30, 33, 35, 36, and 37 volts across the pyrolysis spiral. Some of the mixtures obtained at the various voltages are shown in Table I.

The important information given by these percentages is the ratios. The amount of α -pinene is not important since apparently it can be reduced to a low value by lowering the drop rate. Approximately the same amounts of ocimene were produced by the different voltages, so the optimum operating voltage is that which produces the smallest amounts of alloöcimene and dipentene. The dipentene is the most important impurity to keep at a low value since its removal by distillation is very difficult. It appears that the optimum voltage is 28–30 volts.

The ratios of alloöcimene plus ocimene to dipentene were somewhat better than obtained by hot tube pyrolysis at 350°. By operating at a very high column temperature, a high spiral temperature and low drop rates, a very high concentration of alloöcimene can be obtained if alloöcimene is desired rather than ocimene.

Analysis of product. Separation of ocimene proved to be difficult. Even at 5 mm. it is believed that some ocimene isomerized due to the length of the heating period. The product was distilled at 5 mm. Hg pressure in a protruded packing distillation column, 3.5 cm. O.D. and 140 cm. long. Material boiling at 54° was collected. It contained some dipentene. This distillate was analyzed by the method of Hawkins and Hunt³ for per cent ocimene by isomerizing it and a sample of pure alloöcimene in separate sealed tubes for 1 hr. at about 200°. This heating isomerized the ocimene to alloöcimene and caused some of the alloöcimene formed, and some of the pure alloöcimene, to dimerize. Before heating, the alloöcimene had an n_D^{25} of 1.5424 and the ocimene, 1.4842. After heating, the alloöcimene was 1.5360 and the ocimene 1.5320. The difference between the refractive indices of the heated alloöcimene and dipentene (n_D^{25} , 1.4702) is divided into the difference between the refractive indices of the heated impure ocimene and dipentene. This is justified as the relation between the refractive index and the composition of alloöcimene-dipentene mixtures is nearly linear.⁶ The calculation gave 94% ocimene. Since the ocimene isomerizes almost immediately at 200°, the alloöcimene produced from ocimene and the pure alloöcimene have nearly the same length of time to dimerize. Thus, using the refractive index of the heated pure alloöcimene as equivalent to that of heated pure ocimene is valid.

The 94% ocimene produced, boiling at 54°, at 5 mm., was found to have a refractive index of 1.4842, a density of 0.7953 g./cc. at 25°, a viscosity of 0.680 centipoise, and a surface tension of 25.4 dynes per cm.

The viscosity was obtained with an Ostwald viscometer. The surface tension was obtained with a Colthup and Torly maximum bubble pressure type apparatus.

If the refractive index of the 94% ocimene is corrected

(5) L. A. Goldblatt and S. Palkin, *J. Am. Chem. Soc.*, **63**, 3517 (1941).

(6) R. E. Fuguitt and J. E. Hawkins, *J. Am. Chem. Soc.*, **69**, 319 (1947).

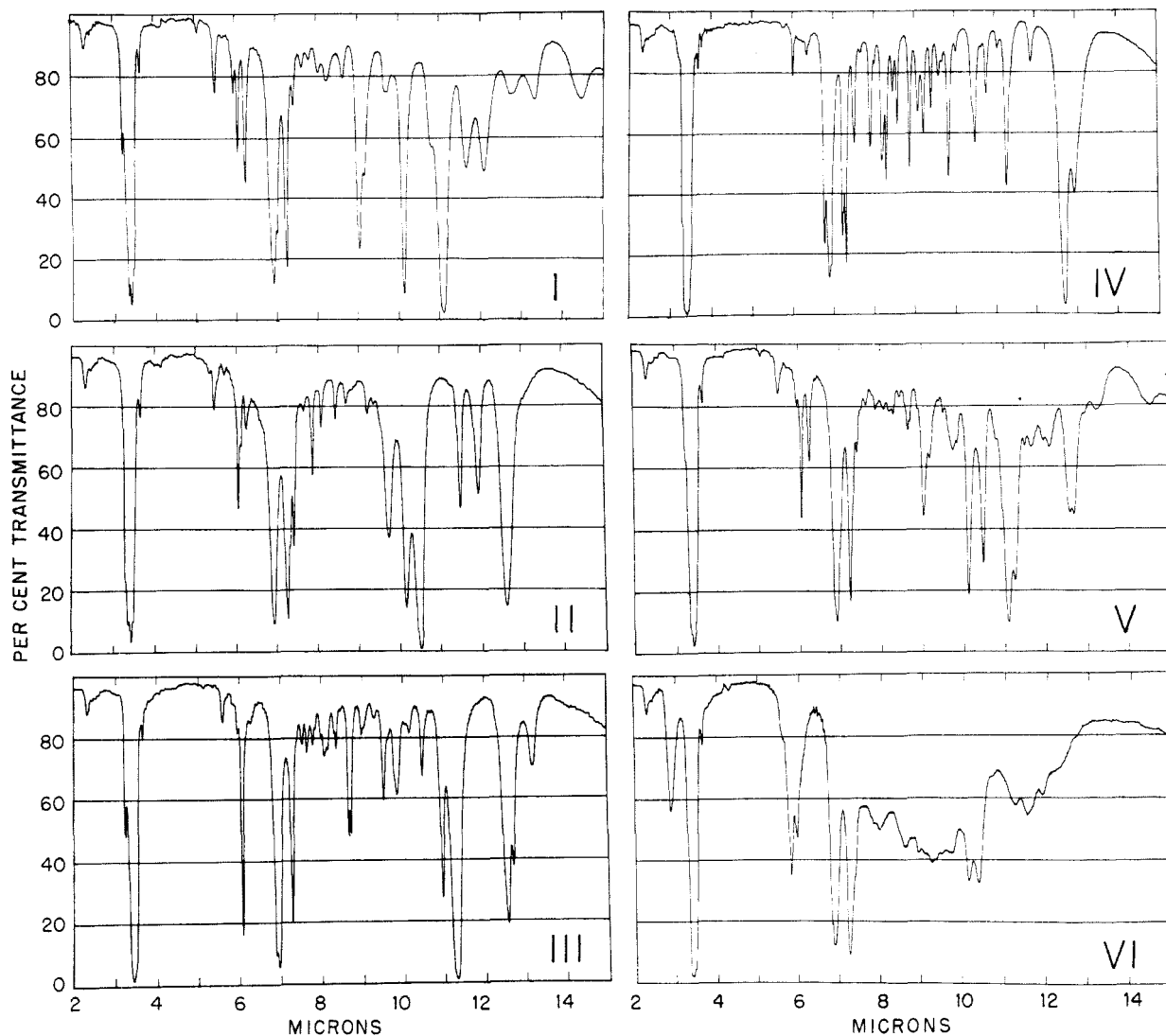


Fig. 2. Infrared absorption spectra (in a 0.0288 mm. cell). I. 94% Ocimene. II. Alloöcimene. III. Dipentene. IV. α -Pinene. V. Synthetic pyrolysis mixture. VI. Alloöcimene dimer.

by dividing the difference between the refractive index of dipentene, 1.4702, and that of the 94% ocimene by 0.94, and adding this to the refractive index of dipentene, a value of n_D^{25} 1.4851 is obtained for pure ocimene. If the density is corrected by dividing the difference between the impure ocimene density found and that of dipentene, 0.8370, by 0.94 and subtracting this from the density of dipentene, a value of 0.7926 at 25° is obtained. These values compare favorably with those of n_D^{20} 1.4873 and density at 20° of 0.8034 reported by O'Connor and Goldblatt.⁴

In order to determine optimum operating conditions of the ocimene apparatus it is necessary to analyze the pyrolysis product. The most convenient available method of analysis was by infrared. The infrared spectra of ocimene, alloöcimene from hot spiral pyrolysis, dipentene, α -pinene, and a synthetic pyrolysis mixture will be found in Figure 2.

These spectra are included as they were obtained with an instrument which was capable of greater resolution than shown by previously published spectra and cover a wider range of wave lengths which furnishes additional informa-

tion.⁴ The spectrum of the dimer is included as it readily forms from alloöcimene and has not been published previously.

The optical densities of the principal pyrolysis components at their characteristic infrared wave lengths also are given in Table II. The wave lengths suitable for quantitative work are given in Table III. The ocimene absorbancies in these tables were corrected for the presence of 6% dipentene by subtracting 0.06 times the dipentene absorbancy and adjusted to 100% ocimene by division by 0.94. An approximate method of analysis was developed using four wave lengths, at each of which only one component was a major absorber and all others absorbed at essentially the same low value. Using the equation of composition and average values of absorbance for the low absorbers, the following relations were developed for a 0.0288 mm. cell. $V_1 \cdot V_4 =$ volume fractions of the various components. $A_s =$ the optical density of the mixture at the particular wave length.

At 12.09 microns, $0.04(1 - V_1) + 0.32 V_1 = A_s$, where $V_1 =$ vol. fraction of ocimene

TABLE II

OPTICAL DENSITY AT CHARACTERISTIC INFRARED WAVE LENGTHS OF PURE COMPONENTS OF PYROLYSIS MIXTURE IN 0.0288 MM. CELL

Part I Alloöcimene		Part II Dipentene	
Wave Length, Microns	Optical Density	Wave Length, Microns	Optical Density
3.42	1.30	3.43	1.6
6.03	0.300	6.05	0.740
6.91	1.02	6.93	1.23
7.24	0.928	7.25	0.670
7.40	0.460	8.65	0.292
7.85	0.223	8.70	0.285
9.73	0.440	10.94	0.530
10.15	0.838	11.27	1.8
10.50	1.7	12.54	0.685
11.47	0.320	12.67	0.440
11.92	0.300		
12.59	0.770		

Part III α -Pinene		Part IV Ocimene	
Wave Length, Microns	Optical Density	Wave Length, Microns	Optical Density
3.40	2.00	3.40	1.10
6.77	0.635	6.05	0.244
6.88	0.925	6.23	0.372
7.22	0.580	6.91	0.892
7.38	0.790	7.24	0.408
7.50	0.285	9.02	0.645
7.89	0.250	10.12	1.08
8.18	0.290	11.10	1.7
8.87	0.313	11.66	0.310
9.21	0.260	12.10	0.292
9.84	0.350		
10.49	0.250		
11.27	0.384		
12.70	1.32		
12.96	0.287		

TABLE III

OPTICAL DENSITY OF PURE COMPONENTS OF PYROLYSIS MIXTURE IN 0.0288 CELL AT INFRARED WAVE LENGTHS MOST USEFUL IN QUANTITATIVE DETERMINATIONS

Wave Length, Microns	Ocimene	Allo- ocimene	Dipentene	α -Pinene
6.05	0.204	0.240	0.740 ^a	0.043
8.65	0.066	0.065	0.292 ^a	0.035
8.70	0.044	0.082	0.285 ^a	0.032
8.87	0.072	0.057	0.040	0.313 ^a
9.02	0.644 ^a	0.046	0.076	0.110
9.73	0.118	0.440 ^a	0.125	0.118
10.94	0.016	0.450	0.530 ^a	0.022
11.64	0.307 ^a	0.064	0.060	0.008
12.09	0.319 ^a	0.066	0.028	0.013
12.96	0.100	0.067	0.078	0.287 ^a

^a Values, used in calculating composition of mixtures, determined at appropriate wave lengths.

At 9.74 microns, $0.12(1 - V_2) + 0.44V_2 = A_s$, where $V_2 =$ vol. fraction of alloöcimene

At 12.96 microns, $0.08(1 - V_3) + 0.29V_3 = A_s$, where $V_3 =$ vol. fraction of α -pinene

At 8.70 microns, $0.05(1 - V_4) + 0.285V_4 = A_s$, where $V_4 =$ vol. fraction of dipentene

In these equations everything but the component being determined, $(1 - V)$, is treated as one component. A synthetic pyrolysis mixture, Fig. 2, was made with the composition in volume per cent as follows, ocimene 47, dipentene 23, alloöcimene 20, and α -pinene 10. This mixture had an optical density at 12.09 microns of 0.168, at 9.74 microns of 0.183, at 12.96 microns of 0.108, and at 8.70 microns of 0.104. Using the above equations, the following values were obtained: ocimene, 46%; dipentene, 23%; alloöcimene, 20%; and α -pinene, 13%. This is an excellent check with the known values.

GAINESVILLE, FLA.

[CONTRIBUTION FROM THE LABORATORY OF BIOCHEMISTRY, NATIONAL CANCER INSTITUTE¹]

Nitration of 1- and 3-Fluorofluorene

KAZUO SUZUKI,² ELIZABETH K. WEISBURGER, AND JOHN H. WEISBURGER

Received April 20, 1959

The nitration of either 1- or 3-fluorofluorene led to a mixture of isomers. In each case, the main product was the 7-nitro derivative, but small amounts of the 2- and 4-nitro compounds were also isolated. The halogen fluorine hinders substitution in the same ring of the polynuclear hydrocarbon fluorene and directs the entering group chiefly into the unsubstituted ring. A number of derivatives of these compounds, including the fluorenones, and the amino and acetylamino derivatives were prepared.

Substitution by the halogen fluorine in molecules with physiological activity has in many cases resulted in a profound alteration of the biological effect tending in general towards an increased activity.³ With the carcinogen *N*-2-fluorenylacetyl-amide substitution of fluorine at the 7-position

served to enhance the carcinogenicity appreciably.⁴ The 7-carbon atom is one of the positions at which hydroxylation occurs during the metabolism of

(1) National Institutes of Health, Public Health Service, U. S. Department of Health, Education, and Welfare.

(2) Visiting Scientist, National Cancer Institute. On leave of absence from Yamaguchi University, Ube, Japan.

(3) (a) E. C. Miller and J. A. Miller, *J. Natl. Cancer Inst.*, **15**, 1571 (1955). (b) J. Fried, *Cancer*, **10**, 752 (1957). (c) J. Fried and A. Borman, *Vitamins and Hormones*, **16**, 303 (1958).

(4) J. A. Miller, R. B. Sandin, E. C. Miller, and H. P. Rusch, *Cancer Research*, **15**, 188 (1955).