

[CONTRIBUTION FROM THE LABORATORIES OF WINTHROP CHEMICAL COMPANY, INC.]

 **$\Delta$ -(3,4-Dicarboxy)-furanvaleric and -acetic Acids**

BY S. ARCHER AND MARGARET G. PRATT

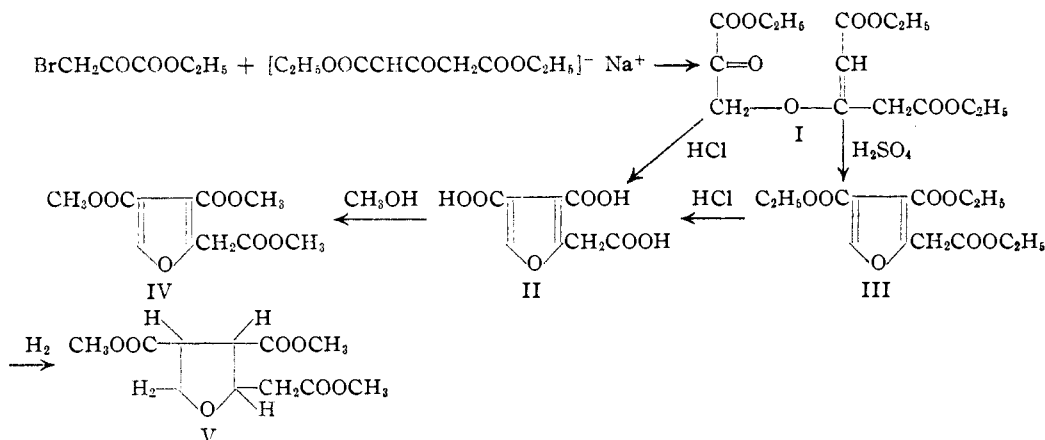
Recently Hofmann<sup>1</sup> reported a method for the preparation of  $\delta$ -(3,4-dicarboxy)-furanvaleric acid. For much the same reasons we were interested in obtaining this and related compounds. Hofmann prepared this substance by partially hydrogenating the condensation product of ethyl acetylenedicarboxylate and  $\delta$ -(2-furan)-valeric acid. The resulting unsaturated bicyclic ester was then heated to remove the elements of ethylene from the molecule. Saponification of the dicarbethoxyfuranvaleric acid yielded the free tri-acid, m. p. 188–190°.

Herewith are reported the preparation of  $\delta$ -(3,4-dicarboxy)-furanvaleric acid and of the related 3,4-dicarboxyfuranacetic acid by a different procedure. Sutter<sup>2</sup> condensed ethyl bromopyruvate with ethyl sodiooxalacetate and then cyclized the crystalline intermediate with hydrochloric acid. He assumed that C-alkylation had occurred in the initial condensation and therefore gave the structure of the product from the acid treatment as 2,3,5-furantricarboxylic acid. However, Reichstein<sup>3</sup> prepared Sutter's acid by partial decarboxylation of furantetracarboxylic acid. Since it

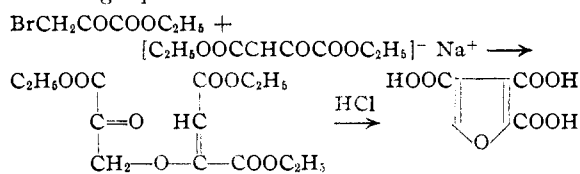
It should be noted that in order to account satisfactorily for the correct triacid it was necessary to postulate that O-alkylation had occurred.

Accordingly, the next higher homolog was prepared in this Laboratory by condensing ethyl sodioacetonedicarboxylate with ethyl bromopyruvate. The oily O-alkylation product was furanized by refluxing with 20% hydrochloric acid. The free acid, II, m. p. 205–206°, was esterified with methanol and sulfuric acid to give a crystalline trimethyl ester, IV, m. p. 66°. The triethyl ester, III, was obtained directly from I by treatment with concentrated sulfuric acid. The viscous high-boiling oil was saponified to the free acid II.

Attempts to hydrogenate the ester, IV, at low pressure with the usual catalysts resulted in failure. At higher temperatures (150°) and pressures (3000 lb./sq. in.) reduction proceeded smoothly in the presence of Raney nickel. The tetrahydro ester, V, a high-boiling oil, yielded a crystalline compound when warmed with hydrazine hydrate. Analysis indicated that a trihydrazide was formed.



is established that  $\alpha$ -acids lose carbon dioxide more readily than  $\beta$ -acids in the furan series, the compound prepared by Sutter must be 2,3,4-furantricarboxylic acid. Reichstein then proposed that the reaction proceeds according to the following equations



In order to prepare the homologous valeric acid by this procedure it was necessary to find a satisfactory method for making  $\beta$ -ketosuberic ester. A modification of Ruggli and Maeder's<sup>4</sup> method was finally employed. The yield of desired ester of suitable purity was 46% of the theoretical based on  $\delta$ -carbethoxyvaleroyl chloride.

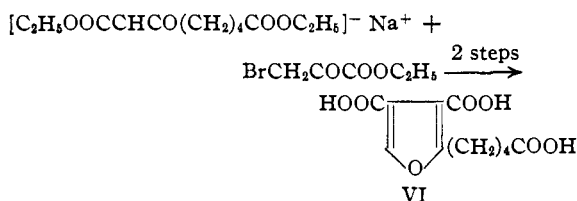
Ethyl hydrogen adipate was converted to the

(4) Ruggli and Maeder, *Helv. Chim. Acta*, **25**, 943 (1943), obtained  $\beta$ -keto adipic ester in an over-all yield of 25% based on  $\beta$ -carbethoxypropionyl chloride. This is better than that obtained by Stevens and Beutel, *THIS JOURNAL*, **65**, 449 (1943). When the procedure of the latter authors was employed for  $\beta$ -ketosuberic ester inferior yields were encountered. Since the main difference between the two methods is the reaction medium, it is best to effect the condensation in ether. However, Stevens' extraction procedure is more satisfactory.

(1) Hofmann, *THIS JOURNAL*, **66**, 51 (1944).(2) Sutter, *Ann.*, **499**, 54 (1932).(3) Reichstein, *Helv. Chim. Acta*, **16**, 276 (1933).

acid chloride which was then condensed with ethyl sodioacetoacetate to give ethyl  $\alpha$ -acetyl- $\beta$ -ketosuberate. This diketo-ester was removed from the reaction mixture by extraction with saturated potassium carbonate solution rather than with the sodium carbonate recommended by Ruggli. The number of extractions was considerably reduced and manipulation was facilitated by the presence of crystalline potassium bicarbonate in the aqueous phase rather than the pasty sodium salt. On ammonolysis the ester gave mainly ethyl  $\beta$ -ketosuberate although some ethyl acetoacetate was formed.

The condensation with ethyl bromopyruvate and subsequent ring closure proceed as for the lower homolog to give VI. After several recrystallizations from water the  $\delta$ -(3,4-dicarboxy)-furanvaleric acid melted at 192–193°. A liquid trimethyl ester was prepared and without purification was converted to a monoamide, m. p. 104°, and a diamide, m. p. 156–157°.



Despite the indications in the literature already cited that the condensation proceeded through an O-alkylation step, the possibility still remained that C-alkylation was occurring with the higher homologs of oxaloacetic ester. If this were true then the acid VI would be  $\delta$ -(2,4-dicarboxy)-furanvaleric acid and not the isomer shown. Doubt as to the correctness of the above structure VI was removed when a direct comparison of the acid in question was made with a sample kindly furnished by Dr. Hofmann. There was no depression when a melting point was taken of a mixture of the two samples.

### Experimental

**Ethyl Pyruvate.**—One kilogram of technical pyruvic acid (55%) was saturated with salt and extracted with six 400-cc. portions of ether. After drying over sodium sulfate the solution was distilled to yield 377 g. of substantially pure acid, b. p. 55–58° (8 mm.). A solution of 300 g. of the keto-acid, 750 cc. of absolute alcohol and 1 liter of carbon tetrachloride was distilled in an apparatus equipped with an automatic separator.<sup>5</sup> When the distillate no longer separated into two layers (seventeen hours) the separator was removed and the residue distilled. The fraction boiling at 146–150° was used for bromination. The yield was 59% of the theoretical.

**Ethyl Bromopyruvate.**—In a three-neck flask bearing a dropping funnel, condenser and gas inlet tube extending to the bottom there was placed 97 g. of ethyl pyruvate. The ester was kept at 65° as 49 cc. of bromine was added during the course of one hour, while bubbling carbon dioxide continuously through the reaction mixture to sweep out the hydrogen bromide. Then the clear golden yellow liquid was distilled to yield 162 g. (88%) of bromi-

nated ester, b. p. 116–121° (27 mm.). A portion was redistilled for analysis, b. p. 92.5–94° (10 mm.).<sup>6</sup>

*Anal.* Calcd. for  $C_8H_{10}O_3Br$ : C, 30.80; H, 3.59. Found: C, 30.50; H, 3.57.

**Ethyl Acetonedicarboxylate.**—The following modification of Ingold's<sup>8</sup> procedure was found to be more convenient than the one described in "Organic Syntheses."<sup>9</sup> To 1134 g. of hydrated citric acid in a large battery jar there was added five pounds of 25% oleum in ten minutes. Stirring was done by hand during the first part of the addition but it was possible to use a mechanical stirrer after about half the acid had been consumed. The reaction proceeded with vigorous foaming and after about a half hour the evolution of gas had practically ceased. The mixture was then cooled and one kilo of ice added in small portions together with powdered dry-ice, the latter serving to keep the temperature from rising. The solid was then filtered, washed with ethyl acetate and dissolved in 1100 cc. of dry ethanol previously saturated with 250 g. of anhydrous hydrogen chloride. The solution was warmed to 45° and then allowed to stand at room temperature for about fourteen hours. The ester, isolated by the usual procedure,<sup>9</sup> boiled at 89–93° (4 mm.) and weighed 374 g. The yield was 34% of the theoretical.

**3,4-Dicarboxyfuranacetic Acid (II).**—To a cooled, stirred suspension of 17.2 g. of sodium sand in 750 cc. of dry ether, 155 g. of ethyl acetonedicarboxylate was added dropwise with stirring during one hour. When all the sodium had reacted the solution was cooled in a freezing mixture and 145 g. of ethyl bromopyruvate was dropped in over a period of two hours. The mixture was then refluxed for one hour to insure complete reaction. At the end of this time an equal volume of water was added to the chilled mixture. The ether layer was separated and then concentrated on the steam-bath without drying. The oily residue was refluxed with two liters of 20% hydrochloric acid for two hours. The solution was decolorized with norite and then allowed to cool in the ice chest overnight. There was deposited 106 g. of the desired tri-acid. A sample twice recrystallized from 20% hydrochloric acid melted at 200–201° when air dried. It analyzed for the monohydrate.

*Anal.* Calcd. for  $C_8H_6O_7 \cdot H_2O$ : C, 41.40; H, 3.13. Found: C, 41.20; H, 3.48.

When dried at 100° (0.5 mm.) for five hours the melting point of the sample rose to 205–206°. It now analyzed for the anhydrous product.

*Anal.* Calcd. for  $C_8H_6O_7$ : C, 44.88; H, 2.80. Found: C, 45.39; H, 2.68.

**Methyl 3,4-Dicarbomethoxyfuranacetate (IV).**—A solution of 10 g. of the tri-acid (II) was refluxed for nine hours with 100 g. of methanol containing 5 g. of concentrated sulfuric acid. Most of the methanol was then removed *in vacuo* and the residue poured onto ice. The ester which crystallized weighed 10.3 g. On crystallization from methanol 6.0 g. of fine needles was obtained, m. p. 63–64°. The compound distilled at 133–135° (0.4 mm.). When the distillate was crystallized from methanol, the melting point rose to 66°.

*Anal.* Calcd. for  $C_{11}H_{12}O_7$ : C, 51.58; H, 4.69. Found: C, 51.29; H, 4.46.

**Ethyl 3,4-Dicarbomethoxyfuranacetate (III).**—This ester was prepared directly from I, by the following procedure. To the cooled residue from the action of 292 g. of ethyl bromopyruvate on the sodio derivative made from 312 g. of ethyl acetonedicarboxylate there was added, slowly with stirring, 2200 cc. of concentrated sulfuric acid. The resulting dark solution was then warmed to 50° and kept there for five minutes before being poured into five liters

(6) Ward, *J. Chem. Soc.*, **123**, 2210 (1923), reports a b. p. 98–100° (10 mm.).

(7) Microanalyses by Miss Esther Bass and Miss Patricia Curran of this laboratory.

(8) Ingold and Nickolls, *J. Chem. Soc.*, **121**, 1642 (1922).

(9) Adams, *et al.*, "Organic Syntheses," Coll. Vol. I, pp. 10, 237.

(5) Clarke and Davis, "Organic Syntheses," Coll. Vol. I, p. 262.

of ice-water. The oil that separated was collected with ether and washed successively with water, 10% sodium carbonate solution, 10% hydrochloric acid and again with water. The dried solution was then distilled to give 195 g. of the ester boiling at 141–145° (0.5 mm.). The yield was 49%.

*Anal.* Calcd. for  $C_{14}H_{18}O_6$ : C, 56.37; H, 6.08. Found: C, 56.07, 56.33; H, 5.49, 5.42.

When refluxed with 20% hydrochloric acid until solution was complete, the ester was converted to the acid, II, m. p. and m. m. p. 201–202°.

**Methyl 3,4-Dicarbomethoxytetrahydrofuranacetate (V).**—A solution of 57 g. of the trimethyl ester, IV, in 500 cc. of methanol was heated at 150° at a pressure of 3000 lb./sq. in. with hydrogen in the presence of Raney nickel. After six hours, the reduction appeared to be over. Distillation of the filtered reaction mixture gave 38 g. of reduced ester boiling at 146–149° (0.6–0.9 mm.); yield 67%. For analysis a portion was redistilled. It then boiled at 140–142.5° (0.2 mm.).

*Anal.* Calcd. for  $C_{11}H_{16}O_7$ : C, 50.77; H, 6.20. Found: C, 51.08; H, 5.80.

When heated with a methanolic solution of hydrazine hydrate the ester gave a crystalline solid which, after being repeatedly heated with hot methanol, melted at 212–214° (dec.). It analyzed for a trihydrazide.

*Anal.* Calcd. for  $C_8H_{12}O_4N_6$ : N, 32.47. Found: N, 32.67, 32.71.

**Ethyl Hydrogen Adipate.**—The procedure described for ethyl hydrogen suberate was used.<sup>10</sup> The residue from the distillation of the half-ester was always added to the next run. In this way 1361 g. of mono-ester, b. p. 177–179° (18 mm.), was prepared from 1314 g. of adipic acid, esterified in portions of 438 g. The average yield was 87%.

**5-Carbomethoxyvaleroyl Chloride.**—Eight hundred and forty-one grams of ethyl hydrogen adipate was added over a period of one-half hour to 720 cc. of thionyl chloride. After heating under reflux for four hours the liquid was distilled. There was obtained 926 g. of acid chloride, b. p. 122–133° (12 mm.). The yield was 96%.

**Ethyl  $\delta$ -Carbomethoxy-valeroylacetate.**—To a cold stirred suspension of ethyl sodioacetate prepared from 120 g. of the ester and 23.8 g. of sodium powder in one liter of dry ether there was added over a period of three hours a solution of 184 g. of 5-carbomethoxyvaleroyl chloride<sup>11</sup> in 300 cc. of ether. After standing at room temperature overnight the ether suspension was shaken with dilute hydrochloric acid. The acid washings were then extracted with three 50-cc. portions of ether. The combined organic layers were then concentrated on the steam-bath. The residue was shaken with three 200-cc. portions of saturated potassium carbonate solution. The extraction mixture separated into three layers; the heavy colorless layer containing suspended potassium bicarbonate, an orange middle layer containing the potassium salt of the desired keto-ester, and the top layer containing the by-products of the reaction. The two lower layers were run off together, chilled and acidified with 3 *N* hydrochloric acid. The oil which separated was taken up in ether, washed, dried and distilled. The ester boiled at 137–141° (0.2 mm.). There was collected 147 g. (56%).

*Anal.* Calcd. for  $C_{13}H_{20}O_6$ : C, 57.38; H, 7.42. Found: C, 58.02; H, 7.98.

The copper salt prepared by adding an alcoholic solution of the ester to an aqueous solution of copper acetate and sodium acetate was isolated as light blue prisms, m. p. 96–97° after several recrystallizations from methanol.

*Anal.* Calcd. for  $C_{26}H_{38}O_{12}Cu$ : C, 51.52; H, 6.30; Cu, 10.49. Found: C, 51.15; H, 6.30; Cu, 10.70.

**Ethyl  $\alpha$ -Acetyl- $\beta$ -ketosuberate.**—When 194 g. of  $\delta$ -carbomethoxy-valeroyl chloride was substituted for the

carbomethoxy derivative in the above experiment, there was obtained 169 g. of the keto-ester, b. p. 140–145° (0.5 mm.). This is 69% of the theoretical quantity.

*Anal.* Calcd. for  $C_{14}H_{22}O_6$ : C, 58.72; H, 7.75. Found: C, 58.91, 59.12; H, 8.12, 8.26.

**Ethyl 7-Carbomethoxy-2-ketoheptate.**—A slow stream of dry ammonia was passed through a solution of 78 g. of ethyl 5-carbomethoxyvaleroylacetate in 200 cc. of dry ether cooled in a freezing mixture. After forty minutes, the gas stream was stopped and the semi-solid mass allowed to stand at room temperature overnight.

The next day two layers were present. They were acidified with 2 *N* hydrochloric acid. The ethereal solution was then shaken with two 50-cc. portions of ice-cold 3 *N* hydrochloric acid. Each shaking was carried out for at least ten minutes. The acid washings were followed by an extraction with 50 cc. of saturated sodium carbonate solution and then with the same quantity of water. After drying the organic layer was distilled to yield 41.3 g. of keto-ester, b. p. 127–130° (0.5 mm.). The yield was 63%.

*Anal.* Calcd. for  $C_{11}H_{18}O_6$ : C, 57.36; H, 7.89. Found: C, 57.49, 57.71; H, 7.95, 7.86.

One gram of the above ester was dissolved in 8 cc. of concentrated hydrochloric acid and the solution then allowed to stand for three days in a vacuum desiccator over potassium hydroxide. The residue was treated with an aqueous solution of semicarbazide hydrochloride. The solid that separated was collected on a filter and crystallized from dilute acetic acid. It melted at 143–144°. This agrees with the m. p. given by Blaise<sup>12</sup> for the semicarbazone of  $\delta$ -acetylvaleric acid, m. p. 144–146°.

**Ethyl  $\beta$ -Ketosuberate.**—This ester was prepared by the procedure given for the corresponding methyl ester. From 156 g. of ethyl  $\alpha$ -acetyl- $\beta$ -ketosuberate there was obtained 87.5 g. (67%) of the desired ester, b. p. 140–141° (0.6 mm.).

*Anal.* Calcd. for  $C_{12}H_{20}O_6$ : C, 59.04; H, 8.26. Found: C, 59.32; H, 8.29.

**$\delta$ -(3,4-Dicarboxy)-furanvaleric Acid (VI).**—To an ethereal solution of the sodio derivative prepared from 136 g. of ethyl  $\beta$ -ketosuberate, and 11.5 g. of sodium sand in 500 cc. of ether was added 97 g. of ethyl bromopyruvate. The mixture was worked up as for the homologous acetic acid. After refluxing with two liters of 20% hydrochloric acid for three and one-half hours, decolorizing with norite, filtering and cooling, 41.7 g. of the desired acid precipitated. Concentration of the mother liquor to half volume gave 4.5 g. more of the acid. The total yield was 46.2 g. or 36%. After recrystallization from water with the aid of norite the crystals melted at 188–189.5°. Further crystallization from the same solvent raised the m. p. to 192–193°.

*Anal.* Calcd. for  $C_{11}H_{12}O_7$ : C, 51.58; H, 4.73. Found: C, 51.44, 51.52; H, 4.91, 4.93.

When the above acid was admixed with the sample furnished by Dr. Hofmann no depression in melting point was observed.

**Ammonolysis of Methyl  $\delta$ -(3,4-Dicarbomethoxy)-furanvalerate. A. Monoamide.**—Crude trimethyl ester prepared from the above acid and methanol with sulfuric acid as the catalyst was dissolved in saturated methanolic ammonia and allowed to stand at room temperature overnight. The solvent was then removed and the solid residue triturated with a small quantity of ether. After crystallization from aqueous methanol it melted at 104°.

*Anal.* Calcd. for  $C_{13}H_{17}O_6N$ : C, 55.14; H, 6.01; N, 4.95. Found: C, 55.34; H, 6.23; N, 4.94.

**B. Diamide.**—The crude trimethyl ester was heated at 100° for three hours with saturated methanolic ammonia in a bomb tube. The solution was then evaporated to dryness and the residue crystallized from aqueous ethanol. The solid that separated appeared to be a mixture of mono- and di-amide. It was leached with boiling ether. On concentration the extracts gave slightly impure mono-

(10) Swann, Oehler and Buswell, "Organic Syntheses," Coll. Vol. II, p. 276.

(11) We wish to thank Mr. W. Boehme of this Laboratory for a supply of this acid chloride.

(12) Blaise and Kohler, *Compt. rend.*, **148**, 490 (1909).

amide, m. p. 99-102°. The ether-insoluble residue which composed the bulk of the original solid was crystallized twice from dilute ethanol to give the pure diamide, m. p. 156-157°.

*Anal.* Calcd. for  $C_{12}H_{16}O_6N_2$ : N, 10.44. Found: N, 10.46.

**Acknowledgment.**—We wish to thank Dr. Klaus Hofmann for his kindness in furnishing a sample of the dicarboxyfuranvaleric acid. Our thanks are also due to Miss Lillian Morrell for technical assistance during the course of the work.

### Summary

1. A satisfactory procedure for preparing ethyl  $\beta$ -ketosuberate in 44% yield based on ethyl hydrogen adipate is presented.

2. A new method for preparing  $\delta$ -(3,4-dicarboxy)-furanvaleric acid and some of its derivatives is described.

3. The preparation of 3,4-dicarboxyfuranacetic acid and some of its derivatives is reported.

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## The Nature of the Sex Attractant of the Female Gypsy Moth\*

BY H. L. HALLER, FRED ACREE, JR., AND S. F. POTTS

The gypsy moth (*Porthetria dispar* (L.)), one of the most serious insect pests of fruit, shade and woodland trees in New England, was accidentally introduced into Massachusetts from France in 1869 (Burgess and Baker<sup>1</sup>). In the last thirty to forty years approximately \$1,700,000 have been spent annually for the control of this pest (Burgess<sup>2</sup>).

The female gypsy moth does not fly, and the male is attracted to the female by scent. As early as 1893 experiments were undertaken in which traps containing unfertilized living females were used to attract the male (Forbush and Fernald).<sup>3</sup> As a control measure these traps were of no value.

The area infested by the moth continued to grow, and in 1913 intensive experiments (Collins and Potts<sup>4</sup>) were initiated to facilitate the finding of new infestations. It was soon found that males were attracted to an extract prepared from the abdominal tips of unfertilized females, and at the present time benzene extracts of the tips are used in scouting traps. Briefly, the bait for each trap is prepared by clipping the tips from 30 unfertilized live females twenty-four to forty-eight hours after emergence, placing them in a cork-sealed bottle with 1 ounce of benzene, and storing at 35° F. until needed for use.

According to Collins and Potts,<sup>4</sup> chemical studies on the extractives were initiated at the Harvard University Medical School in 1925 by W. R. Bloor. From experiments carried out that year, he<sup>5</sup> concluded that the males are attracted

by the odor of a substance produced in the female abdominal tip, and that this relatively stable substance is soluble in fat solvents and slightly soluble in water, and is non-saponifiable. In 1926 the studies were continued by C. H. Fiske.<sup>5</sup> He suspected that the substance was an aldehyde, but he was unable to isolate it. The next year, B. L. Souther<sup>5</sup> working at the same school concluded that the substance was probably an indifferent saturated material—fat, protein, or ester; that it was destroyed by cold concentrated hydrochloric acid and by boiling alcoholic potash; and that it was readily volatile with solvents and continuously generated by hydrolysis of a more complex compound.

In the fall of 1941 the chemical study of the gypsy moth attractant was renewed by the Bureau of Entomology and Plant Quarantine and prior to the flight season in 1942 and 1943 experiments were performed with two lots of a benzene extract of the material. The first lot was prepared as described above from female moths collected in 1941, and the second from female moths collected in 1942. In each case the tips were separated from the benzene solution and washed with benzene. The benzene was then removed from the combined solutions and the residues were treated as described below. Each treatment resulted in one or more fractions, samples of which were tested in the field for attractiveness to male moths in comparison with an aliquot of the starting material. Each fraction was tested in five replicates at the same equivalent concentration of 30 moth tips per 30 ml. of benzene solution per trap.

Included in the tests of 1942 were several chemicals that had been shown to attract males of other species (Götz,<sup>6</sup> Lehman,<sup>7</sup> and Travis<sup>8</sup>) one substance known to occur in insect urine

\* Not copyrighted.

(1) A. F. Burgess and W. L. Baker, U. S. Dept. Agr. Cir. 464, 38 pp. (1938).

(2) A. F. Burgess, *J. Econ. Entomol.*, **33**, 558 (1940).

(3) E. H. Forbush and C. H. Fernald, "The gypsy moth, *Porthetria dispar* (Linn.)." Mass. State Board of Agriculture, Boston, 1896, p. 345.

(4) C. W. Collins and S. F. Potts, U. S. Dept. Agr. Tech. Bull. 339 pp., 1932.

(5) Unpublished report quoted in (4) p. 14.

(6) B. Götz, *Umschau*, **44**, 794 (1940).

(7) R. S. Lehman, *J. Econ. Entomol.*, **25**, 949 (1932).

(8) B. V. Travis, *ibid.*, **32**, 690 (1939).