2-[4-(1-Hexyl)-1-(2-acetoxy-2-phenylethyl)]-piperidine Hydrochloride.—Two samples of this compound were prepared by the acetylation of compound III-7. Each sample of compound III-7 was by a different method. Each salt melted at 169–171° (dec.) and a mixture of the two melted at 168–170° (dec.).

Anal. Calcd. for $C_{21}H_{34}ClNO_2$: Cl, 9.64; N, 3.81. Found: Cl, 9.76; N, 4.02.

2-[4-(1-Octyl)-1-(2-acetoxy-2-phenylethyl)]-piperidine Hydrochloride.—Two samples of compound III-8 (prepared by two different procedures) were esterified by refluxing with acetic anhydride. The reddish oils which resulted could not be crystallized; however, the respective hydrochlorides were obtained and found to be identical, m.p. 152–157°. A mixture of the two melted at 152–156°. A separate analysis for each gave almost identical per cent. composition.

Anal. Calcd. for $C_{28}H_{38}ClNO_2$: Cl, 8.95; N, 3.54. Found: Cl, 9.12; N, 3.54.

2-[4-(1-Nonyl)-1-(2-acetoxy-2-phenylethyl)]-piperidine Hydrochloride.—The above ester was prepared by refluxing the alcohol (III-9) with acetic anhydride. The hydrochloride of the ester was isolated and purified, m.p. 150–156°.

Anal. Calcd. for $C_{24}H_{40}ClNO_2$: Cl, 8.65; N, 3.42. Found: Cl, 8.69; N, 3.32.

2-[4-(5-Nonyl)-1-(2-acetoxy phenylethyl)]-piperidine Hydrochloride.—The acetate was prepared from the parent alcohol (III-10) and isolated as the hydrochloride, m.p. 150–157°.

Anal. Calcd. for $C_{24}H_{40}ClNO_2$: Cl, 8.65; N, 3.42. Found: Cl, 8.83; N, 3.44.

DENTON, TEXAS RECEIVED SEPTEMBER 24, 1951

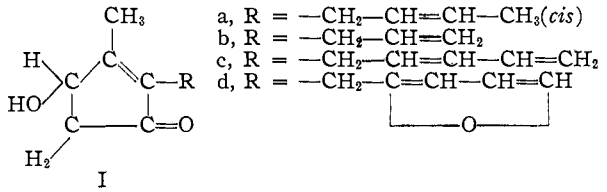
[CONTRIBUTION FROM THE NISSIN CHEMICAL COMPANY AND THE BUREAU OF ENTOMOLOGY AND PLANT QUARANTINE, AGRICULTURAL RESEARCH ADMINISTRATION, U. S. DEPARTMENT OF AGRICULTURE]

Furethrin

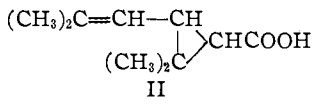
BY MASANAO MATSUI, F. B. LAFORGE, N. GREEN AND MILTON S. SCHECHTER

The preparation of furethrin, a mixture of stereoisomeric insecticidal esters of the type of pyrethrin I but with a 2-furfuryl side chain, is described. The procedures follow those employed in the synthesis of allethrin, a commercially available mixture of synthetic esters of the pyrethrin type, with furfurylacetone as a starting material.

The development of a general method for the synthesis of cyclopentenolones[1] of the type of cinerolone (formula Ia) has led to the preparation of a number of cyclopentenolones of formula I having various substituents for R.[1-3] Acylation of these synthetic cyclopentenolones with the acid



I



II

chloride of natural *d-trans*-chrysanthemum monocarboxylic acid or with the mixture of acid chlorides of synthetic *dl-cis*- and *dl-trans*-chrysanthemum monocarboxylic acids[4] (formula II) furnished insecticidally active esters[1-3] of the pyrethrin or cinerin type. The mixture of esters known as allethrin, produced by acylating 2-allyl-4-hydroxy-3-methyl-2-cyclopenten-1-one (allethrolone) (formula Ib) with a mixture of *dl-cis*- and *dl-trans*-chrysanthemum monocarboxylic acid chlorides, was selected as being the simplest and least expensive of these esters to manufacture. It is now being produced commercially. The presence of unsaturation in the radical R seems to be advantageous for high knock-down and kill of house flies, pyrethrin I, the ester of *d-trans*-chrysanthemum monocarboxylic acid with *d*-pyrethrolone (formula Ic), being one of the most toxic to insects. The cyclopentenolone of formula Id resembles pyrethrolone with respect to the number of carbon atoms and the relative positions of the side chain double bonds. We have synthesized this cyclopentenolone, which we propose to name "furethrolone," by the following steps (Fu = 2-furyl)

$$CH_3COCH{=}CHFu \xrightarrow[\text{catalytic}]{[H]} \underset{\text{III}}{CH_3COCH_2CH_2Fu}$$

$$CH_3COCH_2CH_2Fu \xrightarrow[NaH \text{ or } NaOC_2H_5]{(C_2H_5)_2CO_3} \underset{\text{IV}}{C_2H_5OOCCH_2COCH_2CH_2Fu}$$

$$C_2H_5OOCCH_2COCH_2CH_2Fu \xrightarrow{\text{aq. KOH}} \underset{\text{V}}{KOOCCH_2COCH_2CH_2Fu}$$

$$KOOCCH_2COCH_2CH_2Fu \xrightarrow{CH_3COCHO} \underset{\text{VI}}{CH_3COCHOHCH_2COCH_2CH_2Fu}$$

$$CH_3COCHOHCH_2COCH_2CH_2Fu \xrightarrow{\text{aq. NaOH}} Id$$

The starting material is furfuralacetone, which can be hydrogenated to furfurylacetone. The subsequent steps are the same as those described for the synthesis of cyclopentenolones.[1]

The acylation of furethrolone with the mixture of acid chlorides of *dl-cis*- and *dl-trans*-chrysanthemum monocarboxylic acids furnished a mixture of isomeric esters for which the name "furethrin" is proposed. Its production might be more economical than that of allethrin, owing to the low cost and ready availability of furfuralacetone.

In tests on house flies furethrin proved to be about equal to pyrethrins in toxicity.[5]

(1) M. S. Schechter, N. Green and F. B. LaForge, THIS JOURNAL, **71**, 1517, 3165 (1949).

(2) M. S. Schechter, N. Green and F. B. LaForge, Abstracts, 118th Meeting American Chemical Society, p. 34N, September, 1950.

(3) L. Crombie and S. H. Harper, *Nature*, **164**, 534 (1949); *J. Chem. Soc.*, 1152 (1950); L. Crombie, A. J. B. Edgar, S. H. Harper, M. W. Lowe and D. Thompson, *ibid.*, 3552 (1950); Y. Katsuda, Y. Inouye, A. Nishimura, K. Kitagawa, T. Shinohara and M. Ohno, *Botyu Kagaku*, **16**, 115 (1951).

(4) I. G. M. Campbell and S. H. Harper, *J. Chem. Soc.*, 283 (1945); S. H. Harper, H. W. B. Reed and R. A. Thompson, *J. Sci. Food Agr.*, **2**, 94 (1951); R. Schett, *Beitrag zur Kenntnis der Pyrethrine, Dissertation*, Zurich (1947).

(5) Preliminary data by W. A. Gersdorff and N. Mitlin and by J. Fales, Bureau of Entomology and Plant Quarantine.

Experimental

4-(2-Furyl)-2-butanone (Furfurylacetone) (IV).—Furfurylacetone (III) prepared from furfuryl chloride and ethyl acetoacetate by the procedure of Kirner and Richter[6] showed b.p. 95–97° (18 mm.), $n^{25}D$ 1.4684, d^{25}_4 1.0369; MR_D calcd. 37.64; found 37.03.[7]

The most satisfactory method of preparation was found to be hydrogenation of furfuralacetone with Raney nickel catalyst. The reaction was performed in a rocking autoclave of 1250-ml. capacity, 600 ml. of which was occupied by 544 g. (4 moles) of furfuralacetone, 25 g. of Raney nickel catalyst, and a small quantity of water. The hydrogenation was carried out at 50° and 10 atmospheres. The total volume of hydrogen absorbed corresponded to 120 l. at 760 mm. and 0° (*ca.* 5.4 moles). The product, separated from catalyst and water, was distilled, and the main fraction was collected at 100–104° (23 mm.), yield 440–460 g. (80–83%), $n^{17}D$ 1.4696, d^{15}_4 1.0319.

The 2,4-dinitrophenylhydrazone was obtained as red crystals, m.p. 106–107°.

Anal. Calcd. for $C_{14}H_{14}O_5N_4$: N, 17.61. Found: N, 18.00.

The semicarbazone melted at 143°.

Anal. Calcd. for $C_9H_{13}O_2N_3$: C, 55.39; H, 6.67; N, 21.54. Found: C, 54.72; H, 6.91; N, 21.13.

Ethyl 5-(2-Furyl)-3-oxopentanoate (V).—This β-keto ester was prepared by carbethoxylation of furfurylacetone employing sodium hydride.[8]

The proportions used were 184 g. (1.33 moles) of furfurylacetone, 64 g. (2.66 moles) of sodium hydride, and 314 g. (2.66 moles) of ethyl carbonate. The yield of product boiling at 102–103° (0.7 mm.), $n^{25}D$ 1.4720, was 196 g. (70%).

Anal. Calcd. for $C_{11}H_{14}O_4$: OC_2H_5, 21.4. Found: OC_2H_5, 21.1.

This ester was prepared also by the sodium methylate forced condensation procedure previously described for ethyl 3-oxo-6-heptenoate,[1] employing 130 g. (1 mole) of furfurylacetone. After the ethyl carbonate had been removed by distillation at 20 mm., the reaction product was distilled at 6 mm. Fifty grams of unchanged furfurylacetone, b.p. up to 70°, was recovered, and 40 g. of material of undetermined nature was obtained, which distilled from 70 to 100°, $n^{16}D$ 1.4562. The main fraction, 80 g., was collected at 100–130°, $n^{16}D$ 1.4753. When redistilled it yielded 62 g., b.p. 113–117° at 4 mm., $n^{16}D$ 1.4758.

This ester was also prepared with the use of sodium amide.[9] Fifty-eight grams (1.5 moles) of sodium amide and 400 ml. of ether were placed in a 1.5-l. three-necked flask equipped with thermometer, stirrer, reflux condenser and dropping funnel. Seventy-nine grams (0.5 mole) of furfurylacetone was added at once with stirring, which was continued for 1.5 hours, and then the ether was refluxed for a short time. Heating was discontinued, and 146 g. (1.22 moles) of ethyl carbonate was added as rapidly as possible, with stirring yet without too vigorous refluxing. After about four hours stirring and refluxing, the contents of the flask were cooled and acidified with 100 ml. of glacial acetic acid. The product was isolated as in the previous preparation, yielding 23 g. (21.9%), b.p. 110–120° (3.5 mm.).

3-Hydroxy-7-(2-furyl)-2,5-heptanedione (VI).—To 105 g. (0.5 mole) of cold ethyl 5-(2-furyl)-3-oxopentanoate (V) was added a cold solution of 36 g. of potassium hydroxide (86% assay) (0.55 mole) in 200 ml. of water. The clear solution was allowed to stand for three days in a refrigerator at 5° and then saturated with carbon dioxide. A solution of pyruvaldehyde was prepared by refluxing 95.7 g. (0.55 mole) of pyruvaldehyde diisopropyl acetal with 96 ml. of 2% sulfuric acid solution, with stirring until homogeneous (about one hour) and then for ten minutes longer. The solution was cooled in an ice-bath, neutralized by the addition of powdered sodium bicarbonate in small portions, and added to the saponified β-keto ester solution. The total volume of solution after mixing (including some rinsings) was 575 ml. Within an hour an oil started to separate. The next day the reaction mixture was extracted several times with ether, the combined ether extracts were washed with saturated sodium chloride solution and dried over sodium sulfate, and the ether was distilled off, leaving 105 g. of oil. A portion of this oil was distilled in high vacuum, and the fraction with b.p. 138–142° at 0.5 mm., $n^{25}D$ 1.4977. was collected. The yield calculated from the amount of distilled product was 56% based on ethyl 5-(2-furyl)-3-oxopentanoate. A middle cut taken for analysis had $n^{25}D$ 1.4970.

Anal. Calcd. for $C_{11}H_{14}O_4$: C, 62.84; H, 6.71. Found: C, 62.37; H, 6.92.

2-(2-Furfuryl)-4-hydroxy-3-methyl-2-cyclopenten-1-one (Furethrolone).—Cyclization of crude 3-hydroxy-7-(2-furyl)-2,5-heptanedione (VI) according to the procedure previously described,[1] employing agitation for three hours with about ten volumes of 2% sodium hydroxide solution containing a small amount of hydroquinone, gave over-all yields of 36–39%, b.p. 144–150° at 0.5 mm., $n^{25}D$ 1.530–1.537, based on ethyl 5-(2-furyl)-3-oxopentanoate. Cyclization of distilled 3-hydroxy-7-(2-furyl)-2,5-heptanedione with twenty volumes of 2% sodium hydroxide solution for 3.5 hours gave a 45% yield of product (25% over-all yield based on ethyl-5-(2-furyl)-3-oxopentanoate), b.p. 146–149° at 0.5 mm., $n^{25}D$ 1.5377.

The semicarbazone was prepared and recrystallized from ethyl acetate, m.p. 216.5–217° (dec.).

Anal. Calcd. for $C_{12}H_{15}O_3N_3$: N, 16.85. Found: N, 17.18, 16.99.

The 3,5-dinitrobenzoate was prepared, m.p. 168–169°.

Anal. Calcd. for $C_{18}H_{14}O_8N_2$: C, 55.95; H, 3.65; N, 7.25. Found: C, 55.71; H, 4.28; N, 7.18.

The *p*-nitrobenzoate was prepared, m.p. 108–109°.

Anal. Calcd. for $C_{18}H_{15}O_6N$: C, 63.34; H, 4.43; N, 4.10. Found: C, 63.38; H, 4.74; N, 4.10.

Regeneration of furethrolone by agitation of the semicarbazone with saturated potassium bisulfate solution in the presence of ether for two days gave the pure cyclopentenolone, b.p. 140–141° at 0.3 mm., $n^{25}D$ 1.5410.

Anal. Calcd. for $C_{11}H_{12}O_3$: C, 68.73; H, 6.29. Found: C, 68.40, 68.27, 68.14; H, 6.25, 5.91, 5.94.

Furethrin.—Eleven and seven-tenths grams (0.061 mole) of 2-(2-furfuryl)-4-hydroxy-3-methyl-2-cyclopenten-1-one (furethrolone) was acylated with 11.9 g. (0.064 mole) of the mixture of synthetic *dl-cis-* and *dl-trans*-chrysanthemum monocarboxylic acid chlorides in 75 ml. of benzene containing 7.0 g. (0.089 mole) of pyridine. After about 18 hours water was added to dissolve the separated pyridine hydrochloride, and after dilution with a convenient amount of ether the organic layer was washed several times with sodium bicarbonate solution. Any remaining pyridine was washed out with dilute hydrochloric acid. The ether–benzene solution was then washed with saturated sodium chloride solution and dried, and the solvents were completely removed *in vacuo;* yield 21.0 g., $n^{25}D$ 1.5190.

A portion (*ca.* 10 g.) was distilled and the greater part collected at 187–188° (0.4 mm.) as a pale yellow distillate, $n^{25}D$ 1.5202.

Anal. Calcd. for $C_{21}H_{26}O_4$: C, 73.66; H, 7.65. Found: C, 73.79, 73.98; H, 8.15, 8.26.

Furethrolone was likewise acylated with natural *d-trans*-chrysanthemum monocarboxylic acid chloride to furnish a product, $n^{25}D$ 1.5177.

(6) W. R. Kirner and G. H. Richter, THIS JOURNAL, **51**, 3131 (1929).

(7) E. C. Hughes and J. R. Johnson, *ibid.*, **53**, 737 (1931), give b.p. 95° (15 mm.), $n^{25}D$ 1.4697, d^{25}_4 1.0258, MR_D 37.53 (observed).

(8) S. B. Soloway and F. B. LaForge, *ibid.*, **69**, 2677 (1947); F. B. LaForge, N. Green and W. A. Gersdorff, *ibid.*, **70**, 3707 (1948).

(9) R. Levine and C. R. Hauser, *ibid.*, **66**, 1768 (1944).

OSAKA, JAPAN
BELTSVILLE, MARYLAND
RECEIVED NOVEMBER 19, 1951