[CONTRIBUTION FROM THE U. S. DEPARTMENT OF AGRICULTURE, BUREAU OF ENTOMOLOGY AND PLANT QUARANTINE]

Some New Pyrethrin-type Esters[1,2]

BY YUH-LIN CHEN[3] AND W. F. BARTHEL

RECEIVED MARCH 27, 1953

Five new pyrethrin-type esters were synthesized in seeking compounds of high insecticidal activity and in studying the effect of aryl side chains in the methylcyclopentenolone portions of the molecule. The esters prepared from phenyl- and benzyl-substituted methylcyclopentenolones and *dl*-chrysanthemic acid were of the same order of toxicity as natural pyrethrins. Substitution of methoxyl or methylenedioxy groups in the aryl nucleus greatly decreased the activity.

The general method[4] developed in this Bureau has permitted the preparation of a series of cyclopentenolones (V), one of which, when esterified with *dl*-chrysanthemic acid (VI), is the highly useful pyrethrin-like insecticide known as allethrin and which is now produced commercially.

Some esters in which R in formula VII is an aliphatic side chain have been reported, but none made with the *dl*-acid were as effective as allethrin (R = allyl) or the pyrethrins.[4,5,6] When R is furfuryl, the insecticidal ester has been named "furethrin" and is about equal to the pyrethrins in toxicity to houseflies.[7]

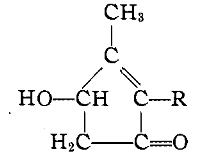
We have undertaken the preparation of a series of substituted cyclopentenolones in which R is an aryl group by essentially the same steps used in the "furethrin"[7] preparation as shown.

$$\underset{\mathrm{I}}{\mathrm{RCH_2COCH_3}} + \mathrm{(EtO)_2CO} \xrightarrow{\mathrm{NaH}}$$

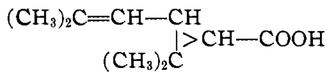
$$\underset{\mathrm{II}}{\mathrm{RCH_2COCH_2COOEt}} \xrightarrow{14\%\ \mathrm{KOH}}$$

$$\underset{\mathrm{III}}{\mathrm{RCH_2COCH_2COOK}} \xrightarrow[\mathrm{H_2O}\ (p\mathrm{H}\ 8.5)]{\mathrm{CH_3COCHO}}$$

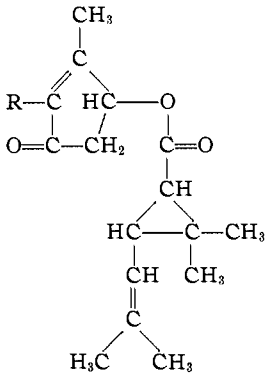
$$\underset{\mathrm{IV}}{\mathrm{RCH_2COCH_2CHOHCOCH_3}} \xrightarrow[\text{cyclization}]{2\%\ \mathrm{NaOH}} \mathrm{V}$$



Va, R = phenyl
b, R = benzyl
c, R = *p*-methoxybenzyl
d, R = *o*-methoxybenzyl
e, R = 3,4-methylene-dioxybenzyl



VI



VII

Where R is phenyl, the phenylacetone (Ia) was obtained commercially, but after carbethoxylation, the yield of β-keto ester (IIa) was only 25% based on phenylacetone. This β-keto ester, when prepared from ethyl acetoacetate by the method of Libermann, *et al.*,[8] was obtained in 28% yield. The benzylacetones (Ib, c, d and e) were made by hydrogenation, at 70–80° and 2000 p.s.i., of the respective benzylidene acetones using nickel-on-kieselguhr as a catalyst.

The γ-benzylacetoacetic esters (IIb, c, d and e) were prepared by carbethoxylation of the benzylacetones using sodium hydride and diethyl carbonate.

The hydroxydiketones (IV) were cyclized directly without isolation. The resulting cyclopentenolones (V) separated as viscous oils, which could neither be distilled without decomposition nor crystallized. The cyclopentenolones were characterized by their crystalline nitrobenzoates. It was possible to obtain the 3,5-dinitrobenzoates of the cyclopentenolones where R = a or b, but it was necessary to prepare the *p*-nitrobenzoates of c, d and e because the corresponding 3,5-dinitro compound would not crystallize.

Each cyclopentenolone was esterified in the usual way[9] with the acid chloride prepared from commercially obtainable synthetic chrysanthemic acid (a mixture of *dl-cis* and *trans* isomers). The esters were viscous oils which could not be distilled. A preliminary purification was obtained by fractionation with solvent as previously reported for natural pyrethrins.[10]

Because of the difficulty in purification, only one ester (VIIe) yielded good analytical data. The data for VIIb and c were acceptable, while the data for VIIa and d left something to be desired.

Attempts to prepare crystalline semicarbazones and 2,4-dinitrophenylhydrazones resulted only in

---

(1) This work was conducted under funds allotted by the Department of the Army to the Bureau of Entomology and Plant Quarantine.

(2) Presented before the Organic Section at the 122nd Meeting of the American Chemical Society, Atlantic City, N. J., September 15, 1952.

(3) Present address: College of Agriculture, National Taiwan University, Taipei, Formosa, China.

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

(5) Y. Inoue, Y. Katsuda, A. Nishimura, K. Kitagawa and M. Ohno, *Botyu Kagaku* (*Kyoto Univ., Japan*), **16**, 153 (1951).

(6) W. A. Gersdorff, *J. Econ. Ent.*, **42**, 532 (1949); *Soap & Sanit. Chem.*, **25** (11), 129 (1949); W. A. Gersdorff and N. Mitlin, *J. Econ. Ent.*, **44**, 70 (1951).

(7) M. Matsui, F. B. LaForge, N. Green and M. S. Schechter, THIS JOURNAL, **74**, 2181 (1952).

(8) D. Libermann, J. Himbert, L. Hengl and G. Kirchoffer, *Compt. rend.*, **229**, 765 (1949).

(9) F. B. LaForge and W. F. Barthel, *J. Org. Chem.*, **12**, 199 (1947).

(10) W. F. Barthel, H. L. Haller and F. B. LaForge, *Soap & Sanit. Chem.*, **20** (7), 121 (1944).

oily products or indefinite mixtures. The esters are listed in Table I.

TABLE I

ESTERS OF CHRYSANTHEMIC ACID

R	Formula	Yield, %[a]	n^{25}D	Analyses, % Calcd. C	Calcd. H	Found C	Found H
a	$C_{22}H_{26}O_3$	76	1.5354	78.07	7.74	76.91	7.14
b	$C_{23}H_{28}O_3$	91	1.5287	78.37	8.01	77.89	7.84
c	$C_{24}H_{30}O_4$	59	1.5262	75.36	7.91	74.79	8.00
d	$C_{24}H_{30}O_4$	88	1.5149	75.36	7.91	74.42	8.45
e	$C_{24}H_{28}O_5$	48	1.5118	72.70	7.12	72.53	7.40

[a] Based on the cyclopentenolone.

Insecticidal Activity

When tested against houseflies, the phenyl and benzyl analogs (R = a, b) were of the same order of toxicity as natural pyrethrins. The substituted benzyl analogs (R = c, d and e) were much less toxic.[11]

Experimental[12]

Benzyl Ketones. Preparation of Benzylacetone (Ib).—Benzalacetone (Eastman Kodak white label) 36.5 g. (0.25 mole), was dissolved in 30 ml. of 95% alcohol and hydrogenated at 70–80° at 2000 p.s.i., using 3 g. of nickel–kieselguhr catalyst. When the reaction stopped as indicated by the end of the pressure drop, the mixture was centrifuged and decanted from the catalyst, and the alcohol removed on the steam-bath. The other benzyl ketones (Ic, d, e) were prepared in a similar manner. The physical properties are given in Table II.

TABLE II

SUBSTITUTED KETONES (I) RCH_2COCH_3

R	B.p., °C.	Mm.	n^{25}D	Yield, %	Reported properties
b	115–116	13	1.5108	89–90	B.p. 115° (13 mm.) $n^{21.7}$D 1.511[a]
c	153–155	15	1.5190	86	B.p. 154° (14.5 mm.) n^{20}D 1.5200[b]
d	143–144	13	1.5201	90	New compound[c]
e	130–131	2	M.p. 55°	90	M.p. 55°, b.p. 164–165° (12 mm.)[d]

[a] A. Klages, *Ber.*, **37**, 2313 (1904). [b] A. Sosa, *Ann. chim.*, 14, 5 (1940). [c] *Anal.* Calcd. for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 73.99; H, 8.09. [d] A. Kaufmann and R. Radosevic, *Ber.*, 49, 676 (1916).

γ-Substituted β-Ketoesters. Preparation of Ethyl γ-Benzylacetoacetate (IIb).—The carbethoxylation was performed with 148 g. (1 mole) of benzylacetone, 48 g. (2 moles) of sodium hydride and 236 g. (2 moles) of diethyl carbonate, according to the method of Soloway and LaForge.[13] Extreme care was used in adding glacial acetic acid and then water to avoid a violent reaction during hydrolysis. The reaction product was distilled in vacuum, 4 g. of forerun discarded, and the β-ketoester collected at 152–163° (4 mm.). The other ketoesters (IIc, d, e) were prepared in a similar manner with the exception of ethyl γ-phenylacetoacetate, which was prepared by the method of Libermann, *et al.*[8] These esters are described in Table III.

Hydroxydiketones. 7-Phenyl-3-hydroxy-2,5-heptanedione (IVb).—Ethyl γ-benzylacetoacetate, 121 g. (0.55 mole), was slowly saponified in the refrigerator at 5° for 3 days with 43 g. (0.65 mole) of potassium hydroxide (85% assay) dissolved in 210 ml. of water. After removal of the nonsaponified portion, 22 g., by extraction with peroxide-free ether, the saponified part (by difference), 86.4 g. (0.45 mole), was adjusted to *p*H 8.5 with dilute sulfuric acid (1:4). Pyruvaldehyde[14] (46.5% assay), 85 g. (0.54 mole), contained in a separate flask was neutralized to *p*H 8.5 with 1% sodium hydroxide solution. The two solutions were mixed in a 1-liter flask, stoppered and kept at room temperature. The solution became turbid after 10 minutes, and after an hour oil began to separate. After standing two days at room temperature, the oily reaction product was extracted with peroxide-free ether. The extract was washed with saturated sodium chloride solution and dried over anhydrous sodium sulfate, and the ether was removed under vacuum using a water-bath at 40°; yield 94 g. or 78%.

The other hydroxydiketones (IVa, c, d, e) were prepared in a similar manner, and the yields of crude hydroxydiketones based on starting β-ketoester are: 6-phenyl-3-hydroxy-2,5-hexanedione (IVa), 91%; 7-(*p*-methoxyphenyl)-3-hydroxy-2,5-heptanedione (IVc), 81%; 7-(*o*-methoxyphenyl)-3-hydroxy-2,5-heptanedione (IVd), 74%; 7-(3,4-methylenedioxyphenyl)-3-hydroxy-2,5-heptanedione (IVe) 78%.

Cyclopentenolones. 2-Benzyl-4-hydroxy-3-methyl-2-cyclopenten-1-one (Vb).—Crude hydroxydiketone (IVb), 24 g., was added, dropwise with stirring during one hour at about 10° under a blanket of nitrogen gas, to 1500 ml. of 2% sodium hydroxide solution containing 0.2 g. of hydroquinone. The mixture was stirred for three hours more at room temperature. It was then extracted with peroxide-free ether, washed with saturated sodium chloride solution and dried over anhydrous sodium sulfate, and the ether was removed under vacuum by warming in a water-bath at 40°. Sixty-three grams of crude cyclopentenolone (Vb) was obtained (57% yield based on β-ketoester).

The other cyclopentenolones (Va, c, d, e) were prepared in a similar manner with the following yields of crude material based on starting β-keto ester: 2-phenyl-4-hydroxy-3-methyl-2-cyclopenten-1-one (Va), 75%; 2-(*p*-methoxybenzyl)-4-hydroxy-3-methyl-2-cyclopenten-1-one (Vc), 66%; 2-(*o*-methoxybenzyl)-4-hydroxy-3-methyl-2-cyclopenten-1-one (Vd), 58%; 2-(3,4-methylenedioxybenzyl)-4-hydroxy-3-methyl-2-cyclopenten-1-one (Ve), 52%.

The 3,5-dinitrobenzoates or *p*-nitrobenzoates were prepared; their melting points and analyses are shown in Table IV.

Esters of Chrysanthemic Acid. 2-Benzyl-4-hydroxy-3-methyl-2-cyclopenten-1-one Ester with Chrysanthemic Acid (VIIb).—Twenty grams (0.1 mole) of crude 2-benzyl-4-hydroxy-3-methyl-2-cyclopenten-1-one was treated with 18.5 g. (0.1 mole) of chrysanthemic acid chloride,[15] using petroleum ether (Skellysolve A) as a solvent, in the presence of 15 ml. of pyridine in a flask protected by a calcium chloride tube. After two days 100 ml. of ether was added and the mixture washed successively with tap water, 5% cold sodium hydroxide solution, cold water, dilute hydrochloric acid, twice with tap water, and finally dried over anhydrous sodium sulfate. The ether was removed under vacuum on a water-bath at 40°. The residual dark-brown viscous oil, which weighed 34 g., was dissolved in approximately 100 ml. of petroleum ether, treated with activated carbon, filtered, and the petroleum ether was removed *in vacuo* at 40°. Thirty-two grams of an amber viscous oil was obtained, n^{25}D 1.5330. The 2,4-dinitrophenylhydrazone was prepared and recrystallized from ethanol, m.p. 140–146°.

Anal. Calcd. for $C_{29}H_{32}N_4O_6$: C, 65.40; H, 6.06; N, 10.52. Found: C, 65.30; H, 5.95; N, 10.37.

The crude ester partially crystallized in a refrigerator after standing several months, but attempts to recrystallize it were unsuccessful.

Since crystalline derivatives of the other esters could not be prepared, they were submitted to partition between nitromethane and petroleum ether (Skellysolve B). Seven grams of crude ester was dissolved in 50 ml. of petroleum

---

[11] The tests on houseflies were conducted by W. A. Gersdorff and N. Mitlin of the Bureau of Entomology and Plant Quarantine.

[12] All boiling points and melting points are uncorrected. All analyses reported in this paper were performed by Mrs. Mary H. Aldridge, Chemistry Dept., University of Maryland.

[13] S. B. Soloway and F. B. LaForge, THIS JOURNAL, **69**, 2677 (1947).

[14] Technical material obtained from Benzol Products Co., Newark, N. J.

[15] The acid chloride was obtained by dissolving 117 g. of technical grade chrysanthemic acid (obtained from Benzol Products Co.) in 130 ml. of petroleum ether (b.p. 28–38°) and adding dropwise during 1 hour 120 g. of purified thionyl chloride in 90 ml. of petroleum ether. After standing overnight, the solvent and excess thionyl chloride were removed at the water-pump and the chrysanthemic acid chloride distilled, b.p. 99–101° at 13 mm. (yield 114 g.). The acid chloride, if not used immediately, was kept in a sealed ampule

TABLE III

β-KETOESTERS (II) $RCH_2COCH_2COOC_2H_5$

R	B.p., °C.	Mm.	$n^{25}D$	Yield, %	Analyses, % Calcd. C	H	Found C	H
a	117–120	2	1.5172	28	[a] B.p. 126–128 (4 mm.), $n^{22}D$ 1.5130			
b	152–163	4	1.5011	60	70.89	7.32	70.82	7.50
c	140–170[b]	0.3	1.5086	51	67.18	7.25	67.00	7.49
d	120–170[b]	.025	1.5083	58	67.18	7.25	66.98	7.13
e	160–191[b]	.02	1.5151	55	63.63	6.10	63.70	6.31

[a] D. Libermann, I. Himbert, L. Hengl and G. Kirchoffer, *Compt. rend.*, **229**, 765 (1949). [b] Bath temperature.

TABLE IV

SUBSTITUTED CYCLOPENTENOLONES

Derivative	R	Formula	M.p., °C.	Analyses, % Calcd. C	H	N	Found C	H	N
3,5-Dinitrobenzoate	a	$C_{19}H_{14}N_2O_7$	166–167	59.69	3.69	7.33	59.75	3.58	7.22
	b	$C_{20}H_{16}N_2O_7$	196–197	60.60	4.07	7.07	61.00	3.82	6.97
p-Nitrobenzoate	c	$C_{21}H_{19}NO_6$	115–116	66.13	5.02	3.68	66.18	5.24	3.96
	d	$C_{21}H_{19}NO_6$	157.5–158.5	66.13	5.02	3.68	66.13	5.08	3.99
	e	$C_{21}H_{17}NO_7$	139.5–140.5	63.79	4.34	3.54	63.28	4.75	3.79

ether and extracted consecutively with five 50-ml. portions of nitromethane (redistilled at 30 mm. pressure). The nitromethane solutions were passed through a column 12 mm. in diameter and 30 mm. long of charcoal (Norite A) that had been wetted with nitromethane, and the initial heat was permitted to dissipate (charcoal heats up when wetted with nitromethane). Care was taken not to let the charcoal get dry between successive aliquots. An 80 mm. vacuum was applied to facilitate the flow through the column.

The first 25 ml. of solution to pass through the column was set aside. The next 100 ml., which contained most of the ester, was placed in a modified Claisen distilling flask[16] and the nitromethane removed under 20 mm. vacuum with a water-bath at 40–50°. When most of the nitromethane was gone, the water-bath was removed and the vacuum maintained for four hours. Dry nitrogen was passed through the ebullition tube at all times to avoid oxidation of the ester. A vacuum of 0.5 mm. drawn through a Dry Ice trap was applied to the residual ester for eight hours at 30° while spread out in a thin layer at the bottom of flask; yield 3.8 g.

Results of analysis, yields and refractive indices of the respective esters (VII) of chrysanthemic acid are given in Table I.

BELTSVILLE, MARYLAND

---

[16] W. F. Barthel, *Ind. Eng. Chem., Anal. Ed.*, **16**, 374 (1944).

[CONTRIBUTION FROM THE CHEMICAL RESEARCH SECTION, PICATINNY ARSENAL]

Identification of Isomers Formed in the Nitration of Carbazole[1]

BY D. B. MURPHY, F. R. SCHWARTZ, J. P. PICARD AND J. V. R. KAUFMAN

RECEIVED APRIL 13, 1953

Direct nitration of carbazole results in the formation of two isomeric compounds. One of these is 1,3,6,8-tetranitrocarbazole. The other, present to the extent of about 10% in the crude product, is believed to be the 1,2,6,8-isomer and evidence is presented in support of this belief.

Several investigators,[2,3,4] in describing the preparation of tetranitrocarbazole, report the separation, by fractional crystallization from acetic acid, of a number of isomers from the products of nitration. The isomer formed in largest amount was later shown to be 1,3,6,8-tetranitrocarbazole.[5] No attempt to determine the structures of the other isomers is recorded, and, considering the techniques used, it is possible that no really effective separation of the products of this reaction has ever been accomplished. The work described here was undertaken with the intention of determining whether a mixture of isomers is formed in the nitration of carbazole, and, if so, of establishing the structures of these isomers.

From a sample of crude tetranitrocarbazole prepared by sulfonation and subsequent nitration of carbazole[6] three fractions, varying in their solubilities, could be separated by repeated fractional crystallization from acetone. The most soluble of these fractions, obtained in small amount, contained about 13% nitrogen, compared with the calculated value of 20.17% for tetranitrocarbazole. Based upon this analysis and the poor resolution obtained in the infrared spectrum of this substance, we believe this to be a mixture of decomposition and condensation products formed in the reaction, together with partially nitrated material. Both the middle fraction and the least soluble fraction, melting at 253–254° and 295–296.0°, respectively, after recrystallization, had nitrogen contents close to the calculated value for tetranitrocarbazole, indicating that they were isomers.

The least soluble fraction was considered most likely to be the 1,3,6,8-isomer, and we accordingly

---

[1] Presented at the Meeting-in-miniature of the North Jersey Section, A.C.S., January 26, 1953.

[2] G. L. Ciamician and P. P. Silber, *Gazz. chim. ital.*, **12**, 272 (1882).

[3] R. Escales, *Ber.*, **37**, 3596 (1904).

[4] H. Raudnitz, *ibid.*, **60**, 743 (1927).

[5] W. Borsche and B. G. B. Scholten, *ibid.*, **50**, 596 (1917).

[6] Casella and Co., German Patent 268,173; French Patent 464,538.