hours,[14] b. p. 130° at 2 mm.; m. p. after crystallization from cyclohexane, 77–78°; reported[14] b. p. 168–170° at 14 mm., m. p. 77–78°.

3',4',5'-Trimethoxy-2-methyl-4,5-methylenedioxybenzophenone (I).—In a 250-ml. three-necked flask were placed 10 ml. (0.084 mole) of 3,4-methylenedioxytoluene, 50 ml. of anhydrous carbon disulfide and 4.5 ml. (0.037 mole) of anhydrous stannic chloride. To this was added slowly with cooling and stirring 10 g. (0.043 mole) of freshly distilled trimethylgalloyl chloride dissolved in 50 ml. of carbon disulfide. The reaction mixture was stirred at ice-bath temperature for six hours; during this time, the product separated as a red complex. The reaction mixture was decomposed with ice-cold 7% hydrochloric acid, extracted with ether, and the ether extract washed with dilute hydrochloric acid, water, dilute sodium hydroxide and with water. The ether solution was dried with calcium chloride, the ether distilled off, and the residue refluxed with a solution of potassium hydroxide in methyl alcohol for twenty minutes. The resulting mixture was diluted with water and extracted with ether. The ether solution was washed with water, dried with calcium chloride, and the ether removed by distillation. The residue was crystallized from methyl alcohol or cyclohexane giving 6.2 g. (43% yield) of product, m. p. 108–110°. The product gave a positive test for the methylenedioxy bridge when warmed with sulfuric acid and a trace of gallic acid.[15]

Anal. Calcd. for $C_{18}H_{18}O_6$: C, 65.45; H, 5.45; OCH_3, 28.15. Found: C, 65.60; H, 5.61; OCH_3, 27.94.

3,4,5-Trimethoxy-α-piperonylacetophenone (III).—In a 100-ml. flask fitted with a condenser and drying tube were placed 50 ml. of absolute alcohol and 0.46 g. (0.02 mole) of sodium. The sodium ethoxide solution thus prepared was cooled in an ice-bath and 5.6 g. (0.02 mole) of ethyl 3,4,5-trimethoxybenzoylacetate[16] was added. Four and one-half grams (0.029 mole) of piperonyl bromide,[17] dissolved in 10 ml. of absolute ether was then added to the cold alcohol solution. Sodium bromide began to precipitate. After ten minutes, the ice-bath was removed, and the reaction allowed to proceed for half an hour while warming up to room temperature. The reaction mixture was then acid. It was diluted with water and extracted with ether. The ether solution was dried, the ether distilled off, and a viscous residual oil obtained. This was hydrolyzed by dissolving in 400 ml. of methanol and adding a solution of 45 g. of barium hydroxide octahydrate in 800 ml. of water at room temperature. A white solid soon formed; after twelve hours, it was removed by filtration. The organic material was separated from inorganic salts by dissolving in chloroform, the chloroform solution dried with anhydrous magnesium sulfate, and the chloroform removed by distillation. There remained 3.8 g. (55% yield for the two steps) of a white crystalline mass which after recrystallization from methanol gave 3.4 g. of product, m. p. 146–147°; reported[9] 96–98°.

Anal. Calcd. for $C_{19}H_{20}O_6$: C, 66.27; H, 5.83; OCH_3, 27.03. Found: C, 66.14; H, 5.95; OCH_3, 26.87.

Dinitrophenylhydrazone of III.—Accurately weighed samples of III dissolved in alcohol reacted with excess dinitrophenylhydrazine in 2 *N* hydrochloric acid to give the 2,4-dinitrophenylhydrazone according to the quantitative procedure of Iddles, *et al.*[18] Quantitative yields were obtained. After two recrystallizations from benzene, approximately half the material remained, m. p. 188.5–189°.

Anal. Calcd. for $C_{25}H_{24}O_9N_4$: C, 57.25; H, 4.61; N, 10.68. Found: C, 57.47; H, 4.62; N, 10.84.

Acknowledgment.—The authors wish to express their appreciation to the National Institute of Health for the financial assistance which made this work possible, and to Mrs. Mary H. Aldridge and Mr. Byron Baer for carrying out the microanalyses.

Summary

1. 3',4',5'-Trimethoxy-2-methyl-4,5-methylenedioxybenzophenone (I) has been prepared by the stannic chloride catalyzed condensation of 3,4-methylenedioxytoluene with trimethylgalloyl chloride.

2. 3,4,5-Trimethoxy-α-piperonylacetophenone (III) has been prepared by an acetoacetic ester type of synthesis.

3. 3,4-Methylenedioxytoluene has been prepared by the hydrogenolysis of piperonyl alcohol. The latter is more resistant to hydrogenolysis over a copper–chromium–barium oxide catalyst than is benzyl alcohol.

(14) Asano and Yamaguti, *J. Pharm. Soc.* (*Japan*), **60**, 34 (1940).
(15) Labat, *Bull. soc. chim. biol.*, **15**, 1344 (1933).
(16) Perkin and Weizmann, *J. Chem. Soc.*, **89**, 1655 (1906).
(17) Robinson and Robinson, *ibid.*, **105**, 1463 (1914).
(18) Iddles, Low, Rosen and Hart, *Ind. Eng. Chem., Anal. Ed.*, **11**, 102 (1939).

COLLEGE PARK, MARYLAND RECEIVED MAY 18, 1949

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY]

Spirobarbituric Acids Containing a Six-membered Carbocyclic Ring

BY ARTHUR C. COPE, PETER KOVACIC[1] AND MARION BURG[1]

Several spirobarbituric acids have been described by Dox and Yoder[2] in which the 5-carbon atom of the barbituric acid nucleus forms part of an unsubstituted cyclobutane or cyclohexane ring, but no pharmacological data were reported for these compounds. The spirobarbituric acids present points of structural similarity and dissimilarity to the 5,5-dialkylbarbituric acids which have led us to prepare a number of such compounds for pharmacological evaluation. In both classes the two acidic hydrogen atoms in the 5-position of the barbituric acid nucleus have been replaced by establishment of carbon-to-carbon linkages, but the spiro compounds differ uniquely from the 5,5-dialkylbarbituric acids in the spatial arrangement of the two rings in perpendicular planes. Since the pharmacological characteristics of 5,5-dialkylbarbituric acids vary widely according to the size and structure of the alkyl substituents, properties of the spiro compounds could not be predicted.

The intermediate esters required for the synthesis of spirobarbituric acids were prepared by the addition of butadiene to diethyl methylene-

(1) Sharp and Dohme Research Associate.
(2) Dox and Yoder, THIS JOURNAL, **43**, 677, 1366, 2097 (1921).

TABLE I

DIETHYL 6-ALKYL-3-CYCLOHEXENE-1,1-DICARBOXYLATES (I)

Alkyl substituents in formula I	Boiling point, °C.	Mm.	Yield, %	$n^{25}D$	d^{25}_4	Formula	Molecular refraction Calcd.	Found	Analyses, % Carbon Calcd.	Found	Hydrogen Calcd.	Found
None[a]	105–108	3	67	1.4540		$C_{12}H_{18}O_4$						
6-Methyl[b]	129–131	10	43	1.4570	1.0466	$C_{13}H_{20}O_4$	62.87	62.52	64.97	64.76	8.38	8.31
6-Ethyl	93–94.5	0.5	33	1.4590	1.0333	$C_{14}H_{22}O_4$	67.52	67.49	66.11	65.79	8.72	8.80
6-Isopropyl	107–108	0.95	7[c]	1.4618	1.0300	$C_{15}H_{24}O_4$	72.11	71.59	67.13	67.14	9.01	8.84
6-*n*-Propyl	114–116	1.3	39	1.4585	1.0215	$C_{15}H_{24}O_4$	72.11	71.74	67.13	67.17	9.01	9.22
6-Isobutyl	132–133	3.5	16	1.4580	1.0091	$C_{16}H_{26}O_4$	76.73	76.33	68.05	67.91	9.28	9.40
3,4,6-Trimethyl[b]	101–103	0.7	73	1.4608	1.0201	$C_{15}H_{24}O_4$	72.11	72.15	67.13	66.94	9.01	9.14
2,5-Endomethylene-6-methyl[b]	99.5–102	1.1	22	1.4659	1.0738	$C_{14}H_{20}O_4$	65.29	65.06	66.64	66.37	7.99	8.06
6-Methylmercaptomethyl	133–134.5	<1	44	1.4905	1.1069	$C_{14}H_{22}O_4S$	75.46	74.86	58.71	58.58	7.74	7.89

[a] Described in ref. 3. [b] Described in ref. 4. [c] The same yield was obtained when the reaction temperature was 190–215°.

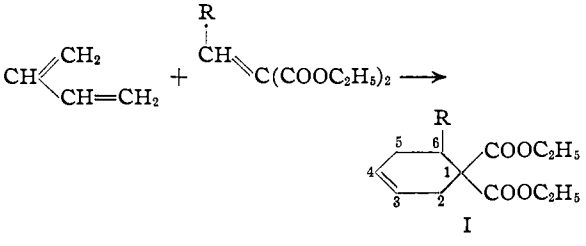
TABLE II

DIETHYL 2-ALKYLCYCLOHEXANE-1,1-DICARBOXYLATES (II)

2-Alkyl substituent in formula II	Boiling point, °C.	Mm.	Yield, %	$n^{25}D$	d^{25}_4	Formula	Molecular refraction Calcd.	Found	Analyses, % Carbon Calcd.	Found	Hydrogen Calcd.	Found
None[a]	111–112	5	94	1.4438								
Methyl[b]	95–96	1	92	1.4490	1.0288	$C_{13}H_{22}O_4$	63.34	63.13	64.43	64.57	9.15	9.42
Ethyl	114.8–115.8	2.8	89	1.4516	1.0181	$C_{14}H_{24}O_4$	67.98	67.87	65.60	65.36	9.44	9.30
n-Propyl	94–97.5	0.4	83	1.4518	1.0063	$C_{15}H_{26}O_4$	72.58	72.43	66.63	66.73	9.69	9.73
Isopropyl	133–134.5	5	85	1.4556	1.0132	$C_{15}H_{26}O_4$	72.51	72.58	66.63	66.78	9.69	9.74
Isobutyl	123–125	2	88	1.4501	0.9929	$C_{16}H_{28}O_4$	77.20	76.63	67.57	67.54	9.92	10.06

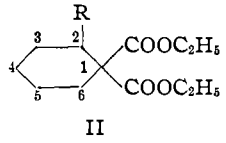
[a] The preparation by a different method is described by Dox and Yoder, THIS JOURNAL, **43**, 1366 (1921). [b] Described in ref. 4 and by Freer and Perkin, *J. Chem. Soc.*, **53**, 206 (1888).

malonate[3] or higher molecular weight diethyl alkylidenemalonates[4] to give esters of type I. Similar adducts were prepared by reaction of 2,3-dimethyl-1,3-butadiene and cyclopentadiene with diethyl ethylidenemalonate.

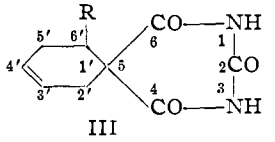


I

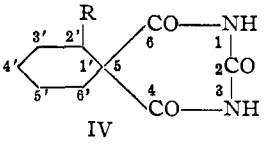
Catalytic hydrogenation of the unsaturated esters yielded corresponding saturated esters (II). Condensation of both classes of esters with urea and thiourea furnished spirobarbituric and thiobarbituric acids (III, IV, V and VI).[5]



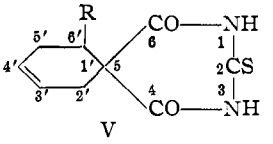
II



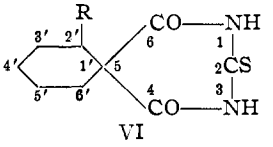
III



IV



V



VI

Unsaturated esters (I) prepared by the diene synthesis are listed in Table I. The butadiene additions proceeded fairly well at 170–180° except in the case of diethyl isobutylidenemalonate, which gave a low yield of adduct. Diethyl isopropylidenemalonate and ethyl isopropylidenecyanoacetate failed to react with butadiene under the conditions investigated. Butadiene reacted with diethyl (2-methylmercaptoethylidene)-malonate to give an adduct (I, R = CH_3SCH_2–), but failed to add to diethyl (3-methylmercaptopropylidene)-malonate, which polymerized when the addition was attempted at 220°. The adduct formed from cyclopentadiene and diethyl ethylidenemalonate decomposed on distillation, except at low pressures, presumably by disproportionation into the original diene and ester. In one case (I, R = *n*-C_3H_7) the unsaturated ester was prepared by heating together the aldehyde (butyraldehyde), diethyl malonate, acetic anhydride and butadiene. The product was isolated in a yield equiva-

(3) Bachmann and Tanner, *J. Org. Chem.*, **4**, 500 (1939).

(4) Alder and Rickert, *Ber.*, **72**, 1983 (1939); U. S. Patent 2,264,354; *C. A.*, **36**, 1615 (1942).

(5) In order to emphasize the relationship of these spiro compounds with barbituric acid the authors have chosen to describe them as derivatives of barbituric acid. By the present *Chemical Abstracts* system these spirobarbituric acids would be classified as diaza spirohydrocarbons.

TABLE III

6′-ALKYLSPIRO-[BARBITURIC ACID-5,1′-3′-CYCLOHEXENE] (III)[5]

Alkyl substitution in formula III	M. p., °C.	Yield, %	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found	Results of pharmacological tests in white mice[b] ND^{50} mg./kg.	ND^{100} mg./kg.	LD^{50} mg./kg.	Ratio LD^{50}/ND^{50}	Duration at ND^{100} Induction, min.	Duration, hr.
None	258.8–259.8	31	$C_9H_{10}N_2O_3$	55.66	55.66	5.19	5.21	14.43	14.38	>800	>800	>800	..	Mild lethargy at 0.5 hr. (800 mg./kg.)	
6′-Methyl	218.5–219	77	$C_{10}H_{12}N_2O_3$	57.68	57.93	5.80	5.78	13.45	13.41	420	550	575	1.3	15–18	3.2
6′-Ethyl	193.6–194.2	34	$C_{11}H_{14}N_2O_3$	59.44	59.33	6.35	6.31	12.61	12.40	245 ± 18	350	530 ± 23	2.16	8–10	1.47
6′-*n*-Propyl	191.5–192.5	68	$C_{12}H_{16}N_2O_3$	60.99	60.93	6.82	6.99	11.85	11.65	126	180	395	3.11	6–8	1.3
6′-Isopropyl	195–197	25	$C_{12}H_{16}N_2O_3$	60.99	61.15	6.82	7.02	11.85	11.65	125	150	408	3.26	6–11	1.0
3′,4′,6′-Trimethyl	150.5–151.5	51	$C_{12}H_{16}N_2O_3$	60.99	61.06	6.82	6.86	11.85	11.63	175	200	455	2.6	10–12	<1.0
6′-Methylmercaptomethyl[a]	168.2–168.6	21	$C_{11}H_{14}N_2O_3S$	51.95	52.04	5.55	5.60	11.02	10.90	325 ± 18	400	790 ± 44	2.43	13–15	1.12

[a] Prepared by Procedure D. [b] Tested by intraperitoneal injection in Carworth Farms strain F′ female mice weighing 16–18 g. Solutions were freshly prepared from the sodium salts for each test. Calculations are based on the equivalent weights of the free acids. Five mice were used at each dose level. The test for narcosis was performed by placing the mice on their left sides on a flat surface and striking their tails with a forefinger, then placing them on their right sides and repeating the process. A mouse which failed to right itself under these conditions was considered to be narcotized. ND^{50} is the dose at which 50% of the mice were narcotized; ND^{100} is the dose at which all were narcotized. LD^{50} signifies the dose at which 50% of the mice were killed.

TABLE IV

2′-ALKYLSPIRO-BARBITURIC ACID-5,1′-CYCLOHEXANE] (IV)[5]

2′-Alkyl substituent in formula IV	M. p., °C.	Yield, %	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found	Results of pharmacological tests in white mice ND^{50} mg./kg.	ND^{100} mg./kg.	LD^{50} mg./kg.	Ratio LD^{50}/ND^{50}	Duration at ND^{100} Induction, min.	Duration, hrs.
None[a]	279.6–280.6	33	$C_9H_{12}N_2O_3$							>800	>800	>800	..	Activity reduced (800 mg./kg.)	
Methyl	219.5–220	62	$C_{10}H_{14}N_2O_3$	57.12	57.15	6.71	6.70	13.32	13.10	185	250	445	2.4	5–6	1.4
Ethyl	194.8–195.2	34	$C_{11}H_{16}N_2O_3$	59.36	59.04	7.19	7.30	12.49	12.38	105 ± 9	150	345 ± 26	3.29	2–5	0.84
n-Propyl	185–185.5	34	$C_{12}H_{18}N_2O_3$	60.48	60.27	7.61	7.68	11.75	11.63	53	75	275	5.18	4–5	.4
Isopropyl	196.2–196.8	20	$C_{12}H_{18}N_2O_3$	60.48	60.45	7.61	7.56	11.75	11.60	67 ± 3	75	274 ± 13	4.12	10–12	.4
Isobutyl	194.2–194.6	25	$C_{13}H_{20}N_2O_3$	61.88	61.91	7.99	7.91	11.11	10.89	90 ± 4	110	217 ± 15	2.41	5–6	.4

[a] Described in ref. 2.

TABLE V

6′-ALKYL-2-THIOSPIRO-[BARBITURIC ACID-5,1′-3′-CYCLOHEXENE] (V)[5]

Alkyl substitution in formula V	M. p., °C.	Yield, %	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found	Results of pharmacological tests in white mice[a] ND^{50}, mg./kg.	ND^{100}, mg./kg.	LD^{50}, mg./kg.	Ratio, LD^{50}/ND^{50}	Duration at ND^{100} Induction, min.	Duration, hr.
None	231.4–233.2	30	$C_9H_{10}N_2O_2S$	51.41	51.45	4.79	4.91	13.33	13.34	>800	>800	>800	..	Mild lethargy at 1.0 hr. (800 mg./kg.)	
6′-Methyl	175–176	57	$C_{10}H_{12}N_2O_2S$	53.55	53.25	5.39	5.47	12.49	12.32	185	250	345	1.8	10–12	3.0
6′-Ethyl	129.2–129.4	13	$C_{11}H_{14}N_2O_2S$	55.44	55.39	5.92	6.09	11.76	11.95	155 ± 19	250	295 ± 24	1.9	4–6	2.54
3′,4′,6′-Trimethyl	171–172	52	$C_{12}H_{16}N_2O_2S$	57.11	56.96	6.39	6.40	11.10	11.03	185	250	335	1.8	3–4	>7.0
6′-*n*-Propyl	143.2–143.8	40	$C_{12}H_{16}N_2O_2S$	57.12	57.22	6.39	6.64	11.10	11.14	150 ± 13	200	310 ± 23	2.06	5–8	4.25

[a] See footnote *b*, Table III.

lent to that obtained if the condensation and diene addition reactions were carried out separately.

The catalytic hydrogenations of the unsaturated esters (I) to saturated esters II (Table II) proceeded rapidly and in good yield in the presence of Adams platinum catalyst.

The spirobarbituric acids (III and IV, Tables III and IV) were prepared by condensing the corresponding esters with urea in the presence of sodium isopropoxide in isopropyl alcohol. Isolation of the spirothiobarbituric acids (Tables V and VI) required a modification of the usual procedure because of the ease with which they were hydrolyzed to dicarboxylic acids. For example, acidification of a cold alkaline solution of 6′-methyl-2-thiospiro-[barbituric acid-5,1′-3′-cyclohexene] by

TABLE VI

2'-ALKYL-2-THIOSPIRO-[BARBITURIC ACID-5,1'-CYCLOHEXANE] (VI)[5]

2'-Alkyl substituent in formula VI	M. p., °C.	Yield, %	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found	Results of pharmacological tests in white mice: ND^{50}, mg./kg.	ND^{100}, mg./kg.	LD^{50}, mg./kg.	Ratio, LD^{50}/ND^{50}	Duration at ND^{100}: Induction, min.	Duration, hr.
None	243.2–243.8	31	$C_9H_{12}N_2O_2S$	50.92	50.98	5.70	5.69	13.20	13.18	>1200	>1200	>1200	..	Lethargy and scratch reflex (1200 mg./kg.)	
Methyl	172–172.5[a]	43	$C_{10}H_{14}N_2O_2S$	53.07	53.34	6.23	6.16	12.38	12.38	175	200	265	1.5	7–12	>3.0
Ethyl	158.4–159.2	20	$C_{11}H_{16}N_2O_2S$	54.97	55.21	6.72	6.67	11.66	11.52	170 ± 20	250	355 ± 27	2.08	3–4	1.27
n-Propyl	150.2–151.0	35	$C_{12}H_{18}N_2O_2S$	56.66	56.50	7.13	7.40	11.02	11.03	159 ± 11	200	253 ± 21	1.59	5–10	1.37

[a] Procedure C gave a crude product, m. p. 150–156.5° (dec.), which contained the corresponding dicarboxylic acid.

the addition of hydrochloric acid gave a mixture of the thiobarbituric acid derivative (V, R = CH_3) and 6-methyl-3-cyclohexene-1,1-dicarboxylic acid. This hydrolysis could be minimized by isolating the crude, dry sodium salt of the thiobarbituric acid derivative and adding it to an excess of cold hydrochloric acid (procedure D). The sodium salts of the spirothiobarbituric acids proved to be sufficiently stable in aqueous solution for pharmacological testing.

Pharmacological

Preliminary pharmacological data which were obtained for the spirobarbituric acid derivatives by Dr. Karl H. Beyer and Mr. S. E. McKinney of Sharp and Dohme, Inc., are included in Tables III–VI. Among the spirobarbituric acid (Tables III and IV) both narcotic activity and toxicity increased with increasing molecular weight, and the compounds with the highest therapeutic ratios were the 6'-isopropyl and *n*-propyl derivatives (formula III) and the 2'-isopropyl and *n*-propyl derivatives (formula IV). Both unsaturated and saturated spirothiobarbituric acids (formulas V and VI) were less active, longer acting and had poorer therapeutic ratios than the corresponding spirobarbituric acids.

Experimental[6]

Diethyl methylenemalonate was prepared from paraformaldehyde and diethyl malonate by the method of Bachmann and Tanner.[3] The crude reaction mixture was distilled through a 20-cm. Widmer column until the distillation temperature reached 116° (43 mm.). Some decomposition occurred at 105–116° (43 mm.). The pale green viscous residue was distilled through a 20 × 1.3 cm. Vigreux column with a heated jacket and the diethyl methylenemalonate fraction which collected at 124–128° (35 mm.) was treated with butadiene at once to prepare diethyl 3-cyclohexene-1,2-dicarboxylate.[3] Other diethyl alkylidenemalonates were prepared by procedures described previously.[7]

Diethyl 6-Alkyl-3-cyclohexene-1,1-dicarboxylates (I). Procedure A.—Conditions similar to those used by Alder and Rickert[4] were employed, which can be illustrated by description of the procedure followed for preparing diethyl 6-*n*-propyl-3-cyclohexene-1,1-dicarboxylate. Diethyl *n*-butylidenemalonate (112.7 g., 0.53 mole) was placed in a 500-ml. steel hydrogenation bomb which had been cooled with Dry Ice. After the ester was cooled to −15°, 115 g. (2.1 moles) of butadiene (previously collected in a Dry-Ice-cooled tube from a commercial cylinder) was added. The mixture was stirred, the bomb closed, and allowed to stand until it reached room temperature, It was then heated for twelve to fourteen hours at 170–180° without shaking. The product was distilled through a 20-cm. Widmer column. About 80 g. of vinylcyclohexene was collected at 20–60 mm., followed by 50 g. of recovered diethyl *n*-butylidenemalonate, b. p. 99–109° (3 mm.). The crude adduct (70 g., b. p. 109–125° at 2.8 mm.) was redistilled through the same column and yielded 52 g. (39%) of diethyl 6-*n*-propyl-3-cyclohexene-1,1-dicarboxylate, b. p. 114–116° (1.3 mm.). The properties of other esters prepared by this procedure are listed in Table I.

Procedure B.—Diethyl malonate (80.1 g., 0.5 mole), freshly distilled butyraldehyde (36.1 g., 0.5 mole), acetic anhydride (51.1 g., 0.5 mole) and butadiene (108 g., 2.0 moles) were mixed in a Dry-Ice-cooled 500-ml. steel hydrogenation bomb. The mixture was heated at 182–195° for twelve and one-half hours without shaking, and the product was isolated by the method described under Procedure A. The yield of diethyl 6-*n*-propyl-3-cyclohexene-1,1-dicarboxylate, b. p. 99–101.8° (0.8 mm.), (32 g., 20.3%) was equivalent to the yield obtained by carrying out the condensation and addition reactions as separate preparations.

Diethyl (2-Methylmercaptoethylidene)-malonate. (a) Methylmercaptoacetaldehyde Diethyl Acetal.—Diethyl bromoacetal[8] was treated with sodium methylmercaptide by an adaptation of the procedure of Barger and Coyne[9] suitable for a larger scale preparation. Absolute ethanol (1.3 l.) was placed in a 3-l. three-necked flask fitted with a reflux condenser and a motor-driven slip-sealed stirrer. Sodium ethoxide was prepared by the addition of 79 g. (3.44 g. atoms) of clean sodium. The solution was cooled in an ice-bath and the reflux condenser was replaced by a spiral condenser cooled with ice-water. A T-tube was attached to the top of condenser which led to a safety trap which was connected to a water aspirator. A screw clamp attached to the open end of the T-tube was used to regulate the aspiration. Methyl mercaptan (100 g., 2.08 moles) was introduced gradually through a gas inlet tube by aspiration during one hour, in an assembly of apparatus similar to that used for introducing bromine in the preparation of bromoacetal,[8] except that the methyl mercaptan was placed in a 200-ml. round-bottom flask (fitted with inlet and outlet tubes) which initially was cooled and subsequently was warmed to control the rate of addition. The inlet tube was replaced by a 500-ml. dropping funnel and 296 g. (1.5 moles) of freshly distilled diethyl bromoacetal was added during twenty-five minutes with stirring. Sodium bromide separated during the addition. The reaction mixture was allowed to stand overnight, filtered,

(6) Melting points are corrected and boiling points are uncorrected. We are indebted to Mr. S. M. Nagy, Mrs. Louise W. Spencer and Mr. Philip H. Towle for analyses.

(7) Cope, Hofmann, Wyckoff and Hardenbergh, THIS JOURNAL, 63, 3452 (1941).

(8) McElvain and Kundiger, "Organic Syntheses," Vol. 23, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 8.

(9) Barger and Coyne, *Biochem. J.*, 22, 1417 (1928).

and the filtrate added to 2 l. of water. The oily layer was removed and the aqueous layer saturated with sodium chloride and extracted with five 100-ml. portions of benzene. The combined oil and extracts were distilled through a 20-cm. Widmer column and yielded 164 g. (67%) of methylmercaptoacetaldehyde diethyl acetal, b. p. 72.5–73.5° (11 mm.).

(b) **Methylmercaptoacetaldehyde.**—Methylmercaptoacetaldehyde diethyl acetal (86.1 g., 0.52 mole) was heated under reflux with 200 ml. of water and 2 ml. of concd. hydrochloric acid for one-half hour. The mixture became homogeneous after five minutes at the reflux temperature. The solution was cooled, extracted with 150 ml. of ether, partially saturated with sodium chloride and again extracted with 150 ml. of ether. The combined extracts were washed with two 100-ml. portions of 10% sodium bicarbonate solution, three times with 250-ml. portions of water, dried over magnesium sulfate and distilled through a 20-cm. Widmer column. The yield of methylmercaptoacetaldehyde, b. p. 93–95° (235 mm.), was 25 g. (53%).

(c) **Diethyl (2-Methylmercaptoethylidene)-malonate.**—Diethyl malonate (62.5 g., 0.39 mole), methylmercaptoacetaldehyde (70 g., 0.78 mole) and acetic anhydride (62.5 g., 0.61 mole) were heated under reflux in an oil-bath at 130° for twenty-four hours. The mixture was fractionated through a 20-cm. Widmer column at atmospheric pressure until the distillation temperature reached 113°. Continuation of the fractionation under reduced pressure yielded a crude product (42 g., b. p. 121–135° at 3 mm.) which was fractionated through a 220 × 8 mm. glass helix-packed, total condensation, variable take-off type column. The yield of diethyl (2-methylmercaptoethylidene)-malonate was 33.5 g. (37%) b. p. 123.5–125.5° (1.5 mm.), $n^{25}D$ 1.4882, d^{25}_4 1.1057; M_D calcd. 59.19, found 60.55 (exaltation 1.36).

Anal. Calcd. for $C_{10}H_{16}O_4S$: C, 51.70; H, 6.94. Found: C, 51.59; H, 6.92.

Diethyl (3-Methylmercaptopropylidene)-malonate.—Diethyl malonate (40 g., 0.25 mole), β-methylmercaptopropionaldehyde[10] (57 g., 0.55 mole) and acetic anhydride (40 g., 0.39 mole) were allowed to react under the conditions described above. Redistillation of the crude product through a 220 × 8 mm. glass helix-packed, total condensation, variable take-off type column yielded 43.8 g. (70.6%) of diethyl (3-methylmercaptopropylidene)-malonate, b. p. 143–145° (2.5 mm.), $n^{25}D$ 1.4885; d^{25}_4 1.0877; M_D calcd. 63.81, found 65.31 (exaltation 1.50).

Anal. Calcd. for $C_{11}H_{18}O_4S$: C, 53.64; H, 7.53. Found: C, 53.70; H, 7.35.

Diethyl 6-(Methylmercaptomethyl)-3-cyclohexene-1,1-dicarboxylate.—Diethyl (2-methylmercaptoethylidene)-malonate (22.5 g., 0.097 mole) was placed in a 60 × 2 cm. Pyrex bomb-tube and cooled in a chloroform–carbon tetrachloride–Dry Ice-bath. Butadiene (27 g., 0.5 mole) was added and the tube was sealed and heated in a bomb furnace at 160–170° for fourteen hours. Distillation yielded 19.4 g. of a crude product, b. p. 123–134.5° (1 mm.) which was redistilled through the helix-packed column described above. The yield of diethyl 6-(methylmercaptomethyl)-3-cyclohexene-1,1-dicarboxylate was 12.5 g. (44%), b. p. 133–133.5° (less than 1 mm.), $n^{25}D$ 1.4905, d^{25}_4 1.1069; M_D calcd. 75.46, found 74.86.

Anal. Calcd. for $C_{14}H_{22}O_4S$: C, 58.71; H, 7.74. Found: C, 58.58; H, 7.89.

Under these conditions no adduct was obtained from butadiene and diethyl (3-methylmercaptopropylidene)-malonate, and most of the ester was recovered. At 220° partial polymerization occurred and the recovery of the ester was reduced to 50%, but no adduct was isolated.

(10) Supplied by U. S. Industrial Chemicals, Inc., through the courtesy of Harry L. Fisher. Described by Hurd and Gershbein, THIS JOURNAL, **69**, 2334 (1947); Catch, Cook, Graham and Heilbron, *Nature*, **159**, 578 (1947); ref. 9.

Diethyl 2-Alkylcyclohexane-1,1-dicarboxylates (II).—Solutions of the unsaturated esters (I) (approximately 50 g.) in dry ethyl acetate (about 50 ml.) were hydrogenated in the presence of 0.5 g. of prereduced Adams platinum catalyst at room temperature and about 25 p. s. i. during one-half to two hours. The properties and yields of the saturated esters (II) which were obtained are listed in Table II.

Barbituric Acid Condensations.—The barbituric acid derivatives described in Tables III and IV were prepared by a modification of a procedure described previously,[11] which is illustrated by the synthesis of 2′-*n*-propylspiro-[barbituric acid-5,1′-cyclohexane] (IV, R = *n*-C_3H_7) (procedure C).

Diethyl 2-*n*-propylcyclohexane-1,1-dicarboxylate (14.8 g., 0.055 mole) and urea (6.6 g., 0.11 mole) were added to the sodium isopropoxide prepared from 2.3 g. (0.1 g. atom) of sodium and 95 ml. of dry isopropyl alcohol, and the mixture was heated under reflux for fifteen hours in an oil-bath at 105°. The isopropyl alcohol was removed under reduced pressure and the solid residue cooled in an ice-bath and dissolved in 100 ml. of cold water. The solution was extracted with three 30-ml. portions of ether, and the combined extracts were washed with water. The combined water washes and aqueous solution were cooled in ice and acidified by dropwise addition of a 50% excess of 20% hydrochloric acid, with stirring. The solid barbituric acid derivative was separated by filtration, washed with water and recrystallized to constant melting point from dilute alcohol. Distillation of the ether extracts resulted in recovery of 4.6 g. of diethyl 2-*n*-propylcyclohexane-1,1-dicarboxylate, b. p. 108° (0.8 mm.), $n^{25}D$ 1.4478.

Thiobarbituric Acid Derivatives.—The thiobarbituric acid derivatives described in Tables V and VI were prepared by a method (procedure D) which may be illustrated by details of the synthesis of 6′-*n*-propyl-2-thiospiro-[barbituric acid-5,1′-3′-cyclohexene] (V, R = *n*-C_3H_7).

Procedure C (above) was followed with 24.3 g. (0.088 mole) of diethyl 6-*n*-propyl-3-cyclohexene-1,1-dicarboxylate, 10.5 g. (0.14 mole) of thiourea and the sodium isopropoxide prepared from 4.0 g. (0.17 g. atom) of sodium and 200 ml. of dry isopropyl alcohol as the reactants. After the period of reflux, distillation of the isopropyl alcohol under reduced pressure left a crude solid mixture containing the sodium salt of 6′-*n*-propyl-2-thiospiro-[barbituric acid-5,1′-3′-cyclohexene]. This solid was washed with ether, collected on a filter, and added in portions with stirring to 250 ml. of 20% hydrochloric acid cooled in an ice-bath. The solid product was separated by filtration and recrystallized to constant melting point from dilute alcohol. No appreciable amount of a carboxylic acid was isolated when this procedure was followed. A similar preparation (I, R = CH_3–) according to procedure C gave a crude product which was in part soluble in aqueous sodium bicarbonate solution. Acidification of the sodium bicarbonate solution precipitated 6-methyl-3-cyclohexene-1,1-dicarboxylic acid, which after recrystallization from acetone–benzene had m. p. 175–176° (dec.).

Anal. Calcd. for $C_9H_{12}O_4$: C, 58.68; H, 6.56; neut. equiv., 92.09. Found: C, 58.60; H, 6.54; neut. equiv., 92.49.

Summary

The preparation, properties and pharmacological assay of a number of spirobarbituric and thiobarbituric acids derived from diethyl 6-alkyl-3-cyclohexene-1,1-dicarboxylates and diethyl 2-alkylcyclohexane-1,1-dicarboxylates and the preparation and properties of these intermediate esters are described.

CAMBRIDGE, MASSACHUSETTS RECEIVED MAY 13, 1949

(11) Cope and Hancock, THIS JOURNAL, **61**, 96 (1939).