Anal. Calcd. for $C_9H_{14}O_2$: C, 70.1; H, 9.2. Found: C, 69.6; H, 9.3.

No further work was done with either the ether of fraction *c* or the yellow fraction *d*.

Nepetalic Anhydride.—A 15-g. sample of the residue remaining from the initial crude fractionation of the neutral portion of the oil was distilled from glass wool in a 25-ml. flask without a fractionating column and 13 g. of a yellow viscous oil, b. p. 200–210° (0.1 mm.), obtained. This viscous oil on standing slowly crystallized. Over a two-month period 2 g. of white crystalline nepetalic anhydride, m. p. 139–140°, was isolated from the semi-crystalline mass by recrystallization from petroleum ether (40–60°).

Nepetalic anhydride also was isolated from a sample of non-crystalline nepetalic acid that had been standing for several years. From a 40-g. sample of this acid 1.8 g. of the anhydride remained as alkali-insoluble material. Upon recrystallization from alcohol it melted at 139–140°; $[\alpha]^{25}D$ +136 (in chloroform); mol. wt. (Rast), 347 (calcd. 350).

Anal. Calcd. for $C_{20}H_{30}O_5$: C, 68.5; H, 8.7. Found: C, 68.7; H, 8.8.

Nepetalic anhydride was obtained from an acetylation of nepetalic acid with acetyl chloride. Fractionation of a solution of 3.9 g. of acetyl chloride and 5.0 g. of nepetalic acid in 5 ml. of carbon tetrachloride that had stood overnight at room temperature yielded 2.4 g. of nepetalic acid acetate,[3] b. p. 120–126° (0.1 mm.) and 2.7 g. of the anhydride, b. p. 203–206° (0.1 mm.). The latter fraction partially crystallized on cooling and after recrystallization from petroleum ether yielded the solid anhydride; m. p. 138–139°.

Hydrolysis of 0.65 g. of the anhydride in a refluxing solution of 2 ml. of concentrated hydrochloric acid in 10 ml. of water over a period of fourteen hours yielded 0.62 g. of nepetalic acid which was identified as the semicarbazone.

Nepetalactone from Nepetalic Anhydride.—In a distilling flask of about 2 ml. capacity 0.5 g. of nepetalic anhydride was carefully heated at its boiling point with a microburner for thirty minutes during which time a small amount of water distilled out. Then the residue was distilled under diminished pressure and 0.4 g. of nepetalactone, b. p. 67–70° (0.1 mm.); $n^{28}D$ 1.4843, was obtained as distillate.

A 10-g. sample of the viscous, non-crystalline material remaining from the petroleum ether crystallization of the anhydride distillate was heated in a metal bath at 280° for two hours. During this time 0.2 g. (38%) of water distilled out. The residue on distillation under diminished pressure yielded 3.9 g. (41%) of nepetalactone which was identified as the semicarbazone of nepetalic acid.

Summary

An investigation of the alkali-insoluble portion (10%) of the volatile oil of catnip shows that it consists of β-caryophyllene (14%), nepetalactone (42%) and nepetalic anhydride (36%). This latter compound is the anhydride of the hydroxylactone form of nepetalic acid.

In addition to these compounds two other substances which comprise not more than 0.5% of the oil have been isolated but not identified.

It is shown that nepetalactone is the component of the oil, the odor of which makes the catnip plant so attractive to certain species of the cat family.

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[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

α-Alkoxyvinyl- and α-Alkoxyethylbarbituric Acids

BY S. M. MCELVAIN AND HOWARD BURKETT[1]

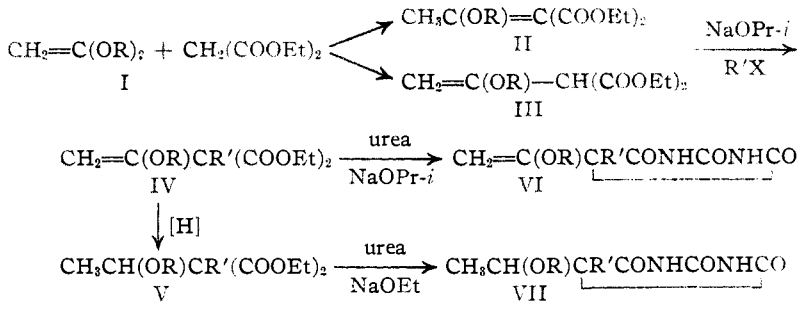
The formation of (α-ethoxyethylidene)-malonic ester (II, R is ethyl) from the reaction of ketene diethyl acetal and malonic ester[2] suggested a study of this reaction with other ketene dialkylacetals[3] (I) and the conversion of the resulting α-alkoxyethylidenemalonic esters into the corresponding 5-(α-alkoxyvinyl)-5-alkyl-barbituric acids (VI) by the sequence of reactions shown below. It seemed possible also that the vinyl group could be hydrogenated at the malonic ester stage (IV) and a series of 5-substituted (α-alkoxyethyl)-barbituric acids (VII) prepared from the saturated malonic esters (V).

In the original study of the reaction between ketene diethyl acetal and malonic ester the (α-ethoxyethylidene)-malonic ester (II), m. p. 26–27°, was obtained in 55% yield. It has been found possible in the present work to increase the yield of this product to 66% and to obtain in addition the isomeric (α-ethoxyvinyl)-malonic ester (III, R is ethyl) in 11% yield. The structure of the latter ester, which is a liquid, is shown by its ozonolysis into formaldehyde, and by the fact that the two isomers yield the same malonic ester and barbituric acid in the reactions shown below. By long heating (125° for twenty hours) with a trace of sodium ethoxide the liquid ester (III) may be converted into its solid isomer (II).

(1) Eli Lilly and Company Fellow, 1940–1942.

(2) Barnes, Kundiger and McElvain, THIS JOURNAL, **62**, 1281 (1940).

(3) McElvain and Walters, *ibid.*, **64**, 1059 (1942).



Only in the case of the compounds (II and III, R is ethyl) derived from ketene diethylacetal was an attempt made to separate the isomers. In each of the other cases the mixture of the isomers was directly alkylated. When this alkylation was carried out in ethyl alcohol the yields of the disubstituted malonic esters (IV) were quite low (20–25%) but with isopropyl or *t*-butyl alcohols as solvents the yields of these malonic esters generally were between 55–85% of the theoretical.

The hydrogenation of the vinyl substituted ester (IV) to the saturated ester (V) was carried out only with the compound in which R = R′ = ethyl. While the hydrogenation went quite satisfactorily, this method did not seem as practicable as the direct introduction of the alkoxyethyl group through the interaction of the appropriate chloroethyl ether prepared from acetaldehyde, the alcohol and hydrogen chloride[4] and the sodio derivative of the mono-substituted malonic ester as illustrated by the reactions

$$CH_3CHO + ROH + HCl \longrightarrow CH_3CHClOR \xrightarrow{NaCR'(COOEt)_2} V$$

It was found necessary to carry out this reaction in the sequence shown, since all attempts to further alkylate a malonic ester containing an α-alkoxyethyl substituent yielded only polymeric products.

As may be seen from Table V in the experimental part, the yields in the conversion of the vinyl substituted malonic esters (IV) into the corresponding barbituric acids were quite low due, in considerable part, no doubt, to the cleavage of the malonic ester into the corresponding acetic ester and derivatives thereof.[5] In fact, in two cases (IV, R is ethyl, R′ is *n*-propyl and R is *n*-butyl, R′ is ethyl) it was not possible to isolate any of the barbituric acid VI even when the condensation was carried out in isopropyl alcohol.

(4) Henze and Murchison, This Journal, **53**, 4077 (1931).
(5) *Cf.* Cope and McElvain, *ibid.*, **54**, 4319 (1932).

In contrast to this behavior, the saturated esters V condensed with urea in ethyl alcohol solution to give good yields of the barbituric acids (VII). In the case of the barbituric acid in which R is *n*-propyl and R′ is methyl-*n*-propylcarbinyl a pair of racemates that had sufficiently different physical properties to allow them to be separated were formed (see Table VI). The corresponding compound in which R is ethyl failed to yield a similar pair of racemates.

Pharmacological Data

The barbituric acids that have been prepared in this work are being studied pharmacologically by Mr. E. E. Swanson of The Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Indiana, who has kindly furnished a preliminary report that is summarized in Table I. Corresponding data for amytal (Sodium Isoamyl Ethyl Barbiturate, Lilly) are included for comparison. The pharmacological values were determined intraperitoneally in white rats, and are expressed as minimum anesthetic dose (M.A.D.) and minimum lethal dose (M.L.D.) in mg. of barbiturate per kg. of animal weight. The "therapeutic index" is the ratio of these values. The pair of racemates in which R′ is the methyl-*n*-propylcarbinyl group are listed in Table I in the same order that they appear in Table VI.

Discussion of the Pharmacological Data

It may be seen from the M.A.D. column of Table I that the 5-(α-alkoxy-ethyl)-5-alkylbarbituric acids (no. 5–16) as a group are more effective anesthetics than the corresponding alkoxyvinyl compounds (no. 2–4). As a matter of fact quite a number of these alkoxyethyl substituted compounds appear to be more effective in producing anesthesia in white rats than is amytal (no. 1), although some of them cause very noticeable preanesthetic tremors or convulsions. Nos. 6 and 13 are particularly striking since each of them has a low anesthetic dose coupled with a sufficiently low toxicity (M.L.D.) to give them decidedly higher therapeutic indices than that shown by amytal. It should be noted also that the duration of the anesthesia produced in the white rat by both 6 and 13 are considerably less than that of amytal.

TABLE I

SUMMARY OF THE PHARMACOLOGICAL DATA

No.	R is	R′ is	M.A.D., mg./kg.	Duration of anesthesia, min.	M.L.D., mg./kg.	Therapeutic index, M.L.D./M.A.D
	5-(α-Alkoxyvinyl)-5-alkylbarbituric Acids $CH_2{=}C(OR)\overline{CR'CONHCONHCO}$					
1	Amytal		90	200	200	2.22
2	Ethyl	Ethyl	200	600	400	2.00
3	Ethyl	Allyl	100	300	210	2.10
4	Isoamyl	Ethyl	120	63	240	2.00
	5-(α-Alkoxyethyl)-5-alkylbarbituric Acids $CH_3CH(OR)\overline{CR'CONHCONHCO}$					
5	Ethyl	Ethyl	150[a]	460	400	2.67
6	Ethyl	*n*-Propyl	80	162	300	3.75
7	Ethyl	*n*-Butyl	150	120	300	2.00
8	Ethyl	Isoamyl	125	102	275	2.02
9	*n*-Propyl	Ethyl	80[b]	150	120	1.50
10	*n*-Butyl	Ethyl	60[b]	150	70	1.16
11	Isoamyl	Ethyl	80[b]	75	120	1.50
12	Ethyl	Allyl	100	300	160	1.60
13	Ethyl	Methyl-*n*-propylcarbinyl	60	108	160	2.67
14	*n*-Propyl	Allyl	50[a]	204	100	2.00
15	*n*-Propyl	Methyl-*n*-propylcarbinyl	300[a]	300	450	1.50
16	*n*-Propyl	Methyl-*n*-propylcarbinyl	120[a]	150	200	1.67

[a] Caused pre-anesthetic tremors. [b] Caused pre-anesthetic convulsions.

There is an interesting difference in the pharmacological behavior of the diastereoisomeric pair of racemates 15 and 16. Although they both have practically the same therapeutic indices, the lower melting (see Table VI) compound (no. 16) is over twice as effective as an anesthetic and twice as toxic as its higher melting isomer.

Experimental

Diethyl α-Ethoxyethylidenemalonate and Diethyl α-Ethoxyvinylmalonate.—One hundred and fifty grams (1.3 moles) of ketene acetal, 105 g. (0.65 mole) of diethyl malonate and 2.2 g. (0.03 mole) of sodium ethoxide were thoroughly mixed and heated by an oil-bath at 125–130° for twelve hours. The reaction mixture was then distilled rapidly. First, 95 g. (0.58 mole) of almost pure ethyl orthoacetate was collected. Following 5 g. of an intermediate fraction, 130 g. of material, b. p. 96–106° (0.4 mm.), $n^{25}D$ 1.4573, was collected. Upon cooling in an ice–salt mixture, this material became a thick slush, which then was poured onto a suction funnel surrounded by a freezing mixture. In this manner 83 g. of diethyl α-ethoxyethylidenemalonate, m. p. 25–27°, was obtained.

The filtrate (47 g.) from this cold filtration was carefully fractionated. After a small forerun, 16.4 g. (11%) of diethyl α-ethoxyvinylmalonate, b. p. 69–70° (0.03 mm.); $n^{25}D$ 1.4380; d^{25}_{25} 1.048; $M^{20}D$, calcd., 57.53; found, 57.62, was collected. This product contained 58.2% ethoxyl (calcd. 58.7%). Following an intermediate fraction, 16.7 g. of diethyl α-ethoxyethylidenemalonate, b. p. 84° (0.03 mm.); m. p. 26–27°; $n^{25}D$ 1.4634; d^{25}_{25} 1.068; $m^{20}D$ calcd., 57.53; found, 59.36, was collected. This exaltation of the molecular refraction would be expected in this structure. The total yield of diethyl α-ethoxyethylidenemalonate was 99.7 g., 66% of theoretical.

Anal. Calcd. for $C_{11}H_{18}O_5$: C, 57.4; H, 7.9; OC_2H_5, 58.7. Found: C, 57.6; H, 7.9; OC_2H_5, 58.6.

The diethyl α-ethoxyvinylmalonate was ethylated and the resulting diethyl ethyl-(α-ethoxyvinyl)-malonate condensed with urea according to the procedures given below. The resulting barbituric acid melted at 188–189° and was identical with the one produced in like manner from diethyl α-ethoxyethylidenemalonate.

The liquid ethoxyvinylmalonic ester could be converted into its solid isomer by the following procedure: 9 g. of diethyl α-ethoxyvinylmalonate was heated with 0.25 g. of sodium ethoxide at 125° for twenty hours. Fractionation of the reaction mixture gave none of the starting material in the pure state but did yield 5.34 g. (59%) of diethyl α-ethoxyethylidenemalonate, b. p. 79–83° (0.03 mm.); m. p. 25–26°; $n^{25}D$ 1.4621.

Ozonolysis of Diethyl α-Ethoxyvinylmalonate.—A solution of 4.7 g. of diethyl α-ethoxyvinylmalonate in 14 ml. of glacial acetic acid and 1 ml. of acetic anhydride was treated with ozonized oxygen until no more was taken up. The solution was then poured into a three-necked flask containing 15 ml. of water, 4 g. of zinc dust, and a few crystals each of hydroquinone and silver nitrate. The flask was equipped with a stirrer and a reflux condenser, the upper end of which was connected to a tube leading to the bottom of a test-tube containing 10 ml. of water. Nitrogen was passed into the flask while it was heated on the steam-bath so that any formaldehyde liberated would be carried over into the test-tube of water. After four hours, the water containing the formaldehyde was poured into a solution of dimethyl dihydroresorcinol in aqueous potassium carbonate and the resulting solution just acidified with acetic acid. The precipitate which was obtained weighed 8 mg., melted at 184–185° and gave no depression when mixed with an authentic specimen prepared from formaldehyde and dimethyldihydroresorcinol.

Similar treatment of the diethyl α-ethoxyethylidenemalonate gave no detectable amount of formaldehyde.

Diethyl α-Alkoxyvinyl-alkylmalonate and Diethyl α-Alkoxyvinyl-malonate Mixtures.—A series of diethyl α-alkoxyethylidenemalonates were prepared by mixing the appropriate dialkyl ketene acetal,[3] diethyl malonate, and sodium ethoxide in the same molecular ratio as given in the previous section and heating the mixture in an oil-bath at the temperature and for the length of time given in Table II. No attempt was made to separate the isomers in these cases, but the material collected over the boiling range indicated in Table II was ethylated without further purification.

Table II

Mixtures of the Isomeric Diethyl α-Alkoxyethylidenemalonates, $CH_3C(OR)=C(COOC_2H_5)_2$ and Diethyl α-Alkoxyvinyl-malonates, $CH_2=C(OR)CH(COOC_2H_5)_2$[a]

R is	Reaction temp., °C.	Reaction time, hr.	B. p., °C.	Mm.	Yield, %
Propyl	185	24	110–112	3	65
n-Butyl	165	3	135–140	2.5	42
n-Butyl	140	24	135–140	2.5	54
i-Amyl	130	24	120–130	0.05	81

[a] These esters were prepared by Mr. Bruce Stevenson, to whom the authors wish to acknowledge their indebtedness.

The α-alkoxyvinyl-alkylmalonic esters were prepared by the following general procedure. To a solution of 2.3 g. (0.1 atom) of sodium in about 15 times its weight of the solvent alcohol shown in Table III, 0.1 mole of the appropriate diethyl α-alkoxyethylidenemalonate was added. The alkyl bromide or iodide was then added to this alkaline solution and the mixture refluxed until it was neutral. After cooling, sufficient water was added to dissolve all of the salt, the oily layer separated and the aqueous layer extracted with ether. The combined ether extract and oily layer was washed with water, dried over anhydrous sodium carbonate and distilled. Since it was practically impossible to obtain analytically pure compounds when an alcohol other than ethyl was used as a solvent, fractions with the ranges of boiling points and refractive indices shown in Table III were used for the preparation of barbituric acids.

Diethyl α-Alkoxyethyl-alkylmalonates.—Diethyl α-ethoxyethyl-ethylmalonate was prepared by catalytic hydrogenation of the corresponding α-ethoxyvinylethylmalonic ester by the following procedure. A solution of 8 g. of the vinyl ester in 70 ml. of absolute ethyl alcohol together with 1 g. of Raney nickel was placed in a steel bomb and shaken with hydrogen at a pressure of 1850 pounds. The hydrogenation proceeded readily at 120°. Fractionation of the product gave 4.62 g. (53%) of diethyl α-ethoxyethyl-ethylmalonate, b. p. 73° (0.04 mm.); $n^{25}D$ 1.4279; d^{25}_{25} 1.000.

Anal. Calcd. for $C_{13}H_{24}O_5$: C_2H_5O, 51.9. Found: C_2H_5O, 51.9.

Diethyl α-ethoxyethyl-malonate was prepared from sodium malonic ester and α-chloro-ethyl ether in 28% yield as in the general procedure described below. It possessed the same properties as the product obtained from the catalytic hydrogenation of α-ethoxyethylidene-malonic ester.[2]

Attempts to ethylate diethyl α-ethoxyethyl-malonate produced only polymeric material. This may be due to a partial elimination of the ethoxyl group as ethyl alcohol and the polymerization of the resulting unsaturated ester. Support for this supposition comes from the fact that the highest ethoxyl analysis for diethyl α-ethoxyethylmalonate prepared by either of the above methods was 57.4% (calcd. 58.2%).

Diethyl α-ethoxyethyl-ethylmalonate was also prepared as follows. In a dry 1-liter 3-necked flask, equipped with an inlet tube, stirrer, and reflux condenser connected to a soda-lime drying tower, which in turn was connected to a gas trap, was placed 0.3 g. of hydrated ferric nitrate. The flask was cooled in a dry-ice–acetone bath and 300 ml. of liquid ammonia added. The stirrer was started, the cooling bath removed, and a small piece of sodium added. As soon as the initial blue color had disappeared, 12.7 g. (0.55 mole) of sodium in small pieces was added rapidly. As soon as all of the sodium had reacted as noted by the disappearance of the blue color, the cooling bath was replaced and 94 g. (0.5 mole) of diethyl ethylmalonate was added from a separatory funnel in a small stream. The reaction mixture was stirred for fifteen minutes with the cooling bath and for fifteen minutes without it. Then 50 ml. of dry ether and 300 ml. of dry benzene were added in a small stream. After the reaction mixture had reached

Table III

Diethyl α-Alkoxyvinyl-alkylmalonates, $CH_2=C(OR)CR'(COOC_2H_5)_2$

R is	R' is	Solvent alcohol	Yield, %	B. p. °C.	Mm.	$n^{25}D$
Ethyl	Ethyl	Ethyl	20	130–133	9	1.4382–1.4400
Ethyl	Ethyl	*t*-Butyl	60	87– 91	0.1	1.4390–1.4402
Ethyl	Allyl	*i*-Propyl	59	92– 96	0.1	1.4469–1.4480
Ethyl	*n*-Propyl	*i*-Propyl	72	97– 98	1.0	1.4370–1.4400
Ethyl	*n*-Propyl	Ethyl	25	81– 84	0.03	1.4322–1.4420
Ethyl	*n*-Butyl	*i*-Propyl	85	88– 91	0.04	1.4400–1.4437
Ethyl	*i*-Amyl	*i*-Propyl	79	84– 90	0.01	1.4412–1.4429
n-Propyl[a]	Ethyl	*i*-Propyl	39	121–130	2.3	1.4400–1.4478
n-Butyl[a]	Ethyl	*i*-Propyl	24	110–120	0.5	1.4380–1.4462
Isoamyl	Ethyl	*i*-Propyl	55	104–110	0.04	1.4400–1.4429

[a] The authors are indebted to Mr. Bruce Stevenson for the preparation of these esters.

TABLE IV

DIETHYL α-ALKOXYETHYL-ALKYLMALONATES, $CH_3CH(OR)CR'(COOC_2H_5)_2$

R is	R' is	Formula	Yield, %	B. p., °C.	Mm.	$n^{25}D$	d^{25}_{25}	$M^{25}D$ Calcd.	$M^{25}D$ Found	Analyses, % Calcd. C	Calcd. H	Found C	Found H
Ethyl	Ethyl	$C_{13}H_{24}O_5$	60	71–72	0.03	1.4282	1.0023	67.3	66.8	59.4	9.3	59.6	9.3
Ethyl	*n*-Propyl	$C_{14}H_{26}O_5$	66	81–82	.03	1.4291	0.9900	71.9	71.5	61.3	9.6	61.1	9.5
Ethyl	*n*-Butyl	$C_{15}H_{28}O_5$	68	85–86	.04	1.4317	.9779	76.5	76.2	62.5	9.8	62.4	9.8
Ethyl	*i*-Amyl	$C_{16}H_{30}O_5$	63	88–89	.03	1.4320	.9673	81.1	80.8	63.5	10.0	63.5	9.9
n-Propyl	Ethyl	$C_{14}H_{26}O_5$	62	77–78	.03	1.4290	.9905	71.8	71.5	61.3	9.6	61.2	9.5
n-Butyl	Ethyl	$C_{15}H_{28}O_5$	76	83–84	.03	1.4306	.9780	76.4	76.4	62.5	9.8	62.3	9.6
i-Amyl	Ethyl	$C_{16}H_{30}O_5$	71	89–90	.03	1.4320	.9699	81.1	81.9	63.5	10.0	63.7	9.9
Ethyl	Allyl	$C_{14}H_{24}O_5$	83	78–79	.04	1.4370	1.0030	71.4	71.1	61.6	8.9	61.7	8.6
Ethyl	Methyl-*n*-propyl carbinyl	$C_{16}H_{30}O_5$	84	83–84	.03	1.4369	0.9814	81.1	80.6	63.5	10.0	63.3	10.1
n-Propyl	Allyl	$C_{15}H_{26}O_5$	82	97–98	.18	1.4388	.9907	76.0	75.8	62.9	9.2	62.8	9.1
n-Propyl	Methyl-*n*-propyl carbinyl	$C_{17}H_{32}O_5$	69	101–102	.06	1.4380	.9726	85.0	85.2	64.5	10.2	64.6	10.2

room temperature, it was refluxed on the steam-bath until all of the ammonia was removed. This was facilitated by passing a slow stream of dry nitrogen into the flask. When all of the ammonia had been removed, the flask was cooled with cold water and 76 g. (0.7 mole) of α-chloroethyl ether added dropwise. After the addition of the chloroether, stirring was continued for about one hour at room temperature and for about ten minutes at the refluxing temperature of the benzene. The reaction mixture was then cooled and 300 ml. of water added. The benzene layer was separated and washed with two 100-ml. portions of water. The combined aqueous portions was extracted with ether. The benzene layer combined with the ether extract was washed with 50 ml. of 10% sodium carbonate, dried over anhydrous sodium carbonate, and finally distilled.

Other members of the series described in Table IV were prepared by the same procedure using the appropriate malonic ester and α-chloroethyl alkyl ether. All of the α-chloro-ethers were prepared by the procedure of Henze and Murchison.[4]

5-α-Alkoxyvinyl-5-alkylbarbituric Acids.—5-α-Ethoxyvinyl-5-ethylbarbituric acid was prepared as follows. To an alcoholic solution of sodium ethoxide, prepared from 4.6 g. (0.20 mole) of sodium and 75 ml. of absolute ethyl alcohol, was added 7.5 g. (0.125 mole) of urea and 17 g. (0.065 mole) of diethyl α-ethoxyvinylethylmalonate. After the mixture had refluxed for twelve hours, the alcohol was removed by distillation, and the residue dissolved in 80 ml. of ice-water. The aqueous solution then was extracted with ether. Evaporation of the ether left 6 g. of oil, the distillation of which gave 2 g. of material that was lower-boiling than the starting material and was probably the corresponding acetic ester $CH_3C(OC_2H_5)=C(C_2H_5)COOC_2H_5$; also, 4 g. of material with the boiling range of the starting ester was obtained. From this latter fraction was isolated 0.2 g. of a solid, m. p. 55–59°, which analyses indicated to be the amide $CH_3C(OC_2H_5)=C(C_2H_5)CONH_2$, corresponding to the above acetic ester.

Anal. Calcd. for $C_8H_{15}O_2N$: N, 8.98. Found: N, 8.92.

Crystallization from 50% ethyl alcohol of the precipitate produced by acidification of the aqueous alkaline solution yielded 3.8 g. (25% of theory) of 5-α-ethoxyvinyl-5-ethyl-barbituric acid. Properties of this compound and the others of this series that were prepared are listed in Table V. Other members of the series were prepared in a similar manner with certain variations. It was not possible to obtain any of either of the barbituric acids in which R and R' are, respectively, ethyl and *n*-propyl or *n*-butyl and ethyl. The time of reflux generally was between ten and twenty hours. Comparison of the yields, using ethyl, *i*-propyl, or *t*-butyl alcohol as the solvent, is shown in columns 3 and 4 of Table V. The ether extractable material from others of the series varied in amount but in no other case was an attempt made to fractionate this material or isolate a pure compound.

5-α-Alkoxyethyl-5-alkylbarbituric Acid.—5-α-Ethoxyethyl-5-ethylbarbituric acid was prepared as follows. To a solution of 3.5 g. (0.15 atom) of sodium in 50 ml. of absolute alcohol was added 6 g. (0.10 mole) of urea and 13 g.

TABLE V

5-(α-ALKOXYVINYL)-5-ALKYLBARBITURIC ACIDS $CH_2=C(OR)\overline{C(R')CONHCONHCO}$

R is	R' is	Formula	Solvent alcohol	Yield, %	M. p., °C.	Analyses, % Calcd. N	Calcd. C_2H_5O	Found N	Found C_2H_5O
Ethyl	Ethyl	$C_{10}H_{14}O_4N_2$	Ethyl	25	189 –190				
Ethyl	Ethyl	$C_{10}H_{14}O_4N_2$	*i*-Propyl	37	189 –190				
Ethyl	Ethyl	$C_{10}H_{14}O_4N_2$	*t*-Butyl	42	189.5–190	12.4	19.9	12.4	19.8
Ethyl	Allyl	$C_{11}H_{14}O_4N_2$	*i*-Propyl	40	158 –160	11.7	18.9	11.2	18.8
Ethyl	*n*-Butyl	$C_{12}H_{18}O_4N_2$	*i*-Propyl	7	169 –170	11.0	17.7	11.2	17.5
Ethyl	*i*-Amyl	$C_{13}H_{20}O_4N_2$	*i*-Propyl	8	165.5–166	10.5		10.4	
n-Propyl	Ethyl	$C_{11}H_{16}O_4N_2$	*i*-Propyl	4.5	177 –179	11.7		11.6	
i-Amyl	Ethyl	$C_{13}H_{20}O_4N_2$	*i*-Propyl	5.4	153 –154	10.5		10.5	

Table VI

5-(α-Alkoxyethyl)-5-alkylbarbituric Acids $CH_3CH(OR)C(R')CONHCONHCO$

R is	R′ is	Formula	Yield, %	M. p., °C.	Analyses, % Calcd. N	Calcd. C_2H_5O	Found N	Found C_2H_5O
Ethyl	Ethyl	$C_{10}H_{16}O_4N_2$	32.5	181 –181.5	12.3	19.8	12.2	19.8
Ethyl	*n*-Propyl	$C_{11}H_{18}O_4N_2$	42	168.5–169	11.5	18.6	11.4	18.4
Ethyl	*n*-Butyl	$C_{12}H_{20}O_4N_2$	43	138 –139	10.9	17.6	10.9	17.5
Ethyl	*i*-Amyl	$C_{13}H_{22}O_4N_2$	44	136 –137	10.4	16.7	10.2	16.6
n-Propyl	Ethyl	$C_{11}H_{18}O_4N_2$	57	177.5–178	11.6		11.5	
n-Butyl	Ethyl	$C_{12}H_{20}O_4N_2$	58	132.5–133	10.9		10.8	
i-Amyl	Ethyl	$C_{13}H_{22}O_4N_2$	70	129.2–130	10.4		10.4	
Ethyl	Allyl	$C_{11}H_{16}O_4N_2$	57	127 –128	11.7	18.7	11.7	18.8
Ethyl	Methyl-*n*-propylcarbinyl	$C_{13}H_{22}O_4N_2$	64	159 –163[a]	10.4	16.7	10.3	16.6
n-Propyl	Allyl	$C_{12}H_{18}O_4N_2$	66	160 –160.5	11.0		11.0	
n-Propyl	Methyl-*n*-propylcarbinyl	$C_{14}H_{24}O_4N_2$	75	210.5–212	9.8		9.5	
n-Propyl	Methyl-*n*-propylcarbinyl	$C_{14}H_{24}O_4N_2$		153.5–154.5	9.8		9.6	

[a] After 3 recrystallizations from 50% alcohol the melting point of this product was 169–169.5°.

(0.05 mole) of diethyl α-ethoxyethylethylmalonate. After the mixture had refluxed eighteen hours, the alcohol was removed by distillation. About 100 ml. of ice-water was added to the residue. The resulting solution was extracted with 75 ml. of ether in three portions. Evaporation of the ether left 0.3 g. of oil, which slowly crystallized upon standing. This material was not characterized. The crude barbituric acid was precipitated by acidification of the aqueous alkaline solution with an excess of concentrated hydrochloric acid. Recrystallization from 35% ethyl alcohol gave 3.7 g. (32.5%) of 5-α-ethoxyethyl-5-ethyl barbituric acid.

Others of the series were prepared by the same procedure. In no case was the amount of material from the ether extract more than 0.5 g. In all cases except the two containing the methyl-*n*-propyl-carbinyl substituent one crystallization of the barbituric acid from 30–50% ethyl alcohol was sufficient to give each of the 5-α-alkoxyethyl-5-alkyl barbituric acids shown in Table VI in a pure state. The mixture of the pair of racemates that contained the methyl-*n*-propyl-carbinyl substituent was obtained in 75% yield, but after their separation into the products that melted as shown in Table VI the yield of each of these products amounted only to about 15%.

Summary

A number of ketene dialkylacetals have been condensed with malonic ester and the resulting mixture of (α-alkoxyethylidene)- and (α-alkoxyvinyl)-malonic esters have been alkylated to the (α-alkoxyvinyl)-alkylmalonic esters. These esters have been condensed with urea to produce the corresponding barbituric acids.

A number of related (α-alkoxyethyl)-alkylmalonic esters also have been prepared by the condensation of the appropriate chloroethers with alkylmalonic esters. The (α-ethoxyethyl)-ethylmalonic ester was also prepared from the (α-ethoxyvinyl)-alkylmalonic ester by catalytic hydrogenation. These malonic esters have been converted into barbituric acids.

A brief summary and a discussion of the pharmacological properties of these barbituric acids are given.

The reaction product from the condensation of ketene diethylacetal with malonic ester has been separated into the isomeric (α-ethoxyethylidene)-malonic ester and (α-ethoxyvinyl)-malonic ester, the structures of which have been proved by ozonolysis.

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