The methyl ester of this substance was made with diazomethane in ether and crystallized from ethanol, m. p. 106–107°.

Anal. Calcd. for $C_{17}H_{20}O_3$: C, 74.97; H, 7.40. Found: C, 74.92; H, 7.43.

The semicarbazone of the acid made by the pyridine–ethanol method, was crystallized from pyridine, m. p. 270–272° (dec.).

Anal. Calcd. for $C_{17}H_{21}N_3O_3$: C, 64.74; H, 6.71. Found: C, 64.64; H, 6.88.

1-Methyl-1,2,3,4,5,6,7,8-octahydroanthracene-2-carboxylic Acid.—The preceding acid (0.5 g.) was hydrogenated at 3 atmospheres in the presence of 0.5 g. of 10% palladium-on-Darco G-60, 1 ml. 60% perchloric acid and 40 ml. acetic acid for two hours. The catalyst was filtered, the solution was shaken with ether and water; the ether was washed free of acetic acid, dried and distilled. The product was crystallized from ethyl acetate, m. p. 218–220°.

Anal. Calcd. for $C_{16}H_{20}O_2$: C, 78.65; H, 8.25. Found: C, 78.72; H, 8.35.

The methyl ester of this substance, made with diazomethane was crystallized from pentane, in which it is very soluble, by cooling in a Dry Ice–acetone-bath. The product had m. p. 42–43°.

Anal. Calcd. for $C_{17}H_{22}O_2$: C, 79.03; H, 8.59. Found: C, 79.10; H, 8.68.

1-Methylanthracene.—The preceding acid (120 mg.) was heated at 300° with 300 mg. of palladium-on-charcoal 5% for 1.5 hours and then at 350° for 3 minutes. The product was dissolved in ether and filtered. The ether solution was washed with 5% sodium carbonate, dried and evaporated; the residue was sublimed in a high vacuum. Material subliming up to 80° was converted to the picrate and this was crystallized from ethanol, m. p. 113–115°. The hydrocarbon was obtained by passing a solution of the picrate in benzene through a column of alumina. Crystallized from pentane it melted at 77°.[10]

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(10) Reported for 1-methylanthracene, m. p. 85–86°, picrate m. p. 113–115°; Fischer and Sapper, *J. prakt. Chem.*, [2] **83**, 203 (1911).

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Barbiturates Containing the 3-Methyl-2-butenyl Group

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Because, as was stated[2] a number of years ago "the replacement of an alkyl group in 5,5-dialkylbarbituric acids by an allyl group frequently leads to an increase in effectiveness, together with a lower degree of increase in toxicity," it was of interest to determine if this therapeutic advantage was retained when the replacement was by a γ,γ-dimethylallyl group, derived from the now readily available isoprene. The present paper describes the preparation of a short series of such substances (I–VII) which are listed in Table I.

(1) National Dairy Research Laboratories Inc., Oakdale, L. I., N. Y.

(2) Volwiler, THIS JOURNAL, **47**, 2236 (1925).

It was shown by Staudinger[3] that hydrogen bromide undergoes 1,4-addition to isoprene and the structure of the resultant 3-methyl-2-butenyl bromide was proved. He also used this isoprenyl bromide to alkylate malonic ester and the thus-produced 3-methyl-2-butenylmalonic ester (VIII) was alkylated[4] with the alkyl halides suitable to give isopropyl isoprenyl malonic ester (IX) and allyl isoprenyl malonic ester (X), the latter of which was also prepared by alkylation of allyl malonic ester with isoprenyl bromide. In the present work all of these reactions were repeated and the malonic esters IX and X were condensed with urea in the Fischer–Dilthey[5] synthesis of the barbituric acids I and IV; I was also prepared by alkylation of isopropylbarbituric acid with isoprenyl bromide. Positive proof of the skeletal structure of isoprenyl malonic ester (VIII) was obtained by its condensation with urea to yield isoprenylbarbituric acid (VII) and catalytic hydrogenation of the latter to the known[2] 5-isoamylbarbituric acid. Ethyl isoprenylmalonic ester (XI), prepared from isoprenyl bromide and ethyl malonic ester, was condensed with urea to produce ethyl isoprenyl barbituric acid (V), and isopropyl isoprenyl thiobarbituric acid (VI) was obtained by the condensation of the malonic ester IX with thiourea. The two N-alkylated derivatives II and III were prepared, in the former case, by N-allylation of the barbituric acid I, and, in the latter case, by the condensation of the malonic ester IX with methylurea.

In general these substances, with the exception of II, have a rather excitatory effect on experimental animals. The oral tolerated dose of I is 100 mg./kg. mouse and the LD_{50} is approximately 200 mg./kg., with death due to convulsions. For III the tolerated dose by subcutaneous injection is around 50 mg./kg. mouse and the LD_{50} is 70 mg./kg.; by intravenous administration the LD_{50} is 12–15 mg./kg. mouse and 5–10 mg./kg. rabbit, with death due to convulsions. IV and V likewise produced spastic convulsions on injection. This reversal of the actions usually found in and associated with the ordinary barbiturates is in agreement with the recent report by Taylor and Noble[6] who described some pharmacological properties of the sodium salt of V.

We are indebted to Dr. N. Ercoli, of this Institute, for the pharmacological results herein presented and to Dr. H. M. Wuest for his suggestions concerning the problem.

Experimental

5-(3-Methyl-2-butenyl)-barbituric Acid, VII.—The following is a procedure representative of the preparation of substances I, III, IV, V, VI and VII. A mixture of

(3) Staudinger, Kreis and Schilt, *Helv. Chim. Acta*, **5**, 743 (1922).

(4) Staudinger, Muntwyler, Ruzicka and Seibt, *ibid.*, **7**, 390 (1924).

(5) Fischer and Dilthey, *Ann.*, **335**, 334 (1904).

(6) Taylor and Noble, *Nature*, **163**, 447 (1949).

TABLE I

BARBITURIC ACIDS[a] $(CH_3)_2C{=}CHCH_2$ substituted at R and R¹, X = O or S

	R	R¹	X	Yield, %	M. p., °C.	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
I	$(CH_3)_2CH$—	H—	O	67	127–128[b,c]	60.50	60.44	7.61	7.23	11.76	11.86
II	$(CH_3)_2CH$—	$CH_2{=}CHCH_2$—	O	47	78–79[c]	64.72	64.84	7.97	7.81	10.07	10.26
III	$(CH_3)_2CH$—	CH_3—	O	31	87–88[d]	61.88	62.02	7.99	7.92	11.10	10.89
IV	$CH_2{=}CHCH_2$—	H—	O	71	104–105[d]	61.04	61.02	6.83	6.88	11.86	11.99
V	C_2H_5—	H—	O	50	155–156[e]	58.92	59.15	7.19	7.07	12.49	12.33
VI	$(CH_3)_2CH$—	H—	S	26	134–135[e]	56.66	56.57	7.13	7.03	11.02	11.43
VII	H—	H—	O	45	186–188[e]	55.10	54.81	6.12	6.10	14.28	14.22

[a] Although some of the pharmacology of 5-ethyl-5-(3-methyl-2-butenyl)-barbituric acid was reported as early as 1945 (Noble, Associate Committee on Drug Medical Research, 7th Meeting, National Research Council, Ottawa, April, 1945; *cf.* Ballem, Noble and Webster, *Can. Med. Assoc. J.*, **58**, 447 (1948)), there appears to be no description of these dimethylallyl barbiturates in the chemical literature. [b] Potentiometric titration of this acid in 50% alcohol indicated, at half-neutralization, that the pK_a was 9.1. [c] Recrystallized from aqueous alcohol. [d] Recrystallized from aqueous ethylene glycol. [e] Recrystallized from methanol.

isoprenyl malonic ester (11.4 g., 0.05 mole), urea (4.5 g., 0.075 mole; or an appropriate amount of thiourea or methylurea) and sodium ethoxide (3.45 g., 0.15 mole, of sodium in 70 cc. of absolute alcohol; in the case of I, IV and V dry sodium ethoxide was used) was heated for eight hours on the steam-bath in a pressure bottle. The precipitated sodium salt was removed by filtration and dissolved in water, or in case no solvent had been used water was added to the entire reaction mixture, and the crude barbituric acid was precipitated by carbon dioxide.

Isoamylbarbituric Acid.—A solution of 2.0 g. of 5-(3-methyl-2-butenyl)-barbituric acid in 45 cc. of absolute ethanol was hydrogenated over 0.1 g. of Adams catalyst for two hours at 48 p.s.i. Considerable material separated from the solution during the reduction. Additional alcohol (100 cc.) was added to take all the separated solid into solution, the catalyst was removed by filtration and the filtrate was chilled to give 5-isoamylbarbituric acid which, after recrystallization, did not depress the m. p. of an authentic sample[2] of the material, m. p. 238–240°, prepared by alkylation of barbituric acid with isoamyl bromide.

Ethyl 3-Methyl-2-butenylmalonic Ester XI.—To a stirred and cooled (2 to 10°) mixture of ethyl malonic ester (62 g., 0.33 mole, Eastman Kodak Co. redistilled, b. p. 95–97° (12 mm.)), isoprenyl bromide (50 g., 0.33 mole) and alcohol (20 cc.) there was slowly added a solution of sodium (7.6 g., 0.33 mole) in alcohol (150 cc.). After thirty minutes refluxing the no-longer basic mixture was worked up in the usual manner to give 53 g. (62% yield) of product, b. p. 131–138° (10 mm.); $n^{25}D$ 1.4450.

Anal. Calcd. for $C_{14}H_{24}O_4$: C, 65.62; H, 9.37. Found: C, 65.18; H, 9.40.

5-Isopropyl-5-(3-methyl-2-butenyl)-barbituric Acid, I.—The following is the alternative preparation of this substance. To a cooled (−5°) and stirred mixture of 5-isopropylbarbituric acid[2] (8.5 g., 0.050 mole) and sodium ethoxide (1.15 g. (0.050 mole) of sodium in 20 cc. of alcohol) there was added during one hour a solution of isoprenyl bromide (7.5 g., 0.050 mole) in alcohol (10 cc.). After 30 minutes additional stirring at −5° the mixture was allowed to warm to room temperature and worked up in the usual manner to give 3.3 g. (27% yield) of pure product, m. p. 128–129°. A portion of the isoprenyl bromide was consumed in a side-reaction, and when the isoprenyl bromide was added all at once and the condensation was carried out at room temperature this side-reaction became predominant. After the reaction was carried out at room temperature the mixture was poured into water and the aqueous mixture was extracted with ether. The extract was washed with 10% sodium hydroxide and then with water until the washings were neutral. After the extract was dried the solvent was removed and the residue was distilled to give 2–3 g., which after redistillation boiled at 102° (750 mm.).

Anal. Calcd. for $C_5H_{10}O$: C, 69.76; H, 11.62. Found: C, 68.87; H, 11.97.

The material is possibly dimethylvinylcarbinol, the b. p. of which is reported[7] to be 98–99° and which has been obtained[8] by treatment of 3-methyl-3-butenyl chloride or bromide with aqueous alkali or even with water. The isomeric 3-methyl-2-butenol-1 is reported[9] to boil at 140°.

1-Allyl-5-isopropyl-5-(3-methyl-2-butenyl)-barbituric Acid, II.—A mixture of 5-isopropyl-5-isoprenylbarbituric acid (11.9 g., 0.050 mole), allyl bromide (6.2 g., 0.050 mole) and cupric sulfate pentahydrate (1.25 g., 0.005 mole) in 25 cc. of 2 *N* sodium hydroxide was refluxed seven hours and then allowed to stand overnight, during which time the crude crystalline product precipitated.

(7) Gadziatzki, *Jahresber.*, 700 (1887).

(8) Claisen, *J. prakt. Chem.*, [2] **105**, 78 (1908).

(9) Courtot, *Bull. soc. chim.*, [3] **35**, 660 (1906); *cf.* also Ultee, *Rec. trav. chim.*, **68**, 483 (1949).

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A Novel Sulfidation Reaction and Its Application to Some Indoles and Pyrroles

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In a recent paper[2] we disclosed a novel reaction whereby 4-substituted-2-aminothiazoles are directly converted to their corresponding bis-(5-thiazolyl) sulfides by making alkaline a solution of the aminothiazole, thiourea and a halogen.

On extending this reaction to other heterocyclic compounds we have found that with certain indoles and pyrroles the corresponding disulfides may be obtained.

In general the procedure was to add to a water–alcohol solution of the compound under investigation, thiourea in amount equivalent to two moles of thiourea per mole of compound, and iodine equivalent to one mole per mole of compound. The solution was then made very alkaline with

(1) Ethyl Corporation Fellow, 1948.

(2) Woodbridge and Dougherty, THIS JOURNAL, **71**, 1744 (1949).