Anal. Calcd. for $C_9H_8O_4$: C, 60.00: H, 4.74; CH_3O, 17.22. Found: C, 59.99; H, 4.70; CH_3O, 17.25.

5-Carboxyvanillic Acid (X). From 5-Carboxyvanillin.—Silver oxide (0.017 mole, freshly prepd. from 5.8 g. of silver nitrate) was covered with 50 cc. of water and treated with 5.1 g. (0.128 mole) of C.P. sodium hydroxide. This mixture at 47° was treated with 3.3 g. (0.017 mole) of 5-carboxyvanillin and heated to 65°, at which point a reaction took place. The source of heat was removed and the temperature rose to 73°. The reaction mixture was cooled and filtered, and the silver precipitate was washed with water. The filtrate was acidified with dilute sulfuric acid and cooled. The white fluffy precipitate was filtered, washed with water, and dried to yield 3.3 g. (94.3%) of 5-carboxyvanillic acid melting at 282°; this did not depress the melting points with a sample of 5-carboxyvanillic acid isolated in the nitrobenzene oxidations described above or with that isolated from metallic oxide oxidations of lignin materials.[4-6]

Anal. Calcd. for $C_9H_8O_6$: C, 50.93; H, 3.80; CH_3O, 14.63. Found: C, 50.88; H, 3.80; CH_3O, 14.60.

Under certain conditions of crystallization from water a dihydrate of 5-carboxyvanillic acid is obtained. This product is obtained as fluffy white needles with the same melting point and ultraviolet absorption spectrum as the anhydrous product. However, during the melting point determination, dehydration is observed at temperatures above 110°.

Anal. Calcd. for $C_9H_8O_6 \cdot 2H_2O$: C, 43.56; H, 4.87; CH_3O, 12.50. Found: C, 43.75; H, 4.77; CH_3O, 12.54.

Drying of this compound at 105° yielded the theoretical amount of moisture.

From 5-Formylvanillic Acid.—Silver oxide was prepared, covered with water, and treated with sodium hydroxide exactly as above. This mixture at 40° was treated with 5-formylvanillic acid in the same manner; a reaction took place raising the temperature to 52°. The reaction mixture was treated as above to yield 100% of 5-carboxyvanillic acid melting at 283–284° and not depressing a mixed melting point with authentic 5-carboxyvanillic acid.

From 5-Formylvanillin.—Similar oxidation of 5-formylvanillin with twice as much silver oxide but with the same amount of alkali resulted in the formation of 5-carboxyvanillic acid as the main product, together with some bisulfite-soluble 5-carboxyvanillin and a little resinous material which was not characterized.

Acknowledgment.—The authors wish to thank Mr. Donald McDonnell for the analyses and spectra reported in this paper.

APPLETON, WISCONSIN

[CONTRIBUTION FROM THE LILLY RESEARCH LABORATORIES]

The Synthesis of 5-Carbethoxyuracils

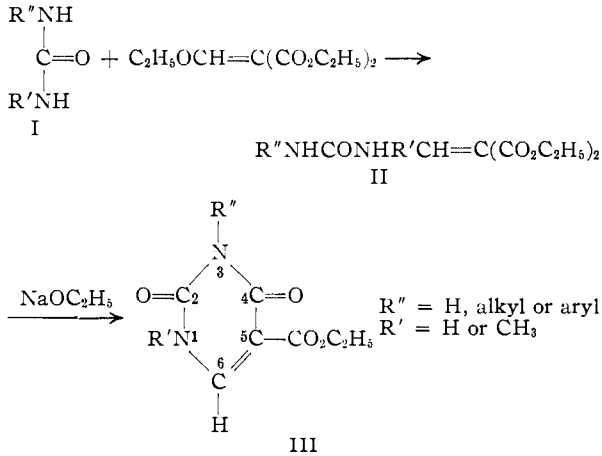
BY CALVERT W. WHITEHEAD

RECEIVED FEBRUARY 15, 1952

Diethyl ethoxymethylenemalonate undergoes condensation with urea and N-substituted ureas. The condensation has been carried out by heating the ethoxymethylenemalonate with N,N′-dimethylurea to obtain directly 1,3-dimethyl-5-carbethoxyuracil; with N-methylurea to obtain 3-methyl-5-carbethoxyuracil and with higher N-alkylureas to obtain alkylureidomethylenemalonates which were converted to the 3-alkyl-5-carbethoxyuracil in the presence of a basic catalyst. The condensation was also carried out with urea and a number of N-alkyl- and N-arylureas with diethyl ethoxymethylenemalonate in alcoholic solution in the presence of a base catalyst to obtain directly the 5-carbethoxyuracil in good yield. These uracils containing a functional ester group made possible the convenient preparation of a number of new heterocyclic acids and amides some of which have shown diuretic activity in animals.

The facility with which diethyl ethoxymethylenemalonate, $C_2H_5OCH{=}C(CO_2C_2H_5)_2$ condenses with basic nitrogen compounds has been demonstrated in reactions with ammonia,[1] amines,[2] acetamidine[3] and ethylisothiourea.[4] The product from the latter reaction was 2-ethylmercapto-5-carbethoxy-6-oxypyrimidine. Wheeler[4] reported that urea showed no sign of reacting with diethyl ethoxymethylenemalonate at 140° and a condensation was not effected on standing in alkaline solutions. Other attempts to condense diethyl ethoxymethylenemalonate with urea or substituted ureas are not found in the literature. An investigation has been made into the condensation of diethyl ethoxymethylenemalonate with urea and N-substituted ureas as a method of synthesizing N-substituted-5-carbethoxyuracils and also as a study of the reactions of diethyl ethoxymethylenemalonate with weakly basic nitrogen compounds.

The condensations proceeded according to the general equation



When diethyl ethoxymethylenemalonate was heated with an equimolar quantity of an N-*mono*-alkylurea at 120°, ethanol was eliminated and the corresponding diethyl alkylureidomethylenemalonate (II) was formed. In the case of the methylureidomethylenemalonate (II, R′ = H, R″ = CH_3), further heating at 150° gave the uracil (III). The higher alkyl homologs did not cyclize when they were heated at 150° and diethyl *n*-propylureido-

(1) L. Claisen, *Ann.*, **297**, 77 (1897).

(2) C. C. Price and R. M. Roberts, THIS JOURNAL, **68**, 1204 (1946).

(3) T. A. Geissman, M. J. Schlatter, I. D. Webb and J. D. Roberts, *J. Org. Chem.*, **11**, 741 (1946).

(4) H. J. Wheeler, T. B. Johnson and C. O. Johns, *Am. Chem. J.*, **37**, 392 (1907).

methylenemalonate actually was distilled under reduced pressure without change. N,N'-Dimethylurea reacted with diethyl ethoxymethylenemalonate at 120° to give the uracil, III (R' = R'' = CH_3) directly, the intermediate ureide, II, not being obtained.

Treatment of the ureides, II, with sodium ethylate in absolute ethanol brought about cyclization to form the uracils, III. A more convenient method was to allow the N-substituted ureas, I, (R' = H, R'' = alkyl or aryl groups), to react with diethyl ethoxymethylenemalonate in ethanol in the presence of one equivalent of sodium ethylate to form the uracils, III, directly and in high yields. Urea itself gave diethyl ureidomethylenemalonate which could be cyclized to the uracil, III, (R' = R'' = H) when refluxed in ethanol in the presence of sodium ethylate.

In the condensation of monosubstituted ureas with diethyl ethoxymethylenemalonate two theoretically possible ureides, II, could be formed. However, only one homogeneous substance was obtained upon cyclization to the uracil, III. The product from methylurea was saponified and decarboxylated to obtain 3-methyluracil melting at 174–175°[5] and not 1-methyluracil which melts at 232°.[6] Also, the product from phenylurea was hydrolyzed to 3-phenyl-5-carboxyuracil, m.p. 240°[7] and decarboxylated to 3-phenyluracil, m.p. 244–246°.[7] This shows the condensation to occur exclusively between the unsubstituted nitrogen of the urea and the ethoxymethylene group of the ester.

The 5-carbethoxyuracils prepared by the methods described are listed in Table I with the over-all yields and the method of preparation indicated.

Amides (Table II) having various degrees of water solubility, were prepared from the esters in the usual manner by heating with the desired amine. Also, the esters were readily saponified to the acids (Table III). Alkylation of a number of the 3-substituted-5-carbethoxyuracils was carried out, using dimethyl or diethyl sulfate (Table I, method C).

The diuretic activity of some of these compounds was determined in catheterized female dogs anesthetized with a barbiturate. Doses of 0.5 g. or 1.0 g. of the uracil were given orally, or doses of 2.5 mg./kg. to 10 mg./kg. were given intravenously. The flow of urine was noted over a four-hour period. The results were compared with those obtained on the same animal when given intravenous doses of a commercially available mercurial diuretic in a dose equivalent to 0.75 to 3.0 mg. of mercury per kg. of body weight. Results of the testing are included in Tables II and III. The pharmacological evaluations were made by K. K. Chen and E. B. Robbins both of this Laboratory.

Acknowledgment.—The author is grateful to W. L. Brown, H. L. Hunter and W. J. Schenck for the microanalyses reported here.

Experimental

Diethyl Ureidomethylenemalonate.—Urea (6.0 g. or 0.1 mole) was added to 150 ml. of ethanol containing sodium ethylate previously prepared from 2.3 g. of sodium. Diethyl ethoxymethylenemalonate (21.6 g. or 0.1 mole) was added and the solution allowed to stand at room temperature in a stoppered flask. After seven days the alcohol was removed under reduced pressure and the residue dissolved in 50 ml. of cold water. The solution was made slightly acid by addition of dilute hydrochloric acid. The solid was filtered off and dried. Recrystallization from alcohol yielded product melting at 197–200°. Repeated recrystallization from alcohol produced 6 g. (21.8%) of product melting at 207–209°.[4]

Anal. Calcd. for $C_9H_{14}N_2O_5$: C, 47.00; H, 6.13; N, 12.30. Found: C, 47.16; H, 6.63; N, 12.58.

5-Carbethoxyuracil.—Diethyl ureidomethylenemalonate (23 g. or 0.1 mole) was dissolved in 200 ml. of absolute alcohol containing 0.1 mole of sodium ethylate, prepared from 2.3 g. of sodium metal. The solution was allowed to stand for 12 hours then heated under reflux for five hours. The alcohol was removed by reduced pressure distillation. Ice-water (50 ml.) was added to dissolve the residue. The product was precipitated by adding cold dilute hydrochloric acid. The solid was filtered off and recrystallized from ethyl alcohol, m.p. 232°, yield 13 g. or 72%.

Anal. Calcd. for $C_7H_8N_2O_4$: C, 45.70; H, 4.35. Found: C, 45.46; H, 4.82.

1,3-Dimethyl-5-carbethoxyuracil.—*sym*-Dimethylurea (44 g. or 0.5 mole) and diethyl ethoxymethylenemalonate (108 g. or 0.5 mole) were mixed in a long-necked flask and heated in an oil-bath at 120° for 24 hours. Upon cooling the mass solidified and was dissolved in hot ethyl acetate. Charcoal was added and the solution filtered. The product was allowed to crystallize, yield 66 g. (62%), m.p. 112°. An analytical sample was prepared by recrystallizing several times from ethyl alcohol, m.p. 112°.

Anal. Calcd. for $C_9H_{12}N_2O_4$: C, 51.20; H, 5.72; N, 13.21. Found: C, 51.02; H, 5.88; N, 12.92.

3-Methyl-5-carboxyuracil.—N-Methylurea (14.8 g. or 0.2 mole) and diethyl ethoxymethylenemalonate (43.2 g. or 0.2 mole) were mixed and heated at 120° for 24 hours. The evolution of alcohol had ceased after this time and the diethyl methylureidomethylenemalonate could not be induced to crystallize. This material was then heated at 150° and the evolution of ethanol continued until the mass solidified. Recrystallization from alcohol yielded 16 g. (41%) of 3-methyl-5-carbethoxyuracil, m.p. 221°.

3-Methyl-5-carbethoxyuracil (10 g.) was added to 50 ml. of 10% sodium hydroxide solution. The solution was warmed on the steam-bath for two hours. The solution was acidified with dilute hydrochloric acid and allowed to cool. The free acid crystallized out and was collected on the filtering funnel and dried, yield 8.5 g. (98%). Crystallization from alcohol gave a product melting at 242°.

Anal. Calcd. for $C_6H_6N_2O_4$: N, 16.47. Found: N, 16.38.

3-Methyluracil.—3-Methyl-5-carboxyuracil (2 g.) was heated in a test-tube placed in a Woods metal bath at 255°. After ten minutes the evolution of carbon dioxide ceased. The test-tube was removed from the bath and its contents dissolved in alcohol. The solution was clarified with charcoal, filtered and allowed to cool. 3-Methyluracil,[5] m.p. 174–175°, was obtained in 90% yield.

Diethyl *n*-Propylureidomethylenemalonate.—N-Propylurea (10.2 g. or 0.1 mole) and diethyl ethoxymethylenemalonate (21.6 g. or 0.1 mole) were mixed and heated in an open flask in an oil-bath at 110° for 12 hours. The resulting oil could not be induced to crystallize and was distilled through a small claisen distilling head, b.p. 165–170° (1 mm.), yield 50%.

Anal. Calcd. for $C_{12}H_{26}N_2O_5$: C, 52.95; H, 7.36; N, 10.29. Found: C, 53.26; H, 7.64; N, 9.88.

3-*n*-Propyl-5-carbomethoxyuracil.—Diethyl *n*-propylureidomethylenemalonate (14.5 g. or 0.05 mole) was dissolved in 50 ml. of methanol. Sodium methylate (2.88 g. or 0.055 mole) was added and the solution allowed to stand 48 hours. It was then heated at 80° for six hours, cooled and poured onto 100 g. of ice. The ice mixture was acidified with dilute hydrochloric acid. The product crystallized immediately and was separated by filtration. It was recrystallized from ethyl alcohol, m.p. 205°, yield 6 g. (56.5%).

Anal. Calcd. for $C_9H_{12}N_2O_4$: C, 51.20; H, 5.72; N, 13.21. Found: C, 51.55; H, 6.08; N, 13.25.

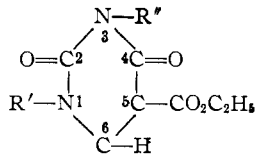
(5) T. B. Johnson and F. W. Heyl, *Am. Chem. J.*, **37**, 628 (1907).

(6) H. J. Wheeler and T. B. Johnson, *ibid.*, **42**, 35 (1909).

(7) L. R. Burger and T. B. Johnson, THIS JOURNAL, **56**, 2754 (1934).

TABLE I

5-CARBETHOXYURACILS



R	R″	Yield, %	M.p., °C.	Empirical formula	Method	Analyses, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
H	C_2H_5	82	219	$C_9H_{12}N_2O_4$	B	51.20	5.72		51.32	6.26	
H	$HOCH_2CH_2$	79	175–176	$C_9H_{12}N_2O_5$	B			12.23			12.30
H	$CH_2=CHCH_2$	80	174	$C_{10}H_{12}N_2O_4$	B			12.46			12.56
CH_3	C_2H_5	76	116	$C_{10}H_{14}N_2O_4$	C			12.38			12.59
CH_3	$(CH_3)_2CH$	78	98	$C_{11}H_{16}N_2O_4$	C			11.64			11.37
H	n-C_4H_9	53	152	$C_{11}H_{16}N_2O_4$	A			11.64			11.57
CH_3	n-C_4H_9	<50	60	$C_{11}H_{16}N_2O_4$[a]	C			11.64			11.91
H	$(CH_3)_2CHCH_2$	62	167	$C_{11}H_{16}N_2O_4$	B	55.00	6.72	11.64	54.69	6.69	11.73
H	$CH_3CH_2CH(CH_2OH)$	82	161	$C_{11}H_{16}N_2O_5$	B	51.45	6.32		51.21	6.52	
CH_3	$(CH_3)_2CHCH_2$	72	119	$C_{12}H_{18}N_2O_4$	C			11.00			10.70
H	Cyclohexyl	49	282	$C_{12}H_{16}N_2O_4$[a]	B	57.12	6.38	11.10	57.19	6.41	11.34
H	p-Cl-C_6H_4-	88	263	$C_{13}H_{11}ClN_2O_4$	B	52.95	3.77		52.60	3.75	
H	n-C_6H_{13}	50	140	$C_{13}H_{20}N_2O_4$	A			10.42			10.64
C_2H_5	$(CH_3)_2CHCH_2$	65	90–90.5	$C_{13}H_{20}N_2O_4$	C			10.42			10.29
CH_3	p-Cl-C_6H_4-		141	$C_{14}H_{13}ClN_2O_4$	C	54.55	4.25	9.07	54.53	4.82	9.05
H	p-CH_3O-C_6H_4-	90	185–194	$C_{14}H_{14}N_2O_5$	B	58.00	4.87		58.00	5.12	
H	p-CH_3-C_6H_4-	97	235	$C_{14}H_{14}N_2O_4$	B	61.40	5.16		61.33	5.21	
H	C_6H_5-CH_2-	90	215	$C_{14}H_{14}N_2O_4$	B	61.40	5.16		61.27	5.67	
H	n-C_7H_{15}	49	133	$C_{14}H_{22}N_2O_4$	B			9.94			10.31
CH_3	C_6H_5-CH_2-	76	79	$C_{15}H_{16}N_2O_4$	C			9.73			9.66
H	$C_6H_5-CH(CH_3)$	77	130	$C_{15}H_{16}N_2O_4$	B	62.65	5.60		62.57	5.74	
H	C_6H_5-$(CH_2)_2$-	84	228	$C_{15}H_{16}N_2O_4$	B			9.73			9.67
H	n-C_8H_{17}-	48	130	$C_{15}H_{24}N_2O_4$	B			9.45			9.94

[a] The methyl ester was obtained when cyclized in methanol.

Condensation of Diethyl Ethoxymethylenemalonate with Higher N-Alkylureas at Elevated Temperatures, Method A.—N-Alkylureas were heated with diethyl ethoxymethylenemalonate at 120° to obtain substituted ureidomethylenemalonates. These were cyclized without further purification to obtain the desired uracils. The following preparation of 3-*n*-amyl-5-carbethoxyuracil is typical of the procedure used. Other uracils similarly obtained are listed in Table I.

3-*n*-Amyl-5-carbethoxyuracil.—*n*-Amylurea (13.0 g. or 0.1 mole) and diethyl ethoxymethylenemalonate (21.6 g. or 0.1 mole) were mixed and heated at 120°. Evolution of ethyl alcohol began immediately. The heating was continued for 24 hours. The resulting sirup was added to 200 ml. of absolute ethanol containing sodium ethylate prepared from 2.3 g. of sodium. The solution was allowed to stand at room temperature for 24 hours. The alcohol was removed under reduced pressure. Water (100 ml.) and ice (100 g.) were added and the mixture acidified with dilute hydrochloric acid. The resulting solid was recrystallized from ethyl alcohol–water mixture, m.p. 152°, yield 6.2 g. (24%).

Anal. Calcd. for $C_{12}H_{18}N_2O_4$: N, 11.01. Found: N, 11.05.

Condensation of Diethyl Ethoxymethylenemalonate with N-Substituted Ureas in Presence of Sodium Ethylate, Method B.—N-Alkyl- and N-arylureas in general were found to give the corresponding uracils directly with diethyl ethoxymethylenemalonate when dissolved in alcohol in the presence of an equal molar quantity of sodium ethylate and allowed to stand at room temperature for several days. This method is exemplified by the following two preparations.

3-α-Hydroxymethyl-*n*-propyl-5-carbethoxyuracil.—N-α-Hydroxymethyl-*n*-propylurea (11.6 g. or 0.1 mole) was added to 200 ml. of absolute ethanol containing sodium ethylate prepared from 2.3 g. or 0.1 mole of sodium. To this was added 21.6 g. or 0.1 mole of diethyl ethoxymethylenemalonate and the solution allowed to stand in a stoppered flask at room temperature for 48 hr. The alcohol was removed under reduced pressure. Cold dilute hydrochloric acid was added until slightly acidic. The water was removed *in vacuo* and the solid residue dissolved in a minimum amount of warm ethyl acetate. The solution was filtered and allowed to cool to yield 21.0 g. (82%) of the crystalline product. An analytical sample was obtained by repeated crystallization from ethyl acetate, m.p. 161°.

Anal. Calcd. for $C_{11}H_{16}N_2O_5$: C, 51.45; H, 6.32. Found: C, 51.21; H, 6.52.

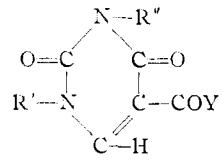
3-Phenyl-5-carbethoxyuracil.—Sodium (4.6 g. or 0.2 g. atom) was allowed to react with 250 ml. of absolute ethanol in a flask fitted with a calcium chloride tube. Phenylurea (27.2 g. or 0.2 mole) and diethyl ethoxymethylenemalonate (43.2 g. or 0.2 mole) were added and the solution allowed to stand at room temperature for three days. The alcohol solution was cooled by adding 100 g. of ice and 200 ml. of cold water. The cold solution was acidified with concentrated hydrochloric acid. The solid was filtered off and dried, yield 46 g. or 88%. This was recrystallized from alcohol, m.p. 230–231°.

Anal. Calcd. for $C_{13}H_{12}N_2O_4$: C, 60.20; H, 4.66. Found: C, 60.20; H, 4.75.

3-Phenyluracil.—3-Phenyl-5-carbethoxyuracil (5.2 g.) was added to 100 ml. of 5% sodium hydroxide solution. This solution was heated to boiling for two hours. It was then cooled, filtered and acidified with hydrochloric acid. The solid was filtered off and dissolved in dilute sodium bicarbonate solution. This was filtered, warmed and acidified. The 3-phenyl-5-carboxyuracil crystallized out, yield 2.5 g., m.p. 243° dec.[7] One gram of the dry acid was placed in a test-tube heated in a Woods metal bath at 243° and held at this temperature for 15 minutes. After the evolution of carbon dioxide had ceased the tube was removed from the bath and the 3-phenyluracil crystallized from hot water,

TABLE II

AMIDES FROM 5-CARBETHOXYURACILS

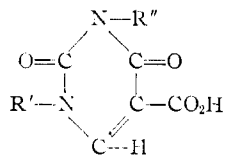


R′	R″	Y	Yield, %	M.p., °C.	Empirical formula	Analyses, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
CH_3	CH_3	$NHCH_3$	100	196	$C_8H_{11}N_3O_3$			21.30			21.15
CH_3	CH_3	NHC_2H_5	95	158	$C_9H_{12}N_3O_3$[b]	51.45	5.76		51.40	6.08	
H	n-C_3H_7	$NHCONH_2$	50	234	$C_9H_{12}N_4O_4$	45.00	5.04		45.30	5.40	
H	$HOCH_2CH_2$–	NHC_2H_5	75	222	$C_9H_{13}N_3O_4$	47.70	5.76		47.95	6.07	
CH_3	CH_3	$NHCH_2CH_2OH$	100	151	$C_9H_{13}N_3O_4$[c,d]	47.60	5.77		47.57	5.90	
H	$HOCH_2CH_2$	$NHCH_2CH_2OH$	60	185	$C_9H_{13}N_3O_5$			17.58			17.45
CH_3	C_2H_5	$NHCH_2CH_2OH$	57	179	$C_{10}H_{15}N_3O_4$			17.45			17.72
C_2H_5	CH_3	$NHCH_2CH_2OH$	70	123	$C_{10}H_{15}N_3O_4$	49.90	6.26		49.00	6.51	
CH_3	CH_3	NHC_4H_9	100	125	$C_{11}H_{17}N_3O_3$			17.58			17.55
CH_3	CH_3	$NHCH_2CH(CH_3)_2$	100	150.5	$C_{11}H_{17}N_3O_3$[c,b]			17.59			17.54
CH_3	$(CH_3)_2CH$–	$NHCH_2CH_2OH$	93	114	$C_{11}H_{17}N_3O_4$[b]			16.45			16.16
CH_3	CH_3	$N(CH_2CH_2OH)_2$	45	122	$C_{11}H_{17}N_3O_5$[d]			15.54			15.33
CH_3	CH_3	NHC_5H_{11}	100	115.5	$C_{12}H_{19}N_3O_3$			16.61			16.39
CH_3	$(CH_3)_2CHCH_2$	$NHCH_2CH_2OH$	49	142	$C_{12}H_{19}N_3O_4$	53.60	7.11	15.61	53.20	7.22	16.10
CH_3	CH_3	$NH(CH_2)_3N(CH_3)_2$	86	89	$C_{12}H_{20}N_4O_3$			20.83			20.83
H	Cyclohexyl	$NHCH_2CH_2OH$	89	232	$C_{13}H_{19}N_3O_4$			14.95			14.89
CH_3	CH_3	NHC_6H_{13}	79	121	$C_{13}H_{21}N_3O_3$	58.50	7.93	15.73	58.24	8.03	15.29
CH_3	CH_3	$NH(CH_2)_3N(C_2H_5)_2$	66	69.5	$C_{14}H_{24}N_4O_3$	56.74	8.16		56.47	8.21	
CH_3	CH_3	NHC_7H_{15}	87	107	$C_{14}H_{23}N_3O_3$			15.01			14.76

[a] Moderate diuresis with oral doses of 0.5 g. and 1 g. [b] Moderate diuresis with intravenous doses of 5–10 mg./kg. [c] Marked diuresis with oral doses of 0.5 g. and 1 g. [d] Marked diuresis with intravenous doses of 5–10 mg./kg.

TABLE III

5-CARBOXYURACILS



R′	R″	Yield, %	M.p., °C.	Empirical formula	Analyses, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
H	CH_3	90	242	$C_6H_6N_2O_4$			16.47			16.38
CH_3	CH_3	90	183	$C_7H_8N_2O_4$[a]	45.60	4.37	15.22	45.80	4.70	15.33
H	C_2H_5	70	179	$C_7H_8N_2O_4$	45.60	4.37		45.65	4.73	
H	n-C_3H_7	90	172–173	$C_8H_{10}N_2O_4$	48.51	5.08	14.12	48.52	5.31	14.40
CH_3	C_2H_5	70	172	$C_8H_{10}N_2O_4$	48.51	5.11		48.42	5.42	
H	$(CH_3)_2CH$	69	192	$C_8H_{10}N_2O_4$	48.51	5.09		48.62	5.42	
CH_3	$CH_2{=}CHCH_2$	70	161–162	$C_8H_{10}N_2O_4$	51.45	5.14		51.43	5.11	
H	$(CH_3)_2CHCH_2$	80	211	$C_9H_{12}N_2O_4$	51.17	5.72		51.02	5.97	
H	$CH_3CH_2CH(CH_2OH)$–	90	166	$C_9H_{12}N_2O_5$	47.40	5.31		47.42	5.81	
CH_3	n-C_4H_9	80	148	$C_{10}H_{14}N_2O_4$			12.75			12.40
C_2H_5	n-C_4H_9	95	107	$C_{11}H_{16}N_2O_4$	55.00	6.72		54.79	6.83	
CH_3	n-C_5H_{11}	74	152	$C_{11}H_{16}N_2O_4$	54.95	6.70	11.65	54.96	6.86	11.13
H	p-Cl-C_6H_4–	98	255 dec.	$C_{11}H_7N_2O_4Cl$	49.60	2.63		49.23	3.00	
H	p-CH_3-C_6H_4–	90	240 dec.	$C_{12}H_{10}N_2O_4$	58.35	4.10		58.75	4.36	
CH_3	n-C_6H_{13}	66	151	$C_{12}H_{18}N_2O_4$	56.65	7.13		56.90	7.07	

[a] Moderate diuresis with oral doses of 0.5 g. and 1 g.

yield 0.6 g., m.p. 242–246°.[7] This product was insoluble in cold sodium bicarbonate solution.

Alkylation of the 3-Substituted-5-carbethoxyuracils, Method C.—Uracils obtained by either method A or B were alkylated with an alkyl sulfate according to the following example.

1-Ethyl-3-*n*-butyl-5-carbethoxyuracil.—3-*n*-Butyl-5-carbethoxyuracil (20 g. or 0.083 mole) was added to 150 ml. of water. Sodium hydroxide (3.4 g. or 0.085 mole) was added and the solution stirred vigorously at 40°. Diethyl sulfate (12.9 g. or 0.084 mole) was added dropwise over a period of one hour. The stirring was continued for another hour. The water was removed under reduced pressure and the solid extracted with ethyl acetate. The ethyl acetate solution was dried over magnesium sulfate, filtered, concentrated and petroleum ether was added to the point of incipient crystallization. Upon cooling the product crystallized out. This was collected and again recrystallized, yield 14.5 g. (65%), m.p. 41–43°.

Anal. Calcd. for $C_{11}H_{20}N_2O_4$: C, 58.20; H, 7.46. Found: C, 58.25; H, 7.70.

Preparation of 5-Carbamyluracils.—The 5-carbethoxyuracil obtained by either method A, B or C was mixed with an equal molar equivalent plus 10% excess of the desired amine and the two heated at 110° for 24 to 48 hours. The amide usually crystallized upon cooling and was recrystallized from hot ethyl acetate. These amides are listed in Table II.

Hydrolysis of the 5-Carbethoxyuracils to the Corresponding Acids.—The 5-carbethoxyuracil obtained by either method A, B or C was added to 5% sodium hydroxide solution (20 ml. for each gram of ester) and heated to reflux temperature. The solution was cooled, filtered through hardened filter paper and acidified with dilute hydrochloric acid. The acid was collected on a filter paper, dried and recrystallized from hot ethanol. The water soluble acids were recovered by evaporating the water solution to dryness under reduced pressure and then extracting with hot alcohol. The 5-carboxyuracils are listed in Table III.

INDIANAPOLIS, INDIANA

[CONTRIBUTION FROM THE RESARCH LABORATORIES OF FLINT, EATON AND CO.]

Isothioureas as Germicides

BY F. J. BANDELIN AND J. V. TUSCHHOFF

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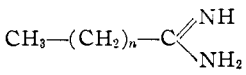
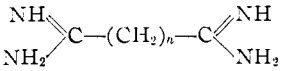
A series of homologous S-alkyl isothioureas and their 1,3-dialkyl derivatives were prepared and investigated for germicidal activity. Several members of the series were found to exhibit marked germicidal activity. Maximum activity against *Staphylococcus aureus* and *Eberthella typhi* occurred when the S-alkyl was either dodecyl or tetradecyl and when the nitrogens were substituted with either methyl or ethyl groups. These compounds exhibited foaming and detergent properties. Data indicate that these compounds have some properties similar to the quaternary ammonium salts.

The antiprotozoal properties of a number of amidines and diamidines have been observed and reported. These compounds were investigated chiefly by British workers for trypanocidal activity. Blaschko and Duthie[1,2] examined a large series of amidines as inhibitors of amine oxidase. Monoamidines of the general type

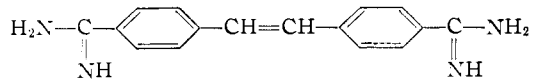


exhibited an increase in inhibition with an increase in the length of the carbon chain up to $n = 10$ with a decrease thereafter. With alkylene diamidines of the general type

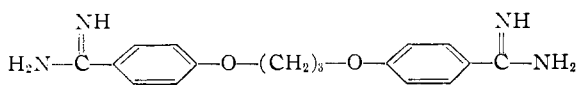


inhibition was found to have reached a maximum at $n = 12$. King, Lourie and Yorke[3,4] showed that alkyl diamidines of the latter type exhibited powerful trypanocidal action both *in vitro* and *in vivo*, the most active in this respect being undecanediamidine which produced almost 100% cures in mice and rabbits infected with *T. rhodesiense*.

Ashley, *et al.*,[5] reported the antibacterial activity of a series of symmetrical aromatic diamidines. Outstanding among these compounds were



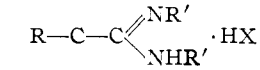
stilbamidine (4,4′-diguanylstilbene), and



propamidine 1,3-bis-(4-guanylphenoxy)-propane. These proved to be valuable chemotherapeutic agents in trypanosomiasis and in leishmanial infections.

More recently Brooks, *et al.*,[6] reported a number of S-alkylisothioureas in a comprehensive study of antitubercular compounds. Because of the similarity and structural relationship of the active moiety with the above compounds we have prepared a series of substituted isothioureas with a large aliphatic residue attached through the sulfur and with monosubstitution of each of the nitrogens with shorter aliphatic chains in order to study the influence of chemical structure upon the antibacterial properties. Since no systematic study of these compounds has appeared we wish to record here the work done in this Laboratory on this problem.

The compounds under investigation have the general type formula:



in which R is used to represent a straight chain alkyl group of 10 to 16 carbon atoms and R′ ranges from hydrogen to *n*-butyl. Hydrochlorides, hydrobromides and hydriodides were prepared from each base. These compounds, when pure, are obtained as fine white, odorless crystals. They are generally insoluble in diethyl ether and benzene, sparingly soluble in acetone and freely soluble in water and in ethanol. They are stable in acid solution and in all but strongly alkaline solutions. Aqueous solutions are nearly tasteless. Table I shows the effect of variation in the chain length of the R and R′ groups upon the germicidal activity.

Experimental

Since these isothiourea alkyl ethers were made by means of well known reactions it is not necessary to give preparational detail for each compound. The reactions employed were those of alkyl halides with thiourea or 1,3-dialkylthioureas to give isothiourea alkyl ether hydrohalides. Temperature and solvent both materially affected the speed of the reaction and the yield. Reactions were carried out

(1) H. Blaschko and R. Duthie, *Biochem. J.*, **39**, 347 (1945a).

(2) H. Blaschko and R. Duthie, *ibid.*, **39**, 478 (1945b).

(3) H. King, E. M. Lourie and W. Yorke, *Ann. Trop. Med. Parasit.*, **32**, 177 (1938).

(4) H. King, E. M. Lourie and W. Yorke, *Lancet*, II, 1360 (1937).

(5) J. N. Ashley, H. J. Barber, A. J. Ewins, G. Newbery and A. D. H. Self, *J. Chem. Soc.*, 103 (1942).

(6) J. D. Brooks, P. T. Charlton, P. E. Macy, D. A. Peak and W. F. Short, *ibid.*, 452 (1950).