droxide. The ethanol was distilled off and replaced by water. Acidification with dilute hydrochloric acid gave clean crystalline products which were removed by filtration. The substituted indoleacetic acids were recrystallized readily from an ethanol–water mixture.

PEARL RIVER, N. Y.

[CONTRIBUTION FROM THE NUTRITION AND PHYSIOLOGY SECTION, RESEARCH DIVISION, AMERICAN CYANAMID CO., LEDERLE LABORATORIES]

Synthesis of Some Substituted Indole-3-butyric Acids[1]

BY MILON W. BULLOCK AND JOHN J. HAND

RECEIVED JUNE 20, 1956

A series of indole-3-butyric esters and acids having substituents in the benzene ring have been prepared from methyl or ethyl 5-formylvalerate and a substituted phenylhydrazine hydrochloride. The intermediate phenylhydrazones were not isolated but were converted directly to the indole derivative by a Fischer indole ring closure.

Indole-3-acetic acid (heteroauxin) and indole-3-butyric acid have been found useful for certain specialized phytological applications such as propagation of plants by cuttings, prevention of preharvest drop of fruit, etc.[2] Indole-3-acetic acid and other phytologically active compounds have been found to have a synergistic effect when used with streptomycin for the control of certain crop diseases.[3] The biological activity of indole-3-acetic acid for some applications is increased by substitutions in the benzene ring.[4] The activity of the closely related indole-3-butyric acids would be expected to be increased by similar structural modifications. A series of substituted indole-3-butyric acids has been prepared for testing.

The compounds were obtained by essentially a one-step Fischer indole synthesis which consisted of the *in situ* formation of the substituted phenylhydrazone of methyl or ethyl 5-formylvalerate under conditions favorable for ring closure to occur.

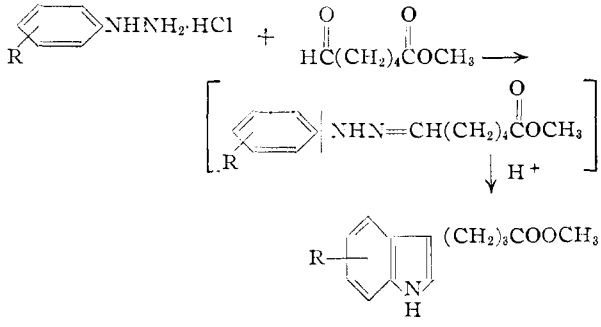

TABLE I

YIELDS AND MELTING POINTS OF PHENYLHYDRAZINE HYDROCHLORIDES

Hydrochloride	Formula	Procedure	Yield, %	M.p., °C.
o-Tolylhydrazine	$C_7H_{11}ClN_2$	A	56.5	195 d.[a]
p-Tolylhydrazine	$C_7H_{11}ClN_2$	A	63	155–160[a]
2,4-Dimethylhydrazine	$C_8H_{13}ClN_2 \cdot 2H_2O$	A	31.5–40	182–184[b]
o-Chlorophenylhydrazine	$C_6H_8Cl_2N_2$	B	50	198–200 d.[c]
m-Chlorophenylhydrazine	$C_6H_8Cl_2N_2$	C	73.5	124–246 d.[d]
p-Chlorophenylhydrazine	$C_6H_8Cl_2N_2$	B	67	221.5–223 d.[e]
2,4-Dichlorophenylhydrazine	$C_6H_9Cl_3N_2$	A	50.3	193–194.5 d.[f]
3-Chloro-2-methylphenylhydrazine	$C_7H_{10}Cl_2N_2$	A	70	239 d.[g]
4-Chloro-2-methylphenylhydrazine	$C_7H_{10}Cl_2N_2$	A	54.2	201–202 d.[h]
5-Chloro-2-methylphenylhydrazine	$C_7H_{10}Cl_2N_2$	A	75.5	215–216 d.[i]
5-Chloro-2-methoxyphenylhydrazine	$C_7H_{10}Cl_2N_2O$	A	58.6	192–193 d.[j]

[a] W. McPherson and G. W. Stratton, THIS JOURNAL, **37**, 908 (1915), prepared the free base but did not report the m.p. of the intermediate hydrochloride. [b] The m.p. of the hydrochloride dihydrate is given as 183° by A. Klauber, *Monatsh. Chem.*, **12**, 212 (1891). [c] F. Graziani, *Chem. Zentr.*, **84**, II, 496 (1913), gave m.p. 194° dec. [d] C. Willgerodt and E. G. Muhe, *J. prakt. Chem.*, [2] **44**, 451 (1891), gave m.p. 235–236° dec. [e] F. Graziani, ref. *c* gave m.p. 225–230° dec. [f] F. D. Chattaway and C. F. B. Pearce, *J. Chem. Soc.*, **107**, 32 (1915), gave the decomposition point as about 210°. [g] *Anal.* Calcd. for $C_7H_{10}Cl_2N_2$: C, 43.54; H, 5.22; N, 14.51; Cl, 36.73. Found: C, 43.23; H, 5.34; N, 14.74; Cl, 36.28. [h] *Anal.* Calcd. for $C_7H_{10}Cl_2N_2$: C, 43.54; H, 5.22; N, 14.51; Cl, 36.73. Found: C, 43.28; H, 5.24; N, 14.47; Cl, 36.68. [i] *Anal.* Calcd. for $C_7H_{10}Cl_2N_2$: C, 43.54; H, 5.22; N, 14.51; Cl, 36.73. Found: C, 43.26; H, 5.09; N, 14.76; Cl, 37.02. [j] F. J. Stevens and D. H. Higginbotham, THIS JOURNAL, **76**, 2206 (1954), gave m.p. 195–196° dec.

Attempts to isolate and purify the intermediate phenylhydrazones were unrewarding. The phenylhydrazones were obtained in low yields as gums which could not be satisfactorily purified. The acidic conditions required for the cyclization reaction will convert any trimerized aldehyde to the reactive monomer so that phenylhydrazone formation and cyclization can occur.

The substituted phenylhydrazine hydrochlorides which were required as intermediates were

(1) Presented in part at the 129th Meeting of the American Chemical Society, Dallas, Texas, April 9, 1956.

(2) F. Skogg, "Plant Growth Substances," University of Wisconsin Press, Madison, Wis., 1951.

(3) R. N. Goodman and D. D. Hemphill, *Science*, **119**, 347 (1954); D. D. Hemphill and R. N. Goodman, *ibid.*, **122**, 122 (1955).

(4) O. L. Hoffman, S. W. Fox and M. W. Bullock, *J. Biol. Chem.*, **196**, 437 (1952).

TABLE II

ESTERS OF INDOLE-3-BUTYRIC ACIDS

Ester	Procedure	Yield, %	M.p., °C.	Recrystn. solvent	Empirical formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Chlorine, % Calcd.	Chlorine, % Found
Methyl indole-3-butyrate	D	7.2	72.5–73	Methanol–water	$C_{13}H_{15}NO_2$	71.86	71.53	6.96	7.37	6.45	6.37		
Ethyl indole-3-butyrate	D	10.4	39–40	Cyclohexane	$C_{14}H_{17}NO_2$	72.70	72.43	7.41	7.52	6.06	6.08		
Methyl 5-methylindole-3-butyrate	F	4.0	69	Cyclohexane	$C_{14}H_{17}NO_2$	72.70	72.43	7.40	7.50	6.06	6.24		
Methyl 7-methylindole-3-butyrate	D	10.0	112–112.5	Cyclohexane	$C_{14}H_{17}NO_2$	72.70	72.59	7.40	7.54	6.06	6.01		
Methyl 5,7-dimethylindole-3-butyrate	E	7.4	97–98	Benzene–cyclohexane	$C_{15}H_{19}NO_2$	73.44	73.50	7.81	7.42	5.71	5.53		
Methyl 5-chloroindole-3-butyrate	D	13.5	77.5–78	Cyclohexane	$C_{13}H_{14}ClNO_2$	62.03	61.80	5.61	5.87	5.57	5.84	14.09	13.80
Ethyl 5-chloroindole-3-butyrate	D	18.0	67	Cyclohexane	$C_{14}H_{16}ClNO_2$	63.28	63.29	6.07	6.26	5.27	5.28	13.34	13.20
Methyl 4- and 6-chloroindole-3-butyrates	D	3.6	94–98	Cyclohexane	$C_{13}H_{14}ClNO_2$	62.03	61.73	5.61	5.78	5.57	5.61	14.09	14.14
Ethyl 4- and 6-chloroindole-3-butyrates	D	13[a]	85–86	Ethanol	$C_{14}H_{16}ClNO_2$	63.28	62.81	6.07	6.40	5.27	5.42	13.34	13.09
Methyl 7-chloroindole-3-butyrate	D	16.8	78–79	Cyclohexane	$C_{13}H_{14}ClNO_2$	62.03	61.61	5.61	5.51	5.57	6.16	14.09	13.86
Ethyl 7-chloroindole-3-butyrate	D	23	65	Cyclohexane	$C_{13}H_{14}ClNO_2$	63.28	62.97	6.07	6.33	5.27	5.22	13.34	12.93
Methyl 5,7-dichloroindole-3-butyrate	D	10.4	107.5–108	Methanol	$C_{13}H_{13}Cl_2NO_2$	54.56	54.35	4.58	4.62	4.90	4.88	24.78	24.50
Methyl 4-chloro-7-methylindole-3-butyrate	F	12.5	111.5–112	Benzene–ligroin	$C_{14}H_{16}ClNO_2$	63.28	63.37	6.07	6.29	5.27	5.37	13.34	13.21
Methyl 5-chloro-7-methylindole-3-butyrate	F	13.7	118.5–119	Methanol	$C_{14}H_{16}ClNO_2$	63.28	63.35	6.07	6.40	5.27	5.50	13.34	13.02
Methyl 6-chloro-7-methylindole-3-butyrate	E	16.7	141	Methanol	$C_{14}H_{16}ClNO_2$	63.28	63.06	6.07	6.26	5.27	5.28	13.34	13.34
Methyl 4-chloro-7-methoxyindole-3-butyrate	F	5.3	158–158.5	Ethanol	$C_{14}H_{16}ClNO_3$	59.68	60.00	5.72	6.15	4.97	5.00	12.59	10.39

[a] Based on mixture of isomers, m.p. 62–63° from which only one isomer was obtained pure.

TABLE III

INDOLE-3-BUTYRIC ACIDS

3-Butyric acid	Yield, %	M.p., °C.	Empirical formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Chlorine, % Calcd.	Chlorine, % Found
5-Methylindole-	79	154–154.5	$C_{13}H_{15}NO_2$	71.86	71.42	6.96	7.04	6.45	6.66		
7-Methylindole-	Quant.	154–155	$C_{13}H_{15}NO_2$	71.86	71.50	6.96	7.08	6.45	6.34		
5,7-Dimethylindole-	94	101–106	$C_{14}H_{17}NO_2$	72.70	73.49	7.41	7.51	6.06	5.52		
5-Chloroindole-	92	142.5–143	$C_{12}H_{12}ClNO_2$	60.64	60.64	5.09	5.24	5.89	6.15	14.95	14.71
4- and 6-Chloroindole-	84	125–130	$C_{12}H_{12}ClNO_2$	60.64	60.77	5.09	5.23	5.89	6.14	14.95	15.35
7-Chloroindole-	Quant.	137–137.5	$C_{12}H_{12}ClNO_2$	60.64	60.81	5.09	5.19	5.89	6.02	14.85	14.93
5,7-Dichloroindole-	99	120–120.5	$C_{12}H_{11}Cl_2NO_2$	52.96	53.04	4.07	4.44	5.15	5.23	26.06	26.43
4-Chloro-7-methylindole-	Quant.	121–122.5	$C_{13}H_{14}ClNO_2$	62.03	61.66	5.61	5.77	5.57	5.65	14.09	14.09
5-Chloro-7-methylindole-	92	114–114.5	$C_{13}H_{14}ClNO_2$	62.03	62.16	5.61	5.88	5.57	5.66	14.09	14.09
6-Chloro-7-methylindole-	96	158	$C_{13}H_{14}ClNO_2$	62.03	62.16	5.61	5.77	5.57	5.61	14.09	14.31
4-Chloro-7-methoxyindole-	73	247–249	$C_{12}H_{12}ClNO_3 \cdot H_2O$	54.65	54.65	5.64	5.88	4.90	4.52	12.41	12.87

prepared by diazotization of the amine hydrochlorides followed by reduction of the diazonium salts to the hydrazines. We have found that two moles of amine can be diazotized in 10 to 15 minutes if a Dry Ice–acetone cooling bath is used. There is no advantage in having the amine hydrochloride in solution as suspensions are diazotized equally well. For phenylhydrazines having no *ortho* substituent sodium sulfite was a satisfactory reducing agent, and the hydrochlorides were generally obtained in a nearly pure state. Stannous chloride reduction was satisfactory for all compounds including those having an *ortho* substituent, but it was always necessary to recrystallize the product to remove tin which is carried down with the precipitate. The yields and melting points of the phenylhydrazine hydrochlorides prepared are summarized in Table I.

The ease of cyclization of the intermediate phenylhydrazones varies considerably. Those with two *ortho–para*-directing groups are cyclized with mild reagents such as alcoholic hydrogen chloride. The unsubstituted and monosubstituted phenylhydrazones require ethanolic sulfuric acid. The yields of ethyl esters cyclized with ethanolic sulfuric acid are superior to those of the methyl esters cyclized with methanolic sulfuric acid. The boiling point of methanol is too low for the ring closure to occur effectively. Boron trifluoride in refluxing methanol was found to give very low yields in this series. The melting points, elemental analyses and yields of the esters prepared are summarized in Table II.

The acids were obtained by saponification of their purified esters in the usual way. Melting points, yields and elemental analyses are in Table III.

Experimental[5]

The following examples illustrate the methods employed for the preparation of the compounds described in this publication. The letters refer to the procedure as given in Tables I and II. The acids listed in Table III were prepared by saponification of their esters with ethanolic or methanolic potassium hydroxide, replacing the alcohol with water and acidifying. The acids were generally recrystallized from a water–ethanol mixture to obtain analytical samples.

o-**Tolylhydrazine Hydrochloride (Procedure A).**—In a 3-liter, 3-neck flask equipped with stirrer, thermometer and dropping funnel were placed 214.3 g. (2 moles) of *o*-toluidine and 750 ml. of water. The mixture was stirred while 750 ml. of hydrochloric acid was added. The reaction flask was placed in a Dry Ice–acetone-bath and cooled rapidly to −20°. The temperature was maintained −15 to −20° while a solution of 142 g. (2 moles) of sodium nitrite in 500 ml. of water was added through a dropping funnel, the tip of which extended nearly to the bottom of the flask. The diazotization required about 10 minutes. The reaction mixture was allowed to warm to 0° and poured with stirring into a solution of 915 g. (4.05 moles) of stannous chloride dihydrate in 1 liter of hydrochloric acid at 0°. The resulting mixture was stored at 0° overnight. The crystals were filtered off and washed with hydrochloric acid and with ether. This gave 363 g. of crude product which contained appreciable amounts of stannic ion. The product was recrystallized from 1100 ml. of water to yield 180.2 g. (1.18 moles, 56.5%) of purified product, m.p. 195° dec. This compound could be prepared in only 13.3% yield by reduction of the diazonium salt with sodium sulfite.

o-**Chlorophenylhydrazine Hydrochloride (Procedure B).**—In a 2-liter, 3-neck flask equipped with thermometer, stirrer and dropping funnel were placed 127.6 g. (1 mole) of *o*-chloroaniline and 250 ml. of water. The mixture was stirred and cooled in an ice-bath while 250 ml. of hydrochloric acid was added as rapidly as the temperature could be kept below 60°. The reaction mixture was cooled rapidly to −5° in a Dry Ice–alcohol-bath and maintained at −5 to −10° while a solution of 69 g. (1 mole) of sodium nitrite in 250 ml. of water was added through a dropping funnel, the tip of which extended nearly to the bottom of the reaction flask. The diazotization required about 10 minutes. The reaction mixture was allowed to warm up to −3° and filtered rapidly through a glass wool plug into a solution of sodium sulfite at 5° which had just been prepared by neutralizing to phenolphthalein a solution of 205 g. (5 moles) of 97% sodium hydroxide in 1.5 liters of water with gaseous sulfur dioxide. The resulting mixture was warmed slowly to 60° and maintained at 60 to 70° for 1 hr. The solution was acidified to litmus with hydrochloric acid and heated on the steam-bath 6 hr. The reaction mixture was treated with activated charcoal and filtered through a layer of Celite filtering aid, one liter of hydrochloric acid, sp. gr. 1.19, was added and the resulting solution allowed to cool. The crystals were filtered off, washed with 3 *N* hydrochloric acid and with ether. The yield was 89 g. (0.503 mole), 50% of crystals, m.p. 198–200° dec.

m-**Chlorophenylhydrazine Hydrochloride (Procedure C).**—One-hundred twenty-seven and six-tenths grams (1 mole) of *m*-chloroaniline was dissolved in 460 ml. of 6 *N* hydrochloric acid and diazotized at 0° by the addition of a solution of 69 g. (1 mole) of sodium nitrite in 150 ml. of water. The cold diazonium salt solution was filtered rapidly and stirred into a cold solution of sodium sulfite which was prepared by adding 225 g. of sodium bisulfite to a solution of 100 g. of sodium hydroxide in one liter of water, cooling to about 25° and adding more sodium bisulfite until the *p*H of the solution was about 8 and finally adding 24 more grams of sodium bisulfite. The reaction mixture was warmed on the steam-bath 1 hr., acidified to litmus and heated an additional 4 hr. The hot solution was treated with decolorizing charcoal and filtered. One liter of hydrochloric acid was added and the solution allowed to cool. The product was filtered off and washed with 320 ml. of 3 *N* hydrochloric acid. The product was recrystallized from a mixture of water and hydrochloric acid. The yield was 131.5 g. (0.735 mole), 73.5%, m.p. 245–246° dec.

Methyl 5-Formylvalerate.[6]—In a 5-liter, 3-neck flask equipped with condenser, sintered glass gas inlet tube and a fast and efficient propeller type stirrer were placed 100 g. of 5% palladium-on-barium sulfate catalyst, 3 liters of mixed xylenes and 3 ml. of quinoline-S poison.[7] A slow stream of hydrogen was passed into the stirring solution while a few ml. of solvent was distilled out through the dry condenser to remove all traces of water, and 1 kg. (5.6 moles) of methyl 5-chloroformylvalerate[8] was added. The reaction mixture was stirred rapidly at reflux while a stream of hydrogen was passed in. After 4 hr. the reduction rate became very slow. Approximately 10 g. of Norit A decolorizing charcoal was added and the solution filtered. The solvent was distilled off under the reduced pressure of a water aspirator and the residue distilled through a 24″ Vigreux column. The fractions distilling 99–100° at 10.7 mm. and having $n^{20}D$ 1.4318 and d^{20} 1.097 were collected as pure product. The yield of pure aldehyde was 319.6 g. (2.21 moles), 39.6%. An additional 25% of material was obtained at an estimated 90% purity by redistilling the higher boiling fractions.

Anal. Calcd. for $C_7H_{12}O_3$: C, 58.31; H, 8.39. Found: C, 58.00; H, 8.49.

The product trimerizes and darkens on standing. It can be stabilized by storage over calcium carbonate or sodium bicarbonate.

Methyl Indole-3-butyrate (Procedure D).—A mixture of 43.4 g. (0.3 mole) of phenylhydrazine hydrochloride, 43.3 g. (0.3 mole) of methyl 5-formylvalerate and 200 ml. of methanol was warmed on the steam-bath a few minutes to obtain a homogeneous solution. Now a solution of 30 ml. of sulfuric acid in 70 ml. of methanol was added and the reaction mix-

(5) All melting points and boiling points are uncorrected. Elemental microanalyses were done by Mr. L. Brancone and staff.

(6) This compound was prepared by essentially the same procedure as used by G. B. Brown, *et al.*, *J. Org. Chem.*, **12**, 160 (1948), for the preparation of ethyl 5-formylvalerate.

(7) R. Adams, "Organic Reactions," Vol. IV, John Wiley and Sons, Inc., New York, N. Y., p. 308.

(8) M. W. Bullock and J. J. Hand, THIS JOURNAL, **78**, 5854 (1956).

ture refluxed 3 hr. The cooled solution was poured into a mixture of ice and water. The product was extracted with 500 ml. of ether. The ether product was washed with water and with saturated sodium bicarbonate solution and dried over sodium sulfate. Distillation of the ether left an oil which was distilled *in vacuo*. The fraction distilling 160–190° at 0.15 mm. and crystallizing in the received was collected as product. The crude ester was recrystallized from a methanol–water mixture to give a yield of 4.7 g. (0.0217 mole, 7.2%) of white plates, m.p. 72–73°. Another recrystallization from the same solvent pair gave pure ester, m.p. 72.5–73°.

Ethyl 5-Chloroindole-3-butyrate (Procedure D).—A mixture of 15.8 g. (0.1 mole) of *p*-chlorophenylhydrazine hydrochloride, 360 ml. of absolute ethanol and 40 ml. of sulfuric acid was refluxed 3 hr. The cooled solution was poured into 2.5 liters of ice-water containing 300 g. of ammonium sulfate. The ester was recovered by extraction with two 250-ml. and one 100-ml. portions of ether. The combined ether extracts were dried over sodium sulfate and distilled leaving 22 g. of black oil. The oil was distilled and the fraction distilling 170–200° at 0.1 mm. collected as product. Recrystallization of the crude ester from cyclohexane gave 4.8 g. (0.018 mole, 18%) of product, m.p. 67°. After an additional recrystallization the m.p. was 69°.

Methyl 6-Chloro-7-methylindole-3-butyrate (Procedure E).—Fifty-seven grams (0.3 mole) of 3-chloro-2-methylphenylhydrazine hydrochloride was dissolved in 300 ml. of hot methanol, and 43.3 g. (0.3 mole) of methyl 5-formylvalerate was added. After gentle warming the reaction mixture refluxed spontaneously several minutes. The methanol was distilled off leaving a mixture of oil and solid materials. The residue was taken up in hot methanol, decolorized with activated charcoal and filtered. From the cooled filtrate 13.3 g. (0.05 mole, 16.7%) of ester, m.p. 140.5–141°, was obtained. After recrystallization from 210 ml. of methanol, the ester had m.p. 141°.

Methyl 5-Chloro-7-methylindole-3-butyrate (Procedure F).—A mixture of 57.8 g. (0.3 mole) of 4-chloro-2-methylphenylhydrazine hydrochloride and 300 ml. of methanol was warmed on the steam-bath to dissolve the hydrochloride. Then 43.3 g. (0.3 mole) of methyl 5-formylvalerate was added. The resulting solution was refluxed 30 minutes and saturated with anhydrous hydrogen chloride. The reaction mixture was refluxed an additional 3 hr. and left standing overnight. The reaction mixture was poured into ice and water and the product recovered by ether extraction. The ether solution was washed with water and with saturated sodium bicarbonate solution and dried over sodium sulfate. Distillation of the solvent left a sticky solid. The crude product was taken up in 100 ml. of hot methanol, treated with decolorizing charcoal and filtered. The filtrate deposited crystals on cooling. The ester was filtered off and washed with cold methanol. The yield was 10.8 g. (0.041 mole), 13.7% of product, m.p. 118.5–119°. The melting point was unchanged after recrystallization from methanol.

PEARL RIVER, N. Y.

[CONTRIBUTION FROM THE COLLEGE OF PHARMACY, UNIVERSITY OF MICHIGAN]

Diuretics. III. 1,3-Dimethyl-9-alkyl- and 1,3,9-Trimethyl-8-alkylthioisoxanthines

BY F. F. BLICKE AND R. L. SCHAAF[1,2]

RECEIVED JUNE 13, 1956

1,3-Dimethyl-5,6-diaminouracil was treated with a variety of alkyl isothiocyanates to form ureido derivatives which were cyclized to 2-alkylamino-4,6-dimethyl-5,7-diketo-4,5,6,7-tetrahydrothiazolo-[5,4-d]pyrimidines and 1,3-dimethyl-8-thiol-9-alkylisoxanthines. The thiol group was removed from the latter with the formation of 1,3-dimethyl-9-alkylisoxanthines. 1,3,9-Trimethyl-8-alkylthioisoxanthines were prepared by alkylation of 1,3,9-trimethyl-8-thiolisoxanthine. None of the compounds tested exhibited diuretic activity.

The substituted isoxanthines described in this paper were synthesized in a search for diuretics.

Treatment of 1,3-dimethyl-5,6-diaminouracil (I)[3] with an alkyl isothiocyanate[4] yielded a 1,3-dimethyl-5-(3-alkylthioureido)-6-aminouracil (II) (Table I). In six instances we were able to cyclize the uracil II, in refluxing hydrochloric acid, to a 1,3-dimethyl-8-thiol-9-alkylisoxanthine (III) (compounds 1–6, Table II).[5] The 8-thiol compounds were converted into 1,3-dimethyl-9-alkylisoxanthines (IV) (compounds 7–11, Table II) by the action of nitrous acid[6] or Raney nickel.

Hitherto it had not been reported that 2-alkylamino-4,6-dimethyl-5,7-diketo-4,5,6,7-tetrahydrothiazolo[5,4-d]pyrimidines (V), compounds which are isomeric with III, are formed during the conversion of compounds of type II into III. The examples of compounds of type V (compounds 1–5, Table III) which were obtained were previously unknown. The structure of a typical representative, 2-hexahydrobenzylamino-4,6-dimethyl-5,7-diketo-4,5,6,7-tetrahydrothiazolo[5,4-d]pyrimidine (V, R = hexahydrobenzyl; XI, R = CH_3) was established by a six-step, unequivocal synthesis from butyl nitrosocyanoacetate. The acetate was reduced with aluminum amalgam to butyl aminocyanoacetate[7] which, without isolation, was converted by hexahydrobenzyl isothiocyanate into 2-hexahydrobenzylamino-4-carbobutoxy-5-aminothiazole (VII). The thiazole reacted with one molecular equivalent of methyl isocyanate to yield a monosubstituted product, 2-(1-hexahydrobenzyl-3-methylureido)-4-carbobutoxy-5-aminothiazole (VIII), and with two molecular equivalents of the same reagent to form a disubstitution product, 2-(1-hexahydrobenzyl-3-

(1) This paper represents part of a dissertation submitted by R. L. Schaaf in partial fulfillment of the requirements for the Ph.D. degree in the University of Michigan, 1955.

(2) The Monsanto Chemical Co. Fellow.

(3) F. F. Blicke and H. C. Godt, Jr., THIS JOURNAL, **76**, 2798 (1954).

(4) The term alkyl (formulas II–V) has been used to include methyl, ethyl, propyl, isopropyl, butyl, allyl, cyclohexyl, benzyl and hexahydrobenzyl.

(5) Although compounds of type III are named in the literature as 8-thiouric acids, we have called them 8-thiolisoxanthines in view of their behavior with alkyl halides and other reagents. H. Biltz and J. Sauer (*Ber.*, **64**, 752 (1931)) stated that 8-thiouric acids frequently act as 8-thiolxanthines.

(6) The first use of nitrous acid to convert thiolisoxanthines (8-thiouric acids) into isoxanthines was mentioned in a German Patent (120,437; *Frdl.*, **6**, 1180 (1900–1902)). The method was used subsequently by H. Biltz, *et al.*, (*Ann.*, **423**, 200 (1921)) and by W. Traube, *et al.* (*ibid.*, **432**, 266 (1923)).

(7) Ethyl nitrosocyanoacetate was reduced with aluminum amalgam to ethyl aminocyanoacetate by A. H. Cook, I. Heilbron and A. L. Levy (*J. Chem. Soc.*, 1594 (1947)) but the experimental details were not reported. We used the procedure described by V. Cerchez (*Bull. soc. chim.*, [4] **47**, 1282 (1930)) for the reduction of diethyl isonitrosomalonate. It might be more advantageous to employ sodium hydrosulfite (see B. F. Tullar, U. S. Patent 2,393,723; *C. A.*, **40**, 2465 (1946)).