solution were dried over sodium sulfate and evaporated. The semi-solid residue was triturated with 100 ml. of 10% potassium hydroxide, filtered and washed with water. The combined filtrate and washings were extracted twice with chloroform and acidified with 25 ml. of hydrochloric acid. Extraction of the acid solution with five 125-ml. portions of chloroform gave a further 6.3 g. of crude α-mercaptobutyramide; total yield 7.5 g. (42%); m.p. 81–91°. It was not purified further in order to avoid partial oxidation to the disulfide.

Anal. Calcd. for C_4H_9ONS: C, 40.31; H, 7.61. Found: C, 40.17; H, 7.51.

α-Mercaptodiethylacetamide.[15]—This intermediate was prepared from α-bromodiethylacetamide (58.2 g., 0.30 mole) by a slight modification of the procedure described above for preparation of α-mercaptobutyramide. Precipitation of potassium bromide was much slower in this case, presumably because of steric hindrance in the fully substituted α-bromoamide. Consequently, a much longer reaction time was required—18 hours at room temperature and 25 hours at reflux temperature. The reaction mixture was made strongly alkaline with potassium hydroxide to avoid partial extraction of the weakly acidic mercaptoamide along with the neutral products. After thorough extraction with chloroform, the alkaline solution was acidified and extracted with chloroform. The α-mercaptodiethylacetamide was obtained as a low melting solid (yield 5.7 g., 12.9%) and was not further purified.

2-Thiono-5-(6-carbomethoxyhexanal)-4-thiazolidone was obtained from methyl pimelaldehydate and rhodanine[16] as yellow crystals, m.p. 116–117°. Microbiological activity against *M. tuberculosis* was 5 γ/mg.

Anal. Calcd. for $C_{11}H_{15}O_3NS_2$: C, 48.33; H, 5.53; N, 5.12. Found: C, 48.24; H, 5.41; N, 5.15.

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[15] This compound has been reported (E. Clemmensen and A. H. C. Heitman, *Am. Chem. J.*, **40**, 298 (1908)) to melt at 147°. Because of this high melting point and because the earlier investigators took no precautions to avoid oxidation, it seems probable that their compound was actually the disulfide. The analytical results obtained by them are in better accord with the disulfide structure than with the α-mercaptodiethylacetamide formulation.

[16] P. L. Julian and B. M. Sturgis, THIS JOURNAL, **57**, 1126 (1935).

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF G. D. SEARLE AND CO.]

Some Alkyl Homologs of Theophylline

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The preparation of a number of 1,3-dialkyl- and 1,3,8-trialkylxanthines is described. The Traube synthesis, starting with a dialkylurea and cyanoacetic acid, is shown to be of general application, and many of the intermediate compounds are characterized.

The dimethylxanthines, theophylline and theobromine, have for many years been used in the treatment of certain cardiac conditions and as diuretics. While in many respects they are quite satisfactory for these purposes, they are far from ideal, since they frequently are not sufficiently potent and may be accompanied by undesirable side effects in larger doses. Since lesser alkylated xanthines are of little or no value, and since caffeine differs appreciably in therapeutic effects, it is obvious that the alkyl groups are highly significant in determining biological activity. Prior to the present investigation of the higher dialkylxanthines the preparation of only a few compounds had been recorded in the literature[1–3] and nothing had been published on their pharmacological activity. In order to permit a systematic evaluation of the effect of substituting larger alkyl groups for the methyl groups in theophylline, the present work was undertaken.

These compounds were prepared by a modification of the Traube[4] synthesis, in which a *sym*-dialkylurea is converted to the corresponding 1,3-dialkylxanthine. Since this synthesis leads readily to 8-alkylated xanthines, and since such products are not found in nature at all it seemed interesting to include them in the present study.

The Traube synthesis appears to be completely general for 1,3-dialkyl or 1,3,8-trialkylxanthines, with only obvious modification of reaction conditions needed in places. One apparent limitation to this generality of application lies in the fact that diisopropylurea was completely inert in the first step, so that it was impossible to prepare this example of a diisoalkylxanthine. The full extent of this limitation was not explored.

Preliminary pharmacological testing of some of these compounds has been completed and is published elsewhere.[5] Some of the lower members of the group, with and without an 8-alkyl substituent, were found significantly active. Activity of higher members of the series was insufficient to be interesting.

Experimental

Reagents.—*sym*-Dialkyl substituted ureas were prepared by passing 1 mole of phosgene gas into a well-stirred mixture of 2 moles of monoalkylamine, 2 moles of sodium hydroxide, 250 cc. of water and 250 cc. of benzene at 10°, or by the action of an alkyl isocyanate on a primary amine in dry ether. Other reagents were of commercial quality and used without further purification.

1,3-Dialkyl-6-aminouracils.—One mole each of a *sym*-dialkylurea and of cyanoacetic acid were heated with 2 moles of acetic anhydride and 250 cc. of acetic acid for three hours at 60°. Acetic acid and excess anhydride were then removed as far as possible under reduced pressure without raising the temperature in the reaction mixture. The residue was dissolved in about two liters of water, made alkaline with sodium carbonate and boiled for about two hours. The products crystallized on cooling giving yields ranging from 70 to 90%. For analysis, they were recrystallized from water or 50% alcohol. Their properties are given in Table I.

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[1] G. Scarlat, *Bull. Soc. Sci. Bucarest*, **13**, 155, through *J. Chem. Soc.*, **88**, [i] 160 (1905).

[2] German Patent 121,224.

[3] W. Traube and W. Nithack, *Ber.*, **39**, 227 (1906).

[4] W. Traube, *ibid.*, **33**, 3035 (1900).

[5] G. V. LeRoy and J. H. Speer, *J. Pharmacol. Exptl. Therap.*, **69**, 45 (1940).

TABLE I

6-AMINOURACILS

Substituents	M.p. ,°C.	Formula	Nitrogen, % Calcd.	 Found
1,3-Diethyl	195°[a]	$C_8H_{13}N_3O_2$	23.0	23.1
1-Butyl-3-ethyl	67–71[b]	$C_{10}H_{17}N_3O_2$	19.9	20.0
1,3-Dibutyl	105–106	$C_{12}H_{21}N_3O_2$	17.7	17.8

[a] Scarlat[1] gives 137°. [b] Probably contaminated with some 1-ethyl-3-butyl isomer which could not be readily separated at this point.

Identical products were obtained using the pyridine–phosphorus oxychloride method described by Traube,[4] though in poorer yield. Neither of these methods (nor the combination of phosphorus oxychloride and acetic anhydride[6]) yielded any product other than unchanged starting material when applied to diisopropylurea. *sym*-Dialkyl substituted ureas will not condense with ethyl cyanoacetate in the presence of sodium ethylate, though this condensation goes smoothly with monoalkylureas.[7]

1,3-Dialkyl-5-nitroso-6-aminouracils were prepared from the crude products of the preceding step exactly as described by Traube,[4] save that 50% alcohol was used as the reaction medium for the ethylbutyl and dibutyl compounds. The yields were 75 to 95%. Their properties are listed in Table II.

TABLE II

5-NITROSO-6-AMINOURACILS

Substituents	M.p., °C.	Formula	Nitrogen, % Calcd.	 Found
1,3-Diethyl	204–206 dec.	$C_8H_{12}N_4O_3$	26.4	26.6
1-Butyl-3-ethyl	189–190	$C_{10}H_{16}N_4O_3$	23.3	23.1
1,3-Dibutyl	211–212	$C_{12}H_{20}N_4O_3$	20.9	21.1

1,3-Dialkyl-5,6-diaminouracils were obtained by the ammonium sulfide reduction described by Traube.[4] The yields were 40 to 90%. The diethyl derivative (m.p. 103–104°) was very soluble in water. The ethyl-butyl derivative was obtained as a semi-crystalline mush and used for the next step without analysis or purification.

The dibutyl derivative was an oil, insoluble in hot or cold water and very soluble in alcohol. Its monohydrochloride crystallized from water in leaflets, m.p. 235°, which turned red upon exposure to air, particularly when they were moist.

Anal. Calcd. for $C_{12}H_{22}N_4O_2 \cdot HCl$: N, 19.3; Cl, 12.2. Found: N, 19.3; Cl, 12.2.

The alkylxanthines were obtained by heating at 110–140° for two hours in an open vessel a mixture of one part of the dialkyldiaminouracil with about four parts of RCOOH, where R is the substituent to be introduced into the 8-position of the final xanthine. A few of the intermediate 5-acylamino derivatives[8] crystallized spontaneously on cooling. These were isolated and purified by crystallization from 50% alcohol. Their properties are listed in Table III.

TABLE III

1,3-DIALKYL-6-AMINO-5-ACYLAMINOURACILS

Alkyl groups	Acyl groups	M.p., °C.	Formula	Nitrogen, % Calcd.	 Found
Dimethyl	Acetyl	275–276	$C_8H_{12}N_4O_3$	26.4	26.6
Dimethyl	Propionyl	257–258	$C_9H_{14}N_4O_3$	24.8	24.6
Dimethyl	Butyryl	229–230	$C_{10}H_{16}N_4O_3$	23.3	23.5
Diethyl	Formyl	260–261[a]	$C_9H_{14}N_4O_3$	24.8	24.9
Dibutyl	Formyl	220	$C_{13}H_{22}N_4O_3$	19.9	19.8

[a] Scarlat[1] gives 235°; Ruttink[8] gives 247°.

Most of these acyl compounds did not crystallize spontaneously. In such cases the excess acid was removed by boiling at atmospheric pressure and the red-brown residue (or the purified acyl derivative where available) was converted to the alkylxanthine by heating in a metal-bath at 275–300° for ten minutes. The crude product was decolorized with Darco in hot 50% or 95% alcohol and allowed to crystallize. One or two recrystallizations served to yield a pure product. Their properties are recorded in Table IV.

TABLE IV

ALKYL XANTHINES

Xanthine	M.p., °C.	Formula	Nitrogen, % Calcd.	 Found
1,3-Dimethyl (Theophylline)	269–270	$C_7H_8N_4O_2$		
1,3,8-Trimethyl	325	$C_8H_{10}N_4O_2$	28.9	28.8
1,3-Dimethyl-8-ethyl	270	$C_9H_{12}N_4O_2$	26.9	26.9
1,3-Dimethyl-8-propyl	256	$C_{10}H_{14}N_4O_2$	25.2	25.0
1,3-Dimethyl-8-isopropyl	271	$C_{10}H_{14}N_4O_2$	25.2	25.1
1,3-Dimethyl-8-isobutyl	234[a]	$C_{11}H_{16}N_4O_2$	23.7	23.0
1,3-Dimethyl-8-(1-ethylpropyl)	220–221	$C_{12}H_{18}N_4O_2$	22.4	22.2
1,3-Diethyl	219–220[b]	$C_9H_{12}N_4O_2$	26.9	27.3
1,3-Diethyl-8-methyl	231–232	$C_{10}H_{14}N_4O_2$	25.2	25.6
1,3,8-Triethyl	193	$C_{11}H_{16}N_4O_2$	23.7	23.9
1,3-Diethyl-8-propyl	170–171	$C_{12}H_{18}N_4O_2$	22.4	22.6
1,3-Diethyl-8-isopropyl	156–157	$C_{12}H_{18}N_4O_2$	22.4	22.3
1,3-Diethyl-8-isobutyl	152–153	$C_{13}H_{20}N_4O_2$	21.2	20.9
1-Ethyl-3-butyl	166	$C_{11}H_{16}N_4O_2$	23.7	23.7
1,3-Dibutyl	189	$C_{13}H_{20}N_4O_2$	21.2	21.3
1,3-Dibutyl-8-methyl	158–159	$C_{14}H_{22}N_4O_2$	20.1	20.3
1,3-Dibutyl-8-ethyl	124	$C_{15}H_{24}N_4O_2$	19.2	18.6

[a] Traube and Nithack[3] give 227°. [b] Scarlat[1] gives 208°; Ruttink[8] gives 212°.

Two of the xanthines (1,3-diethyl-8-propyl and 1,3-diethyl-8-isobutyl) failed to crystallize when the crude product was dissolved in alcohol. They were purified by rapid distillation in vacuum (b.p. about 220° at 3 mm.) and the distillate crystallized from alcohol. While distillation was not tried in other cases, there is no reason to believe that any of the xanthines in Table IV could not be distilled or sublimed without decomposition under reduced pressure.

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(6) B. Hepner and S. Frenkenberg, *Helv. Chim. Acta*, **15**, 350 (1932).

(7) M. Conrad, *Ann.*, **340**, 310 (1905).

(8) J. Ruttink, *Rec. trav. chim.*, **65**, 751 (1946).