1-Acetylimidazolidine-2-thione (100 mg., 0.07 mole) was warmed with 0.7 ml. of 0.1 *N* hydrochloric acid in water until the aqueous phase had evaporated (4 hours). The residue, weighing 71.7 mg. (101%), had the same melting point and mixed melting point as authentic ethylene thiourea.

1,3-Diacetylimidazolidine-2-thione (IV).—Ethylene thiourea (5.1 g., 0.05 mole) was dissolved in 20 ml. of acetic anhydride. The solution turned yellow almost at once and it was refluxed for three hours. The mixture was evaporated to dryness under reduced pressure and the crude needles recrystallized from 10 ml. of methanol; yield 7.35 g. (79%), m.p. 85–87°. The compound was slightly soluble in water; it gave a negative test with copper sulfate in hydrochloric acid.

Anal. Calcd.: C, 45.14; H, 5.41; N, 15.04; S, 17.22. Found: C, 45.18; H, 5.34; N (Kjeldahl), 15.08; S, 17.09.

One gram of III was refluxed for one-half hour with 5 ml. of acetic anhydride. Evaporation to dryness yielded yellow needles of IV, m.p. 84–85.5°.

1,3-Diacetylimidazolidine-2-thione (93 mg., 0.05 mole) was warmed with 0.5 ml. of 0.1 *N* hydrochloric acid in water until the aqueous phase had evaporated (4 hours). The residue, weighing 52.0 mg. (102%) had the same melting point and mixed melting point as authentic ethylene thiourea.

Ultraviolet Spectra.—Spectra were measured in ethanol at appropriate dilutions with a Beckman DU spectrophotometer. Wave lengths of maxima and molar absorptivity were found as follows: ethylene thiourea, 235 mμ (15,000); 2-*n*-butylmercaptoimidazoline HCl, 222 mμ (10,500); acetylimidazolidinethione, 235 mμ (12,500), 270 mμ (11,000), shoulder at 325 mμ (80); diacetylimidazolidinethione, 252 mμ (20,000), 288 mμ (11,000), 375 mμ (54).

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Unsymmetrically N-Substituted Piperazines. IV. N-Alkyl Derivatives

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While alkylation of piperazine by lower alkyl halides gives mixtures from which mono-N-alkyl derivatives are not readily separated, the use of higher alkyl halides permits relatively facile isolation of pure products. Two mono-N-alkylpiperazines have been reported previously, the *n*-lauryl[1] and the *n*-decyl[2] derivatives. The former of these, which possesses considerable antibacterial potency, was also found to have marked fungistatic and fungicidal action. Since infections with pathogenic fungi have aroused increased interest in recent years, several related mono-N-alkylpiperazines were prepared. In this series optimal activity was observed with the decyl and lauryl derivatives.

As 2,5-dimethylpiperazine had become available commercially a somewhat parallel series of N-alkyl derivatives was also prepared from this base. The peak of activity was now found associated with the lauryl and tetradecyl compounds. As between members of the two series having the same N-alkyl group, the 2,5-dimethyl compound was never inferior and usually substantially more active, and, at the same time, less toxic. This difference in toxicity was appreciable after injection (intraperitoneally) and very marked on oral administration which suggests possible use against *Monilia* infections of the digestive tract.

(1) R. Baltzly, J. S. Buck, E. Lorz and W. Schoen, THIS JOURNAL, **66**, 263 (1944).

(2) K. E. Hamlin, A. W. Weston, F. E. Fischer and R. J. Michaels, Jr., *ibid.*, **71**, 2731 (1949).

Microbiological tests in buffered solutions indicate that the fungicidal entity both with these and with related piperazine derivatives (*e.g.*, N-methyl-N′-(*p*-chlorobenzhydryl)-piperazine) is the monocation, activity is greater at *p*H 7–8 than at *p*H 6 or *p*H 5.[3]

The 2,5-dimethylpiperazine used as starting material is preponderantly (over 90%) the *trans* form. The mono-N-alkyl derivatives of such a centrosymmetrical substance should be capable of optical activity. So far none has been resolved.

Three carbamates (II, VI and VIII) and two guanidines (IV and X) were prepared from the corresponding N-alkylpiperazines. Compounds II and VI had hypnotic activity of a low order.

Experimental

The physical properties and analytical data of the compounds reported are shown in Table I. Most of the mono-N-alkylpiperazine dihydrochlorides crystallized from ethanol–ether mixtures in fine platelets. In the cases of the higher members (IX, XVII and XVIII) these platelets were rather waxy and the crystals, once obtained, were sparingly soluble in water. A mono hydrochloride was prepared from XII but its physical properties discouraged further work with mono-cationic salts. Melting points over 220° are uncorrected and may be regarded as only approximate. Some of them are decomposition points and others are attended by decomposition and are markedly dependent on minor variations in technique. Hamlin, Weston and co-workers[2] have reported the melting point of V as 271–274°. The writer has obtained the figure shown in Table I on their material as well as our own but would not expect either value to be duplicated by a third party.

Alkylations.—Ideally these reactions would be best performed in a one-phase system at a *p*H favoring predominance of the mono-valent cation (*p*H 7–8). With benzyl chloride yields of monobenzylpiperazine as high as 72% have been obtained in this fashion. With the higher alkyl halides the ideal conditions are not attainable since the alkyl halides have sparing solubility even in hot alcohol and the reaction takes an inordinate time if the halide is added slowly enough to prevent separation of layers. Buffering is also rather unsatisfactory. Piperazine forms rather insoluble phosphates and while acetates give good buffering, the acetate ion reacts appreciably with the alkyl halide. Thus use of acetate buffer results in small loss through formation of dialkylpiperazine but leaves a considerable neutral fraction, presumably alkyl acetate. On a scale large enough to justify recovery of materials, the most convenient and economical procedure is to employ 2 to 3 equivalents of the piperazine and to ignore buffering possibilities.

The separation of products is greatly facilitated by the facts that the mono-N-alkylpiperazines of these molecular dimensions are more readily extracted from ether by dilute acid than are the dialkyl derivatives and that the dihydrochlorides of the latter are sparingly soluble in water. The general procedure has been to extract the total ether-soluble material with successive portions of dilute hydrochloric acid until crystals began to form. At this point an excess of hydrochloric acid would be added to the ethereal layer and the precipitated solid would be filtered off and washed with ether and water. The washings would then be partitioned, the aqueous layer added to the previous acid extracts and the ethereal layer evaporated. Except when acetate buffers were used in the reactions this neutral residue was generally quite small (less than 5% of the starting halide). The aqueous layers were then basified strongly, the basic oil was taken into ether and dried over potassium carbonate. On distillation, the monoalkylpiperazines came over rather sharply leaving only small residues (1 to 2 cc.) of less volatile material. No attempt was made to investigate further the N,N′-dialkylpiperazines separated in working up the reaction mixtures. The following experiment is given in detail to exemplify the methods used.

(3) The results of the microbiological studies will be reported in more detail by Dr. Marion B. Sherwood of these laboratories.

TABLE I

DERIVATIVES OF PIPERAZINE R—N NR′

Compound no.	R	R′	B.p. of base, °C.	M.p. of salt, °C.	Empirical formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
I	C_8H_{17}	H	144–146[a]	255	$C_{12}H_{26}N_2 \cdot 2HCl$	53.1	53.1	10.4	10.5
II	C_8H_{17}	COOEt[g]		209–210[e]	$C_{15}H_{30}N_2O_2 \cdot HCl$	58.9	58.8	10.2	9.7
III	C_9H_{19}	H	112–115[b]	246–249	$C_{13}H_{28}N_2 \cdot 2HCl$	54.7	54.9	10.6	10.4
IV	C_9H_{19}	$C(NH)NH_2$		>265 dec.	$C_{14}H_{30}N_4 \cdot 2HBr$	40.5	40.3	7.8	7.9
V	$C_{10}H_{21}$	H	156–158[c]	246–248	$C_{14}H_{30}N_2 \cdot 2HCl$	56.2	55.9	10.7	11.1[d]
VI	$C_{10}H_{21}$	COOEt[h,m]		210–212[f]	$C_{17}H_{34}N_2O_2 \cdot HCl$	60.5	60.7	10.5	10.3
VII	$C_{11}H_{23}$	H	131–134[b]	250	$C_{15}H_{32}N_2 \cdot 2HCl$	57.5	57.4	11.0	10.9
VIII	$C_{12}H_{25}$	COOEt[h]		213–214[f]	$C_{19}H_{38}N_2O_2 \cdot HCl$	62.9	63.2	10.8	10.7
IX	$C_{16}H_{33}$	H	160–170[b]	255	$C_{20}H_{42}N_2 \cdot 2HCl$	62.6	62.5	11.6	11.4
X	$C_{16}H_{33}$	$C(NH)NH_2$		>250 dec.	$C_{21}H_{44}N_4 \cdot 2HBr$	49.0	49.3	9.0	8.9

DERIVATIVES OF 2,5-DIMETHYLPIPERAZINE R—N(CH$_3$) N(CH$_3$)—R′

XI	C_9H_{19}	H	113[b]	231–232	$C_{15}H_{32}N_2 \cdot 2HCl$	57.5	57.7	10.9	11.2
XII	$C_{10}H_{21}$	H	115–122[b]	67–68[i]	$C_{16}H_{34}N_2HCl \cdot H_2O$	62.2	62.4	12.1	12.3
				233–233.5	$C_{16}H_{34}N_2 \cdot 2HCl$	58.7	58.9	11.1	11.2
XIII	$C_{10}H_{21}$	CH_3[k]		231–232	$C_{17}H_{36}N_2 \cdot 2HCl$	59.8	59.8	11.2	11.3
XIV	$C_{10}H_{21}$	C_2H_5[l]	143[b]	244 dec.	$C_{18}H_{38}N_2 \cdot 2HCl$	60.8	60.4	11.4	11.2
XV	$C_{11}H_{23}$	H	135–136[b]	228	$C_{17}H_{36}N_2 \cdot 2HCl$	59.8	59.8	11.2	11.0
XVI	$C_{12}H_{25}$	H	142–143[b]	229–231	$C_{18}H_{38}N_2 \cdot 2HCl$	60.8	60.8	11.4	11.2
				247–248	$C_{18}H_{38}N_2 \cdot 2HBr$	48.7	49.1	9.1	9.2
XVII	$C_{14}H_{29}$	H	166.5[b]	231–232	$C_{20}H_{42}N_2 \cdot 2HCl$	62.6	62.9	11.6	11.2
XVIII	$C_{16}H_{33}$	H	180[b]	241–242	$C_{22}H_{46}N_2 \cdot 2HCl$	64.2	63.8	11.8	11.8

[a] At 15 mm. pressure. [b] The pressure in these distillations was below 1 mm. but cannot be given more precisely. [c] At 10 mm. pressure. [d] An air-dried sample was analyzed and the figures obtained were corrected for loss in weight on drying in high vacuum. [e] Crystallized from acetone–ether mixtures. [f] Crystallized from ethyl acetate. [g] Prepared by carbethoxylation of I. [h] Prepared by alkylation of N-carbethoxypiperazine in the presence of potassium carbonate. [i] Calcd. H_2O; 5.8; loss in weight in high vacuum, 5.7. [j] Waxy prisms from ethyl acetate. [k] Prepared by Clarke–Eschweiler reaction on XII. [l] Prepared by hydrogenation of XII in the presence of excess acetaldehyde over platinized charcoal. [m] The base has been reported by Hamlin, Weston and co-workers (ref. 2).

Tetradecyl-2,5-dimethylpiperazine.—To 39 g. (0.34 mole) of dimethylpiperazine dissolved in 375 cc. of 95% ethanol was added 25 cc. of concentrated hydrochloric acid, bringing the *p*H to 8. The solution was stirred and heated to reflux and 110 g. (0.34 mole) of tetradecyl iodide was admitted gradually from a dropping funnel. The rate of addition was such as to minimize layer formation. Addition of iodide was finished after 25 hours. Solid sodium bicarbonate was added at intervals whenever the *p*H was observed to be below 6.5. A total of 29 g. (0.34 mole) of bicarbonate was added during 48 hours. At the end of this time the condenser was removed, and alcohol was allowed to boil off for a further 4 hours. (The times mentioned are considerably greater than actually required since two overnight reflux periods are included. During these periods acid accumulated and must have largely checked the displacement reaction.) After cooling, water, strong alkali and ether were added to the reaction mixture and the ethereal layer was washed with water until the washings were neutral: these washings were discarded. The ethereal layers were then extracted with successive portions of *N* hydrochloric acid until a precipitate began to appear. An excess of 3 *N* hydrochloric acid was added and the solid was filtered off and washed with water and ether. The precipitate weighed 43 g. (= 0.076 mole as ditetradecyldimethylpiperazine dihydrochloride). The residue from the ethereal layer weighed 7 g. (0.02 mole calculated as iodide; 0.03 mole calculated as tetradecyl ethyl ether).

The combined aqueous layers from the acid washings were strongly basified, extracted with ether and the ethereal layer was dried over potassium carbonate. The ethereal solution was removed from the desiccant, evaporated and the residual base was distilled at about 0.5 mm. pressure. The distillate, boiling over a 4° range weighed 42 g. (0.135 mole) of which 24.5 g. came over at 166.5°.

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Unsymmetrically Substituted Piperazines. V. Piperazine Ureas

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Certain N-benzyl-N′-carbamylpiperazines reported in the first paper of this series[1] when administered to mice, exhibited hypnotic properties of good quality. These substances were a third to a half as active as the better barbituric acid hypnotics. Accordingly a number of related compounds were examined to see if an hypnotic of practical utility could be obtained by systematic variations. Data on the ureas so prepared are shown in Table I. Compounds VI, VII and VIII had about the same hypnotic potency as the compounds prepared earlier. Compounds III and IV were quite weak hypnotics.