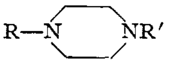
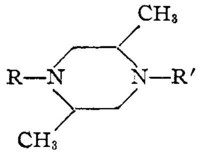
TABLE I

DERIVATIVES OF PIPERAZINE



Compound no.	R	R′	B.p. of base, °C.	M.p. of salt, °C.	Empirical formula	Analyses, %			
						Carbon		Hydrogen	
						Calcd.	Found	Calcd.	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 									
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

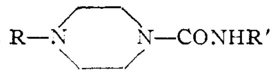
BY RICHARD BALTZLY, SAMUEL W. BLACKMAN AND WALTER S. IDE

RECEIVED JULY 27, 1953

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.

TABLE I

UREAS DERIVED FROM N-MONOSUBSTITUTED PIPERAZINES



Compound no.	R	R′	M.p., °C.	Empirical formula	Analyses, % Carbon		Hydrogen	
					Calcd.	Found	Calcd.	Found
I	$C_6H_5CH_2$	Et	226–228	$C_{24}H_{21}N_3O \cdot HCl$	59.2	59.1	7.8	7.7
II	Me	C_6H_5[a]	134	$C_{12}H_{17}N_3S$	61.2	60.9	7.3	7.0
			208–210	$C_{12}H_{17}N_3S \cdot HCl$	53.0	53.1	6.7	6.8
III	n-C_8H_{17}	H	236–237[e] dec.	$C_{13}H_{27}N_3O \cdot HCl$	56.2	56.1	10.2	10.0
IV	n-$C_{11}H_{23}$	H[b]	231–233[e] dec.	$C_{16}H_{33}N_3O \cdot HCl$	60.1	60.0	10.7	10.3
V	n-$C_{16}H_{33}$	H[c]	222–225[e] dec.	$C_{21}H_{43}N_3O \cdot HCl$	64.6	65.1	11.4	11.6
VI	p-$BrC_6H_4CH_2$	H[d]	238–241[e] dec.	$C_{12}H_{16}BrN_3O \cdot HCl$	43.1	43.2	5.1	5.0
VII	3,4-$Cl_2C_6H_3CH_2$	H	245.5–246.5 dec.	$C_{12}H_{15}Cl_2N_3O \cdot HCl$	44.5	44.6	5.0	4.8
VIII	Ph_2CH	H	203–204	$C_{18}H_{21}N_3O \cdot HCl$	65.1	65.5	6.7	6.5
IX	α-$C_{10}H_7CH_2$	H	203	$C_{16}H_{19}N_3O \cdot HCl$	62.8	62.9	6.6	6.5

[a] Thiourea. [b] The base, crystallized from ether–hexane mixture, melts at 96°. [c] The base crystallizes from hexane in small platelets and melts at 99.5–100.5°. [d] The base crystallizes in needles from 40% ethanol, m.p. 177–179.5°. [e] Platelets.

Experimental

All the ureas were prepared by conventional methods. Compound I was obtained by the reaction of benzylpiperazine[1] with ethyl isocyanate; compound II from methylpiperazine[2] and phenyl isothiocyanate. The other ureas were formed by the reaction of the appropriate bases with nitrourea. Compounds VIII and IX were crystallized from ethanol–ether mixture, the hydrochloride of II from aqueous ethanol and the other compounds of Table I from absolute ethanol.

Intermediates.—N-Octyl-, -undecyl- and -cetylpiperazines[3] and N-benzhydrylpiperazine[4] are known.

N-(*p*-Bromobenzyl)-N′-carbethoxypiperazine.—Carbethoxypiperazine[5] was allowed to react with *p*-bromobenzyl bromide in alcohol in the presence of sodium carbonate. After standing several hours with occasional shaking, water was added to dissolve the inorganic material and the solution was partitioned between ether and water. The ethereal layer was then extracted with dilute hydrochloric acid and the extract was evaporated *in vacuo*. The residual hydrochloride was recrystallized from ethanol–ether mixture, m.p. 223° dec.

Anal. Calcd. for $C_{14}H_{19}BrN_2O_2 \cdot HCl$: C, 46.2; H, 5.5. Found: C, 46.6; H, 5.6.

N-(*p*-Bromobenzyl)-piperazine.—The above carbamate was refluxed 20 hours in 6 *N* hydrochloric acid and the solution was evaporated *in vacuo*. The residual solid, which was unmelted at 290°, was recrystallized from a little water.

Anal. Calcd. for $C_{11}H_{15}BrN_2 \cdot 2HCl$: C, 40.3; H, 5.2. Found: C, 39.9; H, 5.1.

N-(3,4-Dichlorobenzyl)-piperazine.—3,4-Dichlorobenzoic acid was reduced to 3,4-dichlorobenzyl alcohol[6] by lithium aluminum hydride. The alcohol was converted (at least partially) to the chloride by the method of Norris[7] and the latter was added in benzene solution to carbethoxypiperazine in alcohol in the presence of sodium carbonate. The working up, which was similar to that of the *p*-bromobenzyl analog, afforded a product that crystallized in leaflets, melted at 212–213° and was not quite pure as judged by analysis. After hydrolysis with 6 *N* hydrochloric acid, N-(3,4-dichlorobenzyl)-piperazine dihydrochloride, m.p. 257° dec., was obtained. It was crystallized from ethanol-ethyl acetate mixture.

Anal. Calcd. for $C_{11}H_{14}Cl_2N_2 \cdot 2HCl$: C, 41.5; H, 5.1. Found: C, 41.5; H, 5.3.

N-(α-Naphthylmethyl)-piperazine.—The reaction of α-chloromethylnaphthalene with piperazine in 95% ethanol is rather unsatisfactory, presumably due to extensive solvolysis. The base was isolated as the fraction insoluble in water and soluble in dilute acid. It boils at 178° at 1 mm. pressure. The dihydrochloride melts at 273°.

Anal. Calcd. for $C_{15}H_{18}N_2 \cdot 2HCl$: C, 60.2; H, 6.7. Found: C, 60.1; H, 6.6.

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Polarography of Phenyl 2-Thienyl and 2,2′-Dithienyl Ketones

BY R. A. DAY, JR., AND W. A. BLANCHARD

RECEIVED OCTOBER 19, 1953

The effect of aromatic groups in ketones in promoting double-wave formation upon polarographic reduction of the carbonyl group has been pointed out in recent publications.[1,2] Heterocyclic groups, such as thienyl, would be expected from both steric and resonance considerations to impart greater stability than a phenyl group to the dimer assumed to form in basic solution.[3] Thus phenyl 2-thienyl ketone would be expected to form double waves in basic media more readily than benzophenone. Likewise 2,2′-dithienyl ketone should produce double waves more readily than phenyl 2-thienyl ketone.

These two ketones have been prepared and their polarography studied in buffered ethanol–water media over the *p*H range of 1 to 13. The above expectations were found to be true, as shown in Table I.

Phenyl 2-thienyl ketone shows normal behavior in acid media, giving two waves of about equal height at *p*H 3.2 and 4.1.[4] The second wave is masked by discharge of hydrogen at *p*H 1.0. The two waves are merged at *p*H 5.1 into one wave of full height. The half-wave potential of this single wave becomes progressively more negative as the *p*H is increased. The larger increase at *p*H 8.1 is usually noted on change to a borate buffer. At *p*H 10.1 a small second wave is present. This wave increases in height at the expense of the first wave as

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[1] R. A. Day, Jr., S. R. Milliken and W. D. Shults, THIS JOURNAL, **74**, 2741 (1952).

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[4] All *p*H values herein are of the aqueous buffer.