TABLE II

REACTION PRODUCTS

Expt.[a]	DurCOC$_6$H$_4$X (in which X =)	M.p., °C.	Mol. formula	Analyses, % Calcd. C	Calcd. H	Calcd. S	Found C	Found H	Found S
1	*o*-OC$_6$H$_5$	124.5–125.5	C$_{23}$H$_{22}$O$_2$	83.60	6.71	....	83.51	6.83	...
2	*o*-O-C$_6$H$_4$-Br	210.5–211.5	C$_{23}$H$_{21}$O$_2$Br	67.49	5.17	....	67.90	5.31	...
3	*o*-SC$_6$H$_5$	155.5–156.5	C$_{23}$H$_{22}$OS	79.73	6.40	9.25	79.83	6.44	9.19
4	*o*-SCH$_3$	191.5–192.5	C$_{18}$H$_{20}$OS	75.99	7.09	11.27	76.12	7.07	11.49
5	*o*-OC$_6$H$_5$	124.5–125.5							
6	*o*-O-C$_6$H$_4$-NO$_2$	156–157	C$_{23}$H$_{21}$NO$_4$	73.58	5.64	3.73[b]	73.86	5.64	3.66[b]
7	*p*-OC$_6$H$_5$	146–147.5	C$_{23}$H$_{22}$O$_2$	83.60	6.71	....	83.63	6.90	....

[a] These numbers correspond to the experiments enumerated in Table I. [b] These values are for nitrogen.

treated with 7.5 g. of potassium permanganate in 240 ml. of water; the yield of sulfone was 82%. After recrystallization from methanol, it melted at 195.3–196.3°.

Anal. Calcd. for C$_{18}$H$_{20}$O$_3$S: C, 68.30; H, 6.37; S, 10.13. Found: C, 68.32; H, 6.51; S, 10.23.

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Unsymmetrically-Substituted Piperazines. VII.

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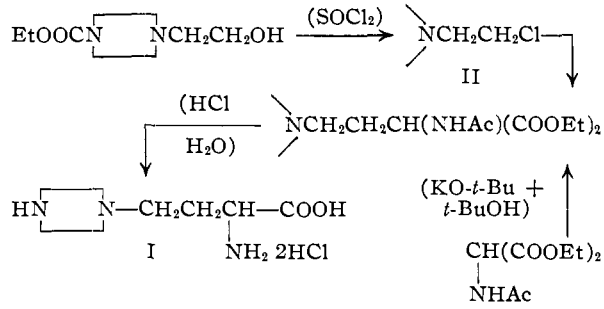
Some unsymmetrically-substituted piperazines prepared in connection with a continuing program[1] for the synthesis and pharmacological evaluation of such compounds were found to possess a moderate order of anthelmintic activity against *Syphacia obvelata*, a mouse pinworm.[2] The preparation and properties of some of the piperazines prepared, most of which have polar substituents, are reported here.

The synthetic routes used, in general, involved the alkylation of N-carbethoxypiperazine[3] by the appropriate halide in a suitable solvent, using an additional equivalent of the amine and filtering at the end of the alkylation to remove amine hydrohalide, or using potassium carbonate or sodium ethoxide to bind the acid which was produced. This procedure served to eliminate the tedious separations and low yields which frequently accompany the direct mono-alkylation of piperazine. 1-Nonyl-4-carbethoxypiperazine was prepared by treating 1-nonylpiperazine[1] with ethyl chlorocarbonate, and converting the hydrochloride so produced to the base with the theoretical amount of sodium ethoxide in ethanol.

Hydrolytic removal of the carbethoxyl group was accomplished by heating with constant-boiling aqueous hydrochloric acid under reflux, the preferred procedure[3] for the extremely water-soluble lower piperazine homologs, and subsequent conversion of the resulting hydrochlorides to the bases with sodium ethoxide in anhydrous ethanol. The carbethoxyl group was removed from 1-octyl-4-carbethoxypiperazine at a reasonable rate by heating it under reflux with aqueous ethanolic sodium hydroxide, provided that vigorous stirring was used. The resulting 1-octylpiperazine was converted by a Schotten–Baumann reaction to its *p*-nitrobenzoyl derivative, whose water-insoluble hydrochloride was reduced by hydrogen and Adams catalyst to 1-octyl-4-p-aminobenzoylpiperazine, the piperazine analog of a piperidine reported[4] to have antitubercular and amoebastatic activity.

For the preparation of the very water-soluble amino acid α-piperazinopropionic acid (Table, line 13), ethyl α-(4-carbethoxypiperazino)-propionate (Table, line 12) was hydrolyzed with boiling aqueous barium hydroxide under reflux. Treatment with carbon dioxide, and subsequent boiling of the solution, allowed the barium to be removed as carbonate. The success of this procedure indicates that the amino acid exists as a zwitterion, as would be expected.

The amino acid I, modelled as a possible antimetabolite to histidine, was prepared in excellent yield as outlined in the partial formulas.



Potassium *t*-butoxide in *t*-butyl alcohol[5] was used as the condensing agent, to ensure the absence of side reactions. The initial condensation product could not be crystallized readily, and so was converted without purification to the amino acid.

The details of the procedure used to recover 2-(4-benzylpiperazino)-propanol from the lithium aluminum hydride reduction of the corresponding propionic acid are given in the Experimental section, since they illustrate some minor modifications of the

(1) For the previous paper of this series, see R. Baltzly, THIS JOURNAL, **76**, 1164 (1954).

(2) H. W. Brown, K. F. Chan and K. L. Hussey, *Am. J. Trop. Med. Hyg*, **3**, 504 (1954).

(3) T. S. Moore, M. Boyle and V. M. Thorne, *J. Chem. Soc.*, 39 (1929).

(4) P. Truitt, G. Sammons and D. Zachry, THIS JOURNAL, **74**, 5961 (1952).

(5) The *t*-butyl alcohol was dried by storing it over calcium hydride at a temperature over its m.p., venting the hydrogen produced. The dry *t*-butyl alcohol produced in this way requires no distillation for synthetic purposes, but is simply decanted from the hydride as needed. It is neutral to test paper.

more usual methods, which have been found to enable the ready recovery of the water-soluble piperazine alcohols from such reductions, essentially free of inorganic salts.

1-Methyl-4-carbamylpiperazine was prepared from 1-methylpiperazine and aqueous nitrourea,[6] and 1-methyl-4-nitrosopiperazine was made by treatment of aqueous 1-methylpiperazine with nitrous acid. A future report will deal with the use of the carbamyl and the nitroso functions as protecting groups in the synthesis of other substituted piperazines.

Approximate pK_a values were determined from the pH at the mid-points of the titration curves of 1-methyl-4-nitrosopiperazine (5.93), of 1-methyl-4-benzoylpiperazine (6.78), of 1-propargyl-4-carbethoxypiperazine (5.44) and of 1-methyl-4-carbethoxypiperazine (7.31) in water on titration with hydrochloric acid. The lowering of the pK_a due to substitution of a propargyl for a methyl group is seen to be 1.9 units, which is about the middle of the range of values found[7] for some simpler amines. Substitution of a benzoyl or a nitroso group for the carbethoxyl of 1-methyl-4-carbethoxypiperazine decreased the value of the pK_a, as would be expected, although the magnitude of the changes was somewhat greater than was expected.

Acknowledgment.—The author wishes to acknowledge many helpful discussions with Dr. R. Baltzly, and to thank S. W. Blackman for the elemental analyses reported. He is indebted to E. Magnien and Frances M. Smith for skilled technical assistance.

Experimental

1-β-Chloroethyl-4-carbethoxypiperazine (II).—Fifty grams (0.25 mole) of 1-β-hydroxyethyl-4-carbethoxypiperazine[3] dissolved in 150 ml. of anhydrous ether was added in 15 minutes to a solution of 36 g. (0.3 mole) of thionyl chloride in 300 ml. of anhydrous ether contained in a flask equipped with stirrer and reflux condenser. After the spontaneous boiling had subsided, the reaction mixture, from which a thick oil which soon solidified had separated, was heated under reflux for six hours, and allowed to stand overnight. The solid was then removed by filtration and washed with ether, yielding 65 g., m.p. 183–188°. A portion was recrystallized four times to a constant m.p. of 194° by adding anhydrous ether to incipient turbidity to its solution in hot absolute ethanol.

Anal. Calcd. for $C_9H_{18}N_2O_2Cl_2$: C, 42.03; H, 7.05. Found: C, 42.10; H, 7.07.

2-Amino-4-piperazinobutyric Acid (I).—To a solution of 6.9 g. (0.173 mole) of potassium in 150 ml. of dry *t*-butyl alcohol[5] was added 31 g. (0.143 mole) of ethyl α-acetamidomalonate, the temperature being maintained just above the freezing point of the solvent. While the resulting solution was stirred, a suspension of 40.5 g. (0.157 mole) of 1-β-chloroethyl-4-carbethoxypiperazine in 150 ml. of dry *t*-butyl alcohol and a solution of 6.9 g. (0.17 mole) of potassium in 150 ml. of dry *t*-butyl alcohol were added simultaneously during 15 min. The reactants, protected by a sodium hydroxide trap, were stirred and heated under reflux an additional 8 hours and allowed to remain overnight. Filtration and evaporation of the filtrate *in vacuo* yielded a sirup, which was heated under reflux with 450 ml. each of water and concentrated hydrochloric acid for 3 days. Removal of the solvent from this gave an oil which crystallized on scratching and was recrystallized from water–ethanol

(6) T. L. Davis and K. C. Blanchard, THIS JOURNAL, **51**, 1790 (1929); R. Baltzly, *et al.*, *ibid.*, **66**, 263 (1944). The hydrochloride has been made in 72% yield by another method [S. Kushner, *et al.*, *J. Org. Chem.*, **13**, 144 (1948)].

(7) K. N. Campbell, F. C. Fatora, Jr., and B. K. Campbell, *ibid.*, **17**, 1141 (1952).

TABLE I

Substituent 1	Substituent 4	Method[a]	Preparation Time, hr.	Preparation Temp., °C.[b]	%	B.p., base °C.	B.p., base Mm.	Salt M.p., °C.	Salt Recryst.	Equiv. wt. Calcd.	Equiv. wt. Found	Calcd.[c] C	Calcd.[c] H	Found[c] C	Found[c] H
CH_3–	–NO	W[d]	1/2	−5 to 0	93	93–95	8	166–167[n]	A-E	129[g]	130[g]	36.26	7.82	35.88	7.82
CH_3–	$-CONH_2$	W[d]	1/2	[m]	76	121 (m.p.)		.....	B[e]			50.38[g]	9.15[g]	50.52[g]	9.15[g]
CH_3–	$-COC_6H_5$	W[f]	1/4	0	75	114–116	0.04	142.5–143[p]	AW-A	204[g]	202[g]	45.10	5.53	44.83	5.42
n-C_9H_{17}–	*p*-$NO_2C_6H_4CO$-	W[f]	1 1/2	10	100	.....		201.5–202[n]	D[e]			59.44	7.88	58.90	7.80
n-C_9H_{17}–	*p*-$NH_2C_6H_4CO$-	AW[d]	3/4	R	59	.....		220[n]	AW			64.47	9.12	64.93	8.87
n-C_9H_{19}–	–COOEt	A[d]	1	B	59	.....		187–190[n]	EA			59.88	10.36	59.89	10.54
$HC\equiv C-CH_2$–	–COOEt	E[h]	3	B	98	88–89	0.03	174.3–175[n]	A-EA-E	196[g]	201[g]	Cl−	15.36	Cl−	15.24
$PhCH_2$–	$HOCH_2CHOHCH_2$-	A[i]	10	B	58	143–160	0.2	234–236[o]	AW			52.01	6.86	52.49	7.10
H–	$HOCH_2CHOH-CH_2$-	MW[j]	1	R	93	101–103 d.	.1	169–171[o]	M, MW			36.06	7.78	36.18	8.05
$PhCH_2$–	$-CH(CH_3)COOEt$	AW[k]	26	B	74	105–111	.2	217.5–218.2[p]	A-E			N[l]	8.02	N[l]	7.76
H–	$-CH(CH_3)CH_2OH$	MW[j]	1	45	82	.....		203–203.5[p]	M-E			38.72	8.35	38.62	8.15
$EtOOCCH(CH_2)$–	–COOEt	Ac-B[h]	18	B	74	108	.7	140.5–141.5[n]	A-E			48.89	7.86	48.51	7.78
$HOOCCH(CH_3)$–	–H	W[d]	16	B	82	.....		270 dec.[e]	I-W			53.14[g]	8.92[g]	52.97[g]	9.31[g]
S—C=C—C=C—CH_2–	–COOEt	Ac[h]	48	R	73	122–134	.04	217–217.5[n]	A-B-E			Cl−	12.20	Cl−	12.23

[a] Solvents: A = absolute ethanol, AW = 95% ethanol, Ac = acetone, B = benzene, D = dioxane, E = absolute ether, EA = ethyl acetate, I = isopropyl alcohol, M = methanol, MW = 95% methanol–5% water. [b] R = room temp., about 22–28°, B = b.p. of solution. [c] For the salt given. [d] See text. [e] Free base. [f] Schotten–Baumann reaction. [g] The product darkened in light if wet with dioxane. [h] Two moles of amine/mole halide was used. [i] One mole of sodium ethoxide/mole halide was used. [j] 5% Pd-on-charcoal and H_2 in Parr shaker on corresponding N-benzyl compound. [k] Potassium carbonate, 1 mole/mole bromoester, was used. [l] Kjeldahl. [m] 10 min. at 60°, 10 min. to reach 100°, and 10 min. at 100°. [n] Monohydrochloride of base. [o] Dihydrochloride of base. [p] Methiodide.

and water–ethanol–ethyl acetate, m.p. 258–259° (slow heating) or 278–281° (rapid heating), with decomposition. It gave a strong blue ninhydrin test.

Anal. Calcd. for $C_8H_{19}N_3O_2Cl_2$: C, 36.93; H, 7.36; Cl, 27.25. Found: C, 37.12; H, 7.86; Cl, 27.60.

2-(4-Benzylpiperazino)-propanol.—The reduction of 31 g. (0.112 mole) of ethyl 2-(4-benzylpiperazino)-propionate by 7.6 g. (0.2 mole) of lithium aluminum hydride in ether was carried out in the usual way. After 5 hours under reflux, the solution was treated with 18 ml. of water which must be added *dropwise* with stirring, initially at a maximum rate of one drop each few seconds, since the reaction mixture tends to foam as the hydrogen is involved. After the water had been added and the reaction mixture stirred an additional 10 minutes to ensure the destruction of all of the hydride, 9 g. of Dry Ice in small pieces was added through the condenser over 5 minutes with stirring, to decompose any lithium alkoxide. Filtration, washing of the solids with anhydrous ether, removal of the solvent and distillation of the remaining oil gave 22.5 g. (86%), b.p. 111–130° at 0.3 mm. The dihydrochloride was recrystallized from absolute ethanol, m.p. 239.8° dec.

Anal. Calcd. for $C_{14}H_{24}N_2OCl_2$: C, 54.72; H, 7.87. Found: C, 54.73; H, 8.20.

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Hydroxylation of Benzene in a Solution of Hydrogen Peroxide and Copper Sulfate

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The formation and reactions of hydroxyl radicals in aqueous solutions have been the object of numerous investigations.[1] Wieland[2] observed that hydrogen peroxide in the presence of cupric ions degrades stable organic compounds, like benzoic acid, to carbon dioxide and water. Since Baxendale[1c] reported that cuprous ions generate hydroxyl radicals from hydrogen peroxide, it seemed probable that the reaction described by Wieland proceeds through the intermediate formation of phenols. On treating benzene under suitable conditions with aqueous hydrogen peroxide and copper sulfate we were able to isolate phenol from the reaction mixture. Salicylic acid was obtained by treating sodium benzoate in a similar manner.

Experimental

Hydroxylation of Benzene.—Two grams of copper sulfate in 100 ml. of distilled water and 25 ml. of 30% hydrogen peroxide was vigorously agitated on a shaking machine for 14 hr. with 150 ml. of benzene. After 14 hours the mixture was filtered in order to break up the emulsion. The black aqueous layer was acidified with 6 *M* sulfuric acid and then extracted with successive portions of methylene chloride. The benzene and the methylene chloride were extracted with dilute sodium hydroxide and the alkaline extracts were acidified and treated with decolorizing carbon. The resulting clear solution was extracted with methylene chloride. The organic layer was dried and the solvent was removed leaving 0.14 g. of long needles, m.p. 37°, with the characteristic odor of phenol. It was converted into tribromophenol (0.30 g.) by bromine water, and recrystallized from dilute alcohol, m.p. 92° (uncor.). The experiment was repeated with a reaction time of 65 hr. and gave 0.37 g. of the crude product and 0.86 g. of the brominated derivative.

Hydroxylation of Sodium Benzoate.—Fifty ml. of a 0.2 *M* solution of sodium benzoate, adjusted to *p*H 4 with excess acid, was mixed with an equal volume of a 0.4% solution of hydrated copper sulfate. On the addition of 12 ml. of 30% hydrogen peroxide the solution turned green and some green precipitate settled out. The volume of the system was made up to 500 ml. with distilled water and it was allowed to stand for 13 hr. At the end of that period the yellow brown solution was acidified with 6 *M* sulfuric acid and extracted with ethyl ether. After drying the extract the solvent was removed, leaving 1 g. of a light brown crystalline residue. On the addition of dilute ferric nitrate to an aqueous solution of the product, an intensely violet color developed. The absorption spectra in 0.00040 *M* aqueous ferric nitrate of a 0.014% solution of salicylic acid and a 0.19% solution of the product were compared. At the 530 mμ absorption maximum the values of log I/I_0 were 0.63 and 0.55, respectively. The yield of 0.04 g. of salicylic acid was estimated colorimetrically.

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Nitrohydroxy Aromatic Ketones. I. Nitrohydroxyacetophenones

BY SHIAM SUNDER JOSHI AND HARI SINGH

RECEIVED NOVEMBER 23, 1953

Though simple in structure, only a few nitrohydroxyacetophenones are described in the literature. These have been prepared in general by nitration of hydroxyketones or their derivatives and by acetylation of nitrophenols. By direct nitration, 3-nitro-4-hydroxy-,[1] 3-nitro-6-hydroxy-[2] and 3-nitro-2-hydroxy-5-methylacetophenones[2,3] were obtained. The oximes and acetyl derivatives of hydroxyacetophenones have also been employed.[4–6]

It has been reported that the nitro group inhibits direct acetylation[7] or migration of the acetyl group under the influence of aluminum chloride.[8,9] However, 3-nitro-4-hydroxyacetophenone has been obtained recently by both reactions.[10] It had been obtained earlier from 2-nitroanisole[11,12] and by hydrolysis of 4-bromo-3-nitroacetophenone.[13] The present investigation confirms other reports[14,15] that inhibition due to the nitro group may be overcome by proper experimental conditions.

The literature also records the formation of picric acid during the attempted dinitration of *o*-hydroxyacetophenone.[5] 3,5-Dinitro-6-hydroxyacetophenone was obtained in this Laboratory as a result of

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