tained pure because both were very hygroscopic. The picrate and picrolonate were obtained as well-characterized crystalline salts.

**Picrate.**—Prepared in and recrystallized from absolute ethanol, the picrate formed yellow elongated prisms which softened at 210° and melted, with decomposition, at 218.5–219.5° (cor.).

*Anal.* Calcd. for $C_{14}H_{18}N_4O_8$: C, 45.41; H, 4.89. Found: C, 45.57; H, 5.06.

**Picrolonate.**—Prepared in and recrystallized from absolute ethanol, the picrolonate formed yellow elongated prisms, m. p. 182.5–183.5° (cor.). It is interesting that the melting point of the racemic 1-methyl-7-hydroxypyrrolizidine picrolonate is almost the same as that of retronecanol picrolonate, m. p. 184–185°.[19] These picrolonates, of course, are not identical.

*Anal.* Calcd. for $C_{18}H_{23}N_5O_6$: C, 53.33; H, 5.72; N, 17.28. Found: C, 53.26; H, 5.71; N, 17.32.

## Summary

1. 1-Methyl-7-ketopyrrolizidine has been synthesized through ethyl 3-methylpyrrolidine-2-carboxylate (obtained from γ-picoline) by addition to ethyl acrylate followed by a Dieckmann cyclization and hydrolysis. The final product probably was a mixture of two racemates. By condensation with *l*-menthydrazide a single pure 1 - methyl - 7 - ketopyrrolizidine - *l* - menthydrazone was isolated. This was different from the *l*-menthydrazone of retronecanone in melting point and rotation.

2. Optically active ethyl 3-methylpyrrolidine-2-carboxylate was converted to the corresponding optically active 1-methyl-7-ketopyrrolizidine by a similar series of reactions. By treatment of the reaction mixture with hydroxylamine, a pure optically-active 1 - methyl - 7 - ketopyrrolizidine oxime resulted, which was identical with retronecanone oxime in melting point and rotation. The identity was verified further by the preparation of identical picrates and picrolonates.

3. It has been proved that the keto group in retronecanone is in the 7-position. From this it may be deduced that the secondary hydroxyl group in retronecanol, retronecine, platynecine, desoxyretronecine, heliotridine, and oxyheliotridane is in the 7-position.

4. It has been shown that in the reduction of desoxyretronecine, retronecine, and esters of retronecine to give retronecanol, asymmetric reduction has taken plaec with the exclusive formation of one stereochemical configuration of the $C_1$-$CH_3$.

5. Reduction of retronecanone in neutral and acid solutions gave a mixture of corresponding hydroxy compounds, from which retronecanol could not be isolated.

(19) Konovalova and Orekhov, *Bull. soc. chim.*, [5] **4**, 1285 (1937).

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[CONTRIBUTION FROM THE BURROUGHS WELLCOME & CO. U. S. A. EXPERIMENTAL RESEARCH LABORATORIES]

# The Preparation of N-Mono-substituted and Unsymmetrically Disubstituted Piperazines

BY RICHARD BALTZLY, JOHANNES S. BUCK, EMIL LORZ AND WILLIAM SCHÖN

The direct alkylation of piperazine produces a mixture of substitution products from which the isolation of mono-substituted compounds is difficult or impossible when the substituting group is relatively small. Because of this the belief has arisen that mono-substitution products are not formed, although examination of reported experiments shows only that they were not isolated. A similar situation has prevailed in regard to acylation, although even mono-acetylpiperazine can be obtained easily by logical manipulation.

In Table I are shown the yields of mono- and di-substituted piperazines from a number of reactions, together with the reaction conditions. It seems indicated that in the ideal case where the entire reaction takes place in one homogeneous phase, equimolecular proportions of reactants result in the 1:2:1 proportions of piperazine, mono-substituted piperazine and di-substitution product predicted on general considerations.

Major deviations from these proportions would be expected if a salt of piperazine itself (such as the dihydrochloride which is sparingly soluble in absolute ethanol) were to precipitate during the reaction, or if the acylating or alkylating agent were to form a second liquid phase, thus tending to extract preferentially mono-substituted piperazine already present.

The yields here recorded compare favorably with those claimed for more involved procedures.[1] The argument by which Moore[1a] was led to operate at low *p*H is probably valid. The second benzylation recorded in Table I, run at *p*H about 3.5 gave a proportion of mono-benzyl to dibenzyl piperazine of about 5–1. Similarly a proportion of 2.7–1 was observed in the carbethoxylation, where a low *p*H must have existed toward the end of the reaction. As a preparative method with moderately priced chemicals, however, the buffering procedures seem unprofitable.

From the mono-substituted piperazines that were thus rendered available a number of unsymmetrically disubstituted derivatives have been prepared. These are characterized in Table II.

(1) (a) Moore, Boyle and Thorn, *J. Chem. Soc.*, 39 (1929); (b) Jacobi, *Ber.*, **66**, 113 (1933). The methods described in these papers are two-phase acylations at low *p*H. The conditions are difficult to reproduce exactly and it is doubtful if yields significantly above 50% should be expected from them.

TABLE I

PRODUCTS OF REACTION OF PIPERAZINE WITH VARIOUS REAGENTS

| Reagent | Moles of reagent | Moles of piperazine | Solvent | Reaction time, hr. | Reaction temp., °C. | Mono-substituted piperazine: Moles obt. | Mono-substituted piperazine: B. p., °C. | Mono-substituted piperazine: Pressure, mm. Hg | Moles of disubstituted piperazine obt. |
|---|---|---|---|---|---|---|---|---|---|
| $C_6H_5CH_2Cl$ | 0.5 | 0.5[a] | 300 cc. abs. EtOH | 20 | 25–30 | 0.15–0.16 | 154–160 | 18 | 0.1 |
| | | | | | | | 145–147 | 12 | |
| $C_6H_5CH_2Cl$ | .5 | .5[b,c] | 500 cc. 50% MeOH | 80 | 65 | .26 | 127–130 | 2 | .05 |
| $p$-$ClC_6H_4CH_2Cl$ | .5 | .5[a] | 300 cc. abs. EtOH | 20 | 25–30 | .20 | 140–142 | 2.5 | .1 |
| $p$-$MeOC_6H_4CH_2Cl$ | .5[d] | .5[a] | 250 cc. abs. EtOH | 20 | 25–30 | .14 | 150 | 2.5 | ..[e] |
| $C_6H_5CH_2CH_2Br$ | .5 | .5[a] | 300 cc. abs. EtOH | 40 | 80 | .09 | 150–152 | 8 | ..[e] |
| $n$-$C_{12}H_{25}Br$ | .12 | .17[b] | 170 cc. 90% EtOH | 20 | 80 | .05 | 140 | 1/4 | .017 |
| $CH_2—CH_2$ \ O / | .33 | .5[a] | 500 cc. abs. EtOH | 72 | 25 | .17 | 122–123 | 10 | .06 |
| $CH_2—CH_2$ \ O / | .30 | .60[b] | 300 cc. abs. EtOH | 72 | 25 | .16 | 122–123 | 10 | ..[g] |
| ClCOOEt | .5 | .5[b] | 350 cc. 85% EtOH | 1[f] | 40–50 | .27 | ..... | .. | .1[g] |
| $(CH_3CO)_2O$ | .5 | .5[b] | 300 cc. HAc | 1[f] | 50 | .2 | ..... | .. | ..[g] |

[a] Piperazine hexahydrate used. [b] Anhydrous piperazine used. [c] This run was made at about the *p*H specified by Moore.[1a] [d] 0.5 mole of anisyl alcohol was treated with gaseous HCl and the crude but dry and neutral product used directly. [e] Disubstituted product not isolated. [f] At end of hour soln. was allowed to cool and stand overnight. [g] 15% of original piperazine recovered.

Since, further, the benzyl group can be removed by catalytic hydrogenation,[2] preferably with palladium, a variety of mono-substituted piperazines that would be difficult to separate from a reaction mixture can be obtained pure. The lower alkyl piperazines can also be prepared by alkylating N-piperazine ethyl carboxylate, but this intermediate is unsuitable with more labile systems for which the debenzylation procedure appears preferable.

## Experimental

**Benzylations.**—Data on the preparations are given in Table I. On completion of the reaction, the solution was evaporated *in vacuo*, and the residue partitioned between ether and sodium hydroxide solution. After drying over potassium hydroxide or potassium carbonate the ethereal extract was evaporated and the residual oil distilled *in vacuo*.

In the preparations with *p*-chlorobenzyl and anisyl chlorides and in one run with benzyl chloride considerable solid separated toward the end of the reaction. These solids were filtered off and recrystallized from alcohol; the mother liquors added to the filtrate, and the whole worked up as indicated above. The recrystallized solids were the fairly pure dihydrochlorides of the respective disubstituted piperazines. In these cases very little disubstituted compound was found in the distillation.

In some cases a small amount of piperazine was present in the first fraction of the mono-benzyl derivative. This could be removed by washing in ether solution with water or dilute alkali.

In view of the considerable reaction of benzyl chlorides with water and alcohols, it is likely that the yields could be improved by additon of excess benzyl chloride, possibly with sodium acetate for buffering.

In the reactions of piperazine with lauryl and phenethyl bromides heating was required. The poor yield of phenethylpiperazine was presumably due to loss of hydrogen bromide. The corresponding di-substituted piperazines were very high-boiling and the *bis*-phenethylpiperazine decomposed at the pressure used instead of distilling.

**Reaction with Ethylene Oxide.**—The only significant differences from the procedure of Kitchen and Pollard[3] were in the proportions of reactants (see Table I) and the reaction temperature.

**Carbethoxylation.**—One-half mole (43 g.) of anhydrous piperazine was dissolved in 300 cc. of 95% ethanol. To this was added, with mechanical stirring, 54 g. (0.5 mole) of ethyl chlorocarbonate. The solution warmed itself fairly rapidly (thirteen minutes) to 50° whereupon water cooling was used to keep the temperature below 50°. At this point solid began to separate and 50 cc. of water was added to restore it to solution. The addition of the ethyl chlorocarbonate required about thirty minutes. Shortly thereafter solid was again observed and two types of crystal were apparent. The solution was allowed to stand overnight. The solid was filtered off and washed with 10 cc. of absolute ethanol. The undissolved crystals were piperazine dihydrochloride.

The filtrate, which was acid to congo red, was evaporated *in vacuo*. The residue was dissolved in water and extracted twice with ether. The ethereal extract, on evaporation, yielded 24 g. of N,N'-piperazine *bis*-ethylcarboxylate, a gum that crystallized from hexane and then melted at 49°. The aqueous layer was again taken down *in vacuo* and extracted with a minimum of absolute alcohol, a small residue of piperazine dihydrochloride being again separated. The yellow solution on addition of ethyl acetate and ether, and cooling deposited flesh-colored crystals of piperazine N-ethylcarboxylate hydrochloride. Recrystallization from absolute alcohol with charcoaling gave a colorless product melting at 145°.

**Acetylation.**—One-half mole (43 g.) of anhydrous piperazine was dissolved in 300 cc. of glacial acetic acid. To this was added with stirring 51 g. (0.5 mole) of acetic anhydride. The addition took fifteen minutes during which the temperature rose from 48 to 54°. Stirring was continued for one-half hour and the solution was allowed to stand overnight. Fifty cc. of concentrated hydrochloric acid was then added and the solution was evaporated *in vacuo*. The residue, a thick, red-brown sirup was extracted with 300 cc. of hot benzene to remove the diacetylpiperazine. The benzene-insoluble material was treated with absolute ethanol and the resulting solution filtered off from piperazine dihydrochloride. On addition of ether and standing in the refrigerator the acetylpiperazine hydrochloride crystallized. The crude product weighed 33 g. and melted at 150°. After three recrystallizations from alcohol–ether mixture the melting point was 183°.[1b]

From the intermediates whose preparation is described above a variety of unsymmetrical piperazines has been

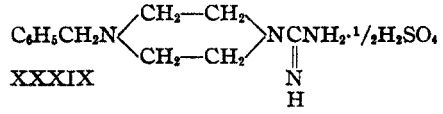
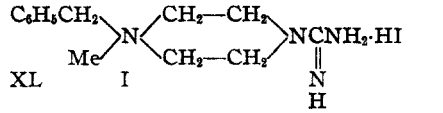
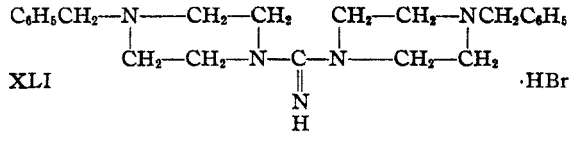
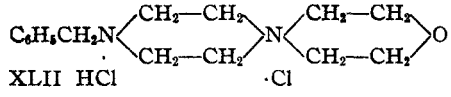
(2) *Cf.* among others Buck and Baltzly, THIS JOURNAL, **63**, 1964 (1941).

(3) Kitchen and Pollard, *J. Org. Chem.*, **8**, 338 (1943).

TABLE II

| No. | R | R′ | Appearance,[a] crystallizing solvent[b] | M. p., °C. | Empirical formula | Analyses, % Calcd. C | Calcd. H | Found C | Found H |
|---|---|---|---|---|---|---|---|---|---|
| | Mono-alkylpiperazine dihydrochlorides RN(CH$_2$—CH$_2$)$_2$NH·2HCl | | | | | | | | |
| I | $C_6H_5CH_2$— | ..... | Flat needles, A | 253 | $C_{11}H_{18}N_2Cl_2$ | 53.00 | 7.28 | 53.14 | 7.54 |
| II | $p$-$MeOC_6H_4CH_2$— | ..... | A | 263 dec. | $C_{12}H_{20}ON_2Cl_2$ | 51.61 | 7.23 | 51.49 | 7.55 |
| III | $p$-$ClC_6H_4CH_2$— | ..... | Flat needles, A | 296 dec. | $C_{11}H_{17}N_2Cl_3$ | 46.55 | 6.04 | 46.46 | 6.23 |
| IV | $C_6H_5CH_2CH_2$— | ..... | A | 252 | $C_{12}H_{20}N_2Cl_2$ | 54.75 | 7.66 | 54.83 | 7.90 |
| V | $n$-$C_{12}H_{25}$— | ..... | Slender needles, AA-E | Dec. >220 | $C_{16}H_{36}N_2Cl_2$ | 58.69 | 11.09 | 58.96 | 10.97 |
| VI | $HOCH_2CH_2$— | ..... | A | 189.5 | $C_6H_{16}ON_2Cl_2$ | 35.48 | 7.94 | 35.37 | 7.87 |
| VII | $CH_3$— | ..... | Aq-M | 110 (hydrate) | $C_5H_{14}N_2Cl_2$ | 34.69 | 8.16 | 34.62 | 8.58 |
| VIII | $C_2H_5$— | ..... | AA | 203–205 | $C_6H_{16}N_2Cl_2$ | 38.48 | 8.62 | 38.27 | 8.70 |
| | Mono-alkylpiperazine amide hydrochlorides RN(CH$_2$—CH$_2$)$_2$NCOR′·HCl | | | | | | | | |
| IX | $C_6H_5CH_2$— | $C_6H_5$— | Prisms, A | 245 | $C_{18}H_{21}ON_2Cl$ | 68.27 | 6.69 | 68.24 | 6.79 |
| X | $C_6H_5CH_2CH_2$— | $C_6H_5$— | Leaflets, A | 246 | $C_{19}H_{23}ON_2Cl$ | 68.96 | 7.01 | 69.19 | 6.81 |
| XI | $p$-$ClC_6H_4CH_2$— | $C_6H_5$— | Leaflets, A | 265 | $C_{18}H_{20}ON_2Cl_2$ | 61.52 | 5.74 | 61.79 | 5.96 |
| XII | $p$-$MeOC_6H_4CH_2$— | $C_6H_5$— | A-E | 234 | $C_{19}H_{23}O_2N_2Cl$ | 65.78 | 6.69 | 65.92 | 7.08 |
| XIII | $p$-$MeOC_6H_4CH_2$— | $C_6H_5CH_2$— | Silky leaflets, A-E | 225 | $C_{20}H_{25}O_2N_2Cl$ | 66.56 | 6.98 | 66.64 | 6.95 |
| XIV | $p$-$ClC_6H_4CH_2$— | $C_6H_5CH_2$— | A | 241 | $C_{19}H_{22}ON_2Cl_2$ | 62.47 | 6.08 | 62.63 | 6.38 |
| | Dialkylpiperazine dihydrochlorides RN(CH$_2$—CH$_2$)$_2$NR′·2HCl | | | | | | | | |
| XV | $C_6H_5CH_2$— | Me— | M | 250 dec. | $C_{12}H_{20}N_2Cl_2$ | 54.73 | 7.66 | 54.70 | 7.81 |
| XVI | $C_6H_5CH_2$— | Et— | AA | 250 dec. | $C_{13}H_{22}N_2Cl_2$ | 56.29 | 8.00 | 56.03 | 7.93 |
| XVII | $C_6H_5CH_2$— | $n$-$C_{12}H_{25}$— | Waxy solid, AA | Dec. >250 | $C_{23}H_{42}N_2Cl_2$ | 66.16 | 10.13 | 66.23 | 10.09 |
| XVIII | Dimethiodide of XVII | | AA | 225 dec. | $C_{25}H_{46}N_2I_2$ | 47.76 | 7.38 | 47.97 | 7.48 |
| XIX | $C_6H_5CH_2$— | —$CH_2CH_2OH$ | Platelets, A-Æ | 225 | $C_{13}H_{22}ON_2Cl_2$ | 53.23 | 7.60 | 53.18 | 7.81 |
| XX | $n$-$C_{12}H_{25}$— | $n$-$C_{12}H_{25}$— | A | .... | $C_{28}H_{60}N_2Cl_2$ | 67.82 | 12.21 | 67.64 | 12.33 |
| XXI | $C_6H_5CH_2$— | 3,4-$(MeO)_2$-$C_6H_3CO·CH_2$— | Glittering leaves, A | Dec. 250–270 | $C_{21}H_{28}O_3N_2Cl_2$ | 59.00 | 6.61 | 59.08 | 6.85 |
| XXII | $C_6H_5CH_2$— | 3,4-$(OH)_2$-$C_6H_3CO·CH_2$— | A | Dec. 255 | $C_{19}H_{24}O_3N_2Cl_2$ | 57.13 | 6.06 | 57.30 | 6.07 |
| XXIII | $p$-$ClC_6H_4CH_2$— | 3,4-$(OH)_2$-$C_6H_3COC·H_2$— | A | Dec. >200 | $C_{19}H_{23}O_3N_2Cl_3$ | 52.59 | 5.35 | 52.54 | 5.71 |
| XXIV | $p$-$MeOC_6H_4CH_2$— | 3,4-$(HO)_2$-$C_6H_3COCH_2$— | A-Æ | 230–231 | $C_{20}H_{25}O_4N_2Cl_2$ | 61.12 | 6.42 | 61.41 | 6.64 |
| XXV | $C_6H_5CH_2$— | 3,4-$(HO)_2$-$C_6H_3CHOH·CH_2$— | A-E | Dec. >210 | $C_{19}H_{26}O_3N_2Cl_2$ | 56.84 | 6.54 | 56.97 | 6.86 |
| XXVI | $p$-$MeOC_6H_4CH_2$— | 3,4-$(HO)_2$-$C_6H_3CHOH·CH_2$— | AA-Æ | 175 | $C_{20}H_{28}O_4N_2Cl_2$ | 55.67 | 6.55 | 55.45 | 6.65 |
| | N-Alkyl-N′-benzoyloxyethylpiperazine dihydrochlorides RN(CH$_2$—CH$_2$)$_2$NCH$_2$CH$_2$OCO$C_6H_4$R′·2HCl | | | | | | | | |
| XXVII | H | H | Aq-Ac | 208–210 | $C_{13}H_{20}O_2N_2Cl_2$ | 50.80 | 6.56 | 50.54 | 6.76 |
| XXVIII | Et | H | Needles, AA | 245 dec. | $C_{15}H_{24}O_2N_2Cl_2$ | 53.73 | 7.22 | 53.86 | 7.48 |
| XXIX | $C_6H_5CH_2$— | H | Platelets, AA | 245 | $C_{20}H_{26}O_2N_2Cl_2$ | 60.44 | 6.60 | 60.59 | 6.57 |
| XXX | $C_6H_5CH_2$— | Cl | Needles, AA | 242 | $C_{20}H_{25}O_2N_2Cl_3$ | 55.60 | 5.84 | 55.78 | 6.08 |
| XXXI | $C_6H_5CH_2$— | $NO_2$ | Meshed needles, Aq-Ac-HCl | 236–237 | $C_{20}H_{25}O_4N_3Cl_2$ | 54.29 | 5.71 | 54.19 | 6.00 |
| XXXII | $C_6H_5CH_2$— | $NH_2$·HCl | Buff crystals, Aq-M-Æ | 258–260 dec. | $C_{20}H_{28}O_2N_3Cl_3$ | 53.49 | 6.29 | 53.50 | 6.39 |
| XXXIII | $C_6H_5CH_2$— | —$NHCOCH_3$ | Plates, A-E | 229 dec. | $C_{22}H_{29}O_3N_3Cl_2$ | 58.12 | 6.44 | 58.60 | 6.77 |
| | Mono-alkylpiperazine urea hydrochlorides RN(CH$_2$—CH$_2$)$_2$NCONHR′·HCl | | | | | | | | |
| XXXIV | $C_6H_5CH_2$— | H | Leaflets, A | 238.5–239 | $C_{12}H_{18}ON_3Cl$ | 56.35 | 7.10 | 56.46 | 7.03 |
| XXXV | $p$-$ClC_6H_4CH_2$— | H | Leaflets, A | 264 | $C_{12}H_{17}ON_3Cl_2$ | 49.65 | 5.91 | 49.59 | 5.86 |
| XXXVI | $p$-$ClC_6H_4CH_2$— | $C_6H_5$— | Leaflets, A | 258 dec. | $C_{18}H_{21}ON_3Cl_2$ | 59.00 | 5.78 | 59.05 | 5.90 |
| XXXVII | $HO·CH_2CH_2$— | H | AA-E | 177 | $C_7H_{15}O_2N_3Cl$ | 40.10 | 7.69 | 40.10 | 7.35 |
| XXXVIII | $C_6H_5COOCH_2CH_2$— | H | AA-E | 205 dec. | $C_{14}H_{29}O_2N_3Cl$ | 53.59 | 6.42 | 53.87 | 6.63 |

TABLE II (*Concluded*)

| No. | Compounds | Appearance,[a] crystallizing solvent[b] | M. p., °C. | Empirical formula | Analyses, % Calcd. C | Calcd. H | Found C | Found H |
|---|---|---|---|---|---|---|---|---|
| | Miscellaneous piperazine derivatives | | | | | | | |
| XXXIX |  | Glossy plates, A-Ac | 220 dec. | $C_{12}H_{19}N_4O_2S_{1/2}$ | 53.91 | 7.17 | 54.15 | 7.38 |
| XL |  | Hexagonal plates, M | 219–220 dec. | $C_{13}H_{22}N_4I_2$ | (N) | 11.48 | (N) | 11.60 |
| XLI |  | AA-E | 229 | $C_{23}H_{32}N_5Br$ | 60.24 | 7.02 | 60.00 | 7.11 |
| XLII HCl |  | A-E | Solid to 280 | $C_{15}H_{24}ON_2Cl_2$ | 56.41 | 7.58 | 56.59 | 7.78 |

[a] Appearance is given only when form is macroscopically characteristic. [b] A = 95% EtOH, AA = absolute EtOH, M = MeOH, E = $Et_2O$, Æ = ethyl acetate, Ac = acetone, Aq = $H_2O$.

prepared. Pertinent data on these substances are given in Table II. Most are characterized as hydrochlorides.

**Aralkylpiperazine Amides.**—The benzoates of benzyl, *p*-chlorobenzyl, anisyl and phenethyl piperazines (IX–XII) were prepared by the Schotten–Baumann method. The phenylacetyl derivatives (XIII, XIV) of anisyl and *p*-chlorobenzyl piperazines were obtained by the action of phenylacetyl chloride in boiling benzene on the appropriate bases.

**Di-alkylpiperazines.**—Benzylpiperazine was reacted in alcoholic solution with methyl and ethyl iodides and with lauryl bromide. The latter required heating to complete the reaction. The methylated and ethylated bases (XV and XVI) were obtained by distillation of the liberated and benzoylated bases from the reaction. Benzyl laurylpiperazine was crystallized as the hydrochloride (XVII). Methylbenzylpiperazine is better prepared from benzylpiperazine by the Clarke–Eschweiler method.[4] Unlike dibenzylpiperazine, benzyl laurylpiperazine forms a dimethiodide (XVIII) without much difficulty. Presumably this is because the monomethiodide (on the lauryl end?) is relatively soluble and is not withdrawn from reaction whereas dibenzylpiperazine forms a rather insoluble monomethiodide that precipitates from solution and reacts further only on prolonged treatment.

Benzyl β-hydroxyethylpiperazine (XIX) resulted from the action of ethylene oxide on benzylpiperazine.

The substituted benzylphenacylpiperazines (XXI–XXIV) were produced by the reaction of the appropriate monosubstituted piperazines with chloroacetocatechol and bromo-acetoveratrone in ethyl acetate solution. Reduction of XXII and XXIV with platinum oxide platinum black at room temperature gave the amino-alcohols, XXV and XXVI.

Catalytic reduction of methylbenzylpiperazine and ethylbenzylpiperazine hydrochlorides with palladized charcoal removed the benzyl group forming methyl and ethyl piperazine dihydrochlorides (VII and VIII).

Similarly, hydrogenation of N-benzyl-N′-benzoyloxyethylpiperazine dihydrochloride (XXIX) (made by benzoylation of XIX) gave benzoyloxyethylpiperazine, XXVII.

Ethylation of β-hydroxyethylpiperazine with ethyl iodide followed by benzoylation of the total bases by the Schotten–Baumann method yielded ethylbenzoyloxyethylpiperazine (XXVIII).

(4) Clarke, Gillespie and Weisshaus, THIS JOURNAL, **55**, 4571 (1933).

Benzylhydroxyethylpiperazine (XIX) reacted with *p*-chloro and *p*-nitrobenzoyl chlorides in ether or benzene solution to give XXX and XXXI. Reduction of the latter gave the corresponding *p*-amino compound, XXXII which was acetylated to form the acetamido derivative, XXXIII.

**Urea Derivatives.**—Phenyl isocyanate and *p*-chlorobenzylpiperazine formed the urea, XXXVI. The other ureas recorded in Table II were prepared by the reaction of nitrourea on the appropriate mono-substituted piperazines.

**Guanidines and Quaternary Salts.**—Benzylpiperazine and S-methylisothiourea sulfate in 65% alcohol yielded the guanidine sulfate, XXXIX. The corresponding hydroiodide, m. p. 155–155.5°, was formed from benzylpiperazine and S-methylisothiourea hydroiodide in absolute alcohol and reacted with methyl iodide in methanol to form the guanidine quaternary salt, XL.

The symmetrical guanidine, XLI, resulted when 2 mols of benzylpiperazine and 1 mol of cyanogen bromide were mixed cautiously in absolute ether solution, the ether blown off and the residual mixture heated at 150–160° (oil-bath) for two and one-half hours.

The spiro-quaternary salt, XLII, was prepared by heating benzyl piperazine with β,β′-dichloro-ethyl ether.

The melting points below 250° given in Table II are corrected.

The authors wish to express their gratitude to Mr. W. S. Ide for the many micro-analyses performed in this study.

## Summary

1. When piperazine reacts with acylating and alkylating agents satisfactory yields of monosubstitution product can be isolated provided the substituting group is of moderate size.

2. By catalytic debenzylation of suitable derivatives of monobenzylpiperazine a further variety of mono-substituted piperazines can be prepared.

3. A number of mono-substituted and unsymmetrically disubstituted piperazines have been prepared and characterized.

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