TABLE II

Compd	Mp, °C	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
IIb	264–265	$C_{20}H_{14}N_4Cl_2$	62.9	3.7	14.4	62.6	3.8	14.8
IIc	232–233	$C_{20}H_{28}N_4$	74.1	8.6	17.3	74.2	8.5	17.3
IId	309–310 dec	$C_{19}H_{16}N_5$	72.8	4.9	22.4	72.6	4.8	22.5

needles 7 g, mp 263–264° (lit.[6] mp 264°). Mixture melting point with an authentic sample of VI remained undepressed.

Formation of Benzaldehyde (Va) from 1-Benzoylsemicarbazide (Ia).—An intimate mixture of Ia (18 g, 0.1 mole) and anhydrous sodium carbonate (22 g, 0.21 mole) was heated in a distilling flask in an atmosphere of carbon dioxide at 260–270° in an oil bath for 3 hr. A yellowish oil that distilled was collectd in an ice-cooled receiver, and the evolved gas, which had a definite smell of ammonia, wasp assed successively through sulfuric acid (10%) and potassium hydroxide solution (50%) and was finally collected in an aspirator by downward displacement of water.

The oil (2.5 g) was purified by distillation, bp 178–179° (760 mm) and was identified to be benzaldehyde through its 2,4-dinitrophenylhydrazone, mp 235–236°. Mixture melting point with an authentic sample of the 2,4-dinitrophenylhydrazone of benzaldehyde showed no depression. The gas collected in the aspirator was qualitatively analyzed in a standard Orsat apparatus. Carbon dioxide was absorbed in potassium hydroxide (50%) solution. The trapped oxygen of the system was then absorbed in potassium pyrogallate solution (10 g of pyrogallol in 200 ml of 50% potassium hydroxide solution). Carbon monoxide was absorbed in ammoniacal cuprous chloride solution (23 g of cuprous chloride, 86 ml of liquor ammonia (29%, w/w), and 100 ml of water). The rest of the gas was found to be nitrogen. Under an analogous condition, Ib and Ic afforded *p*-chlorobenzaldehyde (Vb), (semicarbazone, mp 218–220° (lit.[11] mp 218–220°)) and isonicotinaldehyde (Vc) (characterized as its thiosemicarbazone, mp 220–222° (lit.[12] mp 221°), respectively.

Registry No.—Ia, 2845-79-6; Ib, 2845-81-0; Ic, 2845-80-9; Id, 15129-13-2; Ie, 3064-22-0; If, 2880-02-6; IIa, 15129-16-5; IIb, 15129-17-6; IIc, 15129-18-7; IId, 15215-85-7; IId picrate, 15128-81-1; IIIa, 1152-32-5; IIIb, 15152-50-8; Va, 100-52-7; Va 2,4-dinitrophenylhydrazone, 1157-84-2; VI, 4329-75-3; VII, 2845-82-1.

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The Reductive Ring Cleavage of 1,3-Disubstituted Imidazolium Iodides by Sodium Borohydride

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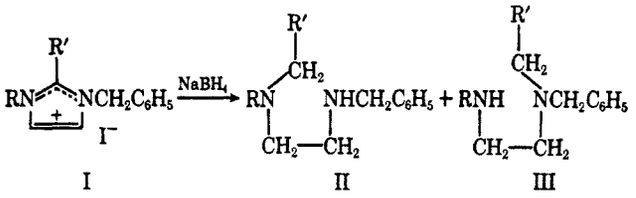
The use of sodium borohydride ($NaBH_4$) to effect reduction of heterocyclic quaternary salts is now a well-established and widely utilized procedure[1] leading to partially or totally reduced ring systems. Among the monocyclic nitrogenous systems having been investigated are pyridinium, pyrazinium, and thiazolium salts.

Our own interest in the imidazoles prompted the study of the effect of $NaBH_4$ on some simple, dissimilarly substituted imidazolium iodides of type I.

The preparation of quaternary salts Ia–e was carried out in acetonitrile and offered no unusual difficulties (see Table I). Aryl-containing substituents were chosen to facilitate isolation and characterization of the reaction products. In the imidazoles, entering quaternizing groups always come to reside on N-3. This fact, suggested by the observation of Sarasin[2] that thermal decomposition of the methiodide of 1-methyl-5-chloroimidazole gave 1-methyl-4-chloroimidazole, was proved unequivocally by nmr measurements on the dimethylimidazolium ion.[3] Our own work led us to note that the 1-methyl-3-benzylimidazolium iodide, prepared by the reaction of 1-methylimidazole with benzyl iodide, was identical with the salt obtained from 1-benzylimidazole and methyl iodide.

The reaction of the quaternary salts with $NaBH_4$ was carried out using a large excess of reducing agent in refluxing 95% alcohol; the hydrolyzed crude reaction mixtures were analyzed by vapor phase chromatography. In all cases examined reductive ring cleavage occurred, giving mixtures consisting of two isomers (93–99% of total) present in unequal amounts. Upon reducing Ia the major (85%) and minor (8%) components were identified as N,N-dimethyl-N′-benzylethylenediamine (IIa) and N,N′-dimethyl-N-benzylethylenediamine (IIIa) by comparing the chromatogram of the crude mixture with that of a mixture of authentic amines. From the reaction mixture, IIa was isolated by crystallization of the bishydrochloride salt which was identical with authentic material.



I II III

a, R = CH_3; R′ = H
b, R = C_2H_5; R′ = H
c, R = n-C_3H_7; R′ = H
d, R = CH_3; R′ = CH_3
e, R = C_2H_5; R′ = CH_3

Parallel behavior was noted upon reducing Ib–e. The major fraction produced from Ib was identical with the one isolated from Id and is, of necessity, N-methyl-N-ethyl-N′-benzylethylenediamine (IIb ≡ IId). Compound Ie gave the known N,N-diethyl-N′-benzylethylenediamine (IIe), whereas Ic, by analogy, furnished N-methyl-N-propyl-N′-benzylethylenediamine (IIc). In all cases separation of type II from III was carried out *via* the hydrochloride salts.

The postulated structures IIa–e were further substantiated by nmr data. Whereas types II and III could not be distinguished in D_2O, spectra in sulfuric acid clearly showed spin coupling with the NH^+ protons. In compound IIa the methyls are split into a

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TABLE I

PROPERTIES OF THE IMIDAZOLIUM SALTS

Imidazolium iodide	Yield, %	Mp, °C	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
1-Methyl-3-benzyl (Ia)	97	113–114	$C_{11}H_{13}IN_2$	44.02	4.37	9.33	44.02	4.34	9.27
1-Ethyl-3-benzyl (Ib)	69	82.5–83	$C_{12}H_{15}IN_2$	45.87	4.81	8.92	45.57	4.83	8.96
1-*n*-Propyl-3-benzyl (Ic)[a]	...	...	$C_{13}H_{17}IN_2$	...	...	...	...	...	...
1,2-Dimethyl-3-benzyl (Id)	62	153–154	$C_{12}H_{15}IN_2$	45.87	4.81	8.92	45.96	4.91	8.70
1-Ethyl-2-methyl-3-benzyl (Ie)	79	123–124	$C_{13}H_{17}IN_2$	47.57	5.22	8.54	47.43	5.23	8.54
1-Methyl-3-phenethyl	86	99–100	$C_{12}H_{15}IN_2$	45.87	4.81	8.92	45.60	4.78	8.96

[a] Failed to crystallize after prolonged standing. The crude reaction mixture was repeatedly scrubbed with benzene and the resulting oil was used in the $NaBH_4$ reduction.

TABLE II

REACTION PRODUCTS OF 1,3-DISUBSTITUTED IMIDAZOLIUM IODIDES AND SODIUM BOROHYDRIDE

Substrate	Isomer distribn of reaction mixture,[a] % (r.r.t.[g] compared with quinoline) II	III	Isolated II, % (mp, °C, bishydrochloride salt)
Ia	85 (0.9)	8	71 (206–207[b])
Ib	81 (1.24)	15	50 (173–174[c])
Ic	80 (1.55)	16	53 (154–155[d])
Id	93 (1.23)	6	65 (173–174[c])
Ie	77 (1.50)	22.5	38 (162.5–163[e])
1-Methyl-3-phenethylimidazolium iodide	91 (1.32)	3	61 (223–224[f])

[a] Analyses were carried out on a Varian Aerograph Hy-FiA-600 B using a 1-m stainless steel column having a 1/8-in. external diameter. Chromosorb W (80–100 mesh) coated with 5% Carbowax 20M and 5% sodium hydroxide (w/w) was used as filler. [b] N. B. Chapman and H. Taylor, *J. Chem. Soc.*, 1908 (1961), report mp 205–206°. [c] *Anal.* Calcd for $C_{12}H_{20}N_2 \cdot 2HCl$: C, 45.87; H, 4.81. Found: C, 45.96; H, 4.91. [d] *Anal.* Calcd for $C_{13}H_{22}N_2 \cdot 2HCl$: C, 55.91; H, 8.66; N, 10.03. Found: C, 55.89; H, 8.59; N, 9.92. [e] N. K. Kochetkov and N. V. Dudykina, *Zh. Obshch. Chim.*, **29**, 1659 (1959), give mp 164–167°. *Anal.* Calcd for $C_{13}H_{22}N_2 \cdot 2HCl$: C, 55.91; H, 8.66; N, 10.03. Found: C, 55.72; H, 8.77; N, 10.12. [f] This compound has been described as free base by R. Wegler and G. Pieper, *Ber.*, **83**, 1 (1950). *Anal.* Calcd for $C_{12}H_{20}N_2 \cdot 2HCl$: C, 54.34; H, 8.36. Found: C, 54.35; H, 8.34. [g] Relative retention time.

doublet at τ 7.48 (J = 4.5 cps) and in IIa–e the benzyl protons are seen as poorly resolved triplets.

The results of Table II show that $NaBH_4$ cleaves the imidazolium ring predominately between C-2 and the nitrogen bearing the benzyl group. To determine whether this specific fission is a function of the benzyl substituent, we also subjected 1-methyl-3-phenethylimidazolium iodide to the $NaBH_4$ reduction. This time cleavage took place almost exclusively (92%) between C-2 and N-3, giving N,N-dimethyl-N′-(2-phenethyl)ethylenediamine, identified by nmr measurements (doublet at τ 7.52 (J = 3 cps)). These results would imply that at some stage of the reduction attack of hydride ion on the electrophilic center C-2 occurs in a sterically controlled fashion away from the bulky N substituent, be it benzyl or phenethyl. Alternately, ring cleavage could be caused by hydrolysis of intermediate imidazolines, followed by further reduction of the resulting aminoaldehydes, with the final isomer distribution governed by the charge distribution in the imidazolinium species.[4]

Experimental Section

1-Benzylimidazole.—To a solution of 23 g (1.0 mole) of sodium in 350 ml of dry methanol was added a solution of 68 g (1.0 mole) of imidazole in 100 ml of methanol. Approximately 350 ml of solvent was distilled off, whereupon 200 ml of dimethylformamide was added and solvent removal was resumed until the internal temperature reached 125°. The mixture was cooled to 30°. Addition of 126.5 g (1.0 mole) of benzyl chloride resulted in a moderately exothermic reaction; the temperature rose to 80° despite external cooling. After stirring for 2 hr the solution was poured onto 1.5 l. of water and the crude product was extracted into benzene. The organic solution was, in turn, extracted with 3 *N* hydrochloric acid from which the base was liberated with sodium hydroxide. It was extracted into benzene. Drying of the organic phase and removal of solvent left an oil which was poured into petroleum ether (bp 30–60°) to give 132 g (84%) of colorless product: mp 70–71° (lit.[5] mp 71–72°).

1-Benzyl-2-methylimidazole[5] was prepared as above in 75% yield. It solidified on standing and had mp 46–47°.

1-Phenethylimidazole.—Analogous treatment of the sodium salt of imidazole with phenethyl bromide furnished 32% of product, bp 140–145° (0.175 mm).

Anal. Calcd for $C_{11}H_{12}N_2$: N, 13.42; Found: N, 13.28.

Preparation of the 1,3-disubstituted imidazolium iodides (see Table I) is exemplified by the synthesis of Ia.

1-Methyl-3-benzylimidazolium Iodide (Ia). A.—A solution of 47.4 g (0.30 mole) of 1-benzylimidazole, 45 g (0.32 mole) of methyl iodide, and 150 ml of acetonitrile was boiled under reflux for 2 hr. Cooling, addition of 500 ml of isopropyl ether, and seeding gave 87 g (92%) of product, mp 112–113°. An analytical sample (acetone) melted at 113–114°.

B.—To a solution of 21.8 g (0.10 mole) of benzyl iodide in 80 ml of acetonitrile was added 10 g (0.12 mole) of 1-methylimidazole, causing spontaneous refluxing. Upon completion of the exotherm, the mixture was kept at reflux for 0.5 hr. Addition of isopropyl ether to the cooled solution gave 23 g of quaternary salt, mp 110–111°, which was in all respect identical with Ia described above.

The Reaction of 1,3-Disubstituted Imidazolium Iodides (Ia–e) with $NaBH_4$. General Procedure.—To a solution of 0.10 mole of the imidazolium salt in 300 ml 95% ethanol at 55° was added portionwise 0.5 mole of $NaBH_4$. After the mixture had ceased foaming, it was heated under reflux for 1 hr. The solvent was removed *in vacuo*; 300 ml of water was added to the residue. The reaction products were taken up in ether and were analyzed by vapor phase chromatogaphy (see Table II). Addition of isopropyl alcohol–hydrogen chloride to the dried organic phase gave a mixture of crude salts of II and IIIa–e from which pure component IIa–e was readily obtained upon recrystallization.

Registry No.—Ia, 15095-61-1; Ib, 15095-62-2; Id, 15095-63-3; Ie, 15095-64-4; IIb bishydrochloride salt, 15095-65-5; IIc bishydrochloride salt, 15095-66-6; IId bishydrochloride salt, 15095-65-5; IIe bishydrochloride salt, 15095-68-8; sodium borohydride, 1303-74-8; 1-methyl-3-phenethylimidazylium iodide, 15095-69-9; N,N-dimethyl-N′-(2-phenethyl)ethylenediamine, 15095-70-2.

(4) The author acknowledges the latter suggestion of referee 1.
(5) R. G. Jones, *J. Am. Chem. Soc.*, **71**, 383 (1949).

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A Convenient Synthesis of 2,5-Piperazinediones[1a]

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We have developed a simple and convenient one-step conversion of unblocked dipeptides, or their hydrobromide salts, to cyclic dipeptides (3,6-dialkyl-2,5-piperazinediones). Cyclization occurs on heating in phenol just below the boiling point of phenol; the reaction does not appear to be accompanied by significant side reactions. Cyclic dipeptides prepared in this manner are listed in Tables I and II. As Table II indicates, cyclization in hot phenol is effective in cases where one of the amino acid residues of the dipeptide is potentially sensitive; it has been achieved in excellent yield with L-seryl-L-tyrosine, L-methionyl-L-tyrosine, and glycyl-L-tryptophan, among other peptides. When the reaction is carried out under nitrogen, there is no discoloration of the reaction mixture; only piperazinediones and traces of starting materials are detected by thin layer chromatography of the crude reaction products.

TABLE I

PREPARATIONS OF PREVIOUS REPORTED 2,5-PIPERAZINEDIONES *via* HEATING DIPEPTIDES IN PHENOL

		Mp, °C	
Dipeptide used	Yield, %	Obsd[a]	Reptd
Gly-Val	84	264–265	260–266[b]
Gly-Leu	22	250–251	254–255[c]
Leu-Gly	39	250–251	254–255[c]
Gly-DL-Phe	54	282–283	277–280[d]
Gly-Tyr	78	287–288.5	295[e]
Gly-Trp	91	299.5–300.5	292–303[f]
Gly-His·2HBr	50	244–245[g]	242–243[g]
Leu-Tyr	99	295–296	310[h]

[a] All melting points with partial decomposition; corrected values given. [b] E. Fischer and H. Schiebler, *Ann.*, **363**, 142 (1908). [c] E. Fischer, *Ber.*, **39**, 2914 (1906). [d] E. Fischer and P. Blank, *Ann.*, **354**, 4 (1907). [e] E. Fischer and W. Schrauth, *ibid.*, **354**, 28 (1907). [f] K. Hofmann and S. Lande, *J. Am. Chem. Soc.*, **83**, 2286 (1961). [g] J. Sheehan and D. McGregor, *ibid.*, **84**, 3000 (1962); however, see Experimental Section. [h] E. Fischer, *Ber.*, **37**, 2498 (1904).

Heating a dipeptide in phenol does not result in loss of optical activity. Where the initial dipeptide contains two optically active amino acid residues, racemization, if it occurred, would lead to formation of diastereomeric cyclic dipeptides, but formation of diastereomers is not observed on cyclizing L-leucyl-L-tyrosine and D-leucyl-L-tyrosine by this method; each of these peptides affords a single product, as described in the Experimental Section. Proton magnetic resonance studies, described elsewhere,[2] confirm that the LL dipeptide yields the piperazinedione with the side chains *cis* and the DL isomer yields the ring with the side chains *trans*.

Protonation of the dipeptide terminal amino group by hydrogen bromide does not prevent cyclization; presumably the amine hydrobromide dissociates under the reaction conditions. The crude hydrobromides of both L-leucyl-L-tyrosine (prepared by dissolving the free dipeptide in 30% hydrogen bromide in acetic acid, then precipitating with anhydrous ether) and glycyl-L-histidine (prepared by dissolving benzyloxycarbonylglycyl-L-histidine in 30% hydrogen bromide in acetic acid, then precipitating with anhydrous ether) have successfully been used as starting materials.

A cyclization procedure similar to that reported here, but using molten β-napthol at 135–140°, was reported some years ago;[3] the solvent was removed by ether extraction. Only optically inactive peptides were examined, so that racemization, if any, was undetected. Phenol, however, is undoubtedly a solvent preferable to β-napthol: it has a lower melting point, is readily available in pure form, can be easily removed by sublimation, and is soluble in water, from which many of the piperazinediones can be crystallized.

Unsymmetrical cyclic dipeptides commonly have been prepared by generating a free dipeptide methyl or ethyl ester from an N-protected dipeptide ester; the blocked ester is obtained by standard peptide synthetic methods and the free dipeptide ester generally cyclizes with very little encouragement. It is likely that a dipeptide ester salt, such as the hydrobromide obtained on removal, say, of an N-carbobenzyloxy group, would also cyclize in hot phenol. This might offer advantages in terms of product purification, since no base would have to be added to free the amino group for reaction. In any event, given the free dipeptides, many of which are commercially available, the use of hot phenol is clearly the cyclization method of choice.

Use of phenol, rather than ethylene glycol[4], as a solvent for the thermal cyclodimerization of amino acids to amino acid anhydrides might also appear advantageous in some cases, because dark by-products, common when glycol is the solvent, are not formed in phenol. However, although DL-phenyalanine does undergo dimerization in phenol, L-tyrosine is too insoluble, and is recovered unchanged after heating for 5 hr at 150°. The phenol method is thus not likely to be general for cyclodimerization of amino acids. On the other hand, all the dipeptides used dissolved in phenol shortly after heating was begun and no failures to cyclize were noted.

(1) (a) This work was supported in part by National Science Foundation, Grant No. GB 4514, and by a grant from the U. S. Public Health Service, 1R01 GM 14059. (b) National Science Foundation College Teacher Research Participant, 1966, 1967.

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