Some Extensions of von Braun (BrCN) Reaction on Organic Bases, Part III

Salimuzzaman Siddiqui*, Sabira Begum, and Bina S. Siddiqui
H. E. J. Research Institute of Chemistry
University of Karachi, Karachi-32/Pakistan

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vom Braun Cyanogen Bromide Reaction

In continuation of studies on some extensions of von Braun BrCN reaction on organic bases, work on diisobutylamine and di-2-butylamine, has led to various substituted ureas and N-imino-ethyl ether derivatives. In contrast to previous observations, reduction of their cyanamides with zinc/HCl gave the amido derivatives instead of diamines.

Introduction

Some extensions of von Braun (BrCN) reaction to the conessine series of alkaloids, leading to the formation of urea, diamine, carbinolamine and guanido derivatives, have been reported in an earlier communication [1]. Subsequently these reactions have been carried out on a number of bases including Harmala [2] and Ephedra alkaloids [3] as well as simpler aliphatic and aromatic amines [1, 3] to determine the range of their applicability, relating to studies in the correlation of structure and physiological activity.

The present paper deals with the extension of these studies to diisobutylamine and di-2-butylamine, which have furnished the following derivatives in good yields:

1. Diisobutylamine, $R = H$
2. N-cyano-diisobutylamine, $R = -CN$
3. N-amido-diisobutylamine, $R = -C=NH$
4. N,N-diisobutyl,N,N-dimethylurea, $R = -CON(CH_3)_2$
5. N,N-diisobutyl,N-acetylene, $R = -CONHCOCH_3$
6. N,N-diisobutyl,N-benzoylurea, $R = -CONHCOOC_6H_5$
7. Diisobutylamine-N-iminoethyl ether, $R = -C=NH\ OCH_3$
8. Di-2-butylamine, $R = H$
9. N-cyano-di-2-butylamine, $R = -CN$
10. N-amido-di-2-butylamine, $R = -C=NH$
11. N,N-di-2-butyl,N,N-dimethylurea, $R = -CON(CH_3)_2$
12. N,N-di-2-butyl,N-acetylene, $R = -CONHCOCH_3$
13. N,N-di-2-butyl,N-benzoylurea, $R = -CONHCOOC_6H_5$
14. Di-2-butylamine-N-iminoethylether, $R = -C=NH\ OCH_3$

The structures of these products have been arrived at through chemical and spectral data, described in the experimental. The preparations of the products 2 and 3 have been recorded through different routes [4, 5].

It may be noted in this context that in contrast to previous observations the cyanamides of diisobutylamine and di-2-butylamine failed to yield diamines on reduction with zinc and hydrochloric acid and gave instead the respective amido derivatives, the structures of which were confirmed through mixed melting points and spectral data.

* Reprint requests to Prof. Dr. S. Siddiqui.
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Attempts to obtain the diamines using other reducing agents (Fe/HCl, LiAlH₄, NaBH₄, Na/EtOH) proved fruitless. However, on treatment with sodium and ethanol in cold both the cyanamides afforded the corresponding imino ethyl ether derivatives, resulting from the nucleophilic attack of the ethoxide, formed during the reaction, on electrophilic carbon of the cyano group.

When the same reaction was carried out at room temperature it resulted in the formation of a mixture of three compounds which could be identified as iminoethyl ether derivatives, unreacted cyanamides and the parent bases.

The guanido derivatives obtained so far only from the cyanamides of the conessine series of alkaloids (i.e.) failed to be formed in the case of these amines also.

**Experimental**

Melting and boiling points were recorded in glass capillary tubes and are uncorrected. IR spectra were measured on a Unicam SP 200 G spectrometer. Proton NMR spectra were determined on JEOL PMX-60 instrument with TMS as internal reference. Mass spectra were recorded on MAT 112 with GC/MS with computer MAT 188. The purity of the samples was checked on TLC (silica gel).

**N-Cyano diisobutylamine**

To a solution of 5 g of diisobutylamine in 20 ml of ether was added 4.8 g of freshly prepared cyanogenbromide [6] (1.2 mole) with cooling and stirring. The white crystalline hydrobromide of the base that separated out was filtered and washed well with ether. The ethereal solution was extracted out with dilute acetic acid to remove any unreacted base then washed with water with the addition of little dilute ammonia and extracted out with ethyl acetate. After working up the ethyl acetate solution in the usual manner and removing the solvent N-amido diisobutylamine was obtained in a crystalline form. On recrystallization with methanol-water it formed colourless fine needles which showed m.p. 73-75 °C. It is soluble in usual solvents and insoluble in water.

**Characterization of N-amido diisobutylamine**

The IR spectrum in CHCl₃ showed bands at 3400 cm⁻¹ and 3520 cm⁻¹ (amide N-H stretching), 1640 cm⁻¹ (amide C=O stretching) and 1580 cm⁻¹ (amide NH bending). Mass spectrum showed molecular ion peak at m/e 172.15755 (calcd for C₆H₁₀N₂O 172.1555) which was in accordance with the molecular formula C₆H₁₀N₂O for N-amido diisobutylamine. Other significant peaks were observed at m/e 157 (10%) = (M-15)+, 129 (75%) = (M-C₆H₄)+, 128 (5%) = (M-CO-NH₂)+, 86 (100%) = (M-C₆H₁₄)+, 44 (60%) = (O=O=C-NH₂).

The H¹ NMR spectrum in CDC₃ showed a twelve-protons doublet at δ 0.96 [4(CH₃)], a four-protons doublet at δ 3.1 [2(CH₂)] and two-protons broad signal at δ 4.5 (CONH₂) and two-protons multiplet extending from δ 1.7 to 2.3 [2(CH)].

**Methylation of N-amidonisobutylamine-N,N-diisobutyl N,N-dimethylurea**

0.5 g of N-amidonisobutylamine was taken in 2 ml of toluene and refluxed on the water bath with 50 mg of sodium metal for 24 h. The activated sodium complex was taken in 2 ml of 40% aqueous solution of formic acid and refluxed with 2 ml of 40% formaldehyde for 10 h. The reaction mixture was basified with dilute ammonia and extracted out with ethyl acetate. The oily residue left on removal of the solvent after washing and drying crystallized out on keeping at room temperature overnight. On recrystallization from methanol it formed colourless elongated rods m.p. 150-151 °C. It is sparingly soluble in petroleum ether, soluble in ether, ethylacetate, chloroform and methanol.

The mass spectrum showed the molecular ion peak at 200 (52%) which was in agreement with the molecular formula C₆H₁₂N₂O for dimethyl derivative of the amide. Other diagnostic peaks were observed at m/e 185 (20)% = (M-15)+, 156 [7] (52%) = [M-N(CH₃)₂]+, 86 (100%) = [M-2(C₆H₄)]+, 57 (82%) = (CH₃)₂CO. In the IR spectrum (CHCl₃) N-H stretching or bending vibrations were not present. It however showed carbonyl absorption at 1660 cm⁻¹.
Acetylation of N-amidodiisobutylamine-N,N-diisobutyl-N-acetylatedurea

The activated sodium complex of 250 mg of the amide prepared as described above, was refluxed with 2 ml of freshly distilled acetic anhydride and a few drops of dry pyridine for 6 h. On working up the reaction mixture in the usual manner, acetyl N-amidodiisobutyl amine was obtained as colourless amorphous solid (yield theoretical). On rubbing with petroleum ether it formed small rods m.p. 169–170 °C. It is soluble in ether, ethylacetate and methanol. It did not show the molecular ion peak in the mass spectrum, but on subjecting it to FI technique a peak appeared at m/e 214 corresponding to molecular formula C11H22N2O2. Diagnostic peaks appeared at m/e 171 (40%) = (M-43)+, 156 (2/4) = [M-C2H5]+, 128 (38%) = [C6H5C=NH]+, 86 (100%) = [M-2(C2H5)]=, 82 (2/4) = (C4H9)+. Its 1H NMR spectrum showed a peak at 3400 cm⁻¹ (amide N-H), and 1620 cm⁻¹ bending vibration. Its 13C NMR spectrum afforded two peaks at δ 142 (O-CH2) and 3430 cm⁻¹ for amido group, 1620 cm⁻¹ (acetyl and urea carbonyl stretchings).

Benzoylation of N-amidodiisobutylamine-N,N-diisobutyl-N-benzoylurea

2 ml freshly distilled benzoyl chloride was added to the activated sodium complex of 250 mg of the amide and refluxed for 6 h. The reaction mixture was basified with dilute aqueous alkali and exhaustively extracted out with ether. Ether layer was washed well with water, dried (Na2SO4) and concentrated. On cooling in ice chest chromatographically pure crystalline benzoyl N-amido-diisobutylamine was obtained. On recrystallization from ether it formed colourless shining plates melting at 50–51 °C (yield 200 mg). It is soluble in common organic solvents.

It did not show the molecular ion peak in the mass spectrum. Diagnostic peaks appeared at m/e 233 (10%) = (M-43)+, 192 (40%) = [M-C2H5]+, 165 (100%) = [C6H5C=NH]+, 77 (30%) = (C6H5)+, 57 (10%) = (C2H5)+, and 43 (6%) = (C2H3)+. In the IR spectrum (KBr) a peak was observed at 3400 cm⁻¹ (amide N-H), and between 1620 cm⁻¹–1640 cm⁻¹ (benzoyl and urea carbonyl stretchings).

Diisobutylamine-N-iminoethyl ether

250 mg of diisobutylamine cyanamide was taken in 10 ml absolute alcohol and to it was added 50 mg of sodium metal with efficient cooling. After about 1 h the reaction mixture was acidified with dilute acetic acid and extracted out with ethyl acetate, for the removal of the unreacted cyanamide. The aqueous acidic layer was basified with dilute ammonia and extracted out with ethyl acetate. On working up the ethyl acetate layer, N-imino-ethyl ether derivative was obtained as a colourless semi-crystalline solid, which formed small rods on rubbing with petroleum ether m.p. 92–93 °C (yield 100 mg). It is soluble in chloroform, methanol and acetone, insoluble in ether, petroleum ether and water. It showed molecular ion peak at m/e 200.18996 (calculated for C12H25N2O = 200.18985) corresponding to the molecular formula C12H25N2O for the diisobutylamine-N-iminoethyl ether. Other diagnostic peaks appeared at m/e 185 (4%) = (M-CH3)+, 157 (12%) = (M-43)+, 142 (12%) = (M-43-15)+, 128 (11%) = [C6H5C=NH]+, 86 (100%) = [M-2(C2H5)]=, 72 (20%) = (C6H5-O-C=N-H)+, and 57 (38%) = (C2H5)+. Its 1H NMR spectrum in CHCl3 showed peaks at 3400 cm⁻¹ (NH stretching) and 1120 cm⁻¹ (C-O-C stretching). Its 1H NMR spectrum afforded two protons quartet at δ 3.9 (O-C2H5CH3) and three-protons triplet at δ 1.4 (O-C2H3CH3).

N-Cyano-di-2-butylamine

To a solution of 5 g of di-2-butylamine in ether was added ethereal solution of cyanogen bromide (1.2 mole) with cooling and constant stirring. After one hour stirring the reaction mixture was worked up as described for N-cyanodiisobutylamine. Chromatographically pure N-cyano-di-2-butylamine was ultimately obtained as colourless oily mass (yield 2.5 g, b.p. 87–88 °C). It is soluble in common organic solvents and insoluble in water. The molecular formula C16H18N2 was confirmed by mass spectrometry M⁺ = 254.14679 (calculated for C16H18N2 = 254.14699). Its 1H NMR spectrum in CHCl3 showed C=N stretching vibration at 2200 cm⁻¹.

Partial hydrolysis of N-cyano-di-2-butylamine-N-amido di-2-butylamine

1 g of N-cyano di-2-butylamine was heated with 15 ml of dilute hydrochloric acid (3.6 N) at 70–80 °C for about 5 h, when the cyanamide went into solution. Heating was continued for further one hour and the reaction mixture was worked up as described for the amido derivative of diisobutylamine. On crystallisation from dilute methanol, N-amido-di-2-butylamine was obtained as colourless slender rods m.p. 61–62 °C. It is soluble in common organic solvents.

Characterization of N-amido-di-2-butylamine

The IR spectrum in CHCl3 showed a peak at 1640 cm⁻¹ for C=O stretching of the amido group, two peaks at 3340 cm⁻¹ and 3430 cm⁻¹ for amido NH2 stretchings and a band at 1580 cm⁻¹ for N–H bending vibration.

The mass spectrum showed molecular ion peak at m/e 172.15742 (calculated for C6H20N2O = 172.15755) in agreement with the molecular formula C6H20N2O for N-amido-di-2-butylamine. The presence of amido group was shown by diagnostic fragments at m/e 128.
N-amido-di-2-butylamine was obtained as colourless dimethylurea N-amido-di-2-butylamine-N,N-di-2-butyl-N-N-Methylation of N-amido-di-2-butylamine-N,N-di-2-butyl-N-N

Methylation of 250 mg of N-amido-di-2-butylamine was carried out in exactly the same manner as described for N-amido-diisobutylamine. Dimethyl N-amido-di-2-butylamine was obtained as colourless fine needles from methanol, m.p. 102–103 °C (yield 210 mg). It is soluble in methanol, chloroform, ethyl acetate, sparingly soluble in ether and insoluble in petroleum ether. It afforded molecular ion at m/e 200 (10%) which was in agreement with the molecular formula, C_{n}H_{m}N_{o}, for the dimethyl-N-amido-di-2-butylamine. In IR spectrum (CHCl_{3}) N-H stretching and bending vibration were not observed, but a peak appeared at 1630 cm^{-1} for urea carbonyl function.

Acetylation of N-amido-di-2-butylamine-N,N-di-2-butyl-N.

The activated sodium complex of 250 mg of N-amido-di-2-butylamine, prepared as described for N-amido-diisobutylamine, was refluxed with 2 ml of freshly distilled acetic anhydride for 4 h. On working up the reaction mixture in the usual manner acetyl N-amido-di-2-butylamine was obtained as colourless amorphous powder, which formed small rods on rubbing with petroleum ether m.p. 91–92 °C (yield theoretical). It is soluble in methanol, ethylacetate and chloroform, sparingly soluble in ether and insoluble in petroleum ether and water. The molecular formula C_{14}H_{22}N_{2}O_{2} was confirmed by mass spectrometry which showed M^{+} 214 (2%). Other diagnostic fragments were observed at m/e 185 (12%) = (M-29)^{+} and 43 (42%) = (COCH_{3})^{+}. IR spectrum in CHCl_{3} showed a peak at 3400 cm^{-1} (amide N-H), 1680 cm^{-1} and 1620 cm^{-1} (acetyl and urea carbonyl stretchings).

Benzylation of N-amido-di-2-butylamine-N,N-di-2-butyl-N.

2 ml benzoyl chloride was added to the activated sodium complex of 250 mg of N-amido-di-2-butylamine. The reaction mixture was refluxed for about 6 h, cooled and treated with dilute aqueous alkali. The oily product thereby obtained was washed well with water and taken up in ether. On removing the solvent from the ethereal solution after drying (Na_{2}SO_{4}), the benzoyl derivative was obtained as white crystallize. On recrystallization from ether it formed rectangular plates and melted at 85–86 °C.

The mass spectrum showed molecular ion peak at m/e 276 (2%) corresponding to the molecular formula C_{14}H_{24}N_{2}O_{2} for benzoyl N-amido-di-2-butylamine. Other diagnostic peaks appeared at 148 (20%) = (0^{+}=C-\text{NH}-\text{COOCH}_{3}), 105 (100%) = (\text{COOCH}_{3})^{+} and 77 (98%) = (\text{C}_{6}H_{5})^{+}. IR spectrum in KBr showed peaks at 3420 cm^{-1} (amide N-H) and between 1650 cm^{-1}–1680 cm^{-1} (benzoyl and urea carbonyl stretchings).

Di-2-butylamine-N-iminoethylether

This compound was obtained from the cyanamide of di-2-butylamine in exactly the same manner as described for disobutylamidine-N-iminoethyl ether. It formed colourless small rods from ether-petroleum ether m.p. 100–101 °C which showed M^{+} peak at m/e 200.18991 (caled for C_{14}H_{24}N_{2}O = 200.1885) corresponding to the molecular formula C_{14}H_{24}N_{2}O. Other prominent peaks appeared at 185 (5%) = (M-15)^{+}, 128 (9%) = (\text{C}_{6}H_{5}N)^{+}, 86 (34%) = (\text{M-2(C}_{6}H_{5})^{+} , 72 (26%) = (\text{C}_{6}H_{5}O-C=\text{NH}^{+} and 57 (80%) = (\text{C}_{6}H_{5})^{+}. Its IR spectrum in CHCl_{3} showed peaks at 3400 cm^{-1} (NH-stretching) and 1130 cm^{-1} (C-O-C stretching of O-Et group). Its H{^1} NMR spectrum showed two-protons quartet at δ 4.1 (OCH_{3}-CH_{3}) and three-protons triplet at δ 1.4 (OCH_{3}-CH_{3}).