Some Extensions of von Braun (BrCN) Reaction on Organic Bases: Part II

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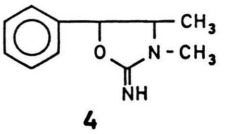
von Braun Cyanogen Bromide Reaction

Extensions of von Braun Cyanogen bromide reaction on Ephedra alkaloids and simpler bases have resulted in synthesis of substituted oxazolidines and a whole series of nitrogen analogues of ephedrine, desoxy ephedrine and simpler amines. The general applicability and limitations of such extension of the reaction are also discussed.

In an earlier communication Siddiqui and Bina [1] reported some extensions of von Braun BrCN reaction on the conessine series of alkaloids, which appeared to provide a novel route for the synthesis of therapeutically active nitrogenous compounds including substituted ureas, diamines, carbinol amines and guanidine derivatives. However, it was noted by them that dimethyl α-napthylamine and diethyl amine do not form guanidine derivatives. Further limitations were observed in the case of harmala and Rauwolfia alkaloids [2, 3]. Tetrahydroharmine yielded only urea derivative, while the Rauwolfia bases sandwicine and isosandwicine failed to yield any of the above mentioned derivatives. In view of these observations it was considered of interest to ascertain the applicability, limitations and variations of these reactions with cyanamides of Ephedra alkaloids and other simpler aliphatic and aromatic amines.

The present work deals with the cyanamides of ephedrine (**1**), O-acetyl ephedrine (**2**) and desoxyephedrine (**3**) which were obtained as oily liquids through the action of BrCN. Attempts were made to obtain from ephedrine cyanamide an N-amide, introducing a urea moiety in the molecule, through careful partial hydrolysis with 20% hydrochloric acid. However, the resulting uniform oily product did not show the presence of amide group in the IR and NMR spectra. Ir could be identified through physical and chemical characterization, and spectral studies as 2-imino-3,4-dimethyl-5-phenyl oxazolidine (**4**) (yield 1 g; 100%). The protonation of the nitrile nitrogen promotes nucleophilic attack from the hydroxyl group resulting in a cyclized product. This constituted a better method of preparation than that described by Fodor *et al.* [4] which involves a rather cumbersome three steps process resulting apparently in low yield.



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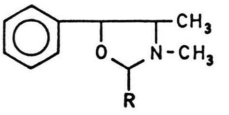
Reduction of **4** with zinc and hydrochloric acid furnished colourless glistening rods of 2-amino-3,4-dimethyl-5-phenyloxazolidine (**5**), m.p. 99 °C (yield 1.01 g; 95%). Further, the amino derivative (**5**) has yielded 2-hydroxy-3,4-dimethyl-5-phenyl oxazolidine (**6**) as colourless fluffy needles, m.p. 92 °C (yield 0.84 g; 83.6%) through careful reaction with nitrous acid. Both these products were hitherto unreported in literature and their structures as shown below, were confirmed through physical and chemical characterization along with spectral data.



5: R = NH_2
6: R = OH

Partial hydrolysis and reduction were also carried out in basic or neutral medium to obtain the urea derivative and diamine, directly from ephedrine cyanamide. The known hydrolysis procedures and catalytic reduction at atmospheric pressure, failed to furnish the desired products. Reduction of the ephedrine cyanamide and O-acetyl ephedrine cyanamide with lithium aluminium hydride resulted in elimination of cyano group and reformation of the parent base. Bouveault Blanc reduction of ephedrine cyanamide on the other hand, afforded, a crystalline compound m.p. 105 °C (yield 0.782 g; 63%), the spectral data of which did not correspond to the diamine, and which could ultimately be identified as ephedrine-N-imino ethyl ether (**7**) formed due to nucleophilic attack of the ethoxide ion on the

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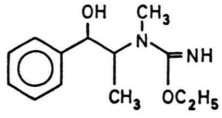
electrophilic nitrile carbon followed by abstraction of proton from the solvent.



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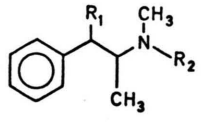
In order to prevent hydroxyl induced cyclization ephedrine was converted into desoxy ephedrine by the method of Schmidt [5]. As a result of extension of von Braun reaction on desoxy ephedrine it has been possible to obtain from desoxy ephedrine cyanamide (**3**) an N-amide (**8**) (yield 0.98 g; 89%) through partial acid hydrolysis. On the other hand, through reduction with zinc and hydrochloric acid, a diamine (**9**) has been obtained (yield 0.777 g; 76%). Further, the diamine has yielded a carbinol amine (**10**) through reaction with nitrous acid (yield 0.613 g; 61%). The structure of these products as shown below, have been arrived at through spectral data and the formation of various derivatives, which are described in the experimental.



1: $R_1 = OH$, $R_2 = CN$;
2: $R_1 = OAc$, $R_2 = CN$;
3: $R_1 = H$, $R_2 = CN$;
8: $R_1 = H$, $R_2 = CONH_2$;
9: $R_1 = H$, $R_2 = CH_2NH_2$;
10: $R_1 = H$, $R_2 = CH_2OH$.

Parallel studies to a large number of aliphatic and aromatic amines afforded a whole series of nitrogen analogues the structures of which were arrived through spectral data and the formation of various derivatives. These are listed in Table I in the experimental. It may be noted in the context of this data that out of 40 derivatives obtained in the present work, 26 have not so far been reported in literature. The others were prepared through different routes, but their yields were significantly lower than in present work.

In view of the results obtained in the present investigations and earlier findings (l. c.) the following observations may be noted with regard to the application of the cited reactions on the cyanamides of various bases.

1. These reactions are applicable to a large variety of bases containing a primary, secondary or tertiary nitrogen atom.

2. The cyanamides of alkaloidal and simpler bases in which the nitrogen atom occurs in a ring system, generally resist reduction to diamines. The same holds good in many cases where the amino group is attached to the ring, due probably to steric hindrance.

3. The urea derivatives could be prepared from the cyanamides of all types of bases, but in the case of alkaloids the formation of such derivatives appears to be sterically conditioned. Thus the alkaloids sandwicine, isosandwicine, ajmaline and isoajmaline, which have tautomeric carbinolamine and aldehyde-imine structures, do not yield urea or any other of the derivatives on mild hydrolysis or reduction [3, 6]. In the case of tetrahydroharmine also, the urea derivative could not be obtained through the normal procedure, and only through hydrolysis with the help of basic hydrogen peroxide [2].

4. The yields of various derivatives obtained in these reactions are excellent and the extension of von Braun BrCN reaction should have economic viability in the synthesis of a large number of potential therapeutic agents.

Experimental

Cyanamide derivatives of Ephedra alkaloids

The cyanamide of ephedrine and desoxyephedrine were prepared by treating their chloroform solution with freshly prepared ethereal solution of BrCN, under good cooling and mechanical stirring for 1 h. The crystalline hydrobromide formed in the reaction was filtered and washed with ether. On removal of the solvent from filtrate and washings, after washing and drying yielded cyanamide derivatives as colourless viscous liquids. The similar work up with N-methyl-O-acetyl ephedrine provided O-acetyl ephedrine cyanamide.

Ephedrine cyanamide (2-methylcyanamide-1-phenyl propanol-1) colourless liquid

Analysis for $C_{11}H_{14}N_2O$

Found	C 69.49	H 7.30	N 14.53,
Calcd	C 69.47	H 7.34	N 14.73.

Mass spectrum: M^+ 190; IR ν_{max} 3300 cm^{-1} (OH group), 2250 cm^{-1} (C≡N) and 3040, 1620 and 1490 cm^{-1} (aromatic ring); NMR ($CDCl_3$): δ 7.4 m (5H, benzene ring), δ 5.00 d (1H, CHOH, $J = 6.3$), δ 2.38 s (3H, N-methyl) and δ 1.11 d (3H, C-methyl, $J = 4.7$).

O-Acetyl ephedrine cyanamide (2-methyl cyanamide-1-phenylpropane-1-O-acetate) colourless liquid

Analysis for $C_{13}H_{16}N_2O_2$

Found	C 67.31	H 7.00	N 12.10,
Calcd	C 67.24	H 6.89	N 12.07.

Mass spectrum: M^+ 232; IR ν_{max} 2250 (C≡N), 1730 (C=O group), 1230 (C–O stretching) and bands due to aromatic ring; NMR ($CDCl_3$): δ 7.5 m (5H, benzene ring), δ 5.2 d (1H, HOAc, $J = 6.3$), δ 2.39 s (3H, N-methyl), δ 2.29 s (3H, $COCH_3$), δ 1.11 d (3H, C-methyl, $J = 4.7$).

Desoxy ephedrine cyanamide (2-methyl cyanamide-1-phenylpropane) colourless liquid

Analysis for $C_{11}H_{14}N_2$

Found	C 75.80	H 8.09	N 16.11,
Calcd	C 75.86	H 8.04	N 16.09.

Mass spectrum: M^+ 174; IR ν_{max} 2250 (C≡N) and 3040, 1620, 1490 cm^{-1} (benzene ring); NMR ($CDCl_3$): δ 7.3 m (5H, benzene ring), δ 3.2 m (1H, methine proton), δ 2.82 d (2H, benzylic protons, $J = 6.28$), δ 2.35 s (3H, N-methyl) and δ 1.14 d (3H, C-methyl, $J = 4.73$).

Substituted Oxazolidines

2-Imino-3,4-dimethyl-5-phenyloxazolidine: 1 g ephedrine cyanamide was suspended in 10 ml of 20% hydrochloric acid and mechanically stirred with occasional warming till a clear solution was obtained. The reaction mixture was basified with ammonia and extracted out with ethyl acetate. The basic oily residue left on removal of the solvent was taken up in ether and treated with ethereal HCl. The resulting hydrochloride crystallized from methanol in shining needles m.p. 235 °C.

Analysis for $C_{11}H_{14}N_2O$. HCl

Found	C 58.53	H 6.74	N 12.12	Cl 15.15,
Calcd	C 58.40	H 6.63	N 12.39	Cl 15.48.

Spectral studies were carried out with the liquid base. Mass spectrum: M^+ 190; IR ν_{max} 3390 (imine NH), 1660 (C=N of imines), 1140 (C–O–C stretching of ethers) and 3040, 1610 and 1490 cm^{-1} (aromatic bands); NMR ($CDCl_3$): δ 7.48 m (5H, aromatic protons), δ 5.2 d (1H, C-5 proton, $J = 6.32$), δ 3.5 m (1H, C-4 proton), δ 2.28 s (3H, N–CH_3) and δ 1.2 d (3H, C–CH_3, $J = 4.73$).

2-amino-3,4-dimethyl-5-phenyl oxazolidine

1 g imino derivative referred to above, was heated with zinc dust and 10% aqueous HCl on water bath for half an hour the solution was filtered and basified with ammonia after prior addition of ammonium chloride. The liberated base was extracted out with ethyl acetate and after usual work up crystallized out from methanol as colourless glistening rods m.p. 99 °C.

Analysis for $C_{11}H_{16}N_2O$

Found	C 68.63	H 8.29	N 14.29,
Calcd	C 68.75	H 8.33	N 14.58.

Mass spectrum: M^+ 192; IR ν_{max} 3400, 3350 (N–H-stretching), 1545 (N–H bending), 1140 (C–O–C stretching) and bands due to aromatic ring; NMR ($CDCl_3$): δ 7.5 m (5H, aromatic protons), δ 5.8 s (1H, C-2 proton), δ 5.1 d (1H, C-5 proton, $J = 6.32$), δ 3.5 m (1H, C-4 proton), δ 2.38 s (3H, N–CH_3) and δ 1.2 d (3H, C–CH_3, $J = 4.74$). Methylation of the amino product with formaldehyde and formic acid afforded N,N-dimethyl derivative (m.p. 112 °C). On the other hand, acetylation and benzoylation yielded N,N-diacetyl and N,N-dibenzoyl derivatives which melted at 82 °C and 80 °C respectively.

2-Hydroxy-3,4-dimethyl-5-phenyl oxazolidine

To a solution of 1 g amino base in 10% hydrochloric acid was added a 10% cold aqueous solution of sodium nitrite (1.2 mole) and after 15 min, the reaction mixture was extracted out with ethyl acetate. The darkish ethyl acetate layer was treated with ether and petroleum ether which threw out the resinous impurities. The nearly colourless solution gave a light yellow residue which crystallized from methanol as fluffy needles, m.p. 92 °C.

Analysis for $C_{11}H_{15}NO_2$

Found	C 68.41	H 7.71	N 7.32,
Calcd	C 68.39	H 7.77	N 7.25.

Mass spectrum: M^+ 193; IR ν_{max} (KBr): 3302 (OH), 1140 (C–O–C stretching), 1055 (C–OH stretching of secondary carbinols in five membered ring), and bands due to aromatic ring; NMR ($CDCl_3$): δ 7.45 m (5H, aromatic protons), δ 5.9 s (1H, CHOH), δ 5.1 d (1H, C-5 proton, $J = 6.33$), δ 3.4 m (1H, C-4 proton), δ 2.38 s (3H, N–CH_3) and δ 1.1 d (3H, C–CH_3, $J = 4.74$). The carbinol amine afforded crystalline O-acetyl (m.p. 102 °C) and O-benzoyl (m.p. 100 °C) derivatives through acetic anhydride and benzoyl chloride respectively.

Ephedrine-N-iminoethyl ether

1 g of ephedrine cyanamide was taken up in 10 ml absolute alcohol and to it was added 100 mg of sodium metal. After half an hour the reaction mixture was extracted out with ethyl acetate with the addition of saline. On working up the ethyl acetate extract N-imino ethyl ether derivative was obtained as colourless rectangular plates from methanol which melted at 105 °C (yielded 0.782 g, 63%).

Analysis for $C_{13}H_{20}N_2O_2$

Found	C 65.94	H 8.22	N 11.90,
Calcd	C 66.10	H 8.47	N 11.86.

Mass spectrum: M^+ 236; IR ν_{max} 3400 cm^{-1} (N–H-stretching), 3300 cm^{-1} (OH group), 1120 cm^{-1} (C–O–C stretching of O–Et group) and bands due to aromatic ring; NMR ($CDCl_3$): δ 7.4 m (5H, benzene

ring), δ 5.00 d (1H, CHOH, $J = 6.13$), δ 3.9 q (2H, O–CH_2–CH_3), δ 2.38 s (3H, N–CH_3), δ 1.4 t (3H, O–CH_2–CH_3) and δ 1.11 d (3H, C–CH_3, $J = 4.73$).

Derivatives of desoxy ephedrine

Desoxy ephedrine urea (2-methylamino-1-phenyl-propane urea): Ephedrine cyanamide (1 g) was taken in 20% aqueous hydrochloric acid and stirred at 60 °C for 1 h when it went into solution. Stirring was continued for further 10 min after which the solution was cooled, basified with ammonia and extracted out with ethyl acetate. The product crystallized out from methanol as colourless shining plates m.p. 120 °C.

Analysis for $C_{11}H_{16}N_2O$

Found	C 68.69	H 8.38	N 14.32,
Calcd	C 68.75	H 8.33	N 14.58.

Mass spectrum: M^+ 192, other prominent fragments at *m/e* 177 $(M–CH_3)^+$, 148 $(M–CONH_2)^+$ and 44 $(CONH_2)^+$; IR ν_{max} (KBr): 3500, 3430 (NH_2 stretchings of amide), 1670 (C=O stretching of amide), 1580 (N–H bending) and bands due to aromatic ring at 3040, 1610 cm^{-1}; NMR ($CDCl_3$): δ 7.3 m (5H, aromatic protons), δ 6.87 s (2H, $CONH_2$), δ 3.3 m (1H, methine proton), δ 2.78 d (2H, benzylic protons, $J = 6.3$), δ 2.36 s (3H, N–CH_3) and δ 1.15 d (3H, C-methyl, $J = 4.73$). The N,N-dimethyl (m.p. 112 °C), diacetyl (m.p. 116 °C) and dibenzoyl (m.p. 97 °C) derivatives of desoxy ephedrine urea were obtained by treating its activated sodium complex in toluene with formic acid/formaldehyde, acetic anhydride and benzoyl chloride respectively.

N-Aminomethyl desoxyephedrine

Desoxyephedrine cyanamide (1 g) was taken in 15% aqueous HCl and heated with zinc dust on water bath till it went into solution. The heating was continued for about half an hour after which the unreacted zinc was filtered off and the filtrate ammoniated after adding ammonium chloride. The product crystallized out from methanol as colourless rectangular plates, m.p. 135 °C.

Analysis for $C_{11}H_{18}N_2$

Found	C 74.22	H 10.20	N 15.64,
Calcd	C 74.15	H 10.11	N 15.73.

Mass spectrum: M^+ 178, other diagnostic fragments at *m/e* 163 $(M–CH_3)^+$, 148 $(M–CH_2NH_2)^+$ and 30 $(H_2C=NH_2)^+$; IR ν_{max} (KBr): 3420, 3390 (NH stretchings), 1590 (N–H bending) and aromatic bands; NMR ($CDCl_3$): δ 7.3 m (5H, aromatic protons), δ 3.43 s (2H, –N–CH_2–N), δ 3.2 m (1H, methine proton), δ 2.75 d (2H, benzylic protons, $J = 6.33$), δ 2.35 s (3H, N–CH_3) and δ 1.46 d (3H, C–CH_3, $J = 4.74$).

The acetylation, benzoylation and methylation of N-aminoethyl desoxyephedrine was carried out in exactly the same manner as described earlier in oxazolidines. N,N-dimethyl m.p. 126 °C; N,N-diacetyl m.p. 106 °C; and N,N-dibenzoyl derivatives m.p. 101 °C.

N-Hydroxy methyl desoxyephedrine

1 g N-amino methyl derivative was taken in 10% aqueous HCl and 1.2 mole of sodium nitrite in cold aqueous solution was added on to it. The N-hydroxymethyl derivative was obtained on usual work up as colourless shining needles from methanol m.p. 120 °C.

Analysis for $C_{11}H_{17}NO$

Found	C 73.81	H 9.51	N 7.79,
Calcd	C 73.74	H 9.49	N 7.82.

Mass spectrum: M^+ peak 179, other diagnostic fragments at *m/e* 164 $(M–CH_3)^+$, 161 $(M–H_2O)^+$, 148 $(M–CH_2OH)^+$ and 31 $(H_2C=OH)^+$; IR ν_{max} (KBr): 3400–3300 (OH stretching), 1060 (–C–O stretching of carbinols) and 3040, 1610, 1490 cm^{-1} (aromatic bands); NMR ($CDCl_3$): δ 7.3 m (5H, aromatic protons), δ 3.6 s (2H, N–CH_2OH), δ 3.1 m (1H, methine proton), δ 2.74 d (2H, benzylic protons, $J = 6.34$), δ 2.35 s (3H, N–CH_3) and δ 1.13 d (3H, C–CH_3, $J = 4.73$).

Treatment of carbinol amine with acetic anhydride and benzoyl chloride provided the corresponding acetate (m.p. 113 °C) and benzoate (m.p. 110 °C) respectively.

Aliphatic and aromatic amines

A number of aliphatic and aromatic amines were converted into the corresponding cyanamides in exactly the same manner as desoxy ephedrine. Partial hydrolysis with 20% hydrochloric acid converted them into the crystalline urea derivatives. On the other hand, reduction with zinc and hydrochloric acid yielded the N-aminomethyl analogues which were liquids in most of the cases and separated from the reaction mixture as crystalline dihydrochlorides. The aminomethyl derivatives were carefully reacted with nitrous acid to obtain N-hydroxymethyl analogues, characterized through their crystalline acetates. The whole series of the derivatives obtained is listed in the following table and the new compounds being marked with asteriks. The analytical and spectral data have been provided in the table in respect of new products as well as those which have already been reported in the literature, liquid in character and have not been characterized through any crystalline derivatives.

Table I.

S. No.	Name of substance with structure	m.p. [°C]	Analysis Found [%] / Calculated [%] C	H	N	Cl	M^+ peak	IR ν_{max} ($CHCl_3$) [cm^{-1}]	$^1H_1$ NMR ($CDCl_3$) δ	Yield[a] g (%)
1	Ethyl methyl canamide [7] $CH_3-CH_2-N-(CH_3)-CN$	1[b]	57.17 57.14	9.54 9.52	33.83 33.33		84	2250	–	1.4 (100)
2	Propyl cyanamide* $CH_3-CH_2-CH_2-NH-CN$	1	57.11 57.14	9.54 9.52	33.34 33.33		84	3400, 2250	3.2t(2H,HN–$C\underline{H}_2$–CH_2), 0.84t(3H,C–CH_3), 1.25m(2H,CH_2)	1.4 (100)
3	Pentyl cyanamide [8] $CH_3-(CH_2)_3CH_2-NH-CN$		64.32 64.28	10.81 10.71	24.86 25.00		112	3420, 2250	–	1.28 (100)
4	3-Methyl butyl cyanamide* $CH_3-CH(CH_3)-(CH_2)_2-NH-CN$	1	64.63 64.28	10.63 10.71	25.02 25.00		112	3410, 2250	3.1t(2H,NH–$C\underline{H}_2$–CH_2), 0.82t(3H,C–CH_3)	1.28 (100)
5	Bis (1-methyl ethyl)cyanamide [9] $[(CH_3)_2CH]_2N-CN$	1	66.70 66.66	11.13 11.11	22.16 22.22		126	2250	–	1.2 (100)
6	Octyl cyanamide* $CH_3-(CH_2)_7-CN$	64	70.20 70.12	11.64 11.68	18.14 18.18		154	3420, 2250	3.2t(2H,CH_2–$C\underline{H}_2$–NH), 0.8t(3H,C–CH_3)	1.19 (100)
7	Methyl ethyl urea* $CH_3-CH_2-N(CH_3)-CO-NH_2$	68	47.09 47.05	9.93 9.8	27.12 27.45		102	3500, 3400, 1650, 1580	6.81bs(2H,$CONH_2$), 3.15q(2H,N–CH_2), 2.36s(3H,N–CH_3), 0.90t(3H,C–CH_3)	1.09 (90)
8	Propyl urea [10] $CH_3-(CH_2)_2NH-CO-NH_2$	110	–	–	–	–	–	–	–	1.06 (88)
9	Pentyl urea [11] $CH_3-(CH_2)_4-NH-CO-NH_2$	99	–	–	–	–	–	–	–	1.0 (87)
10	3-Methyl butyl urea [12, 13] $CH_3-CH-(CH_3)-(CH_2)_2-NH-CO-NH_2$	94	–	–	–	–	–	–	–	1.0 (87)
11	Bis (1-methyl ethyl)urea [14] $[(CH_3)_2-CH_2]-N-CO-NH_2$	103–4	–	–	–	–	–	–	–	1.1 (89)
12	Octyl urea [15] $CH_3(CH_2)_7-NH-CO-NH_2$	96	–	–	–	–	–	–	–	1.01 (91)
13	N-Aminomethyl ethyl methyl amine* $CH_3-CH_2-N(CH_3)-CH_2-NH_2$	1	–	–	–	–	88	3500, 3440, 1585	3.61s(2H,N–$C\underline{H}_2$–NH_2), 3.1q(2H,N–CH_2), 2.36s(3H,N–CH_3), 0.88t(3H,C–CH_3)	0.9 (89)
	–di HCl	38	29.82 30.00	8.95 8.75	17.3 17.5	43.92 43.75	–	–	–	
14	N-Aminomethyl propylamine* $CH_3(CH_2)_2-NH-CH_2-NH_2$	1	–	–	–	–	88	3500, 3450, 1580	3.61s(2H,N–$C\underline{H}_2$–NH_2), 3.1t(2H,N–$C\underline{H}_2$–CH_2), 0.84t(3H,C–CH_3), 1.25m(2H,CH_2)	0.88 (84)
	–di HCl	68	29.91 29.81	8.82 8.69	17.30 17.39	43.91 44.09	–	–	–	–
15	N-Amino methyl pentylamine* $CH_3-(CH_2)_4-NH-CH_2-NH_2$	1	–	–	–	–	116	3500, 3450, 1585	3.61s(2H,N–$C\underline{H}_2$–NH_2), 3.1t(2H,N–$C\underline{H}_2$–CH_2) 0.82t(3H,C–CH_3)	0.93 (90)
	–di HCl	146	38.17 38.09	9.44 9.5	14.51 14.81	37.56 37.56	–	–	–	–
16	N-Amino methyl-3-methyl butyl-amine* $CH_3-CH(CH_3)-(CH_2)_2NH-CH_2NH_2$	1	–	–	–	–	116	3450, 3500, 1590	3.61s(2H,N–$C\underline{H}_2$–NH_2), 3.1t(2H,N–$C\underline{H}_2$–CH_2), 0.81d(6H,C–CH_3)	0.9 (89)
	–di HCl	138	38.29 38.09	9.62 9.52	14.81 14.81	37.91 37.56	–	–	–	–
17	N-Aminomethyl-bis(1-methyl)-ethylamine* $[(CH_3)_2-CH]_2-N-CH_2-NH_2$	1	–	–	–	–	130	3500, 3450, 1590	3.8h(2H,C–CH), 3.61s(2H,N–$C\underline{H}_2$–NH_2), 1.2d(12H,C–CH_3)	0.93 (91)
	–di HCl	131	41.21 41.37	9.72 9.85	13.84 13.79	35.17 34.97	–	–	–	–
18	N-Aminomethyl octylamine* $CH_3-(CH_2)_7-NH-CH_2-NH_2$	48	68.50 68.35	13.99 13.92	17.50 17.72		159	3500, 3450, 1580	3.61s(2H,N–$C\underline{H}_2$–NH_2), 3.1t(2H,CH_2–$C\underline{H}_2$–NH), 0.79t(3H,C–CH_3)	1.03 (90)

Continued Table I.

No.	Name of substance with structure	m.p. [°C]	Analysis Found [%] / Calculated [%] C	H	N	Cl	M^+ peak	IR ν_{max} ($CHCl_3$) [cm^{-1}]	$^1H_1$ NMR ($CDCl_3$) δ	Yield[a] g (%)
19	N-Hydroxymethyl ethyl methyl amine* $CH_3-CH_2-N(CH_3)-CH_2OH$	1	–	–	–	–	89	3250–3400, 1055	4.23s(2H,N–C̲H̲$_2$–OH), 3.2q(N–C̲H̲$_2$–CH$_3$), 2.36s(3H,N–CH$_3$), 0.89t(3H,C–CH$_3$)	0.52 (52)
	-acetate	148	55.10 54.96	9.83 9.92	10.64 10.68		–	–	–	–
20	N-Hydroxymethyl propylamine* $CH_3-(CH_2)_2-NH-CH_2OH$	1	–	–	–	–	89	3460, 3250–3400, 1055	4.23s(2H,N–C̲H̲$_2$–OH), 3.1t(N–C̲H̲$_2$–CH$_2$), 1.35m(2H,C–CH$_2$), 0.84t(3H,C–CH$_3$)	0.56 (56)
	-N-Acetyl acetate	136	55.89 55.49	8.53 8.67	8.00 8.09		–	–	–	–
21	N-Hydroxymethyl pentylamine* $CH_3-(CH_2)_4-NH-CH_2OH$	1	–	–	–	–	117	3460, 3250–3400, 1050	4.23s(2H,N–C̲H̲$_2$OH), 3.1t(2H,N–C̲H̲$_2$–CH$_2$), 0.83t(3H,C–CH$_3$)	0.59 (59)
	-N-Acetylacetate	157	59.51 59.70	9.54 9.45	7.01 6.96		–	–	–	–
22	N-Hydroxymethyl-3-methyl butylamine* $CH_3-CH(CH_3)-(CH_2)_2-NH-CH_2-OH$	1	–	–	–	–	117	3460, 3250, 3400, 1050	4.22s(2H,N–C̲H̲$_2$–OH), 3.1t(2H,N–C̲H̲$_2$–CH$_2$), 0.87d(6H,C–CH$_3$)	0.50 (50)
	N-Acetylacetate	151	59.80 59.70	9.41 9.45	6.89 6.96		–	–	–	–
23	N-Hydroxymethyl bis (1-methyl ethyl)amine* $[(CH_3)_2CH]_2-N-CH_2-OH$	1	–	–	–	–	131	3250–3400, 1055	4.23s(2H,N–C̲H̲$_2$–OH), 3.85h(2H,N–C̲H̲(CH$_3$)$_2$, 0.95d(12H,C–CH$_3$)	0.51 (51)
	-acetate	166	62.21 62.42	10.48 10.98	8.17 8.09		–	–	–	–
24	N-Hydroxymethyl octylamine* $CH_3(CH_2)_7-NH-CH_2-OH$	80	67.84 67.92	13.41 13.20	8.9 8.80		159	3460, 3200–3390, 1050	4.22s(2H,N–C̲H̲$_2$–OH), 3.1t(2H,N C̲H̲$_2$–CH$_2$), 0.8t(3H,C–CH$_3$)	0.62 (62)
25	Pyrrolidine cyanamide [9] C_4H_8N-CN	1	62.89 62.50	8.13 8.33	29.36 29.16		96	2250	–	1.35 (100)
26	N-Methylcyclohexyl cyanamide [16] $C_6H_{11}N(CH_3)-CN$	1	69.32 69.56	10.30 10.14	20.36 20.28		138	2250	–	1.08 (100)
27	Pyrrolidine urea* $C_4H_8N-CO-NH_2$	212	52.91 52.63	8.42 8.77	24.17 24.56		114	3500, 3450, 1680, 1590	6.5s(2H,CONH$_2$), 3.4t(4H,α-methylene protons), 2.2qn(4H,β-methylene protons)	1.01 (87)
28	N-Methyl cyclohexyl urea* $C_6H_{11}-N-(CH_3)-CO-NH_2$	79	61.13 61.53	10.55 10.25	17.79 17.94		156	3500, 3460, 1680, 1590	6.5s(2H,CONH$_2$), 2.38s(3H,N–CH$_3$), 3.6m(1H,N–CH)	1.06 (94)
29	N-Methylaniline cyanamide* $C_6H_5-N-(CH_3)-CN$	1	72.40 72.72	6.32 6.06	21.27 21.21		132	2250	7.2m(5H,aromatic protons), 2.52s(3H,N–CH$_3$)	1.09 (100)
30	*p*-Anisidine cyanamide* *p*-$C_6H_4(OCH_3)-NH-CN$	84	64.86 64.86	5.71 5.40	18.86 18.91		148	3420, 2220, 1625, 1250	7.2–7.4m (4H,aromatic protons), 3.7s(3H,O–CH$_3$)	1.2 (100)
31	1-Phenethyl cyanamide* $C_6H_5-CH(CH_3)-NH-CN$	104	73.55 73.97	6.98 6.89	19.45 19.17		146	3425, 2240, 1620	7.1m(5H,aromatic protons), 3.1q(1H,HN–C̲H̲–CH$_3$), 0.8d(3H,CH–C̲H̲$_3$)	1.2 (100)

Continued Table I.

S. No.	Name of substance with structure	m.p. [°C]	Analysis Found [%] Calculated [%] C	H	N	Cl	M^+ peak	IR ν_{max} ($CHCl_3$) [cm^{-1}]	$^1H_1$ NMR ($CDCl_3$) δ	Yield g (%)
32	3-Phenylpropylcyanamide [16] C_6H_5–$(CH_2)_3$–NH–CN	130	–	–	–	–	–	–	–	1.18 (100)
33	N-Methylaniline urea [17] C_6H_5–N(CH_3)–CO–NH_2	82	–	–	–	–	–	–	–	1.13 (100)
34	*p*-Anisidine urea [18] *p*-C_6H_4(OCH_3)–NH–CO–NH_2	166	–	–	–	–	–	–	–	1 (91)
35	1-Phenethyl urea* $C_6H_5CH(CH_3)$–NH–CO–NH_2	110	65.98 65.85	7.49 7.31	17.30 17.07		146	3500, 3460, 1685, 1590	7.1 m (5H, aromatic protons), 6.75 bs (1H, NHCO), 6.12 s (2H, $CONH_2$), 3.1 q (1H, HN–C<u>H</u>–CH_3), 0.8 d (3H, CH–C<u>H</u>$_3$)	1.12 (100)
36	3-Phenylpropyl urea [19] C_6H_5–$(CH_2)_3$–NH–CO–NH_2	145	–	–	–	–	–	–	–	1.02 (91)
37	N-Aminomethyl-1-phenethyl amine* C_6H_5–$CH(CH_3)NH$–CH_2–NH_2	106	72.53 72.00	9.10 9.33	18.36 18.66		150	3498, 3400, 1588	7.1 m (5H, aromatic protons), 3.6 s (2H, NH–C<u>H</u>$_2$–NH_2), 3.1 q (1H, HN–C<u>H</u>–CH_3), 0.8 d (3H, CH–C<u>H</u>$_3$)	0.90 (88)
38	N-Aminomethyl-3-phenyl propylamine* C_6H_5–$(CH_2)_3$–NH–CH_2–NH_2	138	73.00 73.17	9.61 9.75	17.38 17.01		164	3500, 3450, 1590	7.1 m (5H, aromatic protons), 3.6 s (2H, NH–C<u>H</u>$_2$–NH_2), 3.1 t (2H, N–C<u>H</u>$_2$–CH_2), 2.7 t (C_6H_5–C<u>H</u>$_2$)	0.88 (86)
39	N-Hydroxymethyl-1-phenethyl-amine* C_6H_5–CH(CH_3)–NH–CH_2–OH	94	71.90 71.52	8.47 8.60	9.05 9.27		151	3460, 3250–3400, 1055	4.2 s (2H, N–C<u>H</u>$_2$–OH), 3.1 q (1H, N–C<u>H</u>–CH_3), 0.79 d (3H, CH–C<u>H</u>$_3$)	0.63 (63)
40	N-Hydroxymethyl-3-phenyl propylamine* $C_6H_5(CH_2)_3$–NH–CH_2–OH	120	72.39 72.72	9.20 9.09	8.57 8.48		165	3465, 3260–3400, 1055	7.1 m (5H, aromatic protons), 4.2 s (2H, N–C<u>H</u>$_2$–OH), 3.1 t (2H, N–C<u>H</u>$_2$–CH_2), 2.7 t (C_6H_5–C<u>H</u>$_2$)	0.62 (62)

s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet and h = heptet.
* Refers to new compounds; [a] yields refer to 1 g reactants in each case; [b] = liquid.

[1] S. Siddiqui and B. S. Siddiqui, Z. Naturforsch. **35b,** 1049 (1980).
[2] N. Afza and S. Siddiqui, Pak. J. Sci. Ind. Res. **22,** 6, 290 (1979).
[3] A. Malik, N. Afza, N. Sultana, and S. Siddiqui, Heterocycles **16,** No. 7 (1981).
[4] G. Fodor K. Koezka, and L. Szekeres, Acta Chim. Acad. Sci. Hung. **1,** 377 (1951).
[5] E. Schmidt, Arch. Pharm. **251,** 320 (1913).
[6] S. Siddiqui, S. A. Warsi, M. Alauddin, and V. U. Ahmad, Pak. J. Sci. Ind. Res. **2,** 86 (1959).
[7] D. Martin and W. M. Brause, J. Prakt. Chem. **312** (5), 812 (1971).
[8] C. Wentrup, Tetrahedron **27** (6), 1281 (1971).
[9] A. Joneyzk, Z. Ochal, and M. Makosza, Synthesis **12,** 882 (1978).
[10] C. Mauguin, Ann. Chim. Phys. **22,** 343 (1911).
[11] R. J. Grout and M. W. Partridge, J. Chem. Soc. **1960,** 3340.
[12] T. Curtius, W. Sieber, F. Nadenheim, O. Hambach, and W. Ritter, J. Prakt. Chem. **125,** 195 (1930).
[13] J. Bougault and U. Leboucq, Bull. Soc. Chim. Fr. **47,** 602 (1930).
[14] Van der Zande, Rec. Trav. Chim. Pays-Bas **8,** 231 (1889).
[15] F. Henry, R. Harry, and T. H. Arnold, J. Org. Chem. **23,** 1107 (1958).
[16] S. C. Cherkofsky, U. S. Patent No. 3, 954 (1976); C. F., C. A., 85; 37260r.
[17] T. L. Davis and K. C. Balnchard, J. Am. Chem. Soc. **51,** 1800 (1929).
[18] Kolekhoff, Ber. **16,** 376 (1883).
[19] P. Borgua, L. Vicarini, and G. Calderara, Farmaco. Ed. Sci. **34** (4), 338 (1976).