Some piperazino analogues of methadone and related ketones: a novel conversion of an *N*-carbethoxy to a triethylmethyl group

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Received November 21, 1968

A number of derivatives of methadone and related compounds have been prepared, where the dimethylamino group has been replaced by a 4-substituted piperazino function. The preparation of these compounds involved the reaction of *N*-ω-cyanoalkyl-*N'*-carbethoxy piperazines with ethyl magnesium bromide, and various products were obtained. These included replacement of the *N'*-carbethoxy group by a triethylmethyl function and cleavage of the carbethoxy group. In some cases the ω-cyano group reacted to give the corresponding ketone. Reactions of 1-benzyl-4-carbethoxy piperazine with ethyl magnesium bromide and phenyl magnesium bromide gave no evidence for the formation of the triethylmethyl group. However, cleavage of the carbethoxy group occurred and there was evidence for the formation of the corresponding amide.

Canadian Journal of Chemistry, 47, 2413 (1969)

Introduction

Structural modifications of the narcotic analgesic methadone (**1***a*) involving replacement of the terminal dimethylamino group by an alicyclic *t*-basic function have led to several potent compounds, two of which, namely dipipanone (**1***b*) and phenadoxone (**1***c*), have been used clinically (1, 2). The *N'*-methylpiperazino analogue (**1***d*) has also been examined and is significantly active as an analgesic being half as potent as methadone in mice (3). In analgesics based upon 4-phenylpiperidine (e.g. pethidine) and those in which this structural unit forms part of a polycyclic molecule (e.g., dromoran), substitution of *N*-methyl by arylalkyl functions such as 2-phenethyl and 3-phenpropyl generally yields a more potent product (2), while oxygenated functions [e.g. $(CH_2)_4OH$ and $(CH_2)_2OEt$] effectively raise the activity of pethidine (4).

In the light of these findings, it was considered of interest to examine piperazino analogues of methadone and related compounds which carried aryl–alkyl and oxygenated-alkyl *N'*-substituents.

The general route used to prepare the desired methadone analogues is illustrated for one series in Scheme 1. *N'*-Carbethoxy intermediates (**2**) rather than those unsubstituted at this position were chosen on account of the need to avoid active hydrogen sites in certain of the reactions, and also because of the possibility of subsequent replacement of *N'*-CO_2Et in the ketone **3** by a variety of R substituents. It was recognized that the *N'*-CO_2Et group in the cyanide **2** might provide a further point of Grignard attack but this was not considered a disadvantageous complication since it could lead directly to the N'H analogue of **3**. Other piperazino cyanides subjected to the same reaction sequence were the trimethylene analogue **4** and the branched chain derivatives **5***a* and **5***b*. The latter pair both resulted when diphenylacetonitrile was alkylated with *N*-2-chloropropyl-*N'*-carbethoxy piperazine and their structures were established by converting one member to the corresponding *N'*-methyl derivative, previously prepared by an unambiguous route (5).

Reaction of the cyanides **2**, **4**, and **5** with ethyl magnesium bromide (excess of reagent in benzene at the reflux temperature) led in all cases to basic mixtures from which crystalline products could in some instances be isolated as hydrochloride salts. Further evidence of reaction pathways was provided by the nature of products obtained from the uncrystallizable residues after hydrolysis and *N'*-alkylation procedures. With the exception of the highly hindered cyanide **5***b*, all substrates suffered attack at the cyano function and were converted to corresponding ethyl ketones. These were isolated as the *N'*-alkylated products required for pharmacological evaluation. Direct evidence of the removal of the *N'*-CO_2Et group was only obtained in the case of cyanide **4**, through the isolation of the

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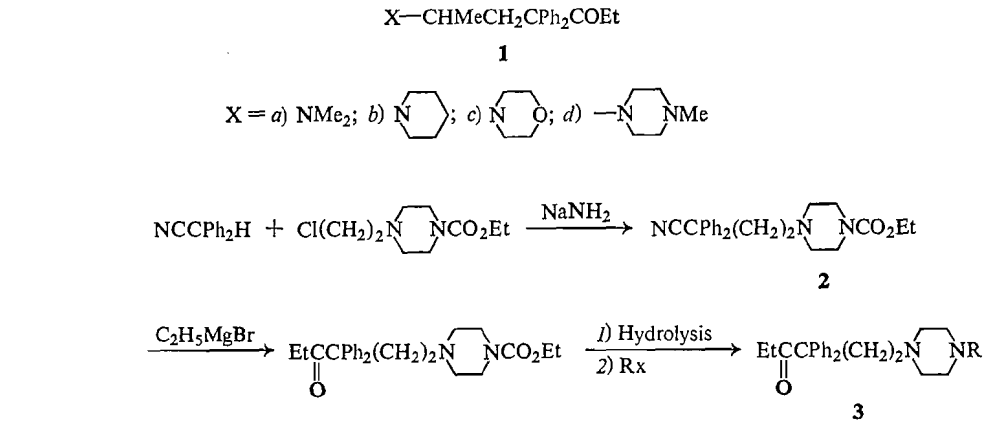
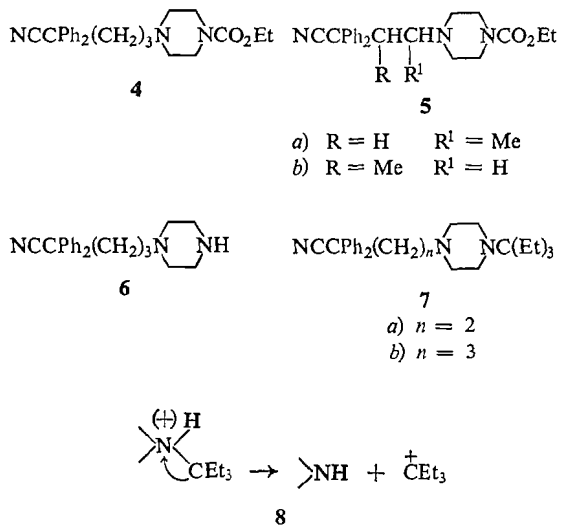


SCHEME 1



sec-amine **6** as a hydrochloride, while an unexpected reaction between the *N*-carbethoxy group and ethyl magnesium bromide, namely its conversion to a triethylmethyl function, was detected in two cases. Structural evidence for the cyanide 2-ethyl Grignard reaction product **7***a* is detailed below:

(*1*) The cyano group of this product is intact because the infrared spectrum of the free base shows a typical $\nu C{\equiv}N$ band at 2280 cm^{-1} (obscured in the salt by the broad $\nu N^{+}H$ band); the *N*′-CO_2Et group has been modified, however, since the pronounced $\nu C{=}O$ band near 1700 cm^{-1} of the precursor cyanide is absent, as are other bands in the carbonyl stretching region (1800–1620 cm^{-1}).

(*2*) The 60 MHz proton magnetic resonance (p.m.r.) spectrum of the salt demonstrates the presence of three identical *C*-ethyl groups (a 9 proton deformed triplet near 9 τ and a 6 proton multiplet near 8.25 τ). Their identity is supported by the fact that these signals were not further resolved when a spectrum was recorded at 100 MHz (Fig. 1).

(*3*) The mass spectrum of the hydrochloride showed a peak of highest *m/e* ratio at 403, corresponding with the dihydrochloride monohydrate of **7***a*. Prominent peaks consistent with likely fragments were found at 374 (loss of Et), 304 (loss of CEt_3), 192 (due to $NCCPh_2$), and 112 (due to $CH_2CH_2N{=}CH{-}N$), while a peak at 99 (CEt_3) was also recorded.

(*4*) Elemental analysis of the salt supported the dihydrochloride monohydrate structure **7***a*. Evidence for water of crystallization was provided by a loss on drying determination and infrared characteristics (broad band near 3500 cm^{-1}) of the salt.

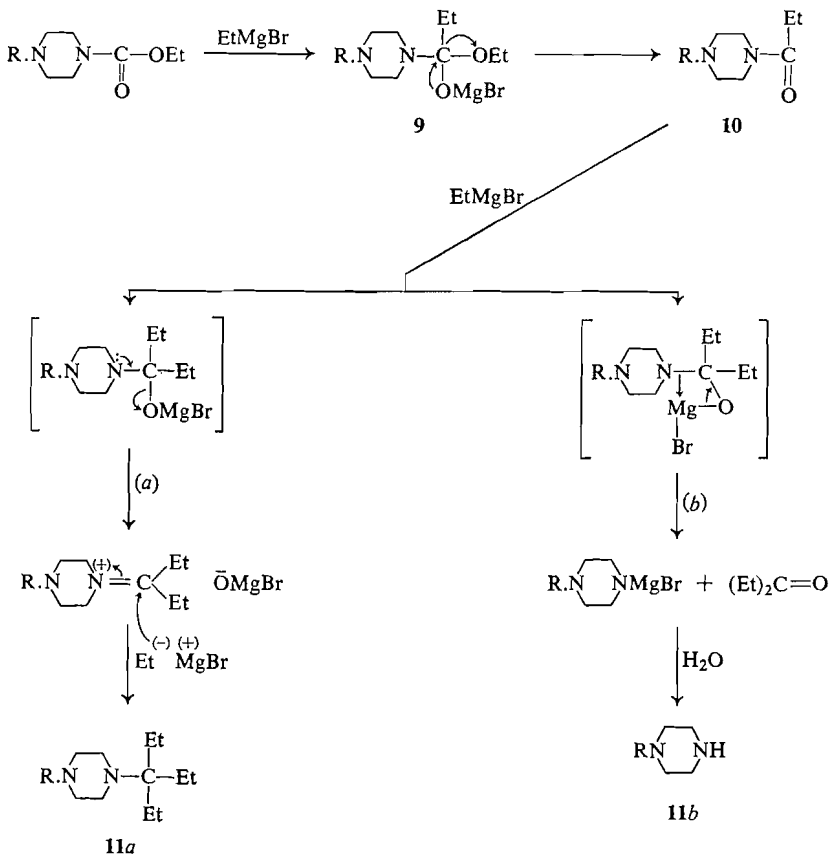
A dihydrochloride monohydrate, isolated from the cyanide 4-ethyl Grignard reaction product, was similarly assigned the *N*-triethylmethyl structure **7***b* on the basis of analytical and infrared spectroscopic evidence. Its *N*′-substituent could be removed under acid conditions (18% HCl—H_2O at the reflux temperature) giving the *sec*-base **6**, and this unusual result (most *N*-alkyl derivatives are stable towards acids) may be attributed to resonance stabilization of the triethyl carbonium ion **8**, a likely reaction intermediate. *N*-Alkyl fission of certain benzhydryl-

amines with water or mineral acid represents an analogous example (6).

Literature data upon the fate of an *N*-carbethoxy group following attack by an organometallic reagent is sparse [chemically *N*-carbethoxy piperazines are substituted urethanes, a class to which no reference is made in standard works on the Grignard reaction (7, 8)], and a tentative reaction mechanism for (*a*) its conversion to a triethylmethyl function and (*b*) its removal is given below (Scheme 2).

Although the amide **10**, proposed as a common intermediate for both pathways, was not detected in reactions involving **3** and **4**, the analogous benzamide was isolated in 28% yield from the analogous reaction between phenyl magnesium bromide and *N*-benzyl-*N'*-carbethoxy piperazine. Treatment of this *N*-benzyl derivative with ethyl magnesium bromide gave *N*-benzyl piperazine (loss of the N'-CO_2Et group) together with the impure *N'*-propionyl amide (infrared evidence). No evidence for pathway (*a*) was obtained in either reaction of the simpler piperazine derivative. Although Scheme 2 depicts N'-CO_2Et loss via the amide **10**, the secondary amine **11***b* might also form upon initial Grignard attack through cleavage of the N—C rather than O—C bond within the complex **9**. However, amides have already been shown to react with Grignard reagents to yield *t*-alkyl amines (9) and secondary amines (10) analogous to **11***a* and **11***b* respectively.

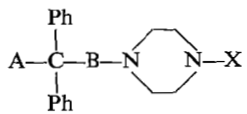
A number of compounds described in this work were evaluated for analgesic activity after subcutaneous injection in mice by a pinch tail method and a modification of the hot plate method described by Janssen and Jageneau (11). Only three compounds showed activity at a dose range of 100 mg/kg, namely **12**, **20**, and **21** (Table I), with approximately 10–15% of the



SCHEME 2

TABLE I

Compounds isolated* by alkylation of the product between ethyl magnesium bromide and the amino cyanides **2**, **4**, **5***a* and **5***b*



Compound	A	B	X	m.p. (°C)	Molecular formula	Analysis							
						Calculated				Found			
						C	H	N	Equiv.	C	H	N	Equiv.
12	COC_2H_5	$(CH_2)_2$	$(CH_2)_3C_6H_5$	215–217	$C_{31}H_{40}Cl_2N_2O$	70.6	7.6	5.3	263	69.9	7.8	5.1	260
13	CN	$(CH_2)_2$	$(CH_2)_3C_6H_5$	278–280	$C_{29}H_{35}Cl_2N_3$†			8.4	248			8.3	250
14	CN	$(CH_2)_2$	$CH_2CH{=}CHC_6H_5$	250–252	$C_{29}H_{33}Cl_2N_3$	70.5	6.7	8.5	247	70.0	6.4	8.7	250
15	COC_2H_5	$(CH_2)_2$	CH_2CH_2OH	210–211	$C_{24}H_{34}Cl_2N_2O\cdot H_2O$	61.3	7.7	6.0	235.5	61.7	7.8	6.2	237
16	CN	$(CH_2)_2$	CH_2CH_2OH	239–240	$C_{22}H_{29}Cl_2N_3O\cdot H_2O$	59.9	7.1	9.5	220	59.7	7.0	9.7	222
17	COC_2H_5	$(CH_2)_3$	$(CH_2)_2C_6H_5$	254	$C_{31}H_{40}Br_2N_2O$	60.4	6.5	4.5	308	60.9	6.8	4.8	311
18	COC_2H_5	$(CH_2)_3$	$(CH_2)_3C_6H_5$	274	$C_{32}H_{42}Br_2N_2O$	61.0	6.7	4.5	315	60.6	6.8	4.7	318
19	COC_2H_5	$(CH_2)_3$	$CH_2CH{=}CHC_6H_5$	249	$C_{32}H_{40}Cl_2N_2O$	70.2	7.5	5.2	270	70.4	7.4	5.8	267
20	COC_2H_5	$(CH_2)_3$	CH_2CH_2OH	244.5	$C_{25}H_{36}Cl_2N_2O_2$	64.2	7.8	6.0	235	64.1	7.8	6.3	230
21	COC_2H_5	$CH_2\cdot CH(CH_3)$	$(CH_2)_2C_6H_5$	232	$C_{31}H_{39}BrN_2O$	69.5	7.3	5.2	268	68.9	7.5	5.3	266
22	COC_2H_5	$CH_2\cdot CH(CH_3)$	$(CH_2)_3C_6H_5$	214	$C_{32}H_{41}BrN_2O$	69.9	7.5	5.1	275	69.5	8.0	5.2	273

*As the mono- or di-hydrohalide salts.
†Anal. Calcd.: Cl, 14.3. Found: Cl, 14.0.

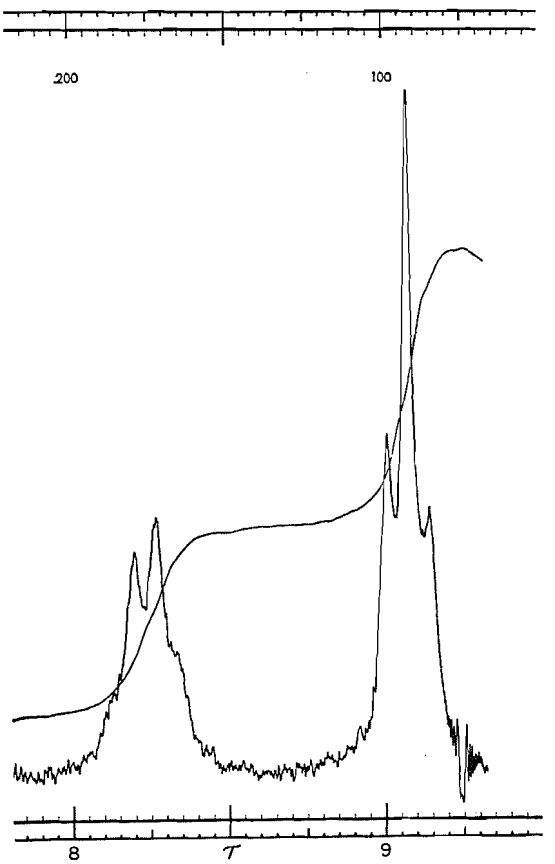


FIG. 1. The 100 MHz proton magnetic resonance spectrum of *7a* in DMSO-d_6.

activity of methadone. None of the cyanides possessed analgesic activity.

Experimental

All melting points and boiling points are uncorrected. The infrared spectra were determined on Unicam SP 100 and Unicam SP 200 spectrophotometers. The proton magnetic resonance (p.m.r.) spectra were recorded on Perkin–Elmer R 10 and Varian HA-100 instruments in dimethyl sulfoxide, operating at 60 and 100 MHz/s respectively with TMS as standard. Equivalent weights of bases and salts were determined by titration with 0.02 *N* perchloric acid in glacial acetic acid with Oracet Blue B as indicator. Microanalyses were performed by Mr. G. S. Crouch, School of Pharmacy, University of London, Dr. G. Weiler and Dr. F. B. Strauss, Microanalytical Laboratory, Oxford, and Mr. M. Ellison, Chesterford Park Research Station, Saffron Waldon, Essex. All organic extracts were washed several times with water and dried over anhydrous sodium sulfate prior to removal of the solvent. Unless otherwise stated, compounds were recrystallized from ethanol or 96% ethanol.

3-(4-Carbethoxypiperazino)-1,1-diphenylpropyl Cyanide (2)

Sodamide (8.6 g) was added to a solution of diphenylacetonitrile (37.6 g) in dry benzene (280 ml) under nitrogen. The mixture was stirred for 1 h and heated under reflux for 4.5 h during which time a further 230 ml of benzene were added. On cooling, a solution of 1-(2-chloroethyl)-4-carbethoxy piperazine (38.5 g) in dry benzene (100 ml) was added and the mixture heated under reflux for 5.5 h. After standing overnight, the excess of sodamide was decomposed with water and the organic extract separated; removal of benzene gave an oil which solidified on trituration with petroleum ether (b.p. 40–60 °C) to give the aminocyanide **2** as yellow crystals (70 g). An analytical sample, melted at 111.5–112.5 °C.

Anal. Calcd. for $C_{23}H_{27}N_3O_2$ (equiv., 377): C, 73.1; H, 7.3. Found (equiv., 372): C, 73.5; H, 7.3.

It gave a hydrochloride m.p. 176.5–178 °C.

Anal. Calcd. for $C_{23}H_{28}ClN_3O_2$ (equiv., 414): C, 66.7; H, 6.8; Cl, 8.6; N, 10.2. Found (equiv., 413): C, 66.6; H, 6.9; Cl, 8.5; N, 10.3.

4-(4-Carbethoxypiperazino)-1,1-diphenylbutyl Cyanide (4)

Reaction between diphenylacetonitrile and 1-(3-chloropropyl)-4-carbethoxy piperazine using the method described in the previous experiment gave the aminocyanide **4**, as pale-yellow crystals, m.p. 139 °C.

Anal. Calcd. for $C_{24}H_{29}N_3O_2$ (equiv., 391): C, 73.6; H, 7.5; N, 10.7. Found (equiv., 390): C, 73.6; H, 7.5; N, 10.9.

Preparation and Proof of Structure of the Isomeric Cyanides 5a and 5b

Diphenylacetonitrile (37.6 g) was condensed with 1-(2-chloropropyl)-4-carbethoxy piperazine (41.3 g) using the method described previously to give an oil (72.0 g), which yielded pale-yellow crystals (40.0 g) from ethanol, m.p. 119–122 °C. Recrystallization gave **5a**, m.p. 122 °C.

Anal. Calcd. for $C_{24}H_{29}N_3O_2$ (equiv., 391): C, 73.7; H, 7.4; N, 10.7. Found (equiv., 392): C, 74.4; H, 7.4; N, 10.8.

The hydrochloride melted at 177–178 °C.

Anal. Calcd. for $C_{24}H_{30}ClN_3O_2$ (equiv., 427.5): C, 67.4; H, 7.0; Cl, 8.3; N, 9.8. Found (equiv., 428): C, 67.1; H, 7.2; Cl, 8.2; N, 9.3.

Evaporation of the combined ethanolic mother liquors gave an oil (28.0 g) which could not be crystallized. A solution of the oil in a mixture of equal parts of benzene and petroleum ether (b.p. 40–60 °C) was chromatographed on alumina, followed by elution with petroleum ether containing increasing concentrations of benzene gave the isomeric cyanide **5b** (23.0 g), m.p. 113–114 °C from ethanol. It gave a hydrochloride, m.p. 124–125.5 °C.

Anal. Calcd. for $C_{24}H_{30}ClN_3O_2$ (equiv., 427.5): C, 67.4; H, 7.0; Cl, 8.3. Found (equiv., 430): C, 66.8; H, 7.1; Cl, 8.3.

5a (15.0 g) was heated under reflux for 6 h with 20% alcoholic potassium hydroxide solution (100 ml). After removal of the alcohol the reaction product was extracted with chloroform to give 3-piperazino-1,1-diphenylbutyl cyanide (11.0 g), the picrate crystallizing from acetone as solvated needles, m.p. 208–210 °C.

Anal. Calcd. for $C_{21}H_{25}N_3 \cdot 2C_6H_3N_3O_7 \cdot C_3H_6O$: C, 51.7; H, 4.5; N, 15.1. Found: C, 52.0; H, 4.6; N, 15.9.

This cyanide (3.2 g), 90% formic acid (1.2 g) and 36% formaldehyde solution (0.5 g), were heated under reflux for 6 h after which time hydrochloric acid was added and the formic acid and formaldehyde removed by distillation. Basification of the reaction mixture and extraction with chloroform gave an oil which solidified on titration with petroleum ether (b.p. 40–60 °C) to give a solid (3.3 g) which on recrystallization from petroleum ether (b.p. 80–100 °C) gave 3-(4-methylpiperazino)-1,1-diphenylbutyl cyanide, m.p. 107 °C, lit. m.p. 108–110 °C (5).

Calcd. for $C_{22}H_{27}N_3$: equiv., 166.5. Found: equiv., 168.

Reaction of Ethyl Magnesium Bromide with 3-(4-Carbethoxypiperazino)-1,1-diphenylpropyl Cyanide (2)

A solution of **2** (12.0 g) in dry benzene (100 ml) was added to a solution of ethyl magnesium bromide (prepared from 13.9 g of ethyl bromide and 3.05 g of magnesium) in ether (90 ml). After removal of the ether the mixture was stirred at room temperature for 4 h and then heated under reflux for 16 h. On cooling the product was decomposed with ice and dilute hydrochloric acid and the benzene layer was separated. Basification of the aqueous phase followed by extraction with ether and subsequent evaporation of the solvent gave an oil (12.2 g) which could not be crystallized. The oil (9.05 g) was dissolved in ethanol and treated with ethanolic hydrochloric acid and stored one month at 1 °C when **7***a* separated as the dihydrochloride monohydrate (2.8 g), m.p. 190 °C from ethanol.

Anal. Calcd. for $C_{27}H_{39}Cl_2N_3 \cdot H_2O$ (equiv., 247): C, 65.6; H, 8.4; Cl, 14.3; N, 8.5. Found (equiv., 245): C, 65.8; H, 8.3; Cl, 14.1; N, 8.7. Loss of H_2O at 120 °C.

Anal. Calcd. for 1 H_2O: 3.6. Found: 3.85.

ν(Nujol): 3450 (OH), 670,710 (monosub., aromatic) cm^{-1}; ν(neat, free base), 2280 (CN) cm^{-1}: p.m.r. characteristics in DMSO-d_6: 9.03 (deformed triplet, 9H), 8.23 (multiplet, 6H), 6.90 (triplet, 2H), 2.56 (multiplet, 10H). Prominent *m/e* peaks: 403(**7***a*), 374[loss of C_2H_5], 304 [loss of $C(C_2H_5)_3$], 192[due to NC.C. $(C_6H_5)_2$], 112 [due to CH_2CH_2N⟨⟩N], 99[due to $C(C_2H_5)_3$].

The residue (30 g) from the mother liquors of several batches was heated under reflux with 18% hydrochloric acid (300 ml) for 5.5 h. The free base recovered from the aqueous phase was an oil **A** which could not be crystallized or converted to a solid salt. It was characterized by alkylation as follows.

2-Phenylethyl Bromide

A mixture of the oil **A** (5.3 g), 2-phenylethyl bromide (1.6 g), sodium bicarbonate (2.0 g), and ethanol (25 ml) was heated under reflux for 5.5 h. After removal of the inorganic matter by filtration, the ethanol was removed and the resultant oil basified with ammonia and extracted with ether. Evaporation of the solvent gave an oil which when treated with ethanolic hydrochloric acid gave 3-[4-(2-phenylethylpiperazino)]-1,1-diphenylpropyl cyanide dihydrochloride (2.5 g), m.p. 264–266 °C. An analytical sample melted at 266–267 °C.

Anal. Calcd. for $C_{28}H_{33}Cl_2N_3$ (equiv., 241): C, 69.7; H, 6.9; N, 8.7. Found (equiv., 244): C, 69.0; H, 7.0; N, 9.0.

Further alkylated derivatives together with compounds isolated from the aminocyanides **4**, **5***a*, and **5***b* were prepared by similar procedures. Relevant analytical and physical data are given in Table I.

Reaction of Ethyl Magnesium Bromide with 4-(4-Carbethoxypiperazino)-1,1-diphenylbutyl Cyanide (4)

Ethyl magnesium bromide (prepared from 65.4 g ethyl bromide and 14.6 g magnesium) was reacted with **4** (58.6 g) using the conditions described previously.

The product (55 g) was acidified with ethanolic hydrogen chloride and fractionally crystallized from ethanol to give

(i) 4-piperazino-1,1-diphenylbutyl cyanide dihydrochloride (6) (5.0 g), m.p. 260–261 °C from ethanol.

Anal. Calcd. for $C_{21}H_{27}Cl_2N_3$ (equiv., 196): C, 64.2; H, 6.9; Cl, 18.1; N, 10.7. Found (equiv., 198): C, 64.2; H, 6.8; Cl, 18.4; N, 10.9.

(ii) 4-(4-triethylmethylpiperazino)-1,1-diphenylbutyl cyanide dihydrochoride monohydrate (7b) m.p.. 180–182 °C.

Anal. Calcd. for $C_{28}H_{41}Cl_2N_3 \cdot H_2O$ (equiv., 254): C, 66.1; H, 8.6; N, 8.3. Found (equiv., 256): C, 66.3; H, 8.4; N, 8.5. Its infrared spectrum was similar to that of **7***a*.

A mixture of **7***b* (30.0 g) and 18% hydrochloric acid (300 ml) was heated under reflux for 6 h. The free base, recovered as usual, was acidified with ethanolic hydrochloric acid to give 4-piperazino-1,1-diphenylbutyl cyanide dihydrochloride, m.p. and mixture m.p. 260–261 °C.

Hydrolysis of residues from the mother liquors of the Grignard reaction product, carried out as before, gave an oil from which 7-piperazino-4,4-diphenylheptan-3-one dihydrochloride monohydrate m.p. 105–110 °C was obtained.

Anal. Calcd. for $C_{23}H_{32}Cl_2N_2O \cdot H_2O$ (equiv., 220): C, 62.6; H, 7.8; N, 6.3; Cl, 16.0. Found (equiv., 222): C, 62.5; H, 8.2; N, 6.3; Cl, 15.5.

ν(Nujol): 3350(H_2O), 1700(CO) cm^{-1}.

Reaction of Ethyl Magnesium Bromide with 3-(4-Carbethoxypiperazino)-1,1-diphenylbutyl Cyanide 5a

Reaction between the cyanide **5***a* (39 g) and ethyl magnesium bromide (prepared from 43.1 g of ethyl bromide and 8.8 g magnesium) gave an oil (35.0 g) from which an unidentified solid **A** (11 g) separated as a hydrochloride. This salt was hydrolyzed with 18% hydrochloric acid as usual and the product alkylated with 2-phenylethyl bromide to give 3-[4-(2-phenylethylpiperazino)]-1,1-diphenylbutyl cyanide dihydrobromide m.p. 282 °C, undepressed by an authentic sample of the salt prepared in the following manner. The carbethoxy group of **5***a* (15.0 g) was hydrolyzed with 20% alcoholic potassium hydroxide solution (100 ml) and the product alkylated.

Anal. Calcd. for $C_{29}H_{35}Br_2N_3$ (equiv., 292): C, 59.5; H, 6.0; Br, 27.3; N, 7.2. Found (equiv., 294): C, 59.6; H, 6.1; Br, 27.4; N, 7.1.

Hydrolysis of the residues from the mother liquors remaining after solid **A** had separated (18.0 g) with excess 18% hydrochloric acid gave 6-piperazino-4,4-diphenylheptan-3-one (14.0 g)' identified as the picrate, m.p. 259–260 °C (from acetone).

Anal. Calcd. for $C_{23}H_{30}N_2O \cdot 2C_6H_3N_3O_7$: C, 51.9; H, 4.5; N, 13.8. Found: C, 50.6; H, 4.6; N, 13.5.

Reaction of Ethyl Magnesium Bromide with 3-(4-Carbethoxypiperazino)-1,1-diphenyl-2-methylpropyl Cyanide 5b

Ethyl magnesium bromide (prepared from 4.4 g of ethyl bromide and 1.0 g of magnesium) was reacted with **5b** (3.9 g) using the method described previously to give an oil **B** (3.6 g) which failed to solidify or form a crystalline salt.

Hydrolysis of the Oil B

Hydrolysis of **B** (3.4 g) with 18% hydrochloric acid (30 ml) gave another oil **C** (2.7 g) which similarly failed to solidify or give a crystalline derivative.

Alkylation of the Oil C

Alkylation of **C** (2.0 g) with 2-phenylethyl bromide gave 3-[4-(2-phenylethyl)piperazino]-1,1-diphenyl-2-methylpropyl cyanide dihydrobromide (2.8 g) m.p. 297–299 °C.

Anal. Calcd. for $C_{29}H_{35}Br_2N_3$ (equiv., 293): C, 59.5; H, 6.0; Br, 27.3; N, 7.2. Found (equiv., 294): C, 59.7; H, 6.2; Br, 27.2; N, 7.1.

The compound was also prepared from **5b** by hydrolysis and subsequent alkylation with 2-phenylethyl bromide by the methods described previously.

Reaction of Phenyl Magnesium Bromide with 1-Benzyl-4-carbethoxy Piperazine

1-Benzyl-4-carbethoxy piperazine (12.5 g) and phenyl magnesium bromide (from 17.5 g phenyl bromide and 2.6 g of magnesium) were reacted under conditions described previously, except that the time of heating under reflux was 4 h. Treatment of the crude reaction product with ethanolic hydrobromic acid gave a solid, fractionally crystallizing from ethanol to give

(i) 1-benzyl-4-benzoyl piperazine hydrobromide (1.35 g) m.p. 250 °C. An analytical sample, melted at 257–259 °C, undepressed when mixed with an authentic sample prepared below.

Anal. Calcd. for $C_{18}H_{21}BrN_2O$ (equiv., 361): C, 59.8; H, 5.9; Br, 22.1; N, 7.8. Found (equiv., 370): C, 60.4; H, 6.2; Br, 21.7; N, 8.1. Benzoylation of 1-benzyl piperazine gave 1-benzyl-4-benzoyl piperazine hydrochloride m.p. 247.5–248.5 °C (lit. m.p. 245 °C (12)).

Calcd. for $C_{18}H_{21}ClN_2O$: equiv., 315.5. Found: equiv., 317.

Liberation of the free base followed by treatment with ethanolic hydrobromic acid yielded an authentic sample of 1-benzyl-4-benzoyl piperazine hydrobromide.

(ii) 1-benzyl-4-carbethoxy piperazine hydrobromide (0.94 g) m.p. 215.5–217 °C. Recrystallization raised the m.p. to 219.5–220.5 °C, undepressed when mixed with an authentic sample prepared below.

Calcd. for $C_{14}H_{21}BrN_2O_2$: equiv., 329. Found: equiv., 325.

1-Benzyl-4-carbethoxy piperazine, prepared from an authentic sample of the hydrochloride, on treatment with ethanolic hydrobromic acid gave an authentic sample of the salt, m.p. 227–227.5 °C. Found: equiv., 327.

Evaporation of the ethanolic mother liquors gave an oil (1.62 g) from which no further crystalline material could be isolated.

Reaction between Ethyl Magnesium Bromide and 1-Benzyl-4-carbethoxy Piperazine

1-Benzyl-4-carbethoxy piperazine (9.64 g) was reacted with ethyl magnesium bromide (from 9.36 g ethyl bromide and 2.07 g of magnesium) under the conditions of the previous experiment to give a golden oil (8.01 g). Treatment of the oil with ethanolic hydrochloric acid gave a solid which was fractionally crystallized from ethanol and ether–ethanol to give

(i) 1-benzyl piperazine dihydrochloride (1.79 g), 239 °C decomp.). An analytical sample melted at 256 °C (lit. m.p. 253° C (12)).

Anal. Calcd. for $C_{11}H_{18}Cl_2N_2$: C, 53.0; H, 7.3. Found: C, 53.0; H, 7.3.

(ii) 1-benzyl-4-carbethoxy piperazine hydrochloride (2.15 g) m.p. 210–212 °C. Recrystallization raised the m.p. to 215.5–217.5 °C, undepressed when mixed with an authentic sample.

(iii) a fawn solid (2.40 g). The infrared spectrum (Nujol) indicated the presence of 1-benzyl-4-carbethoxy piperazine hydrochloride (vCO, 1710 cm^{-1}) and a small peak at 1650 cm^{-1} (tertiary amide) indicated the presence of 1-benzyl-4-propionyl piperazine hydrochloride.

Acknowledgments

We should like to thank Mr. R. F. Branch of the School of Pharmacy, Chelsea College of Science and Technology, and Professor J. A. Elvidge of the Department of Chemistry, University of Surrey for profitable discussions. We are grateful to Smith, Kline & French Laboratories who undertook the pharmacological testing and provided samples of the cyanides **2**, **4**, and **5**. Dr. D. H. Williams of the University Chemical Laboratories, Cambridge, kindly determined the 100 MHz proton magnetic resonance spectrum.

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