Synthesis of Bi- and Tri-cyclic Tetrazepinones

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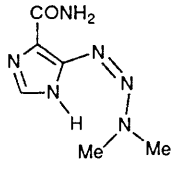
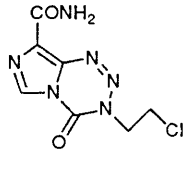
Diazotization of *N,N'*-dialkyl-*N*-(*o*-aminophenyl) ureas **7**, **13** and **17** gave 3,5-dimethyl-3*H*-1,2,3,5-benzotetrazepin-4(5*H*)-one **8**, 3-methyl-6,7-dihydro-1,2,3,5-tetrazepino[7,6,5-*ij*]quinolin-4(3H)-one **14** and 3-methyl-6,7-dihydro[1,4]oxazino[4,3,2,5-*ef*]-1,2,3,5-benzotetrazepin-4-one **19**. The structures of these bi- and tri-cyclic systems were confirmed by ^{1}H, ^{13}C and ^{15}N NMR data. X-Ray diffraction of compound **14** shows that the tetrazepinone ring is nonplanar.

Dimethyltriazene **A** (Dacarbazine) shows antineoplastic activity against malignant melanoma.[1,2] Its mechanism of action is based on metabolic demethylation to generate the monoalkyltriazene,[2–4] the cytotoxicity of which is due to its ability to methylate DNA.[5] Imidazotetrazinone **B** (Mitozolomide), a cyclic analogue of **A**, has recently been shown to release a similar metabolite upon hydrolysis[6,7] and to display potent activity against leukaemia, murine xenografts, Lewis lung and colon carcinoma.[8] One of its advantages over dimethyltriazene **A** is that it can generate the cytotoxic monoalkyltriazene without the host metabolic activation.[9]



A



B

Those results suggest that other cyclic compounds containing the N=N–N-(alkyl)–CO–N moiety may be precursors of monoalkyltriazenes and display similar or more pronounced antitumour activity. In light of these considerations, we have undertaken the synthesis of a novel seven-membered 1,2,3,5-tetrazepin-4-one ring system which contains, like compound **B**, both the ureido function and the alkyltriazene linkage.

We report here the synthesis of bi- and tri-cyclic tetrazepinone derivatives, based on an adaptation of the strategy developed for the synthesis of **B**.[10] ^{15}N NMR data were used to confirm their structures. We also report the confirmation of one of the structures by X-ray diffraction.

Results and Discussion

The approach we chose to study was the diazotization of substituted monoureas of type **3**. The diazonium salt can then cyclize to provide either substituted benzotriazole of type **4** or benzotetrazepinone of type **8**.

Treatment of the commercially available 2-nitrophenyl isocyanate **1** with methylamine provided **2**, which was reduced catalytically to give the amine **3**. Diazotization gave the triazole **4**, m.p. 70 °C. The triazole structure was assigned from the ^{1}H NMR spectrum which showed a methyl signal at 3.15 ppm as a doublet, coupled with the NH proton at 7.31 ppm, which appeared as a broad singlet. The stability of this compound allowed the recording of a Standard Pulse ^{15}N NMR spectrum at the natural abundance level (Fig. 1). Four distinct peaks were observed and their assignments are based on literature values.[11,12] Specific labelling by carrying out diazotization with $Na^{15}NO_2$ showed that the signal at −12 ppm corresponded to

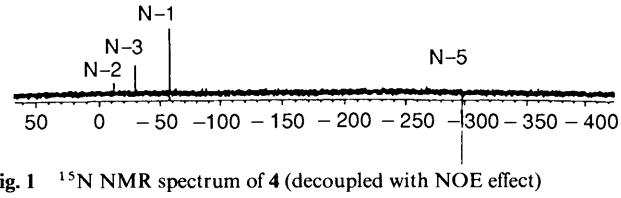
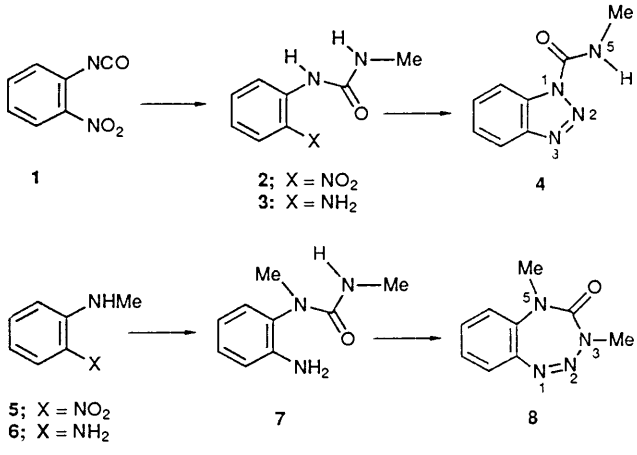


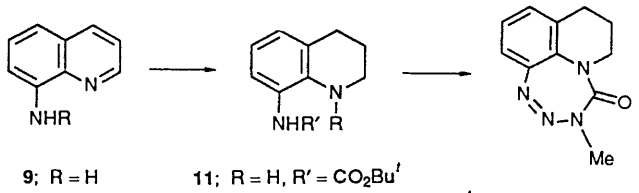
Fig. 1 ^{15}N NMR spectrum of **4** (decoupled with NOE effect)

the central nitrogen N-2. Chemical shift values of −58 and −29 ppm were assigned to N-3 and N-1 and the more shielded nitrogen N-5 resonated at −298 ppm with a one-bond NH coupling constant value of 90 Hz.[11]



Scheme 1

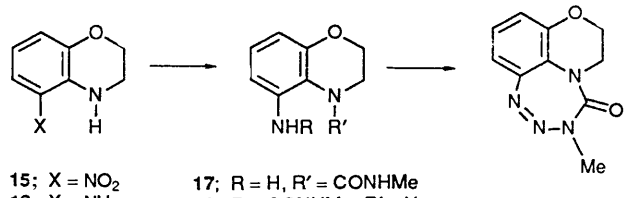
Since replacement of the methyl group in **3** by other alkyl or aryl groups seemed not to affect the mode of cyclization, it was decided to alkylate the amino group carrying the carbamoyl function. *N*-Methyl-2-nitroaniline **5** was reduced to the corresponding amine **6**, and the resulting diamine selectively carbamoylated with methyl isocyanate to provide **7**. Diazotization, followed by adjustment of the pH of the solution to 8, gave **8** as a yellow powder, m.p. 40 °C, in 52% yield (Scheme 1). Its elemental composition was confirmed by its microanalysis and chemical ionization mass spectrum which, in addition to MH^+, showed a large $MH^+ - 28$ peak due to the loss of nitrogen. In the ^{1}H NMR spectrum, the two methyl signals appeared as singlets and in the ^{15}N NMR spectrum, the central nitrogen of the triazene function showed up as a quartet ($^3J_{NH}$ = 2.70 Hz) at +72 ppm, as confirmed by carrying out the diazotization with $Na^{15}NO_2$. The fact that the peak showed up as a quartet ($^3J_{NH}$) confirmed the presence of the N(2)–N(3)–CH_3 moiety. The value of the chemical shift of N-2 is similar to those previously reported for the central nitrogens in 1-aryl-3,3-dialkyltriazenes (*ca.* 70 ppm).[13–15]



9; R = H
10; R = CO_2Bu^t

11; R = H, R' = CO_2Bu^t
12; R = CONHMe, R' = CO_2Bu^t
13; R = CONHMe, R' = H

14



15; X = NO_2
16; X = NH_2

17; R = H, R' = CONHMe
18; R = CONHMe, R' = H

19

Scheme 2

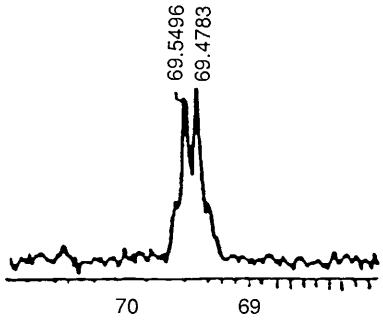
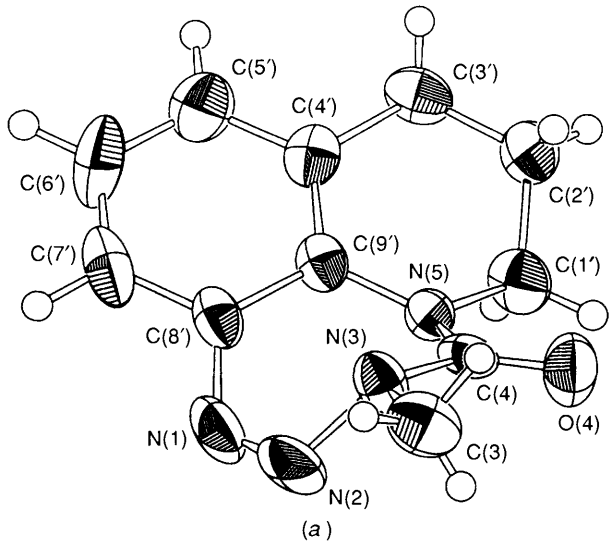


Fig. 2 ^{15}N NMR spectrum of the N-2 specifically labelled compound **14**

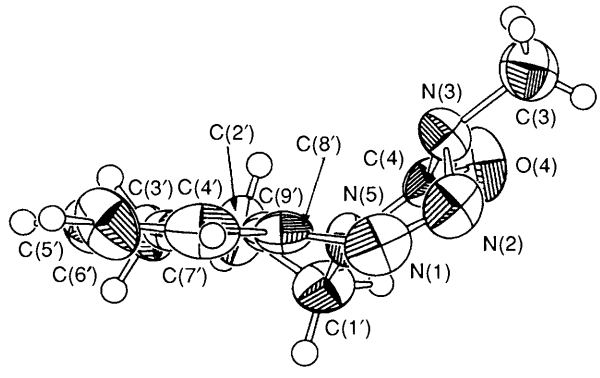
The tricyclic tetrazepinone **14** was prepared as shown in Scheme 2. 8-Aminoquinoline as its *tert*-butoxycarbonyl derivative **10** upon catalytic reduction gave the tetrahydroquinoline **11**. This after conversion into the urea **12** by methyl isocyanate, was hydrolysed to the amino urea **13**. Diazotization followed by adjustment of the pH to 8, gave the tetrazepinone **14**, the structure of which was assigned on the basis of ^1H, ^{13}C, ^{15}N NMR spectral results, chemical ionization mass spectroscopy and elemental analysis. In addition to MH^+, the mass spectrum showed a large $MH^+ - 28$ peak due to loss of nitrogen. In the ^{15}N NMR spectrum the resonance for the central nitrogen atom appeared as a quartet at 69.50 ppm ($^3J_{NH}$ = 2.70 Hz; Fig. 2).

The synthesis of the morpholino analogue of **19** proceeded in a similar fashion. 2-Amino-3-nitrophenol was treated with dibromoethane under basic condition and the resulting nitrobenzoxazine **15** reduced to **16**. Treatment with 1 equiv. of methyl isocyanate gave **17** as the major product which was separated by chromatography from the minor product **18**. Diazotization with $NaNO_2$ or $Na^{15}NO_2$ followed by neutralization, gave **19**. The structure assigned was based on elemental analysis and NMR data. In the ^1H NMR spectrum, the methyl signal appears as a singlet at 3.43 ppm, and the OCH_2CH_2N moiety as a pair of triplet at 4.24 and 3.82 ppm. As in the tetrazepinones **8** and **14**, the central nitrogen of the triazene function showed up as a quartet at 68.50 ppm ($^3J_{NH}$ = 2.70 Hz).

In order to further ascertain the structure and geometry of the 1,2,3,5-tetrazepinone ring, the X-ray structure of compound **14** was determined. As shown in Fig. 3*a*, N-5, N-3 and O-4 were found to be coplanar as expected for a ureido moiety. However, nitrogen N-2 of the N(1)=N(2) bond deviated from the plane of the aromatic ring by 0.5384 Å (Fig. 3*b*). This deviation



(*a*)



(*b*)

Fig. 3 ORTEP views[23] of the crystallographically determined molecular structure for compound **14** (50% probability ellipsoid). For clarity arbitrary thermal parameters were assigned to the hydrogen atoms.

makes the 1,2,3,5-tetrazepinone an essentially nonplanar seven-membered ring. Its geometry is strikingly different from that of the 1,2,3,5-tetrazinone ring in compound **B** for which N-2 does not significantly deviate from planarity as conclusively demonstrated by X-ray diffraction results.[16] The geometry of the tetrazepinone ring is similar to that of the diazepinone ring system in the diazepam-related drugs, the X-ray structures of which were recently described by Gilman.[17]

It is noteworthy that ^1H and ^{13}C chemical shifts of all tetrazepinones were slightly more deshielded than in their ureido precursors. Values around 2.70 ppm for the methyl doublets were observed for ureas **7**, **13** and **17**, whereas they occur at *ca.* 3.20 ppm for the methyl singlets in the tetrazepinones. The same trend was observed for the carbonyl ^{13}C chemical shifts which were around 159 ppm in the ureas and around 161 ppm in the corresponding tetrazepinones. This is in agreement with the fact that the electron withdrawing effect of the diazo group decreases the electron density at the nitrogen and carbon atoms in the ureido moiety. It is also interesting to notice the striking difference between the chemical shift of the central nitrogen (N-2) in the benzotriazole **4** (−12 ppm) and in the tetrazepinones **8**, **14** and **19** (around +70 ppm). In **4**, the greater shielding of the central nitrogen (N-2) is due to the fact that it experiences additional screening from the electronic current in the aromatic triazole ring. In the non-aromatic tetrazepinones, the chemical shift values are analogous to those

Table 1 Non-hydrogen atom fractional co-ordinates for compound **14**

Atom	*x*	*y*	*z*
O(4)	0.118(1)	0.3758(6)	0.6868(9)
N(5)	0.370(1)	0.3321(6)	0.842(1)
N(3)	0.337(1)	0.4116(6)	0.602(1)
N(2)	0.439(1)	0.3437(8)	0.549(1)
N(1)	0.574(1)	0.3226(8)	0.641(1)
C(1′)	0.300(1)	0.2929(8)	0.963(1)
C(2′)	0.334(1)	0.3619(9)	1.097(1)
C(3′)	0.513(1)	0.3776(8)	1.173(1)
C(4′)	0.611(1)	0.3765(8)	1.062(1)
C(5′)	0.777(2)	0.3971(9)	1.117(1)
C(6′)	0.871(1)	0.395(1)	1.017(2)
C(7′)	0.801(2)	0.370(1)	0.863(2)
C(8′)	0.634(1)	0.3527(8)	0.799(1)
C(9′)	0.536(1)	0.3557(7)	0.899(1)
C(4)	0.265(2)	0.3706(8)	0.713(1)
C(3)	0.222(2)	0.455(1)	0.464(2)

Table 2 Non-hydrogen bond lengths (Å) for compounds **14**

O(4)–C(4)	1.21(2)	C(1′)–C(2′)	1.51(2)
N(5)–C(1′)	1.51(2)	C(2′)–C(3′)	1.48(2)
N(5)–C(9′)	1.40(1)	C(3′)–C(4′)	1.50(2)
N(5)–C(4)	1.33(1)	C(4′)–C(5′)	1.39(2)
N(3)–N(2)	1.49(2)	C(4′)–C(9′)	1.42(2)
N(3)–C(4)	1.45(2)	C(5′)–C(6′)	1.38(2)
N(3)–C(3)	1.45(2)	C(6′)–C(7′)	1.36(2)
N(2)–N(1)	1.23(1)	C(7′)–C(8′)	1.39(2)
N(1)–C(8′)	1.41(2)	C(8′)–C(9′)	1.41(2)

Table 3 Non-hydrogen bond angles (°) for compound **14**

C(1′)–N(5)–C(9′)	115.6(8)	C(5′)–C(4′)–C(9′)	119(1)
C(1′)–N(5)–C(4)	117(1)	C(4′)–C(5′)–C(6′)	122(1)
C(9′)–N(5)–C(4)	123(1)	C(5′)–C(6′)–C(7′)	119(1)
N(2)–N(3)–C(4)	111.8(9)	C(6′)–C(7′)–C(8′)	122(1)
N(2)–N(3)–C(3)	109(1)	N(1)–C(8′)–C(7′)	118(1)
C(4)–N(3)–C(3)	115(1)	N(1)–C(8′)–C(9′)	122(1)
N(3)–N(2)–N(1)	119(1)	C(7′)–C(8′)–C(9′)	119(1)
N(2)–N(1)–C(8′)	124(1)	N(5)–C(9′)–C(4′)	120(1)
N(5)–C(1′)–C(2′)	107.1(9)	N(5)–C(9′)–C(8′)	121.2(9)
C(1′)–C(2′)–C(3′)	112(1)	C(4′)–C(9′)–C(8′)	119(1)
C(2′)–C(3′)–C(4′)	115.2(9)	O(4)–C(4)–N(5)	125(1)
C(3′)–C(4′)–C(5′)	120(1)	O(4)–C(4)–N(3)	119.0(9)
C(3′)–C(4′)–C(9′)	120(1)	N(5)–C(4)–N(3)	116(1)

of the central nitrogen in open-chain 1-aryl-3,3-dialkyltriazenes. Electron delocalization occurs to a much lesser extent and N-3 shows significant sp^3 character, as confirmed by X-ray diffraction results (Fig. 2*a*).

Experimental

M.p.s were measured on a Gallenkamp block and are uncorrected. Thin-layer and flash chromatography were performed on silica gel 60 F_{254} aluminium plates and Merck Silica Gel 60 (230–400 mesh) respectively. ^{1}H NMR spectra were recorded on a Varian XL-200 at 200 MHz. ^{13}C NMR spectra were obtained at 75.40 MHz on a Varian XL-300. All ^{1}H NMR spectra were run in $CDCl_3$ or in [$^2H_6$] DMSO. Chemical shifts are reported downfield from TMS and *J* values are in Hz. Low and high resolution mass spectra were recorded in a HP 5984A or LKB 9000 and Du Pont 21-492B instruments.

Compounds **1**, **5**, **9** and **15** were obtained from Aldrich Chemical Co.

^{15}N NMR spectra were taken at 30.40 MHz on a Varian XL-300 and chemical shifts are reported upfield from nitromethane, which was used as external standard. The 90° pulse width was 18 μs and the pulse interval was set at 3 s and the temperature of the probe was 20 °C. Spectra were obtained after 100 scans for the ^{15}N enriched compounds when sample concentrations were 0.10 M in $CDCl_3$ (gated coupled)[11] and after 1024 scans for the natural abundance spectrum at a 0.80 M concentration (decoupled with NOE effect).

All reactions were monitored by thin layer chromatography (TLC).

N′-(2-*Aminophenyl*)-N′-*methylurea* **3**.—To a stirred solution of compound **1** (2 g, 12.20 mmol) in methylene dichloride (10 cm^3) was added dropwise 40% aqueous methylamine (2.5 cm^3). The mixture was stirred for 15 min after which the pale yellow precipitate was filtered off and hydrogenated in methanol (25 cm^3) containing a 10% Pd–C catalyst (300 mg), at 3 atm for 20 min. The mixture was filtered and evaporated to give a white powder (1.8 g, 89.4%) which was recrystallized from methanol; m.p. 170 °C; ν_{max}(KBr)/cm^{-1} 3415 (NH, NH_2) and 1676 (C=O); δ_H([$^2H_6$] DMSO) 8.0 (br s, 1 H, ArN*H*CO), 7.86 (d, *J* 7.86, 1 H, Ar), 7.26–7.17 (m, 2 H, Ar), 7.02 (t, *J* 7.94, 1 H, Ar), 6.00 (br quartet, *J* 4.36, 1 H, CON*H*CH_3), 5.20 (s, 2 H, NH_2) and 3.10 (d, *J* 4.6, 3 H, CONHCH_3); δ_C($CDCl_3$) 156.70(s), 140.70(s), 125.40(s), 124.00(d), 123.60(d), 116.52(d), 115.50(d) and 26.30(q).

N-*Methyl*-1H-*benzotriazole*-1-*carboxamide* **4**.—To a solution of **3** (1 g) in 5M HCl (20 cm^3), was added 17% aqueous of sodium nitrite (2.5 cm^3) dropwise at 0 °C with constant stirring. The resulting white precipitate was extracted with methylene dichloride and purified on silica gel with a 4:3:2 mixture of chloroform–hexane–ethyl acetate to give **4** (0.9 g, 85%); m.p. 70 °C; ν_{max}(KBr)/cm^{-1} 3380–3210 (NH) and 1744 (C=O); δ_H($CDCl_3$) 8.30 (d, *J* 8.30, 1 H, Ar), 8.10 (d, *J* 8.40, 1 H, Ar), 7.70 (t, *J* 8.24, 1 H, Ar), 7.45 (t, *J* 8.20, 1 H, Ar), 7.31 (br s, 1 H, CON*H*CH_3) and 3.15 (d, *J* 5.00, 3 H, CONHCH_3); δ_C($CDCl_3$) 150.00(s), 146.00(s), 132.00(d), 125.00(d), 120.00(d), 114.00(d) and 25.00(q); δ_N($CDCl_3$) −12.22(s), −29.28(s), −58.00(s) and −298.48 (d, $^1J_{NH}$ 90) (Found: C, 54.9; H, 4.6; N, 32.05. Calc. for $C_8H_8N_4O$: C, 54.54; H, 4.58; N, 31.80%).

N-(2-*Aminophenyl*)-N,N′-*dimethylurea* **7**.—*N*-Methyl-2-nitroaniline **5** (4 g) was catalytically reduced to *N*-methyl-*o*-phenylenediamine **6** according to the method described for compound **3**. It was obtained as a brown liquid (2.6, 81%). The amine **6** (2 g) was dissolved in chloroform (100 cm^3) and the solution stirred at 0 °C with 1 equiv. of methyl isocyanate. After 30 min the brown solution was concentrated under reduced pressure and purified on silica gel (methanol–CCl_4, 4:1) to give **7** as a brown oil that solidified with time (2.5 g, 86%); m.p. 180 °C; ν_{max}(KBr disc)/cm^{-1} 3400, 3200 (NH_2, NH), 3000 (CH) and 1686 (C=O); δ_H($CDCl_3$) 7.2–6.8 (m, 4 H, Ar), 4.75 (br s, 2 H, NH_2), 4.25 (br s, 1 H, CONHCH_3), 3.16 (s, 3 H, ArN(CH_3)CO) and 2.70 (d, *J* 4.6, 3 H, CONHCH_3); δ_C($CDCl_3$) 159.50(s), 144.20(s), 129.00(d), 128.00(s), 118.00(d), 116.20(d), 34.80(q) and 26.50(q).

3,5-*Dimethyl*-3H-1,2,3,5-*benzotetrazepine*-4(5H)-*one* **8**.—To a solution of **7** (2 g) in 10 cm^3 of 2% HCl was added dropwise 8% aqueous sodium nitrite (5 cm^3) at 0 °C. The mixture was then extracted with methylene dichloride to remove impurities and the pH of the clear aqueous layer was adjusted to 8 with 5% aqueous sodium hydrogen carbonate. The precipitate that formed was extracted with methylene dichloride and purified on silica gel (ethyl acetate–hexane; 7:3) to give **8** as a yellow powder (1.1 g, 52%); m.p. 40 °C (effervescence at 100 °C); ν_{max}($CHCl_3$)/cm^{-1} 3000 (C–H) and 1680 (C=O); δ_H($CDCl_3$) 7.45–7.08 (m, 4 H, Ar), 3.40 (s, 3 H, ArN(CH_3)CO) and 3.23 (s, NCH_3); δ_C($CDCl_3$) 162.00(s), 142.30(s), 138.50(s), 132.00(d),

128.00(d), 124.50(d), 121.00(d), 38.00(q) and 36.00(q); $\delta_N(CDCl_3)$ 72.00 (q, $^3J_{NH}$ 2.70, N-2); *m/z* (Cl, NH_3) 191.09 ($MH^+ - N_2$, 28.72%), 134.00 (MH^+ – MeNCO, 14.91); (Found: C, 57.0; H, 5.5; N, 24.3%; M^+, 191.0932. Calc. for $C_9H_{10}N_4O$: C, 56.83; H, 5.30; N, 29.46%; *M*, 191.0933).

8-(N-tert-*Butoxycarbonylamino*)-1,2,3,4-*tetrahydroquinoline* **11**.—A solution of 8-aminoquinoline **9** (2g) and di-*tert*-butyldicarbonate (3.5 g, 1.15 eq) in dioxane (50 cm^3) was heated at reflux for 3 days under nitrogen. Evaporation under reduced pressure gave **10** as a brown oil which was sufficiently pure to be used for further reactions; $\delta_H(CDCl_3)$ 9.00 (br s, 1 H, N*H*CO_2Bu^t), 8.70 (d, 1 H, *J* 4.2, Ar), 8.40 (d, 1 H, *J* 4.2, Ar), 8.40 (d, ^{1}H, *J* 8.00, Ar), 8.10 (d, 1 H, *J* 8, Ar), 7.5–7.30 (m, 3 H, Ar) and 1.80 (s, 9 H, CO_2Bu^t). A solution of **10** and 10% Pd–C (1 g) in methanol (30 cm^3) was hydrogenated at 3 atm overnight. Filtration and evaporation gave a colourless crystalline residue in quantitative yield; m.p. 110 °C; $\nu_{max}(CHCl_3)/cm^{-1}$ 3400, 3200 (NH_2, NH), 3000 (CH) and 1715 (C=O); $\delta_H(CDCl_3)$ 7.10 (d, *J* 7.50, 2 H, Ar), 6.72 (d, *J* 7.50, 2 H, Ar), 6.63 (t, *J* 7.20, Ar), 6.20 (br s, N*H*CO_2Bu^t), 3.28 (t, *J* 6.3, 2 H, $CH_2H_2CH_2NH$), 2.80 (t, *J* 6.40, 2 H, $CH_2H_2CH_2NH$), 1.88 (quintet, *J* 6.3, 2 H, $CH_2CH_2CH_2NH$) and 1.50 (s, 9 H, CO_2Bu^t).

8-(N-tert-*Butoxycarbonylamino*)-N-*methyl*-1,2,3,4-*tetrahydroquinoline*-1-*carboxamide* **12**. A solution of **11** (2.8 g, 11.3 mmol) and methyl isocyanate (0.7 cm^3, 1 equiv.) in chloroform (25 cm^3) was stirred for 26 h. The solvent was evaporated to give a white crystalline residue in quantitative yield; m.p. 135 °C; ν_{max}(KBr)/cm^{-1} 3300 (NH), 3000 (CH), 1716 and 1653 (C=O); $\delta_H(CDCl_3)$ 7.84 (d, *J* 8, 1 H, Ar), 7.16 (t, *J* 8, 1 H, Ar), 6.87 (d, *J* 8, 1 H, Ar), 6.76 (s, 1 H, N*H*CO_2Bu^t), 4.60 (br quartet, 1 H, CON*H*CH_3), 3.60 (br, 2 H, $CH_2CH_2CH_2NCO$), 2.74 (d, *J* 4.70, 3 H, COHNCH_3), 2.68 (t, *J* 7.30, 2 H, $CH_2CH_2CH_2NCO$), 1.94 (quintet, *J* 6.70, 2 H, $CH_2CH_2CH_2NCO$ and 1.64 (s, 9 H, Bu^t).

N-*Methyl*-8-*aminotetrahydroquinoline*-1-*carboxamide* **13**.—A suspension of **12** (1.5 g) in trifluoroacetic acid–water (85:15; 10 cm^3) was stirred overnight. Dilution with water (20 cm^3) and neutralization with 5% aqueous sodium hydrogen carbonate gave a deprotected urea as a brown solid (0.7 g, 70%); m.p. 130 °C; ν_{max}(KBr disc)/cm^{-1} 3380, 3300 (NH), 3000 (CH) and 1638 (C=O); $\delta_H(CDCl_3)$ 6.95 (t, *J* 8.00, 1 H, Ar), 6.60 (d, *J* 8.00, 2 H, Ar), 4.95 (br s, 1 H, NH), 3.83 (br s, 4 H, $CH_2CH_2CH_2NCO$, NH_2 overlap), 2.76 (d, *J* 4.70, 3 H, CONHCH_3) 2.60 (t, *J* 7.24, $CH_2CH_2CH_2NCO$) and 1.90 (quintet, *J* 7.00, $CH_2CH_2CH_2$-NCO).

3-*Methyl*-6,7-*dihydro*-1,2,3,5-*tetrazepino*[7,6,5-*ij*]*quinolin*-4(3H)-*one* **14**.—To a solution of **13** (0.7 g, 0.5 mmol) in 5% HCl (10 cm^3) was added dropwise at 0 °C with stirring 5% aqueous sodium nitrite (5 cm^3). Extraction with methylene dichloride (2 × 20 cm^3) removed impurities. The clear aqueous layer containing the diazonium salt was adjusted to pH 8 with 5% aqueous Na_2CO_3 at 0 °C. It affords brown precipitate which was extracted with methylene dichloride. Evaporation of the extract gave a pure brown powder (0.55 g, 76%); m.p. 85 °C (effervescence at 100 °C); $\nu_{max}(CHCl_3)/cm^{-1}$ 3030 (CH) and 1690 (C=O); $\delta_H(CDCl_3)$ 7.25–7.00 (m, 3 H, Ar), 4.24 (t, *J* 5.72, 2 H, $CH_2CH_2CH_2NCO$), 3.33 (s, 3 H), 2.80 (t, *J* 6.66, 2 H, $CH_2CH_2CH_2NCO$) and 1.88 (quintet, *J* 6.1, 2 H, CH_2CH_2-CH_2NCO); $\delta_C(CDCl_3)$ 161.00(s), 142.50(s), 135.97(s), 132.39(d), 131.20(s), 126.23(d), 124.98(d), 44.81(t), 38.12(quartet), 28.53(t) and 23.07(t); $\delta_N(CDCl_3)$ 70 ($^3J_{NH}$ 2.7, N-2); *m/z* (Cl, NH_3) 217.10 (MH^+, 100%), 189.00 ($MH^+ - N_2$) 160.00 (53.00) (Found: C, 61.1; H, 5.55; N, 25.9%; *M* + 1, 217.1089. Calc. for $C_{11}H_{12}N_4O$: C, 61.09; H, 5.53; N, 25.91%; *M* + 1, 217.1089).

5-*Nitro*-2,3-*dihydro*-1,4-*benzoxazine* **15**.—2-Amino-3-nitrophenol (3 g, 19 mmol) of DMF (15 cm^3) and 1,2-dibromomethane (2.7 cm^3) was heated to reflux and KOH (0.75 g, 2 equiv.) was added portionwise. After 2 d under reflux the solution was poured into water (30 cm^3) at 0 °C. Filtration and column chromatography of the red filtrate on silica gel (ethyl acetate–hexane; 2:3) gave yellow crystals (1.5 g, 43%); m.p. 100 °C; $\nu_{max}(CHCl_3)/cm^{-1}$ 3300 (NH) and 1531 (NO_2); $\delta_H(CDCl_3)$ 7.90 (br s, 1 H, NH), 7.74 (d, *J* 8.70, 1 H, Ar), 6.90 (d, *J* 8.70, 1 H, Ar), 6.60 (t, *J* 8.77, 1 H, Ar), 4.24 (t, *J* 4.50, 2 H, OCH_2CH_2NH) and 3.64 (q, *J* 4.7, 2 H, OCH_2CH_2NH); MS *m/z* (EI) 180 (M^+, 42.00%) and 134 ($M - NO_2$, 26).

5-*Amino*-2,3-*dihydro*-1,4-*benzoxazine* **16**.—A solution of the benzoxazine **15** (0.7 g) and 10% Pd–C catalyst (0.3 g) in methanol (15 cm^3) was hydrogenated at 3 atm in a Parr hydrogenator. Filtration and evaporation gave a brown liquid in quantitative yield. ν_{max}(KBr disc)/cm^{-1} 3300, 3200 (NH_2, NH) and 3000 (CH); $\delta_H(CDCl_3)$ 6.65 (t, *J* 8.40, 1 H, Ar), 6.4 (t, *J* 8.20, 2 H, Ar), 4.18 (t, *J* 4.50, 2 H, OCH_2CH_2NH), 3.42 (t, *J* 4.30, 2 H, OCH_2CH_2NH) and 3.10 (br s, 3 H, NH, NH_2).

5-*Amino*-N-*methyl*-2,3-*dihydro*-1,4-*benzoxazine*-4-*carboxamide* **17**.—Compound **16** (0.7 g) was dissolved in chloroform (25 cm^3) and methyl isocyanate (0.2 cm^3, 1 equiv.) was added dropwise at 0 °C. The mixture was stirred for 5 h, after which it was concentrated under reduced pressure and chromatographed on silica gel (ethyl acetate–hexane, 1:1) to give a white crystalline residue (0.4 g, 41%); $\delta_H(CDCl_3)$ 6.90 (t, *J* 8.00, 1 H, Ar) 6.30 (m, 2 H, Ar), 5.60 (br s, NH), 4.2 (t, *J* 4.53, 2 H, OCH_2CH_2NCO), 3.80 (br s, 4 H, OCH_2CH_2NCO, NH_2 overlap) and 2.80 (d, *J* 4.6, 2 H, $CONHCH_3$); $\delta_C(CDCl_3)$ 159.13(s), 150.54(s), 142.79(s), 128.69(d), 116.25(s), 109.11(d), 108.82(d), 67.46(t), 43.37(t) and 28.91(q).

3-*Methyl*-6,7-*dihydro*[1,4]*oxazino*[4,3,2-e]-1,2,3,5-*benzotetrazepin*-4(3H)-*one* **19**.—To a solution of urea (0.4 g, 5 mmol) in 5% HCl (15 cm^3) was added dropwise at 0 °C with stirring, aqueous sodium nitrite (5 cm^3). The mixture was stirred for an additional 10 min after which it was adjusted to pH 9 with 5% aqueous sodium hydrogen carbonate and extracted with methylene dichloride (3 × 5 cm^3). Evaporation of the extract gave **19** (0.25 g, 60%) as a pure brown powder; m.p. 110 °C; ν_{max}(KBr disc)/cm^{-1} 3000 (C–H) and 1691 (C=O); $\delta_H(CDCl_3)$ 7.20–6.90 (m, 3 H, Ar), 4.24 (t, *J* 4.30, 2 H, OCH_2CH_2NCO), 3.82 (t, *J* 4.36, 2 H, OCH_2CH_2NCO) and 3.43 (s, 3 H, $CONCH_3$); $\delta_C(CDCl_3)$ 161.00(s), 146.53(s), 142.43(s), 126.00(d), 124.17(s), 120.60(d), 119.20(d), 66.38(t), 41.40(d) and 38.12(q); $\delta_N(CDCl_3)$ 68.5 (q, $^3J_{NH}$ 2.7) (Found: C, 55.55; H, 4.75; N, 25.35. Calc. for $C_{10}H_{10}O_2N_4$: C, 55.04; H, 4.62; N, 25.6%).

X-Ray Crystallography.—Crystals of compound **14** were obtained from slow evaporation of 1:1 ethyl acetate–hexane mixture.

Crystal data. $C_{11}H_{12}N_4O$, $M = 216.24$. Monoclinic, $a = 8.621(2)$, $b = 14.450(2)$, $c = 8.891(2)$ Å, $b = 108.81(2)°$, $V = 1048.5(5)$ Å^3 (by least-squares refinement on diffractometer angles for 20 automatically centred reflections) space group $P2_1/n$ (alt. $P21/c$, no. 14), $Z = 4$, $D_x = 1.370$ g cm^{-3}. Small yellow needles, thermosensitive. Crystal dimensions: 0.10 × 0.10 × 0.10 mm, μ(Mo-$K\alpha$) = 7.21 cm^{-1}.

Data collection and processing. Rigaku AFC6S diffractometer, $\omega - 2\theta$ mode with ω scan width = 1.52 + 0.30 tan θ, scan speed 32 deg min^{-1}, graphite-monochromated Mo-$K\alpha$ radiation, temperature: 20 ± 1 °C; 1746 reflections measured 1630 unique after absorption correction (max. min. transmission factors = 1.00, 0.95) giving 742 with $I > 2\sigma(I)$. The intensities of three representative reflections remained constant

throughout data collection indicating crystal and electronic stability (no decay correction was applied). The data were corrected for Lorentz and polarization effects. Low temperature data was not available.

Structure analysis and refinement. All non-hydrogen atom-positions from direct methods[18] using the TEXSAN crystallographic software package of Molecular Structure Corporation.[19] All hydrogen-atom positions from a Fourier difference map. All positional and thermal parameters (non-hydrogen atoms: anisotropic; hydrogens; isotropic) and an extinction parameter were refined by full-matrix least square. Final R and R' were 0.087 and 0.072 for 742 observed reflections and 152 variable parameters. The weighting scheme $w = 4F_o^2/\sigma^2(\mathbf{F}_o^2)$ obtained from counting statistics gave satisfactory agreement analyses. The maximum and minimum peaks on the final difference Fourier map corresponded to 0.28 and -0.33 eÅ^{-3}, respectively. Neutral atom scattering factors were taken from Cromer and Waber.[20] Anomalous dispersion effects were included in F_{calc};[21] the values for $\Delta f'$ and $\Delta f''$ were those of Cromer.[22] Figures were drawn with ORTEPII.[23]*

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* A complete list of bond lengths and angles, hydrogen atom coordinates and thermal parameters has been deposited at the Cambridge Crystallographic Data Centre. For details of the deposition scheme see 'Instruction for Authors', *J. Chem. Soc., Perkin Trans. 1*, 1991, issue 1.

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