G. W. H. Cheeseman and S. G. Greenberg

Department of Chemistry, Queen Elizabeth College,
University of London, Campden Hill, London, W8 7AH, England

Received July 11, 1978

The title compounds are prepared by the reaction of carbonyl compounds with 1-(2′-aminomethylphenyl)pyrrole hydrochloride.

J. Heterocyclic Chem., 16, 241 (1979).

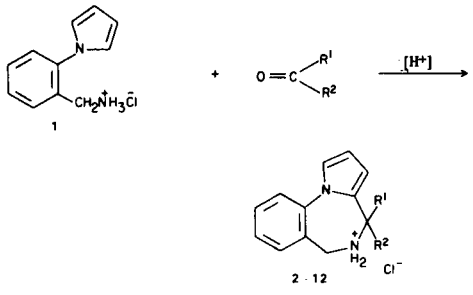
Since the discovery of the central nervous system (CNS) activity of the 1,4-benzodiazepines (1), several clinically useful drugs have been found which contain a heterocyclic moiety fused onto the seven-membered ring (2). Amongst the first of these tricyclic systems to be investigated were the pyrrolo[1,2-*a*]benzodiazepines (3), which are now accessible by several routes (3-9).

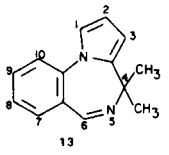
We now report the preparation of several new pyrrolo-[1,2-*a*][1,4]benzodiazepines (Table) by reaction of 1-(2′-aminomethylphenyl)pyrrole hydrochloride (**1**) with carbonyl compounds (Scheme). Diazepines have previously been prepared from the pyrrole (**1**) by reaction with several aldehydes (4,7) and ethyl pyruvate (7). We have found that a range of ketones may be used in this reaction (Table).

The pyrrole (**1**) is conveniently prepared by reduction of 1-(2′-cyanophenyl)pyrrole with sodium dihydro*bis*(2-methoxyethoxy)aluminate, and is used as the hydrochloride (7). Ring closure of **1** with carbonyl compounds to give the diazepines (**2-12**) was monitored by observation of the nmr signals of the pyrrolic hydrogens. Acid catalysis was necessary for the preparation of compounds **4-7**, methanolic hydrogen chloride or (preferably) maleic acid being used for this purpose. Diazepines could not be obtained by this procedure from such ketones as benzyl methyl ketone and acetophenone.

Compound **4** was treated with 1-naphthyl isocyanate to give the corresponding urea. Naphthyl ureas were similarly prepared from several of the other diazepines to facilitate isolation and characterization (see Table). Compound **4** was oxidized by manganese dioxide in toluene to the 4*H*-pyrrolobenzodiazepine (**13**). This preparation represents a new route to 4*H*-pyrrolo[1,2-*a*][1,4]benzodiazepines.

Diazepines **4**, **10** and **13** did not have a significant level of CNS activity.





13

0022-152X/79/020241-04$02.25

EXPERIMENTAL

Melting points were determined with a Gallenkamp melting point apparatus, and are uncorrected. Infrared spectra were recorded on a Unicam SP200 spectrometer, with Nujol mulls or liquid films. Ultra-violet spectra were recorded on a Unicam SP800A spectrometer, using 96% ethanol as solvent. Nuclear magnetic resonance spectra were recorded at 60 MHz on a Perkin-Elmer R12B spectrometer, and are quoted in parts per million downfield from internal TMS. In the ^{1}H nmr spectra of the pyrrolobenzodiazepines, the chemical shifts of the NH protons were sometimes concentration dependent. Mass spectra were recorded at 70 eV on an AEI MS30, MS50 or MS902 mass spectrometer; peak abundances are quoted as a percentage of the base peak. No attempts were made to optimise reaction conditions for yield.

1-(2′-Aminomethylphenyl)pyrrole (**1**).

To a stirred solution of sodium dihydro*bis*(2-methoxyethoxy)-aluminate (100 ml. of 70% w/w solution in toluene) in dry toluene (100 ml.) was added dropwise, over one hour, a solution of 1-(2′-cyanophenyl)pyrrole (16.8 g., 0.1 mole) in dry toluene (50 ml.). After 1.5 hours, aqueous sodium hydroxide (10%, 100 ml.) was cautiously added. The aqueous layer was separated off and extracted with toluene. The combined organic layers were washed with saturated sodium chloride solution, dried (magnesium sulfate) and evaporated, and the residue vacuum-distilled. The product (12.6 g., 73%; b.p. 112°/1.8 mm, n_D^{25} 1.593) was converted into its hydrochloride by treatment with ethereal hydrogen chloride (4,7); nmr (deuteriochloroform): 1.15 (2H, s, NH_2, exchangeable), 3.7 (2H, s, CH_2), 6.25-6.4 (2H, m, H-3,4), 6.75 - 6.9 (2H, m, H-2,5), 7.2 - 7.65 (4H, m, H-3′ to 6′).

General Procedure for the Preparation of 5,6-Dihydro-4*H*-pyrrolo-[1,2-*a*][1,4]benzodiazepines.

A solution of 1-(2′-aminomethylphenyl)pyrrole hydrochloride (0.005 mole) and the carbonyl compound (0.005 mole) in methanol (10 ml.) or *N*,*N*-dimethylformamide (10 ml.) was heated at 65-70° for 1-3 hours. The reaction was monitored by examining the pyrrolic region of the ^{1}H nmr spectrum of a sample of the reaction mixture. If cyclisation was not occurring, then methanolic hydrogen chloride (*ca.* 0.001 mole) or maleic acid (*ca.* 0.001

Table

5,6-Dihydro-4*H*-pyrrolo[1,2-*a*][1,4]benzodiazepines

Compound No.	R^1	R^2	Reactant	Yield (f) (%)	M.p. (°C) (e)	Formula	Found (%) C	H	N	Required (%) C	H	N
2	CCl_3	H	chloral (b)	25	190 dec. (g)	$C_{24}H_{18}Cl_3N_3O$	61.2	4.1	8.8	61.2	3.85	8.9
3	$C_6H_5CH{=}CH$-(a)	H	cinnamaldehyde (b)	76	165-167 dec. (g)	$C_{31}H_{25}N_3O$	81.6	5.5	9.25	81.7	5.5	9.2
4	CH_3	CH_3	acetone (c,d)	50	78.5-79 (f)	$C_{14}H_{16}N_2$	79.1	7.5	13.1	79.2	7.6	13.2
5	C_2H_5	CH_3	ethyl methyl ketone (c,d)	70	140-141.5 dec. (g)	$C_{26}H_{25}N_3O$	78.8	6.85	10.6	79.0	6.4	10.6
6	-$(CH_2)_4$-		cyclopentanone (c,d)	76	108-109 dec. (g)	$C_{27}H_{25}N_3O$	79.5	6.45	9.95	79.6	6.2	10.3
7	-$(CH_2)_5$-		cyclohexanone (c,d)	64	192 dec. (g)	$C_{28}H_{27}N_3O$	79.7	6.5	9.95	79.8	6.5	10.0
8	CH_3CO	CH_3	diacetyl (c)	37	83-84 (f)	$C_{15}H_{16}N_2O$	74.6	6.7	11.8	75.0	6.7	11.7
9	$CO_2C_2H_5$	$CO_2C_2H_5$	diethyl ketomalonate (b)	41	– (g,h)	$C_{29}H_{27}N_3O_5$	70.1	5.3	8.35	70.0	5.5	8.4
10	-CONHCONHCO-		alloxan (monohydrate) (c)	83	218 dec. (f)	$C_{15}H_{12}N_4O_3$	60.8	4.1	18.8	60.8	4.1	18.9
11	-COC_6H_4CO-		ninhydrin (c)	82	227-228 dec. (f)	$C_{20}H_{14}N_2O_2$	76.2	4.4	9.2	76.4	4.5	8.9
12	-$CONHC_6H_4$-		isatin (b)	43	215 dec. (f)	$C_{19}H_{15}N_3O$	75.55	5.1	14.0	75.7	5.0	13.9

(a) E-isomer. (b) Solvent = *N,N*-dimethylformamide. (c) Solvent = methanol. (d) Additional acid required. (e) Data in this and subsequent columns refer to the isolated product (*i.e.*, either the free base or the naphthyl urea). (f) Free base. (g) 1-Naphthyl urea. (h) Analytical sample had indefinite m.p.

mole) was added. Heating was continued until the reaction was essentially complete (1-3 hours).

After cooling, and filtration if a solid had precipitated, the reaction mixture was evaporated to dryness under reduced pressure. Water and ether were added to the combined solids, and the aqueous solution or suspension separated and made alkaline with dilute ammonium hydroxide. The product was extracted into ether or dichloromethane, the organic extracts were washed with water, dried (magnesium sulfate) and evaporated. The residue was purified by crystallization or sublimation, or converted to the corresponding 1-naphthyl urea for analysis. The derivative was prepared in dry petrol (80-100°) and crystallized from the same solvent.

4-Trichloromethyl-5,6-dihydro-4*H*-pyrrolo[1,2-*a*][1,4]benzodiazepine (**2**).

This compound was prepared as an oil from the amine hydrochloride (**1**) (1.03 g.) and freshly distilled chloral (0.5 ml.); ir: ν max 3380-3300 (w) (NH) cm^{-1}; uv: λ max 251 nm; nmr (deuteriochloroform): δ 2.85 br (1H, s, NH, exchangeable), 3.85 (2H, ABq, J 14Hz, CH_2), 4.8 (1H, s, H-4), 6.3-6.5 (1H, m, H-3), 6.6-6.75 (1H, m, H-2), 7.0-7.1 (1H, m, H-1), 7.3-7.6 (4H, m, H-7 to 10). This compound was further characterised as the 1-naphthyl urea.

5,6-Dihydro-4-(E-2′-phenylethenyl)-4*H*-pyrrolo[1,2-*a*][1,4]benzodiazepine (**3**).

This compound was prepared as an oil from the amine hydrochloride (**1**) (0.63 g.) and cinnamaldehyde (0.43 g.); uv: λ max 250.5, 283 sh, 291.5 nm. It was characterised as the 1-naphthyl urea.

5,6-Dihydro-4,4-dimethyl-4*H*-pyrrolo[1,2-*a*][1,4]benzodiazepine (**4**).

This compound was prepared as a crystalline solid from the amine hydrochloride (**1**) (15.0 g.) and acetone (50 ml.) in methanol (100 ml.) containing methanolic hydrogen chloride (*ca.* 0.02 mole), and purified by vacuum sublimation (yield 7.7 g.); ir: ν max 3500 (w) (NH) cm^{-1}; uv: λ max 250 nm; nmr (deuteriochloroform): δ 1.25 (6H, s, 2 x CH_3), 1.9 (1H, s, NH, exchangeable), 3.75 (2H, s, CH_2), 6.15-6.35 (2H, m, H-2,3), 6.9-7.05 (1H, m, H-1), 7.2-7.5 (4H, m, H-7 to 10); ms: m/e 197 (100%, M^+-CH_3), measured 197.1070, M^+ - CH_3 requires 197.1079 (10).

The 1-naphthyl urea had m.p. 154-156°.

Anal. Calcd for $C_{25}H_{23}N_3O$: C, 78.7; H, 6.1; N, 11.0. Found: C, 78.7; H, 6.0; N, 11.2.

The *N*-trifluoroacetyl derivative (prepared with trifluoroacetic anhydride) had m.p. 88.5-89° after crystallisation from pentane and vacuum sublimation; ir: ν max 1690 (s) (CO) cm^{-1}; uv: λ max 251 nm; nmr (deuteriochloroform): δ 1.7 (6H, s, 2 x CH_3), 4.4 (2H, s, CH_2), 6.2-6.5 (2H, m, H-2,3), 6.9-7.05 (1H, m,H-1), 7.25-7.6 (4H, m, H-7 to 10); ms: m/e 308 (M^+).

Anal. Calcd. for $C_{16}H_{15}F_3N_2O$: C, 62.3; H, 4.9; N, 9.1. Found: C, 62.4; H, 4.9; N, 9.2.

4-Ethyl-5,6-dihydro-4-methyl-4*H*-pyrrolo[1,2-*a*][1,4]benzodiazepine (**5**).

This compound was prepared as an oil from the amine hydrochloride (**1**) (1.03 g.) and ethyl methyl ketone (10.0 g.) with methanolic hydrogen chloride (*ca.* 0.001 mole); ir: ν max 3400 (w) (NH) cm^{-1}; uv: λ max 251 nm; nmr (deuteriochloroform): δ 0.55 (3H, t, J = 7 Hz, CH_3 of ethyl), 1.35 (3H, s, CH_3), 1.4 (2H, q, J = 7 Hz, CH_2 of ethyl), 1.95 (1H, s, NH, exchangeable), 3.8 (2H, ABq, J = 13 Hz, ring CH_2), 6.1-6.4 (2H, m, H-2,3), 6.9-7.05 (1H, m, H-1), 7.2-7.5 (4H, m, H-7 to 10).

This compound was further characterised as the 1-naphthyl urea.

5,6-Dihydro-4*H*-pyrrolo[1,2-*a*][1,4]benzodiazepine-4-spiro-1′-cyclopentane (**6**).

This compound was prepared as an oil from the amine hydrochloride (**1**)(0.61 g.) and cyclopentanone (0.52 g.) with methanolic hydrogen chloride (*ca.* 0.001 mole); uv: λ max 249 nm; nmr (deuteriochloroform): δ 1.0-2.0 (9H, m, cyclopentyl H + NH), 3.7 (2H, s, CH_2), 6.15-6.45 (2H, m, H-2,3), 6.8-7.05 (1H, m, H-1), 7.2-7.6 (4H, m, H-7 to 10). This compound was characterised as the 1-naphthyl urea.

5,6-Dihydro-4*H*-pyrrolo[1,2-*a*][1,4]benzodiazepine-4-spiro-1′-cyclohexane (**7**).

This compound was prepared as an oil from the amine hydrochloride (**1**) (1.08 g.) and cyclohexanone (5.0 g.) with methanolic hydrogen chloride (*ca.* 0.001 mole); ir: ν max 3300 (m) (NH) cm^{-1}; uv: λ max 250 nm; nmr (deuteriochloroform): δ 0.7-2.2 (10H, m, cyclohexyl H), 2.8 br (1H, s, NH, exchangeable), 3.7 (2H, s, CH_2), 6.2-6.4 (2H, m, H-2,3), 6.85-7.0 (1H, m, H-1), 7.1-7.45 (4H, m, H-7 to 10). The product was further characterised as the 1-naphthyl urea.

4-Acetyl-5,6-dihydro-4-methyl-4*H*-pyrrolo[1,2-*a*][1,4]benzodiazepine (**8**).

This compound was prepared as a crystalline solid from the amine hydrochloride (**1**) (2.82 g.) and freshly distilled diacetyl (1.27 g.), and purified by vacuum sublimation; ir: ν max 3300 (w) (NH), 1700 (s) (CO) cm^{-1}; uv: λ max 251 nm; nmr (deuteriochloroform): δ 1.5 (3H, s, CH_3), 1.55 (3H, s, $COCH_3$), 3.6 (1H, s, NH, exchangeable), 3.7 (2H, s, CH_2), 6.4-6.6 (2H, m, H-2,3), 7.0-7.15 (1H, m, H-1), 7.25-7.45 (4H, m, H-7 to 10); ms: m/e 197 (100%, $M^+ - COCH_3$).

4,4-Di(ethoxycarbonyl)-5,6-dihydro-4*H*-pyrrolo[1,2-*a*][1,4]benzodiazepine (**9**).

This compound was prepared as a yellow oil from the amine hydrochloride (**1**) (2.06 g.) and diethyl ketomalonate (1.68 g.), with the exclusion of atmospheric moisture; ir: ν max 3300 (w) (NH), 1730 br (s) (CO) cm^{-1}; uv: λ max 251 nm; nmr (deuteriochloroform): δ 1.1 (6H, t, J = 7 Hz, 2 x CH_3), 3.25 br (1H, s, NH, exchangeable), 3.8 (2H, s, ring CH_2), 4.05 (4H, q, J = 7 Hz, 2 x CH_2), 6.3-6.5 (2H, m, H-2,3), 7.0-7.15 (1H, m, H-1), 7.3-7.6 (4H, m, H-7 to 10); ms: m/e 255 (100%, $M^+ - CO_2C_2H_5$). This product was further characterised as the 1-naphthyl urea.

5,6-Dihydro-4*H*-pyrrolo[1,2-*a*][1,4]benzodiazepine-4-spiro-5′-(2′, 4′, 6′-trioxo)pyrimidine (**10**).

This compound was prepared by heating under reflux a solution of the amine hydrochloride (**1**) (10.53 g.) and alloxan monohydrate (7.95 g.) in methanol (100 ml.) for 3 hours. After cooling and evaporation of solvent, the residue was triturated with a solution of potassium hydrogencarbonate (5.0 g.) in water (50 ml.). The resulting potassium salt was filtered off, dissolved in water (170 ml.) and the solution brought to *p*H 6 with dilute acetic acid (20% v/v, 5 ml.). The product was filtered off, and again purified *via* its potassium salt. The solid obtained was crystallised from aqueous ethanol (1:3), and the analytical sample was recrystallised from ethanol-*N*,*N*-dimethylformamide-water (4:1:1) and rigorously dried by heating at 140° *in vacuo* over phosphorus pentoxide; ir: ν max 3600 (w), 3500 (w), 3400 (w) (NH), 1760 (s), 1720 (s), 1700 (s) (CO) cm^{-1}; uv: λ max 248.5, 283 sh nm; nmr (DMSO-d_6): δ 3.5 br (2H, 2 x NH), 3.95 (2H, s, CH_2), 6.2-6.35 (2H, m, H-2,3), 6.8 br (1H, NH), 7.05-7.2 (1H, m, H-1), 7.2-7.6 (4H, m, H-7 to 10); ms: m/e 296 (100%, M^+), measured 296.0908, $C_{15}H_{12}N_4O_3$ requires 296.0909.

5,6-Dihydro-4*H*-pyrrolo[1,2-*a*][1,4]benzodiazepine-4-spiro-2′-(1′, 3′-dioxo)indan (**11**).

This compound was prepared as a yellow solid from the amine hydrochloride (**1**) (1.02 g.) and ninhydrin (0.91 g.), and purified by crystallisation from acetone-ethanol; ir: ν max 3352 (w) (NH), 1740 (m) and 1700 (s) (CO) cm^{-1}; uv: λ max 227, 246 nm; nmr (deuteriochloroform): δ 2.5 br (1H, s, NH, exchangeable), 4.05 (2H, s, CH_2), 5.85-6.3 (2H, m, H-2,3), 6.95-7.1 (1H, m, H-1), 7.25-7.55 (4H, m, H-7 to 10), 7.65-8.1 (4H, m, H-4′ to 7′); ms: m/e 314 (100%, M^+).

5,6-Dihydro-4*H*-pyrrolo[1,2-*a*][1,4]benzodiazepine-4-spiro-3′-oxindole (**12**).

This compound was prepared as an orange solid from the amine hydrochloride (**1**) (1.03 g.) and isatin (0.68 g.), and purified by crystallisation from aqueous ethanol; ir: ν max 3300 (w) (NH), 1730 (s) (split) (CO) cm^{-1}; uv: λ max 249 nm; nmr (deuteriochloroform): δ 2.4 br (1H, s, N(5)H, exchangeable), 4.1 (2H, s, CH_2), 5.95-7.65 (11H, m, aromatic H), 8.65 br (1H, s, N(1′)H, exchangeable); ms: m/e 301 (20%, M^+), 272 (100%, $M^+ - CO - H$).

4,4-Dimethyl-4*H*-pyrrolo[1,2-*a*][1,4]benzodiazepine (**13**)(11).

Manganese dioxide (70%) (7.5 g.) was added to a solution of the 5,6-dihydro compound (**4**) (10.4 g.) in dry toluene (50 ml.). The mixture was stirred and heated under reflux for 24 hours, then filtered, and the solid washed with dry toluene (2 x 25 ml.). The combined filtrate and washings were evaporated *in vacuo* and the residue induced to crystallise by trituration with petrol (40-60°). Crystallisation from chloroform-petrol (40-60°) gave the product as pale yellow crystals (7.6 g. 74%), m.p. 81-83°. A colourless specimen, m.p. 81.5-82° (softens 81°) was obtained by repeated vacuum sublimation; ir: ν max 1650 (m) (C=N) cm^{-1}; uv: λ max 238, 267, 318 nm; nmr (deuteriochloroform): δ 1.55 (6H, s, 2 x CH_3), 6.1-6.5 (2H, m, H-2,3), 7.0-7.2 (1H, m, H-1), 7.2-7.65 (4H, m, H-7 to 10), 8.4 (1H, s, H-6); ms: m/e 210 (92%, M^+), 195 (100%, $M^+ - CH_3$), measured 210.1153, $C_{14}H_{14}N_2$ requires 210.1157.

Anal. Calcd. for $C_{14}H_{14}N_2$: C, 80.0; H, 6.7; N, 13.3. Found: C, 80.1; H, 6.9; N, 13.4.

Acknowledgement.

We thank Queen Elizabeth College for the award of a Nicholas Reaearch Scholarship (to S. G. G.) and the University of London Intercollegiate Research Services Scheme at the School of Pharmacy for some of the mass spectra. Mass spectra were also obtained from P.C.M.U. (Harwell). We should like to express our appreciation to Dr. R. E. Rodway for his help and valuable discussion.

REFERENCES AND NOTES

(1) For a recent review, see S. Garattini, E. Mussini and L. O. Randall, "The Benzodiazepines", Raven Press, New York, N.Y., 1973.

(2) See, for example, R. B. Moffett, *J. Heterocyclic Chem.*, **13**, S-123 (1976).

(3) E. E. Garcia, J. G. Riley and R. I. Fryer, *J. Org. Chem.*, **33**, 1359 (1968).

(4) G. W. H. Cheeseman and M. Rafiq, *J. Chem. Soc. C*, 2732 (1971).

(5) G. W. H. Cheeseman and S. G. Greenberg, *Chem. Ind. (London)*, 916 (1974).

(6) G. De Martino, M. Scalzo, S. Massa, R. Giuliano and M.

Artico, *Farmaco, Ed. Sci.*, **27**, 980 (1972).

(7) S. Raines, S. Y. Chai and F. P. Palopoli, *J. Heterocyclic Chem.*, **13**, 711 (1976).

(8) Y. Kayama, T. Hara, K. Itoh and T. Sunami, *ibid.*, **14**, 171 (1977).

(9) T. Hara, Y. Kayama, T. Mori, K. Itoh, H. Fujimori, T. Sunami, Y. Hashimoto and S. Ishimoto, *J. Med. Chem.*, **21**, 263 (1978).

(10) The molecular ion at m/e 212 is of very low abundance.

(11) Prepared with the help of Mrs. S. Wilkinson.