Synthesis of Pyrrolo[1,2-*a*]naphtho[1,8-*ef*][1,4]diazepines

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The title compounds **9-12** were prepared from *N*-(8-nitronaphthyl)pyrrole (**3**).

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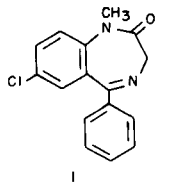
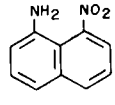
In this paper we report a further development of our investigation of the cyclisation reactions of *N*-arylpyrroles aimed at the synthesis of novel heterocyclic systems of potential biological interest [1]. We noted that in many biologically active 1,4-diazepines such as diazepam **1**, a benzene ring is fused to the *f* bond of the diazepine ring and an aryl substituent is present at position 5 [2]. We thought it would be of interest to combine these two structural features by examining the effect of fusing a naphthalene ring to the *e* and *f* bonds of a 1,4-diazepine. Such a system has proved to be accessible by the cyclisation of appropriately substituted *N*-naphthylpyrroles and we now report the synthesis of pyrrolo[1,2-*a*]naphtho[1,8-*ef*][1,4]diazepine (**9**) and three derivatives of this ring system compounds **10, 11**, and **12**.

We used 1-amino-8-nitronaphthalene (**2**) as starting material for our preparative work. This was obtained from 1-aminonaphthalene by the literature method [3,4] which involved protection of the amino group by formation of a phthaloyl derivative, nitration, and de-protection by treatment with hydrazine. We found it essential to use milder conditions in the terminal step of de-protection than those recommended in the literature. Thus in order to avoid much concomitant tar formation, the reaction was carried out at 0° in ethanol rather than at the boiling point of the solvent.



1



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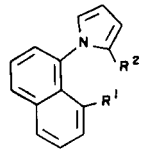
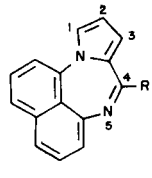
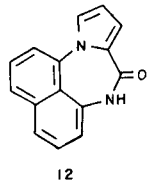


3, $R^1 = NO_2$ $R^2 = H$
4 $R^1 = NO_2$ $R^2 = CHO$
5, $R^1 = NH_2$ $R^2 = H$
6, $R^1 = NHCOCH_3$ $R^2 = H$
7, $R^1 = NHCOC_6H_5$ $R^2 = H$
8, $R^1 = NHCOOC_2H_5$ $R^2 = H$



9, R = H
10, $R = CH_3$
11, $R = C_6H_5$



12

Ring closure of the acetamido **6** and benzamido **7** compounds to the corresponding 4-methyl- and 4-phenylpyrrolonaphthodiazepines **10** and **11** was effected with phoshoryl chloride. Zinc chloride was used to cyclise the ethoxycarbonylamino compound **8** to the 4-oxo derivative **12** in accordance with literature precedent [7].

Biological screening of the tetracyclic compounds **9, 10, 11** and **12** failed to reveal any useful level of CNS activity. It was found that uniquely in this series, the parent compound **9** was a severe skin and respiratory irritant.

The substituted pyrrolonaphthodiazepines **10, 11** and **12** were prepared by cyclisation of the acylaminopyrroles **6, 7** and **8**. These intermediates were obtained by acylating *N*-(8-aminonaphthyl)pyrrole (**5**) with acetic anhydride, benzoyl chloride, and ethyl chloroformate, respectively. The amino compound was isolated as an unstable red oil on reduction of *N*-(8-nitronaphthyl)pyrrole (**3**) with iron powder in the presence of ferrous sulphate. Attempts to carry out the catalytic reduction of the nitro compound with hydrogen gas and a palladium on charcoal catalyst were not successful, as were attempts to prepare the desired amino compound **5** by the reaction of commercially available 1,8-diaminonaphthalene with 2,5-diethoxytetrahydrofuran.

EXPERIMENTAL

The ir spectra of solids were taken as Nujol mulls. Nmr spectra were measured at 60 MHz in deuterochloroform on either a Perkin-Elmer R12B or a Brücker WP60 spectrometer. All signals integrated for the expected number of protons. Mass spectral measurements were recorded at an ionising voltage of 70 eV on a Kratos MS25 machine equipped with a DS 50S data system.

1-Amino-8-nitronaphthalene (**2**).

A mixture of 4-,5- and 8-nitrophthalo-1-naphthylimides (154 g, 0.48 mole) was suspended in ethanol (300 ml) and hydrazine (98%, 250 ml) was added dropwise to the stirred and ice-cooled suspension. When the addition was complete, the ice-bath was removed and the reaction mixture was stirred at room temperature for a further 45 minutes. It was then poured into 2*M* sulphuric acid (2 *l*) at such a rate that the temperature did not rise above 50°. After cooling, the precipitate was filtered off and extracted with several portions of 2*M* sulphuric acid (1.5 *l* in all). The combined filtrate and washings were cooled and made alkaline by the cautious addition of aqueous ammonia. After standing for 16 hours at room temperature, the resulting precipitate was filtered off, dried, and crystallised from light petroleum (bp 60-80°) to give 1-amino-8-nitronaphthalene as vermilion crystals (19.9 g, 34%), mp 87-88° (lit [8] 88-89°, [4] 96-97°) ir: 3400, 3300 cm^{-1} (NH_2); 1520, 1350 (NO_2).

Anal. Calcd. for $C_{10}H_8N_2O_2$: C, 63.82; H, 4.29; N, 14.89. Found: C, 63.74; H, 4.35; N, 14.89.

N-(8-Nitronaphthyl)pyrrole (**3**).

A mixture of 1-amino-8-nitronaphthalene (7.79 g, 0.041 mole), 2,5-diethoxytetrahydrofuran (6.31 g, 0.048 mole) and glacial acetic acid (75 ml) was heated under reflux for 15 minutes. The dark brown residue obtained after removal of solvent, was dissolved in chloroform, and the solution treated with charcoal. Addition of light petroleum (bp 60-80°) precipitated the product (7.69 g, 78%) which after crystallisation from methanol had mp 97°; ir: 1530, 1360 cm^{-1} (NO_2); nmr: δ 6.2 (dd, H-3 and H-4), 6.8 (dd, H-2 and H-5), 7.6-8.4 (m, naphthalenoid); ms: 238 (M^+), 221.

Anal. Calcd. for $C_{14}H_{10}N_2O_2$: C, 70.58; H, 4.23; N, 11.76. Found: C, 70.09; H, 4.27; N, 11.55.

N-(8-Nitronaphthyl)pyrrole-2-carboxaldehyde (**4**).

Freshly distilled phosphoryl chloride (5.27 g, 0.034 mole) was added dropwise with stirring at 0°, to *N,N*-dimethylformamide (2.36 g, 0.032 mole). The mixture was stirred at room temperature for 15 minutes and then diluted with 1,2-dichloroethane (50 ml). After cooling to 5°, a solution of *N*-(8-nitronaphthyl)pyrrole (6.16 g, 0.026 mole) in 1,2-dichloroethane (50 ml) was added dropwise with stirring, the temperature during addition being kept below 5°. The reaction mixture was heated under reflux for 20 minutes, cooled, and then treated with a solution of hydrated sodium acetate (26.2 g, 0.19 mole) in water (75 ml). The mixture was heated under reflux for 15 minutes, cooled, and the organic layer separated. The aqueous layer was extracted with ether (4 x 25 ml), the organic layers were combined, washed with aqueous sodium carbonate, and dried (magnesium sulfate). After filtration and removal of solvent, the residue was crystallised from a mixture of chloroform and light petroleum (bp 60-80°) to give the carboxaldehyde as yellow crystals (5.09 g, 74%), mp 107-108°; ir: 1660 cm^{-1} (C=O); 1520, 1350 (NO_2); nmr: δ 6.35 (dd, H-4), 6.95 (dd, H-3), 7.2-8.0 (H-5 and naphthalenoid), 9.35 (s, C*H*O); ms: 266 (M^+), 220 (M^+ -NO_2).

Anal. Calcd. for $C_{15}H_{10}N_2O_3$: C, 67.66; H, 3.79; N, 10.52. Found: C, 67.62; H, 3.51; N, 10.23.

Pyrrolo[1,2-*a*]naphtho[1,8-*ef*][1,4]diazepine (**9**).

N-(8-Nitronaphthyl)pyrrole-2-carboxaldehyde (1.77 g, 0.0067 mole) was suspended in water (40 ml). Iron powder (2.32 g, 0.041 mole) and ferrous sulphate (0.47 g, 0.0017 mole) were added and the stirred mixture was heated under reflux for 2 hours. Ethanol (20 ml) and charcoal (0.2 g) were then added. The mixture was heated under reflux for a further 30 minutes and filtered while still hot. The residue was extracted with boiling ethanol (2 x 25 ml) and the combined filtrate and washings concentrated under reduced pressure to about one third of its original volume. The product was extracted into chloroform (4 x 20 ml) and the solid obtained by evaporation of the dried (magnesium sulfate) extracts crystallised from light petroleum (bp below 40°). The diazepine (0.62 g, 43%), which was a severe skin and respiratory irritant, was obtained as a yellow crystalline solid of mp 82-84°; nmr: δ 6.4 (dd, H-2), 6.75 (dd, H-3), 7.25-7.75 (m, H-1 and naphthalenoid), 8.0 (s, H-4); ms: 218 (M^+), 191 (M^+ -HCN).

Anal. Calcd. for $C_{15}H_{10}N_2$: C, 82.54; H, 4.62; N, 12.83. Found: C, 82.21; H, 4.45; N, 12.49.

N-(8-Aminonaphthyl)pyrrole (**5**).

N-(8-Nitronaphthyl)pyrrole (2.10 g, 0.0088 mole) was suspended in water (40 ml). Iron powder (3.04 g, 0.054 mole) and ferrous sulphate (0.51 g, 0.0018 mole) were added and the stirred mixture heated under reflux for 3 hours. Ethanol (20 ml) and charcoal (0.2 g) were then added and the mixture heated under reflux for a further 30 minutes. The residue obtained on filtration of the hot reaction mixture, was extracted with boiling ethanol (20 ml). The combined filtrate and washings were reduced to about one third of their original volume by vacuum distillation and the product extracted into chloroform (4 x 20 ml). The combined extracts were treated with charcoal and dried (magnesium sulfate). After filtration and removal of solvent, the amino compound (1.84 g) was obtained as a red oil which was used without further purification; ir: 3500, 3400 cm^{-1} (NH_2).

N-(8-Acetamidonaphthyl)pyrrole (**6**).

N-(8-Aminonaphthyl)pyrrole [prepared by reduction of 2.10 g (0.0088 mole) of the 8-nitro compound] was dissolved in glacial acetic acid (10 ml). Acetic anhydride (2.70 g, 0.027 mole) was added and the reaction mixture was set aside at 4° for 16 hours. After removal of solvent by vacuum distillation, the residue was poured onto crushed ice and the *p*H of the mixture adjusted to 11 by the cautious addition of aqueous sodium hydroxide. The product was isolated by extraction with chloroform (4 x 25 ml). The combined extracts were treated with charcoal and dried (magnesium sulfate). After filtration and removal of solvent, the residue was crystallised from a mixture of chloroform and light petroleum (bp 60-80°). Recrystallisation from methanol gave colourless crystals of the acetamido compound (1.14 g, 52% overall), mp 121°; ir: 3250 cm^{-1} (NH), 1660 (C=O); nmr: δ 1.7 (s, CH_3), 6.3 (dd, H-3 and H-4), 6.6 (dd, H-2 and H-5), 7.0-7.6 (m, naphthalenoid); ms: 250 (M^+).

Anal. Calcd. for $C_{16}H_{14}N_2O$: C, 76.78; H, 5.64; N, 11.19. Found: C, 76.23; H, 5.57, N, 11.25.

4-Methylpyrrolo[1,2-*a*]naphtho[1,8-*ef*][1,4]diazepine (**10**).

Freshly distilled phosphoryl chloride (15.1 g, 0.098 mole) was added to powdered *N*-(8-acetamidonaphthyl)pyrrole (1.32 g, 0.0053 mole) and the mixture stirred at room temperature for 3 hours in an atmosphere of dry nitrogen. Most of the excess of phosphoryl chloride was then removed by vacuum distillation. The residue was poured onto crushed ice with vigorous stirring and solid sodium hydrogen carbonate was added portionwise until the *p*H of the mixture was stable at 7. The product was isolated by extraction with chloroform (4 x 25 ml) and the combined extracts were dried (magnesium sulfate). After filtration and removal of solvent, crystallisation of the residue from light petroleum (bp below 40°) gave the 4-methyl compound (0.81 g. 66%), mp 115°; nmr: δ 2.4 (CH_3), 6.2 (dd, H-2), 6.6 (dd, H-3), 7.1-7.5 (m, H-1 and naphthalenoid); ms: 232 (M^+), 217 (M^+ -CH_3).

Anal. Calcd. for $C_{16}H_{12}N_2$: C, 82.73; H, 5.21; N, 12.06. Found: C, 83.02; H, 5.34; N, 11.82.

4-Phenylpyrrolo[1,2-*a*]naphtho[1,8-*ef*][1,4]diazepine (**11**).

N-(8-Aminonaphthyl)pyrrole [prepared by reduction of 2.26 g (0.0095 mole) of the 8-nitro compound] was dissolved in dry pyridine (5 ml). Freshly distilled benzoyl chloride (1.42 g, 0.010 mole) was added and the reaction mixture was stirred at 20° for 16 hours. After removal of solvent by vacuum distillation, water and ether were added, the ether layer

separated, and the aqueous layer extracted with three further 20 ml portions of ether. The combined ethereal layers were washed successively with dilute hydrochloric acid and sodium hydrogen carbonate solution, treated with charcoal and dried (magnesium sulfate). After filtration and removal of solvent the residual, oily benzoyl derivative **7** [1.72 g, ir: 3400 cm^{-1} (NH), 1650 (C=O)] was dissolved in freshly distilled phosphoryl chloride (8.35 g, 0.054 mole). The solution was stirred at 40° for 2 hours in an atmosphere of dry nitrogen. Excess of phosphoryl chloride was removed by vacuum distillation and ice-water was cautiously added to the residue followed by solid sodium hydrogen carbonate until the *p*H of the mixture was stable at 7. The product obtained by extraction with chloroform (4 x 20 ml) was applied to a silica gel column (Merck Type 60). Elution with carbon tetrachloride under a pressure of 10 psi resulted in the separation of an orange-coloured component. This was crystallised from light petroleum (bp 40-60°) to give the 4-phenyl compound (0.41 g, 15% overall), mp 94-95° dec; nmr: δ 6.4 (dd, H-2), 6.7 (dd, H-3), 7.3-8.0 (m, H-5, benzenoid and naphthalenoid); ms: 294 (M^+), 217 ($M^+ - C_6H_5$).

Anal. Calcd. for $C_{21}H_{14}N_2$: C, 85.69; H, 4.79; N, 9.52. Found: C, 85.28; H, 4.98; N, 9.68.

N-(8-Ethoxycarbonylaminonaphthyl)pyrrole (**8**).

N-(8-Aminonaphthyl)pyrrole [prepared by reduction of 2.08 g (0.0087 mole) of the 8-nitro compound] was dissolved in dry pyridine (40 ml). The solution was stirred and cooled to 0° and ethyl chloroformate (2.28 g, 0.0210 mole) was added dropwise. The reaction mixture was stirred at 20° for 16 hours and then concentrated by vacuum distillation. Ether (40 ml) was added to the residue, the ethereal solution washed with dilute hydrochloric acid (3 x 20 ml), treated with charcoal and dried (magnesium sulfate). After filtration and removal of solvent, and crystallisation of the residue from a mixture of chloroform and light petroleum (bp 60-80°), the product (1.42 g, 58%) was obtained as colourless needles. An analytical specimen of mp 68° was obtained by crystallisation from light petroleum (bp 40-60°); ir: 3500 cm^{-1} (NH), 1740 (C=O); nmr: δ 1.2 (t, CH_3), 4.0 (q, CH_2), 6.0 (br, NH, deuterium oxide exchangeable), 6.4 (dd, H-3 and H-4), 6.8 (dd, H-2 and H-5), 7.3-8.1 (m, naphthalenoid); ms: 280 (M^+), 207 ($M^+ - CO_2C_2H_5$).

Anal. Calcd. for $C_{17}H_{16}N_2O_2$: C, 72.84; H, 5.75; N, 9.99. Found: C, 73.19; H, 5.82; N, 10.11.

4-Oxo-5*H*-pyrrole[1,2-*a*]naphtho[1,8-*ef*][1,4]diazepine (**12**).

Finely powdered anhydrous zinc chloride (2.03 g, 0.015 mole) was added to a solution of *N*-(8-ethoxycarbonylaminonaphthyl)pyrrole (1.03 g, 0.0037 mole) in 1,2-dichlorobenzene (40 ml). The stirred mixture was heated under reflux for 1 hour, then steam-distilled to remove 1,2-dichlorobenzene. The residue was extracted with chloroform (3 x 25 ml), the chloroform extracts combined, treated with charcoal and dried (magnesium sulfate). After filtration and removal of most of the chloroform, light petroleum (bp 60-80°) was added to precipitate the crystalline product (0.57 g, 66%). Recrystallisation from a mixture of chloroform and light petroleum (bp below 40°) gave an analytical sample, mp 190-196° dec; ir: 3200 cm^{-1} (NH), 1650 (C=O); nmr: δ 6.45 (dd, H-2), 6.95 (dd, H-3) 7.25-7.75 (m, H-1 and naphthalenoid), 8.4 (br, H-5, deuterium oxide exchangeable); ms: 234 (M^+), 205 ($M^+ - HCO$).

Anal. Calcd. for $C_{15}H_{10}N_2O$: C, 76.91; H, 4.30; N, 11.96. Found: C, 76.54; H, 4.33; N, 12.09.

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