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SYNTHESIS OF PYRROLO[1,2-*a*][1,6]BENZODIAZONINES FROM PYRROLO[1,2-*a*][1,4]BENZODIAZEPINES AND ALKYNES CONTAINING ELECTRON-ACCEPTOR SUBSTITUENTS

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It has been established that the reaction of pyrrolo[1,2-a][1,4]benzodiazepines with activated alkynes gives pyrrolo[1,2-a][1,6]benzodiazonines as the products of diazepine ring expansion. In the case of pyrrolo[1,2-a][1,4]benzodiazepine, substituted with formyl group at the pyrrole ring, both expansion and cleavage of the diazepine fragment can occur.

Keywords: pyrrolo[1,2-*a*][1,4]benzodiazepines, pyrrolo[1,2-*a*][1,6]benzodiazonines, activated alkynes, diazepine ring expansion, diazepine ring opening.

Benzodiazonines show high and diverse biological activity, *viz*. nervous system excitation, antidepressant and antihypertensive effects [1], and they are CCK_2 receptor antagonists [2]. The diazonine ring occurs in the composition of alkaloids such as teleocidin and lyngbyatoxin [3]. However, methods for synthesizing condensed diazonines are extremely limited and pyrrolobenzodiazonines have not been reported in the literature at all. We have carried out an expansion of the azepine ring in hexahydroazepinoindoles by two carbon atoms using activated alkynes and have synthesized azoninoindoles in 64-88% yields [4].

The diazepine ring in tetrahydrobenzo[1,4]diazepines proved resistant to the action of dimethyl acetylenedicarboxylate (DMAD) and to methyl propiolate. Benzodiazepines containing a lactam fragment

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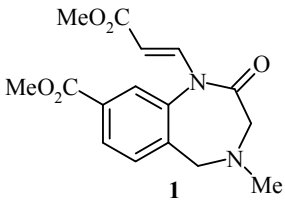
react quite readily by several routes. The principal of these is an *N*-vinylation of the amide fragment to form type **1** compounds and the formation of compounds **2**, **3** as the products of a Stevens rearrangement. The expected benzodiazonine **4** was isolated in only a single case in 4% yield [5].



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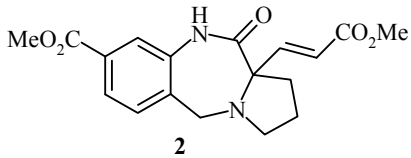

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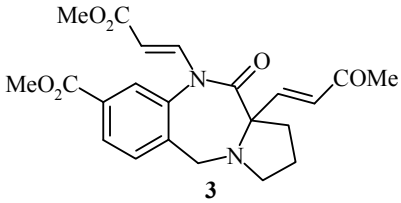

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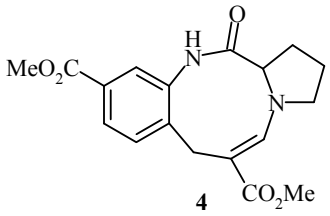

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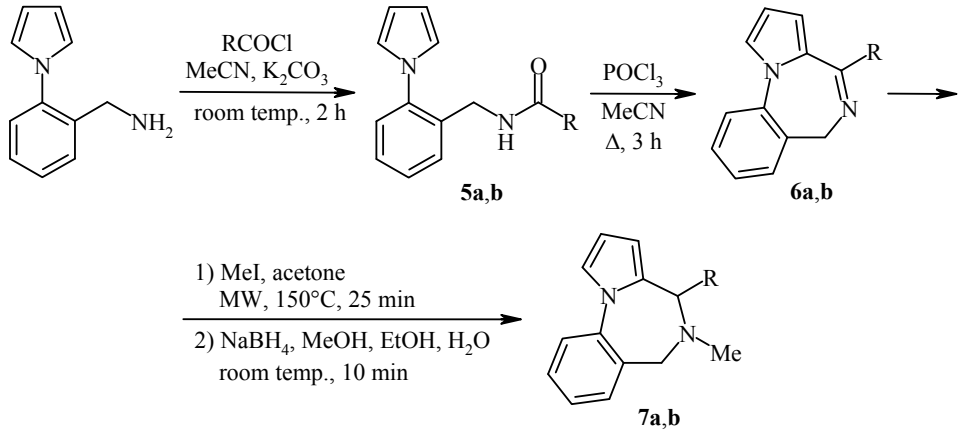
This work relates to a study of the reaction of pyrrolo[1,2-*a*][1,4]benzodiazepines with acetylacetylene, methyl propiolate, or DMAD as a result of which pyrrolo[1,2-*a*][1,4]benzodiazonines have been synthesized for the first time.

4-Phenyl- and 4-(thien-2-yl)-substituted pyrrolobenzodiazepines **7a**,**b** were prepared *via* a multistage synthesis. Using a Bischler-Napieralski reaction the *N*-(*o*-aminomethylphenyl)pyrrole through the corresponding amides **5a**,**b** was converted to the dihydropyrrolobenzodiazepines **6a**,**b**. Methylation with methyl iodide and subsequent reduction of the quaternary salt with sodium borohydride gave pyrrolobenzodiazepines **7a**,**b**.

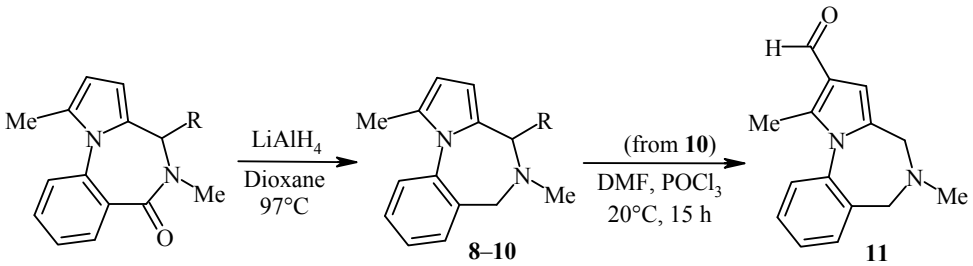


a R = Ph, **b** R = 2-thienyl

1-Methyl-substituted pyrrolo[1,2-*a*][1,4]benzodiazepines **8**-**10** were prepared by the reduction of the corresponding pyrrolobenzodiazepines [6]. A Vilsmeier-Haack reaction of the pyrrolobenzodiazepine **10** gave the aldehyde **11**.

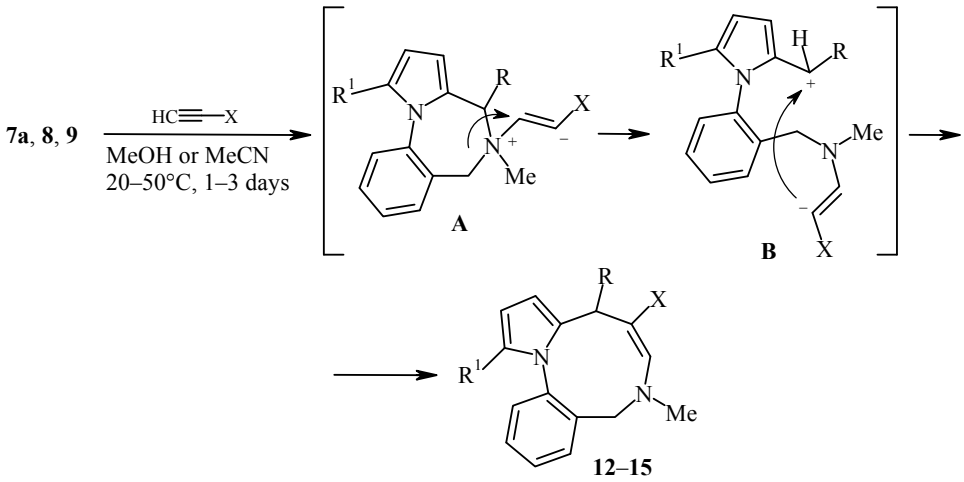
All of the reactions of the pyrrolobenzodiazepines with alkynes gave multicomponent mixtures and were accompanied by marked tarring.

The diazepine **7a** reacted with acetylacetylene in methanol at 30ºC and in acetonitrile at 50ºC over 1 day. Chromatography of the reaction mixtures gave the pyrrolobenzodiazonine **12** in 28 and 25% yields, respectively. The diazepine **7a** reacted more slowly with methyl propiolate in acetonitrile at 50ºC over 3 days. The diazonine **13** was isolated from the reaction mixture in 22% yield.



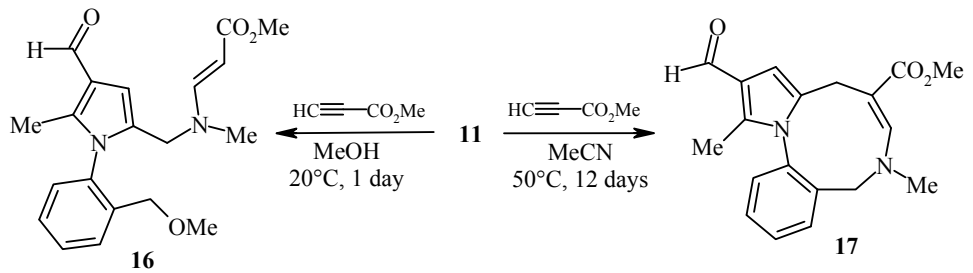
8 R = Ph, **9** R = Me, **10** R = H

The methyl-substituted at pyrrole ring pyrrolobenzodiazepine **8** reacted with methyl propiolate in methanol at 20ºC over 1 day similarly to compound **7a** to yield a multicomponent mixture from which the pyrrolobenzodiazonine **14** can be chromatographically isolated. The 1,4-dimethyl-substituted diazepine **9** reacted with methyl propiolate and acetylacetylene both in methanol and in acetonitrile at 20°C over 3 days to give a multicomponent mixtures. Only in the reaction with methyl propiolate could the pyrrolo[1,2-*a*]-[1,6]benzodiazonine **15** be isolated in 18% yield.



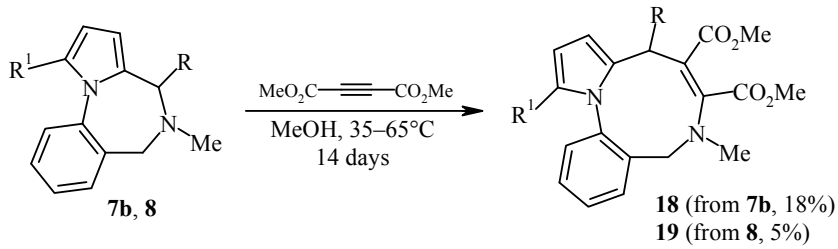
12–**14** R = Ph, **15** R = Me; **12**, **13** R^1 = H, **14**, **15** R^1 = Me; **12** X = COMe, **13**–**15** X = CO_2Me

Carrying out the reaction of the pyrrolobenzodiazepine **10** (without the phenyl group at position 4) with methyl propiolate in methanol a multicomponent mixture was obtained which was assumed to contain the products of vinylation of the pyrrole ring and polymeric type products but these could not be separated chromatographically. With the aim of lowering the activity of the pyrrole ring, its formylation was carried out under Vilsmeier-Haack conditions to give the pyrrolo[1,2-*a*][1,4]benzodiazepinecarbaldehyde **11**. However, its reaction with methyl propiolate in methanol was little selective as before. None the less, column chromatography of the reaction mixture gave a 7% yield of the product of cleavage of the diazepine fragment, namely the pyrrolylmethylamino acrylate **16**. This reaction in acetonitrile gave the pyrrolobenzodiazonine **17** in an 8% yield.



We believe that the reaction of the alkynes with diazepines **7a**, **8**, **9**, **11** begins with the formation of an ammonium type zwitterion of type **A** *via* addition of the tertiary nitrogen to the triple bond. The cleavage of the C(4)–N^+ bond then follows to generate cation **B** which is stabilized by the substituent donor effect. Formation of an alternative benzyl cation seems less likely. One of the routes for the reaction of **B** is the formation of diazonines. After formation of the type **A** zwitterion in the case of diazepine **11**, the formaion of the carbocation of type **B** becomes impossible, and bimolecular nucleophilic processes begin to predominate [7].

Diazepines **7b** and **8** did not react with DMAD in acetonitrile upon prolonged heating and with an excess of the reagent. In methanol multicomponent mixtures are obtained from which respectively the pyrrolobenzodiazonines **18** and **19** could be isolated in low yields.



7b, **8**

18 (from **7b**, 18%)
19 (from **8**, 5%)

18 R = 2-thienyl, R^1 = H; **19** R = Ph, R^1 = Me

The structure of all of the pyrrolo[1,2-*a*][1,6]benzodiazonines **12-15, 17-19** was confirmed by spectroscopic data. Their mass spectra showed molecular ions corresponding to the empirical formulae. The ^{1}H NMR spectra of compounds **12-15**, **17** showed singlet signals for the enamine fragment H-7 protons in the region 7.32-7.61 ppm and also signals for the NCH_2 groups at 3.78-3.94 ppm. The ^{1}H NMR spectrum of pyrrole **16** was characterized by the presence of a singlet for the methoxy group protons of the CH_2OCH_3 at 3.11 ppm and two doublets with J = 13.1 Hz for the protons of the vinyl group at 4.57 and 7.33 ppm.

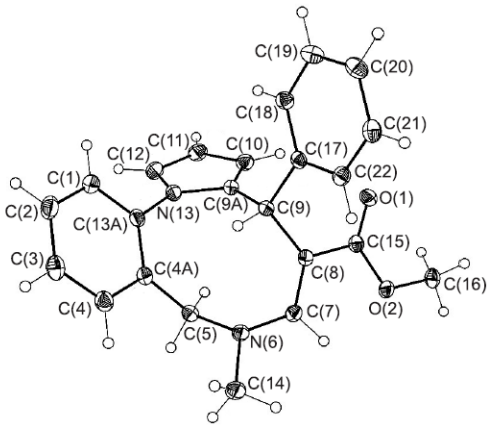


Fig. 1. Molecular structure of compound **13** with representation of atoms by thermal vibration ellipsoids of 50% probability.

The structure of compound **13** was confirmed by X-ray structural analysis (Fig. 1). Compound **13** is polycyclic and contains three fused rings, *viz*. the five-membered pyrrole, six-membered benzene, and nine-membered diazonine. The conformation of the central nine-membered ring can be regarded as a distorted "chair" with the atoms C(4A), N(13), C(13A), C(7), and C(8) deviating from the mean square plane of the remaining ring atoms by -1.479, -0.672, -1.716, 1.007, and 1.057 Å, respectively. The angle between the planes of the pyrrole and fused benzene (C(1)–C(2)–C(3)–C(4)–C(4A)–C(13A)) rings is 56.5°. The compound **13** molecule has an *E*-configuration of substituents at the C(7)=C(8) double bond. Due to conjugation, the carboxyl

substituent lies in the plane of the C(7)=C(8) double bond (torsion angle C(7)=C(8)–C(15)=O(1) 180.0(1)°). The nitrogen atom N(6) has a trigonal-pyramidal configuration (sum of valence angle values at the N(6) atom 354.9°) whereas the N(13) atom is planar (sum of valence angles at N(13) 360.0°). Compound **13** is chiral and has one asymmetric center at the C(9) carbon atom. The compound **13** crystal occurs as a racemate.

Thus, we have shown for the first time the possibility of synthesizing pyrrolobenzodiazonines by a domino reaction of pyrrolobenzodiazepines with activated alkynes. The process of expanding the diazepine ring occurs *via* cleavage of the C(4)–N bond in the initially formed zwitterionic ammonium salt which is formed through a Michael addition of the tertiary nitrogen to the triple bond. The substituent at position C-4 of the pyrrolobenzodiazepine ring stabilizes the carbocation formed *via* cleavage of the bond indicated above.

EXPERIMENTAL

IR spectra were recorded on an Infralum FT-801 Fourier spectrometer for KBr pellets (for crystalline substances) or as a film (for oils). ^{1}H NMR spectra were recorded on a Bruker WP-400 instrument (400 MHz) using $CDCl_3$ with TMS as internal standard. LC-MS spectra for compounds **11**, **13**, **16** were recorded on a system consisting of an Agilent 1100 liquid chromatograph and an Agilent Technologies LC/MSD VL, ELSD Sedex 75 mass spectrometer. The mass spectra of the remaining compounds were recorded on a Thermo Scientific MAT 95XL chromato-mass spectrometer (EI, 70 eV). Elemental analysis was performed on a Carlo Erba 1106 instrument. Melting points were determined on an SMP 10 instrument. TLC was carried out on Sorbfil plates with fixed silica gel layer and visualized using $KMnO_4$ and H_2SO_4. The chromatographic separation used Fluka-507C neutral alumina (0.05-0.15 mm) and Merck silica gel (230-400 mesh). Microwave activation of the quaternization of pyrrolobenzodiazepines **7a**,**b** was carried out using a Monowave 300 Anton Paar type microwave oven.

Preparation of *N*-[2-(1*H*-Pyrrol-1-yl)benzyl]benzamides 5a,b (General Method). PhCOCl or thiophene-2-carbonyl chloride (64 mmol) was added dropwise to a solution of calcined K_2CO_3 (10.5 g, 75 mmol) and 2-(1-pyrrolyl)benzylamine (10.0 g, 58 mmol) in absolute MeCN at 20°C. The mixture was stirred for 2 h (monitoring by TLC using EtOAc–hexane (1:2) as eluent), solvent was evaporated *in vacuo*, and water (40 ml) was added to the residue. The precipitate formed was filtered off and crystallized from a mixture of EtOAc–hexane (1:3).

***N*-[2-(1*H*-Pyrrol-1-yl)benzyl]benzamide (5a)**. Yield 13.5 g (84%), light-brown crystals, mp 138-139°C. IR spectrum, ν, cm^{-1}: 3340 (NH), 1628 (CO). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 4.58 (2H, d, *J* = 6.1, C$\underline{H}_2$NH); 5.95 (1H, br. s, NH); 6.38 (2H, t, *J* = 2.1, H-3,4 pyrrole); 6.84 (2H, t, *J* = 2.1, H-2,5 pyrrole); 7.30-7.33 (1H, m, H Ar); 7.35-7.40 (4H, m, H Ar, H Ph); 7.44-7.47 (1H, m, H Ph); 7.53-7.55 (1H, m, H Ph); 7.62-7.65 (2H, m, H Ph). Mass spectrum, *m*/*z* (I_{rel}, %): 276 [M]$^+$ (1), 169 (13), 155 (100), 105 (34), 77 (54). Found, %: C 78.21; H 5.80; N 10.08. $C_{18}H_{16}N_2O$. Calculated, %: C 78.24; H 5.84; N 10.14.

***N*-[2-(1*H*-Pyrrol-1-yl)benzyl]thiophene-2-carboxamide (5b)**. Yield 14.7 g (90%), brown crystals, mp 119-120°C. IR spectrum, ν, cm^{-1}: 3319 (NH), 1624 (CO). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 4.54 (2H, d, *J* = 6.4, C$\underline{H}_2$NH); 5.80 (1H, br. s, NH); 6.40 (2H, t, *J* = 2.4, H-3,4 pyrrole); 6.84 (2H, t, *J* = 2.4, H-2,5 pyrrole); 7.03 (1H, dd, *J* = 4.6, *J* = 3.7, H-4 thiophene); 7.31–7.34 (2H, m, H Ar); 7.35-7.39 (2H, m, H Ar); 7.44 (1H, br. d, *J* = 4.6, H-3 thiophene); 7.53 (1H, dd, *J* = 3.7, *J* = 4.6, H-5 thiophene). Mass spectrum, *m*/*z* (I_{rel}, %): 282 [M]$^+$ (1), 155 (100), 154 (54), 111 (30). Found, %: C 68.10; H 5.05; N 9.87. $C_{16}H_{14}N_2OS$. Calculated, %: C 68.06; H 5.00; N 9.92.

Preparation of 6*H*-Pyrrolo[1,2-*a*][1,4]benzodiazepines 6a,b (General Method). $POCl_3$ (30.0 g, 196 mmol) was added dropwise to a solution of the amide **5a**,**b** (49 mmol) in absolute MeCN (80 ml) under an argon atmosphere. The mixture was refluxed for 3 h monitoring by TLC using EtOAc–hexane (1:3) as eluent. The solvent was evaporated, and the dark oil was poured into 25% ammonia solution and extracted with EtOAc (400 ml). The extract was dried over $MgSO_4$, and the solvent was evaporated *in vacuo*. The residue was triturated in ether, and the precipitate was filtered off.

4-Phenyl-6*H*-pyrrolo[1,2-*a*][1,4]benzodiazepine (6a). Yield 9.4 g (74%), beige crystals, mp 110-111°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 4.64 (2H, br. s, CH_2N); 6.40-6.45 (1H, m, H-3); 6.46-6.49 (1H, m, H-2); 7.26-7.30 (1H, m, H Ar); 7.32-7.42 (5H, m, H-1, H Ar, H Ph); 7.49 (2H, d, *J* = 7.5, H Ph); 7.69 (2H, d, *J* = 7.5, H Ph). Mass spectrum, *m*/*z* (I_{rel}, %): 282 $[M]^+$ (94), 230 (12), 181 (8), 154 (100), 128 (34). Found, %: C 83.65; H 5.43; N 10.81. $C_{18}H_{14}N_2$. Calculated, %: C 83.69; H 5.46; N 10.84.

4-(2-Thienyl)-6*H*-pyrrolo[1,2-*a*][1,4]benzodiazepine (6b). Yield 11.9 g (92%), beige crystals, mp 160-162°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 4.38 (1H, br. d, *J* = 10.5) and 4.81 (1H, br. d, *J* = 10.5, CH_2N); 6.46 (1H, t, *J* = 3.6, H-2); 6.83 (1H, dd, *J* = 1.4, *J* = 3.6, H-3); 7.02 (1H, dd, *J* = 3.7, *J* = 4.6, H-4'); 7.26-7.30 (1H, m, H-8); 7.33–7.35 (1H, m, H-1); 7.36-7.39 (3H, m, H-7,9,5'); 7.42 (1H, d, *J* = 3.7, H-3'); 7.49 (1H, d, *J* = 7.3, H-10). Mass spectrum, *m*/*z* (I_{rel}, %): 264 $[M]^+$ (100), 263 (92), 236 (30), 155 (52), 154 (83). Found, %: C 72.74; H 4.53; N 10.62. $C_{16}H_{12}N_2S$. Calculated, %: C 72.70; H 4.58; N 10.60.

Preparation of 5,6-Dihydro-4*H*-pyrrolo[1,2-*a*][1,4]benzodiazepines 7a,b (General Method). A mixture of the diazepine **6a**,**b** (2.7 mmol) and MeI (1.93 g, 13.6 mmol) in absolute acetone (10 ml) underwent microwave irradiation (50 W) at 150°C over 25 min. The solvent was evaporated *in vacuo*. The residue was dissolved in a mixture of MeOH (16 ml) and 60% aqueous EtOH (24 ml), and $NaBH_4$ (0.09 g, 2.5 mmol) was added at 20ºC. A precipitate was formed after 10 min. Water (50 ml) was added to the reaction mixture, and the precipitated crystals were filtered off and dried in air.

5-Methyl-4-phenyl-5,6-dihydro-4*H*-pyrrolo[1,2-*a*][1,4]benzodiazepine (7a). Yield 0.68 g (92%), beige crystals, mp 96-98°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.24 (3H, s, NCH_3); 3.51 (1H, d, *J* = 14.0) and 4.13 (1H, d, *J* = 14.0, CH_2N); 3.93 (1H, s, 4-CH); 5.48 (1H, d, *J* = 2.8, H-2); 6.15 (1H, t, *J* = 2.8, H-3); 6.96 (1H, d, *J* = 1.4, H-1); 7.27-7.30 (3H, m, H Ph); 7.35 (2H, t, *J* = 6.9, H Ph); 7.41-7.49 (4H, m, H Ar). Mass spectrum, *m*/*z* (I_{rel}, %): 274 $[M]^+$ (20), 197 (100), 154 (18), 42 (16). Found, %: C 83.21; H 6.58; N 10.25. $C_{19}H_{18}N_2$. Calculated, %: C 83.18; H 6.61; N 10.21.

5-Methyl-4-(2-thienyl)-5,6-dihydro-4*H*-pyrrolo[1,2-*a*][1,4]benzodiazepine (7b). Yield 0.62 g (82%), beige crystals, mp 90-91°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.37 (3H, s, NCH_3); 3.50 (1H, d, *J* = 14.0) and 4.10 (1H, d, *J* = 14.0, CH_2N); 4.36 (1H, s, 4-CH); 5.85 (1H, br. s, H-3); 6.21 (1H, br. s, H-2); 6.91-6.97 (3H, m, H-1, H Ar); 7.29-7.34 (3H, m, H Ar); 7.41-7.45 (3H, m, H-3',4',5'). Mass spectrum, *m*/*z* (I_{rel}, %): 280 $[M]^+$ (54), 197 (100), 155 (100), 154 (46), 97 (24). Found, %: C 72.79; H 5.81; N 10.02. $C_{17}H_{16}N_2S$. Calculated, %: C 72.82; H 5.75; N 9.99.

Preparation of 5,6-Dihydro-4*H*-pyrrolo[1,2-*a*][1,4]benzodiazepines 8-10 (General Method). The corresponding pyrrolo[1,2-*a*][1,4]benzodiazepin-6-one (20.0 mmol) was added portionwise to a suspension of $LiAlH_4$ (1.52 g, 40.0 mmol) in absolute dioxane (30 ml) at 0-5°C under an argon atmosphere. The mixture was heated at 97°C for 1-4 h, cooled, and treated sequentially with water (5 ml), 15% aqueous NaOH solution (5 ml), water (5 ml) again, and then stirred for 1 h. The precipitate formed was filtered off and washed with CH_2Cl_2. The filtrate was separated and dried over $MgSO_4$, and the solvent was evaporated *in vacuo*.

1,5-Dimethyl-4-phenyl-5,6-dihydro-4*H*-pyrrolo[1,2-*a*][1,4]benzodiazepine (8). The reaction was carried out for 4 h (TLC monitoring, eluent EtOAc–hexane, 1:3). Yield 0.45 g (78%), beige crystals, mp 160-161°C (Et_2O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.18 (3H, s, 1-CH_3); 2.30 (3H, s, NCH_3); 3.49 (1H, d, *J* = 13.7) and 4.04 (1H, d, *J* = 13.7, CH_2N); 3.79 (1H, s, 4-CH); 5.37 (1H, d, *J* = 2.9, H-2); 5.91 (1H, d, *J* = 2.9, H-3); 7.28-7.34 (4H, m, H Ar); 7.38-7.40 (2H, m, H Ph); 7.45-7.49 (3H, m, H Ph). Mass spectrum, *m*/*z* (I_{rel}, %): 288 $[M]^+$ (38), 273 (64), 211 (100), 197 (24). Found, %: C 83.26; H 6.95; N 9.68. $C_{20}H_{20}N_2$. Calculated, %: C 83.30; H 6.99; N 9.71.

1,4,5-Trimethyl-5,6-dihydro-4*H*-pyrrolo[1,2-*a*][1,4]benzodiazepine (9). The reaction was carried out for 1 h (TLC monitoring, eluent EtOAc–hexane, 1:1). Yield 0.38 g (83%), yellow oil. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.44 (3H, d, *J* = 6.4, 4-CH_3); 2.29 (3H, s, 1-CH_3); 2.31 (3H, s, NCH_3); 3.02 (1H, d, *J* = 6.4, 4-CH); 3.41 (1H, d, *J* = 13.3) and 3.55 (1H, d, *J* = 13.3, CH_2N); 6.04 (1H, d, *J* = 3.4, H-2); 6.13 (1H, d, *J* = 3.4, H-3); 7.28-7.35 (3H, m, H Ar); 7.40-7.45 (1H, m, H Ar). Mass spectrum, *m*/*z* (I_{rel}, %): 226 $[M]^+$ (22), 211 (100), 170 (18), 154 (9), 105 (7). Found, %: C 79.64; H 8.07; N 12.31. $C_{15}H_{18}N_2$. Calculated, %: C 79.61; H 8.02; N 12.38.

1,5-Dimethyl-5,6-dihydro-4*H*-pyrrolo[1,2-*a*][1,4]benzodiazepine (10). The reaction was carried out for 3.5 h (TLC monitoring, eluent EtOAc–hexane, 1:1). Yield 0.36 g (85%), yellow oil. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.33 (3H, s, 1-CH_3); 2.38 (3H, s, NCH_3); 3.19 (1H, d, *J* = 11.7) and 3.57 (1H, d, *J* = 11.7, 6-CH_2); 3.25-3.34 (1H, m) and 3.39-3.49 (1H, m, 4-CH_2); 6.03 (1H, d, *J* = 2.8, H-3); 6.14 (1H, d, *J* = 2.8, H-2); 7.27-7.31 (2H, m, H Ar); 7.39-7.44 (2H, m, H Ar). Mass spectrum, *m*/*z* (I_{rel}, %): 212 $[M]^+$ (100), 197 (96), 180 (28), 168 (55), 154 (83), 42 (25). Found, %: C 79.25; H 7.57; N 13.27. $C_{14}H_{16}N_2$. Calculated: C 79.21; H 7.60; N 13.20.

1,5-Dimethyl-5,6-dihydro-4*H*-pyrrolo[1,2-*a*][1,4]benzodiazepine-2-carbaldehyde (11). $POCl_3$ (0.4 g, 2.8 mmol) was added dropwise and slowly to a flask containing DMF (0.6 g, 8.5 mmol) cooled to -5°C. The mixture was stirred at 20ºC for 40 min. A solution of the pyrrolobenzodiazepine **10** (0.3 g, 1.4 mmol) in DMF (3 ml) was added dropwise (TLC monitoring, eluent EtOAc–hexane, 1:1). After 15 h, the solution was basified with 10% Na_2CO_3 solution to pH 10 and extracted with Et_2O. The extract was dried over $MgSO_4$, and the solvent was evaporated. Yield 0.1 g (31%), yellow crystals, mp 109-111°C (Et_2O). IR spectrum, ν, cm^{-1}: 1658 (CHO). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.35 (3H, s, 1-CH_3); 2.57 (3H, s, NCH_3); 3.15 (1H, d, *J* = 12.6) and 3.54 (1H, d, *J* = 12.6, 4-CH_2); 3.25 (1H, d, *J* = 13.8) and 3.48 (1H, d, *J* = 13.8, 6-CH_2); 6.58 (1H, s, H-3); 7.28 (1H, d, *J* = 7.9, H Ar); 7.36-7.48 (3H, m, H Ar); 9.94 (1H, s, CHO). Mass spectrum, *m*/*z*: 241 $[M+H]^+$. Found, %: C 74.92; H 6.75; N 11.63. $C_{15}H_{16}N_2O$. Calculated, %: C 74.97; H 6.71; N 11.66.

1-(6-Methyl-9-phenyl-6,9-dihydro-5*H*-pyrrolo[1,2-*a*][1,6]benzodiazonin-8-yl)ethanone (12). A. Acetylacetylene (0.09 g, 1.3 mmol) was added to a solution of the benzodiazepine **7a** (0.30 g, 1.1 mmol) in MeOH (10 ml). The reaction was carried out for 1 day at 30°C (TLC monitoring, eluent EtOAc–hexane, 1:5). The solvent was distilled off *in vacuo*. The oil obtained was crystallized from EtOAc. Yield 0.11 g (28%).

B. Acetylacetylene (0.15 g, 2.2 mmol) was added to a solution of the benzodiazepine **7a** (0.30 g, 1.1 mmol). The reaction was carried out for 1 day at 50°C (TLC monitoring, eluent EtOAc–hexane, 1:5). Solvent was evaporated *in vacuo*, and the oil produced was crystallized from EtOAc. Yield 0.09 g (25%), white crystals, mp 197-199°C. IR spectrum, ν, cm^{-1}: 1641 (COMe), 1598 (C=C). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.14 (3H, s, $COCH_3$); 3.31 (3H, s, NCH_3); 3.94 (2H, s, CH_2N); 4.92 (1H, s, 9-CH); 6.39-6.40 (1H, m, H-10); 6.60-6.64 (1H, m, H-11); 6.70-6.71 (1H, m, H-12); 6.89-7.04 (3H, m, H Ar); 7.09-7.14 (3H, m, H Ar, H Ph); 7.35-7.38 (3H, m, H Ph); 7.48 (1H, s, H-7). Mass spectrum, *m*/*z* (I_{rel}, %): 342 $[M]^+$ (17), 299 (26), 254 (20), 247 (47), 154 (76), 43 (100). Found, %: C 80.62; H 6.51; N 8.13. $C_{23}H_{22}N_2O$. Calculated, %: C 80.67; H 6.48; N 8.18.

Methyl 6-Methyl-9-phenyl-6,9-dihydro-5*H*-pyrrolo[1,2-*a*][1,6]benzodiazonine-8-carboxylate (13). Methyl propiolate (0.2 g, 3.1 mmol) was added to a solution of the benzodiazepine **7a** (0.4 g, 1.3 mmol) in MeCN (10 ml) and stirred at 50C for 72 h (TLC monitoring, eluent EtOAc-hexane, 1:3). Solvent was distilled off *in vacuo*. The residue was chromatographed on a silica gel column (*d* 1.8 cm, *l* 18 cm) using EtOAc–hexane (1:15) as eluent. Yield 0.09 g (22%), white crystals, mp 164-165°C (Et_2O). IR spectrum, ν, cm^{-1}: 1687 (CO_2Me), 1606 (C=C). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.25 (3H, s, NCH_3); 3.90 (2H, s, CH_2N); 4.49 (3H, s, CO_2CH_3); 4.98 (1H, br. s, 9-CH); 6.41 (1H, t, *J* = 3.2, H-11); 6.58 (1H, dd, *J* = 1.8, *J* = 3.2, H-10); 6.72 (1H, dd, *J* = 1.8, *J* = 3.2, H-12); 7.04-7.06 (3H, m, H Ph); 7.12-7.16 (2H, m, H Ph); 7.34-7.39 (3H, m, H Ar); 7.53-7.55 (1H, m, H Ar); 7.61 (1H, s, H-7). Mass spectrum, *m*/*z*: 359 $[M+H]^+$. Found, %: C 77.05; H 6.22; N 7.79. $C_{23}H_{22}N_2O_2$. Calculated, %: C 77.07; H 6.19; N 7.82.

Methyl 6,12-Dimethyl-9-phenyl-6,9-dihydro-5*H*-pyrrolo[1,2-*a*][1,6]benzodiazonine-8-carboxylate (14). Methyl propiolate (0.24 g, 2.8 mmol) was added to a solution of the benzodiazepine **8** (0.404 g, 1.4 mmol) in MeOH (10 ml) and stirred at 50°C for 24 h (TLC monitoring, eluent EtOAc–hexane, 1:3). Solvent was distilled off *in vacuo*, and the residue was separated by column chromatography on silica gel (*l* 18 cm, *d* 1 cm) using EtOAc–hexane (1:7) as eluent. Yield 0.027 g (5%), white crystals, mp 187-189°C (EtOAc–hexane, 1:3). IR spectrum, ν, cm^{-1}: 1690 (CO_2Me), 1606 (C=C). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.10 (3H, s, 12-CH_3); 3.23 (3H, s, NCH_3); 3.46 (3H, s, CO_2CH_3); 3.85 (2H, s, CH_2N); 4.85 (1H, s, 9-CH); 6.12 (1H, d,

J = 3.1, H-11); 6.42 (1H, d, *J* = 3.1, H-10); 7.02-7.06 (1H, m, H Ar); 7.08-7.15 (4H, m, 3H Ar, H Ph); 7.23-7.25 (1H, m, H Ph); 7.32-7.40 (2H, m, H Ph); 7.53 (1H, s, H-7); 7.55-7.57 (1H, m, H Ph). Mass spectrum, *m*/*z* (I_{rel}, %): 372 $[M]^+$ (30), 313 (52), 204 (61), 202 (100), 168 (48), 154 (52), 42 (32). Found, %: C 77.35; H 6.46; N 7.48. $C_{24}H_{24}N_2O_2$. Calculated, %: C 77.39; H 6.49; N 7.52.

6,9,12-Trimethyl-6,9-dihydro-5*H*-pyrrolo[1,2-*a*][1,6]benzodiazonine-8-carboxylate (15). Methyl propiolate (0.24 g, 2.9 mmol) was added to the pyrrolobenzodiazepine **9** (0.34 g, 1.5 mmol) in MeOH (10 ml). The reaction was carried out for 1 day at 20°C (TLC monitoring, eluent EtOAc–hexane, 1:5). Solvent was removed *in vacuo*, and the oil obtained was crystallized from Et_2O. Yield 0.08 g (18%), white crystals, mp 140-142°C. IR spectrum, ν, cm^{-1}: 1733 (CO_2Me), 1615 (C=C). ^1H NMR spectrum, δ, ppm (*J*, Hz): 1.35 (3H, d, *J* = 6.9, 9-CH_3); 2.04 (3H, s, 12-CH_3); 3.15 (3H, s, NCH_3); 3.50-3.45 (1H, m, 9-CH); 3.38 (3H, s, CO_2CH_3); 3.79 (2H, s, CH_2N); 6.00 (1H, d, *J* = 3.1, H-10); 6.35 (1H, d, *J* = 3.1, H-11); 7.32 (1H, s, H-7); 7.39-7.45 (3H, m, H Ar); 7.58-7.55 (1H, m, H Ar). Mass spectrum, *m*/*z* (I_{rel}, %): 310 $[M]^+$ (53), 263 (38), 252 (48), 202 (100), 180 (86), 167 (61), 154 (46), 106 (55). Found, %: C 73.57; H 7.11; N 9.06. $C_{19}H_{22}N_2O_2$. Calculated, %: C 73.52; H 7.14; N 9.02.

Methyl (2*E*)-3-[({4-Formyl-1-[2-(methoxymethyl)phenyl]-5-methyl-1*H*-pyrrol-2-yl}methyl)(methyl)-amino]acrylate (16). Methyl propiolate (0.27 g, 3.2 mmol) was added to a solution of the pyrrolobenzodiazepine carbaldehyde **11** (0.53 g, 2.2 mmol) in MeOH (15 ml). The reaction was carried out for 1 day at 20°C (TLC monitoring, eluent EtOAc). Solvent was removed *in vacuo***,** and the residue was chromatographed on an alumina column (*d* 1.8 cm, *l* 18 cm) using EtOAc–hexane (1:7) as eluent. Solvent was removed *in vacuo*, and the yellow oil obtained was crystallized from Et_2O. Yield 0.07 g (7%), white crystals, mp 96-97°C. IR spectrum, ν, cm^{-1}: 1655 (CHO). ^1H NMR spectrum, δ, ppm (*J*, Hz): 2.20 (3H, s, 5-CH_3); 2.92 (3H, br. s, NCH_3); 3.11 (3H, s, $CH_2OC\underline{H}_3$); 3.60 (3H, s, CO_2CH_3); 3.98-4.09 (4H, m, $C\underline{H}_2OMe$, CH_2N); 4.57 (1H, d, *J* = 13.1, $NC\underline{H}$=CH); 6.72 (1H, s, H-3); 7.20 (1H, d, *J* = 7.5, H Ar); 7.29 (1H, d, *J* = 7.5, H Ar), 7.33 (1H, d, *J* = 13.1, CH=C$\underline{H}$COOMe); 7.45 (1H, t, *J* = 6.9, H Ar); 7.51 (1H, d, *J* = 6.9, H Ar); 9.90 (1H, s, CHO). Mass spectrum, *m*/*z*: 357 $[M+H]^+$. Found, %: C 67.46; H 6.72; N 7.81. $C_{20}H_{24}N_2O_4$. Calculated, %: C 67.40; H 6.79; N 7.86.

Methyl 11-Formyl-6,12-dimethyl-6,9-dihydro-5*H*-pyrrolo[1,2-*a*][1,6]benzodiazonine-8-carboxylate (17). Methyl propiolate (0.15 g, 1.8 mmol) was added to a solution of the pyrrolobenzodiazepine carbaldehyde **11** (0.29 g, 1.2 mmol) in MeCN (17 ml). The reaction was carried out for 12 days at 50°C (TLC monitoring, eluent EtOAc). Solvent was removed *in vacuo*, and the residue obtained was recrystallized from a mixture of Et_2O and hexane. Yield 0.03 g (8%), white crystals, mp 180-182°C. IR spectrum, ν, cm^{-1}: 1649 (CO_2Me), 1620 (C=C). ^1H NMR spectrum, δ, ppm (*J*, Hz): 2.34 (3H, s, 12-CH_3); 2.63 (1H, d, *J* = 15.6) and 3.80 (1H, d, *J* = 15.6, 9-CH_2); 3.25 (3H, s, NCH_3); 3.74 (3H, s, CO_2CH_3); 3.78 (1H, d, *J* = 15.1) and 3.86 (1H, d, *J* = 15.1, CH_2N); 6.59 (1H, s, H-10); 7.24 (1H, d, *J* = 7.3, H-4); 7.45 (1H, s, H-7); 7.46-7.54 (2H, m, H-2,3); 7.63 (1H, d, *J* = 7.3, H-1); 9.89 (1H, s, CHO). Mass spectrum, *m/z* (I_{rel}, %): 324 $[M]^+$ (14), 265 (15), 202 (21), 167 (18), 59 (66), 42 (100). Found, %: C 70.39; H 6.18; N 8.71. $C_{19}H_{20}N_2O_3$. Calculated, %: C 70.35; H 6.21; N 8.64.

Dimethyl 6-Methyl-9-(2-thienyl)-6,9-dihydro-5*H*-pyrrolo[1,2-*a*][1,6]benzodiazonine-7,8-dicarboxylate (18). DMAD (0.44 g, 3.1 mmol) was added to a solution of the pyrrolobenzodiazepine **7b** (0.35 g, 1.3 mmol) in MeOH (12 ml). The reaction was carried out for 13 days at 35°C (TLC monitoring, eluent EtOAc–hexane, 1:10). Solvent was removed *in vacuo*, and the residue was chromatographed on a silica gel column (*l* 15, *d* 1.8 cm) using EtOAc–hexane (1:10) as eluent. Yield 0.99 g (18%), colorless crystals, mp 206-207°C (EtOAc–hexane, 1:3). IR spectrum, ν, cm^{-1}: 1733 (CO_2Me), 1688 (CO_2Me), 1573 (C=C). ^1H NMR spectrum, δ, ppm (*J*, Hz): 3.02 (3H, s, NCH_3); 3.58 (3H, s, CO_2CH_3); 3.89 (3H, s, CO_2CH_3); 3.99 (1H, d, *J* = 15.1) and 4.07 (1H, d, *J* = 15.1, CH_2N); 5.33 (1H, s, 9-CH); 6.36 (1H, t, *J* = 3.2, H-11); 6.59-6.60 (1H, m, H-3'); 6.64-6.65 (1H, m, H-10); 6.67-6.68 (1H, m, H-12); 6.82 (1H, dd, *J* = 3.7, *J* = 5.0, H-4'); 7.03 (1H, d, *J* = 5.0, H-5'); 7.36-7.43 (3H, m, H Ar); 7.53 (1H, d, *J* = 7.8, H Ar). Mass spectrum, *m*/*z* (I_{rel}, %): 422 $[M]^+$ (3), 363 (5), 331 (3), 260 (6), 154 (15), 59 (100). Found, %: C 65.32; H 5.29; N 6.65. $C_{23}H_{22}N_2O_4S$. Calculated, %: C 65.39; H 5.25; N 6.63.

Dimethyl 6,12-Dimethyl-9-phenyl-6,9-dihydro-5*H*-pyrrolo[1,2-*a*][1,6]benzodiazonine-7,8-dicarboxylate (19). DMAD (0.60 g, 4.2 mmol) was added to a solution of the pyrrolobenzodiazepine **8** (0.29 g, 1.0 mmol) in MeOH (20 ml) and refluxed for 14 h (TLC monitoring, eluent EtOAc–hexane, 1:7). Solvent was removed *in vacuo*, and the residue was chromatographed on a silica gel column (*l* 26 cm, *d* 1.8 cm) using EtOAc–hexane (1:8) as eluent. Yield 0.02 g (5%), colorless crystals, mp 230-232°C (Et_2O). IR spectrum, ν, cm^{-1}: 1736 (CO_2Me), 1688 (CO_2Me), 1573 (C=C). ^1H NMR spectrum, δ, ppm (*J*, Hz): 2.03 (3H, s, 12-CH_3); 2.96 (3H, s, NCH_3); 3.47 (3H, s, CO_2CH_3); 3.86 (3H, s, CO_2CH_3); 3.90 (1H, d, *J* = 15.0) and 3.94 (1H, d, *J* = 15.0, CH_2N); 5.08 (1H, s, 9-CH); 6.08 (1H, d, *J* = 3.1, H-10); 6.22 (1H, br. s, H-11); 7.08 (1H, t, *J* = 6.9, H-4); 7.13-7.20 (4H, m, H Ph); 7.25-7.26 (1H, m, H Ph); 7.36 (1H, t, *J* = 7.1, H-2); 7.38 (1H, t, *J* = 7.1, H-3); 7.52-7.55 (1H, m, H-1). Mass spectrum, *m*/*z* (I_{rel}, %): 430 $[M]^+$ (30), 371 (12), 168 (38), 154 (32), 59 (100). Found, %: C 72.48; H 6.11; N 6.55. $C_{26}H_{26}N_2O_4$. Calculated, %: C 72.54; H 6.09; N 6.51.

X-ray Structural Analysis of Compound 13. Crystals of compound **13** ($C_{23}H_{22}N_2O_2$, *M* 358.43) were grown from a mixture of EtOAc and hexane and are triclinic with space group *P*1. At 100 K: *a* 8.7269(4), *b* 9.1525(5), *c* 12.0253(6) Å, α 80.874(1), β 83.560(1), γ 75.925(1)°; *V* 917.15(8) $Å^3$; *Z* 2; d_{calc} 1.298 g/cm^3; *F*(000) 380; μ 0.083 mm^{-1}. Unit cell parameters and intensities of 12040 reflections (5329 independent with R_{int} 0.024) were measured on an automatic, three-circle diffractometer fitted with Bruker APEX-II CCD bicoordinate detector (λMoKα radiation, graphite monochromator, φ- and ω-scanning, θ_{max} 60º). To obtain the data, X-ray absorption was calculated using the SADABS program [6]. The structure was solved by the direct method and refined in F^2 full-matrix least squares analysis in the anisotropic approximation for non-hydrogen atoms. The hydrogen atoms were placed in the geometrically calculated positions and included in the refinement in the isotropic approximation with fixed positions ("rider" model) and thermal parameters (U_{iso}(H) = 1.2U_{eq}(C)). The final values of the probability factors were R_1 0.041 for 4329 independent reflections with $I > 2\sigma(I)$ and wR_2 0.107 for all independent reflections, *GOOF* 1.002. All calculations were performed using the SHELXTL program package [7]. Tables of atomic coordinates, bond lengths, valence angles, and anisotropic temperature parameters for compound **13** have been placed at the Cambridge Crystallographic Data Center (deposit CCDC 902180).

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