

Gregory L. Karrick and Norton P. Peet*

Merrell Dow Research Institute, Indianapolis Center, 9550 Zionsville Road,
Indianapolis, IN 46268
Received October 9, 1985

Recently reported [1] syntheses of 6-methyl-1,2,4,5-tetrahydro-1,4-dioxo-3*H*[1,2]diazepino[5,6-*b*]indole (**5**) and 4-hydroxy-6-methyl-3*H*[1,2]diazepino[5,6-*b*]indole (**12**) were reinvestigated and shown to be in error. The correct assignments for these respective structures are 3-amino-1,9-dihydro-9-methyl-2*H*-pyrido[4,3-*b*]indol-2,4(3*H*)-dione (**6**) and 3-amino-3,9-dihydro-9-methyl-2*H*-pyrido[4,3-*b*]indol-2-one (**13**). Condensation of **6** and **13** with *p*-nitrobenzaldehyde produced benzylidene derivatives, which confirmed the presence of the amino groups.

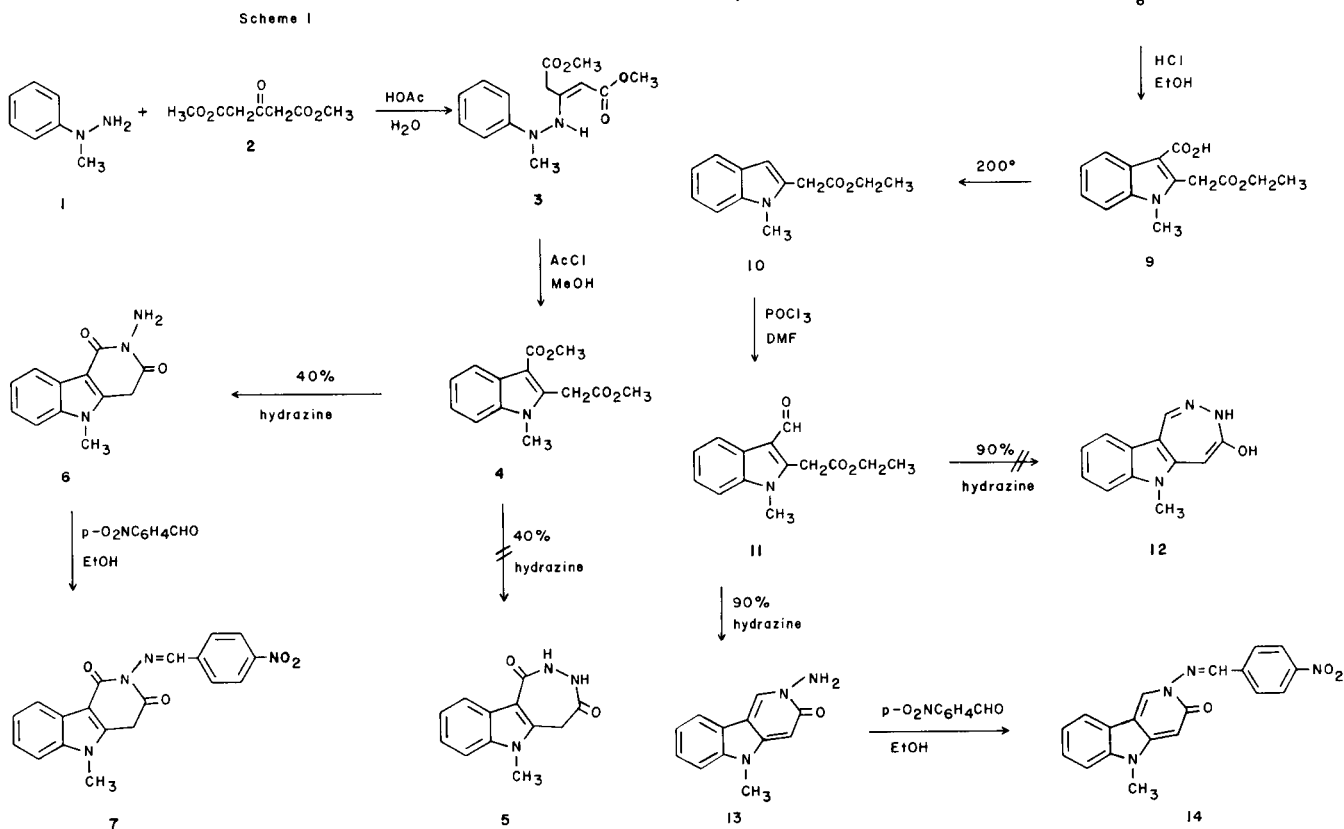
J. Heterocyclic Chem., **23**, 1055 (1986).

A recent paper by Monge, *et al.* [1] describes syntheses of diazepino[5,6-*b*]indoles **5** (Scheme 1) and **12** (Scheme 2). We have reinvestigated these syntheses and found the resulting structures to be incorrectly assigned. The respective compounds are, instead, pyrido[4,3-*b*]indoles **6** and **13**.

1-Methyl-1-phenylhydrazine (**1**) was condensed with dimethyl acetone-1,3-dicarboxylate (**2**) to yield enediester **3** as shown in Scheme I. Interestingly, this structure was earlier described by Bahadur, Bailey, Middleton and Peach [2] as the imino tautomer. Our ¹H nmr spectrum (deuteriochloroform) clearly showed that **3** was tautomeriz-

ed as shown: the allylic methylene group appeared at δ 3.20 and the vinyl hydrogen appeared at δ 4.63. The infrared spectrum of **3** showed one normal, saturated ester carbonyl band at 1730 cm⁻¹, and another carbonyl band at 1660 cm⁻¹, indicative of an α,β -unsaturated, hydrogen-bonded ester.

Compound **3** underwent the Fisher indole synthesis



when treated with methanolic hydrogen chloride, to provide **4**. Subsequent treatment of **4** with aqueous hydrazine, as described by Monge, *et al.* [1], did not give diazepinoindole **5**. Pyridoindole **6** was produced instead. The amino group in **6** appeared in the ^1H nmr spectrum (dimethylsulfoxide- d_6) as a broad signal at δ 5.5. Its presence was confirmed by treatment of **6** with *p*-nitrobenzaldehyde in ethanol to produce *p*-nitrobenzylidene derivative **7**.

The second part of our reinvestigation is shown in Scheme 2. Hydrolysis of diester **4** with sodium hydroxide gave 3-carboxy-1-methyl-1*H*-indole-2-acetic acid (**8**). Esterification of **8** under controlled conditions gave monoester **9**. The internal anhydride of **8** is probably first formed with ethanolic hydrogen chloride in this conversion. Regiospecific ring-opening of the anhydride with ethanol in the expected fashion would give **9**. Decarboxylation of **9** was readily accomplished by thermolysis at 200°. Vilsmeier formylation of **10** gave 3-formyl-1-methyl-1*H*-indole-2-acetic acid ethyl ester (**11**). Treatment of aldehyde-ester **11** with aqueous hydrazine, as described by Monge, *et al.* [1], did not give diazepinoindole **12**. The product of this reaction was, instead, pyridoindole **13**. The amino group in **13** appeared as a singlet at δ 6.2 in the ^1H nmr spectrum (dimethylsulfoxide- d_6). Again, the presence of the amino group in **13** was established chemically, by preparing *p*-nitrobenzylidene derivative **14** from **13** and *p*-nitrobenzaldehyde in ethanol.

In previous studies we have established that compounds purported to be benzotriazepinones were actually aminoquinazolinones, by preparing benzylidene derivatives [3,4]. In addition, we have recently prepared a benzylidene derivative of an *N*-aminopyridone, which was incorrectly assigned as a diazepinone [5].

EXPERIMENTAL

All melting points are uncorrected. The ir spectra were recorded with Perkin-Elmer Model 727B and Model 1310 spectrophotometers, nmr spectra with Varian EM-360A and Varian XL-300 (multinuclear probe) spectrometers, and mass spectra with a Finnigan gc/ms Model 4023 (electron impact and chemical ionization) mass spectrometer. Combustion analyses for C, H and N were performed by Merrell Dow Analytical Laboratories, Cincinnati, Ohio.

3-(2-Methyl-2-phenylhydrazino)-2-pentenedioic Acid Dimethyl Ester (**3**).

To a solution of 35.6 g (0.198 mole) of dimethyl 1,3-acetonedicarboxylate (Aldrich) in 160 ml of acetic acid was added 25.0 g (0.198 mole) of 1-methyl-1-phenylhydrazine (Aldrich). The mixture was heated to reflux, cooled and added to 480 ml of water. The resulting oil solidified on standing. The solid was collected, washed with water and recrystallized from methanol to give 38.4 g (70%) of **3**, mp 89-91° (lit [2] mp 93-94°); ir (Nujol): 3240 and 3190 (NH), 1730 (C=O), 1660 (C=O), 1600 (C=C) cm^{-1} ; nmr (deuteriochloroform): δ 9.51 (broad s, 1H, NH), 7.41-7.07 (m, 2H, aromatic), 7.04-6.71 (m, 3H, aromatic), 4.68 (s, 1H, CH), 3.69 (s, 3H, OCH₃), 3.54 (s, 3H, OCH₃), 3.22 (s, 2H, CH₂), 3.10 (s, 3H, NCH₃); ms: (70 eV, chemical ionization, methane) 279 ($M^+ + 1$), 307 ($M^+ + 29$), 319 ($M^+ + 41$).

3-Carboxy-1-methyl-1*H*-indole-2-acetic Acid Dimethyl Ester (**4**).

To 40 ml of cold methanol was added, dropwise, 9.38 g (0.119 mole) of acetyl chloride. The resulting solution was added to 20.0 g (76.0 mmoles) of **3** in 150 ml of methanol. The mixture was heated at reflux for 90 minutes, cooled and poured into 150 ml of water. The resulting precipitate was collected, washed with water and recrystallized from methanol-water to give 16.2 g (82%) of **4**, mp 97-98° (lit [2] mp 100-101°); ir (Nujol) 1730 (C=O), 1690 (C=O) cm^{-1} ; nmr (deuteriochloroform): δ 8.21-7.95 (m, 1H, H at 4-position), 7.35-7.09 (m, 3H, aromatic), 4.35 (s, 2H, CH₂), 3.95 (s, 3H, NCH₃), 3.75 (s, 3H, OCH₃), 3.72 (s, 3H, OCH₃); ms: (70 eV, chemical ionization, methane) 262 ($M^+ + 1$), 290 ($M^+ + 29$), 302 ($M^+ + 41$).

3-Amino-1,9-dihydro-9-methyl-2*H*-pyrido[4,3-*b*]indol-2,4(3*H*)-dione (**6**).

A solution of 2.10 g (8.04 mmoles) of **4** in 20 ml of 40% aqueous hydrazine was heated at reflux for 24 hours. The solution was concentrated to dryness, and the resulting solid was collected, washed with water and recrystallized from ethanol-water to give 400 mg (22%) of **6**, mp 235-238° (lit [1] mp 239-240°); ir (Nujol): 3320 and 3240 (NH₂), 1705 (C=O), 1650 (C=O) cm^{-1} ; nmr (dimethylsulfoxide- d_6): δ 7.98 (d, J = 6.95 Hz, 1H, H at 5-position), 7.60 (d, J = 7.69 Hz, 1H, H at 8-position), 7.31-7.26 (m, 2H, aromatic), 5.5 (broad s, 2H, NH₂), 4.36 (s, 2H, CH₂), 3.73 (s, 3H, NCH₃); ms: (70 eV, chemical ionization, methane) 230 ($M^+ + 1$), 258 ($M^+ + 29$), 270 ($M^+ + 41$).

Anal. Calcd. for C₁₂H₁₁N₃O₂: C, 62.87; H, 4.84; N, 18.33. Found: C, 62.48; H, 4.90; N, 18.49.

1,9-Dihydro-9-methyl-3(((4-nitrophenyl)methylene)amino)-2*H*-pyrido[4,3-*b*]indole-2,4(3*H*)-dione (**7**).

A solution of 300 mg (1.31 mmoles) of **6** and 200 mg (1.31 mmoles) of *p*-nitrobenzaldehyde (Aldrich) in 45 ml of ethanol was heated at reflux for 21 hours. The resulting precipitate was collected, washed with ethanol and recrystallized from 2-methoxyethanol to afford 200 mg (42%) of **7**, mp 242-244°; ir (Nujol): 1705 (C=O), 1675 (C=O), 1510, 1345, and 860 (NO₂) cm^{-1} ; nmr (dimethylsulfoxide- d_6): δ 8.86 (s, 1H, NCH), 8.41 (d, J = 8.8 Hz, 2H, aromatic), 8.20 (d, J = 8.8 Hz, 2H, aromatic), 7.99 (d, J = 6.4 Hz, 1H, H at 5-position), 7.66 (d, J = 8.3 Hz, 1H, H at 8-position), 7.35-7.29 (m, 2H, aromatic), 4.55 (s, 2H, CH₂), 3.80 (s, 3H, NCH₃); ms: (70 eV, electron impact) *m/e* 363 (molecular ion).

Anal. Calcd. for C₁₉H₁₄N₄O₄: C, 62.98; H, 3.89; N, 15.46. Found: C, 62.73; H, 4.01; N, 15.21.

3-Carboxy-1-methyl-1*H*-indole-2-acetic Acid (**8**).

A solution of 7.10 g (27.2 mmoles) of **4** in 100 ml of 1*N* sodium hydroxide was heated at reflux for 1 hour. The solution was diluted with an equal volume of water and acidified with concentrated hydrochloric acid. The resulting white precipitate was collected, washed with water and recrystallized from ethanol to give 5.77 g (91%) of **8**, mp 245-247° (lit [2] mp 261°); ir (Nujol): 3275-2200 (OH), 1700 (C=O), 1650 (C=O) cm^{-1} ; nmr (dimethylsulfoxide- d_6): δ 12.0 (very broad s, 2H, OH), 8.15-7.88 (m, 1H, H at 4-position), 7.59-7.00 (m, 3H, aromatic), 4.39 (s, 2H, CH₂), 3.74 (s, 3H, NCH₃); ms: (70 eV, electron impact) *m/e* 233 (molecular ion).

3-Carboxy-1-methyl-1*H*-indole-2-acetic Acid Ethyl Ester (**9**).

A solution of 9.05 g (38.8 mmoles) of **8** in 190 ml of 0.4% ethanolic hydrogen chloride was heated at reflux for 20 minutes. The white crystals which formed on cooling were collected and oven-dried to afford 6.36 g (63%) of **9**, mp 194-195° (lit [1] mp 202-203°); nmr (deuteriochloroform): δ 8.32-8.07 (m, 1H, H at 4-position), 7.40-7.10 (m, 3H, aromatic), 4.40 (s, 2H, CH₂), 4.18 (q, J = 7 Hz, 2H, OCH₂), 3.72 (s, 3H, NCH₃), 1.30 (t, J = 7 Hz, 3H, CH₃); ms: (70 eV, electron impact) *m/e* 261 (molecular ion).

1-Methyl-1*H*-indole-2-acetic Acid Ethyl Ester (**10**).

A 14.1-g (54.0 mmoles) quantity of **9** was heated under nitrogen at 200° until gas evolution ceased. The residue was purified by Kugelrohr distillation [bp ca. 130° (0.500 mm Hg)]. The distilled oil crystallized on standing to give 11.4 g (97%) of **10**, mp 45.5-47° (lit [1] mp 46-48°); nmr

(deuteriochloroform): δ 7.59-7.33 (m, 1H, H at 4-position), 7.22-6.87 (m, 3H, aromatic), 6.30 (s, 1H, vinyl), 4.07 (q, J = 7 Hz, 2H, OCH₂), 3.68 (s, 2H, CH₂), 3.50 (s, 3H, NCH₃), 1.17 (t, J = 7 Hz, 3H, CH₃); ms: (70 eV, electron impact) m/e 217 (molecular ion).

3-Formyl-1-methyl-1*H*-indole-2-acetic Acid Ethyl Ester (**11**).

To a 100-ml three-necked round bottom flask fitted with a mechanical stirrer, a dropping funnel, and a drying tube was added 9 ml of dimethylformamide. The flask was cooled in an ice bath and 1.36 g (8.87 mmoles) of phosphorus oxychloride (MCB) was slowly added. The cooling bath was removed and the mixture was stirred for 30 minutes at room temperature. The mixture was cooled with an ice bath and a solution of 1.30 g (5.98 mmoles) of **10** in 8 ml of dimethylformamide was added so that the temperature of the reaction mixture was maintained in the range of 8-10°. The mixture was then warmed for 2 hours at 39° in an oil bath. The resulting yellow-red solution was poured over 30 g of crushed ice and neutralized to pH 8 by careful addition of 9*N* sodium hydroxide. The solution was heated to reflux and cooled in a refrigerator. The resulting crystals were collected, washed with water and recrystallized from ethanol to give 930 mg (63%) of **11**, mp 110-112° (lit [1] mp 111-112°); ir (Nujol): 1730 (C=O), 1660 (C=O) cm⁻¹; nmr (dimethylsulfoxide-*d*₆): δ 10.07 (s, 1H, CHO), 8.21-7.94 (m, 1H, H at 4-position), 7.65-7.04 (m, 3H, aromatic), 4.41 (s, 2H, CH₂), 4.11 (q, J = 7 Hz, 2H, OCH₂), 3.74 (s, 3H, NCH₃), 1.19 (t, J = 7 Hz, 3H, CH₃); ms: (70 eV, chemical ionization, methane) 246 (M⁺ + 1), 274 (M⁺ + 29), 286 (M⁺ + 41).

3-Amino-3,9-dihydro-9-methyl-2*H*-pyrido[4,3-*b*]indol-2-one (**13**).

To a solution of 4.50 g (18.3 mmoles) of **11** in 200 ml of ethanol was added 66 ml of 90% aqueous hydrazine. The volume was reduced to 80 ml by boiling the solution for 1 hour, and the cream-colored crystals which formed were collected, washed with water and oven-dried to give 2.56 g (66%) of **13**, mp 163-165° (lit [1] mp 167-168°); ir (Nujol): 3275 and 3185 (NH₂), 1670 (C=O), 1620 (C=C) cm⁻¹; nmr (dimethylsulfoxide-*d*₆): δ 8.72

(s, 1H, H at 1-position), 7.90 (dd, J = 6 Hz and 2 Hz, 1H, H at 5-position), 7.41-6.94 (m, 3H, aromatic), 6.20 [s, 3H, NH₂ (deuterium-oxide exchangeable) and H at 4-position], 3.55 (s, 3H, NCH₃); ms: (70 eV, chemical ionization, methane) 214 (M⁺ + 1), 242 (M⁺ + 29), 254 (M⁺ + 41).

Anal. Calcd. for C₁₂H₁₁N₃O: C, 67.59; H, 5.20; N, 19.71. Found: C, 67.20; H, 5.20; N, 19.78.

3,9-Dihydro-9-methyl-3-[[[(4-nitrophenyl)methylene]amino]-2*H*-pyrido[4,3-*b*]indol-2-one (**14**).

A solution of 300 mg (1.41 mmoles) of **13** and 220 mg (1.44 mmoles) of *p*-nitrobenzaldehyde (Aldrich) in 45 ml of ethanol was heated at reflux for 20 hours. The resulting precipitate was collected, washed with ethanol and recrystallized from 2-methoxyethanol to afford 340 mg (70%) of **14**, mp 244-246°; ir (Nujol): 1690 (C=O), 1630 (C=N), 1520, 1345, and 840 (NO₂) cm⁻¹; nmr (deuteriochloroform): δ 8.34 (s, 1H, H at 1-position), 8.32 (d, J = 8.8 Hz, 2H, aromatic), 8.04 (d, J = 8.8 Hz, 2H, aromatic), 7.75 (d, J = 7.8 Hz, 1H, H at 5-position), 7.46-7.40 (m, 1H, H at 8-position), 7.27 (s, 1H, N=CH), 7.23-7.17 (m, 2H, aromatic), 6.17 (s, 1H, H at 4-position), 3.57 (s, 3H, NCH₃); ms: (70 eV, electron impact) m/e 346 (molecular ion).

Anal. Calcd. for C₁₉H₁₄N₄O₃: C, 65.89; H, 4.07; N, 16.18. Found: C, 65.55; H, 4.07; N, 16.14.

REFERENCES

- [1] A. Monge, J. A. Palop, T. Goni, A. Martinez and E. Fernandez-Alvarez, *J. Heterocyclic Chem.*, **21**, 381 (1984).
- [2] G. A. Bahadur, A. S. Bailey, N. W. Middleton and J. M. Peach, *J. Chem. Soc., Perkin Trans. I*, 1688 (1980).
- [3] N. P. Peet and S. Sunder, *J. Org. Chem.*, **40**, 1909 (1975).
- [4] N. P. Peet, S. Sunder and D. L. Trepanier, *Indian J. Chem.*, **14B**, 701 (1976).
- [5] N. P. Peet and S. Sunder, *Heterocycles*, **24**, 393 (1986).