Studies on the Synthesis of Heterocyclic Compounds. III. Preparation of Some Pyrazolo[3,4-*c*][1,5]benzodiazocin-10(11*H*)one Derivatives.

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Starting from the readly available *N*-methyl-*N*-(1-phenyl-3-R-pyrazol-5-yl)-2-nitrobenzamides (**1a,b**), the pyrazoles, 4-acetyl substituted **2a,b**, were prepared in high yield. Reduction of **2a** gave the amino derivative **4a**, which was cyclized to the desired pyrazolo[3,4-*c*][1,5]benzodiazocin-10(11*H*)one (**5a**). Compound **2b** afforded 5b directly. Compound **5b** was also prepared by the action of phosphorus oxychloride on *N*-methyl-*N*-(1,3-diphenylpyrazol-5-yl)-2-acetamidobenzamide (**6b**).

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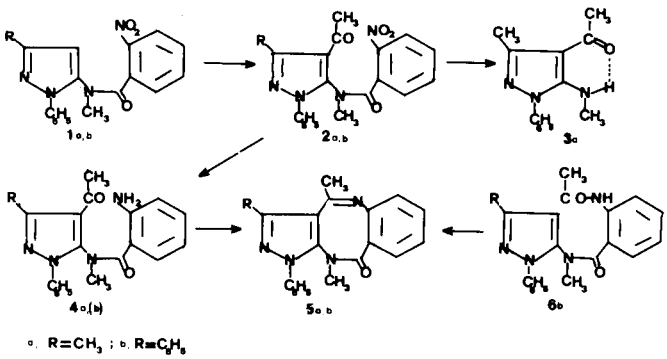
The main part of our research has been devoted to synthetic methods leading to new ring systems containing the pyrazole moiety as a carrier system for potential drugs. The discovery of the marked antidepressant property of some compounds derived from the diazocine ring fused to the pyrazole nucleus (1) and the easy availability in our hands of *N*-methyl-*N*-(1-phenyl-3-*R*-pyrazol-5-yl)-2-nitrobenzamides **1a,b**, prompted us to develop a synthetic route to certain compounds derived from the benzodiazocine ring fused to the pyrazole nucleus, namely, pyrazolo[3,4-*c*][1,5]benzodiazocin-10(11*H*)ones, in order to investigate their therapeutic utility.

Previously, in the course of synthetic work in this laboratory, we undertook the synthesis of the title compounds starting from *N*-methyl-*N*-(1-phenyl-3-methylpyrazol-5-yl)-2-acetamidobenzamide, which has been reported to be formed from the acetylation (2) of *N*-methyl-*N*-(1-phenyl-3-methylpyrazol-5-yl)-2-aminobenzamide (3). However, when this compound was subjected to the action of phosphorus oxychloride under Bischler-Napieralski reaction conditions, an unexpected macroheterocycle was obtained (2).



a, R=CH_3 ; b, R=C_6H_5

Because this procedure was unsuccessful in producing the desired pyrazolobenzodiazocines **5**, an alternative synthetic route was sought. Therefore, the present paper describes the synthesis of the novel pyrazolo[3,4-*c*][1,5]benzodiazocin-10(11*H*)ones, starting from the readily obtainable *N*-methyl-*N*-(1-phenyl-3-R-pyrazol-5yl)-2-nitrobenzamides (**1a,b**) (3). The reaction sequence involved is outlined in the Scheme. Compounds **1a,b** were first converted to the 4-acetylsubstituted pyrazoles **2a,b** *via* acetylation with acetic anhydride; **2a**, in turn, was reduced in the presence of palladium on charcoal to form the amino derivative **4a** in 85% yield. Compound **4a** was cyclized in refluxing benzene with azeotropic removal of water to give **5a**. Further, compound **2b** on reduction spontaneously cyclized to **5b**.

The structural assignment of all the new compounds was made on the basis of correct elemental analysis and spectroscopic data (nmr, *ir*). Further, a chemical structural proof for compound **2a** was accomplished (Scheme). Thus, *N*-methyl-*N*-(1-phenyl-3-methyl-4-acetylpyrazol-5-yl)-2-nitrobenzamide (**2a**), by the action of alkali, afforded 4-acetyl-1-phenyl-3-methyl-5-methylaminopyrazole **3a**, as shown by comparison with an authentic sample (2).

In the last phase of this work, an attempt was made to cyclize *N*-methyl-*N*-(1,3-diphenylpyrazol-5-yl)-2-acetamidobenzamide (**6b**) to give 1,3-diphenyl-4,11-dimethylpyrazolo[3,4-*c*][1,5]benzodiazocin-10(11*H*)one (**5b**). The inability of **6b** to tautomerize in a similar manner as the 3-methylsubstituted derivatives, causing an anomalous cyclization reaction (2), prompted us to ascertain whether the phenyl group at position 3 of the pyrazole nucleus of *N*-(1,3-diphenylpyrazol-5-yl)-2-acetamidobenzamide (**6b**) affects the course of the Bischler-Napieralski reaction. Refluxing **6b** in phosphorus oxychloride for 1 hour left the desired pyrazolobenzodiazocine **5b** in 50-55% yield. This compound was identical in all respects to a sample of 1,3-diphenyl-4,11-dimethylpyrazolo[3,4-*c*][1,5]benzodiazocin-10(11*H*)one.

The tricyclic ring system compounds **5** were identified by the usual analytical and spectroscopic data (nmr, ir), and by the molecular weight determined by mass

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spectroscopy (Experimental).

EXPERIMENTAL

Melting points were determined on Buchi-Tottoli apparatus and are uncorrected. Ir spectra were determined in nujol mulls with a Perkin-Elmer Infrared 299 spectrophotometer. A Joel-JMS-01-SG-2 mass spectrometer was employed for determination of low resolution 75 eV mass spectra. Nmr spectra (deuterochloroform) were obtained with a Varian 60 MHz spectrometer (TMS as internal reference).

General Procedure for the Preparation of *N*-methyl-*N*-(1-phenyl-3-*R*-4-acetylpyrazol-5-yl)-2-nitrobenzamides (**2a,b**).

A mixture of compounds **1a,b** (3) (6 mmoles), acetic anhydride (12 ml.) and one drop of sulphuric acid was refluxed for 3 hours and then evaporated to dryness under reduced pressure. The viscous oil which remained was washed with ice-water (3 x 100 ml.). It solidified on standing as a pink mass, which was filtered and recrystallized from ethanol, yield 70-75%.

Compound **2a**.

This compound had m.p. 130-132°; ir: 1660-1680 cm^{-1} (CO); nmr: δ 2.46 (3H, s, CH_3), 2.48 (3H, s, CH_3), 2.82 (3H, s, CH_3), 7.28-8.20 (9H, m, C_6H_5 and C_6H_4) (4); ms: M^+ 378 (20), 379 (6, M^+ +1), 363 (4), 317 (4), 303 (4), 302 (5), 301 (19), 290 (15), 289 (34), 243 (10), 230 (4), 229 (25), 228 (100), 227 (11), 226 (10), 214 (5), 213 (7), 212 (10), 186 (34), 185 (6), 184 (7), 151 (5), 150 (49), 122 (18), 106 (20), 105 (6), 104 (25), 93 (4), 92 (16), 91 (23), 81 (18), 80 (95), 79 (11), 78 (32), 77 (63), 76 (66), 53 (8), 52 (15), 51 (64), 50 (23), 44 (38).

Anal. Calcd. for $C_{20}H_{18}N_4O_4$: C, 63.48; H, 4.80; N, 14.81. Found: C, 63.57; H, 4.91; N, 14.77.

Compound **2b**.

This compound had m.p. 170-172°; ir: 1670-1690 cm^{-1} (CO); nmr: δ 2.20 (3H, s, CH_3), 2.86 (3H, s, CH_3), 7.30-8.30 (14H, m, 2 x C_6H_5 and C_6H_4) (4); ms: M^+ 440 (10), 441 (M^+ +1, 10), 363 (4), 352 (4), 351 (6), 305 (7), 291 (20), 290 (90), 276 (5), 275 (5), 248 (10), 220 (5), 151 (6), 150 (62), 145 (4), 144 (4), 143 (15), 142 (99), 129 (12), 128 (8), 127 (30), 118 (7), 116 (6), 115 (13), 106 (9), 105 (8), 104 (28), 103 (5), 102 (15), 92 (10), 91 (18), 90 (4), 89 (7), 78 (37), 77 (80), 76 (85), 75 (15), 74 (8), 65 (10), 64 (11), 63 (11), 52 (20), 51 (100), 50 (40), 43 (45), 39 (14), 30 (27).

Anal. Calcd. for $C_{25}H_{20}N_4O_4$: C, 68.17; H, 4.58; N, 12.72. Found: C, 68.20; H, 4.70; N, 12.65.

N-Methyl-*N*-(1-phenyl-3-methyl-4-acetylpyrazol-5-yl)-2-aminobenzamide (**4a**).

Compound **2a** (3 mmoles) was dissolved in ethanol (200 ml.) and hydrogenated in a Parr apparatus at 45-50 psi in the presence of 10% palladium on charcoal (500 mg.). The oil remaining **4a**, after filtering the catalyst and evaporating the solvent, was characterized as the hydrochloride derivative, m.p. 210-214° (ethanol-ether); ir: 1650 (CO), 1680 (CO), 1920, 1980 and 2250 cm^{-1} (broad) (ammonium); ms: m^+ 348 (molecular weight of the free base).

N-Methyl-*N*-(3,1-diphenylpyrazol-5-yl)-2-acetamidobenzamide (**6b**).

A mixture of *N*-methyl-*N*-(1,3-diphenylpyrazol-5-yl)-2-aminobenzamide (3) (6 g.) and acetic anhydride (30 ml.) was stirred at room temperature for 8 hours. The precipitate was collected and recrystallized from ethanol (yield 75%), m.p. 171-173°; ir: 3290 (NH), 1650 (CO), 1700 cm^{-1} (CO); nmr (deuterochloroform): δ 1.90 (3H, s, CH_3), 3.50 (3H, s, CH_3), 6.62 (1H, s, pyrazole CH), 6.70-8.30 (14H, m, 2 x C_6H_5 and C_6H_4), 8.90 (1H, broad, NH, exchangeable).

Anal. Calcd. for $C_{25}H_{22}N_4O_2$: C, 73.15; H, 5.40; N, 13.65. Found: C, 73.18; H, 5.36; N, 13.66.

1-Phenyl-3,4,11-trimethylpyrazolo[3,4-*c*][1,5]benzodiazocin-10-(11*H*)one (**5a**).

Crude **4a** (1 g.) in 150 ml. of anhydrous benzene and traces of *p*-toluensulfonic acid was heated under reflux with stirring for 24-26 hours using a Dean-Stark trap. After cooling, the solution was evaporated to dryness under reduced pressure. The residue was tritured with a few ml. of ethanol and then, on standing, a crystalline product was separeted and recrystallized from ethanol, yield 30-32%, m.p. 198-200°; ir: 1670 cm^{-1} (CO); nmr: δ 2.26 (3H, s, CH_3), 2.54 (3H, s, CH_3), 2.86 (3H, s, CH_3), 6.80-7.64 (9H, m, C_6H_5 and C_6H_4); ms: M^+ 330 (32), 331 (7, M^+ +1), 329 (12), 302 (4), 287 (4), 273 (9), 247 (5), 197 (8), 156 (4), 155 (7), 154 (6), 140 (5), 128 (7), 120 (16), 118 (7), 117 (12), 116 (7), 115 (12), 114 (5), 105 (4), 104 (5), 103 (7), 102 (6), 93 (4), 92 (12), 91 (23), 90 (8), 89 (9), 80 (24), 79 (7), 77 (100), 76 (26), 66 (5), 65 (16), 64 (13), 63 (8), 57 (4), 56 (100), 51 (28), 50 (10), 42 (11), 39 (21).

Anal. Calcd. for $C_{20}H_{18}N_4O$: C, 72.70; H, 5.49; N, 16.96. Found: C, 72.68; H, 5.44; N, 16.92.

1,3-Diphenyl-4,11-dimethylpyrazolo[3,4-*c*][1,5]benzodiazocin-10-(11*H*)one (**5b**).

By Reductive Heterocyclization of **4b**.

Compound **5b** was directly obtained by hydrogenation of **4b** by the same procedure used for **4a**. The solid which separated was recrystallized from ethanol yield 55-60% m.p. 258-260°; ir: 1670 cm^{-1} (CO); nmr: δ 2.40 (3H, s, CH_3), 3.00 (3H, s, CH_3), 6.80-7.64 (14H, m, 2 x C_6H_5 and C_6H_4); ms: M^+ 392 (60), 393 (17, M^+ +1), 391 (22), 364 (8), 350 (4), 349 (11), 335 (4), 320 (4), 309 (6), 259 (4), 196 (6), 176 (4), 175.5 (9), 115.5 (5), 105 (3), 91 (15), 77 (15), 76 (5), 56 (100).

Anal. Calcd. for $C_{25}H_{20}N_4O$: C, 76.51; H, 5.14; N, 14.28. Found: C, 76.64; H, 5.27; N, 14.21.

By Action of Phosphorus Oxychloride on **6b**.

A mixture of **6b** (7 mmoles) and phosphorus oxychloride (25 ml.) was refluxed for 1 hour. Excess phosphorus oxychloride was evaporated under reduced pressure and the reaction mixture was poured into crushed ice mixed with solid sodium bicarbonate and extracted with chloroform (3 x 50 ml.). The organic layers were washed with water, dried (sodium sulfate) and concentrated under reduced pressure to dryness to give a residue which, crystallized from ethanol, gave the product **5b** (yield 45%), m.p. 258-260° (ethanol), which was identical in all respects with a sample of 1,3-diphenyl-4,11-dimethylpyrazolo[3,4-*c*][1,5]benzodiazocin-10(11*H*)one prepared by the above mentioned method.

4-Acetyl-1-phenyl-3-methyl-5-methylaminopyrazole (**3a**).

Compound **2a** (2 mmoles) was dissolved in ethanol (6 ml.) and 4 ml. of aqueous 5*N* potassium hydroxide were added. The mixture was refluxed for 5 hours and then diluted with water. The solid which precipitated was filtered and extracted several times with boiling petroleum ether (b.p. 40-60°). The combined ether extracts were evaporated to a small volume, when a crystalline material, **3a**, separated, m.p. 113-115° (petroleum ether). The product was identified by comparison with an authentic sample (2) (R_f, m.p. and mixed m.p., ms and ir).

REFERENCES AND NOTES

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(3) S. Plescia, G. Daidone, V. Sprio, E. Aiello, G. Dattolo and G. Cirrincione, *ibid.*, 15, 1339 (1978).

(4) In addition to the reported signals, there appeared two sharp signals in the range of δ 2.2-2.8 of very low intensity, which could be attributed to the presence of different isomers as a consequence of the partial double bond character of the amide group.