Studies on the Synthesis of Heterocyclic Compounds. Part VIII. A Facile Synthesis of New Pyrazolo[3,4-*b*]benzazepine-4,9-diones

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2-Carbomethoxybenzoyl chloride reacted with some 5-methylamino-1-phenyl-3-*R*-pyrazoles to yield *N*-methyl-1-phenyl-3-*R*-pyrazol-5-yl)-2-carbomethoxybenzamides. These products were readily transformed into the corresponding acid, which in turn, refluxed in phosphorus oxychloride afforded the tricyclic system, 1-phenyl-3-*R*-pyrazolo[3,4-*b*]benzazepine-4,9-dione.

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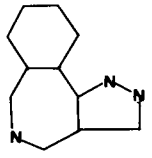
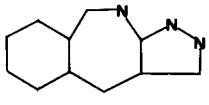
The 3(5)-aminopyrazole derivatives are useful starting materials for synthesis of various pyrazoloazines from sequential condensation and ring closure reactions involving exocyclic and endocyclic nitrogen atoms or the electron rich 4-carbon, as reported in previous papers, from our laboratories (1-3).

An examination of the current literature shows that industrial laboratories are reporting a number of pyrazolo[4,3-*c*]benzazepines of type I prepared as antidepressant and anxiolytics (4-6). Moreover, the only



I



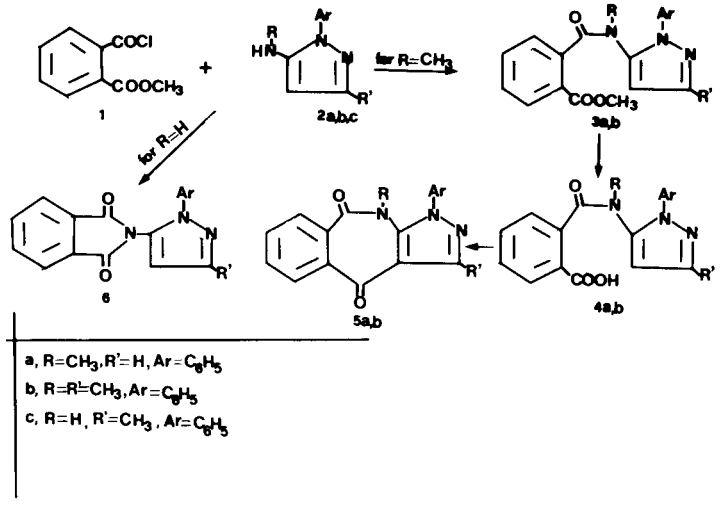
II

reported synthesis (7) of a pyrazolo[3,4-*b*]benzazepine derivative of type II used 5-amino-4-phthalidylpyrazole followed by catalytic hydrogenation and successive heterocyclization of the amino acid.

In view of current interest in the biological activities shown by this tricyclic ring system, we now seek to use the 5-methylaminopyrazoles **2a,b** as precursors of the new pyrazolo[3,4-*b*]benzazepine-4,9-diones **5a,b** (8). In the present work the new synthesis of this heterocyclic ring system was achieved by the reaction sequence outlined in the scheme. Thus, action of 2-carbomethoxybenzoyl chloride (**1**) on 5-methylaminopyrazoles **2a,b** in chloroform in the presence of triethylamine gave the expected condensation products **3a,b**, valuable intermediates toward the synthesis of tricyclic system **5**. The ester moiety in **3** was readily hydrolyzed to yield the acid **4**, which in turn, when refluxed in phosphorus oxychloride formed the new pyrazolo[3,4-*b*]benzazepine derivative **5**. Elemental analysis, molecular weight, ir and nmr spectra were in agreement with the assigned structures (see Experimental). Moreover, it was apparent that the amino group of the 5-aminopyrazoles would have to be monoblocked (*e.g.* R = CH_3) to realize fruitful results. In fact, treatment of 5-amino-1-phenyl-3-methylpyrazole (**2c**) with 2-carbomethoxybenzoyl chloride (**1**) produced the phthalimidopyrazole **6**, as was indicated by its spectral and analytical data.

EXPERIMENTAL

Melting points were determined on Buchi-Tottoli apparatus and are uncorrected. Ir spectra were determined in nujol mulls with a Perkin-Elmer 299 spectrophotometer. A Jeol-JMS-Ol-SG-2 mass spectrometer was employed for determination of low resolution 75eV mass spectra.



Nmr spectra were determined with a Varian EM-360 60MHz spectrometer (TMS as internal reference).

N-Methyl-(1-phenyl-3-*R*-pyrazol-5-yl)-2-carbomethoxybenzamides (**3a,b**).

To a refluxed solution of 5-methylamino-1-phenyl-3-*R*-pyrazole **2a** (9), **b** (2) (10 mmoles) and 2-carbomethoxybenzoyl chloride **1** (10) (20 mmoles) in 150 ml of dry chloroform was added triethylamine (3 ml) in three portions, each 1 ml, over a period of 3 hours. The solution was evaporated under reduced pressure, the residue was mixed with water (150 ml) and extracted with diethyl ether (3 × 50 ml). The organic layer was shaken with a 20% aqueous sodium hydroxide (2 × 50 ml), then washed with water (100 ml) and dried over anhydrous sodium sulfate. After removal of the ether the resulting residue was recrystallized from ethanol (yield 75%).

Compound **3a**.

The product melted at 114-116°; ir: cm^{-1} 1720 (CO) 1670 (CO); nmr (deuterochloroform): δ 3.50 (s, 3H, CH_3) 3.90 (s, 3H, CH_3) 6.20-8.00 (m, 11H, C_6H_5, C_6H_4, pyrazole H_3 and H_4) (12).

Anal. Calcd. for $C_{19}H_{17}N_3O_3$: C, 68.05; H, 5.11; N, 12.53. Found: C, 67.95; H, 5.12; N, 12.63.

Compound **3b**.

The product melted at 138-141°; ir: cm^{-1} 1720 (CO) 1670 (CO); nmr (deuterochloroform): δ 2.15 (s, 3H, CH_3) 3.50 (s, 3H, CH_3) 3.90 (s, 3H, CH_3) 6.00-8.10 (m, 10H, C_6H_5, C_6H_4 and pyrazole H) (12).

Anal. Calcd. for $C_{20}H_{19}N_3O_3$: C, 68.75; H, 5.48; N, 12.03. Found: C, 68.81; H, 5.37; N, 12.12.

N-Methyl-(1-phenyl-3-*R*-pyrazol-5-yl)-2-carboxybenzamides (**4a,b**).

To a solution of the ester **3** (1 g) in ethanol (10 ml), a solution of 4% aqueous hydroxide (30 ml) was added. The mixture was refluxed until solution and then allowed to stand for 12 hours. The alcohol was removed *in vacuo* and the residual solution was washed with ether, treated with hydrochloric acid until *p*H 5. The precipitate was filtered off and crystallized from ethanol (yield 85%).

Compound **4a**.

The product melted at 190-193°; ir (hexachlorobutadiene): 3200-2500 cm^{-1} (broads bands, OH) 1720 (CO) 1660 (CO); nmr (DMSO-d_6): δ 2.90 (s, 3H, CH_3) 6.30-8.30 (m, 11H, C_6H_5, C_6H_4, pyrazole H_3 and H_4) 8.50 (broad, 1H, OH, exchangeable) (12).

Anal. Calcd. for $C_{18}H_{15}N_3O_3$: C, 67.28; H, 4.71; N, 13.08. Found: C, 67.14; H, 4.71; N, 13.19.

Compound **4b**.

The product melted at 172-174°; ir (hexachlorobutadiene): 3100-2300 cm^{-1} (broad bands, OH) 1710 (CO) 1670 (CO); nmr (DMSO-d_6, determined at 80 MHz): δ 2.10 (s, 3H, CH_3) 3.30 (s, 3H, CH_3) 6.30-7.80 (m, 10H, C_6H_5, C_6H_4 and pyrazole H) 13.26 (broad, 1H, OH exchangeable) (12).

Anal. Calcd. for $C_{19}H_{17}N_3O_3$: C, 68.05; H, 5.11; N, 12.53. Found: C, 68.14; H, 5.08; N, 12.49.

Pyrazolo[3,4-*b*]benzazepine-4,9-diones (**5a,b**).

Compound **5a**.

A mixture of **4a** (3 g), phosphorus oxychloride (40 ml) and 0.3 ml of water was refluxed for 5 hours. Excess phophorus oxychloride was evaporated under reduced pressure and the reaction mixture was poured into crushed ice and adjusted to *p*H 8 with sodium bicarbonate. The mixture was extracted with chloroform (3 × 50 ml), the combined extracts were washed with water, dried (sodium sulfate) and the chloroform was evaporated. The residue (3.1 g) was then chromatographed on a column of silica gel with 15% of water (440 g), using diethyl ether as the eluent. The initial eluate F_{1-37} (each 20 ml) was neglected. The combined fractions 38-52 (each 20 ml) were evaporated and the product was recrystallized from ethanol (yield 25%), mp 144-146°; ir: cm^{-1} 1660-1620 (CO); nmr (deuterochloroform): δ 3.18 (s, 3H, CH_3) 7.35-8.50 (m, 10H, C_6H_5, C_6H_4 and pyrazole H); ms: m/e 303 (M^+).

Anal. Calcd. for $C_{18}H_{13}N_3O_2$: C, 71.27; H, 4.32; N, 13.86. Found: C, 71.35; H, 4.32; N, 13.83.

Compound **5b**.

A mixture of **4b** (6 g), phosphorus oxychloride (60 ml) and 0.5 ml of water was refluxed for 5 hours. Excess phophorus oxychloride was evaporated under reduced pressure and the reaction mixture poured into crushed ice was adjusted to *p*H 8 with sodium bicarbonate and extracted with chloroform (3 × 50 ml). The organic layers were washed with water, dried (sodium sulfate) and concentrated under reduced pressure to dryness to give a residue (5.1 g) which was then chromatographed on a column of silica gel with 15% of water (440 g), using diethyl ether as eluent. The initial eluate F_{1-32} (each 20 ml) was neglected. The combined fractions 33-52 (each 20 ml) were evaporated and the residue was recrystallized from ethanol (yield 28%); mp 168-170°; ir: cm^{-1} 1660 (CO) 1630 (CO); nmr (DMSO-d_6): δ 2.35 (s, 3H, CH_3) 3.00 (s, 3H, CH_3) 7.40-8.40 (m, 9H, C_6H_5 and C_6H_4); ms: m/e 317 (M^+).

Anal. Calcd. for $C_{19}H_{15}N_3O_2$: C, 71.91; H, 4.76; N, 13.24. Found: C, 72.01; H, 4.84; N, 13.23.

Phthalimidopyrazole **6**.

To a refluxed solution of equimolar amounts (10 mmoles) of 5-amino-1-phenyl-3-methylpyrazole (**2c**) (11) and 2-carbomethoxybenzoyl chloride (**1**) (10) in 100 ml of dry chloroform was added triethylamine in five portions, each 0.7, 0.35, 0.18, 2 × 0.9 ml, respectively, over a period of 3 hours. The solution was evaporated and the residue was mixed with water (150 ml) and extracted with ether (3 × 50 ml). The organic layers were shaken with aqueous saturated sodium bicarbonate, dried (sodium sulfate) and then were evaporated to give a residue, which recrystallized from ethanol (yield 50%), mp 124-126°; ir cm^{-1}: 1790 and 1730 (CO); nmr (deuterochloroform): δ 2.40 (s, 3H, CH_3) 6.40 (s, 1H, pyrazole H) 7.30-8.20 (m, 9H, C_6H_5 and C_6H_4).

Anal. Calcd. for $C_{18}H_{13}N_3O_2$: C, 71.27; H, 4.32; N, 13.86. Found: C, 71.47; H, 4.44; N, 13.93.

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(12) In addition to the reported signals, there appeared signals in the range of 2-3 δ of 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.