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Studies on 2,3-Dioxopyrrolidines. Synthesis of Piperazine, Pyrrolo[4,5-*b*]indole, Pyrazino[5,6-*b*]indole and Arylazo Derivatives of Amino Acids

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2,3-Dioxopyrrolidines **1** convert into 2,4-diketopiperazines **2** in one pot-reaction with hydrazoic acid. The pyrrolo[4,5-*b*]indole **6** was obtained by cyclization of p-methoxyphenylhydrazone **4** prepared *via* Japp-Klingemann reaction of **1a** with p-methoxyphenyldiazonium chloride. Compound **5** undergoes Schmidt reaction to give the pyrazino[5,6-*b*]indole derivative **6**. Reaction of **1b** with some aryldiazonium chlorides yields arylhydrazono-β-alanines **8** and **9**. Phenylhydrazonoglycine derivative **11** was synthesized *via* Schmidt reaction to **10** with hydrazoic acid.

Key words: piperazine, pyrroloindoles, pyrazinoindoles, Schmidt reaction, Japp-Klingemann reaction

Substituted 2,3-dioxopyrrolidines are reported as inhibitors of blood platelet aggregation [1] and aldose reductase [2]. Condensed heterocycles, having fused 2,3-dioxopyrrole nucleus, have attracted little attention, but some interest has come from physiologically active, *Amaryllidacease* [3] and *Erythrina* [4,5] alkaloids bearing this ring system. A part of our studies [6–10] has focused on exploring the synthetic potentialities of 2,3-dioxopyrrolidine derivatives as key intermediates for the synthesis of some new heterocycles containing fused pyrrole nucleus. The present work reports a novel synthesis of heterocycles and amino acid derivatives starting from 1-aryl-4-carbomethoxy-2,3-dioxopyrrolidines (**1**).

RESULTS AND DISCUSSION

Schmidt reaction cyclic ketones affords lactams [11]. This method was used for synthesis of piperidones and homopiperidones [12]. In the present work, the heterocyclic ketones **1** were subjected to Schmidt reaction by treatment with NaN_3 in the presence of 90% H_2SO_4. The 2,3-piperazindione derivatives **(2)** were identified as the reaction products, according to the study reported by Schmidt *et al*. [13]. The reaction proceeds *via* insertion of the nitrene between the carbonyl group at C-3 and

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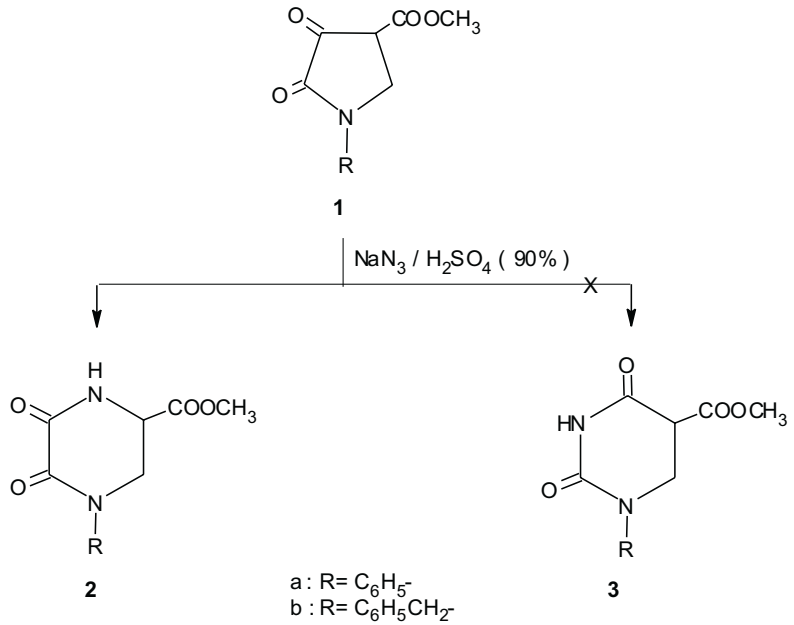
the substituted C-4 of the compound **1**. The ^{1}H NMR spectrum revealed a signal of the proton at nitrogen at δ = 7.10 ppm confirming the structure **2** and ruling out the pyrimidine derivatives **(3)** as products.

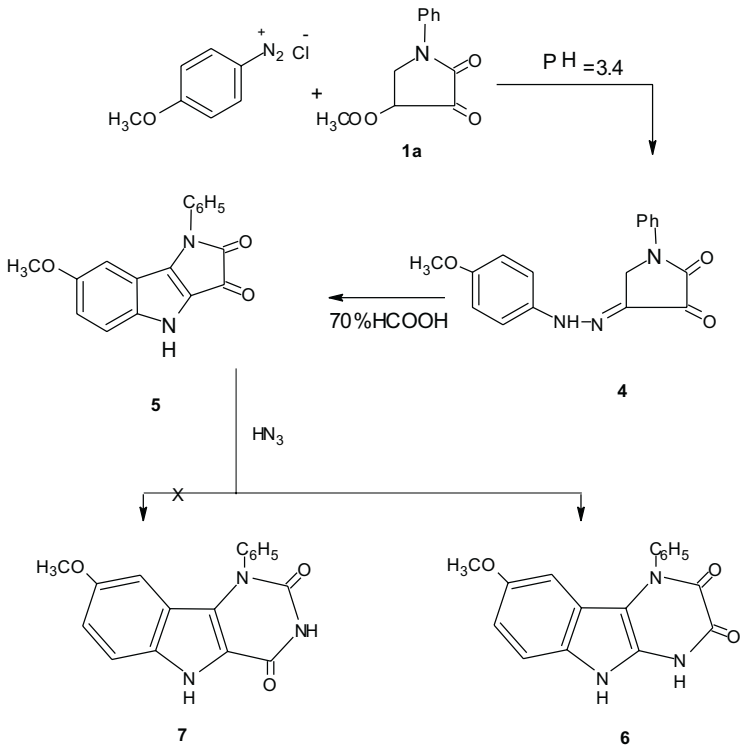


The skeleton of *Physostiga Venesosum* and *Calyeanthaceous* alkaloids [14] contains the pyrrolo[2,3-*b*] indole ring system. The β-ketoester **1a** could be used as a precursor of new 3H-pyrrolo[4,5-*b*]indole derivative **(5)** by the Fischer indole synthesis [15]. The key step is the preparation of p-methoxyphenylhydrazone **(4)** by a Japp-Klingemann reaction of p-methoxyphenyl diazonium chloride with **1a** at pH = 3.4. Then the hydrazone **4** was cyclized by heating under reflux in 70% formic acid. The absence of the signal of the pyrrole CH_2-5 protons and the appearance, that of indolic NH in the NMR spectrum gave a confirmation to structure of **5**.

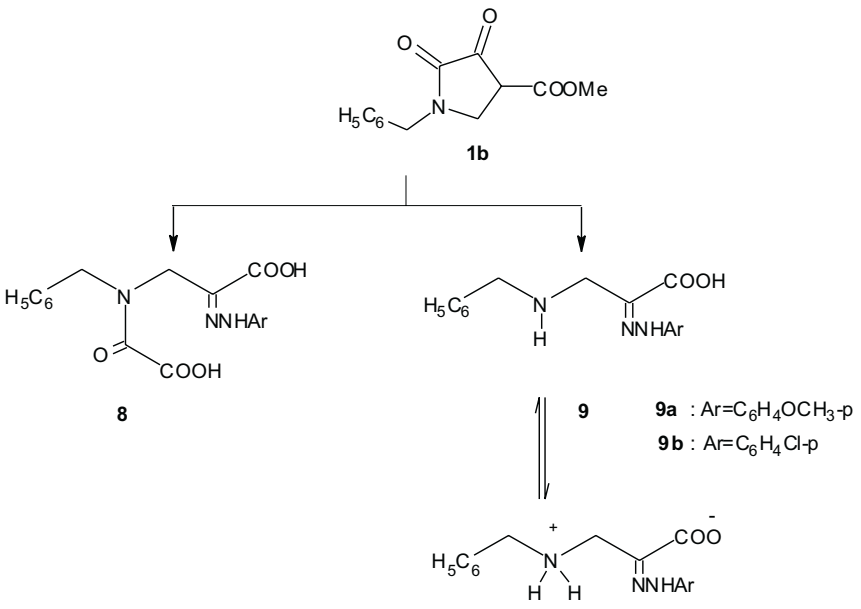
In the reaction of cyclic ketones **5** with hydrazoic acid two isomeric structures **6** and **7** could be proposed for the reaction product. For the formed product we assigned the structure of pyrazino[5,6-*b*]indole **6**.

It is known, that Japp-Klingemann reaction of cyclic β-ketoesters, *e.g.* 2-ethoxy-carbonyl-cyclopentanone results in openning of the ring and the formation of arylazo derivatives of adipic acid [16]. Thus, the Japp-Klingemann reaction of 1-aryl-4-methoxycarbonyl-2,3-dioxopyrrolidines **(1)** with aryldiazonium chlorides in 2.5% aqueous NaOH was expected to produce the α-arylazo-β-alanine **9** and **10**. The structures of **9** and **10** were proved by analytical and spectral data. The NMR spectrum showed the signals of the protons of the two carboxylic group of **9** at δ = 10.22 and 12.51, where the disappearance of the signals of protons of NH and COOH group of **10** due to its presence as zwitterion.

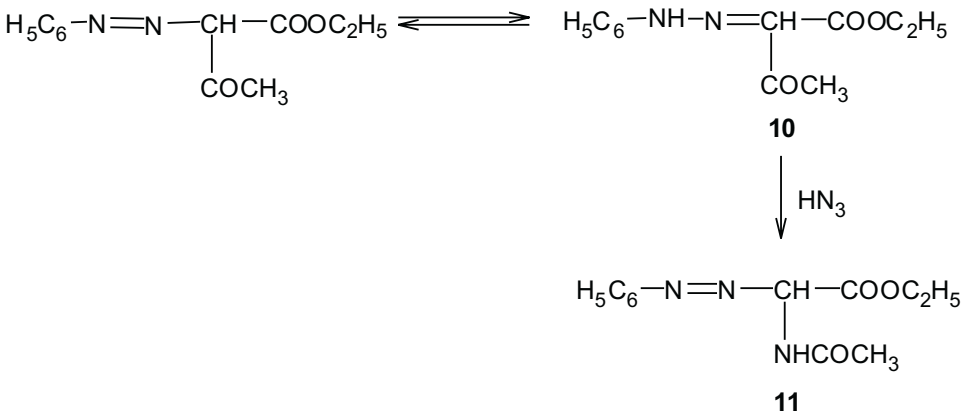
Scheme 1



Scheme 2



The ethyl α-phenylhydrazonoacetoacetate (**10**) subjected to the Schmidt reaction with hydrazoic acid at 0–5°C in chloroform led to the product **11**. Its IR spectrum revealed the bands at 3450, 3210 and 1650 cm^{-1} corresponding to the two NH groups and the amide CO respectively, and ^1H NMR spectrum indicated the singlet of the amide NH group at 8.75 and the azo group at 14.9.



EXPERIMENTAL

^1H NMR spectra were recorded on a Bruker AC-250 (MHz) FT NMR in DMSO as a solvent with TMS as an internal standard. Melting points were measured in an open pyrex capillaries instrument and are uncorrected. IR (cm^{-1}) spectra were obtained on a Pye Unicam sp-883 Perkin-Elmer spectrophotometer in KBr, as a film in liquids.

1-Phenyl (or benzyl)-5-carbomethoxypiperazine-2,3-dione (2a,b). A solution of **1** (0.01 mol) in 30 ml chloroform was added to sulphuric acid (90%, 10 ml) at 0°C with stirring, followed by addition of 0.65 g (0.01 mol) of sodium azide. After stirring for 1 hr at 0°C, the reaction mixture was stirred at room temperature for 4 h, then diluted with ice-water, basified with ammonium hydroxide and extracted with chloroform. The chloroform solution was dried on anhydrous sodium sulphate and evaporated to give an oil. Treating with ethyl acetate gave colourless crystals.

1-Phenyl-5-methoxycarbonylpiperazine-2,3-dione (2a) was obtained as colourless crystals, yield 75%; m.p. 184°C; υ_{max}: 3300 (NH), 1730 (CO-ester), 1685 (NCO) and 1675 (-NHCO). ^1H NMR δ_H: 3.72 (d, 2H, CH_2), 3.91 (s, 3H, CH_3), 4.40 (m, 1H, CH), 7.00–7.51 (m, 6H, NH+aromatic). Anal. for $C_{12}H_{12}N_2O_4$ (248.24); Calcd. C, 58.06; H, 4.87. Found, C, 58.05; H, 4.87%.

1-Benzyl-5-methoxycarbonylpiperazine-2,3-dione (2b) was obtained as colourless crystals; yield 70%; m.p. 198°C (decomp.); υ_{max}: 3310 (NH), 1730, 1680 (CO groups). ^1H NMR δ_H: 3.60 (d, 2H, CH_2), 3.91 (s, 3H, CH_3), 4.35 (m, 1H, CH_2), 4.42 (s, 2H, CH_2), 7.10 (s, 1H, NH), 7.39–7.76 (m, 5H, aromatic). Anal. for $C_{13}H_{14}N_2O_4$ (262.26); Calcd. C, 59.53; H, 5.38. Found, C, 59.51; H, 5.38.

1-Phenyl-2,3-dioxopyrrolidine-4-(p-methoxyphenyl)hydrazone (4). p-Methoxyphenyldiazonium chloride (0.01 mol) was added to compound **1a** (0.01 mol) in 50 ml of acetic acid – sodium acetate buffer solution (pH = 3.4) at 0–5°C. The product that precipitated after standing for 24 h at 10°C was filtered and recrystallized from ethanol to afford yellow crystals; m.p. 220°C; yield 78%; υ_{max}: 3300 (NH), 1710 (CO five-membered), 1680 (CO pyrrole) and 1600 (C=N). ^1H NMR δ_H: 3.64 (s, 3H, CH_3), 4.41 (s, 2H, CH_2), 7.35–7.9 (m, 9H, aromatic); 10.91 (s, 1H, NH). Anal. for $C_{17}H_{15}N_3O_3$ (309.31); Calcd. C, 66.01; H 4.89. Found, C, 66.00; H, 4.89.

7-Methoxy-1-phenyl-3H-dioxopyrrolo[4,5-*b*]indole-2,3-dione (5). Compound **5** (0.01 mol) in formic acid (50 ml, 70%) was heated under reflux for 5 h and then left to stand overnight at room temperature. After pouring into ice-water, the precipitated solid was filtered and crystallized from ethanol to form red crystals; yield 80%; m.p 227°C; υ_{max}: 3400 (NH), 1700 (CO five membered), 1670 (CO amide), and 1600 (C=C). ^{1}H NMR δ_H: 3.72 (s, 3H, CH_3), 7.43–7.89 (m, 9H, aromatic+NH). Anal. for $C_{17}H_{12}N_2O_3$ (292.29); Calcd. C, 69.85; H, 4.14. Found, C, 69.82; H, 4.12.

1,2,3,4-Tetrahydro-7-methoxy-1-phenyl-5H-pyrazino[5,6-*b*]indole-2,3-dione (6). Compound **6** (0.01 mol) in chloroform 30 ml and sulphuric acid (90%, 10 ml) was treated with sodium azide (0.01 mol) at 0–7°C, following the same procedure described for the preparation of **2**. Compound **7** formed as red crystals from ethanol; yield 65%; m.p. 263°C; υ_{max}: 3420 (amidic NH and indolic NH), 1700 (-CONPh) and 1670 (-CONH). ^{1}H NMR δ_H: 3.75 (s, 3H, CH_3), 7.21 (s, 1H, NH), 7.40–7.81 (m, 8H, aromatic), 8.29 (s, 1H, NH). Anal. for $C_{17}H_{13}N_3O_3$ (307.29); Calcd. C, 66.44; H, 4.26; Found, C, 66.41; H, 4.25.

α-Arylhydrazono-N-benzyl-β-alanine (8, 9a,b). To 0.01 mol of **1**b, aqueous sodium hydroxide (50 ml, 2.5%) was added, left to stand at 0–5°C for 24 h. The mixture was diluted with 50 ml of water and p-methoxyphenyl diazonium chloride (0.01 mol) was added. The pH of the medium was adjusted at 7–8 by adding 2 g of sodium bicarbonate. The solid product that separated after standing overnight at 0–5°C was filtered and recrystallized from ethanol to give the reaction product.

3-(N-Benzyl-N-oxalo)amino-2-phenylhydrazonopropionic acid (8) was obtained as yellow crystals; yield 60%; m.p. 166°C; υ_{max}: 3450 (NH), 1730 (CO), 1715 (CO), 1615 (C=N). ^{1}H-NMR δ_H: 3.91 (s, 2H, CH_2), 4.26 (s, 2H, CH_2), 7.54–7.89 (m, 5H, aromatic), 10.22 (s, 1H, COOH), 12.51 (s, 1H, COOH), 14.11 (s, 1H, NH). Anal. for $C_{18}H_{17}N_3O_5$ (355.34). Calcd. C, 60.84; H, 4.82. Found, C, 61.20; H, 5.10.

3-(N-Benzylamino)-2-(4-methoxyphenyl)hydrazonopropionic acid (9a) was obtained as brownish-red crystals; yield 45%; m.p. 151°C; υ_{max}: 3400 (NH), 3250 (NH), 1700 (CO acid), 1605 (N=C). ^{1}H NMR δ_H: 3.21 (s, 2H, CH_2), 3.61 (s, 3H, CH_3), 4.1 (s, 2H, CH_2), 7.49–7.81 (m, 9H, aromatic), 12.3 (s, 1H, NH). Anal. for $C_{17}H_{19}N_3O_3$ (313.34); Calcd. C, 65.16; H, 6.11. Found, C, 65.11; H, 6.01

3-(N-Benzylamino)-2-(4-chlorophenyl)hydrazonopropionic acid 9b was obtained as yellow crystals; yield 50%; m.p. 157°C; υ_{max}: 3400 (NH), 3250 (NH), 1700 (CO acid), 1605 (N=C). ^{1}H NMR δ_H: 3.21 (s, 2H, CH_2), 4.1 (s, 2H, CH_2), 7.49–7.81 (m, 9H, aromatic), 12.3 (s, 1H, NH). Anal. for $C_{16}H_{16}N_3O_2Cl$ (317.5); Calcd. C, 60.47; H, 5.08. Found, C, 60.45; H, 5.45.

Ethyl N-acetylaminooxoacetate phenylhydrazone (11). Compound **10** (0.01 mol) in 30 ml chloroform was added to sulphuric acid (90% , 10 ml) at 0°C with stirring, followed by addition of 0.65 g (0.01 mol) of sodium azide. Following the same procedure described for the preparation of **2**, compound **11** was obtained as yellow crystals; yield 71%; m.p. 162°C; υ_{max}: 3450 (NH), 3200 (NH), 1710 (CO, ester), 1655 (CO amide), 1605 (C=N). ^{1}H NMR δ_H: 1.30 (t, 3H, CH_3), 2.81 (s, 3H, CH_3), 3.25 (s, 1H, CH), 4.22 (q, 2H, CH_2), 7.40 (m, 5H, , aromatic), 8.75 (s, 1H, NH), 14.19 (s, 1H, NH). Anal. for $C_{12}H_{15}N_3O_3$ (249.26); Calcd. C, 57.83; H, 6.07. Found, C, 57.58; H, 6.00.

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