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Synthesis of Some New Pyrimido[5,4-*a*]Indolizines[a]

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Summary. The synthesis of new pyrimido[5,4-*a*]indolizines by reaction of 2-aminoindolizine-1-carbonitrile or ethyl 2-aminoindolizine-1-carboxylate with various electrophilic reagents is described. The structure of the products was confirmed by their elemental analysis and IR, ^{1}H NMR, and mass spectra. The results of a preliminary antimicrobial screening are also presented.

Keywords. 2-Aminoindolizine; Cyclization; Heterocycles; Pyrimido[5,4-*a*]indolizine.

Introduction

Indolizine (pyrrolo[1,2-*a*]pyridine) is an important ring system in view of its similarity to indole; it is found in many natural products, mainly in its hydrogenated state. Like indole, it has a 10π-electron system, which confers aromaticity, in contrast to its pyrrolizine and quinolizine analogs. Consequently, there is both theoretical and practical interest in this heterocyclic system. Most of the work on indolizines has been focused to the search for drugs [1].

Due to the pharmacological, biological, physiological, and medicinal significance of substituted and fused pyrimidines [2], it was of interest to synthesize compounds containing a pyrimidine ring fused with the indolizine system. However, to the best of my knowledge and rather surprisingly, pyrimido[5,4-*a*]indolizines have not been described. Thus, the present work describes, in view of the promising biological properties of their indole analogs, the synthesis of new pyrimido[5,4-*a*]indolizine derivatives from the corresponding 2-aminoindolizines.

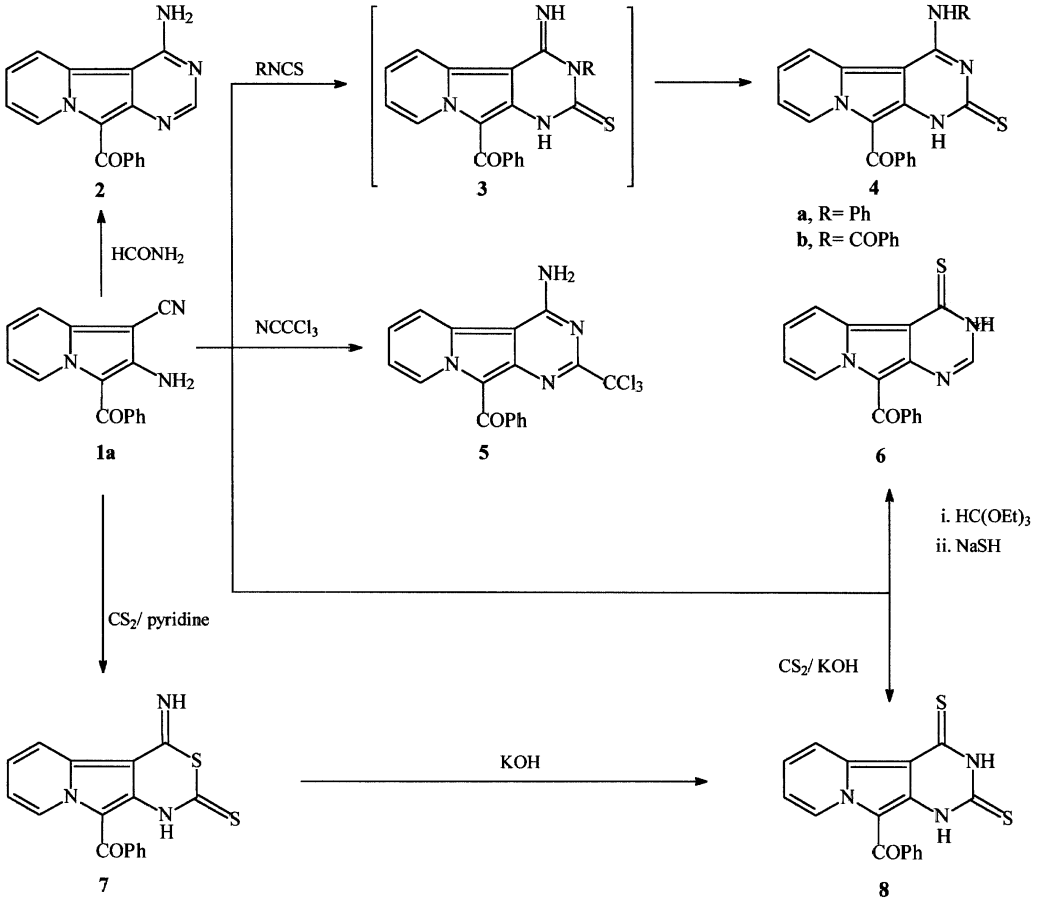
Results and Discussion

A cyano or ester group located in *ortho* position relative to an amino group is considered as a versatile site for the preparation of various polycyclic systems. The present work describes the utilization of 2-aminoindolizine-1-carbonitrile (**1a**) or ethyl 2-aminoindolizine-1-carboxylate (**1b**) in the synthesis of various fused pyrimido[5,4-*a*]indolizines.

[a] Dedicated to the memory of Prof. Dr. *Abd El-Hamid Attia*

The starting materials, 2-amino-3-benzoylindolizine-1-carbonitrile (**1a**) and ethyl 2-amino-3-benzoylindolizine-1-carboxylate (**1b**), were obtained by reaction of 2-bromo-1-phenacylpyridinium salt with malononitrile or ethyl cyanoacetate under the influence of the *Hünig* base, followed by cyclization [3]. Compounds **1a** and **1b** were then subjected to reactions with electrophilic reagents affording the various pyrimido[5,4-*a*]indolizines **2–14** (Schemes 1 and 2). The reaction of **1a** or **1b** with formamide in the presence of acetic anhydride under reflux afforded the fused 4-aminopyrimidine **2** or the fused pyrimidin-4(3*H*)-one **9**, respectively. Their ^{1}H NMR spectra showed the CH-pyrimidine signal at 6.71 ppm for **2** and at 6.83 ppm for **9**. The IR spectrum of **2** showed the absence of a CN group band present in the spectrum of **1a**; the presence of the amino group was indicated by bands at 3412 and 3323 cm^{-1}.

Isothiocyanates reacted with **1a** in refluxing *DMF*, affording the fused 4-aminopyrimidine-2(1*H*)-thione derivative **4a** and **4b**. With **1b**, the fused 3-phenyl-2-(1*H*) thioxopyrimidine-4(3*H*)-one derivative **10** was obtained. The formation of substituted 4-aminopyrimido[5,4-*a*]indolizines **4** presumably involved the intermediate **3**, an isomerization commonly referred to as the *Dimroth* rearrangement



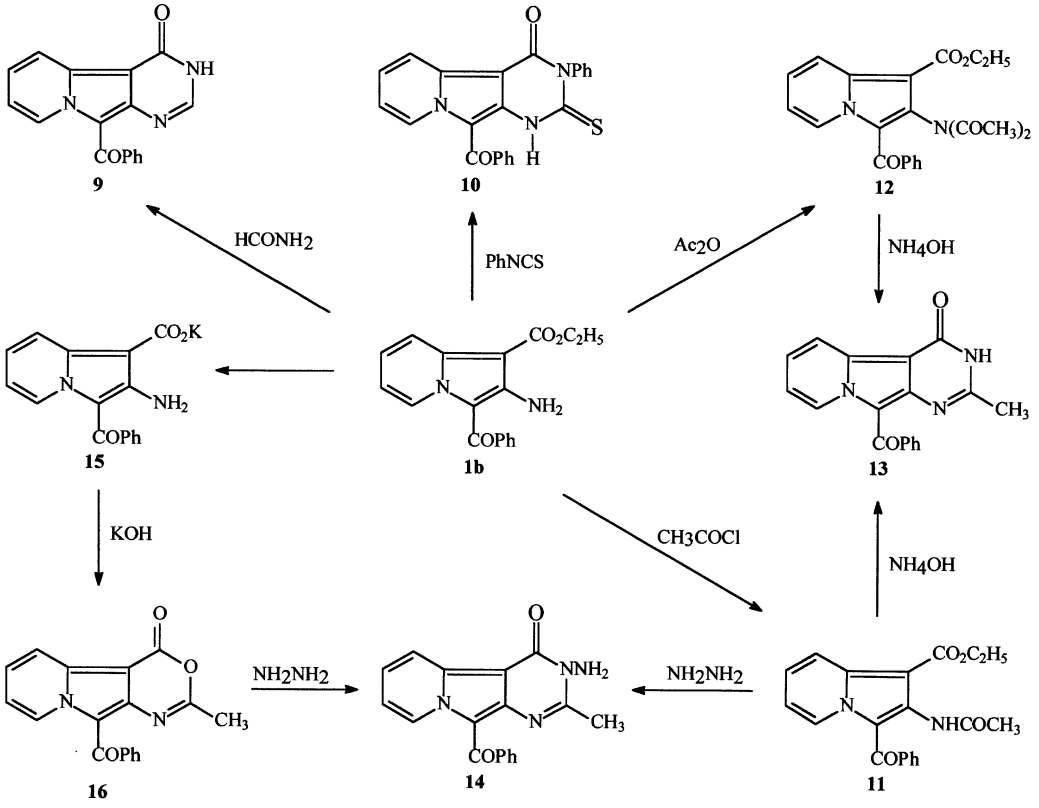
Scheme 1

[4]. Analytical data and spectroscopic properties were found to be in good agreement with the assigned structures **4** and **10**.

Compound **1a** reacted with trichloroacetonitrile in the presence of triethylamine to afford the amine **5**. Its IR spectrum revealed the absence of a band at 2220 cm^{-1} corresponding to the cyano group, and its mass spectrum showed an M^+-peak at $m/z = 404$ corresponding to the molecular formula $C_{18}H_{11}Cl_3N_4O$. In a one-pot reaction, **1a** was converted to the fused pyrimidine-4(3*H*)-thione derivative **6** when subjected to the action of ethyl orthoformate in the presence of acetic anhydride followed by treatment with an ethanolic solution of sodium hydrogen sulfide [5].

The products obtained from the reaction of **1a** with carbon disulfide varied according to the reaction medium. In pyridine, the 6-imino-1,3-thiazine-2(1*H*)-thione **7** was formed, whereas in the presence of aqueous potassium hydroxide the pyrimidinedithione **8** was obtained. Under the action of aqueous potassium hydroxide, compound **7** rearranged to **8** *via* a 1,3-thiazine-pyrimidine rearrangement in accordance with previous findings [4]. These results indicated that the formation of **8** proceeded *via* the 1,3- thiazine **7**, which irreversibly isomerized to the corresponding dithione under the reaction conditions.

The amino group of **1b** was acetylated with acetyl chloride to give the monoacetyl compound **11**, which was further treated with ammonia or with



Scheme 2

hydrazine hydrate affording the fused pyrimidinone **13** or 3-aminopyrimidinone **14**, respectively. Product **13** was also obtained by treatment of the diacetyl derivative **12** obtained by hydrolysis of **1b** in acetic anhydride with ammonium hydroxide. On the other hand, heating of **1b** in alcoholic potassium hydroxide solution gave **15**, which upon refluxing in acetic anhydride afforded the expected 1,3-oxazinone **16**. The latter product was further treated with hydrazine hydrate to give **14**.

All new compounds were preliminarily tested for their antimicrobial activity against microorganisms representing fungi (*Aspergillus niger*) and becteria (*Pseudomonas aeruginosa, Bacillus subtilis*, and *Staphylococcus aureus*). Compound **13** inhibitied *B. subtilis* (equal to oxytetracycline), whereas compounds **1b**, **2**, and **4a** showed an observable activity against *S. aureus* (higher than the standard). The tested compounds, however showed no inhibitory activity against *A. niger* and *P. aeruginosoa*.

Exprimental

All melting points were taken on a Büchi-510 melting point apparatus and are uncorrected. Microanalyses were performed at the Microanalysis Unit, Cairo University; their results were in good agreement with the calculated values. The IR spectra were recrded on a Unicam sp-1000 pu spectrophotometer. The ^{1}H NMR spectra were recorded on an EM-390 Varian spectrometer, and MS were measured at 70 eV with a NG 2AB-3F mass spectrometer. Reactions monitoring and purity control of the synthesized compounds were performed by TLC (silica gel, aluminum sheets $60F_{254}$, Merck).

Antimicrobial testing

Antimicrobial screening was performed using the bioassay technique of antibiotics specified in the U.S. Pharmacopoeia at 50γ/cm^3. Antibiotic medium No. 2 was used as the base agar in the plate assay using bacterial cultures. *Czapeck* agar medium was used with fungal cultures. Filter paper disks (5 mm in diameter) were saturated with solutions of the compounds to be tested and applied to agar plates seeded with the appropriate organism. After incubation for 24 h at 37°C, the diameters of the zones of inhibition were measured. Oxytetracycline was used as a standard.

4-Amino-10-benzoylpyrimido [5,4-a]indolizine (**2**; $C_{17}H_{12}N_4O$)

A solution of 783 mg (3 mmol) **1a** in 5 cm^3 formamide and 3 drops of acetic anhydride was heated at 150°C for 10 h. The solvent was distilled off in vacuum, and the oily residue was triturated with H_2O to give a dark brown solid which was collected by filtration to give 540 mg (63%) **2**.

M.p.: 237–240°C (aq. dioxane); IR (KBr): $\nu = 3412$, 3323 (NH_2), 1635 (CO) cm^{-1}; ^{1}H NMR (*DMSO*-d_6, δ, 90 MHz): 5.75 (s, NH_2, exchangeable with D_2O), 6.71 (s, 1H pyrimidine), 7.1 (dd, H_7), 7.55 (s, C_6H_5) 7.6 (dd, H_6), 8.1 (d, H_5), 9.45 (d, H_8); MS: *m/z* (%) = 288 (M^+, 100).

4-Anilino-10-benzoylpyrimido[5,4-a]indolizine-2(1H)-thione (**4a**; $C_{23}H_{16}N_4OS$)

To a solution of 780 mg; (3 mmol) **1a** in 10 cm^3 *DMF* containing 0.5 cm^3 triethylamine, 405 mg (3 mmol) phenyl isothiocyanate were added, and the reaction mixture was refluxed for 5 h. Excess solvent was distilled off in vacuum, the oily residue was triturated with H_2O and then hot EtOH, and the precipitate was collected by filtration to give 650 mg (55%) **4a**.

M.p.: 293–295°C (aq. dioxane); IR (KBr): $\nu = 3300$ (NH), 1635 (CO) cm^{-1}; ^1H NMR (*DMSO*-d_6, δ, 90 MHz):7.1 (dd, H_7) 7.45–7.6 (m, $2C_6H_5+H_6+NH$, exchangeable with D_2O), 8.15 (d, H_5) 9.4 (d, H_8), 10.5 (br s, NH, exchangeable with D_2O); MS: *m/z*(%) = 396 (M^+, 100).

4-Benzamido-10-benzoylpyrimido[5,4-a]indolizine-2(1H)-thione (**4b**; $C_{24}H_{16}N_4O_2S$)

4b was prepared as **4a** using 498 mg (3 mmol) benzoyl isothiocyanate.

Yield 890 mg (70%); m.p.: 305–307°C (dioxane); IR (KBr): $\nu = 3375$(NH), 1673, 1665 (CO) cm^{-1}; ^1H NMR (*DMSO*-d_6, δ, 90 MHz): 6.95 (dd, H_7), 7.35–7.85 (m, $2C_6H_5+H_6+NH$, exchangeable with D_2O), 8.25 (d, H_5), 9.35 (d, H_8), 10.5 (s, NH, exchangeable with D_2O); MS: *m/z* (%) = 424 (M^+, 0.66), 105 (100).

4-Amino-10-benzoyl-2-(trichloromethyl)-pyrimido[5,4-a]indolizine (**5**; $C_{18}H_{11}Cl_3N_4O$)

To a solution of 783 mg (3 mmol) **1a** and 0.5 cm^3 triethylamine in 25 cm^3 dioxane, 440 mg (3 mmol) trichloroacetonitrile were added, and the reaction mixture was refluxed for 10 h. Excess solvent was distilled off, and the oily residue was triturated with *THF* to give 450 mg (37%) **5**.

M.p.: 197–199°C (dioxane/petroleum ether 60–80°C); IR (KBr): $\nu = 3345$, 3320 (NH_2), 1665 (CO) cm^{-1}; ^1H NMR (*DMSO*-d_6, δ, 90 MHz): 5.45 (s, NH_2, exchangeable with D_2O), 6.97 (t, H_7), 7.5 (dd, H_6), 7.57 (s, C_6H_5), 7.98 (d, H_5), 9.26 (d, H_8); MS: *m/z* (%) = 404 (M^+, 18).

10-Benzoylpyrimido[5,4-a]indolizine-4(3H)-thione (**6**; $C_{17}H_{11}N_3OS$)

A solution of 783 mg (3 mmol) **1a** in a mixture of 10 cm^3 ethyl orthoformate and 3 cm^3 acetic anhydride was refluxed for 3 h. Excess solvent was distilled off in vacuum; the oily residue was dissolved in 20 cm^3 1 *M* ethanolic NaSH solution, refluxed for 8 h, and left overnight. The reaction mixture was concentrated to half of its volume, treated with cold H_2O, and acidified with acetic acid (*pH* = 3). The separated greenish solid was collected by filtration to give 775 mg (85%) **6**.

M.p.: 290–293°C (*DMF*/H_2O); IR (KBr): $\nu = 3470$ (NH), 1645 (CO) cm^{-1}; ^1H NMR (*DMSO*-d_6, δ, 90 MHz): 6.71 (s, 1H pyrimidine), 7 (dd, H_7), 7.56 (s, C_6H_5), 7.6 (dd, H_6), 8.1 (d, H_5), 9.43 (d, H_8), 12.3 (br s, NH, exchangeable with D_2O); MS: *m/z* (%) = 305 (M^+, 42%).

10-Benzoyl-4-imino[1,3]thiazino[5,4-a]indolizine-2(1H)-thione (**7**; $C_{17}H_{11}N_3OS_2$)

A solution of 1.3 g (5 mmol) **1a** in 5 cm^3 dry pyridine and 10 cm^3 carbon disulfide was refluxed on a water bath at 80°C for 10 h and then left overnight. Excess solvent was distilled off under reduced pressure, the residue was triturated with H_2O and then with EtOH, and the separated solid was filtered off to give 1.1 g (65%) **7**.

M.p.: 313–316°C (*DMF*/H_2O); IR KBr): $\nu = 3435$ (NH), 3345 (NH), 1645 (CO) cm^{-1}; ^1H NMR (*DMSO*-d_6, δ, 90 MHz): 7.1 (dd, H_7), 7.51–7.7 (shouldered s, C_6H_5+NH), 7.75 (t, H_6), 7.8 (s, NH), 8.15 (d, H_5), 9.25 (d, H_8), precipitation on addition of D_2O; MS: *m/z* %) = 337 (M^+, 1%).

10-Benzoylpyrimido[5,4-a]indolizine-2,4(1H,3H)-dithione (**8**; $C_{17}H_{11}N_3OS_2$)

Method A: To a solution of 783 mg (3 mmol) **1a** in 10 cm^3 10% alcoholic potassium hydroxide, 10 cm^3 carbon disulfide was added. The reaction mixture was refluxed for 3 h, cooled, poured onto water, and neutralized with 1 *M* HCl. The solid was filtered off, washed washed with water, and dried to afford 0.48 g (50%) **8**.

M.p.: 315–317°C; IR (KBr): $\nu = 3365$ (NH), 1647 (CO) cm^{-1}; ^1H NMR (*DMSO*-d_6, δ, 90 MHz): 7.1 (dd, H_7), 7.3 (s, 2NH, exchangeable with D_2O), 7.55 (s, C_6H_5), 7.75 (t, H_6), 8.6 (d, H_5), 9.35 (d, H_8); MS: *m/z* (%) = 337 (M^+, 12%).

Method B: A solution of 0.32 g (1 mmol) **7** in 5 cm^3 10% alcoholic potassium hydroxide was refluxed for 1 h. The reaction mixture was cooled, poured into H_2O, and neutralized with 1 *M* HCl to give product **8** as identified by its melting point, mixed melting point, and chromatographic behavior in comparison with an authentic sample from method A.

10-Benzoylpyrimido[5,4-a]indolizine-4(3H)-one (**9**; $C_{17}H_{11}N_3O_2$)

A mixture of 626 mg (2 mmol) **1b** suspended in 10 cm^3 formamide and 3 drops acetic anhydride was heated at 150°C for 6 h. Excess solvent was distilled off in vacuum, and the dark oily residue was refluxed in acetone for 30 min and then left to cool. The separated solid was collected by filtration to give 279 mg (48%) **9**.

M.p.: 205–207°C (EtOH); IR (KBr): $\nu = 3310$ (NH), 1716, 1645 (CO) cm^{-1}; ^1H NMR (*DMSO*-d_6, δ, 90 MHz): 6.83 (s, 1H, pyimidinone), 7.1 (dd, H_7), 7.5–7.7 (m, C_6H_5+H_6), 8.1 (d, H_5), 9.45 (d, H_8); MS: *m/z* (%) = 289 (M^+, 14%).

10-Benzoyl-3-phenyl-2-thioxopyrimido[5,4-a]indolizine-4(3H)-one (**10**; $C_{23}H_{15}N_3O_2S$)

A mixture of 924 mg (3 mmol) **1b**, 405 mg (3 mmol) phenyl isothiocyanate, and 0.5 cm^3 triethylamine in 10 cm^3 *DMF* was heated at 120°C for 3 h. Excess solvent was distilled off, and the resulting mass was triturated with H_2O and then with acetone to give 540 mg (45%) **10**.

M.p.: 226–228°C (*DMF*/H_2O); IR (KBr): $\nu = 3348$ (NH), 1690, 1645 (CO) cm^{-1}; ^1H NMR (*DMSO*-d_6, δ, 90 MHz): 7.2 (dd, H_7), 7.4–7.7 (m, C_6H_5+H_6), 8.25 (d, H_5), 9.3 (d, H_8), 10.5 (s, NH, exchangeable with D_2O); MS: *m/z* (%) = 397 (M^+, 14%).

Ethyl 2-acetamido-3-benzoylinodolizine-1-carboxylate (**11**; $C_{20}H_{18}N_2O_4$)

To a suspension of 1.54 g (5 mmol) **1b** in 20 cm^3 dry dioxane, 430 mg (5.5 mmol) acetyl chloride were added dropwise with vigorous stirring. The resulting viscous mass was stirred for additional 30 min at room temperature and then at 80°C for 1 h. The mixture was cooled, poured onto crushed ice, and neutralized with NH_4OH. The formed solid was filtered off and crystallized from dioxane/H_2O (charcoal) to afford 900 mg (53%) **11**.

M.p.: 147–149°C; IR (KBr): $\nu = 3410$ (NH), 1683, 1665, 1645 (CO) cm^{-1}; ^1H NMR (*DMSO*-d_6, δ, 90 MHz): 1.3 (t, CH_3), 2.3 (s, CH_3), 4.35 (q, CH_2), 6 (br s, NH, exchangeable with D_2O), 7.18 (dd, H_7), 7.43 (t, H_6), 7.55 (m, C_6H_5), 8.23 (d, H_5), 9.33 (d, H_8); MS: *m/z* (%) = 350 (M^+, 2%).

Ethyl 3-benzoyl-2-(diacetamino)indolizine-1-carboxylate (**12**; $C_{22}H_{20}N_2O_5$)

A mixture of 924 mg (3 mmol) **1b** and 10 cm^3 acetic anhydride was refluxed for 2 h. Excess solvent was distilled off, and the oily residue was treated with H_2O and left overnight. The obtained solid was filtered off and dried to afford 930 mg (80%) **12**.

M.p.: 167–169°C; IR (KBr): $\nu = 1727$, 1668, 1645 (CO) cm^{-1}; ^1H NMR ($CDCl_3$, δ, 90 MHz): 1.4 (t, CH_3), 2.1 (s, $2CH_3$), 4.3 (q, $2CH_2$), 7.2 (t, H_7), 7.3–7.6 (m, C_6H_5+H_6), 8.25 (d, H_5), 9.27 (d, H_8); MS: *m/z* (%) = 392 (M^+, 7%).

10-Benzoyl-2-methylpyrimido[5,4-a]indolizine-4(3H)-one (**13**; $C_{18}H_{13}N_3O_2$)

Method A: A suspension of 1.05 g (3 mmol) **11** in 25 cm^3 30% NH_4OH was stirred at room temperature for 8 h and left standing for 2 days. The solid was filtered off and washed with 5% KOH

solution and H_2O. The filtrate was treated carefully with acetic acid, and the formed solid was collected and washed with H_2O to afford 300 mg (30%) **13**.

M.p.: 209–211°C (EtOH); IR (KBr) $\nu = 3296$ (NH), 1675, 1645 (CO) cm^{-1}; ^1H NMR (*DMSO*-d_6, δ, 90 MHz): 1.3 (s, CH_3), 6.97 (t, H_7), 7.48 (t, H_6), 7.57 (s, C_6H_5), 7.95 (d, H_5), 9.26 (d, H_8); MS: *m/z* (%) = 303 (M^+, 39%).

Method B: A suspension of 392 mg (1 mmol) **12**. in 15 cm^3 30% NH_4OH was stirred at room temperature for 8 h and left standing for 2 days. The reaction mixture was treated as above affording 200 mg (65%) **13**; m.p.: 209–211°C.

3-Amino-10-benzoyl-2-methylpyrimido[5,4-a]indolizine-4(3H)-one (**14**; $C_{18}H_{14}N_4O_2$)

Method A: To a solution of 350 mg (1 mmol) **11** in 25 cm^3 absolute EtOH, 2 cm^3 hydrazine hydrate were added, and the reaction mixture was refluxed for 3 h. Excess solvent was distilled off, and the residue was triturated with H_2O. The obtained solid was collected by filtration, washed with H_2O, and dired to give 160 mg (50%) **14**.

M.p.: 237–239°C (dioxane); IR (KBr): $\nu = 3420$, 3340 (NH_2), 1685, 1645 (CO) cm^{-1}; ^1H NMR (*DMSO*-d_6, δ, 90 MHz): 1.3 (s, CH_3), 5.6 (s, NH_2, exchangeable with D_2O), 7 (t, H_7), 7.5 (t, H_6), 7.6–7.75 (m, C_6H_5), 8.1 (d, H_5), 9.26 (d, H_8); MS: *m/z* (%) = 318 (M^+, 4%).

Method B: A mixture of 304 mg (1 mmol) **16** in 30 cm^3 absolute EtOH and 2 cm^3 hydrazine hydrate was refluxed for 2 h and then treated as above to give 240 mg (80%) **14**; m.p.: 238–239°C (decomposition).

10-Benzoyl-2-methyl[1,3]oxazino[5,4-a]indolizine-4-one (**16**; $C_{18}H_{12}N_2O_3$)

A stirred suspension of 1.6 g (5 mmol) **1b** in 10 cm^3 5% ethanolic KOH solution was heated at 80°C for 1 h. The reaction mixture was left to cool, and the fine brownish white crystals formed were separated by filtration to give the corresponding potassium salt (1.7 g (95%) **15**, m.p.: 190°C). A solution of 1.6 g (4.5 mmol) **15** in 25 cm^3 acetic anhydride was refluxed for 3 h and then left to cool. The formed solid was separated by filtration, washed with H_2O, and dried to give 1 g (73%) **16**.

M.p.: 201–203°C (EtOH); IR (KBr): $\nu = 1762$, 1645 (CO) cm^{-1}; ^1H NMR (*DMSO*-d_6, δ, 90 MHz): 1.33 (s, CH_3), 7.2 (t, H_7), 7.4–7.7 (m, C_6H_5+H_6), 8.3 (d, H_5), 9.3 (d, H_8); MS: *m/z* (%) = 304 (M^+, 97%).

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