New Routes to the Pyrrolo[2,1-*a*]isoquinoline System

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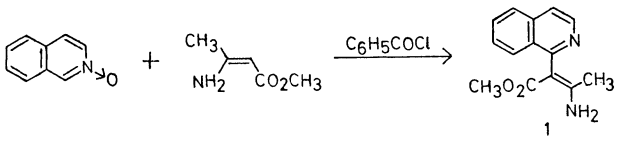
Synopsis. Some derivatives of the title ring system were prepared from methyl α-(1-isoquinolyl)-β-aminocrotonate and ethyl α-(1-isoquinolyl)-β-amino-β-ethoxyacrylate in moderate to good yields *via* their quaternary salts.

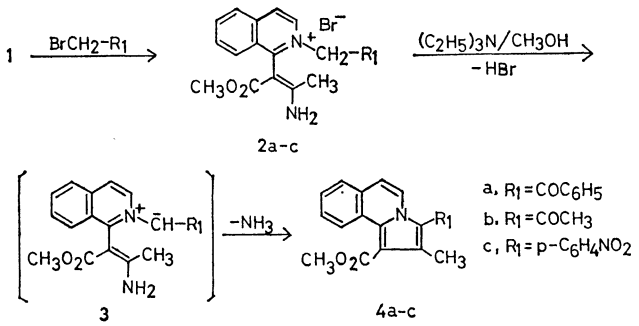
Although several methods for the preparation of pyrrolo[2,1-*a*]isoquinoline system have been reported, the yields of the products are usually poor.[1]

In the course of our recent study of the convenient synthesis of heteroarylacetic esters, methyl α-(1-isoquinolyl)-β-aminocrotonate (**1**) was prepared in a moderate yield (58%) as an intermediate compound for methyl 1-isoquinolylacetate, from isoquinoline 2-oxide and methyl β-aminocrotonate in the presence of benzoyl chloride.[2] The ready availability of **1** and its unique

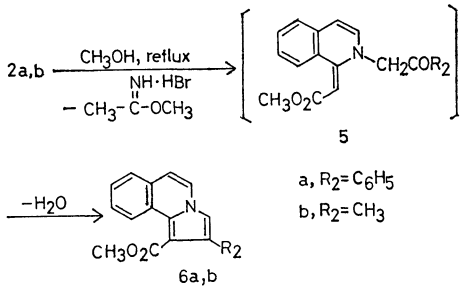


structure, possessing a reactive enaminic substituent at the 1-position of the isoquinoline ring, prompted us to determine the utility of this compound for the synthesis of fused isoquinoline systems. In this paper, we wish to describe the efficient synthesis of pyrrolo-[2,1-*a*]isoquinoline system from **1**. In addition, a related synthesis of the same system from ethyl α-(1-isoquinolyl)-β-amino-β-ethoxyacrylate(**7**) will also be described.

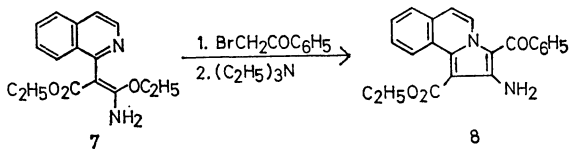
Compound **1** was allowed to react with phenacyl bormide or bromoacetone in chloroform under reflux for 1 h to give quaternary salts **2a**, **b** in about 90% yields. When these salts were treated with excess triethylamine in methanol in order to generate the ylides, **3**, a successive cyclization occurred and two pyrrolo[2,1-*a*]isoquinoline derivatives, **4a** and **4b**, were obtained in 93% and 77% yields respectively. This cyclization can be well explained in terms of the intramolecular nucleophilic attack of the ylidic carbanion on a β-carbon atom in the crotonate moiety, followed by the elimination of ammonia. The intermediacy of the ylides was shown by the development of a deep-red color at the initial stage of the reactions. Although the yield was not satisfactory (23%), Compound **4c** was obtained in a similar manner from **1** and *p*-nitrobenzyl bromide without isolating the intermediate quaternary salt, **2c**.



On the other hand, when quaternary salts **2a** and **2b** were heated in methanol under the reflux temperature for an appropriate time, pyrrolo[2,1-*a*]isoquinoline derivatives of another type, **6a** and **6b**, were obtained in 85% and 92% yields respectively. The structures of these unexpected compounds were fully supported by the results of microanalyses and the spectral data. In addition, the Compound **6b** thus obtained was completely identical with an authentic sample prepared from methyl 1-isoquinolylacetate and bromoacetone using Bragg's method.[3] Although we have not conducted experiments to establish the reaction mechanism, it is reasonable to assume that the reaction is initiated by the nucleophilic attack of methanol on a β-carbon of **2**, which causes the elimination of methyl acetimidate. The intermediate enamine, **5**, thus formed gives **6** by spontaneous dehydrative cyclization.



Recently, Yamanaka *et al.* reported the synthesis of ethyl α-(1-isoquinolyl)-β-amino-β-ethoxyacrylate(**7**).[4] The structural resemblance of **7** to **1** suggested that the above cyclization methods are also applicable to this compound. In fact, the quaternization of **7** with phenacyl bromide and subsequent treatment with triethylamine afforded 2-aminopyrrolo[2,1-*a*]isoquinoline derivative **8** in a 66% yield. In this case, the elimination of ethanol occurred in preference to that of ammonia.



Experimental

All the melting points are uncorrected. The NMR spectra were recorded on a Hitachi R-20B spectrometer for a solution in deuteriochloroform, using TMS as the internal standard. The IR spectra were obtained in Nujol mulls with a Hitachi EPI-2 spectrometer. The UV spectra were determined for solutions in 95% ethanol with a Hitachi 323 spectrometer.

*Preparation of Quaternary Salts (**2a, b**). General Procedure*: A solution of 2.51 g (10 mmol) of hemihydrate of **1** and the appropriate α-bromoketone (10 mmol) in 25 ml of chloroform was refluxed for 1 h. The precipitated yellow solid of **2** was collected by filtration, washed with ether, and then recrystallized from methanol–ether. If the quaternary salt was not precipitates from the reaction mixture, the chloroform was removed by evaporation and the residual oil was crystallized by trituration with ether. The quaternary salt **2a** was thus obtained in a 92% yield; mp 190.5 °C (dec). IR: 3330, 3230, and 3160 cm^{-1} (NH_2), 1692 and 1672 cm^{-1} (C=O). The quaternary salt **2b** was obtained in a 90% yield; mp 148—149 °C (dec). IR: 3350, 3240, and 3160 cm^{-1} (NH_2), 1723 and 1672 cm^{-1} (C=O).

*Methyl 3-Benzoyl-2-methylpyrrolo[2,1-a]isoquinoline-1-carboxylate (**4a**).* Triethylamine (2 ml) was added to a solution of 1.00 g of **2a** in 20 ml of chloroform. The solution turned a deep red and was gradually decolorized. After several minutes, a crystalline compound began to precipitate. After having been allowed to stand overnight, the precipitates were collected by filtration, giving 0.72 g (94%) of **4a** as pale yellow needles. An analytical sample was purified by recrystallization from ethanol; mp 151.5—152.5 °C. IR: 1695 and 1612 cm^{-1} (C=O). UV max: 216^{sh} (log ε 4.40), 273 (4.60), 320 (4.13), 368^{sh} (4.12), and 382 nm (4.18). NMR; δ 2.07 (s, 3H, CH_3), 3.95 (s, 3H, $COOCH_3$), 7.01 (d, 1H, H-6, J=7.5 Hz), 7.3—7.9 (m, 5H arom, 3H, H-7, H-8, H-9), 8.6—8.9 (m, 1H, H-10), and 8.94 ppm (d, 1H, H-5, J=7.5 Hz). Found; C, 77.02; H, 4.92; N, 4.11%. Calcd for $C_{22}H_{17}NO_3$: C, 76.95; H, 4.99; N, 4.08%.

*Methyl 3-Acetyl-2-methylpyrrolo[2,1-a]isoquinoline-1-carboxylate (**4b**).* This compound was prepared from **2b** in a 77% yield in a manner similar to that described above; colorless prisms; mp 124.5—125.5 °C. IR: 1702 and 1623 cm^{-1} (C=O). UV max: 224^{sh} (log ε 4.19), 249 (4.30), 274 (4.57), 284 (4.48), 323 (4.11), 340 (3.91), 357 (4.15), and 375 nm (4.12). NMR: δ 2.51 (s, 3H, CH_3 or $COCH_3$), 2.53 (s, 3H, $COCH_3$ or CH_3), 3.96 (s, 3H, $COOCH_3$), 6.94 (d, 1H, H-6, J=7.5 Hz), 7.35—7.6 (m, 3H, H-7, H-8, H-9), 8.2—8.5 (m, 1H, H-10), and 9.52 ppm (d, 1H, H-5, J=7.5 Hz). Found: C, 72.43; H, 5.32; N, 5.07%. Calcd for $C_{17}H_{15}NO_3$: C, 72.58; H, 5.37; N, 4.98%.

*Methyl 2-Methyl-3-(p-nitrobenzyl)pyrrolo[2,1-a]isoquinoline-1-carboxylate (**4c**).* A mixture of 2.51 g (10 mmol) of hemihydrate of **1**, 2.16 g (10 mmol) of *p*-nitrobenzyl bromide, and 25 ml of chloroform was refluxed for 3 h. The chloroform was then removed by evaporation, and the residual oil was dissolved in 20 ml of methanol. Triethylamine (4 ml) was added to the solution, and the reaction mixture was allowed to stand at room temperature for 2d. The precipitated orange prisms were collected by filtration to give 0.72 g of **4c**; mp 192.5—193.5 °C. The filtrate was evaporated, and the residue was passed through a colum of silica gel, using chloroform as the eluent. From the first orange band, an additional 0.09 g of **4c** was obtained; mp 189—192.5 °C. The total yield was 0.81 g (23%). An analytical sample was purified by recrystallization from ethanol; mp 192.5—193.5 °C. IR: 1682 cm^{-1} (C=O), 1510 and 1346 cm^{-1} (NO_2). UV max: 253^{sh} (log ε 4.42), 269^{sh} (4.55), 277 (4.65), 332 (4.11), and 388 nm (4.00). NMR: δ 2.30 (s, 3H, CH_3), 3.96 (s, 3H, $COOCH_3$), 6.80 (d, 1H, H-6. J=7.5 Hz), 7.3—7.7 (m, 2H arom, 4H, H-5, H-7, H-8, H-9). 8.31 (near d, 2H arom) and 8.9—9.1 ppm (m, 1H, H-10). Found: C, 70.15; H, 4.50; N, 7.77%. Calcd for $C_{21}H_{16}N_2O_4$: C, 69.99; H, 4.48; N, 7.77%.

*Methyl 2-Phenylpyrrolo[2,1-a]isoquinoline-1-carboxylate (**6a**).* A solution of 0.5 g of **2a** in 20 ml of methanol was refluxed for 2 d. The solution was then evaporated, and the residue was extracted with chloroform. The extract was washed with water, dried over sodium sulfate, and evaporated. The residue was recystallized from methanol to give 0.29 g (85%) of **6b** as colorless plates; mp 91.5—92.5 °C. IR: 1690 cm^{-1} (C=O). UV max: 253^{sh} (log ε 4.42), 274^{sh} (4.62), 281 (4.68), and 329 nm (4.08). NMR: δ 3.65 (s, 3H, $COOCH_3$), 6.62 (d, 1H, H-6, J=7.5 Hz), 7.03 (s, 1H, H-3), 7.1—7.7 (m, 5H arom, 4H, H-5, H-7, H-8, H-9), and 8.7—8.95 ppm (m, 1H, H-10). Found: C, 79.62; H, 4.90; N, 4.69%. Calcd for $C_{20}H_{15}NO_2$: C, 79.71; H, 5.02; N, 4.65%.

*Methyl 2-Methylpyrrolo[2,1-a]isoquinoline-1-carboxylate (**6b**).* A solution of 0.5 g of **2b** in 20 ml of methanol was refluxed for 17 h and then worked up in a manner similar to that described for **6a**. Recrystallization from methanol afforded 0.29 g (92%) of **6b** as colorless needles; mp 139—140 °C. IR: 1675 cm^{-1} (C=O). UV max; 223 (log ε 4.44), 243 (4.15), 272^{sh} (4.45), 281 (4.62), and 331 nm (4.06). NMR: δ 2.30 (s, 3H, CH_3), 3.88 (s, 3H, $COOCH_3$), 6.64 (d, 1H, H-6, J=7.5 Hz), 6.80 (s, 1H, H-3), 7.3—7.6 (m, 4H, H-5, H-7, H-8, H-9), and 9.15—9.4 ppm (m, 1H, H-10). Found: C, 75.56; H, 5.50; N, 5.93%. Calcd for $C_{15}H_{13}NO_2$: C, 75.30; H, 5.48; N, 5.85%.

Unequivocal Synthesis of Methyl 2-Methylpyrrolo[2,1-a]isoquinoline-1-carboxylate. A solution of 2.24 g (11 mmol) of methyl 1-isoquinolylacetate and 0.77 g (5.5 mmol) of bromoaceone in 10 ml of acetone was refluxed for 17 h. The solution was then evaporated, and the residue was extracted with chloroform. The extract was washed with water, dried over sodium sulfate, and evaporated. The residue was subsequently recrystallized from methanol, giving 0.67 g (50%) of methyl 2-methylpyrrolo[2,1-*a*]isoquinoline-1-carboxylate; mp 138—140 °C. This compound was shown to be identical with Compound **6b** by a comparison of the IR spectra and by a mixed-melting-point determination.

*Ethyl 2-Amino-3-benzoylpyrrolo[2,1-a]isoquinoline-1-carboxylate (**8**).* A solution of 2.86 g (10 mmol) of **7** and 1.99 g (10 mmol) of phenacyl bromide in 25 ml of chloroform was refluxed for 1 h. The solution was then evaporated, and the residual oil was dissolved in 20 ml of methanol. After triethylamine (4 ml) has been added to this solution, the reaction mixture was allowed to stand overnight at room temperature. The yellow needles thus precipitated were collected by filtration to give 2.38 g (66%) of **8**; mp 155—156 °C. An analytical sample was purified by recrystallization from ethanol; mp 155—156 °C. IR: 3450 and 3300 cm^{-1} (NH_2), 1683 cm^{-1} (C=O). UV max: 214^{sh} (log ε 4.46), 228^{sh} (4.40), 287 (4.62), and 362 nm (4.30). NMR: δ 1.39 (t, 3H, $COOCH_2C\underline{H}_3$, J=7 Hz), 4.38 (q, 2H $COOC\underline{H}_2$-CH_3, J=7 Hz), 5.97 (broad s, 2H, NH_2), 6.80 (d, 1H, H-6, J=7.5 Hz), 7.3—7.7 (m, 5H arom, 3H, H-7, H-8, H-9), 8.56 (d, 1H, H-5, J=7.5 Hz) and 9.0—9.25 ppm (m, 1H, H-10). Found: C, 73.93; H, 5.06; N, 7.90%. Calcd for $C_{22}H_{18}N_2O_3$: C, 73.73; H, 5.06; N, 7.82%.

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4) H. Yamanaka, M. Komatsu, S. Ogawa, and S. Konno, *Chem. Pharm. Bull.*, **27**, 806 (1979).