CHEMISTRY OF PYRROLIZINES; REACTIONS WITH CYANOGEN BROMIDE AND TRIFLUOROACETIC ANHYDRIDE

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Abstract—Interaction of the pyrrolizine 3 with cyanogen bromide in a tetrahydrofuran/water mixture affords addition to the enamine double bond with formation of 5 which can be aromatized to 6 by silica gel. Reaction of 6 with cyanogen bromide in the same solvent mixture yields the indoline 8a which structure is proved in a chemical way by conversion of the product into the aldehyde 8d. The different reaction pathway is discussed in terms of steric hindrance by the ester groups. Treatment of 6 with trifluoroacetic anhydride gives the trifluoroacylated compound 11. Removal of the sterically hindered ester groups in 6, with acetic acid in quinoline at 200 °C, is accompanied by the simultaneous decarboxylation to yield the pyrrolo[1,2-α]indole 13.

Recently we reported that the reactions of 3-(1-pyrrolidinyl) thiophenes I and 1-pyrrolidinyl cycloalkenes 2 with dimethyl acetylenedicarboxylate in polar solvents give pyrrolizines instead of the cyclobutene derivatives that are formed in apolar solvents. Since the 1H-pyrrolo[1,2-α]indole system is the chemical backbone of the anti-tumor antibiotic mitomycin 2 we are currently exploring the possibility of modification of our pyrrolizines and the conversion of these into analogues of mitomycins. Since the structures of the mitomycins were first elucidated, several approaches to their synthesis have been reported and a total synthesis was accomplished via compound 1 by Kishi et al. However, the number of steps and the low overall yield renders the synthesis of a large number of derivatives very difficult.

The experiments described in this paper have been carried out with the readily accessible 5,7,7a,8,9,10-hexahydro-7-methoxy-6H-benzo[g]pyrrolo[1,2-α]indole-7-acetic acid methyl ester (3, E = COOCH3) as a model system. Our first objective was to study the conversion of the pyrrolizine system into an azocine 4 via reaction with cyanogen bromide or trifluoroacetic anhydride in a similar way to that described by Kametani et al. In azocine 4 R2 must be converted in several steps into a keto function which can serve 1) to introduce a handle for the aziridine group, 2) to remove one of the ester groups and 3), via the acetal, for the introduction of the methoxy group. Surprisingly, we found a mode of reaction which is different from known reactions of pyrrolizines with both cyanogen bromide and trifluoroacetic anhydride.

RESULTS AND DISCUSSION

Reactions with cyanogen bromide. Reactions of tertiary amines with cyanogen bromide (the van Braun reaction) are normally carried out in inert solvents such as diethyl ether, chloroform or benzene. However, Albright et al., 9 however, used mixtures of tetrahydrofuran and water or alcohols and Rönsch carried out the reaction in the presence of magnesium oxide. Using these conditions they were able to introduce directly a hydroxy- or an alkoxy group instead of a bromine atom.

The pyrrolizine 3 was reacted with cyanogen bromide in a mixture of tetrahydrofuran and water (25:10) at room temperature to give a product which was not the
expected azocine 4a in 89% yield. According to the mass spectrum and elemental analysis the elemental composition of the reaction product was C_{21}H_{23}BrN_{2}O_{4} indicating that a bromine and not an OH group was incorporated. In the 'H NMR spectrum the characteristic N-CH signal at δ 4.60 ppm (dd, J = 5.5 and 11 Hz) was still present and the 13C NMR spectrum showed that the absorptions of the original double bond were replaced by -C-Br and -C-CN signals at δ 73.0 and 72.1 ppm. On the basis of these data we concluded that the reaction product was 6a-bromo-7-carboxy-1la-cyano-5,6a,7,7a,8,9,10,11a-octahydro-6H-benzo[g]pyrrolo[1,2-a]indole-7-acetic acid, dimethyl ester 5. Obviously addition of cyanogen bromide had taken place at the more reactive enamine double bond.1

Due to the polarization of cyanogen bromide we would expect that the bromine attacks at the β-enamine carbon atom having the highest electron density.

Reaction of compound 5 in the presence of silica gel gave rise to the formation of 7-carboxy-7a,8,9,10-tetrahydro-7H-benzo[2]pyrrolo[1,2-a]indole-7-acetic acid, dimethyl ester 6 which could be crystallized from the crude reaction mixture in 30-40% yield.

Direct aromatization of pyrrolizine 3 with diisopentyl disulfide or N-bromosuccinimide gave, according to the 'H NMR spectra of the crude reaction mixtures, higher yields of pyrrolizine 6. However it was difficult to isolate pure 6. In the case of the reaction with N-bromosuccinimide the pyrrolizine 6 could not be separated by chromatography from a product which contains a bromine atom in the aromatic ring.

Because pyrrolizine 6 does not possess the reactive enamine double bond of 5 and is therefore more closely related to the dihydroindole skeleton of mitomycin C we have carried out further reactions with 6. Reaction of pyrrolizine 6 with cyanogen bromide in tetrahydrofuran-water (25:10) at 40°C gave a 1:1 reaction product in 72% yield as was shown by mass spectrometry (M^+ 444.072, calc for C_{21}H_{23}BrN_{2}O_{4} 444.069) and the elemental analysis. The 'H NMR spectrum showed the characteristic N-CH signal at δ 5.07 ppm (dd, J = 5.5 and 8 Hz) indicating that the C(7a)-N bond had not reacted, however a definite structure assignment could not be made. Assuming that there were two possibilities viz. 1) reaction of cyanogen bromide with the N-CH bond and 2) reaction with the N-CH₂-bond, we decided to replace the bromine atom by a hydroxyl function which after oxidation is converted into either a keto- or an aldehyde group. This would prove either one of the two possible structures (7a or 8a) in a chemical way. Attempts to substitute the bromine atom for a hydroxyl group with silver(I) oxide in an acetone-water mixture failed. The result was a very complicated reaction mixture in which no product could be identified. However, reaction with potassium acetate in the presence of 18-crown-6 in acetonitrile at reflux temperature according to Liotta et al. resulted in the formation of the corresponding acetate 8b in 86% yield. This compound could be smoothly converted into the alcohol 8c with sodium carbonate in 72% yield. Oxidation with pyridinium chlorochromate in dichloromethane, ultimately leads to the formation of 3-carboxy-1-cyano-2-(2-formyl)benz[g]indoline-3-acetic acid, dimethyl ester 8d in 80% yield. The structure of 8d was proven by its spectral data. Conclusive evidence for the aldehyde structure are the absorptions in the 'H NMR spectrum at δ 9.87 ppm and in the 13C NMR spectrum at δ 199.5 ppm. From this result we concluded that in the pyrrolizine 6 cyanogen bromide had reacted with the N-CH₂-bond with formation of 8a. In the spectra of the crude reaction mixtures we could not demonstrate the presence of the azocine 7b.

In their work Kametani et al. reacted a compound that resembles our pyrrolizine namely 5,8-diacetoxy-2,3,9,9a-tetrahydro-7-methoxy-6-methyl-1H-pyrrolo[1,2-a]indole 9 with cyanogen bromide and they observed that the von Braun reaction of 9 gave 7,10-diacetoxy-5-bromo-1-cyano-1,2,3,4,5,6-hexahydro-8-methoxy-9-methyl-1-benzazocine 10a in 56% yield, consequently reaction with the N-CH₂-bond. They did not mention the presence of compounds originating by reaction with the N-CH₂-bond.

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the 'H NMR spectrum showed the presence of a methyl group at δ 2.32 ppm and an N--CH$_2$-group at δ 4.50 ppm (J = 7 Hz); signals of methoxy- or acid groups were absent. The 'H NMR spectrum resembled that of the known 2, 3-dihydro-9-methyl-1H-pyrrolo[1,2-a]indole. 17

We assume that the formation of 13 occurs via the intermediate diacid 12 which eliminates two moles of carbon dioxide. This was proven by heating the diacid 12 in quinoline at 200°C which also resulted in formation of 13. This diacid 12 could be prepared by reaction of the pyrrolizine 6 with potassium tert-butoxide in dimethylsulfoxide according to Bartlett et al. 16 Because this diacid is very soluble in water and difficult to separate from salts, attempts to isolate the diacid in a pure state failed. However, the 'H NMR spectrum clearly revealed the absence of the ester groups. The IR- and mass spectrum further supported this structural assignment.

To our knowledge this conversion of 3 via 6 into 13 represents the first synthesis of derivatives of the 9, 10-dihydro-8H-benzo[9]pyrrolo[1,2-a]indole system.

**EXPERIMENTAL**

M.ps were determined with a Reichert melting point apparatus and are uncorrected. 1H and 13C NMR spectra were recorded with a Bruker WP80-FT and a Varian XL-100 spectrometer, respectively, in CDCl$_3$ with TMS as internal standard. Mass spectra were obtained with a Varian Mat 311A spectrometer and IR spectra with a Perkin-Elmer 257 spectrophotometer. Elemental analyses were carried out by the Analytical Section of the Institute for Organic Chemistry TNO, Utrecht, The Netherlands, under the supervision of Mr. W. J. Buis. Pyrrolizine 3 was prepared as described. 1

6a-Bromo-7-carboxy-11a-cyano-5, 6a, 7, 7a, 8, 9, 10, 11a-octahydro-6H-benzo[9]pyrrolo[1,2-a]indole-7-acetic acid, dimethyl ester 5

To a soln of 3 (17.1 g, 0.05 mol) in 400 ml THF/H$_2$O (25:10) were added magnesium oxide (4.0 g, 0.1 mol) and, dropwise, a soln. of cyanogen bromide (10.6 g, 0.1 mol) in 100 ml THF/H$_2$O (25:10) at room temp. After stirring for 1 h the magnesium oxide was filtered off and the filtrate concentrated in vacuo to about 1/10 of the original volume. The crude 3 was crystallized from the filtrate. 5 was collected on a sintered glass filter, successively washed twice with MeOH and Et$_2$O and dried over CaCl$_2$ (yield 89%). 5 could be used without further purification for the preparation of 6. A sample of 5 was recrystallized from MeOH. M.p. 133-135.5°C; 1H NMR: δ 7.6-7.1 (m, 4H, Ar), δ 4.60 (dd, J = 5.5 Hz); 13C NMR: δ 183.3 and 183.2; IR (keV): 3270, 1691, 1587, 1529, 1462, 1351, 1288, 1238, 1123, 1056, 1018, 978, 865, 707, 621, 542, 410.

We concluded that we were not able to convert the pyrrolizine 6 into the azocines 7 either with cyanogen bromide or with trifluoroacetic anhydride. A reason that in pyrrolizine 6 cyanogen bromide does not react with the annulating N--CH$_2$-bond might be the presence of the bulky ester groups which possibly prevent an attack at the C(7a) position. Therefore we have subsequently tried to remove these ester groups first.

**Removal of the ester groups.** With classical methods such as sodium hydroxide or hydrogen chloride in water or dioxane, concentrated sulphonic acid or trifluoroacetic acid we were not able to remove the ester groups.

Kametani et al. 18 found that the pyrrolo[1,2-a]indole 9 reacted with trifluoroacetic anhydride in a sealed tube at 150°C to yield 7, 10-diacetoxy-1,2,3,4,5,6-hexahydro-8-methoxy-9-methyl-5-trifluoroacetoxy-1-trifluoroacetyl-1-benzazocine 10b. Under the same conditions the pyrrolizines 3 and 6 reacted with trifluoroacetic anhydride to give complicated reaction mixtures from which no pure compound could be isolated. However, the reaction of pyrrolizine 3 with trifluoroacetic anhydride at reflux temperature (40°C) is fast yielding a salt which was isolated. The mass spectrum showed a parent peak at m/e 341 (starting pyrrolizine 3) and in addition fragments originating from trifluoroacetic anhydride. Treatment of the salt with sodium bicarbonate in water gave the starting pyrrolizine 3.

Pyrrolizine 6 reacted with trifluoroacetic anhydride at room temperature to give 7-carboxy-7a,8,9,10-tetrahydro-4-(trifluoroacetyl)-7H-benzo[g]pyrrolo[1,2-a]indole-7-acetic acid, dimethyl ester 11 which was isolated in 78% yield. The structure of 11 was proven by spectroscopic methods. The mass spectrum and elemental analysis showed that only a CF$_3$CO-group had been introduced. Besides, in the 1H NMR spectrum the characteristic N--CH$_2$-absorption at δ 5.10 ppm (dd, J = 5 and 12 Hz) is still present. On the basis of these data the azocine structure 7c could be excluded. Comparison of the 1H NMR spectra of the product and of pyrrolizine 6 showed essential differences in the aromatic patterns; the spectrum of the reaction product exhibited only five aromatic hydrogen atoms. Therefore we concluded that an electrophilic aromatic substitution had taken place. One of the aromatic hydrogens in the 1H NMR spectrum is shifted downfield to δ 9.26 ppm (dd) (influence of the nearest CF$_3$CO-group) and showed a J$_{ortho}$ of 8 Hz and J$_{meta}$ of 1.5 Hz so that the only possibility is that the CF$_3$CO-group had been introduced at the C(4) position.

In the literature it has been reported that trifluoroacetic anhydride is capable of effecting trifluoroacetylation in reactive aromatic and heterocyclic nuclei. 19 In the case of Kametani et al. 18 trifluoroacetylation is not possible because in pyrrolo[1,2-a]indole 9 all aromatic positions are blocked.

To a soln of 3 (17.1 g, 0.05 mol) in 400 ml THF/H$_2$O (25:10) were added magnesium oxide (4.0 g, 0.1 mol) and, dropwise, a soln. of cyanogen bromide (10.6 g, 0.1 mol) in 100 ml THF/H$_2$O (25:10) at room temp. After stirring for 1 h the magnesium oxide was filtered off and the filtrate concentrated in vacuo to about 1/10 of the original volume. The crude 3 was crystallized from the filtrate. 5 was collected on a sintered glass filter, successively washed twice with MeOH and Et$_2$O and dried over CaCl$_2$ (yield 89%). 5 could be used without further purification for the preparation of 6. A sample of 5 was recrystallized from MeOH. M.p. 133-135.5°C; 1H NMR: δ 7.6-7.1 (m, 4H, Ar), δ 4.60 (dd, J = 5.5 Hz); 13C NMR: δ 183.3 and 183.2; IR (keV): 3270, 1691, 1587, 1529, 1462, 1351, 1288, 1238, 1123, 1056, 1018, 978, 865, 707, 621, 542, 410.

We assume that the formation of 13 occurs via the intermediate diacid 12 which eliminates two moles of carbon dioxide. This was proven by heating the diacid 12 in quinoline at 200°C which also resulted in formation of 13. This diacid 12 could be prepared by reaction of the pyrrolizine 6 with potassium tert-butoxide in dimethylsulfoxide according to Bartlett et al. 16 Because this diacid is very soluble in water and difficult to separate from salts, attempts to isolate the diacid in a pure state failed. However, the 1H NMR spectrum clearly revealed the absence of the ester groups. The IR- and mass spectrum further supported this structural assignment.

To our knowledge this conversion of 3 via 6 into 13 represents the first synthesis of derivatives of the 9, 10-dihydro-8H-benzo[g]pyrrolo[1,2-a]indole system.
7-Carboxy-7a,8,9,10-tetrahydro-7H-benzo[g]pyrrolo[1,2-a]indole-7-acetic acid, dimethyl ester 6

Silica gel (60 g) was added to a soin of 5 (6.0 g, 13 mmol) in 150 ml CHCl3. The resulting slurry was stirred for 20-24 h at room temp. The silica gel was filtered off on a sintered glass filter and washed with water, dried with MgSO4 and subsequently concentrated in vacuo. The resulting oil solidified upon the addition of a small amount of MeOH. Purification by trituration with MeOH afforded the pure 6 in 30-40% yield. M.p. 148-150°; 1H NMR: 88.2-7.95 (m, 1H, Ar), 87.5-7.3 (m, 5H, Ar), 85.07 (dd, J = 5.5 and 8 Hz, N-CH-), 83.75 and 3.73 (s, OCH3), 83.6-2.8 (m, 2H, CH2Br), 82.82 (part of AB-q, J = 18 Hz, CH2E), 82.4-2.0 (m, 2H, -CH2-). 13C NMR: 8171.7 and 171.0 (s, C = O), 8135.3 (s), 134.7 (s), 128.6 (d), 127.0 (d), 126.0 (d), 125.2 (s), 122.0 (s), 121.2 (d) and 120.6 (d) (Ar), 8113.9 (s, C = N), 8073.0 (s), 7893.6 (s), 7823.8 (d, N-CH-), 854.5 [s, C(E)CH2E], 853.2 and 52.3 (q, OCH3 and CH2Br- signals). IR (KBr): 1721 cm⁻¹ (CO). MS: M⁺ 446.087, Calc. 446.084. (Found: C, 56.20, H, 5.21; N, 6.10. Calc. for C21H21BrN2O4 (447.33): C, 56.41; H, 5.15; N, 6.26%).

3-Carboxy-1-cyano-2-(3-carboxy-l-cyanobenz[g]indoline-3-acetic acid, dimethyl ester 6c

To a solution of sodium carbonate (2 g) in 90 ml of a 1:1:1 mixture of H2O, MeOH and THF 8b (1.0 g, 2.4 mmol) was added. After stirring for 3.5 h at room temp the reaction was complete. Most of the MeOH and THF were removed under reduced pressure. The resulting residue was dissolved in CHCl3, washed with water and dried with MgSO4. The solvent was evaporated to give an oil which solidified upon the addition of a few drops of EtOAc. Purification by trituration with diisopropyl ether and recrystallization from CHCl3/light petroleum (60/80) gave pure 8c in 72% yield. M.p. 126.5-128°; 1H NMR: 88.5-8.3 (m, 1H, Ar), 87.9-7.3 (m, 5H, Ar), 85.10 (dd, J = 5.5 and 8 Hz, N-CH-), 83.8-3.5 (m, 2H, HO-CH2-), 83.74 (s, 6H, OCH3), 83.58 and 2.84 (AB-q, J = 18 Hz, CH2E), 82.3-1.5 (m, 4H, -CH2-). 13C NMR: 8170.2 (CH3Br), 8160.2 (m, 4H, -CH2-). IR (KBr): 3480 cm⁻¹ (OH), 2222 cm⁻¹ (C = N), 1729 cm⁻¹ (C = O). MS: M⁺ 382.155, Calc. 382.153. (Found: C, 66.13; H, 5.96; N, 7.33%).

3-Carboxy-1-cyano 2- (3-hydroxypropyl)benz[g]indoline-3-acetic acid, dimethyl ester 8d

To a suspension of pyridinium chlorochromate (0.27 g, 1.3 mmol) in 3 ml CHCl3, a soln. of 8c (0.30 g, 0.8 mmol) in 3 ml CH2Cl2 was added. The resulting mixture was stirred for 3h the black reaction mixture was passed through a short florisil column with CHCl3/CH2Cl2 1:1 as the eluent. The solvents were evaporated in vacuo and the residue was treated with a small amount of diisopropyl ether to give a solid product 8d. Trituration with diisopropyl ether and recrystallization from EtOAc afforded pure 8d in 80% yield. M.p. 134°-135°. H NMR: 89.26 (s, 1H, H- = O), 86.8-8.2 (m, 3H, Ar), 85.7-7.5 (m, 5H, Ar), 85.06 (dd, J = 6 and 8 Hz, N-CH-), 83.6-2.82 (AB-q, J = 18 Hz, CH2E), 83.2-1.8 (m, 2H, -CH2). 13C NMR: 8159.5 (s, H- = O), 8171.7, 8171.3 (s, 1H, O), 8135.3 (s), 134.7 (s), 128.6 (d), 126.7 (d), 125.2 (s), 122.0 (s), 121.2 (d) and 120.6 (d) (Ar), 8113.9 (s, C = N), 8073.0 (s), 7893.6 (s), 7823.8 (d, N-CH-), 854.5 [s, C(E)CH2E], 853.2 and 52.3 (q, OCH3), 840.4 (s, H2C-CH = O), 838.4 and 2.82 (AB-q, J = 18 Hz, CH2E). 1H NMR: 89.26 (dd, J = 6, Jo,ho = 1.5 Hz, 1H, Ar), 8.82-7.3 (m, 4H, Ar), 8.50 (dd, J = 5 and 12 Hz, N-CH-), 84.3-3.9 (m, 1H, N-CH2-), 83.8-3.3 (m, 1H, N-CH-), 83.75 and 3.75 (s, OCH3), 83.66 and 2.85
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\[ \text{AB-q, } J = 18 \text{Hz}, \text{CH}_2\text{E}, 8.2-4.7 (m, 3H), 8.1-7.0 (m, 1H) \]

\[ ^{13}C \text{ NMR: } 81.78 \text{.7 (q, O=-~-CF}_3\text{)}, 81.72 \text{.0 and } 17.14 \text{ (s, C=O), 81.56} \text{.1 (s), 135.4 (s), 130.2 (d), 126.6 (d), 125.2 (d), 124.7 (d), 121.7 (s), 121.5 (s) and 115.4 (s) (Ar), 81.17 \text{.3 (q, J = 288 Hz, CF}_3\text{)}, 85.29 \text{.3 (t, -CH}_2\text{E), 85.30} \text{.6 and } 52.1 \text{ (q, OCH}_3\text{), 85.16 \text{ (t, N--CH}_2-\text{), 83.93 \text{ (t, CH}_2\text{E), 83.91} \text{.4 (m, 2x--CH}_2-\text{). IR (KBr): 1748} \text{ and 1730 (sh) cm }^{-1} \text{ (C=O, esters), 1662cm }^{-1} \text{ (O=~--CF}_3\text{). MS: M + 435.128, Calc. 435.129. (Found: C, 60.73; H, 4.61; N, 3.18. Calc. for C}_{22}H_{20}F_{a}NO_{s}(435.40): C, 60.69; H, 4.63; N, 3.22%).} \]

9, 10-Dihydro-7-methyl-8H-benzo[g]pyrrolo[1,2-a]indole 13.

To a soln of 6 (2.04g, 6.0 retool) in 12 ml quinoline was added dry acetic acid (6.12 ml, 108 mmol) under a slow stream of N\(_2\). The reaction mixture was heated at 200 \(^\circ\) for 40 h. Most of the quinoline was removed under reduced pressure. The residue, dissolved in CH\(_2\)Cl\(_2\), was passed through a short column of florisil. After removal of the solvent the resulting solid was purified by trituration with light petroleum (60-180) affording 13 in 36% yield. A sample was recrystallized from ethanol M.p. 151.0-152.5°; ~H NMR: 88.3-8.15 (m, 1H, Ar), 8.0-7.8 (m, 1H, Ar), 7.7-7.25 (m 4H, Ar), 4.50 (t, J =7Hz, N-CH\(_2--\)), 3.1-2.5 (m, 4H, -CH\(_2--\)), 2.32 (s, CH\(_3\)) 13C NMR: 81.39.8 (s), 129.9 (s), 128.6 (d), 124.7 (d), 122.4 (d), 120.0 (d), 119.1 (d), 118.9 (d), 102.3 (s) (sp\(^2\)-carbon atoms), 84.7 (t, N-CH\(_2--\)), 82.81 and 22.4 (t, -CH\(_2--\)), 89.0 (q, CH\(_3\)). MS: M' 435.120, Calc. 435.40: C, 60.69; H, 4.63; N, 3.22%.

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