Synthesis of Substituted Pyrrolo[1,2-*a*][1,3]diazepine. A Correction

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The structure of a formerly described pyrrol[1,2-*a*][1,3]diazepine is corrected by synthesis. The correction is discussed by comparing physicochemical data and synthetic procedures for both substances.

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In 1976, Sowell and De Witt Blanton reported the synthesis of a new substituted pyrrolo[1,2-*a*][1,3]diazepine. In 1985, we reported the synthesis of pyrrolo[1,2-*a*]- and [2,3-*d*]heterobicycles from acyloines, amino acid derivatives and malononitrile [2]. In the case of ethyl 4-aminobutyrate as a primary amine we should obain the same product as described by Sowell and De Witt Blanton. Scheme I shows both synthetic routes. However, comparing the physico-chemical data of both products, there are some differences in the melting point, ir, uv, and ^{1}H-nmr spectra, whereas the elemental analyses and ms are identical (see Table 1). In order to avoid errors in the literature,

Table 1

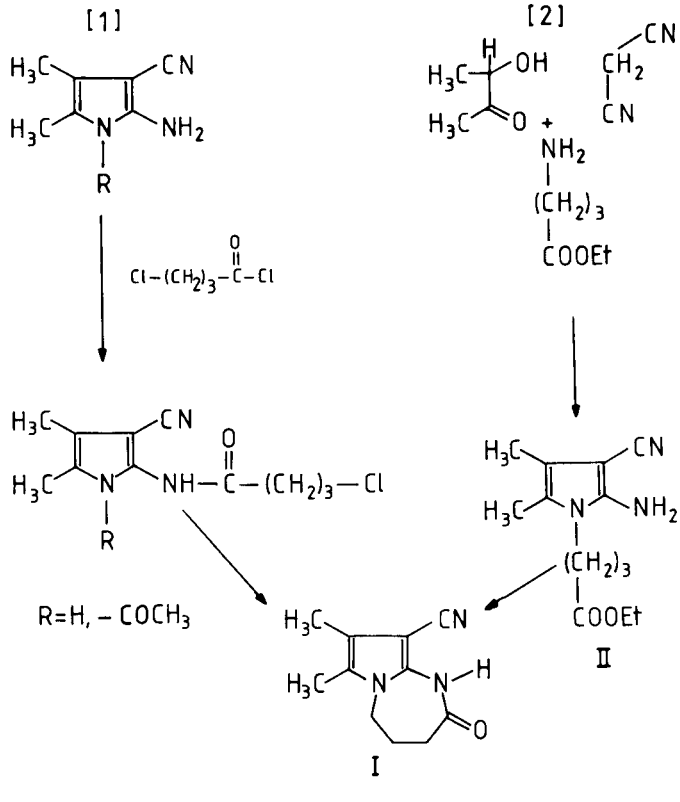
Physicochemical Data of the Pyrrolo[1,2-*a*][1,3]diazepines

According to Reference:		[1a]	[2]
Melting Point	(°C)	181-182	217-218
IR	(cm^{-1})		
NH		3300	3200
CO		1670	1680
UV	(nm)		
CH_3OH		287	271
CH_3OH/NaOH		287	292
^{1}H-NMR (ppm)			
$CDCl_3$/resp	d_6-DMSO		
NH		10.55/10.55 s	8.05/10.0 s
2 × CH_3		2.15, 2.05/ s	2.05/ s
		2.10, 2.00 s	2.15, 2.05 s
3 × CH_2		4.10 t	3.95 t
		2.2-2.8 m/	2.1-2.6 m/
		3.85 t,	3.90 t,
		2.0-2.6 m	2.2-2.26 m
MS (70 eV)		m/e 203	m/e 203

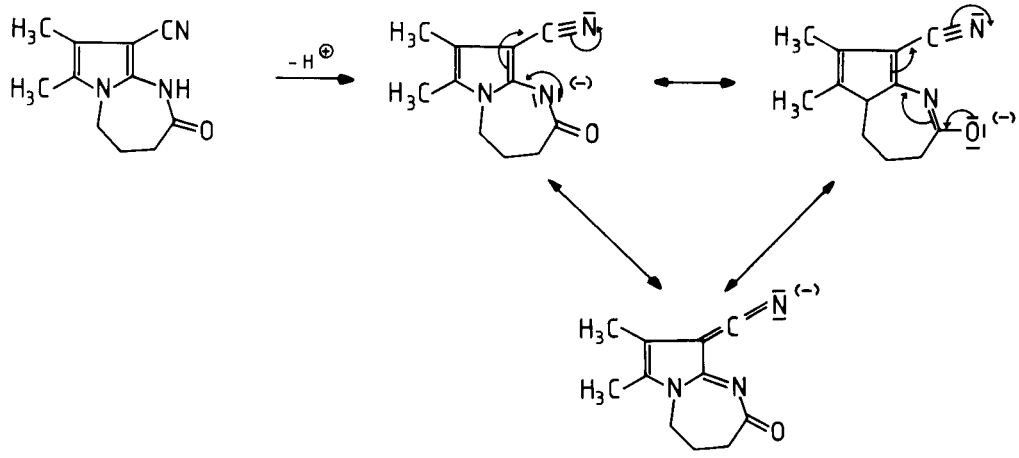
we resynthesized the pyrrolodiazepine according to [1a]. The direct comparison of both substances gave the same results, that is, both products are not identical.

In general, it is possible that the reaction yields, in addition to compound I, the isomeric compounds III and IV in both cases. The formation of III should be possible *via* acyl transfer from N2 to N1 in the procedure described by Sowell or from N1 to N2 in our synthetic route. By means of the ^{1}H-nmr spectrum the formation of III was excluded because of the exchangeable proton on the nitrogen occuring at 10.0 ppm, instead of about 4 ppm. The formation of IV seemed to be favoured because of different nucleophilic activity of the endo- and exocyclic nitrogen atoms, and because of the possibility to form a five-membered instead of a seven-membered ring system. Two examples in literature served as a proof for this view: Cooper [3] described

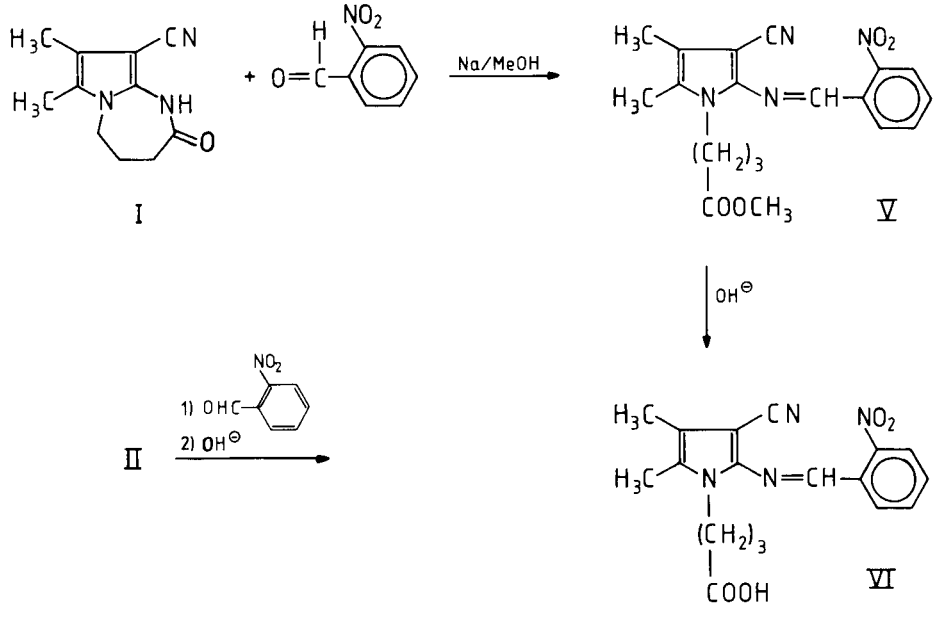
Scheme 1



Scheme 2

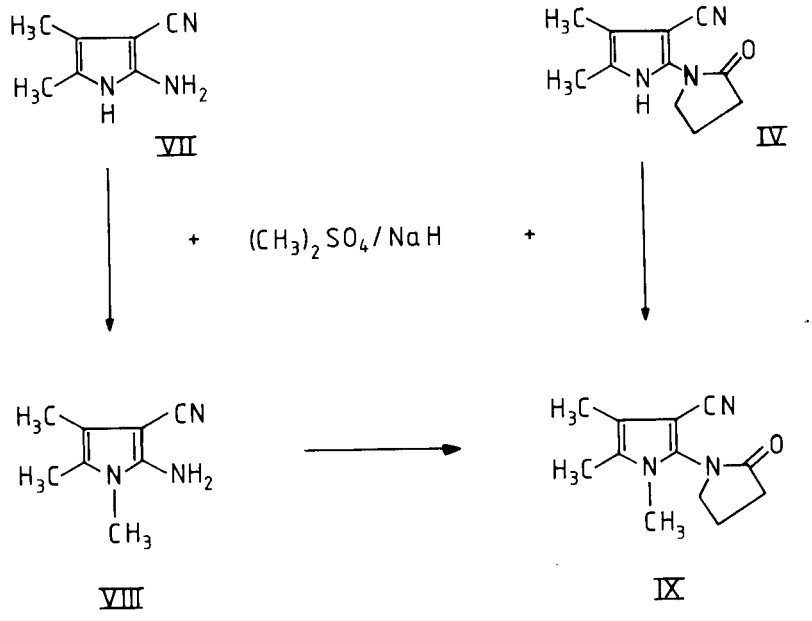


Scheme 3

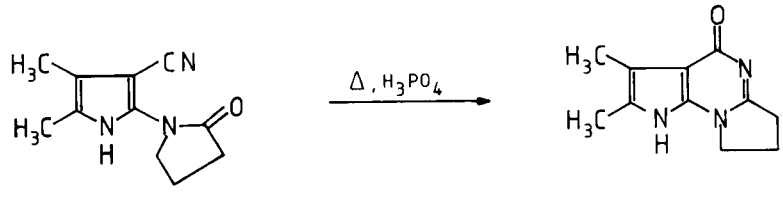


the formation of a cyclopropyl pyrrolyl ketone instead of an expected tetrahydropyrrolopyridine from a 2-acylpyrrole derivative. The reaction described by Manhas and coworkers [4] yielded a thienylbutyrolactam from 2-amino-3-cyanothiophene and 4-chlorobutyryl chloride. Therefore we were convinced that both procedures resulted in either compound I or compound IV only. If this view was correct, one should be able to distinguish between both substances analytically. Recording the uv spectra in alkaline solution, the spectrum of compound I, assuming I to undergo salt formation, would show a remarkable bathochromic shift (Scheme 2). As expected, only one substance, namely our synthetic product, showed this behaviour (see Table 1). Furthermore, both substances I and IV were treated with 2-nitrobenzaldehyde/sodium in hot methanol. Only our compound I gave a ring-opening reaction and yielded the azomethine V. The ester group in V easily hydrolysed to the corresponding pyrrolylbutyric acid VI. Compound VI was independently synthesized from II by condensation with 2-nitrobenzaldehyde and hydrolysis of the ester function (Scheme 3). The results of the reactions mentioned above, can only be explained if structure IV is assumed for the compound described by Sowell and De Witt Blanton [1a]. Selective methylation confirmed these results. The pyrrole VII [5] was selectively methylated at N1 [6] to yield VIII, after acylation and ring closure (Scheme 4), accor-

Scheme 4



Scheme 5



ding to [1a] resulted in IX. On the other hand, methylation of IV gave the identical product IX. As a last proof, we cyclisized IV in boiling phosphoric acid to the tricycle X, while it was impossible to cyclisize I in the same manner (Scheme 5).

Structural assignments of the substances were made on the basis of elemental analyses, infrared spectra and ^{1}H-nmr spectra. These data are presented in the Experimantal part and in Table 1.

EXPERIMENTAL

General Information: see [2].

9-Cyano-7,8-dimethyl-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrrolo[1,2-*a*][1,3]-diazepine (I) (experimental details see [2]).

1-(3′-Carbomethoxypropyl)-2-(2″-nitrobenzylideneamino)-3-cyano-4,5-dimethylpyrrole (V).

To a solution of I (1.0 g, 5 mmoles) in methanol was added 2-nitrobenzaldehyde (0.7 g, 7 mmoles) and a solution of sodium (0.23 g, 10 mmoles) in 30 ml of methanol. After heating on a steam bath until an orange colour appeared, the solution was cooled and diluted with water (*ca* 40 ml). The precipitate which formed was collected and recrystallized from ethanol, yield 0.51 g (30%), mp 175-178°; ir: 2200 and 1730 cm^{-1}; ^{1}H-nmr: (ppm) 2.04 (s, 3H, CH3 at C-4 or C-5), 2.17 (s, 3H, CH3 at C-4 or C-5), 2.55 (m, 4H, 2 × CH_2), 3.5 (s, 3H, $-OCH3$), 4.05 (m, 2H, CH_2), 7.7 (m, 4H, arom), 8.93 (s, 1H, CH); ms: (70 eV) m/e 369 (M+), 339, 270.

Anal. Calcd. for $C_{19}H_{24}N_4O_4$: C, 61.94; H, 5.47; N, 15.21. Found: C, 61.81; H, 5.31; N, 15.47.

1-(3′-Carboxypropyl)-1-(2″-nitrobenzylideneamino)-3-cyano-4,5-dimethylpyrrole (VI).

a) A solution of 5.0 g of sodium hydroxide in 50 ml of water was stirred on a steam bath with V (5.4 g, 15 mmoles). After V was dissolved, the reaction mixture was cooled and neutralized with hydrochloric acid (10%) until a brown precipitate was formed; yield 2.0 g (70%) mp >300°; ir: 2200, 1690 cm^{-1}; ^{1}H-nmr: (ppm) 2.15 (s, 3H, CH_3 at C4 or C5), 2.25 (s, 3H, CH_3 at C4 or C5), 2.65 (m, 4H, 2 × CH_2), 4.2 (m, 2H, CH_2), 7.9 (m, 4H, arom), 9.1 (s, 1H, CH), *ca* 11.5 (s, 1H, COOH); ms: (70 eV) 355 (M$^+$), 341, 324, 270.

Anal. Calcd. for $C_{18}H_{18}N_4O_4$: C, 61.01; H, 5.12; N, 15.81. Found: C, 60.87; H, 5.21; N, 15.67.

b) A mixture of II (2.49 g, 10 mmoles) and *o*-nitrobenzaldehyde (1.51 g, 10 mmoles) and 0.1 g of *p*-toluenesulfonic acid in dry toluene was refluxed with the aid of a Dean-Stark trap. When 1.8 ml of water was collected the reaction was stopped and the solvent removed under reduced pressure. The red precipitate was worked up as described for VIa.

1-Methyl-2-(2'-oxo-*N*'-pyrolidinyl)-3-cyano-4,5-dimethylpyrrole (IX).

a) To a solution of IV (2.03 g, 10 mmoles) in 60 ml of THF was added sodium hydride (80%) (0.29 g, 10 mmoles). After 30 minutes a solution of *p*-toluenesulfonicmethylate in 10 ml of THF was added dropwise with cooling into the reaction mixture. After stirring overnight the solvent was removed under reduced pressure and the formed precipitate recrystallized from ethanol, yield 1.6 g (75%); mp, 135-137°; ir: 220, 1705 cm^{-1}; ^{1}H-nmr: (ppm) 2.00 (s, 3H, CH3 at C-4 or C-5), 2.10 (s, 3H, CH3 at C-4 or C-5), 2.40 (m, 4H, 2 × CH_2), 3.65 (m, 2H, CH_2), 3.10 (s, 3H, CH_3); ms: (70 eV) m/e 218 (M+), 189, 175, 162.

Anal. Calcd. for $C_{12}H_{15}N_3O$: C, 66.34; H, 6.96; N, 19.34. Found: C, 66.70; H, 7.06; N, 19.68.

b) Compound IX was prepared from VIII according to ref [1a].

6,7-Dimethyl-5-oxo-1,2,3,5-tetrahydro-8*H*-dipyrrolo[1,2-*a*:3',2'-*e*]pyrimidine (X).

A solution of IV (2.02 g, 10 mmoles) in 100 ml of phosphoric acid (85%) was refluxed for 6 hours. After cooling, crushed ice and ammonia (25%) was added until the *p*H 7. The precipitate which formed was recrystallized from DMF, yield 1.44 g (71%), mp 206-208°; ir: 3360, 1670 cm^{-1}; ^{1}H-nmr: (ppm) 1.90 (s, 3H, CH_3 at C-4 or C-5), 2.10 (s, 3H, CH_3 at C-4 or C-5), 2.50 (m, 4H, 2 × CH_2), 3.80 (m, 2H, CH_2), 10.4 (s, 1H, NH); ms: (70 eV) m/e 204 (M+), 178, 164, 145.

Anal. Calcd. for $C_{11}H_{13}N_3O$: C, 65.00; H, 6.45; N, 20.68. Found: C, 65.02; H, 6.94; N, 20.23.

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