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Synthesis and Electrophilic Bromination of 2-Methyl-9-carbethoxy-1,3,4,7-tetraazacycl[3.3.3]azine

OLOF CEDER and KENNETH ROSÉN

Department of Organic Chemistry, University of Göteborg and Chalmers Institute of Technology, Fack, S-402 20 Göteborg, Sweden

The synthesis of the 1,3,4,7-tetraazacycl[3.3.3]azine, *7*, is described. Electrophilic bromination of this compound occurs in position 6.

The condensation between equimolar amounts of 2,4-diaminopyrimidine, *1*, and ethyl 2-cyano-3-ethoxyacrylate, *2*,[1] can occur either at the 2- or 4-amino group. In the first case the recently reported[2] 1,3,6,7-tetraazacycl-azine *8* (*cf.* Chart 1) is eventually formed and in the second the isomeric system *7* should finally result. The present communication describes the synthesis, proof of structure, and electrophilic bromination of 2-methyl-9-carbethoxy-1,3,4,7-tetraazacycl[3.3.3]azine, *7*, along with spectral studies on *7* and its 6-bromoderivative *9*. The sequence utilized to prepare *7* is the same as the one earlier[2] used to obtain *8*.

Condensation of 2,4-diaminopyrimidine, *1*, with one mol of ethyl 2-cyano-3-ethoxyacrylate, *2*, in refluxing benzene led to a *ca.* 1:3 mixture of *3* and *4*, from which *3* was isolated by fractional crystallization from methanol. The two isomers could not be separated by thin-layer chromatography. The structural proof of *3* is based on the following data. The mass spectrum shows a molecular ion peak at $m/e = 233$ and in the IR spectrum, bands at 2180 (CN), 3200 – 3400 (NH_2), and 1680 cm^{-1} (ester carbonyl) are present. The NMR spectrum displays the expected types of protons (*cf.* Experimental) and it is very similar to the spectrum of *4*.[5] In the spectrum of *3* no evidence for a mixture of geometrical isomers, which is present in the spectrum of *4*, can be discovered.

On acetylation of an aromatic, primary amine, the proton adjacent to the amino group suffers a considerable chemical-shift change.[2,3] This method, earlier used[2] to determine the structure of *4*, was now applied to *3*. In an aminopyrimidine system the above-mentioned change is 97 – 117 Hz (at 60 MHz).[4] The present results are summarized in Chart 1. The shift-changes,

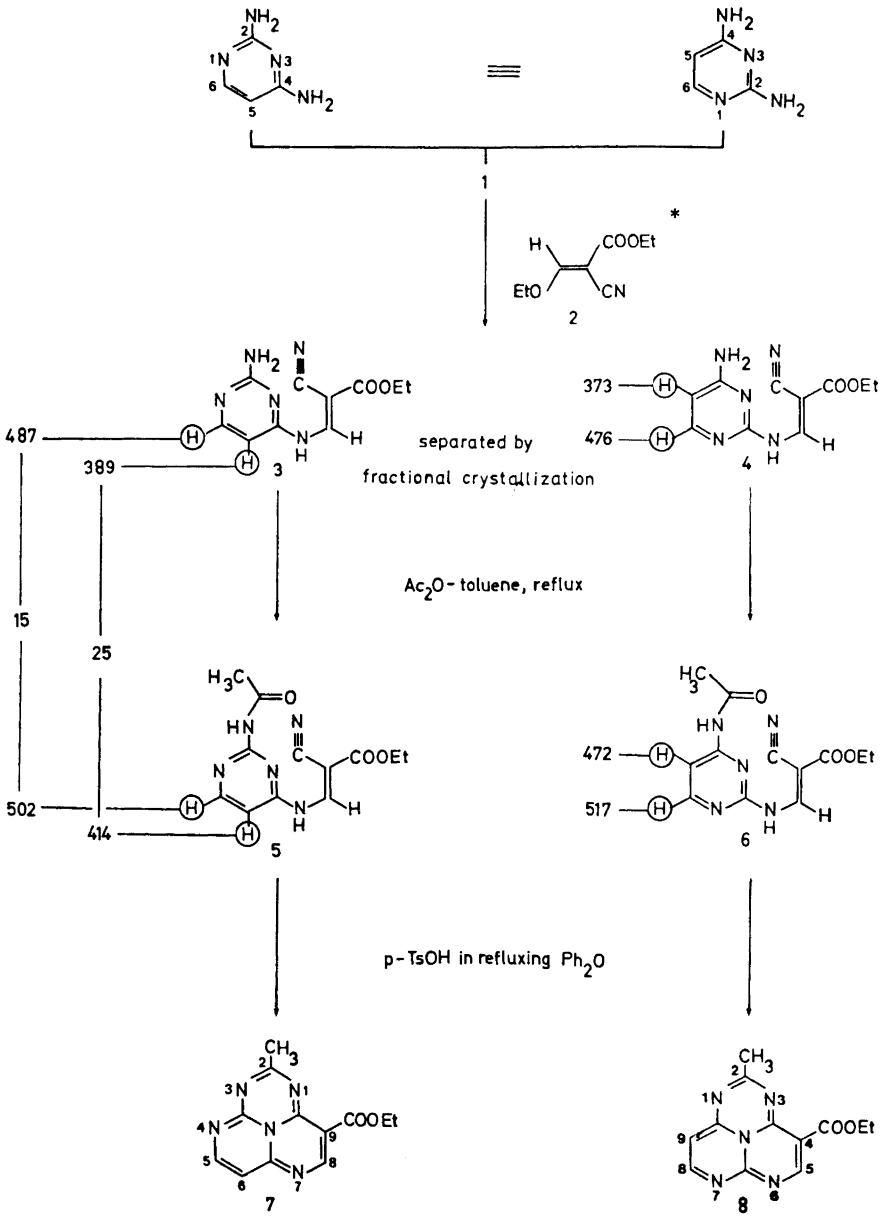


Chart 1. Reaction scheme for the formation of *7* and chemical-shift changes of H-5 and H-6 in *3* and *4* on acetylation. * For configurational assignment of *2*, *cf.* Ref. 2.

25 and 15 Hz for H-5 and H-6, respectively, are in complete accord with structures *3* and *5*.

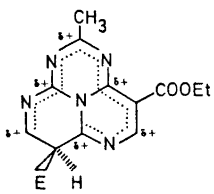
The final ring closure of *5* to *7* was achieved, as before,[2] in diphenyl ether at 250° in the presence of a catalytic amount of *p*-toluenesulfonic acid. The yield in the last step was 45 %. The deep-red cyclazine *7* has a molecular weight of 257 (MS) and the elemental analyses are in agreement with the molecular formula $C_{12}H_{11}N_5O_2$. The IR spectrum, which lacks amino and cyano absorption, has a carbonyl band at 1638 cm^{-1}. The UV spectrum (*cf.* Experimental) is very similar to the spectrum of *8*.[6] The chemical shifts for the "corresponding" protons in *7* and in *8* are, as would be expected, very similar (*cf.* Table 1). The mass spectra of *7* and *8*[2] show identical fragmentation patterns, including an abundance of doubly-charged ions.

Table 1. Chemical-shift values for the protons in *7* and *8* ($CDCl_3$).

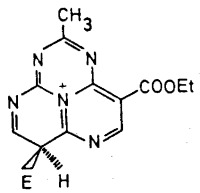
Cpd.	"Corresponding" aromatic protons						CH_3	CH_3-CH_2-O	
7	8.10	(H-8)	7.67	(H-5)	6.12	(H-6)	2.20	1.33,	4.29
8	8.22	(H-5)	7.74	(H-8)	5.75	(H-9)	2.09	1.29,	4.20

Attempts to decarboxylate *7* by the method used to prepare 1,3,6-triazacycl[3.3.3]azine and its 2-methyl homolog [7] from their 4-carbethoxy derivatives (diphenyl ether, traces of *p*-toluenesulfonic acid, 100 – 258°, 1 – 3 h) were not successful, since *7* is unstable under these conditions.

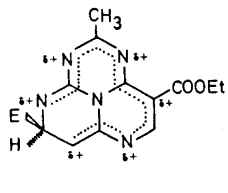
From an argument using resonance structures, one can predict that an electrophile (E) should attack at C-6. For the intermediates resulting from substitution in this position one can draw, in addition to the six resonance forms with the positive charge on carbon atoms as represented by *7a*, three structures with the charge on the central nitrogen atom. These, represented by *7b*, are the only ones where all atoms have full octets. For substitution in position 5, there are four resonance forms with the positive charge on peripheral nitrogen atoms and two with the charge on carbon atoms. In all these forms, represented by *7c*, the atom carrying the charge contains a sextet and no resonance structure with the charge on the central nitrogen atom can be drawn.



7a

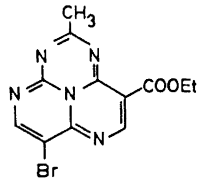


7b

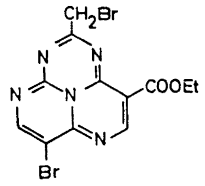


7c

In order to verify the above prediction, *7* was treated with *N*-bromosuccinimide in chloroform at room temperature. A 86 % yield of 6-bromo-9-carbethoxy-2-methyl-1,3,4,7-tetraazacycl[3.3.3]azine, *9*, was obtained. Its mass spectrum shows molecular ion peaks at $m/e = 335$ and 337 (intensity 1:1), which is in agreement with the formula $C_{12}H_{10}N_5O_2Br$. In the NMR spectrum of *7* the H-5 and H-6 signals appear as two doublets centered at 7.67 and 6.12 ppm, respectively. In the spectrum of *9*, the signal at higher field has vanished and the lower-field signal remains as a singlet at 7.96 ppm. Therefore, substitution has occurred at C-6. The H-8 singlet is found at 8.25 ppm.



9



10

There seems to be no significant difference between the strength of the conditions necessary to monobrominate *7* and *8*. The monobromo compound *9* seems to be much more stable than the 9-bromoderivative of its isomer *8*, and it can be handled and stored without any particular precautions. The higher stability of system *7* is also demonstrated by bromination with bromine in glacial acetic acid. In that medium at room temperature, *8* was completely destroyed and no identifiable products could be isolated. The same treatment of *7* at 20° or 50° yielded a blue dibromo compound (molecular ion peaks at 413, 415, and 417, intensities 1:2:1), stable under normal conditions (*cf.* Experimental). This compound also resulted when *9* was treated with bromine in glacial acetic acid as described above. We believe that it has structure *10* since electrophilic bromination is not likely to occur on carbon atoms adjacent to a nitrogen atom (*cf. 7a* and *7c*) and since the corresponding methyl group in the 1,3,6-triazacycl[3.3.3]azine system reacts easily under these conditions.[8]

EXPERIMENTAL

General. Nuclear magnetic resonance (NMR) spectra were recorded with a Varian Model A-60 spectrometer, using tetramethylsilane as internal reference. Ultraviolet and visible spectra were measured in ethanol with a Cary Model 15 spectrophotometer. Mass spectra were determined with a GEC-AEI MS 902 instrument at the Department of Medical Biochemistry, University of Göteborg. Thin-layer chromatography (TLC) was performed on Silica Gel GF_{254} (Merck) according to Stahl and the spots were visualized by means of short-wave ultraviolet light. For column chromatography, silica gel (0.05 – 0.2 mm; Merck), and neutral aluminium oxide (Fluka) were used.

Condensation of 2,4-diaminopyrimidine with ethyl 2-cyano-3-ethoxyacrylate. To a suspension of 8.8 g (0.08 mol) of 2,4-diaminopyrimidine, *1*, in 1 l of benzene was added 13.5 g (0.08 mol) of ethyl 2-cyano-3-ethoxyacrylate, *2*. The reaction mixture was heated under reflux for 72 h. After cooling to room temperature, the reaction mixture was filtered to remove a small amount of brown, solid material and the benzene was evaporated under reduced pressure. The solid residue was dissolved in boiling methanol, cooled in an ice bath and the precipitate (of *4*) then formed was removed by filtration.

The mother liquor was evaporated under reduced pressure and the remaining solid was washed with cold methanol to remove traces of starting material. This evaporation-washing procedure was repeated three times. After drying at 70°/2 torr, 1.7 g (9 %) of yellow, solid *3*, m.p. 184 – 186°, showing one spot on TLC (EtOAc; $R_F = 0.63$) was obtained. IR (KBr): 3200 – 3400 (NH), 2180 (CN), 1680 (C=O) cm^{-1}; NMR (dimethyl sulfoxide-d_6): doublet ($J = 5$ Hz) at 8.08 (1 H, H-6), doublet ($J = 5$ Hz) at 6.45 (1 H, H-5), vinyl singlet at 9.02 and NH absorption at 6.58 ppm; MS: *m/e* 233 (M^+). No NMR signals arising from compound *4* were detectable.

Acetylation of 3 to 5. A suspension of 1.0 g (0.004 mol) of *3* in 70 ml of *p*-xylene and 3 ml of acetic anhydride was heated under reflux for 24 h. The resulting solution was allowed to cool to room temperature and the white, crystalline solid, which had precipitated, was separated by filtration. Yield: 0.6 g of pure *5* (51 %). NMR (dimethyl sulfoxide-d_6): broad NH at 10.10 (2 H), vinyl singlet at 9.01 (1 H), doublet ($J = 5$ Hz) at 8.33 (1 H, H-6), doublet ($J = 5$ Hz) at 6.88 (1 H, H-5), quartet at 4.20 (2 H, CH_2), singlet at 2.22 (3 H, CH_3), and triplet at 1.26 (3 H, CH_3) ppm. MS: *m/e* 275 (M^+).

Cyclization of 5 to 7. To a solution of 210 mg of *5* in 30 ml of refluxing diphenyl ether was added 5 mg of *p*-toluenesulfonic acid. The solution immediately became deeply red-brown. Refluxing was continued for 15 min. The now turbid reaction mixture was allowed to cool to room temperature, and was then poured on to a column of 8 g of aluminium oxide, packed in petroleum ether. A red band was eluted with 250 ml of chloroform. The eluate containing this material was collected and evaporated under reduced pressure to yield 90 mg (45 %) of a deep-red solid, m.p. 157 – 159°. The NMR spectrum ($CDCl_3$), IR, and mass spectral data are reported above. UV: λ_{max} at 221 ($\varepsilon = 13\,900$), 236 ($\varepsilon = 10\,150$), 315 ($\varepsilon = 12\,050$), 337 ($\varepsilon = 15\,720$), 348 ($\varepsilon = 13\,200$), 492 ($\varepsilon = 490$), 521 ($\varepsilon = 744$), and 556 ($\varepsilon = 639$). (Found: C 55.96; H 4.58; N 27.03. Calc. for $C_{12}H_{11}N_5O_2$: C 56.03; H 4.31; N 27.22).

Bromination of 7 with NBS. A solution of 40 mg of *7* and 90 mg of *N*-bromosuccinimide in 8 ml of chloroform was stirred at *ca.* 25°. The formation of *9* was followed by TLC (EtOAc; $R_F = 0.27$). After 30 h, all starting material had been converted to *9*. The volume of the reaction solution was reduced to *ca.* 5 ml under reduced pressure and succinimide and unreacted NBS were then removed by filtration. The filtrate was poured on to a column of silica gel (2.5 × 25 cm) and the product was eluted with 150 ml of chloroform-ethyl acetate (1:3). Yield: 45 mg (86 %). Mass and NMR spectral data are reported above.

Bromination of 7 with bromine in glacial acetic acid. To a solution of 5 mg of *7* in 0.5 ml of glacial acetic acid was added a solution of 7 mg of bromine in 0.2 ml of glacial acetic acid. The mixture was allowed to stand at room temperature and the reaction was followed by analytical TLC (EtOAc). A blue-violet band appeared and after 4 h the acetic acid was removed *in vacuo* and the brown residue was applied on to a preparative silica-gel plate, which was developed in ethyl acetate. The blue-violet band was scraped off and extracted with chloroform. MS: *m/e* 413, 415, and 417 (M^+, intensity 1:2:1), in agreement with the composition $C_{12}H_9N_5O_2Br_2$.

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