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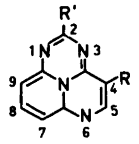
Some Reactions of the 2-Methyl-1,3,6-triazacycl[3.3.3]azine System

OLOF CEDER and KARIN VERNMARK

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

The following properties of the 2-methyl-1,3,6-triazacycl[3.3.3]azine system have been studied: the reactivity of the methyl group, catalytic hydrogenation, nitration, alkylation, and nucleophilic substitution. Hydrogenation leads to a dihydro derivative, alkylation to a mixture of *N*-alkylated products, and attack by piperidine proceeds *via* an aryne intermediate.

The present communication describes some further properties and reactions of the earlier prepared 2-methyl-1,3,6-triazacycl[3.3.3]azine,* *1*,[1–3] and its 4-cyano derivative *2*.[1,4,5]



1 R=H, R'=Me
2 R=CN, R'=Me
3 R=CN, R'= CH=CHPh
8 R=NH_2, R'=Me
9 R=Br, R'=Me

Methyl groups on carbon atoms adjacent to nitrogen in aromatic heterocycles often display considerable reactivity, *e.g.* in 2-methylpyrimidine.[8] The NMR spectrum of *2* in CF_3COOD showed that the methyl protons had exchanged to 50 % after 10 min, while the intensity of all other proton signals remained unchanged for several hours. In a CF_3COOD solution containing a trace of concentrated DCl, exchange of H-5 was also observed from a small decrease in its NMR signal after *ca.* 2 h. Reaction of *2* with benzaldehyde in the presence of $ZnCl_2$ gave the styryl compound *3*.[8] Attempts to convert *3* to the corresponding aldehyde by ozonolysis were unsuccessful since the cyclazine system was decomposed by ozone.

Catalytic hydrogenation of *2* yielded two products, *4* and *5*, of the same molecular weight. The structure of *4*, 5,6-dihydro-*2*, follows from the presence of a CH_2 signal (not coupled with the NH in DMSO-d_6) and an A_2X-type absorption in the aromatic region of the NMR spectrum. In air, on TLC plates, and on sublimation, *4* is smoothly oxidized back to *2*. A mass spectrum of *4* shows a small molecular ion and a large M − 2 ion indicating that aromatization takes place in the mass spectrometer also. Compound *5*, isomeric with *4* and showing the same behavior, is probably the 1,2- or 2,3-dihydro compound, but lack of material did not allow a structural assignment. The parent compound *1* is more resistant to catalytic hydrogenation than *2* and most of the starting material is recovered unchanged when the conditions are the same as those used above.

The central nitrogen atom in cyclazines is completely non-basic [6] and in azacyclazines protonation occurs on the peripheral *N*-atoms.[2,9] When *1* is treated with methyl iodide, a mixture of three quaternary salts, *6a* − *c* is formed in the ratio 85:10:5 (NMR, *cf.* Experimental). The major component is probably the 6-methylated compound, *6a*, since alkylation of N-6 is sterically less hindered than that of N-1 and N-3; the NMR chemical shift values do not allow a distinction between *6b* and *6c*, respectively. Attempts to alkylate *2* with methyl iodide were unsuccessful also under forcing conditions. On the other hand, *2* reacted smoothly with methyl fluorosulfonate to form a mixture of two quaternary salts in a 95:5 ratio (NMR, *cf.* Experimental). Again, the major component is probably the 6-methyl derivative, *7a*.

* For definitions and nomenclature of cyclazines, *cf.* Refs. 6 and 7.

None of the methods available to date for the synthesis of azacycl[3.3.3]azines has led to amino compounds which could be converted into diazonium salts. When *2* was heated in polyphosphoric acid (PPA) containing $NH_2OH.H_2SO_4$,[10] a small yield of the 4-amino compound *8* was obtained. This conversion is not synthetically useful, however.

Treatment of *1* with $Cu(NO_3)_2-Ac_2O$ produced the three isomeric 4-, 7-, and 9-nitro compounds. All three possessed the same R_F-value in the solvent systems tried and they could not be separated. Nitration, like bromination, of *1*[3] proceeded very smoothly and rapidly and the mixture of derivatives was produced in 40 % yield.

In order to investigate the behavior of the 1,3,6-triazacycl[3.3.3]azine system toward nucleophiles, 4-bromo-*1*, *9*, was refluxed for *ca.* 2 days with piperidine. Instead of the expected substitution product, the 5-piperidino derivative resulted. Its structure was supported by NMR-shift reagent studies (*cf.* Experimental). This reaction therefore seems to require an elimination-addition process *via* the 4,5-dihydro derivative.[11] The conditions used in the present case are notably mild for the generation of such an intermediate.

EXPERIMENTAL

General spectrometric conditions and chromatographic procedures were the same as those described in Ref. 13.

The ozonization experiment was performed according to the following procedure: The reaction solution was kept at −60 °C by the use of a dry ice−ethanol bath. A mixture of 3 % of ozone in oxygen, produced by a Welsbach Model T-23 ozonator, was passed through the solution at a rate of 70 ml/min. The reaction was continued until elemental iodine was liberated from a 1 % aqueous solution of potassium iodide through which the effluent gases were passed. Excess of ozone was then removed by passing a stream of nitrogen through the solution for 20 min.

Preparation of 4-cyano-2-styryl-1,3,6-triazacycl[3.3.3]azine, 3. To a mixture of 170 mg (0.81 mmol) of *2* in 3 ml (29.6 mmol) of benzaldehyde a small amount of $ZnCl_2$ was added. The solution was kept at 110 °C for 20 min, during which time it turned dark-green. Some of the benzaldehyde was evaporated under reduced pressure. Chromatography of the residue on 15 g of silica gel (EtOAc−$CHCl_3$); 1:9) gave 110 mg of product from which benzoic acid was eliminated by sublimation at 120°/2 Torr. Purification of the sublimation residue by preparative TLC (EtOAc) yielded 60 mg (25 %) of a green solid *3*, m.p. 235−238 °C. IR: 2230 (C≡N), 1630 cm^{-1} (C=C), UV: λ_{max} (ε) 215 (17 450), 238 (13 960), 295 sh. (7280), 352 (51 200), 378 sh. (27 850), 388 sh. (18 940), 397 (21 200), 407 sh. (5050) in ethanol and 555 sh. (200), 600 (326), 643 (410), 707 (315 nm in acetone). NMR ($CDCl_3$): δ 5.94 (1 H, d, H-7 or H-9), 6.11 (1 H, d, H-7 or H-9), 6.41 (1 H, d, vinyl proton), 7.12 (1 H, t, H-8), 7.6−7.3 (6 H, m, phenyl protons and H-5), 7.78 (1 H, d, vinyl proton), $J_{7,8}=J_{8,9}=8.2$, J(vinyl protons) = 15.8 Hz (indicating *trans* configuration). MS: $M^+=297.096\pm0.004$. Calc. for $C_{18}H_{11}N_5$: 297.1014.

Ozonolysis of 3. A solution of 15 mg of *3* in 30 ml of CH_2Cl_2 was ozonized for 7 min. The blue solution had then turned yellow. To destroy the ozonides, a small amount of Pd/C was added and the solution was hydrogenated for 16 h. After filtration and evaporation, a yellow sirup was obtained in which no blue or green compounds could be detected by TLC.

Catalytic hydrogenation of 2 *to* 4 *and* 5. A mixture of 1 g of *2* and 100 mg (10 %) Pd/C in 250 ml of abs. ethanol was shaken under H_2 (3.1 atm.) for three days in a Parr hydrogenation apparatus. Unreacted starting material and catalyst were removed from the solution by filtration. After the solution was evaporated to dryness, 700 mg of a green solid remained which was purified by column chromatography on silica gel with EtOAc-$CHCl_3$ (1:3) as the eluent. Yield: 200 mg (20 %) of a yellow product *4*, m.p. 243 °C. Preparative TLC (EtOAc-MeOH; 3:1) separated *5* ($R_F=0.45$) from *4* ($R_F=0.37$) giving < 1 % yield of *5*. *4* IR: 3480 (NH), 2200 cm^{-1} (C≡N), UV:λ_{max} (ε) 262 (1055), 346 (2250), 377 sh. (1290), 410 sh. (690) nm, NMR (DMSO-d_6): δ 2.15 (3 H, s, CH_3), 3.88 (2 H, s, CH_2), 6.30 (2 H, d, H-7 and H-9), 7.67 (1 H, t, H-8), $J_{7,8}=J_{8,9}=8.0$ Hz, MS: $M^+=211$, *5* MS: $M^+=211$.

Catalytic hydrogenation of 1. A mixture of 42 mg of *1* and 7 mg of (10 %) Pd/C in 20 ml of abs. ethanol was hydrogenated as described above. During three days the solution did not change color and no hydrogenation product could be detected by TLC.

Methylation of 1 *to* 6a−c. A solution of 73 mg (0.39 mmol) of *1* in 3 ml (48.1 mmol) of CH_3I in a sealed tube was kept at 60 °C for 4 h. Unreacted starting material was dissolved in $CHCl_3$ and the remaining red product was isolated by filtration, washed with $CHCl_3$, and dried. Yield: 75 mg (95 %) of *6*. The three N-CH_3 signals indicate the presence of the three isomers *6a−c*. NMR (D_2O) of the major isomer: δ 2.14 (3 H, s, 2-CH_3), 3.27 (3 H, s, N-CH_3), 5.55 (1 H, d, H-4), 6.61 (2 H, d, H-7 and H-9), 7.36 (1 H, d, H-5), 7.88 (1 H, t, H-8), $J_{4,5}=7.7$, $J_{7,8}=J_{8,9}=8.6$ Hz. The two minor

isomers have their methyl signals at 2.20, 3.06 and 2.23, 3.13, respectively. The ring-proton signals overlap and are therefore difficult to assign. The integral ratio for the three methyl groups in *6a–c* is 17:2:1, respectively. Electrophoresis (pyridine-AcOH-H_2O; 20:5:220) of *6* was performed on cellulose plates (400 V) and showed the presence of only one spot, hereby proving the existence of only monomethylated *1* in the mixture. The electrophoresis was carried out on a Camag Thin Layer Electrophoresis apparatus.

Methylation of 2 (a) with methyl iodide. One hundred mg (0.47 mmol) of *2* and 0.7 ml (11.3 mmol) of CH_3I in a sealed tube were reacted for 17–24 h at different temperatures between 20 and 100 °C. At lower temperatures, the starting material was recovered unchanged, but at higher temperatures it was destroyed. No methylated product could be isolated.

(b) with methyl fluorosulfonate. To a suspension of 100 mg (0.47 mmol) of *2* in 4 ml of CH_3CN, 1 g (8.8 mmol) of CH_3OSO_2F was added dropwise. The blue solution turned red and after 1 min, 5 ml of CH_2Cl_2 was added. The red precipitate which formed was collected by filtration, washed with CH_2Cl_2 and air-dried. Yield: 40 mg (37 %). The red amorphous product, *7*, was very unstable in the solid state and from an MeOH or H_2O solution the starting material was reformed almost immediately. The NMR signals of the methylated product indicated the presence of two isomers in a 95:5 ratio. NMR (CF_3COOD) of the major isomer: δ 2.38 (3 H, s, 2-CH_3), 3.99 (3 H, s, *N*-CH_3), 6.95 (1 H, d, H-7 or H-9), 7.27 (1 H, d, H-7 or H-9), 8.04 (1 H, t, H-8), 8.25 (1 H, s, H-5), $J_{7,8}=J_{8,9}=8.5$ Hz.

Preparation of 4-amino-1,3,6-triazacycl[3.3.3]azine, 8. A mixture of 257 mg (1.2 mmol) of *2* and 612 mg (4.7 mmol) of $NH_2OH.H_2SO_4$ in 5 ml of PPA was heated to 190 °C. Ice water was added and the solution was neutralized with 10 % aqueous $NaHCO_3$ and then extracted with chloroform. The extract was dried ($MgSO_4$) and evaporated to dryness. Preparative TLC (EtOAc-MeOH; 3:1) yielded 9 mg (4 %) of a green solid, *8*, m.p. 220 °C. IR: 3450, 3310 cm^{-1} (NH), UV: λ_{max} (ε) 213 (9900), 237 (11 770), 263 (13 460), 307 (9100), 353 (10 840), 394 (6240), 531 sh. (40), 577 (130), 629 (190), 691 (150) nm, NMR ($CDCl_3$): δ 1.65 (3 H, s, CH_3), 5.10 (1 H, d, H-7 or H-9), 5.76 (1 H, d, H-7 or H-9), 6.46 (1 H, q, H-8), 6.99 (1 H, s, H-5), $J_{7,8}=8.7$, $J_{8,9}=7.4$ Hz, MS: $M^+=199.084\pm0.003$. Calc. for $C_{10}H_9N_5$: 199.0858.

Acetylation of 8. To a solution of 2 mg of *8* in 0.5 ml of *p*-xylene, 1 drop of acetic anhydride was added. The mixture was kept at 30 °C for 5 min, then evaporated to dryness yielding a green solid. TLC (EtOAc-MeOH; 1:1) showed the presence of a blue compound with almost the same R_F value as *8*, m.p. 207 °C. MS: $M^+=241$.

Nitration of 1. To a solution of 80 mg of $Cu(NO_3)_2.3H_2O$ in 2 ml of acetic anhydride, 40 mg of *1* was added. The mixture was left at room temperature for 25 min and it was then neutralized with aqueous $NaHCO_3$ (10 %), yielding a green solution which was extracted with chloroform. The combined extracts were dried ($MgSO_4$) and then evaporated to dryness. On preparative TLC (EtOAc-MeOH; 3:1) of the dark-green product, only one band ($R_F=0.42$) was observed. Extraction of this band yielded 20 mg of a green solid, m.p. 180–182 °C. The NMR spectrum ($CDCl_3$) showed it to be a mixture of three isomers. The methyl groups have the chemical shift values 1.91, 2.01 and 2.08 ppm and the integral ratio of these signals is 1:1.5:1, MS: $M^+=229$.

Reaction of 4-bromo-2-methyl-1,3,6-triazacycl[3.3.3]azine 9, *with piperidine*. A mixture of 90 mg of 4-bromo-*1* in 8 ml of piperidine was kept at 80–90 °C for two days. The solution was evaporated to dryness. Column chromatography on 4 g of silica gel with EtOAc as the eluent, gave a red product which was further purified by preparative TLC (EtOAc-MeOH; 3:1). Yield: 20 mg (22 %), m.p. 125–127 °C. UV: λ_{max} (ε) 234 (15 820), 260 (17 940), 285 sh. (17 270), 309 (25 800), 325 sh. (19 820), 367 sh. (4760), 428 sh. (160), 450 sh. (260), 480 sh. (470), 513 (650), 552 (540) nm. NMR ($CDCl_3$): δ 1.62 (6 H, s, piperidine protons), 1.84 (3 H, s, CH_3), 3.51 (4 H, s, piperidine protons), 5.02 (1 H, s, H-4), 5.55 (1 H, d, H-7 or H-9), 5.90 (1 H, d, H-7 or H-9), 6.95 (1 H, t, H-8), $J_{7,8}=J_{8,9}=8.3$ Hz, MS: $M^+=267.146\pm0.002$. Calc. for $C_{15}H_{17}N_5$: 267.1484.

Lanthanide-shift measurements. The different Δ_{Eu}-values [12] were determined as follows: a weighed amount of the actual substance was dissolved in dry $CDCl_3$ and known amounts of Eu(fod)$_3$-d_{27} dissolved in the same solvent were added. After each addition, the NMR tube was left spinning in the probe for about 15 min before the NMR spectrum was determined. The Δ_{Eu}-values obtained in *ca.* 0.15 M solution and at shift reagent/substrate ratios from 0 to 2 are summarized in Table 1.

Table 1. Δ_{Eu}-values for the protons in 5-piperidino-*1*.

Proton	Δ_{Eu}
H-4	3.8
H-7	0.8
H-8	0.8
H-9	5.4
2-CH_3	5.0
Piperidine	0.3 and 0.8

The high value for the 2-methyl protons indicates that the coordination of Eu takes place preferably at N-1 and N-3. The chemical shift value of the one-proton singlet (δ 5.02) and the high Δ_{Eu}-value for the same proton indicate that H-4 is present. Therefore we conclude that the piperidine moiety is located in the 5-position. The low degree of coordination at the 6-position is therefore a result of the steric hindrance of the piperidine moiety.

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REFERENCES

1. Ceder, O. and Andersson, J. E. *Acta Chem. Scand. 26* (1972) 596.
2. Ceder, O. and Vernmark, K. *Acta Chem. Scand. 27* (1973) 3259.
3. Ceder, O. and Samuelsson, M. L. *Acta Chem. Scand. 29* (1975) 867.
4. Ceder, O., Andersson, J. E. and Johansson, L. E. *Acta Chem. Scand. 26* (1972) 624.
5. Ceder, O. and Samuelsson, M. L. *Acta Chem. Scand. 27* (1973) 2095.
6. Windgassen, Jr., R. J., Saunders, Jr., W. H. and Boekelheide, V. *J. Am. Chem. Soc. 81* (1959) 1459.
7. Ceder, O. and Beijer, B. *J. Heterocycl. Chem. In press.*
8. Holland, A. *Chem. Ind. London* (1954) 786.
9. DePompei, M. and Paudler, W. W. *J. Org. Chem. 41* (1976) 1661.
10. Snyder, H. R., Elston, C. T. and Kellom, D. B. *J. Am. Chem. Soc. 75* (1953) 2014.
11. Den Hertog, H. J. and Van der Plas, H. C. *Adv. Heterocycl. Chem. 4* (1965) 121.
12. Demarco, P. V., Elzey, T. K., Lewis, R. B. and Wenkert, E. *J. Am. Chem. Soc. 92* (1970) 5734.
13. Ceder, O. and Vernmark, K. *Acta Chem. Scand. To be published.*

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