Alkylation of Tetrazolo[1,5-a]pyridine and Its Benzologues (Annelation Effect)

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Tetrazolo[1,5-a]pyridine (1) and its angularly and linearly fused benzologues tetrazolo[1,5-a]quinoline (4), tetrazolo[5,1-a]isoquinoline (7), and tetrazolo[1,5-b]isoquinoline (10), respectively, were alkylated by methyl iodide, dimethyl sulfate, trimethyloxonium, and triethyloxonium salts to give mixtures of 1- and 2-alkyl compounds in different ratios. While tetrazoles 1 and 4 afforded mainly 1-alkyl compounds, tetrazole 7 yielded predominantly 2-alkyl compound. Comparison of the linearly (10) and angularly fused (4 and 7) analogues showed that besides steric factors the annelation effect influences also the regioselectivity of these reactions. A satisfactory correlation was found between densities of the MO representations of the lone electron pairs calculated by CNDO/2 and the experimental findings.

Recently we have reported[1] that direct phenylation of tetrazolo[1,5-a]pyridine (1) as well as of its angular benzologues with diphenyliodonium salt results mainly in N-1 arylated product unless this position is sterically hindered (e.g., selective formation of 2-phenyltetrazolo[5,1-a]isoquinoline was found).

As a continuation of the above studies and of our earlier efforts on electrophilic reactions of fused heteroaromatic systems[2] we decided to investigate the alkylaton of the differently fused tetrazoles in detail. In this area, very little has been published earlier: Glover et al. found[3] that tetrazolo[1,5-a]pyridine (1) reacts with methyl iodide to give 1-methyltetrazolopyridinium salt **2**; the structure was proved by an independent synthesis. According to patent literature,[4] the alkylation of tetrazolo[1,5-a]quinoline (4) with ethyl iodide afforded the 3-ethyl compound **5** (corresponding to the 1-substitution of **1** because of the different numbering). No verification of the structure, however, was given in this publication.

This study compares the alkylation of fused tetrazoles with three methylating agents which differ in their soft and hard character[5] (methyl iodide, dimethyl sulfate, and trimethyloxonium tetrafluoroborate), and triethyloxonium tetrafluoroborate. The latter reagent was chosen to assess the dependence of these alkylations on steric factors.

The bicyclic (1) and angular tricyclic (4 and 7) tetrazoles exist exclusively as tetrazole isomers,[6] while 3-azidoisoquinoline (11) and the linear tetrazolo[1,5-b]isoquinoline (10) are in equilibrium both in solid phase and in solutions.[7] The presence of the ring-opened azide isomer **11** is responsible for the fact that alkylation of this compound is successful only with a trialkyloxonium reagent.

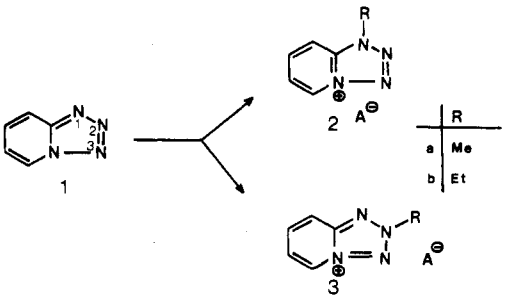
Mixtures obtained from the alkylation reactions were worked up so that, in every case, the crude product was first isolated to enable detection of all components formed in the reaction (Scheme I).

Structure elucidation of the alkylated products was carried out by ^{1}H NMR. Reaction of bicycle **1** with methyl iodide afforded a mixture of intensity ratio of 24:1 as revealed by the methyl signals.

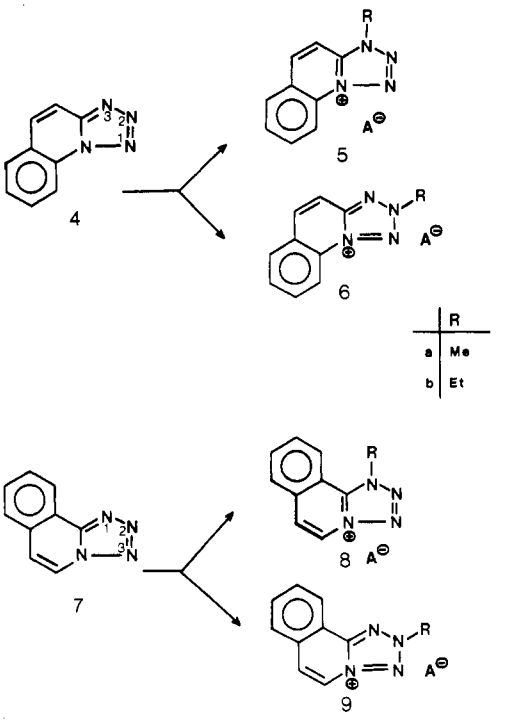
By comparison with the literature,[3] 1-methyl-tetrazolo-[1,5-a]pyridinium salt (**2**) was formed as main product and the minor product therefore had to be considered as 2-methyl compound **3**. (Formation of the 3-methyl isomer could be excluded by proton NMR as shown below).

Similarly, methylation of the angularly fused tricyclic tetrazoles **4** and **7** with methyl iodide afforded mixtures containing two isomers in a ratio of 10:1 and 3:2, respectively (Scheme II). Assignments of the proton signals to the components was straightforward on the basis of signal

Scheme I



Scheme II



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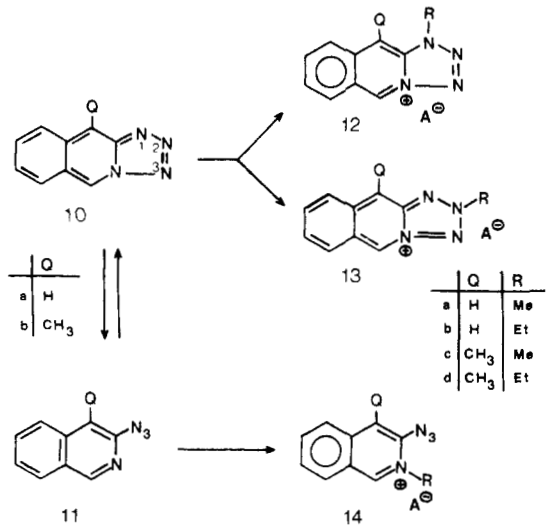
0022-3263/88/1953-0973$01.50/0

Scheme III



intensities. Differential nuclear Overhauser effect (DNOE) measurements as shown (see supplementary material) indicated that the major component in each experiment was the 1-methylated product (according to numbering of bicycle **1**), isomers **5** and **8**.

Saturation of the more intense methyl singlet at 4.62 ppm in the ^{1}H NMR spectrum of the mixture of **5** + **6** resulted in a significant enhancement of intensities of H-4 at 8.57 ppm [J(H-5,H-4) = 9.4 Hz]. Irradiation of the weaker methyl line at 5.01 ppm had, however, no influence on the aromatic signal intensities. Similarly, no effect on H-9 doublet pair of the isomers (at 8.88 and 8.73 ppm, respectively) was observed which finding excludes the 3-methyl structure for both components. Results of similar DNOE experiments on the mixture of **8** + **9** were in accordance with the above findings. Irradiation of the methyl line at 4.91 ppm corresponding to the main product results in a very strong intensity enhancement of the corresponding H-10 doublet pair at 8.98 ppm. The stronger effect in **8** as compared to **5** is due to the smaller distance between the methyl group and the "peri" H-10 atom in compound **8**. No DNOE signal of H-10 was observed in case of saturation of the methyl signal at 4.99 ppm for the minor component **9**. As the H-5 doublet (at 9.48 and 9.43 ppm) of both isomers **8** and **9** proved to be insensitive to saturation of the methyl group, the 3-methyl alternative structure could safety be ruled out.

Two derivatives of the linearly fused tetrazolo[1,5-*b*]-isoquinoline ring system (**10**)—the unsubstituted (**10a**) and 10-methyl-substituted (**10b**) compounds—were subjected to alkylation reactions (Scheme III). Assignment of the proton NMR spectra to the isomeric alkyltetrazolium structures was accomplished in the case of compound **10b**. Because of the lack of azide band in IR spectrum, the two components found in this spectrum were considered as 1- and 2-methyl isomers. On the basis of the chemical shifts of the related compounds (**2**, **3**, **5**, **6**, **8**, and **9**) we concluded that 1-methyl compound **12a** was obtained in majority. (CH_3, 4.81 ppm, while for the minor component 5.02 ppm was measured).

On the basis of the above assignements the isomeric ratios observed with different reagents could easily be established by comparison of integrals of the different methyl signals. In the spectra of the ethylated products, comparison of the methylene signals was used to determine the position of the ethyl group introduced.

Table I. Percent of 1-Alkylated Isomers in the Reaction Mixtures[a]

start tetrazole	Me_2SO_4	MeI	Me_3O^+-BF_4^-	Et_3O^+-BF_4^-	products
1	85	96	86	75	**2** and **3**
4	95	91	90	60	**5** and **6**
7	60	60	40	20	**8** and **9**
10a			100	95	**12a,b** and **13a,b**
10b			83	52	**12c,d** and **13c,d**

[a] These entries express the ratio of the 1-alkylated products related to the total 1-alkyl/(1-alkyl + 2-alkyl) × 100 with a limit of reproducibility of ±2%.

Results of alkylations obtained by ^{1}H NMR are summarized in Table I. From this comparison, the following conclusions can be drawn.

(A) With respect to the reagent: (i) dimethyl sulfate and methyl iodide react in rather similar manner and give nearly the same isomeric ratios; (ii) trimethyloxonium salt leads preferably to 2-methyl compound; (iii) in all cases, a relatively high ratio of 2-alkyl product was formed with triethyloxonium salt compared to the trimethyloxonium reagent.

(B) With respect to the reactant: (i) Ring systems **1** and **4** gave similar ratios with a slightly more preference of 2-methylation in the latter case. (ii) Alkylation of **4** is essentially different from that of **7**. Thus, in the case of the isoquinoline isomer **7** a relatively high ratio of 2-methyl compound was observed with all reagents; moreover, predominant formation of 2-ethyl salt **9b** (80%) allowed isolation of this compound in acceptable yield. (iii) The unsubstituted linearly fused tetrazole (**10**) resulted in the 1-methyl-substituted salt **12** as main product in a higher ratio than isomer **4** or bicycle **1**. On the contrary, presence of 10-methyl substituent (**10b**) highly assisted the formation of 2-methyl salt (**13c**), too. This effect was found even more pronounced with the ethylation of this compound.

These results show that the regioselectivity of alkylation of these fused tetrazoles is controlled by a combination of steric and electronic factors. The steric effect always favours to an attack at the easiest approachable point (rather at N-2 than at N-1 according to the numbering of **1**)[8]. This steric control is demonstrated by comparison of methylation of **4** with that of **7**, or by the increased amount of 2-substituted compounds **13c,d** with the methyl-substituted linear ring system **10b**. Similarly, the unambiguous trend that 2-substituted products were preferred in ethylations compared to methylations can evidently be ascribed also to steric reasons.

The other essential effect orienting alkylation is the heteroaromatic electronic distribution. In our earlier studies[9] we found several examples for the effect of the type of fusion of heteroaromatic systems on the regioselectivity. The present findings also show that, in addition to the steric conditions, this annelation effect also plays important role. Furthermore, Table I shows that the annelation effect can lead to an opposite result compared to the steric effect. For rationalization of this annelation effect semiempirical CNDO/2 calculations[10] have been

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Table II. Electronic Distribution of the Highest Occupied π (HOMO) and the Highest n Orbital of Compound 1 at Centers N-1, N-2, and N-3

center	$c^2_{HOMO(\pi)}$	c^2_n	$c^2_{px} + c^2_{py}$	c^2_s
N-1	0.28	0.38	0.31	0.07
N-2	0.00	0.31	0.25	0.06
N-3	0.27	0.11	0.10	0.01

carried out for the starting tetrazole systems (**1**, **4**, **7**, and **10**). On the basis of mechanistic considerations, the nucleophilic attack of the heteroaromatic system on the alkylating agent is supposed to proceed in the plain of the fused ring system. Therefore, besides the HOMO orbitals, the orbital coefficients of those orbitals having non negligable density only in this plain and lying the nearest to the HOMO have also been calculated.

Table II comprises these values for the three possible centers of **1** available for electrophiles. On the left sides of the columns, the c^2_{HOMO} densities are listed whereas on the right, the c^2_n coefficients of the highest orbital of that symmetry mentioned above are shown. These figures clearly show that for electronic reasons, N-1 is highly preferred for an electrophylic attack followed by N-2, whereas the calculated value for N-3 lower by one order of magnitude.

Our earlier results[1] found with arylation of these heterocycles can also be interpreted by these electronic density values. The very low value for N-3 centers gives a good explanation for the lack of either arylation of alkylation at N-3. It is interesting to note that not only the total electronic density but also their p-character—favoring the nucleophilicity—of center N-3 is extremely low.

We believe that the above considerations provide a good explanation for the regioselective alkylations of bicyclic and differently fused tricyclic tetrazoles. Furthermore, the finding that in appropriate cases 1- and 2-alkyltetrazolium salts can conveniently be prepared in acceptable yields is of preparative importance. The study on reactivity of these new azolium salts is in progress.

Experimental Section

Melting points were determined on a Büchi apparatus and are uncorrected. The IR spectra were recorded with a Specord 75 IR apparatus. The NMR spectra were determined in dimethyl sulfoxide-d_6 solutions at room temperature on a Bruker WM-250 FT-spectrometer controlled by an ASPECT 2000 computer. TMS was used as internal standard. The quantum chemical calculations were carried out by IBM 3031 computer.

Methylation of Tetrazoles. Method A: Methylation with Methyl Iodide. A solution of the appropriate tetrazole compound (2 mmol) in absolute acetonitrile (5 mL) was refluxed with methyl iodide (3 mL) for 4 h. The precipitated crystals were filtered off and washed with ether to give crude *N*-methyl salt.

Data of products (starting tetrazole, yield, mp): **1**, 56%, 177–180 °C; **4**, 72%, 198–200 °C; **7**, 50%, 162–165 °C.

Method B: Methylation with Dimethyl Sulfate. A mixture of dimethyl sulfate (1 mL) and a solution of the appropriate tetrazole (2 mmol) in acetonitrile (5 mL) was refluxed for 1 h. The reaction mixture was then evaporated, and the residue was dissolved in water (5 mL) and was mixed with 40% tetrafluoboric acid. The resulting crude *N*-methyl salt was precipitated as colorless crystals.

Data of products (starting tetrazole, yield, mp): **1**, 91%, 118–130 °C; **4**, 93%, 256–267 °C; **7**, 95%, 165–171 °C.

Method C: Methylation with Trimethyloxonium and Triethyloxonium Tetrafluoborates. A solution of the tetrazole compound (1 mmol) in absolute dichloromethane (5 mL) was stirred at 20 °C with 0.16 g (1.1 mmol) of trimethyloxonium tetrafluoborate or with 0.2 g (1.1 mmol) of triethyloxonium tetrafluoborate, respectively, for 20 h. The reaction mixture was then treated with ether (10 mL), and the resulting precipitate was filtered off.

Data of products (starting tetrazole, alkyl group introduced, yield, mp): **1**, Me, 90%, 121–129 °C; Et, 86%, 89–100 °C; **4**, Me, 96%, 230–251 °C; **4**, Et, 80%, 188–210 °C; **7**, Me, 85%, 178–209 °C; **7**, Et, 65%, 119–125 °C.

1-Methyltetrazolo[1,5-*a*]pyridinium Tetrafluoborate (2a). The crude product obtained from tetrazolo[1,5-*a*]pyridine (**1**) by using method B was recrystallized from acetonitrile–ether to give pure 1-methyl compound **2a**: mp 131–135 °C (75%); ^{1}H NMR (dimethyl sulfoxide-d_6 9.80 (d, 1 H, H-5), 8.70 (d, 1 H, H-8), 8.60 (t, 1 H, H-7), 8.02 (t, 1 H, H-6), 4.53 (s, 3 H, CH_3) ppm. Anal. Calcd for $C_6H_7BF_4N_4$ (222.13): C, 33.44; H, 3.17; N, 25.22. Found: C, 33.19; H, 2.96; N, 25.09.

3-Methyltetrazolo[1,5-*a*]quinolinium Tetrafluoborate (5a). The crude product obtained from tetrazolo[1,5-*a*]quinoline (**4**) by using method B was recrystallized from acetonitrile–ether to give pure 1-methyl compound **5a**; mp 267–269 °C (80%); ^{1}H NMR (dimethyl sulfoxide-d_6) 9.08 (d, 1 H, H-5), 8.88 (dd, 1 H, H-9), 8.57 (d, 1 H, H-4), 8.50 (d, 1 H, H-6), 8.28 (t, 1 H, H-8), 8.11 (t, 1 H, H-7), 4.62 (s, 3 H, CH_3) ppm; IR (KBr) 3300, 2900, 1610, 1600, 1500, 1060, 810, 800, 760 cm^{-1}. Anal. Calcd for $C_{10}H_9BF_4N_4$ (272.03): C, 44.15; H, 3.33; N, 20.60. Found: C, 43.98; H, 3.02; H, 20.39.

2-Ethyltetrazolo[5,1-*a*]isoquinolinium Tetrafluoroborate (9b). The crude product obtained from tetrazolo[5,1-*a*]isoquinoline (**7**) by using method C was recrystallized three times from a mixture of acetone and ethyl acetate to give pure 2-ethyl compound **9b**: mp 138–140 °C (35%); ^{1}H NMR (dimethyl sulfoxide-d_6) 9.42 (d, 1 H, H-5), 8.78 (dd, 1 H, H-10), 8.41 (d, 1 H, H-6), 8.40 (dd, 1 H, H-7), 8.22 (t, 1 H, H-8), 8.12 (t, 1 H, H-9), 5.30 (q, 2 H, CH_2), 1.80 (t, 3 H, CH_3) ppm; IR (KBr) 3010, 2980, 1620, 1510, 1470, 1440, 1060, 790, 740, 690 cm^{-1}. Anal. Calcd for $C_{11}H_{11}BF_4N_4$ (286.06): C, 46.18; H, 3.88. Found: C, 46.05; H, 3.69.

1-Ethyltetrazolo[1,5-*b*]isoquinolinium Tetrafluoroborate (12b). The crude product obtained from tetrazolo[1,5-*b*]isoquinoline (**10a**) with triethyloxonium tetrafluoroborate by using method C was recrystallized from acetic acid to give colorless needles: mp 185–187 °C (65%); ^{1}H NMR (dimethyl sulfoxide-d_6) 10.95 (s, 1 H, H-5), 9.36 (s, 1 H, H-10), 8.48 and 8.37 (2 d, 2 H, H-6,9), 8.15 and 7.98 (2 t, 2 H, H-7,8); 5.04 (q, 2 H, CH_2), 1.70 (t, 3 H, CH_3) ppm; IR (KBr) 3080, 2950, 1620, 1500, 1450, 1060, 880, 740 cm^{-1}. Anal. Calcd for $C_{11}H_{11}BF_4N_4$ (286.06): C. 46.18; H, 3.88. Found: C, 45.91; H, 3.72.

Registry No. **1**, 274-87-3; **2a** (A^- = I^-), 57024-09-6; **2a** (A^- = BF_4^-), 112483-28-0; **2b** (A^- = BF_4^-), 112483-30-4; **3a** (A^- = I^-), 112483-31-5; **3a** (A^- = BF_4^-), 112483-33-7; **3b** (A^- = BF_4^-), 112483-35-9; **4**, 235-25-6; **5a** (A^- = I^-), 112483-36-0; **5a** (A^- = BF_4^-), 112483-38-2; **5b** (A^- = BF_4^-), 112483-40-6; **6a** (A^- = I^-), 112483-41-7; **6a** (A^- = BF_4^-), 112483-43-9; **6b** (A^- = BF_4^-), 112483-45-1; **7**, 1443-60-3; **8a** (A^- = I^-), 112483-46-2; **8a** (A^- = BF_4^-), 112483-48-4; **8b** (A^- = BF_4^-), 112483-50-8; **9a** (A^- = I^-), 112483-51-9; **9a** (A^- = BF_4^-), 112483-53-1; **9b** (A^- = BF_4^-), 112483-55-3; **10** (Q = H), 33459-64-2; **10** (Q = Me), 75949-22-3; **12a**, 112483-57-5; **12b**, 112483-59-7; **12c**, 112483-61-1; **12d**, 112483-63-3; **13b**, 112483-65-5; **13c**, 112483-67-7; **13d**, 112483-69-9.

Supplementary Material Available: ^{1}H NMR DNOE spectra of compounds **5** and **6** and **8** and **9**, respectively (2 pages). Ordering information is given on any current masthead page.

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