Syntheses in the Pyridazine Series. XXX. Protonation and Quaternization Studies on Imidazo[1,2-*b*]pyridazines and *s*-Triazolo[4,3-*b*]pyridazines

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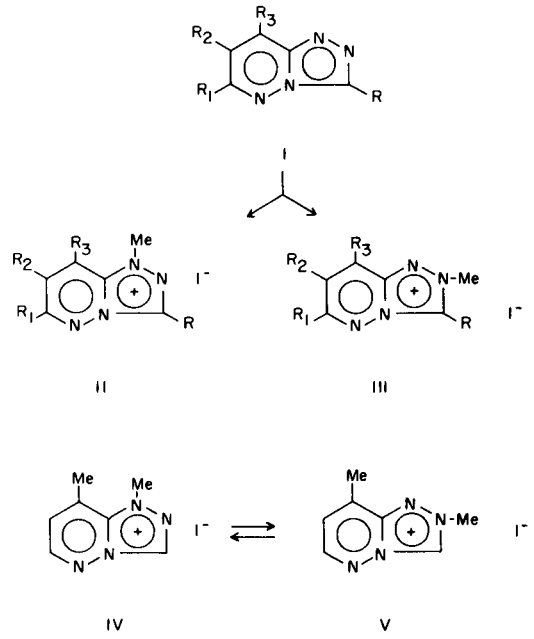
Sterically unhindered *s*-triazolo[4,3-*b*]pyridazines form N_1-methiodides, whereas 3- and/or 8-substituted analogs form a mixture of N_1- and N_2-methiodides. In some cases thermal rearrangement occurred. Imidazo[1,2-*b*]pyridazines form N_1-methiodides and here also steric interactions were observed as evidenced by the NMR spectra.

A recent report by Becker and Böttcher (1) about quaternizations of *s*-triazolo[4,3-*b*]pyridazines claimed that this reaction occurred exclusively at N_2, evidence being based on chemical degradation studies. In the light of investigations on the analogous *s*-triazolo[4,3-*a*]-pyridines (2,3) and as a result of our continuous interest in this bicyclic system (4, and references cited therein), it seemed worthwhile to investigate protonation and *N*-methylation by applying NMR techniques.

Upon considering the calculated electron densities (5) (Table I) for *s*-triazolo[4,3-*b*]pyridazine and some of its methyl analogs, it became evident that the most basic centre is at N_1. In fact, methylation of *s*-triazolo[4,3-*b*]pyridazine and its 6-methyl and 7-methyl analogs with methyl iodide have been found to give exclusively the N_1-methylated products. Since it is well known that the site of quaternization may be influenced in particular by steric and inductive effects, we have also investigated in detail some compounds where steric effects were anticipated. Thus, 3-methyl-*s*-triazolo[4,3-*b*]pyridazine afforded under the same reaction conditions a mixture of N_1- and N_2-methiodides in a ratio of about 67:33 as concluded from the integral ratio of the relative peaks in the NMR spectrum. Similarly, 8-methyl-*s*-triazolo[4,3-*b*]pyridazine afforded the N_1- and N_2-methiodides in 35:65 ratio, whereas in the case of the 3,8-dimethyl analog this ratio of N_1-:N_2-methiodide was 21:79.



These results clearly indicate the importance of both effects, the steric and inductive. From MO calculations it becomes evident that an introduction of a methyl group at position 8 does not significantly alter the relative electron densities at both ring nitrogens which are involved in quaternizations. On the other hand, a methyl group at position 3 clearly affects the electron density at N_2 by its inductive effect. Consequently, combination of both effects causes position 2 to be favoured over position 1 in methylation of 3,8-dimethyl-*s*-triazolo[4,3-*b*]pyridazine.

The NMR spectra of the quaternized compounds and isomeric products have been recorded and are tabulated (Table II). Taking into consideration the signals for H_3 of the quaternized 8-methyl compound, or the signal for the methyl group at position 3 of the 3-methyl or 3,8-dimethyl compounds, one would expect that the signal for H_3 of the N_2-methiodide (III, R = R_1 = R_2 = H, R_3 = Me) would occur at a lower field than that of the isomeric N_1-methiodide (II, R = R_1 = R_2 = H, R_3 = Me) as a consequence of the deshielding effect due to the proximity of the more positive ring nitrogen. Indeed, this effect was observed and in a similar manner, with the 3-methyl analogs, the

TABLE I

Calculated Electron Densities for *s*-Triazolo [4,3-*b*]pyridazine and Imidazo[1,2-*b*]pyridazine

Position of Substituent		Positions 1	2	3	4	5	6	7	8	9
s-Triazolo[4,3-*b*]pyridazines										
H	A	1.320	1.221	0.956	1.566	1.095	0.952	0.963	0.954	0.936
	B	0.281	0.019	0.212	0.016	0.180	0.020	0.127	0.120	0.025
3-CH_3	A	1.326	1.274	0.912	1.584	1.136	0.954	0.970	0.954	0.945
	B	0.263	0.049	0.191	0.022	0.162	0.017	0.122	0.094	0.037
8-CH_3	A	1.313	1.224	0.955	1.569	1.171	0.951	1.015	0.911	0.947
	B	0.248	0.010	0.182	0.018	0.209	0.017	0.161	0.119	0.010
3,8-diCH_3	A	1.318	1.277	0.911	1.587	1.176	0.952	1.022	0.910	0.957
	B	0.241	0.034	0.171	0.024	0.191	0.015	0.153	0.095	0.021
Imidazo[1,2-*b*]pyridazine										
H	A	1.321	1.048	1.079	1.565	1.144	0.956	0.977	0.955	0.956
	B	0.212	0.039	0.299	0.007	0.168	0.008	0.137	0.083	0.046

A = total π-electron density
B = frontier electron density

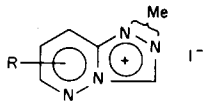
signals for the methyl group in compounds III (R = Me, $R_1 = R_2 = R_3 = H$; or $R = R_3 = Me$, $R_1 = R_2 = H$) appear at a lower field than for the corresponding N_1-methiodides (II, R = Me, $R_1 = R_2 = R_3 = H$; or $R = R_3 = Me$: $R_1 = R_2 = H$). Moreover, deshielding of the 8-methyl group is greater for N_1-methiodides (II) as compared to the N_2-methiodides (III, $R = R_1 = R_2 = H$, R = Me; or $R = R_3 = Me$, $R_1 = R_2 = H$). The same effect is also exerted on a 3-methyl group by the adjacent N_2-methyl group. These observations are comparable to those made recently on simple quaternized pyridazines (6,7) and *s*-triazolo[4,3-*a*]pyridines (3).

Under the reaction conditions employed, quaternization of *s*-triazolo[4,3-*b*]pyridazines was irreversible and the products were stable compounds, but upon heating they lost the *N*-methyl group. However, if they were heated in a sealed tube at higher temperatures, in some cases rearrangement was observed. In this manner, 1,8-dimethyl-*s*-triazolo[4,3-*b*]pyridazinium iodide (IV), when heated in a sealed tube at 255° for 45 minutes, was transformed into a mixture which consisted of the starting material (IV) and the 2,8-dimethyl isomer (V) in a ratio of 65:35 as indicated by NMR analysis. On the other hand, when the pure 2,8-dimethyl isomer (V) was heated similarly at 215° for 25 minutes it afforded a mixture of the starting material (V) and the 1,8-dimethyl isomer (IV) in the ratio of 67:33 as calculated from the NMR spectrum. As these results indicate, there is somewhat less tendency for rearrangement of the N_2-methyl isomer into the N_1-methyl isomer as in the case of *s*-triazolo-[4,3-*a*]pyridines (3), which may be ascribed to the somewhat diminished basicity of the bicyclic system under investigation.

MO calculations for imidazo[1,2-*b*]pyridazine (Table I) clearly indicate that N_1 is the most basic nitrogen in this bicycle and quaternization would therefore be expected to take place at this position. Thus far, only two quaternized imidazo[1,2-*b*]pyridazines have been reported (8,9) and for 2-methyl-6-methoxyimidazo[1,2-*b*]pyridazine, when quaternized with *p*-chlorobenzyl chloride forcing reaction conditions had to be applied (9). Alkylation at N_1 was postulated by analogy with the known protonation at N_1 (10). Evidence for N_1-methylation, which proceeds under more severe reaction conditions than in the *s*-triazolo[4,3-*b*]pyridazine series, comes from correlation of the chemical shifts for the N_1-methyl groups of compounds where there is no steric hindrance, with those compounds which have attached at position 8 a

TABLE II

NMR Data for *s*-Triazolo[4,3-*b*]pyridazine Methiodides

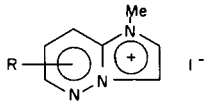


R	Position of Me	Chemical Shifts (τ)										Coupling Constants (cps)			
		H_3	H_6	H_7	H_8	3-CH_3	6-CH_3	7-CH_3	8-CH_3	N_1-CH_3	N_2-CH_3	$j_{6,7}$	$j_{7,8}$	$j_{6,8}$	$j_{3,8}$
H	1	0.31	0.95	2.00	1.36	—	—	—	—	5.62	—	4.5	9.5	2.0	~0.5
7-CH_3	1	0.17	1.05	—	1.55	—	—	7.32	—	5.70	—	—	—	2.0	~0.8(a)
6-CH_3	1	0.55	—	2.00	1.55	—	7.19	—	—	5.64	—	—	9.5	—	—
3-CH_3	1	—	0.80	1.89	1.25	7.08	—	—	—	5.71	—	4.5	9.5	2.0	—
3-CH_3	2	—	0.80	1.89	1.25	6.90	—	—	—	—	5.64	4.5	9.5	2.0	—
8-CH_3	1	0.64	1.11	2.11	—	—	—	—	7.00	5.42	—	4.5	—	—	(b)
8-CH_3	2	0.33	1.21	2.35	—	—	—	—	7.23	—	5.51	4.5	—	—	(b)
3,8-diCH_3	1	—	1.08	2.15	—	7.08	—	—	7.05	5.51	—	4.5	—	—	(b)
3,8-diCH_3	2	—	1.17	2.38	—	6.89	—	—	7.28	—	5.63	4.5	—	—	(b)

NMR spectra were recorded as solutions in deuterium oxide with sodium trimethylsilylpropane sulfonate as internal standard.
(a) $j_{H_8, 7\text{-}CH_3}$ = 1.2 cps. (b) $j_{H_7, 8\text{-}CH_3}$ = 1.2 cps.

TABLE III

NMR Data for Imidazo[1,2-*b*]pyridazine Methiodides

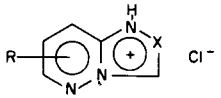


R	Chemical Shifts (τ)									Coupling Constants (cps)				
	H_2	H_3	H_6	H_7	H_8	6-CH_3	7-CH_3	8-CH_3	N_1-CH_3	$j_{2,3}$	$j_{6,7}$	$j_{7,8}$	$j_{6,8}$	$j_{3,8}$
H	1.80	1.61	1.00	2.05	1.40	—	—	—	5.77	2.0	4.5	9.5	1.5	1.0
6-CH_3	1.90	1.67	—	2.21	1.56	7.25	—	—	5.81	2.0	—	9.5	—	1.0
6-Cl, 8-CH_3	1.90	1.60	—	2.24	—	—	—	7.05	5.61	2.0	—	—	—	(a)
7,8-diCH_3	2.02	1.72	1.17	—	—	—	7.42	7.17	5.62	2.0	—	—	—	(b)

NMR spectra were recorded as solutions in deuterium oxide with sodium trimethylsilylpropane sulfonate as internal standard.
(a) $j_{H_7,8\text{-}CH_3}$ = 1.5 cps. (b) $j_{7\text{-}CH_3,\ 8\text{-}CH_3} \sim$ 0.5 cps.

TABLE IV

NMR Data for *s*-Triazolo[4,3-*b*]pyridazine Hydrochloride Salts and Imidazo[1,2-*b*]pyridazine Hydrochloride Salts

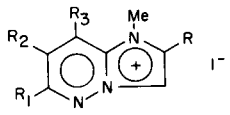


R	X	Chemical Shifts (τ)										Coupling Constants (cps)				
		H_2	H_3	H_6	H_7	H_8	2-CH_3	3-CH_3	6-CH_3	7-CH_3	8-CH_3	$j_{2,3}$	$j_{6,7}$	$j_{7,8}$	$j_{6,8}$	$j_{3,8}$
H	N	—	0.25	0.84	2.12	1.38	—	—	—	—	—	—	4.5	9.5	2.0	—
3-CH_3	N	—	—	0.91	2.04	1.40	—	7.00	—	—	—	—	4.5	9.5	2.0	—
6-CH_3	N	—	0.27	—	2.05	1.45	—	—	7.17	—	—	—	—	9.5	—	1.0
7-CH_3	N	—	0.24	0.95	—	1.55	—	—	—	7.25	—	—	—	—	2.0	1.0(a)
8-CH_3	N	—	0.28	1.18	2.28	—	—	—	—	—	7.20	—	4.5	—	—	—(b)
H	C-CH_3	—	1.82	1.12	2.22	1.62	7.38	—	—	—	—	—	4.5	9.5	1.5	1.0(c)
7,8-diCH_3	CH	1.80	1.56	1.16	—	—		—	—	7.32	7.24	2.0	—	—	—	—(d)
7,8-diCH_3	C-CH_3	—	1.86	1.22	—	—	7.30	—	—	7.36	7.30	—	—	—	—	-(c)(e)
6-Cl-7,8-diCH_3	CH	1.80	1.56	—	—	—	—	—	—	7.32	7.17	2.0	—	—	—	—(d)

NMR spectra were recorded as solutions in deuterium oxide with sodium trimethylsilylpropane sulfonate as internal standard.
(a) $j_{H_8,7\text{-}CH_3}$ = 1.2 cps; (b) $j_{H_7,\ 8\text{-}CH_3}$ = 1.2 cps; (c) $j_{H_3,2\text{-}CH_3}$ = 1.0 cps; (d) $j_{7\text{-}CH_3,8\text{-}CH_3}$ = 1 cps; (e) $j_{7\text{-}CH_3,\ 8\text{-}CH_3} \sim$0.5 cps.

TABLE V

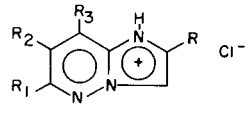
Imidazo[1,2-*b*]pyridazine Methiodides



R	R_1	R_2	R_3	M.P., °C	Formula	Anal., % Calcd. C	H	N	Found C	H	N
CH_3	H	H	H	285-286	$C_8H_{10}IN_3$	34.93	3.66	15.28	34.83	3.83	15.09
H	CH_3	H	H	207	$C_8H_{10}IN_3$	34.93	3.66	15.28	35.21	3.73	15.05
H	Cl	H	H	276-277	$C_7H_7ClIN_3$	28.45	2.39	14.22	28.49	2.52	14.20
CH_3	Cl	H	H	255-257	$C_8H_9ClIN_3$			13.58			13.42
H	Cl	CH_3	H	268-270	$C_8H_9ClIN_3$			13.58			13.55
H	Cl	H	CH_3	261-263	$C_8H_9ClIN_3$	31.04	2.93	13.58	31.30	3.28	13.56
H	H	CH_3	CH_3	275	$C_9H_{12}IN_3$	37.39	4.18	14.53	37.48	4.40	14.49
CH_3	H	CH_3	CH_3	>330	$C_{10}H_{14}IN_3$	39.62	4.65	13.86	39.88	4.89	13.81
H	Cl	CH_3	CH_3	280	$C_9H_{11}ClIN_3$	33.41	3.53	12.98	33.20	3.54	12.71
CH_3	Cl	CH_3	CH_3	292-294	$C_{10}H_{13}ClIN_3$	35.58	3.88	12.44	35.77	4.04	12.70

TABLE VI

Imidazo[1,2-*b*]pyridazinium Chlorides



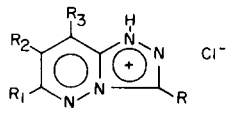
R	R_1	R_2	R_3	M.P., °C	Formula	Anal., % Calcd. C	H	N	Found C	H	N
CH_3	H	H	H	210-212	$C_7H_8ClN_3$	49.56	4.75	24.78	49.55	4.92	24.73
CH_3	Cl	H	H	238	$C_7H_7Cl_2N_3$	41.20	3.46	20.59	41.08	3.78	20.43
H	Cl	CH_3	H	218	$C_7H_7Cl_2N_3$			20.59			20.59
H	H	CH_3	CH_3	245	$C_8H_{10}ClN_3$	52.33	5.49	22.88	52.41	5.73	22.84
CH_3	H	CH_3	CH_3	267-268	$C_9H_{12}ClN_3$	54.69	6.12	21.26	54.49	6.28	21.31
H	Cl	CH_3	CH_3	>310	$C_8H_9Cl_2N_3$	44.06	4.16	19.26	43.93	4.42	19.22
CH_3	Cl	CH_3	CH_3	280-282	$C_9H_{11}Cl_2N_3$	46.57	4.78	18.10	46.71	4.95	17.83

methyl group and therefore a peri interaction would be expected (Table III). Again, as discussed above for *s*-triazolo[4,3-*b*]pyridazines, quaternization of 6-chloro-8-methyl- and 7,8-dimethylimidazo[1,2-*b*]pyridazines is reflected by a significant deshielding of the N_1-methyl group.

The NMR spectra of protonated *s*-triazolo[4,3-*b*]-pyridazines and imidazo[1,2-*b*]pyridazines were also recorded (Table IV). The most prominent feature of these spectra is that signals for all ring protons are shifted to more deshielded positions than in the unprotonated compounds. As a consequence of protonation, the electron

TABLE VII

s-Triazolo[4,3-*b*]pyridazinium Chlorides



R	R_1	R_2	R_3	M.P., °C	Formula	Anal., % Calcd. C	H	N	Found C	H	N
H	H	H	H	170-171	$C_5H_5ClN_4$	38.35	3.22	35.79	38.60	3.44	36.05
CH_3	H	H	H	184-186	$C_6H_7ClN_4$	42.24	4.14	32.84	42.04	4.35	32.98
H	CH_3	H	H	169-170	$C_6H_7ClN_4$	42.24	4.14	32.84	42.43	4.28	32.96
H	H	CH_3	H	188-190	$C_6H_7ClN_4$	42.24	4.14	32.84	42.33	4.45	32.86
H	H	H	CH_3	192-194	$C_6H_7ClN_4$	42.24	4.14	32.84	42.20	4.32	33.10

density in the bicycle becomes smaller due to electron withdrawal from the ring system. This electron deficiency is transmitted from the ring carbons to C-H bonds and displacement of signals toward lower field is observed. In addition to such observations in the pyridine series (11), the same effects were observed with some protonated azoles (12) where the resulting cations are stabilized by an amidinium type of resonance.

Taking into account the basicities of the ring nitrogens in the systems under investigation, the site of protonation evidently coincides with the site of *N*-methylation, although quaternization is kinetically controlled and protonation gives a thermodynamically-determined product. Our assessment also corroborates the conclusion reached by Armarego (10), who on the basis of ionization and UV spectral measurements, proposed N_1-protonation for imidazo[1,2-*b*]pyridazines.

EXPERIMENTAL (13)

Imidazo[1,2-*b*]pyridazine (8) and its 2-methyl- (8), 7-methyl- (14), 7,8-dimethyl- (14), 2,7,8-trimethyl- (14), and 6-chloro-7,8-dimethyl- analogs (14) were prepared according to the procedures developed and described earlier. *s*-Triazolo[4,3-*b*]pyridazine (15) and its 3-methyl- (4), 7-methyl- (4), 8-methyl- (4) and 3,8-dimethyl- (4) analogs were prepared by catalytic dehalogenation of their 6-chloro derivatives. 6-Methyl-*s*-triazolo[4,3-*b*]pyridazine was obtained from 3-hydrazino-6-methylpyridazine and formic acid according to the procedure described by Libermann and Jacquier (16).

General Procedure for the Preparation of Imidazo[1,2-*b*]pyridazinium Methiodides.

The corresponding imidazo[1,2-*b*]pyridazine (0.005-0.01 mole) was heated with excess methyl iodide (1.5-3.0 g.) in a solution of methanol (10-15 ml.) under reflux for 4 hours. Upon cooling, the crystals which separated were filtered off and crystallized from ethanol (yields; 10-36%). The methiodides and their analytical data are presented in Table V.

General Procedure for the Synthesis of Imidazo[1,2-*b*]pyridazinium Chlorides.

A solution of the corresponding imidazo[1,2-*b*]pyridazine (0.005-0.01 mole) in absolute ethanol (5-10 ml.) was saturated at room temperature with hydrogen chloride. The crystals, which separated were collected and crystallized from ethanol (yields; 23-93%). The salts and their analytical data are given in Table VI.

General Procedure for the Preparation of *s*-Triazolo[4,3-*b*]pyridazinium Chlorides.

A solution of the corresponding *s*-triazolo[4,3-*b*]pyridazine (0.005 mole) in ethanol (10 ml.) was treated with concentrated hydrochloric acid (0.5 ml.). The reaction mixture was evaporated *in vacuo* to dryness and the residue was crystallized from ethanol. The salts and the pertinent analytical data are given in Table VII.

s-Triazolo[4,3-*b*]pyridazinium Methiodide (II, R = R_1 = R_2 = R_3 = H).

To a solution of *s*-triazolo[4,3-*b*]pyridazine (1.2 g., 0.01 mole) in methanol (5 ml.) was added methyl iodide (5.67 g., 0.04 mole), the reaction flask was closed and the mixture was shaken at room temperature for 5 minutes. The reaction mixture was allowed to stand at room temperature for 24 hours and then while stirring diethyl ether (25 ml.) was added slowly to precipitate the quaternary salt. The salt was collected, washed with diethyl ether (25 ml.) and dried *in vacuo*. The crude salt (0.7 g., 27%; m.p. 250-268°) was crystallized from ethanol to give the pure 1-methyl isomer (0.4 g.), m.p. 269-271°.

Anal. Calcd. for $C_6H_7IN_4$: C, 27.50; H, 2.69; N, 21.38. Found: C, 27.50; H, 2.68; N, 21.39.

The combined filtrates and washings were evaporated *in vacuo* to about 2 ml. and diethyl ether (20 ml.) was added to precipitate the unreacted parent compound (0.5 g.).

In practically the same way, the following *s*-triazolo[4,3-*b*]-pyridazinium methiodides were formed.

6-Methyl-*s*-triazolo[4,3-*b*]pyridazine.

This compound afforded the crude methiodide (m.p. 140-175°) which was treated (0.7 g.) with hot acetone (50 ml.), the mixture was filtered while hot, and the residue was washed with diethyl ether (15 ml.) and then dried *in vacuo*. The pure 1,6-dimethyl compound (II, R = R_2 = R_3 = H, R_1 = CH_3) was obtained in 35% yield, m.p. 230-232°.

Anal. Calcd. for $C_7H_9IN_4$: C, 30.45; H, 3.29; N, 20.29. Found: C, 30.55; H, 3.68; N, 20.55.

From the combined filtrates some unreacted starting bicyclic compound (0.2 g.) was isolated after evaporation of the solvents.

1,7-Dimethyl-*s*-triazolo[4,3-*b*]pyridazinium Iodide (II, R = R_1 = R_3 = H, R_2 = CH_3).

The crude product was washed with diethyl ether and dried *in vacuo* and appeared to be sufficiently pure for analysis. The yield was 51%, m.p. 293-294°.

Anal. Calcd. for $C_7H_9IN_4$: C, 30.45; H, 3.29; N, 20.29. Found: C, 30.59; H, 3.32; N, 20.22.

8-Methyl-*s*-triazolo[4,3-*b*]pyridazine.

This compound afforded the crude quaternized product (3.1 g.) with m.p. 213-216°. The corresponding signals for the 8-methyl group of the corresponding methiodides appeared in the NMR spectrum as two peaks at τ = 7.00 and 7.23 with an integral ratio of 35:65 for the 1-methyl (II, R = R_1 = R_2 = H, R_3 = CH_3) and 2-methyl derivative (III, R = R_1 = R_2 = H, R_3 = CH_3), respectively. The crude mixture of methiodides, after treatment with hot acetone (800 ml.), was filtered while still hot and the residue was crystallized from ethanol to give the pure 1,8-dimethyl isomer (0.5 g.) m.p. 296-297°.

Anal. Calcd. for $C_7H_9IN_4$: C, 30.45; H, 3.29; N, 20.29. Found: C, 30.35; H, 3.46; N, 20.53.

The acetone extract was evaporated *in vacuo* to dryness and the residue was extracted with cold absolute ethanol (5 portions of 100 ml.) at -5°. The solution was evaporated to dryness and the extraction procedure with cold ethanol at -5° was repeated 10 times. The combined residues were crystallized from ethanol and ethyl acetate (1:1) giving the pure 2,8-dimethyl isomer (III, R = R_1 = R_2 = H, R_3 = CH_3), m.p. 221-223°.

Anal. Calcd. for C_7H_9IN: C, 30.45; H, 3.29; N, 20.29. Found: C, 30.79; H, 3.55; N, 20.36.

3-Methyl-*s*-triazolo[3,4-*b*]pyridazine.

This compound afforded the crude methiodides in about 50% yield. The product consisted of the 1,3-dimethyl and 2,3-dimethyl isomers in a ratio of 67:33 as indicated by NMR analysis. The crude mixture of methiodides (0.64 g.) was treated with hot acetone (80 ml.), was filtered while still hot, and the residue was washed with diethyl ether (20 ml.) and dried *in vacuo*. The purification procedure was repeated giving the pure 1,3-dimethyl isomer (II, R_1 = R_2 = R_3 = H, R = CH_3) (0.1 g.), m.p. 227-229°.

Anal. Calcd. for $C_7H_9IN_4$: C, 30.45; H, 3.29; N, 20.29. Found: C, 30.80; H, 3.34; N, 20.21.

The acetone extract was evaporated to dryness *in vacuo* and the residue was repeatedly recrystallized from ethanol. However, the product (0.1 g.) was not the pure 2,3-dimethyl isomer since NMR spectral examination revealed that it contained about 20% of the 1,3-dimethyl isomer.

3,8-Dimethyl-*s*-triazolo[4,3-*b*]pyridazine.

This compound (2.18 g.) was quaternized with methyl iodide (8.52 g. in 30 ml. of methanol) as described for the parent compound, except that the mixture was allowed to stand at room temperature for 48 hours. The methiodides were separated by addition of diethyl ether (30 ml.), were collected by filtration, washed with diethyl ether (40 ml.) and dried *in vacuo*. The crude product (1.5 g.) melted at 217-221° and an NMR spectral examination revealed that it contained a mixture of the 1,3,8-trimethyl and 2,3,8-trimethyl isomers in the ratio of 21:79. The product was treated with hot acetone (200 ml.), filtered while hot, and the residue was washed with diethyl ether (30 ml.). The pure 1,3,8-trimethyl isomer (0.4 g.) (II, R_1 = R_2 = H, R = R_3 = CH_3) had m.p. 240-241°.

Anal. Calcd. for $C_8H_{11}IN_4$: C, 33.09; H, 3.82; N, 19.31. Found: C, 33.39; H, 4.08; N, 19.34.

The acetone extract was evaporated to dryness and the residue was crystallized from ethanol and ethyl acetate as described in the case of the formation of methiodides of 8-methyl-*s*-triazolo[4,3-*b*]-pyridazine. NMR analysis showed, however, that the 2,3,8-trimethyl isomer was contaminated with about 20% of the 1,3,8-trimethyl isomer.

Thermal Rearrangement of 1,8-Dimethyl-*s*-triazolo[4,3-*b*]pyridazinium Iodide (IV) into 2,8-Dimethyl-*s*-triazolo[4,3-*b*]pyridazinium Iodide (V) and Vice Versa.

The pure 1,8-dimethyl isomer (IV, 0.15 g.) was heated in a sealed tube in an oil bath at 255° for 45 minutes. The partially sintered product was dissolved in deuterium oxide, the solution was filtered and the NMR spectrum was recorded immediately. The signal ratios of the 8-methyl peak of both isomers revealed that the isomeric methiodides were present in admixture in the ratio of 65:35 (IV:V).

In a similar manner the pure 2,8-dimethyl isomer (V) was heated in a sealed tube at an oil bath temperature of 215° for 25 minutes. An NMR spectral analysis showed that the product consisted of both isomers, the 2,8-dimethyl and 1,8-dimethyl derivative, in a ratio of about 67:33 (V:IV).

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