Pyridazines. LIX. An Unusual Reaction of Azidoazolopyridazines with Diethylamine

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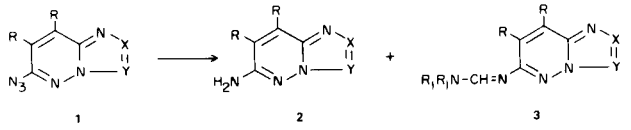
6-Azidoazolopyridazines and 6-azidopyridotetrazolopyridazines react in the presence of diethylamine to give various products. Among them, the corresponding diethylaminomethyleneamino derivatives were formed in a novel reaction.

In previous work on azidoazoloazines we have shown that these compounds may undergo several types of transformations. Besides azido-tetrazolo isomerizations and cycloadditions there were observed also reactions based upon decomposition of the azido group and which most probably involve nitrenes as reactive intermediates. The products which are formed in such reactions result either from dimerization or from insertion of nitrenes into a C-H group and/or hydrogen abstraction from the solvent (1-4).



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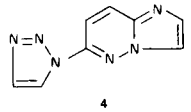
We wish to report here on a novel type of reaction of azidoazolopyridazines and their tricyclic analogs in the presence of diethylamine. Besides the anticipated amino derivatives, the corresponding diethylaminomethyleneamino derivatives were also formed. When a solution of 6-azidotetrazolo[1,5-*b*]pyridazine (**1**, R = H, X = Y = N) in diethylamine was heated under reflux for 10 hours, the corresponding amino derivative (**2**, R = H, X = Y = N) and diethylaminomethyleneamino derivative (**3**, R = H, R_1 = Et, X = Y = N) were formed in a ratio of 2.4:1. Both compounds could be separated by tlc. The dimethyl analog (**1**, R = Me, X = Y = N), however, afforded after 240 hours both derivatives, **2** and **3** (R = Me, R_1 = Et, X = Y = N) in the ratio of 1:3.2. Similar reaction with 6-azidotriazolo[4,3-*b*]pyridazine (**1**, R = H, X = N, Y = CH) afforded after 45 hours the corresponding derivatives **2** and **3** (R = H, R_1 = Et, X = N, Y = CH) in ratio of 1:45.

The reaction of 6-azidoimidazo[1,2-*b*]pyridazine (**1**, R = H, X = Y = CH) with diethylamine was more complex (46 hours of reflux) and besides the amino (**2**, R = H, X = Y = CH) and diethylaminomethyleneamino derivatives



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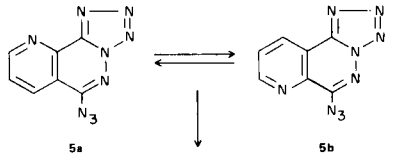

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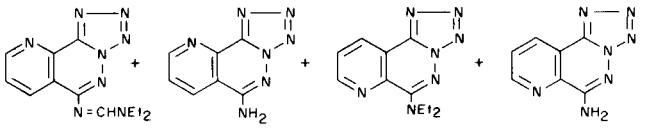

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(**3**, R = H, R_1 = Et, X = Y = CH) the triazole (**4**) was also isolated and identified. The mentioned compounds were formed in ratio of 1:31:16.

The extension of this reaction to 6-azidopyrido[2,3-*d*]-tetrazolo[1,5-*b*]pyridazine (**5a**) for which we have shown that in solution it exists in equilibrium with the isomeric 6-azidopyrido[3,2-*d*]tetrazolo[1,5-*b*]pyridazine (**5b**) gave after 120 hours a mixture of four compounds. Thus, **6**, **7**, **8** and **9** were formed in ratio of about 35:1:3:15. As in previous cases the amino derivatives **7** and **9** are formed by hydrogen abstraction from the solvent by the intermediate nitrene. Compound **8** is obviously formed in a nucleophilic displacement of the azido group after isomerization of **5a** into **5b**.

Although the mechanism of formation of diethylaminomethyleneamino derivatives lacks firm interpretation one may postulate that they are formed in some kind of transformation of intermediate nitrenes. We assume that the -CH= group of diethylaminomethyleneamino derivatives as well as the -CH=CH- moiety of the triazole part

of **4** originate from the diethylamine molecule. Moreover, the formation of the corresponding 6-amino derivatives is best interpreted by attack of the azolopyridazine nitrene, comparable to the thermally generated and highly electrophilic phenylnitrene (5), on diethylamine.

Finally, it should be mentioned that a very facile and almost quantitative azido into amino group transformation could be observed when azidoazolopyridazines were allowed to react with acetylacetone in an ethanolic solution and in the presence of triethylamine. In this manner, the isomeric **5a** and **5b** immediately formed the corresponding amino compounds **7** and **9**.

All diethylaminomethyleneamino derivatives could be hydrolyzed in dilute acetic acid or with ethanolic potassium hydroxide solution into the corresponding amino derivatives.

EXPERIMENTAL (6)

6-Diethylaminomethyleneaminotetrazolo[1,5-*b*]pyridazine (**3**, X = Y = N, R = H, R_1 = Et).

A mixture of the azido compound (**1**, X = Y = N, R = H) (1.0 g.) and diethylamine (20 ml.) was heated under reflux for 10 hours. Excess solvent was removed *in vacuo*, some chloroform was added and the amino compound (**2**, X = Y = N, R = H, 310 mg.) was filtered off. The filtrate was evaporated to dryness and the residue purified by tlc (Merck DC-Fertigplatten Aluminumoxid F 254 (type T), chloroform as solvent). Upon elution of the strongly fluorescent spot with methanol there were obtained 130 mg. of the compound (**3**, X = Y = N, R = H, R_1 = Et) which was then crystallized from chloroform and *n*-hexane, m.p. 105°; mass spectrum: M^+ = 219; nmr spectrum (in deuteriochloroform): τ 2.82 (d, H_7), 1.99 (d, H_8), 1.50 (s, -C*H*=N-), 6.35 and 6.50 (q, C*H*$_2$CH$_3$), 8.66 and 8.73 (t, CH$_2$C*H*$_3$); $J_{7,8}$ = 9.7, J_{Et} = 7.2 Hz.

Anal. Calcd. for $C_9H_{13}N_7$: N, 44.72. Found: N, 45.11.

If the above diethylaminomethyleneamino compound was heated under reflux with dilute acetic acid (1:4) for 1 hour or with a 10% solution of potassium hydroxide in ethanol for 10 minutes, the amino compound (**2**, X = Y = N, R = H) was obtained. The 6-dimethylaminomethyleneamino analog (**3**, X = Y = N, R = H, R_1 = Me) was prepared from the corresponding 6-amino compound (10 g.), *N,N*-dimethylformamide dimethylacetal (10 ml.) and benzene (10 ml.). The mixture was heated under reflux for 9 hours, the solvent evaporated to dryness and the product (11 g.) crystallized from chloroform and petroleum ether and then twice from chloroform and *n*-hexane, m.p. 207°; mass spectrum: M^+ = 191.

Anal. Calcd. for $C_7H_9N_7$: N, 51.29. Found: N, 51.33.

When hydrolyzed as described above for the diethylamino analog, the compound was transformed into the 6-amino derivative (**2**, X = Y = N, R = H).

6-Diethylaminomethyleneamino-*s*-triazolo[4,3-*b*]pyridazine (**3**, X = N, Y = CH, R = H, R_1 = Et).

A mixture of the azido compound (**1**, X = N, Y = CH, R = H, 1.0 g.) and diethylamin (250 ml.) was heated under reflux for 45 hours. The solvent was evaporated *in vacuo* and the residue was purified by tlc (DC Fertigplatten Aluminumoxid F 254 (Type T), chloroform as solvent). The spot at the start was eluted with methanol, the solvent evaporated and the residue (100 mg.) sublimed at 230-240°/1 mm. There were obtained 10 mg. of 6-amino-*s*-triazolo[4,3-*b*]pyridazine. Elution of the strongly fluorescent spot with methanol gave compound (**3**, X = N, Y = CH, R = H, R_1 = Et, 450 mg.) which was crystallized from chloroform and *n*-hexane, m.p. 107°; mass spectrum: M^+ = 218; nmr spectrum (in deuteriochloroform): τ = 1.23 (d, H_3), 3.15 (d, H_7), 2.20 (dd, H_8), 1.78 (s, -C*H*=N-), 6.40 and 6.60 (q, C*H*$_2$CH$_3$), 8.70 and 8.75 (t, CH$_2$C*H*$_3$); $J_{7,8}$ = 9.4, $J_{3,8}$ = 0.8, J_{Et} = 7.2 Hz.

Anal. Calcd. for $C_{10}H_{14}N_6$: N, 38.51. Found: N, 38.19.

Hydrolysis, as described above, afforded 6-amino-*s*-triazolo[4,3-*b*]pyridazine.

The analogous 6-dimethylaminomethyleneamino compound (**3**, X = N, Y = CH, R = H, R_1 = Me) was prepared by heating the corresponding 6-amino compound (2.0 g.) and *N,N*-dimethylformamide dimethylacetal (5.0 g.) for 50 minutes. The product (2.25 g.) was crystallized from chloroform and petrol ether, m.p. 169-173°; mass spectrum: M^+ = 190.

Anal. Calcd. for $C_8H_{10}N_6$: N, 44.19. Found: N, 44.18.

The compound could be hydrolyzed to the corresponding 6-amino derivative.

Reaction of 6-Azido-7,8-dimethyltetrazolo[1,5-*b*]pyridazine with Diethylamine.

A mixture of the azido compound (**1**, X = Y = N, R = Me, 1.0 g.) and diethylamine (100 ml.) was heated under reflux for 240 hours. Upon evaporation of the solvent *in vacuo*, the residue was treated with chloroform and filtered. The insoluble part (0.15 g.) was identified as 6-amino-7,8-dimethyltetrazolo[1,5-*b*]pyridazine. The filtrate was evaporated and the residue purified by TLC (DC-Fertigplatten Kieselgel F 254, chloroform and methanol, 20:1, as solvent). The strongly fluorescent spot was eluted with methanol and upon evaporation of the solvent compound **3**, (X = Y = N, R = Me, R_1 = Et) was obtained (0.485 g.). After crystallization from chloroform and *n*-hexane the pure compound had m.p. 95-99°; mass spectrum: M^+ = 247; nmr spectrum (in deuteriochloroform): τ = 7.90 (s, 7-CH$_3$), 7.60 (s, 8-CH$_3$), 1.90 (s, -C*H*=N-), 6.55 and 6.72 (q, C*H*$_2$CH$_3$), 8.72 and 8.80 (t, CH$_2$C*H*$_3$); J_{Et} = 7.2 Hz.

Anal. Calcd. for $C_{11}H_{17}N_7$: N, 39.65. Found: N, 40.01.

Upon hydrolysis the compound was transformed into its 6-amino analog.

Reaction Between 6-Azidoimidazo[1,2-*b*]pyridazine and Diethylamine.

The azido compound (**1**, X = Y = CH, R = H, 1.0 g.) and diethylamine (250 ml.) were heated under reflux for 46 hours. The solvent was evaporated to dryness and the residue submitted to purification by tlc (DC Fertigplatten Aluminumoxid F 254 (Type T), chloroform as solvent). The spot at the point of application of the sample was eluted with methanol, the solvent was evaporated to dryness and the residue (45 mg.) was sublimed at 200-210°/1 mm to give the pure 6-amino compound (**2**, X = Y = CH, R = H, 10 mg.). Elution of the strongly fluorescent spot with methanol and evaporation of the solvent afforded a mixture (0.47 g.) of compounds **3** (X = Y = CH, R = H, R_1 = Et) and **4** in ratio of about 2:1. Both compounds could be separated by tlc (DC-Fertigplatten Kieselgel F 254, chloroform and methanol, 5:1, as solvent). To achieve good separation the same plate was developed three times with the same solvent mixture. Compound **3** (X = Y = CH, R = H, R_1 = Et) had m.p. 198-208°; mass spectrum: M^+ = 217; nmr spectrum (in deuteriochloroform): τ = 2.50 (d, H_2), 2.33 (d, H_3), 3.25 (d, H_7), 2.35 (d, H_8), 1.86

(s, -CH=N-), 6.45 and 6.57 (q, CH_2CH_3), 8.72 and 8.75 (t, CH_2CH_3); $J_{2,3} \cong 1.0$, $J_{7,8} = 9.2$, $J_{Et} = 7.5$ Hz.

Anal. Calcd. for $C_{11}H_{15}N_5$: N, 32.24. Found: N, 32.02.

Compound **4** had m.p. 177-179°; mass spectrum: $M^+ = 186$; nmr spectrum (in deuteriochloroform): τ = 2.14 (d, H_2), 2.07 (d, H_3), 2.02 (d, H_7), 1.94 (d, H_8), 2.12 (d, H_4), 1.53 (d, H_5); $J_{2,3} \cong 1.0$, $J_{7,8} = 9.2$, $J_{4,5} = 1.3$ Hz.

Anal. Calcd. for $C_8H_6N_6$: N, 45.14. Found: N, 45.08.

6-Diethylaminopyrido[3,2-*d*]tetrazolo[1,5-*b*]pyridazine (**8**).

A mixture of 6-chloropyrido[3,2-*d*]tetrazolo[1,5-*b*]pyridazine (0.3 g.) and diethylamine (25 ml.) was heated under reflux for 21 hours. Upon evaporation of the solvent to dryness, water (100 ml.) was added and the residue filtered off. Upon crystallization from aqueous methanol the compound had m.p. 169° (yield 0.18 g.); mass spectrum: $M^+ = 243$; nmr spectrum (in deuteriochloroform): τ = 0.90 (dd, H_8), 2.23 (dd, H_9), 1.20 (dd, H_{10}), 6.02 (q, CH_2CH_3), 8.58 (t, CH_2CH_3); $J_{8,9} = 4.5$, $J_{9,10} = 8.2$, $J_{8,10} = 1.5$, $J_{Et} = 7.2$ Hz.

Anal. Calcd. for $C_{11}H_{13}N_7$: N, 40.31. Found: N, 40.44.

6-Aminopyrido[3,2-*d*]tetrazolo[1,5-*b*]pyridazine (**9**).

A mixture of **5b** (0.1 g.), ethanol (5 ml.), acetylacetone (0.1 g.) and triethylamine (0.03 g.) was heated to boiling, The product which separated was filtered off and washed with ethanol (yield almost quantitative), m.p. over 285°; mass spectrum: $M^+ = 187$; nmr spectrum (in DMSO-d_6): τ = 0.98 (dd, H_8), 2.10 (dd, H_9), 1.26 (dd, H_{10}), 2.60 (broad, NH_2); $J_{8,9} = 4.5$, $J_{9,10} = 8.2$, $J_{8,10} = 1.5$ Hz.

Anal. Calcd. for $C_7H_5N_7$: N, 52.39. Found: N, 52.03.

6-Aminopyrido[2,3-*d*]tetrazolo[1,5-*b*]pyridazine (**7**).

The compound was prepared in analogous way as described above for the isomeric **9**, m.p. over 285°; mass spectrum: $M^+ = 187$, $M\text{-}N_4 = 131$; nmr spectrum (in DMSO-d_6): τ = 1.25 (dd, H_7), 2.10 (dd, H_8), 0.90 (dd, H_9), 2.25 (broad, NH_2); $J_{8,9} = 4.5$, $J_{7,8} = 8.2$, $J_{7,9} = 1.5$ Hz.

Anal. Calcd. for $C_7H_5N_7$: N, 52.39. Found: N, 52.38.

Reaction of 6-Azidopyrido[2,3-*d*]tetrazolo[1,5-*b*]pyridazine with Diethylamine.

The azido compound **5a** (0.8 g.) and diethylamine (100 ml.) were heated under reflux for 120 hours. The product was filtered off (product A) and the filtrate was evaporated to dryness. The residue was mixed with cold chloroform (40 ml.) and the insoluble part was filtered off (70 mg. of compound **9**). The chloroform solution was evaporated to dryness and the residue purified by tlc (DC Fertigplatten Aluminumoxid F 254 (Type T), Merck, chloroform as solvent). The spot with $R_f = 0.58$ was eluted with methanol and sublimed at 170-180°/1 mm (30 mg. of compound **8**).

The product A was dissolved in cold methanol (50 ml.) and filtered. The insoluble part (90 mg.) consisted of compounds **9** and **7** in the ratio of about 8:1. The filtrate was charcoaled, filtered hot and the solvent was evaporated to dryness. After addition of some ether, the product was filtered off. There were obtained 0.35 g. fo compound **6**, m.p. 152-155°; mass spectrum: $M^+ = 270$; nmr spectrum (in DMSO-d_6): τ = 1.28 (dd, H_7), 2.18 (dd, H_8), 0.90 (dd, H_9), 1.47 (s, -CH=N-), 6.30 and 6.45 (q, CH_2CH_3), 8.75 (t, CH_2CH_3); $J_{8,9} = 4.5$, $J_{7,8} = 8.2$, $J_{7,9} = 1.5$, $J_{Et} = 7.2$ Hz.

Anal. Calcd. for $C_{12}H_{14}N_8$: N, 41.46. Found: N, 41.57.

Hydrolysis of compound **6**, as described in the above cases, afforded the corresponding amino compound **7**.

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