# Reaction between 6-Azidoazolopyridazines or 2-Azidopyrido[1,2-*a*]pyrimid-4-one and Some Secondary Aliphatic Amines

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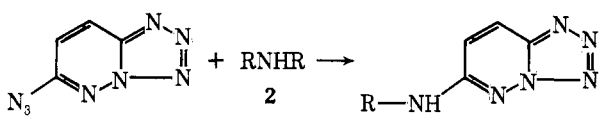
Azidoazoloazines react thermally or photochemically with secondary aliphatic amines to give N- and C-alkylated aminomethyleneamino derivatives. It is proposed that the reaction proceeds via an intermediate imine or enamine with subsequent cycloaddition of the azide. Decomposition of the formed triazoline can take place by several routes to give a mixture of reaction products. 2-Azidopyrido[1,2-*a*]pyrimid-4-one reacts in general in a different manner. Here, the amine is added to the carbonyl bond, the pyrimidine part of the bicycle is cleaved, and finally the azido group is isomerized into a tetrazole ring.

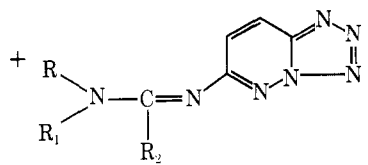
We have previously reported the unusual reaction between a heterocyclic azide and diethylamine.[1,2] To gain more insight into the mechanism of this transformation, we have now studied thermal and photochemical reactions between some higher secondary aliphatic amines and azidoazolopyridazines or 2-azidopyrido[1,2-*a*]pyrimid-4-one.

6-Azidotetrazolo[1,5-*b*]pyridazine (**1**) reacted with dipropylamine (**2a**) under reflux for 50 h to give a mixture of the corresponding amine (**3a**), the *N,N*-dipropylaminomethyleneamino derivative (**4a**), and its ethyl derivative (**4b**). A similar, but easier transformation took place with diisobutylamine (**2c**) or diisopentylamine (**2d**) (6 h and 40 min, respectively) to give unusual products (**4d** and **4e**, or **4f** and **4g**, respectively). Diisopropylamine (**2b**) was very unreactive and only after 285 h at reflux a small amount of the *N*-alkylaminoalkyleneamino derivative (**4c**) could be isolated with much of **3a**. In this manner, in all cases, besides the heterocyclic amine as the major product, also di- or trisubstituted amidines were formed.



**1** + RNHR (**2**) → **3**

| | R | R |
|---|---|---|
| a, | *n*-Pr | a, H |
| b, | *i*-Pr | b, $COCHMe_2$ |
| c, | $Me_2CHCH_2$ | c, $NEt_2$ |
| d, | $Me_2CHCH_2CH_2$ | |
| e, | Et | |



**4**

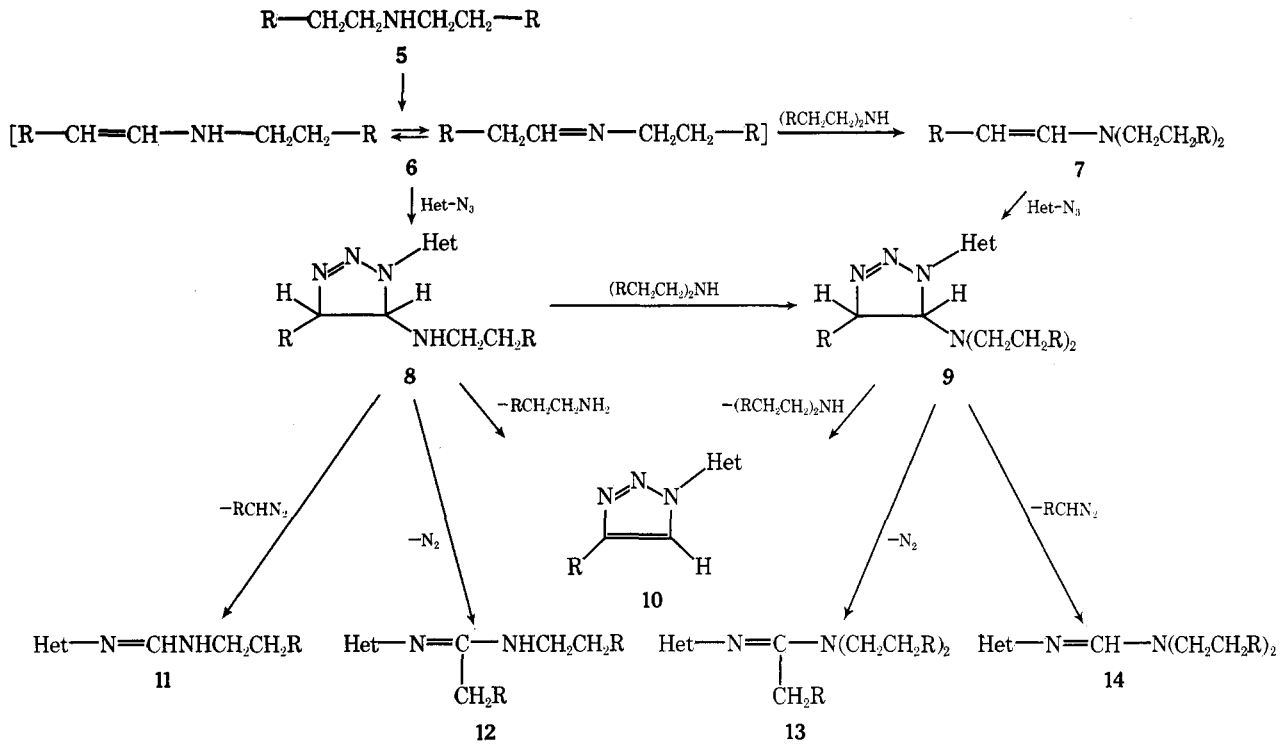
| | R | $R_1$ | $R_2$ |
|---|---|---|---|
| a, | *n*-Pr | *n*-Pr | H |
| b, | *n*-Pr | *n*-Pr | Et |
| c, | H | *i*-Pr | Me |
| d, | H | $Me_2CHCH_2$ | *i*-Pr |
| e, | $Me_2CHCH_2$ | $Me_2CHCH_2$ | *i*-Pr |
| f, | $Me_2CHCH_2CH_2$ | $Me_2CHCH_2CH_2$ | H |
| g, | $Me_2CHCH_2CH_2$ | $Me_2CHCH_2CH_2$ | $Me_2CHCH_2$ |
| h, | H | Et | H |
| i, | $Me_2CHCH_2$ | $Me_2CHCH_2$ | H |
| j, | Et | Et | H |

The above-mentioned results are best explained in terms of an intermediate imine or enamine (**6**), formed by dehydrogenation of the secondary aliphatic amine (**5**). Cycloaddition of the azide on the so-formed double bond[3,4] results in the formation of an unstable triazoline (**8**) which then decomposes in several ways. Elimination of the amine generates the triazole (**10**), whereas elimination of a diazoalkane affords compound **11** or elimination of nitrogen gives the alkylated compound (**12**). It can be anticipated that the *N,N*-dialkylamino derivatives **13** or **14** can be formed in a similar manner. Recently, we have shown that from the decomposition of a substituted triazole, resulting from the reaction between a heterocyclic azide and a 1,3-dicarbonyl compound, under mild reaction conditions a diazo compound is generated and detected.[5] Fragmentation of this type was observed earlier[6] and is operative in several other reactions.[7] No attempts have been made to detect diazoalkanes in our present experiments.

The *N,N*-dialkylamino side chain present in **13** and **14** could be formed in a transamination step from **6** to **7** or from **8** to **9**; the triazoline could then decompose to give either **10** or **13** or **14**. It was established in a separate experiment that the final products are not transaminated. Compound **4d** could not be transformed into **4e** with diisobutylamine under the same reaction conditions as employed for the reaction between **1** and **2c**. The transamination step must therefore occur at an earlier stage, either a conversion of **6** to **7** or **8** to **9**.

For a successful transformation, however, it is necessary that in the first step an unsaturated amine (**6**) be formed. Dehydrogenation of secondary amines can be carried out by a variety of reagents or catalytically.[8] There are no examples of dehydrogenation of a secondary aliphatic amine in the presence of an azide, but there are reports that some amides or amines can act as organic hydrogen abstractors.[9,10] Moreover, partial thermal decomposition of the azide in the reaction mixture gives a nitrenoid species which can abstract hydrogen. In a separate experiment we have treated ethylideneethylamine[11] (**15**) with the azide (**1**) and the reaction proceeded smoothly at room temperature to give the same mixture of products as observed previously in thermal decomposition of the same azide in diethylamine.[1] In a further experiment, a mixture of ethylideneethylamine and diisobutylamine was left to stand at room temperature for several days. The azide (**1**) was added to this reaction mixture and a vigorous reaction was observed. In addition to compound **3a**, the *N,N*-dialkylamino derivative (**4i**) was isolated and identified. This indicates that the ethylamine part of ethylideneethylamine was substituted with the higher secondary amine and that decomposition followed a reaction path similar to the conversion of **9** to **14**.

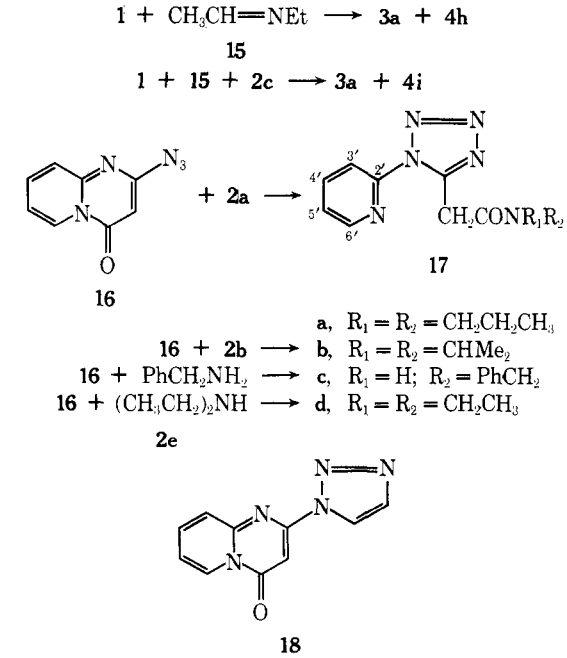
Furthermore, triethylamine reacts thermally in a similar manner as demonstrated previously[1] with diethylamine. Apparently dealkylation must take place during the conver-



sion. This process must be very slow since even after 25 days only partial conversion could be observed. There are known several methods for dealkylation of tertiary amines,[12] but none of them is plausible to explain our results. Heterocyclic amines, which result as the major product from the above reactions, are formed by thermal decomposition of the azides into nitrenes[13] which abstract hydrogens from the solvent, i.e., the secondary amines.

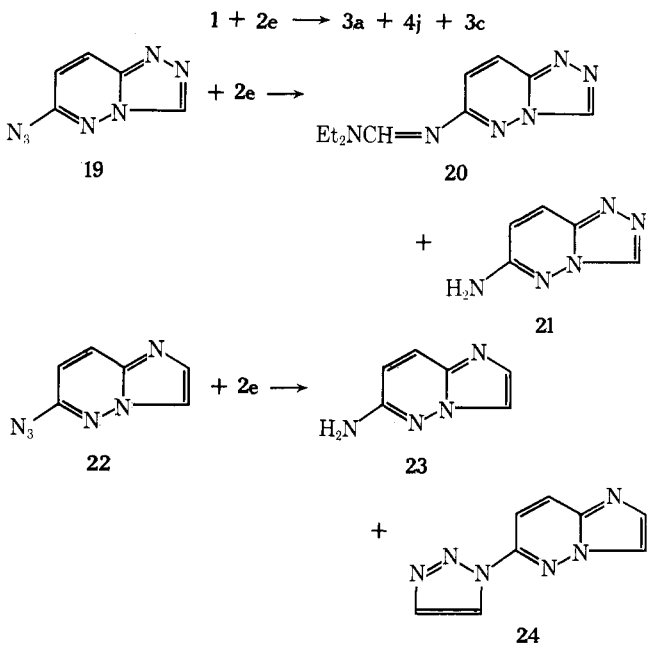
Compound **4d** could be hydrolyzed in 20% acetic acid to give the amide **2b**, in contrast to our previous observations[1] that hydrolysis of similar products afforded the heterocyclic amine (**3a**).

With 2-azidopyrido[1,2-*a*]pyrimid-4-one (**16**), thermal reactions with dipropylamine or diisopropylamine afforded the pyridyltetrazoles **17a** or **17b**. The formation of only these derivatives indicates that in this case the amine acts as nucleophile in an addition reaction to the carbonyl group. This



is followed by ring opening of the pyrimidine part and simultaneous formation of the tetrazole ring. Thus, the nucleophilic addition is faster than the formation of an unsaturated amine and addition of the azide to the formed double bond. This is similar to our previous findings when stronger nucleophiles were employed.[14] Diethylamine reacted partly in the same manner to give **17d**, but in addition compound **18** could be isolated and identified.

Moreover, we have found that the investigated azides react with secondary amines photochemically in almost the same manner as thermally. However, these reactions are less complex, but afford sometimes different reaction products than thermal reactions, since they are performed under less drastic reaction conditions. The azide (**1**) when irradiated at room temperature in the presence of diethylamine for 24 h afforded



in addition to compounds **4j** and **3c** the amine **3a** as the main product. Compound **3c**, however, was not isolated from a thermal decomposition and its formation in a photochemical

Table I[d]

| Reaction components (quantity) | Time, h | Products and yield | Mp, °C | Solvent for crystn | $R_f$ | Formula | Mass spectrum $M^+$, m/e | Solvent | $^1$H NMR data Chemical shifts (δ) and coupling constants (J) |
|---|---|---|---|---|---|---|---|---|---|
| **1** (1 g) + **2a** (40 ml) | 50 | **3a** (104 mg, 12%) | (ref 24) | | | | | | |
| | | **4a** (92 mg, 6%) | 58 | MeOH, hexane | 0.27[a] | $C_{11}H_{17}N_7$ | 247 | $CD_3OD$ | 7.27 (d, $H_7$), 8.15 (d, $H_8$), 8.48 (s, CH=N), $J_{7,8}$ = 9.7 Hz |
| | | **4b** (185 mg, 11%) | bp 208–209 | | 0.41[a] | $C_{13}H_{21}N_7$ | 275 | $CDCl_3$ | 7.02 (d, $H_7$), 7.94 (d, $H_8$), $J_{7,8}$ = 10.0 Hz |
| **1** (2 g) + **2b** (30 ml) | 285 | **3a** (1.43 g, 85%) | | | | | | | |
| | | **4c** (62 mg, 2.3%) | 129 | $CHCl_3$ and hexane | 0.17[b] | $C_9H_{13}N_7$ | 219 | $Me_2SO$-$d_6$ | 7.24 (d, $H_7$), 8.38 (d, $H_8$), 1.20 (d, CH**Me**$_2$), 4.13 (m, C**H**Me$_2$), 2.15 (s, –N=C–$CH_3$), $J_{7,8}$ = 9.8, $J_{i\text{-Pr}}$ = 6.5 Hz |
| **1** (1 g) + **2c** (10 ml) | 6.25 | **3a** (275 mg, 33%) | | | | | | | |
| | | **4d** (200 mg, 12%) | 112–113 | $CHCl_3$ and petroleum ether,[c] MeOH and $H_2O$ | 0.59[a] | $C_{12}H_{19}N_7$ | 261 | $Me_2SO$-$d_6$ | 7.27 (d, $H_7$), 8.44 (d, $H_8$), $J_{7,8}$ = 10.0 Hz |
| | | **4e** (120 mg, 6%) | 168–169 | $CHCl_3$ and petroleum ether,[c] $CHCl_3$ and hexane | 0.67[a] | $C_{16}H_{27}N_7$ | 317 | $CDCl_3$ | 7.04 (d, $H_7$), 7.98 (d, $H_8$), 3.12 (septuplet, C**H**Me$_2$), $J_{7,8}$ = 10.0, $J_{i\text{-Pr}}$ = 7.2 Hz |
| **1** (1 g) + **2d** (6 ml) | 0.66 | **3a** (480 mg, 57%) | | | | | | | |
| | | **4f** (32 mg, 1.7%) | 92–96 | $CHCl_3$ and petroleum ether[c] | 0.50[a] | $C_{15}H_{25}N_7$ | 303 | $CDCl_3$ | 7.23 (d, $H_7$), 8.09 (d, $H_8$), 8.60 (s, CH=N), $J_{7,8}$ = 9.5 Hz |
| | | **4g** (100 mg, 4.5%) | bp 230–231 | | 0.70[a] | $C_{19}H_{33}N_7$ | 359 | $CD_3OD$ | 7.20 (d, $H_7$), 8.22 (d, $H_8$), $J_{7,8}$ = 9.7 Hz |
| **16** (1 g) + **2a** (25 ml) | 170 | **17a** (956 mg, 62%) | 135–136 | MeOH and $H_2O$ (1:2) | 0.58[b] | $C_{14}H_{20}N_6O$ | 288 | $Me_2SO$-$d_6$ | 8.05 (m, $H_{3'}$, $H_{4'}$), 7.55 (m, $H_{5'}$), 8.52 (m, $H_{6'}$) |
| **16** (1 g) + **2b** (50 ml) | 185 | **17b** (975 mg, 63%) | 137–138 | MeOH and $H_2O$ (1:2) | 0.33[a] | $C_{14}H_{20}N_6O$ | 288 | $Me_2SO$-$d_6$ | 7.96 (m, $H_{3'}$, $H_{4'}$), 7.45 (m, $H_{5'}$), 8.45 (m, $H_{6'}$), 5.83 and 6.60 (septuplet, C**H**Me$_2$), $J_{i\text{-Pr}}$ = 6.9 Hz |
| **16** (0.5 g) + $PhCH_2NH_2$ (1 ml) | 1 | **17c** (750 mg, 95%) | 163–164 | EtOH | | $C_{15}H_{14}N_6O$ | 266 ($M^+$-$N_2$) | $Me_2SO$-$d_6$ | 8.45 (m, $H_{6'}$), 7.9–8.2 (m, $H_{3'}$, $H_{4'}$), 7.55 (m, $H_{5'}$), 7.18 (s, $C_6H_5$) |

[a] $CHCl_3$. [b] $CHCl_3$–MeOH, 50:1. [c] Petroleum ether, bp 40–60 °C. [d] Satisfactory analytical data were obtained for all compounds listed.

process can be interpreted via an intermediate nitrene, generated from the azide, and secondary amine. This is similar to the observed formation of a substituted hydrazine in a photochemical decomposition of an aromatic azide in the presence of dimethylamine[15,16] and such insertions are also known with some heteroaromatic azides.[17,18] In a similar manner as **1** the azide **19** afforded a mixture of **20** and **21**, but in the case of 6-azidoimidazo[1,2-*b*]pyridazine (**22**) it was possible to isolate from the reaction mixture besides the amine (**23**) also the triazole (**24**). The isolation and identification of this triazole as well as that of **18** supports the above proposed mechanism of formation of intermediates like **8** or **9**. Compound **24** is a 1-substituted triazole and is apparently photostable, although it has been observed that only 2-substituted 1,2,3-triazoles are photostable and others easily eliminate nitrogen.[19–23]

This is probably not the case with compound **18**, since in a photochemical reaction of compound **16** with diethylamine only **17d** was isolated and no **18** could be detected, which contrasts with the corresponding thermal transformation.

## Experimental Section

Melting points were determined on a Kofler apparatus. Spectral data were obtained from a JEOL C-60HL spectrometer and Hitachi Perkin-Elmer RMU-6L mass spectrometer. Photochemical reactions were carried out in a Rayonet photoreactor RPR-100 at 300 nm.

**General Procedure for Thermal Reaction between 6-Azidotetrazolo[1,5-*b*]pyridazine and an Aliphatic Secondary Amine.** A mixture of the azide (1) and secondary amine was heated under reflux (boiling point of the particular secondary amine). At the end of the reaction, the mixture was evaporated in vacuo to dryness, $CHCl_3$ (40–50 ml) was added, and compound **3a** was filtered off. The filtrate was chromatographed by TLC (DC-Fertigplatten Kieselgel $F_{254}$, 0.5 mm). The separated compounds were eluted and crystallized. The reaction conditions, melting points of the products, yields, NMR, and other data are presented in Table I.

***N*-(Tetrazolo[1,5-*b*]pyridazinyl-6)isobutyramide (3b).** A solution of compound **4d** (50 mg) in diluted acetic acid (1:4, 3 ml) was heated under reflux for 2 h. The reaction mixture was evaporated to dryness and the residue was crystallized from $CHCl_3$ and petroleum ether (bp 40–60 °C): mp 176–179 °C (yield 26 mg, 66%); NMR ($CD_3OD$) $\delta$ 8.66 and 8.45 (d, $H_7$ $H_8$), 2.75 (septuplet, $CHMe_2$), $J_{7,8}$ = 10.5, $J_{CHMe_2}$ = 6.8 Hz; mass spectrum M·+ 206.091475 (calcd for $C_8H_{10}N_6O$, 206.091603).

**Reaction between 1 and Ethylideneethylamine.** Compound 1 (1 g) was added portionwise to ethylideneethylamine (**15**)[11] (3 ml, containing 30% ethylamine). After the vigorous reaction had subsided, the reaction mixture was left to stand at room temperature for 1 h. The mixture was evaporated to dryness, $CHCl_3$ (20 ml) was added, and the product was filtered off and washed with $CHCl_3$ (15 ml). The compound was identified as **3a**.[24] The filtrate was chromatographed by TLC, $CHCl_3$ as solvent. The strongly fluorescent compound with $R_f$ 0.5 was eluted and compound **4h** (31 mg, 3%) was obtained and identified.[1]

**Synthesis of Compound 4i.** A mixture of ethylideneethylamine (**15**, 1.5 ml, containing 30% ethylamine) and diisobutylamine (1.5 ml) was left at room temperature in a sealed vessel for 4 days. To this mixture compound 1 (1 g) was added portionwise. After the vigorous reaction had subsided, the reaction mixture was left at room temperature for 1 h and evaporated to dryness. $CHCl_3$ (20 ml) was added and compound **3a** (220 mg, 26%) was filtered off. The filtrate was purified by TLC and after the strongly fluorescent product with $R_f$ 0.42 was eluted, it was identified as compound **4i**: mp 93–96 °C (37 mg, 2% yield) (from $CHCl_3$ and petroleum ether, bp 40–60 °C); mass spectrum M·+ 275.185839 (calcd for $C_{13}H_{21}N_7$, 275.185834); NMR ($CDCl_3$) $\delta$ 7.25 (d, $H_7$), 8.12 (d, $H_8$), 8.65 (s, CH=N), 2.0 ($CHMe_2$), $J_{7,8}$ = 9.5, $J_{i\text{-}Pr}$ = 7.0 Hz.

**Reaction between 2-Azidopyrido[1,2-*a*]pyrimid-4-one (16) and Diethylamine.** A mixture of compound **16**[14] (0.5 g) and diethylamine (100 ml) was heated under reflux for 115 h. The reaction mixture was evaporated to dryness, ethanol (15 ml) was added, and the product was filtered off. The compound was purified by crystallization from aqueous ethanol and identified as **18**: mp 232–233 °C (yield 80 mg, 14%); NMR (DMF-$d_7$) $\delta$ 6.89 (s, $H_3$), 9.0 (m, $H_6$), 8.18–7.22 (m, $H_7$, $H_8$, $H_9$), 7.82 (d, $H_{4'}$), 8.67 (d, $H_{5'}$), $J_{4',5'}$ = 1.3 Hz; mass spectrum M·+ 213.

Anal. Calcd for $C_{10}H_7N_5O$: C, 56.33; H, 3.31; N, 32.85. Found: C, 56.07; H, 3.52; N, 32.63.

The filtrate was evaporated to dryness, $CHCl_3$ (3 ml) was added, and the solution was treated with charcoal and after 30 min was filtered and poured into hexane (15 ml). The separated product **17d** was crystallized three times from $CHCl_3$ and hexane, mp 88–90 °C (320 mg, 46%), mass spectrum M·+ 260.

Anal. Calcd for $C_{12}H_{16}N_6O$: C, 55.37; H, 6.20; N, 32.29. Found: C, 54.98; H, 6.35; N, 32.60.

Reactions of **16** with other amines were performed in a similar manner and the products **17a**, **17b**, and **17c** are presented in Table I.

**Photochemical Reaction between 1 and Diethylamine.** A mixture of compound 1 (0.8 g) and diethylamine (24 ml) was irradiated in a photoreactor for 24 h at room temperature. The reaction mixture was evaporated in vacuo to dryness, $CHCl_3$ (24 ml) was added, and the separated product was filtered off. It was identified as **3a** (230 mg, 34%). The filtrate was purified by TLC (DC-Fertigplatten $Al_2O_3$ $F_{254}$ T, 1.5 mm, $CHCl_3$ as solvent). The compound with $R_f$ 0.82 was identified as **4j**[1] (182 mg, 17%) and the other compound with $R_f$ 0.55 was crystallized from $CHCl_3$ and hexane and identified as **3c**: mp 88–92 °C (32 mg, 3%); NMR ($CDCl_3$) $\delta$ 7.67 (d, $H_7$), 8.22 (d, $H_8$), $J_{7,8}$ = 10.4 Hz; mass spectrum M·+ 207.

Anal. Calcd for $C_8H_{13}N_7$: C, 46.36; H, 6.32; N, 47.32. Found: C, 46.31; H, 6.03; N, 47.59.

In a similar manner compound **19** (0.5 g) was irradiated in the presence of **2e** (110 h) to give a mixture of **20**[1] (85 mg, 13%), **21** (25 mg, 6%), and starting compound **19** (25 mg). When compound **22** (2 g) was irradiated in the presence of **2e** for 62 h, compounds **23** (145 mg, 9%) and **24**[1] (54 mg, 2%) were isolated and identified.

**Photochemical Reaction of 16 with 2e.** A mixture of the azide **16** (0.34 g) and diethylamine (10 ml) was irradiated for 110 h (at 300, 254, or 350 nm) at room temperature. After evaporation to dryness the residue was dissolved in $CHCl_3$ and purified by TLC (DC-Fertigplatten $Al_2O_3$ $F_{254}$ T, 1.5 mm, $CHCl_3$ as solvent. The compound with $R_f$ 0.53 was eluted and crystallized from $CHCl_3$ and hexane and identified as **17d** (160 mg, 34%).

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**Registry No.**—**1**, 14393-79-4; **2a**, 142-84-7; **2b**, 108-18-9; **2c**, 110-96-3; **2d**, 544-00-3; **2e**, 109-89-7; **3a**, 19195-43-8; **3b**, 59711-30-7; **3c**, 59711-31-8; **4a**, 59711-32-9; **4b**, 59711-33-0; **4c**, 59711-34-1; **4d**, 59711-35-2; **4e**, 59711-36-3; **4f**, 59711-37-4; **4g**, 59711-38-5; **4i**, 59711-39-6; **15**, 1190-79-0; **16**, 55395-31-8; **17a**, 59711-40-9; **17b**, 59711-41-0; **17c**, 59711-42-1; **17d**, 55395-34-1; **18**, 59711-43-2; **19**, 14393-80-7; **22**, 13526-73-3; $PhCH_2NH_2$, 100-46-9.

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