zin-4-ium Bromide (4d, R = Ph).—6-Chloro-3(2H)-pyridazinethione (1.47 g) was dissolved in tetrahydrofuran (50 ml) and under stirring phenacyl bromide (1.99 g) was added. The reaction mixture was left to stand at room temperature for 2 hr, and the separated product was filtered off, washed with some hot tetrahydrofuran and dried *in vacuo*: yield 77%; mp 163–164°; ir (Nujol) 3390 cm^{-1} (OH). *Anal.* Calcd for $C_{12}H_{10}BrClN_2OS$: C, 41.70; H, 2.92; N, 8.11; S, 9.28. Found: C, 41.37; H, 3.10; N, 8.47; S, 9.35.

In an analogous way the **3-methyl analog (4d, R = Me)** was prepared. The reaction mixture was evaporated to half of its original volume, and the residue was cooled on ice, filtered, washed with some tetrahydrofuran and dried *in vacuo*: yield 53%; mp 178–179°; ir (Nujol) 3378 cm^{-1} (OH). The compound is unstable and darkens after exposure on air after 15 min. *Anal.* Calcd for $C_7H_8BrClN_2OS$: C, 29.64; H, 2.84; N, 9.88. Found: C, 30.02; H, 3.30; N, 10.20.

2,3-Dihydropyrido[3,2-*d*]thiazolo[3,2-*b*]pyridazin-4-ium Bromide (5a, X = CH; Y = N; R = R$_1$ = H).—To a solution of pyrido[2,3-*d*]pyridazine-5(6H)-thione (1.63 g) in N,N-dimethylformamide (10 ml), K_2CO_3 (1.4 g) and 1,2-dibromoethane (1.88 g) were added. The reaction mixture was stirred at room temperature for 5 hr and then left to stand on ice overnight. The precipitated mixture of salts was filtered off and the pyridazinium salt was dissolved in hot anhydrous EtOH (about 15 ml). Upon cooling crystals separated and were filtered off and crystallized from EtOH: yield 0.73 g (27%); mp > 330° (at about 320° slow decomposition started). *Anal.* Calcd for $C_9H_8BrN_3S$: C, 38.08; H, 3.13; N, 16.28; S, 12.42. Found: C, 38.32; H, 3.33; N, 16.49; S, 12.09.

In an analogous way the isomeric **2,3-dihydropyrido[2,3-*d*]thiazolo[3,2-*b*]pyridazin-4-ium bromide (5b, X = N; Y = CH; R = R$_1$ = H)** was obtained in 23% yield, mp > 330° (from EtOH and N,N-dimethylformamide, 1:2). *Anal.* Calcd for $C_9H_8BrN_3S$: C, 38.08; H, 3.13; N, 16.28; S, 12.42. Found: C, 38.09; H, 3.63; N, 15.94; S, 12.22.

Registry No.—**2a**, 18599-27-4; **2b** (R_1 = H; R_2 = $PhCOCH_2S$), 18599-28-5; **2b** (R_1 = H; R_2 = $MeCOCH_2S$), 18599-29-6; **2c** (R = Ph), 18598-86-2; **2c**·HBr. (R = Ph), 18621-00-6; **2c** (R = Me), 18592-50-2; **2d** (R = Ph), 18592-51-3; **2d** (R = Me), 18592-52-4; 2-phenacylthiopyridine·HBr, 3166-30-1; **3a** (R = Ph), 18592-54-6; **3b** (R = Ph), 18592-55-7; **3b** (R = Me), 18592-56-8; **3c** (R = Ph), 18592-57-9; **3c** (R = Me), 18592-58-0; **3d** (R = Ph), 18621-01-7; **3d** (R = Me), 18592-59-1; **4a** (R = Ph), 18592-60-4; **4b** (R_1 = Ph), 18592-61-5; **4b** (R_1 = Me), 18592-62-6; **4c** (R = Ph), 18592-63-7; **4c** (R = Me), 18592-64-8; **4d** (R = Ph), 18592-65-9; **4d** (R = Me), 18592-66-0; **5a**, 18592-67-1; **5b**, 18592-68-2.

Acknowledgment.—For valuable suggestions in connection with the nomenclature of some new systems we wish to thank Mr. K. L. Loening, Director of Nomenclature, Chemical Abstracts Service.

1,3-Butadiynes in the Synthesis of Heterocyclic Compounds. I. 2,3-Dihydro-1,4-diazepine, Pyrazole, and Isoxazole Derivatives

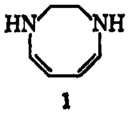
WILLIAM W. PAUDLER AND ANDREW G. ZEILER

Department of Chemistry, Ohio University, Athens, Ohio 45701

Received August 28, 1968

The condensation of 1,3-butadiyne with ethylenediamine has been shown to yield 5(7)-methyl-1H-2,3-dihydro-1,4-diazepine **2** ⇆ **3** rather than the reported 1,2,3,4-tetrahydro-1,4-diazocine (**1**). The reaction of hydrazine with appropriately substituted 1,3-butadiynes afforded pyrazoles **6a–d**, while 1,4-diphenyl-1,3-butadiyne, when treated with hydroxylamine, yielded isoazole **7**. Isomeric isoxazole **9** was also prepared and its structure was proven by nmr and mass spectrometric techniques.

The syntheses of pyrroles, thiophenes and selenophenes by the addition of ammonia, hydrogen sulfide and hydrogen selenide, respectively, to 1,3-butadiynes have recently been the subject of several papers.[1-3] An extension of this reaction utilizing ethylenediamine instead of monoamines has also been described.[4] The condensation product of ethylenediamine with 1,3-butadiyne is reported to afford 1,2,3,4-tetrahydro-1,4-diazocine (**1**).



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In view of our interest in diazocines[5-7] we repeated this reaction and obtained a "compound" which distilled at the reported boiling point [136° (6 mm)]. The nmr spectrum of this material is, however, not in agreement with that expected for 1,2,3,4-tetrahydro-1,4-diazocine (**1**). The nmr spectral data of the compound (*cf.* Experimental Section) show the presence of a methyl group, an olefinic two-proton (AB) system and a four-proton singlet along with an exchangeable one-proton peak. The nmr spectrum of the material obtained by distillation shows, in addition to the absorptions reported in the Experimental Section, a multitude of smaller peaks indicative of impurities. These impurities are no longer present when the reaction mixture is treated under milder conditions than those reported.[4] In fact, the yield of the compound is increased from 55 to 91% and the material crystallizes (mp 72–73°).

The purification process did not alter the molecular formula ($C_6H_{10}N_2$) of the compound. A consideration of the nmr spectrum strongly suggests that the correct structure of this material is the dihydrodiazepine (**2** or **3**). This assignment was readily confirmed by the catalytic reduction of the diazepine material to the known hexahydrodiazepine **4**.[8] The question as to

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(1) J. Reisch and K. E. Schulte, *Angew. Chem.*, **73**, 241 (1961).

(2) K. E. Schulte, J. Reisch, and L. Hoerner, *Chem. Ber.*, **95**, 1943 (1962).

(3) R. F. Curtis, S. H. Hasnain, and J. A. Taylor, *Chem. Commun.*, 365 (1968).

(4) M. F. Shostakovski, I. A. Chekulaeva, and L. V. Kondrat'eva, *Dokl. Acad. Nauk SSSR*, **153**, 1353 (1963).

(5) W. W. Paudler and A. G. Zeiler, *J. Org. Chem.*, **32**, 2425 (1967).

(6) W. W. Paudler and A. G. Zeiler, *Chem. Commun.*, 1077 (1967).

(7) W. W. Paudler, G. R. Gapski, and J. M. Barton, *J. Org. Chem.*, **31**, 277 (1966).

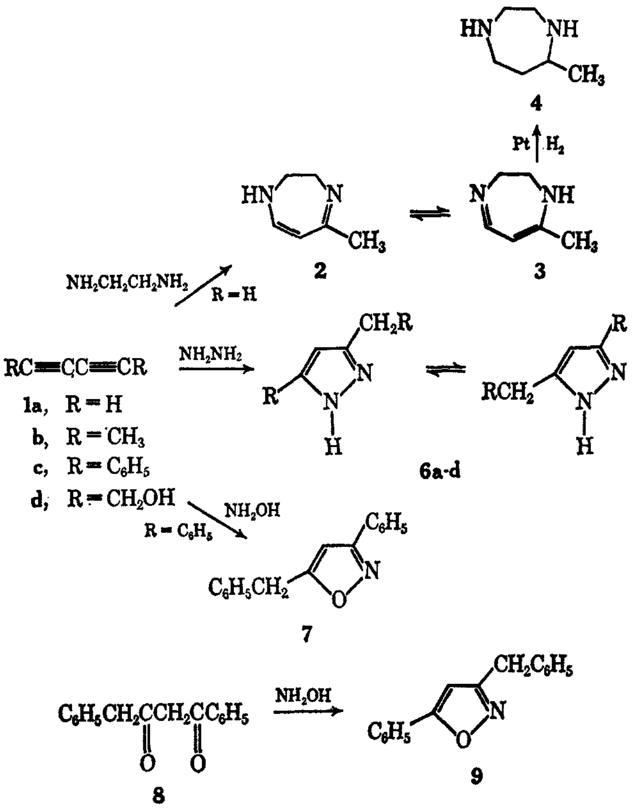
(8) F. Poppelsdorf and R. C. Myerly, *ibid.*, **26**, 131 (1961).

whether we are dealing with tautomer **2** or **3** is still open, but in view of the fact that the methylene protons appear as a four-proton singlet, we suggest that, at least in solution, we are dealing with a rapidly equilibrating system of the two tautomers. The structurally most closely related known dihydrodiazepine is 2,3-dihydro-5,7-dimethyl-1,4-diazepine (**5**). The nmr spectral data for this compound[9,10] listed in the Experimental Section further substantiate our structural assignment for compound **2** (**3**).

The results of this experiment led us to study the reaction of 1,3-butadiynes with other difunctional nucleophiles. Thus, the reaction of 1,3-butadiynes with hydrazine and with hydroxylamine would be expected to yield pyrazoles and isoxazoles, respectively.

The general applicability of this synthetic approach, which involves an over-all 1,3 addition to 1,3-butadiynes, is outlined in Scheme I. The pyrazoles **6a–c** are known compounds[11] and the structures of the appropriate condensation products were readily established. The hydroxymethyl derivative **6d** is unknown, but its structure is clearly established by its elemental analysis, mass spectrometric molecular weight and by a comparison of its nmr spectrum with that of the related pyrazoles **6a–c** (*cf.* Experimental Section).

SCHEME I



The structure of the isoxazole obtained from the condensation of the 1,3-butadiyne **1** (R = C_6H_5) cannot be established by a comparison with a known compound. The structure of the isoxazole obtained from the condensation of the dicarbonyl compound **8** with hydroxylamine has never been established.[11c] The properties of the compound obtained from the 1,3-butadiyne **1** (R = C_6H_5) are, in fact, different from those of the isoxazole obtained from the dicarbonyl compound **8** and hydroxylamine. The structures of the two isoxazoles are, however, readily established from an analysis of their mass spectral fragmentation patterns (*cf.* Experimental Section).

The formation of the ions $[C_6H_5CH_2C_2HN]^+$ and $[C_6H_5CO]^+$ from compound **9**, but not from compound **7**, clearly differentiates between the two isomeric isoxazole structures and allows us to assign them as shown in Scheme I.

Further confirmation of the isoxazole structures is found by an analysis of their nmr spectra. The olefinic isoxazole proton in compound **9** is more deshielded by the phenyl group than the same proton in isoxazole **7**, which is not subject to this deshielding effect, while the reverse is true of the methylene protons which are more deshielded when adjacent to the carbon–carbon double bond of isoxazole **7** than in isoxazole **9**. We are currently in the process of studying the mechanisms and the general applicability of these reactions.

Experimental Section[12]

2,3-Dihydro-5-methyl-1,4-diazepine (2 ⇄ **3**).—To 6.0 g (0.1 mol) of ethylenediamine at 0° was added 3.7 g (0.074 mol) of 1,3-butadiyne.[13] The flask was tightly stoppered and the solution was stirred overnight at 0° (*caution*: at room temperature this reaction can be violent) and at room temperature for 4 hr. The excess ethylenediamine was removed under vacuum (0.1 mm) at room temperature, affording brown crystals. This material was purified by sublimation at 40° (0.1 mm) to yield pale yellow, hygroscopic needles: mp 72–73°; mass spectrum mol wt, 110; 100-MHz pmr (DMSO-d_6), one-proton doublet (τ 3.14, J = 8 cps), one-proton doublet, (5.50, J = 8 cps); four-proton singlet (6.54), methyl singlet (8.08). *Anal.* Calcd for $C_6H_{10}N_2$: C, 65.41; H, 9.15; N, 25.43. Found: C, 65.34; H, 9.28; N, 25.35.

2 ⇄ **3.**—The picrate (from EtOH) had mp 146–147°; 100-MHz pmr (DMSO-d_6); one-proton doublet (τ 2.60, J = 8 cps), one-proton doublet (5.10, J = 8 cps), four-proton singlet (6.44), methyl singlet (7.82). *Anal.* Calcd for $C_{12}H_{13}N_5O_7$: C, 42.48; H, 3.86; N, 20.64. Found: C, 42.79; H, 3.84; N, 20.52.

2,3-Dihydro-5,7-dimethyl-1,4-diazepine pmr[10] spectrum (**CDCl$_3$**) showed a one-proton singlet (τ 5.60), four-proton singlet (6.58), and six-proton singlet (8.12).

2,3-Dihydro-5,7-dimethyl-1,4-diazepine perchlorate pmr[9] spectrum (**DMSO-d_6**) showed a one-proton singlet (τ 4.90), four-proton singlet (6.45), and six-proton singlet (7.7).

Catalytic Reduction of 2.—A solution of 300 mg (2.72 mol) of the diazepine in 50 ml of acetic acid–water (1:1) was hydrogenate in the presence of 0.15 g of prereduced platinum oxide, at atmospheric pressure. The sample required 115.2 ml of hydrogen (calcd 121.8). The catalyst was removed by filtration and most of the solvent was evaporated. The remaining solution was made basic with 10% aqueous NaOH and extracted with chloroform. Evaporation of the chloroform extract gave the crude reduction product (230 mg, 60%) which was isolated as its dipicrate salt: mp 255–256° dec (from EtOH) (lit.[8] mp 256 dec); 100 MHz pmr (DMSO-d_6); methyl doublet (τ 8.75, J = 7.2 cps), two-proton multiplet (7.98), three-proton multiplet (6.67), four-proton singlet (6.56).

3-Methylpyrazole (**6a**).—A solution of 3.2 g (0.1 mol) of hydrazine in 20 ml of ethanol was placed in a Carius tube and cooled to −20°. Butadiyne (3.02 g, 0.06 mol) was then added and the tube was sealed and the reaction mixture was heated at 65° for

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[9] C. Barnett, *Chem. Commun.*, 637 (1967).

[10] H. A. Staab and F. Vogtle, *Chem. Ber.*, **98**, 2701 (1965).

[11] (a) N. K. Kochetkov, *Dokl. Akad. Nauk SSSR*, **82**, 593 (1952). (b) C. Alberti and G. Zerbi, *Farmaco, Ed. Sci.*, **16**, 527 (1961). (c) C. Bulow and H. Grotowsky, *Chem. Ber.*, **34**, 1479 (1901).

[12] Nmr spectra were obtained with a Varian A-60 or HA-100 spectrometer. Mass spectra were obtained with a Hitachi–Perkin-Elmer RMU-6E instrument equipped with a solid sample injector. The ionizing voltage employed was 80 V. Elemental analyses were done by Mrs. K. Decker of this department.

[13] J. B. Armitage, E. R. H. Jones, and M. C. Whiting, *J. Chem. Soc.*, 44 1951).

50 hr. The resulting dark solution was diluted with 100 ml of water and extracted with chloroform. The chloroform extract was dried over anhydrous potassium carbonate and evaporated to dryness to yield 3.58 g (73%) of crude **6a**: bp 205° (754 mm) (lit.[11a] bp 204–205°); mass spectrum mol wt, 82; 60 HMz pmr ($CDCl_3$), CH_3 (τ 7.69); ring protons H_A (2.94), H_B (2.49), J_{AB} = 2 cps.

3-Ethyl-5-methylpyrazole (6b).—A solution of 1 g (0.013 mol) of 2,4-hexadiyne and 1 g (0.03 mol) of hydrazine in 10 ml of ethanol was refluxed for 3 days. Water (50 ml) was added and the mixture was extracted with chloroform. The chloroform extract was dried over potassium carbonate and evaporated to dryness giving 1.12 g (78%) of **6b**: mass spectrum mol wt, 110; 60-MHz pmr ($CDCl_3$), methyl triplet (τ 8.78, J = 7.5 cps), methyl singlet (7.73, methylene quartet (7.34, J = 7.5 cps), one-proton singlet (4.27), picrate from benzene, mp 145–146° (lit.[11b] mp 139–140°).

3-Benzyl-5-phenylpyrazole (6c).—A mixture of 1 g (5 mmol) of 1,4-diphenyl-1,3-butadiyne and 2 g of hydrazine was refluxed for 1 hr. The mixture was diluted with water and extracted with benzene. Evaporation of the benzene extract afforded 1.16 g (99%) of **6c** as white crystals (mp 88–90°). An analytical sample was obtained by recrystallization from cyclohexane: mp 91.5–92.5° (lit.[11c] mp 90.5–91°); mass spectrum mol wt, 234; 60-MHz pmr ($CDCl_3$), two-proton singlet (τ 6.08), one-proton singlet (3.72), ten aromatic protons (2.1–2.8).

3-(β-Hydroxyethyl)-5-hydroxymethylpyrazole (6d).—A solution of 1.1 g (0.01 mol) of 1,6-dihydroxy-2,4-hexadiyne and 1 g of hydrazine in 10 ml of ethanol was refluxed overnight. The solution was decolorized with charcoal and the solvent and excess hydrazine was evaporated under vacuum affording 1.23 g (86%) of **6d** as a viscous, colorless oil: mass spectrum mol wt, 142; 60 MHz pmr (D_2O): two-proton triplet (τ 7.10); two-proton triplet (6.10), two-proton singlet (5.34), one-proton singlet (3.75).

Anal. Calcd for $C_6H_{10}N_2O_2$: C, 50.69; H, 7.09; N, 19.71; Found: C, 50.48; H, 7.15; N, 19.82.

5-Benzyl-3-phenylisoxazole (7).—A mixture of 0.5 g (2.48 mmol) of 1,4-diphenyl-1,3-butadiyne and 2 g of hydroxylamine hydrochloride in 20 ml of pyridine was refluxed under nitrogen for 4 days. The reaction mixture was treated with 100 ml of water and the precipitated solid was collected and dissolved in 5 ml of ether which was then diluted with 30 ml of petroleum ether and cooled on ice. The resulting white crystals (0.29 g, 50%) were purified by sublimation at 80° (0.5 mm): mp 83–84°; 60-MHz pmr spectrum ($CDCl_3$), two-proton singlet (τ 5.92), one-proton singlet (3.83), ten aromatic protons (2.10–2.80); mass spectrum [m/e (%)] 235 (34), 144 (100), 116 (17), 103 (11), 101 (12), 91 (27), 77 (41), 65 (12), 63 (11), 51 (21), 44 (22).

Anal. Calcd for $C_{16}H_{13}NO$: C, 81.61; H, 5.56; N, 5.94. Found: C, 81.75; H, 5.70; N, 6.15.

3-Benzyl-5-phenylisoxazole (9).—Compound **9** was prepared by the method of Bulow and Grotowsky:[11c] mp 91–92°; 60-MHz pmr spectrum ($CDCl_3$), two-proton singlet (τ 6.00), one-proton singlet (3.79), ten aromatic protons (2.18–2.80); mass spectrum [m/e (%)] 235 (100), 144 (46), 130 (15), 116 (15), 105 (23), 103 (10), 101 (10), 92 (24), 91 (75), 89 (15), 77 (50), 65 (35), 63 (49), 51 (28).

Registry No.—**3**, 18761-60-9; **3** picrate, 18753-54-3; **6d**, 18753-55-4; **7**, 18753-56-5.

Diazocine Chemistry. IV. Ring Contractions to Diazepines and Piperidines

WILLIAM W. PAUDLER, ANDREW G. ZEILER, AND GEORGE R. GAPSKI

Department of Chemistry, Clippinger Laboratories, Ohio University, Athens, Ohio

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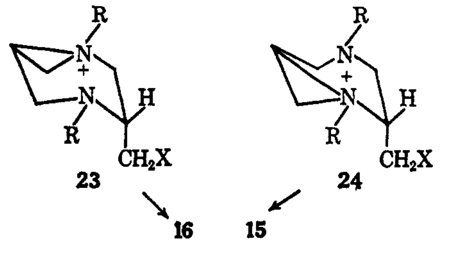
Treatment of *cis*- and *trans*-diazocine derivatives **1** and **2** with thionyl chloride afforded *cis*- and *trans*-diazepines **3** and **5**, respectively. *trans* compound **2** also yielded *trans*-piperazine **4**. Similar ring-contracted diazepines were obtained from *cis*- and *trans*-tetratosyl derivatives **7** and **8**. Free aminediols **11** and **12** were prepared by hydrolysis of N,N′-ditosyl compounds **1** and **2**. *cis*-Diol **13** rearranges, when passed over hot alumina, to 2-methyl- (**14**), 2,5-dimethyl- (**15**), 2,6-dimethyl- (**16**), and 2,3,5-trimethylpyrazine (**17**). The mode of formation of these compounds is described in terms of the involvement of intermediate aziridinium ions.

In connection with efforts directed toward the synthesis of 1,5-diazocine, we investigated the reaction of a mixture of *cis*- and *trans*-1,5-bis(*p*-toluenesulfonyl)-3,7-dihydroxyoctahydro-1,5-diazocine (**1** and **2**) with thionyl chloride and reported the isolation of the ring contracted products **3** and **4**.[1] In an attempt to elucidate the stereochemical consequences of this reaction, we have now studied it in some detail, utilizing the pure diols **1** and **2**.

Treatment of the pure *cis*-diol **1** with thionyl chloride afforded the previously described, but stereochemically nondefined, perhydro-1,4-diazepine **3** as essentially the sole reaction product. Similar treatment of the *trans*-diol with thionyl chloride yielded the *trans*-2,5-di(chloromethyl)piperazine derivative **4** along with a compound (**5**) which is isomeric with the diazepine derivative **3**. That this material is, indeed, a stereoisomer of compound **3** was established by its conversion into perhydro-1,4-diazepine **6**, the same product as was obtained from the reduction of compound **3**. Since the substance resulting from the conversion of the *cis*-diol has a dipole moment of 6.05 D, while the isomer obtained from the transformation of the *trans*-diol has a dipole moment of 4.34 D, we can assign the *cis* configuration to compound **3** and the *trans* configuration to compound **5**.

SCHEME I



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[1] W. W. Paudler and A. G. Zeiler, *J. Org. Chem.*, **32**, 2425 (1967).