# ACETYLENE DERIVATIVES OF 1,2,4-TRIAZOLE

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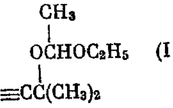
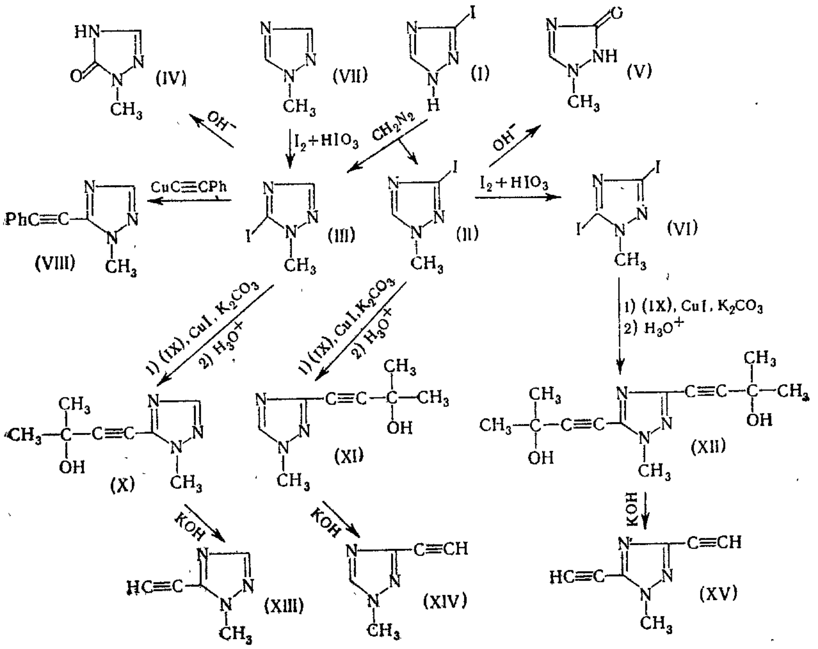
Continuing our study of the preparation and properties of the acetylenic derivatives of five-membered nitrogen heterocycles [1-5], we synthesized some ethynyl-substituted 1,2,4-triazoles by the previously proposed method [6]



$HC\equiv CC(CH_3)_2OCH(CH_3)OC_2H_5$ (IX)

The methylation of 3(5)-iodo-1,2,4-triazole (I) with diazomethane gave a mixture of the 3-iodo-(II) and 5-iodo-1-methyl-1,2,4-triazoles (III) (2 :1) in 89% yield. The (II) and (III) isomers were separated chromatographically, and their structure was established by comparing the experimental dipole moments with those calculated by the additive scheme [7]. The obtained compounds, with mp 90-91° and 102-103°C, respectively have dipole moments of 2.70 ± 0.20 and 3.70 ± 0.20 D (the calculated values for the 5- and 3-iodide are respectively 2.60 and 4.50 D). Despite the substantial difference between the found and calculated values in the second case, which is probably explained by the polarizability of the triazole ring [8], these data make it possible to assign with assurance the structure of 5-iodo-1-methyl-1,2,4-triazole (III) to the low-melting isomer. The made assignment was confirmed by the hydrolysis of (III) to the known 1-methyl-1,2,4-triazolin-5-one (IV) [9].



In an attempt to develop a convenient method for the preparation of 3,5-diiodo-1-methyl-1,2,4-triazole (VI) we studied the direct iodination of 1-methyl-1,2,4-triazole (VII). It could be assumed that the iodine

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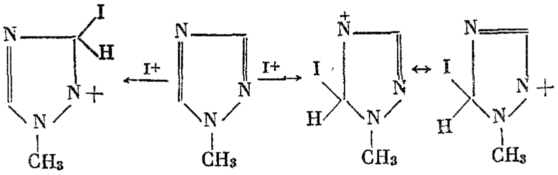
TABLE 1. Acetylene Derivatives of 1-Methyl-1,2,4-triazole

| Compound | Yield, % | T, mp, °C | Empirical formula | N (found/calculated), % | Infrared spectrum (CHCl$_3$), $\nu$, cm$^{-1}$ | NMR spectrum, δ, ppm |
|---|---|---|---|---|---|---|
| (X) | 60 | 54-55 (from petroleum ether) | $C_8H_{11}N_3O$ | 25,65/25,44 | (In CCl$_4$) : 2245 (C≡C), 3612 (OH) | In CCl$_4$ : 3,82 (NCH$_3$), 7,71 (3-H), 1,54 (CH$_3$), 5,78 (OH) |
| (XI) | 64 | 92-93 (from CCl$_4$) | $C_8H_{11}N_3O$ | 25,65/25,44 | 2250 (C≡C), 3603 (OH) | In CH$_2$Cl$_2$. 3,85 (NCH$_3$). 8,15 (5-H), 1,55 (CH$_3$), 5,10 (OH) |
| (XII) | 47 | 107.5-108.5 (from C$_6$H$_6$) | $C_{13}H_{17}N_3O_2$ | 17,07/17,00 | 2255 (C≡C), 3608 (OH) | In CDCl$_3$· 3,87 (NCH$_3$), 1,62 and 1,67 (CH$_3$). 5,01 and 5,51 (OH) |
| (XIII) | 72 | 76 (from petroleum ether) | $C_5H_5N_3$ | 39,15/39,24 | (In CCl$_4$): 2140 (C≡C), 3320 (C≡CH) | In CH$_2$Cl$_2$: 3,92 (NCH$_3$), 3,68 (C≡CH), 7,71 (3-H) |
| (XIV) | 85 | 106-107 | $C_5H_5N_3$ | 39,17/39,24 | 2145 (C≡C), 3315 (C≡CH) | In CH$_2$Cl$_2$: 3,87 (NCH$_3$), 3,13 (C≡CH), 8,05 (5-H) |
| (XV) | 30 | 103 | $C_7H_5N_3$ | 32,02/32,06 | 2144 (C≡C), 3313 (C≡CH) | In CHCl$_3$: 3,88 (NCH$_3$), 3,52 (5-C≡CH), 2,98 (3-C≡CH) |

will primarily replace the hydrogen in the 5 position, since in the intermediate σ-complex the charge is delocalized to a greater degree than in the complex that is formed when the 3 position is attacked



Actually, the oxidative iodination of (VII) with $I_2$ and $HIO_3$ leads only to the monoiodide (III). A second iodine atom cannot be inserted into the 5-iodide molecule (III). However, the presence of iodine in the 3 position of the heterocycle does not completely deactivate the 5 position, and it proved possible to synthesize the 3,5-diiodide (VI) by the direct iodination of 3-iodo-1-methyl-1,2,4-triazole (II).

It is known that halotriazoles are very inert in nucleophilic substitution reactions [10]. In order to check the theoretical possibility of replacing the halogen in such compounds by the acetylene group we condensed iodotriazole (III) with copper phenylacetylide. We obtained phenyl-(1-methyl-1,2,4-triazol-5-yl)acetylene (VIII) in 62% yield under the usual conditions of the acetylide synthesis [11]. This result gave reason to also expect success in the catalytic replacement of the halogen in the triazole ring.

We used CuI in the presence of $K_2CO_3$ as the catalyst [12] in the acetylenic condensation of (II), (III), and (VI) with the acetal derivative of 2-methyl-3-butyn-2-ol (IX). At the end of reaction the crude products were hydrolyzed with dilute HCl in dioxane. The overall yields of the triazolylacetylenic alcohols (X)-(XII) were 50-65%. Compounds (X)-(XII) were cleaved by heating in vacuo at 100-125°, in which connection the ethynyltriazoles were removed from the reaction sphere as they were formed. The yields of the monoacetylenes (XIII) and (XIV) were 70-85%, while the yield of 3,5-diethynyl-1-methyl-1,2,4-triazole (XV) was 30%. The structure of the synthesized compounds was proved by the elemental analysis, IR, and NMR spectral data. It should be mentioned that in the NMR spectra of the ethynyltriazoles the signal of the proton of the ethynyl group in the 5 position is shifted by ~0.5 ppm downfield relative to the signal of the proton of the same group in the 3 position. A similar shift of the signal of the proton of an acetylenic group, adjacent to a methylated ring nitrogen, was observed by us for imidazole and pyrazole derivatives [5, 13].

## EXPERIMENTAL METHOD

The NMR spectra were taken on a JNM-4H-100 spectrometer at 26° (internal standard = HMDS). The IR spectra were taken on a UR-20 instrument.

Methylation of 3(5)-Iodo-1,2,4-triazole (I). To 10.1 g of (I) [14] in 75 ml of absolute alcohol at 10° was gradually added an ether solution of $CH_2N_2$ (from 22.8 g of N-nitrosomethylurea), the mixture was stirred for 2 h, and the solvent was distilled off. The residue was chromatographed on $Al_2O_3$ (V activity) in a 3 : 2 ether–petroleum ether mixture to give the 5-iodo-(III) and 3-iodo-1-methyl-1,2,4-triazoles (II).

The yield of (III) was 3.6 g (33%), mp 90-91° (from petroleum ether). Found: C 17.50; H 2.17; I 60.89%. $C_3H_4IN_3$. Calculated: C 17.24; H 1.93; I 60.73%. NMR spectrum ($CCl_4$, δ, ppm): 3.89 ($NCH_3$); 7.73 (3-H). The yield of (II) was 6.1 g (56%), mp 102-103° (from $CCl_4$). Found: C 17.36; H 2.00; I 60.19%. $C_3H_4IN_3$. Calculated: C 17.24; H 1.93; I 60.73%. NMR spectrum ($CH_2Cl_2$, δ, ppm): 3.85 ($NCH_3$); 7.78 (5-H).

Iodination of 1-Methyl-1,2,4-triazole (VII). A mixture of 9.7 g of (VII) [15], 11.9 g of $I_2$, and 4.1 g of $HIO_3$ in 100 ml of $CH_3COOH$, 25 ml of water, 2.5 ml of $H_2SO_4$, and 25 ml of $CCl_4$ was heated at 75° for 4 h, neutralized with NaOH, and extracted with $CHCl_3$. Recrystallization from petroleum ether gave 10 g (41%) of (III).

1-Methyl-1,2,4-triazolin-5-one (IV). A mixture of 1 g of (III) and 10 ml of 20% aqueous KOH solution was refluxed for 6 h, neutralized with dilute HCl solution, and evaporated to dryness. Sublimation at 150° (1 mm) gave 0.47 g (99%) of (IV), mp 178-179° [9].

1-Methyl-1,2,4-triazolin-3-one (V). A mixture of 3 g of (II) and 30 ml of 20% aqueous KOH solution was refluxed for 40 h, cooled, and extracted with $CHCl_3$. The aqueous layer was neutralized, evaporated to dryness in vacuo, and (V) was extracted from the residue with $CHCl_3$ in a Soxhlet apparatus; the yield was 1.1 g (75%), mp 192-193° (from isobutanol). Found: N 42.31%. $C_3H_5N_3O$. Calculated: N 42.41%.

3,5-Diiodo-1-methyl-1,2,4-triazole (VI). A mixture of 4 g of (II), 9.7 g of $I_2$, and 3.3 g of $HIO_3$ in 20 ml of $CH_3COOH$, 5 ml of hexane, and 2.5 ml of dilute $H_2SO_4$ solution (1 : 4) was heated at 85° for 20 h. After cooling, 500 ml of $CHCl_3$ was added, the mixture was neutralized with NaOH, the organic layer was separated, and the aqueous layer was extracted with $CHCl_3$. We isolated 6 g of crude (VI) from the combined $CHCl_3$ solution; after recrystallization from heptane the yield was 5.2 g (82%), mp 138-139° [16].

Phenyl-(1-methyl-1,2,4-triazol-5-yl)acetylene (VIII). A mixture of 2.1 g of (III) and 2 g of copper phenylacetylide in 35 ml of pyridine was refluxed in a $N_2$ atmosphere for 20 h, diluted with 500 ml of ether, filtered, and the solvent was distilled off. The residue was chromatographed on $Al_2O_3$ (V activity) in benzene to give 1.1 g (62%) of (VIII), mp 70-71° (from petroleum ether). Found: C 72.27; H 5.08; N 22.99%. $C_{11}H_9N_3$. Calculated: C 72.11; H 4.95; N 22.94%. NMR spectrum ($CCl_4$, δ, ppm): 3.95 ($NCH_3$); 7.70 (3-H); 7.3-7.5 m ($C_6H_5$). Infrared spectrum ($CCl_4$, ν, $cm^{-1}$): 2235 ($C \equiv C$).

Acetylenic Condensation. A mixture of 4.2 g of (II), 4.7 g of (IX), 5.7 g of CuI, and 10.4 of $K_2CO_3$ in 30 ml of pyridine was heated in a $N_2$ atmosphere at 112-115° for 18 h, diluted with 500 ml of ether, filtered through a small layer of $Al_2O_3$ (V activity), and the solvents and excess (IX) were distilled off. The crude product (4.9 g) in 13 ml of dioxane and 7 ml of 1 : 1 HCl solution was stirred at 20° for 4 h, diluted with 200 ml of ether, and dried over $K_2CO_3$. The material was chromatographed on $Al_2O_3$ (V activity) in ether to give 2.1 g (64%) of (XI). Alcohols (X) and (XII) were synthesized in a similar manner (Table 1).

5-Ethynyl-1-methyl-1,2,4-triazole (XIV). A finely ground mixture of 100 mg of (X) and 10 mg of KOH was heated carefully at 100° (1 mm) in a vacuum-sublimation apparatus. Here 47 mg (72%) of (XIII) was sublimed. Acetylenes (XIV) and (XV) were obtained in a similar manner (see Table 1).

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## CONCLUSIONS

1. The acetylenic condensation was extended to 1,2,4-triazole derivatives. Some ethynyl-substituted 1-methyl-1,2,4-triazoles were synthesized.

2. The oxidative iodination of 1-methyl-1,2,4-triazole was studied.

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