

The Condensation Reactions of 5-Azidotropolone Derivatives with Active Methylene Compounds¹⁾

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The reactions of 5-azidotropolone (I), its methyl ether (II), and tosylate (XIII) with active methylene compounds were investigated. Several tropolones and azulenes which possess the 1,2,3-triazole ring as a substituent were obtained. The order of reactivities in these reactions were found to be: tropolone tosyl groups > azido groups > tropolone methyl ether groups. The direction of the addition of the azido groups to active methylene compounds was also clarified.

In 1902, Dimroth reported that the reaction of phenyl azide with ethyl acetoacetate gave a 1,2,3-triazole derivative,²⁾ and this type of reactions has been reviewed by Benson and Savell.³⁾

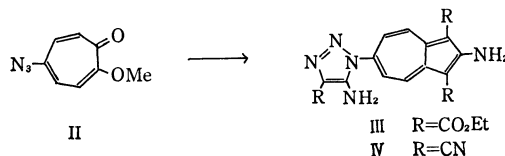
Recently, much attention has been focused on organic azido compounds, because of their interesting 1,3-dipolar characteristics, and on nitrene-formation reactions.⁴⁾ We ourselves have also been interested in azido derivatives of troponoid compounds and have investigated several reactions of 5-azidotropolones.^{1,5)}

Active troponoid compounds have been known to give azulene derivatives or their related compounds by reactions with active methylene compounds.⁷⁾ As a part of our studies of azidotropolones, we have investigated the reactions of 5-azidotropolones with active methylene compounds in order to obtain the 1,2,3-triazole derivatives of troponoid and azulenoid compounds and to investigate their properties.

5-Azidotropolones possess two active centers in their molecules toward active methylene compounds. Therefore, their order of reactivity is interesting. Moreover, if the addition reactions take place, the direction of addition to the azido group must be determined, because the direction will indicate the degree of interaction between the azido group and tropolone moiety.

The treatment of 5-azidotropolone methyl ether (II) with an excess of ethyl cyanoacetate afforded a crystalline substance (III). The elemental analysis of III ($C_{21}H_{23}O_6N_5$) showed that III was a condensation product of II with three moles of ethyl cyanoacetate. The UV and visible spectra of III are agreeable to classifying it as an azulene derivative,⁷⁾ and the NMR

spectrum of III shows two peaks (2H, d, $J=11$ Hz respectively) at 9.10 and 7.46 ppm which correspond to adjacent hydrogens on the seven-membered ring moiety.⁸⁾ The IR spectrum of III shows the existence of two different kinds of amino groups (3545, 3488, and 3380 cm^{-1}) and of ester groups (1680 and 1656 cm^{-1}). Therefore, the structure of III is 2-amino-1,3-diethoxycarbonyl-6*N*-(5'-amino-4'-ethoxycarbonyl-1,2,3-triazol-1-yl)azulene, and the attack of ethyl cyanoacetate takes place at the azido group and the tropolone moiety at the same time. Also, the reaction of II with malononitrile gave 2-amino-1,3-dicyano-6*N*-(5'-amino-4'-cyano-1,2,3-triazol-1-yl)azulene (IV).



When II was treated with a rather weak active methylene compound—diethyl malonate, a sodium salt (V) was obtained. The acid treatment of V afforded a yellow crystalline substance (VI), whose molecular formula was agreeable with $C_{13}H_{13}O_5N_3$; VI also showed a strong absorption at 2140 cm^{-1} in its IR spectrum. These data suggest that VI possesses an azido or diazo group.⁹⁾ If the azido group of II was kept unchanged, VI might be 6-azido-3-ethoxycarbonyl-1-oxaazulan-2-one. However, the UV and visible spectra of VI are not of the oxaazulanone type,^{6,7)} but are very similar with those of tropolone methyl ethers. Thus, the structure of VI is 5 α -diazo- α -ethoxycarbonyl-acetylamino-2-methoxytropolone, and V is the sodium salt of the ring-closed enol tautomer of VI. VI is interchangeable with V upon treatment with sodium hydroxide. This relaxation is also proved by the following fact: when the silver salt of VI was treated with methyl iodide, the enol ether of VI—5-(4'-ethoxycarbonyl-5'-methoxy-1,2,3-triazol-1-yl)-2-methoxytropolone (VII)—was obtained. The existence of this type of ring-chain tautomer was suggested by Dimroth¹⁰⁾ and proved by Leffler.¹¹⁾

9) L. J. Bellamy, "Advances in Infrared Group Frequencies," Methuen, London (1968), pp. 62–64.

10) O. Dimroth, *Ann.*, **373**, 349 (1910).

11) J. E. Leffler and S. K. Lim, *J. Amer. Chem. Soc.*, **78**, 1949 (1956).

1) Presented at 18th Annual Meeting of the Chemical Society of Japan, Osaka, April, 1965.

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2) O. Dimroth, *Ber.*, **35**, 1029 (1902).

3) F. R. Benson and W. L. Savell, *Chem. Rev.*, **46**, 1 (1950).

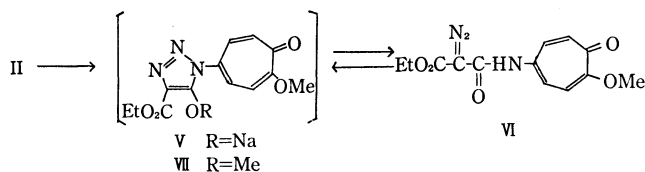
4) G. Lábbe, *ibid.*, **69**, 345 (1969), and the references cited therein.

5) T. Toda, H. Horino, and T. Nozoe, *This Bulletin*, **45**, 226 (1972).

6) T. Nozoe, K. Takase, and H. Matsumura, "Dai Yuki Kagaku," (Comprehensive Organic Chemistry), Vol. 13, ed. by M. Kotake, Asakura Shoten, Tokyo (1960), p. 178.

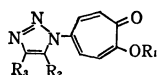
7) a) T. Nozoe and T. Asao, *ibid.*, p. 439. b) T. Nozoe, S. Seto, K. Takase, S. Matsumura, and T. Nakazawa, *Nippon Kagaku Zasshi*, **86**, 346 (1965), and the references cited therein.

8) H. Sugiyama, *Sci. Repts. Res. Inst. Tohoku Univ., Ser. A*, **20**, 34 (1968).



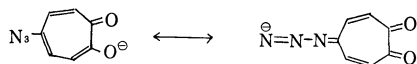
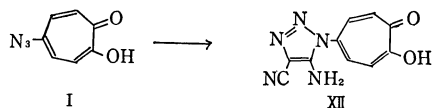
In order to obtain stable triazole derivatives, the reactions of II with suitable active methylene compounds which should not enolized at the C-5 position of the triazole ring were carried out. These compounds were ethyl acetoacetate, acetylacetone, ethyl benzoylacetate and dibenzoylmethane. The products obtained are listed in Table 1. Although the active methylene compounds were used in excess amounts, no azulene or oxaazulene formation was observed in any case. The methoxy groups in the tropone moieties of X and XI were replaced by the ethoxy group of the solvent used during the reactions.

TABLE 1.



	R ₁	R ₂	R ₃
VII	Me	OMe	CO ₂ Et
VIII	Me	Me	CO ₂ Et
IX	Me	Me	COMe
X	Et	Ph	CO ₂ Et
XI	Et	Ph	COPh

Under the same conditions as above, the reaction of I itself with malononitrile, cyano acetoacetate, and other active methylene compounds was examined. The reaction with malononitrile gave the corresponding triazolytropolone (XII). However, with other active methylene compounds it did not give any condensation products, but resulted in the recovery of the starting substances. The reason why the reactivity of the azido group of I is lower than that of II is that the tropolone anion is formed under the reaction conditions and the electron density on the azido group become higher than that of II. This phenomenon is shown below as the resonance contribution of the anion:



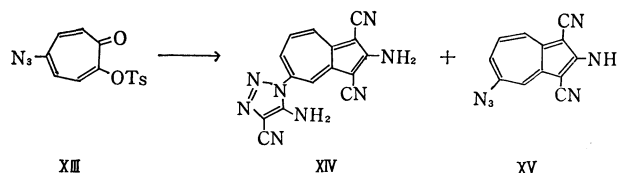
Thus, the condensation reaction did not take place except with a strong, active methylene compound

12) Y. Ikegami, *Kagaku no Ryoiki*, Special Issue, "Infrared Spectra," No. 8, Nanko-Do, Tokyo (1958), p. 33.

such as malononitrile.

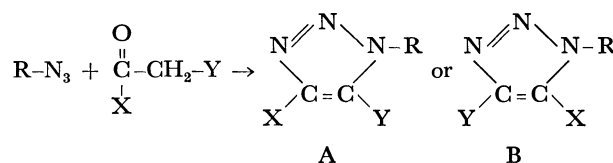
The reaction of the tosylate (XIII) of I with malononitrile afforded an azulene derivative (XIV) which differs from III. The IR spectrum of XII shows absorptions at 877 and 800 cm⁻¹. Those correspond to an isolated hydrogen and the three adjacent hydrogens on the seven-membered ring moiety¹²⁾ of XIV. It had previously been established that 2-halotropones and tropolone tosylates gave abnormal substitution products or addition products in those reactions.^{7,13)} The structure of XIV is 2-amino-1,3-dicyano-5*N*-(5'-amino-4'-cyano-1,2,3-triazol-1-yl)azulene.

When this reaction was carried out under controlled conditions, a minor product (XV) was also obtained in addition to XIV. The elemental analysis (C₁₂H₆N₆), the IR spectrum (2110 cm⁻¹, N₃: 872 and 787 cm⁻¹, an isolated hydrogen and three adjacent hydrogens respectively), and the UV and visible spectra (typical azulene type) all suggested that the structure of XV was 2-amino-5-azido-1,3-dicyanoazulene.



The results obtained above indicate that the order of the reactivity of the each functional group with active methylene compounds is: the tosyl group > the azido group > the methyl ether group.

As far as the 1,3-dipolar character of the azido group is concerned,^{4,14)} there are two possible 1,2,3-triazole ring formation by the reaction of azidotropolones with active methylene compounds. In the cases of phenyl azides, it has been proved that the 1,2,3-triazole derivatives formed are of the A type.^{4,15)}



No special interactions between the 5-azido groups and tropolone moieties were observed in several reactions of 5-azido tropolones.⁵⁾ Therefore, the direction of the addition of the above condensation might be similar to the case of phenyl azides. In order to clarify this question, the following experiments were carried out. The rearrangement of VIII with sodium ethoxide¹⁶⁾ and subsequent hydrolysis afforded *N*-phenyl-1,2,3-triazole dicarboxylic acid. On the other hand, the condensation reaction of methyl *p*-azido-

13) T. Sato, *Nippon Kagaku Zasshi*, **80**, 1342, 1345, 1349 (1959).

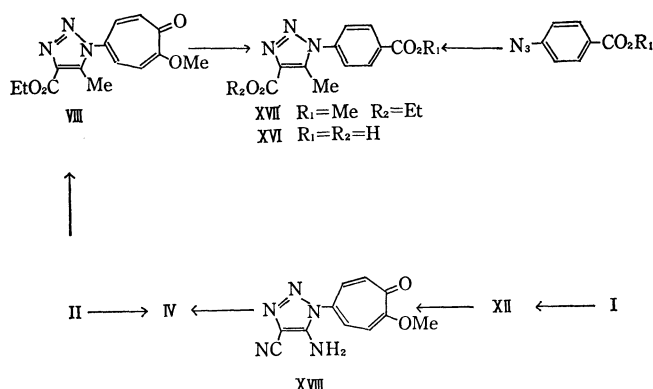
14) R. Huisgen, *Angew. Chem.*, **75**, 604 (1963).

15) M. E. Munk and Y. Y. Kim, *J. Amer. Chem. Soc.*, **80**, 2213 (1964).

16) T. Nozoe, K. Takase, and H. Matsumura, "Dai Yuki Kagaku," (Comprehensive Organic Chemistry), Vol. 13, ed. by M. Kotake, Asakura Shoten, Tokyo (1960), p. 186.

benzoate¹⁷⁾ with ethyl acetoacetate gave the *N*-phenyl-1,2,3-triazole dicarboxylic acid mentioned above. Therefore, the structure of VIII and the direction of the addition of active methylene compounds to II are proved.

When the methyl ether of XII was treated with malononitrile, IV was obtained in a good yield. Therefore, in this case the direction of the addition of the active methylene compounds is proved to be the same as in the case of phenyl azides. Therefore, the influence of the tropolone moiety on the azido group is not strong enough to change the direction of the addition of active methylene compounds to the azido group.



Experimental¹⁸⁾

The Reaction of II with Ethyl Cyanoacetate. Into a solution of 2.1 g of ethyl cyanoacetate and 130 mg of sodium in 10 ml of absolute ethanol, 1.0 g of 5-azido-2-methoxytropone (II) was stirred; the mixture was then allowed to stand overnight. The precipitate formed was collected and extracted with hot benzene to give 1.14 g of yellowish-orange crystals of 2-amino-1,3-diethoxycarbonyl-6*N*-(5'-amino-4'-ethoxycarbonyl-1,2,3-triazol-1-yl)azulene (III), which were recrystallized from benzene; mp 237 °C (dec).

Found: C, 57.34; H, 5.61; N, 15.70%. Calcd for $C_{21}H_{23}O_6N_5$: C, 57.13; H, 5.25; N, 15.87%. λ_{max} , $m\mu$ (log ϵ); 246 (4.3), 332 (4.7), 418 (3.9). ν_{max} (KBr); 3546, 3485, 3380, 1680, 866, 844 cm^{-1} .

The Reaction of II with Malononitrile. Into a mixture of 270 mg of triethylamine and 270 mg of malononitrile in 3 ml of absolute ethanol, 200 mg of II was stirred while the mixture was being cooled in an ice bath. After the mixture had been allowed to stand for 4 hr, the precipitates formed were collected to yield 390 mg of a yellow powder of 2-amino-1,3-dicyano-6*N*-(5'-amino-4'-cyano-1,2,3-triazol-1-yl)azulene (IV), which was subsequently recrystallized from dimethylformamide; mp 280 °C (dec).

Found: C, 60.41; H, 2.75; N, 37.39%. Calcd for $C_{15}H_8N_8$: C, 59.99; H, 2.69; N, 37.32%. λ_{max} , $m\mu$ (log ϵ); 231 (4.49), 328 (5.29), 404 (3.75). ν_{max} ; 3500, 3390, 3280, 2230, 858, 833 cm^{-1} .

The Reaction of II with Diethyl Malonate. Two hundred mg of II were dissolved in a solution of 650 mg of diethyl malonate and 35 mg of sodium in 3 ml of absolute ethanol. After the mixture had stood overnight, the precipitates were

separated and washed with 2 M hydrochloric acid to leave 166 mg of yellow crystals of 5-azido-2-methoxytropone (VI), which were subsequently recrystallized from ethanol; mp 144 °C.

Found: C, 53.46; H, 4.67; N, 14.43%. Calcd for $C_{13}H_{13}O_5N_3$: C, 53.61; H, 4.50; N, 14.43%. λ_{max} , $m\mu$ (log ϵ); 225 (4.41), 244 (4.33 sh), 340 (4.16). ν_{max} ; 2140, 1685, 1630, 881, 857 cm^{-1} .

5-(4'-Ethoxycarbonyl-5'-methoxy-1,2,3-triazol-1-yl)-2-methoxytropone (VII). The precipitate made from a mixture of 1.30 g of II, 2.15 g of diethyl malonate, and 175 mg of sodium in 8 ml of absolute ethanol according to the above method was dissolved in 15 ml of water, and to this we added an excess aqueous solution of silver nitrate. The greenish gray deposits were collected, dried, and weighed (245 mg).

A suspension of this precipitate and 460 mg of methyl iodide in 6 ml of acetone was then refluxed on a water bath for 5 hr. After it had been filtered, the solution was concentrated and the residue was recrystallized from ethanol to afford 87 mg of yellow crystals (VII); mp 211 °C.

Found: C, 54.69; H, 5.19; N, 13.60%. Calcd for $C_{14}H_{15}O_6N_3$: C, 55.08; H, 4.95; N, 13.77%. λ_{max} , $m\mu$ (log ϵ); 224 (4.41), 246 (4.41), 334 (4.17). ν_{max} ; 1721, 1695, 1670, 851, 844 cm^{-1} .

The Reaction of II with Ethyl Acetoacetate. To a solution of 2.24 g of ethyl acetoacetate and 194 mg of sodium in 10 ml of absolute ethanol, 1.4 g of II was added at once with cooling in an ice bath; the mixture was then allowed to stand overnight. The collection of the precipitate and washing with 2 M hydrochloric acid gave 2.20 g of yellow needles of 2-methoxy-5*N*-(4'-ethoxycarbonyl-5'-methyl-1,2,3-triazol-1-yl) tropone (VIII); mp 178 °C from alcohol.

Found: C, 58.30; H, 5.26; N, 14.41%. Calcd for $C_{14}H_{15}O_4N_3$: C, 58.12; H, 5.23; N, 14.53%. ν_{max} ; 1721, 1637, 851, 833 cm^{-1} .

The Reaction of II with Acetylacetone. Into a mixture of 250 mg of acetylacetone and 26 mg of sodium in 2.5 ml of absolute ethanol, 200 mg of II were stirred. After the solution had been allowed to stand overnight, the precipitate produced was collected to yield 242 mg of yellow plates, 2-ethoxy-5*N*-(5'-methyl-4'-acetyl-1,2,3-triazol-1-yl) tropone (IX); mp 170 °C.

Found: C, 60.45; H, 5.28; N, 16.20%. Calcd for $C_{13}H_{13}O_3N_3$: C, 60.22; H, 5.50; N, 16.21%. λ_{max} , $m\mu$ (log ϵ); 243 (4.49), 326 (4.15). ν_{max} ; 1692, 862, 855 cm^{-1} .

The Reaction of II with Ethyl Benzoylacetate. Two hundred mg of II were added to a solution prepared from 434 mg of ethyl benzoylacetate and 26 mg of sodium in 2 ml of ethanol. After it had stood overnight in a refrigerator, the deposits were separated and crystallized from ethanol to afford 402 mg of colorless crystals of 2-ethoxy-5*N*-(4'-ethoxycarbonyl-5'-phenyl-1,2,3-triazol-1-yl) tropone (X); mp 217 °C.

Found: C, 66.54; H, 5.44; N, 11.84%. Calcd for $C_{20}H_{19}O_4N_3$: C, 65.74; H, 5.24; N, 11.50%. λ_{max} , $m\mu$ (log ϵ); 228 (4.52), 246 (4.48 sh), 328 (4.12). λ_{max} ; 1730, 843, 811, 780, 709 cm^{-1} .

The Reaction of II with Dibenzoylmethane. Two hundred mg of II were added to a solution of 560 mg of dibenzoylmethane dissolved in a sodium ethoxide solution (sodium (35 mg) and absolute ethanol (6 ml)). The orange solution was then concentrated, acidified with 2 M hydrochloric acid, and extracted with benzene to give 400 mg of orange prisms of 2-ethoxy-5*N*-(4'-benzoyl-5'-phenyl-1,2,3-triazol-1-yl) tropone (XI), which were subsequently recrystallized from ethanol; mp 164 °C.

17) M. O. Foster and H. M. Judd, *J. Chem. Soc.*, **97**, 259 (1910).

18) All the melting points are uncorrected.

Found: C, 72.65; H, 4.92; N, 10.55%. Calcd for $C_{24}H_{19}O_3N_3$: C, 72.53; H, 4.82; N, 10.57%. $\lambda_{\max}$, $m\mu$ ($\log \epsilon$); 228 (4.46), 252 (4.49), 328 (4.14). $\nu_{\max}$; 1618, 1580, 820, 752, 739, 709 cm^{-1} .

The Reaction of 5-Azidotropolone (I) with Malononitrile.

An alcoholic solution of 200 mg of I, 180 mg of malononitrile, and 410 mg of triethylamine was stirred for 12 hr. The solvent was then evaporated, and the residue was acidified with 2 M hydrochloric acid to afford 95 mg of a brown powder of 5*N*-(5'-amino-4'-cyano-1,2,3-triazol-1-yl)tropolone (XII), which was recrystallized from DMF; mp 256°C (dec).

Found: C, 52.24; H, 3.50; N, 30.30%. Calcd for $C_{10}H_7O_2N_5$: C, 52.40; H, 3.08; N, 30.56%. $\lambda_{\max}$, $m\mu$ ($\log \epsilon$); 227 (4.41); 246 (4.20), 346 (3.88).

The Reaction of I with Ethyl Cyanoacetate. Two hundred mg of I, 170 ml of ethyl cyanoacetate, and 270 mg of triethylamine were treated as above. The precipitates given by acidification, when extracted with ethyl acetate from its mother liquid, afforded about 160 mg of I.

The Reaction of 2-(p-Toluenesulfonyloxy)tropolone (XIII) with Malononitrile.

A suspension of 300 mg of XIII and 204 mg of malononitrile in 2 ml of absolute ethanol was treated with a solution of 100 mg of triethylamine in 2 ml of absolute alcohol. The solution was stirred for 1 hr and then allowed to stand for 7 hr. The precipitates were collected and extracted with hot ethanol. This afforded 69 mg of a brown powder of 5-azido-2-amino-1,3-dicyanoazulene (XV); mp 290°C.

Found: C, 60.97; H, 2.73; N, 36.12%. Calcd for $C_{12}H_6N_6$: C, 61.53; H, 2.58; N, 35.88%. $\lambda_{\max}$, $m\mu$ ($\log \epsilon$); 238 (4.23), 326 (4.45 sh), 336 (4.56), 403 (4.37). $\nu_{\max}$; 3350, 3215, 2220, 2110, 872, 787 cm^{-1} .

The non-extractable residue was recrystallized from DMF to afford a yellowish-orange powder of 2-amino-1,3-dicyano-5*N*-(5'-amino-4'-cyano-1,2,3-triazol-1-yl)azulene (XIV); mp 300°C (dec).

Found: C, 60.36; H, 2.95; N, 36.92%. Calcd for $C_{15}H_8N_8$: C, 59.99; H, 2.69; N, 37.32%. $\lambda_{\max}$, $m\mu$ ($\log \epsilon$); 230 (4.23), 315 (4.27), 238 (4.50), 410 (3.61), 426 (4.80). $\nu_{\max}$; 3400, 3280, 2230, 877, 800 cm^{-1} .

The Determination of the Structures of the Condensed Products.

a) The Condensation Reaction of p-Methoxycarbonylphenyl Azide: To a solution of 150 mg of sodium and 950 mg of ethyl acetate in 2 ml of absolute ethanol, 1.0 g of *p*-methoxycarbonylphenyl azide was added, after which the mixture was cooled in an ice bath. It was allowed to stand for 7 hr, and washed with 2 M hydrochloric acid to afford 1.1 g of

colorless plates of 1*N*-*p*-methoxycarbonylphenyl-4-ethoxycarbonyl-5-methyl-1,2,3-triazol (XVII), which was recrystallized from ethanol; mp 174–175°C.

Found: C, 58.14; H, 5.25; N, 14.64%. Calcd for $C_{14}H_{15}O_4N_3$: C, 58.12; H, 5.23; N, 14.53%. $\nu_{\max}$; 2130, 1718, 1285, 852, 841, 765 cm^{-1} .

A solution of 500 mg of XVI, 3 ml of 2 M sodium hydroxide, and 2 ml of ethanol was refluxed for 1 hr, and then acidified with 6 M hydrochloric acid to give 390 mg of colorless, amorphous 4*N*-(4'-carboxyl-5'-methyl-1,2,3-triazol-1-yl)benzoic acid (XVI), which was subsequently recrystallized from ethanol; mp 235°C (dec).

Found: C, 53.88; H, 3.82; N, 16.75%. Calcd for $C_{11}H_9O_4N_3$: C, 53.44; H, 3.67; N, 17.00%. $\nu_{\max}$; 2940–2860, 2680–2654, 1685, 859 cm^{-1} .

b) The Rearrangement of VIII: A solution of 0.5 g of VIII in a sodium ethoxide mixture (sodium (87 mg) and absolute ethanol (10 ml)) was refluxed for 16 hr on an oil bath. After the evaporation of the solvent and the addition of water, the solution was heated for 1 hr on a water bath. Then it was acidified with 2 M hydrochloric acid and extracted with ethyl acetate, which had itself been extracted with a sodium bicarbonate solution. It was acidified to afford 200 mg of a colorless powder which can be identified with the XVI given in *a*) by a comparison with their IR spectra and by a mixed-melting-point-test.

The Reaction of XII with Ethyl Cyanoacetate. *a)* To a solution of 200 mg of XII in 200 ml of ethyl acetate in 5 ml DMF, an ethereal diazomethane solution was added until no color change was shown by a ferric chloride test. After it had then been allowed to stand overnight, the solution was concentrated to give 141 mg of a gray powder of 5*N*-(5'-amino-4'-cyano-1,2,3-triazol-1-yl)-2-methoxytropolone (XVIII); mp 233°C (dec).

Found: C, 54.78; H, 3.99; N, 28.31%. Calcd for $C_{11}H_9O_2N_5$: C, 54.32; H, 3.73; N, 28.80%.

b) Into a solution of 100 mg of triethylamine and 65 mg of malononitrile in 2 ml of absolute ethanol, 100 mg XVIII was stirred; the mixture was then allowed to stand for 3 days. The precipitates were collected to afford 143 mg of a gray powder which was found to be identical with IV by a comparison with their IR spectra.

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