Reaction of Electron-Deficient 1,2,4-Triazoline-3,5-diones with Electron-Rich Nitrogen Heterocycles

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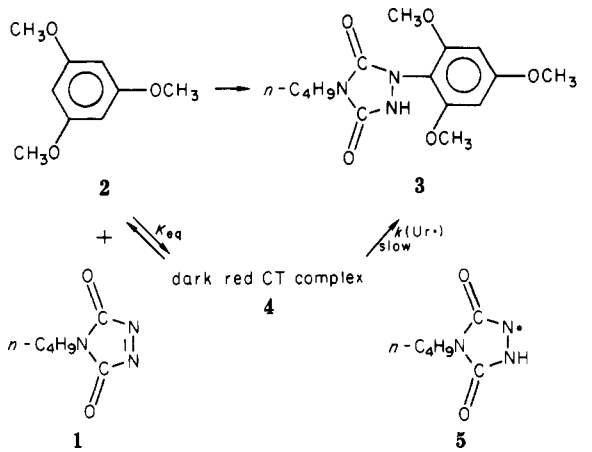
The reaction of 4-substituted 1,2,4-triazoline-3,5-diones (RTAD's) with some electron-rich nitrogen heterocycles has been examined. RTAD's react rapidly with 1-methylindole to give aromatic disubstitution in the 2- and 3-positions along with some polymer. 3-Ethylcarbazole reacts slowly to give a 2:1 polymer. 1-Methylpyrrole reacts rapidly to give 2,5-disubstituted pyrroles. This later reaction is accompanied by some rather spectacular color changes that are due to formation of three different charge-transfer complexes. A mechanism is proposed to account for these reactions involving radical attack on charge-transfer complexes.

In the previous paper,[1] it was reported that 4-substituted 1,2,4-triazoline-3,5-diones (RTAD's) react with polyalkoxybenzenes to give aromatic substitution. A kinetic study of the reaction of *n*-BuTAD (**1**) with 1,3,5-trimethoxybenzene (TMB, **2**) showed the reaction to be first order in TMB and in *n*-BuTAD. However, it was also found



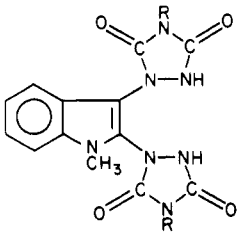
that the rate constant was dependent on how long the methylene chloride solutions of *n*-BuTAD had been exposed to normal laboratory light, before the kinetics were run. Since it was known[2] that photolysis of *n*-BuTAD gives rise to urazolyl radicals (**5**), it was postulated that urazolyl radicals (Ur·) were involved in the rate-determining step. Further it was found that the reaction exhibited an inverse temperature effect; i.e., the reaction rate increased as the temperature was lowered. In order to account for these observations, it was postulated that there was a rapid equilibrium to form a charge-transfer complex (**4**), followed by attack of urazolyl radical on the complex. This would give an overall kinetic expression:

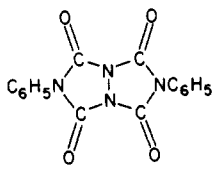
$$-d(n\text{-BuTAD})/dt = K_{eq}k(n\text{-BuTAD})(TMB)(Ur\cdot)$$

Further, the urazolyl radical that is consumed in the rate-determining step must be regenerated in a later step, since the reaction rate does not fall off with time; i.e., the urazolyl radical is a catalyst.

In order to examine the generality of this reaction, we chose next to look at the reaction of RTAD's with electron-rich nitrogen compounds. In our initial attempt we looked at the reaction of RTAD's with indole. A very rapid reaction was observed, but only highly insoluble polymeric material was formed. In order to circumvent this problem, we instead examined the reaction of *N*-methylindole with RTAD's.

A solution of PhTAD in methylene chloride was added dropwise to a solution of *N*-methylindole in methylene chloride at 0 °C. As each drop was added, a faint purple developed that rapidly disappeared. Removal of the solvent, followed by recrystallization from ethyl acetate, gave a 36% yield of a white solid. Elemental analysis indicated that the product was a 2:1 adduct (PhTAD–*N*-methylindole). ^{13}C NMR and ^{1}H NMR indicated clearly that the product was 1-methyl-2,3-bis[1-(4-phenylurazolyl)]indole (**6a**). In an attempt to produce a 1:1





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6a, R = C_6H_5
b, R = *n*-C_4H_9

adduct the above reaction was repeated by using reverse addition; however, only **6a** was obtained (39%). When these two reactants were warmed to the boiling point of the solvent and then rapidly mixed, the solution turned purple as the charge-transfer complex was formed and within 10 s had changed to a yellow-brown. The other product in these reactions appears to be a reddish brown polymer.

Dropwise addition of *n*-BuTAD to *N*-methylindole in methylene chloride at 0 °C gave **6b**. In this case the product was extracted with potassium hydroxide, followed by treatment with charcoal. Acidification gave a crude material, which after recrystallization gave a 28.5% yield of **6b**.

Encouraged by these results we tried the reaction of PhTAD with *N*-ethylcarbazole. On mixing in methylene chloride at room temperature, the reaction immediately turned deep red. After 4 h the red color was gone. The solid that precipitated was filtered to give a 16.2% yield of the triazolotriazole **7**. This compound was identical with that reported by Wald and Wamhoff.[3] The remaining material was polymer showing only broad absorptions at 1.25, 4.15, and 7.13 ppm. Integration indicated that the polymer involved 2 mol of PhTAD and 1 mol of the *N*-ethylcarbazole. The polymer was base soluble, indicating that it contained urazole moities on the aromatic rings. Varying the mole ratio of the reactants from 1:2 to 2:1 did

(1) Hall, J. H. *J. Org. Chem.* **1983**, *48*, 1708.
(2) Hall, J. H.; Bigard, W. E.; Fargher, J. M; Jones, M. L. *J. Org. Chem.* **1982**, *47*, 1459.
(3) Wamhoff, H.; Wald, K. *Chem. Ber.* **1977**, *110*, 1699.

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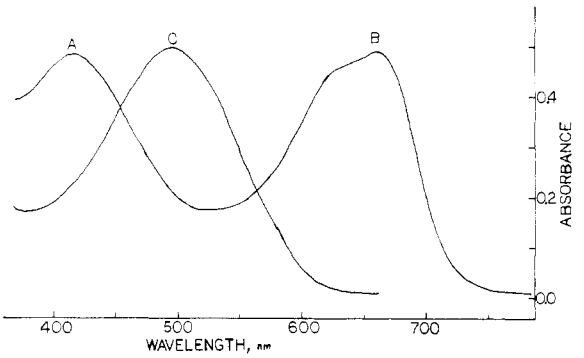
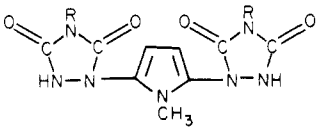


Figure 1. Absorption spectrum of *n*-BuTAD–1-methylpyrrole in methylene chloride showing the yellow complex (A), the blue complex (B), and the polymer (C).

not change the yield of **7** nor the composition of the polymer.

We also looked at the reaction of RTAD's with *N*-methylpyrrole. Since RTAD's are reported to be excellent dienophiles, we expected to get a Diels–Alder adduct. Instead rather startling results were obtained. When the red PhTAD in methylene chloride was added all at once to a solution of *N*-methylpyrrole in methylene chloride, there was an instant color change to Kelly green followed by changes to yellow-brown and then to red-brown, all within 1 min. A precipitate then appeared. The precipitate was identified by ^1H and ^{13}C NMR as 1-methyl-2,5-bis[1-(4-phenylurazolyl)]pyrrole (**8a**) obtained in 60.4% yield. The remaining reddish brown material is a 1:1



8a, R = C_6H_5
b, R = *n*-C_4H_9

polymer with broad absorptions (^1H NMR) at 3.0, 6.2, 6.5, and 7.4 ppm. Repeating the reaction at −60 °C and adding the PhTAD solution dropwise to a solution of *N*-methylpyrrole gave additional information. The red color of the PhTAD disappeared as fast as it was added to give a yellow solution with only a slight green tint. As this solution was allowed to warm, it turned completely yellow. At −15 °C **8a** precipitated. Not until the solution reached about 0 °C did the red-brown color of the polymer appear. Also **8a** apparently is not formed at −60 °C, as it does not precipitate at that temperature even when seeded.

When *n*-BuTAD was reacted with *N*-methylpyrrole at room temperature, similar results were observed and 8b was isolated in 61.5% yield.

In an effort to better define the color changes occurring in these reactions, *n*-BuTAD was reacted with *N*-methylpyrrole in the cell of a UV–vis spectrophotometer. Dilute solutions were rapidly mixed and scanned within 30 s, after mixing. The spectrum showed two maxima at 404 and 660 nm with a shoulder at 630 nm as shown in Figure 1. Thus the Kelly green color is the combination of a blue species (660 nm) and a yellow species (404 nm). Both the blue and the yellow species rapidly disappear, and a new band at 494 nm, due to the polymer, builds in over a period of a few minutes.

If one very rapidly mixes 0.01 M *n*-BuTAD and 0.01 M *N*-methylpyrrole in a 2:1 ratio in the cell of the spectrophotometer and monitors the absorbance of the solution at 404, 520, and 660 nm (separate experiments) as a function of time during the first few seconds of the reaction, the curves shown in Figure 2 are generated. As can be seen, the yellow species is formed first, followed by the blue species. The latter however disappears more rapidly, leaving a yellow solution after about 1 min. After 3 min the solution is essentially colorless. The polymer band grows in very slowly as monitored at 520 nm and does not seem to be related to the disappearance of either the blue or the yellow species. If this same experiment is repeated at −15 °C, there is very little of the blue species; i.e., the solution on mixing turns bright yellow. The bright yellow disappears slowly over a period of about 90 min. When this experiment was repeated at −15 °C by using a 0.01 M solution of *n*-BuTAD that had been exposed to ambient fluorescence light for about 8 h before use to increase the radical concentration, the yellow color disappeared twice as fast. Thus it seems likely that the yellow complex is disappearing by reaction with urazolyl radicals. In addition to the blue and yellow complexes, there is a third complex formed that is deep red. This complex can be seen if a solution of *N*-methylpyrrole is added dropwise to a solution of *n*-BuTAD at −40 °C. As the first few drops hit the solution, it turns deep red (similar to the complex formed with polyalkoxybenzenes and with *N*-methylindole) and then changes rapidly to green (blue and yellow complexes). Under these conditions of excess *n*-BuTAD at −40 °C, the blue and yellow complexes remain stable for several hours.

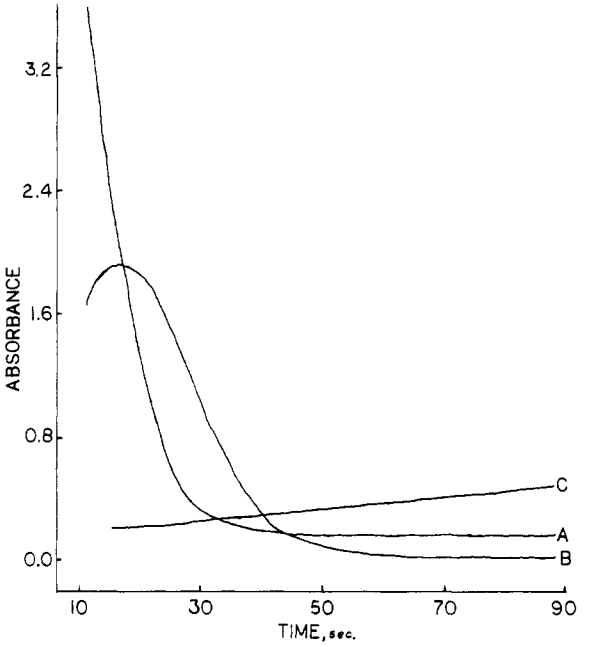


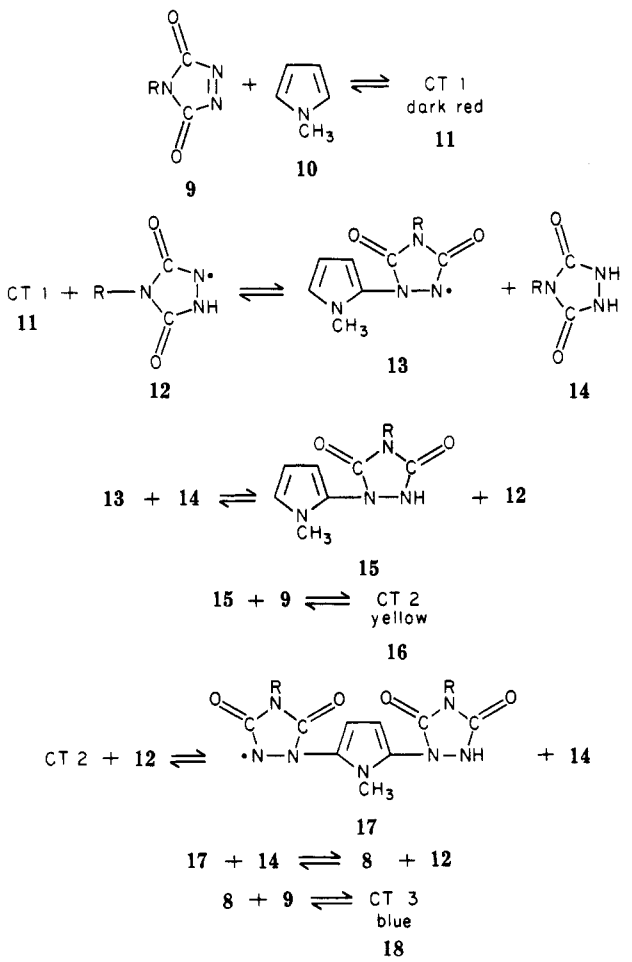
Figure 2. Change in absorbance vs. time at 404 (A), 660 (B), and 520 (C) nm in the reaction of *n*-BuTAD with 1-methylpyrrole.

In order to see if any of these colored species are free radicals, the green solution (blue and yellow complexes) was examined in the ESR from −80 to +50 °C. However, no radical species could be detected other than urazolyl radicals. The solution contained no radical cations or anions.

An understanding of these color changes began to emerge when it was discovered that the blue complex could be generated by mixing the product **8b** with *n*-BuTAD. This result suggested that the deep red, yellow, and blue complexes are complexes formed between the *n*-BuTAD and 1-methylpyrrole, 1-methyl-2-[1-(4-*n*-butylurazolyl)]-pyrrole (**15b**), and 1-methyl-2,5-bis[1-(4-*n*-butylurazolyl)]pyrrole (**8b**), respectively.

It was found that by adding a solution of *n*-BuTAD to a solution of 1-methylpyrrole in a 1:1 molar ratio at −50 °C only a yellow complex could be seen. On warming to

Scheme I



room temperature a 32% yield of **8b** was obtained along with a 27% yield of the monosubstitution product **15b**. Addition of *n*-BuTAD to a solution of **15b** gave the yellow complex. Further addition gave the blue complex of **8b**.

A mechanistic interpretation of the reaction is given in Scheme I. At room temperature, the initially formed dark red complex **11** disappears rapidly. As the reaction proceeds, the monosubstituted compound **15** and the disubstituted compound **8** both form complexes, **16** (yellow) and **18** (blue) and hence the green color. However, as the RTAD is used up, the equilibrium to form complex **18** (blue) reverses and most of the blue disappears to give a yellow solution. The yellow then disappears as **15** is converted into **8**. The reversal of this last step suggests that the entire scheme may be reversible. The fact that **8** is the product at 25 °C is only because it is insoluble in the solvent system and precipitates out of solution shifting the equilibrium.

If a very dilute solution (3.8×10^{-5} M) of **8b** is made in methylene chloride and *n*-BuTAD is added to it, the intense (ϵ 3.5×10^4) blue complex is formed. The intensity of the blue complex increases slowly over the first few minutes. On standing, this color slowly disappears, suggesting that formation of trisubstituted or even tetrasubstituted products may be possible under high dilution.

The fact that at low temperatures, the reaction mixture is yellow suggests that at these temperatures only monosubstitution occurs; i.e., the reaction stops at the formation of **15**. This is consistent with the fact that **8** does not precipitate out until the solution is warmed to about −15 °C.

Presumably this same reaction path applies to the reaction of *N*-methylindole with RTAD's to give **6**. However in this case the product **6** does not form a complex with the RTAD. So the only complex seen is the initial deep red complex. The difference in the two reactions is that in the *N*-methylindole case the equilibrium to form the initial dark red complex is to the left; i.e., there is a fairly high concentration of free *N*-methylindole and free RTAD in solution during reaction. In contrast, the equilibria to form the complexes with the *N*-methylpyrrole lie far to the right, there being only a small amount of free RTAD and *N*-methylpyrrole in the reaction mixture after the first few seconds.

In closely related work, Flitach and Heinrich have reported very low yields of 2-substituted and 2,5-disubstituted products in the reaction of azocarboxylate esters with pyrrole and *N*-methylpyrrole.[4] Higher yields of substitution products were obtained with indolizine[4] and 2-*tert*-butylpyrolo[3,4-*b*]quinoxaline.[5] Nothing is mentioned in these reports about charge-transfer complexes.

Experimental Section

Melting points are uncorrected. The IR spectra were recorded on a Perkin-Elmer 297 spectrophotometer. The ^{1}H NMR spectra were recorded on a 90-MHz Perkin-Elmer R32, and the ^{13}C NMR spectra were recorded on a Nicolet NT-200 spectrometer. The elemental analyses were performed by Gailbraith Laboratories Inc., Knoxville, TN.

The 4-substituted 1,2,4-triazoline-3,5-diones were prepared by oxidation of the urazole with *N*-bromosuccinimide.[5] 4-PhTAD was purified by recrystallization from methylene chloride at −10 °C prior to use. *n*-BuTAD was purified by sublimation. The remaining materials were commercial reagents.

Reaction of 1-Methylindole with 4-Phenyl-1,2,4-triazoline-3,5-dione. A. In 20 mL of methylene chloride was dissolved 0.197 g (1.50 mmol) of 1-methylindole. This solution was cooled to 0 °C and a solution of 0.525 g (3.00 mmol) of 4-phenyl-1,2,4-triazoline-3,5-dione in 40 mL of methylene chloride was added dropwise with stirring over a period of 2 h. As each drop was added, a faint purple could be seen. As the last few drops of azo compound were added, the solution turned light red. On warming to room temperature, the red color disappeared. Removal of the solvent under vacuum gave a reddish orange residue. Recrystallization of the residue from ethyl acetate at −10 °C gave 0.262 g (36.3%) of 1-methyl-2,3-bis[1-(4-phenylurazolyl)]indole: mp 202–205 °C dec; ^{1}H NMR (Me_2SO-d_6, δ) 3.81 (3 H, s), 7.44 (16 H, m); ^{13}C NMR (Me_2SO-d_6, δ) 29.6 (CH_3); 105.3, 120.9, 118.2, 122.3, 110.5 (C-3 to C-7 of indole ring), 123.3 (C-3a of indole), 126.5, 128.8, 128.9, 128.1, 128.4 (*o*-, *m*-, *p*-C's of phenyl), 131.0, 131.4, 132.1 (C-1's of phenyl and C-2 of indole), 152.0, 151.1, 152.7, 153.0 (C=O's); IR (Nujol, cm^{-1}) 3140 (b), 1692, 1722, 1790 (C=O's), 848, 765, 738, 686 (aromatic).

Anal. Calcd for $C_{25}H_{19}N_7O_4$: C, 62.36; H, 3.98; N, 20.37. Found: C, 62.49; H, 4.04; N, 20.38.

B. The above experiment was repeated, adding the 1-methylindole solution dropwise to the 4-phenyl-1,2,4-triazoline-3,5-dione solution; yield 0.280 g (38.8%) of 1-methyl-2,3-bis[1-(4-phenylurazolyl)]indole.

C. Solutions of 1-methylindole and 4-phenyl-1,2,4-triazoline-3,5-diones were prepared as in A. They were warmed to 40 °C. The solutions were rapidly mixed. The solution turned purple and changed to a reddish purple and then to yellow-brown in the first 10 s. After 5 min, the solution was yellow-green. Removal of the solvent, followed by recrystallization from ethylacetate at −10 °C, gave 0.20 g (28.5%) of 1-methyl-2,3-bis[1-(4-phenylurazolyl)]indole.

Reaction of 1-Methylindole with 4-*n*-Butyl-1,2,4-triazoline-3,5-dione. The reaction was carried out as in A above. At the end of the reaction the methylene chloride solution was extracted with 5% potassium hydroxide. The basic extracts were treated with charcoal, filtered, and then acidified with hydrochloric acid. Extraction with methylene chloride, followed by removal of the solvent, gave 0.591 g of crude product. Recrystallization

(4) Flitsch, W.; Heinrich, J. *Tetrahedron Lett.* **1980**, *21*, 3673.
(5) Kreher, R.; Use, G. *Tetrahedron Lett.* **1978**, 4671.

from ethyl acetate gave 0.190 g (28.5%) of 1-methyl-2,3-bis[1-(4-*n*-butylurazolyl)]indole: mp 190–193 °C dec; ^{1}H NMR ($CDCl_3$, δ) 0.91 (3 H, t), 0.94 (3 H, t) 1.1–1.8 (m, 8 H) (m, 3.45 (2 H, t), 3.48 (3 H, s), 3.57 (2 H, t), 7.0–7.7 (4 H, m), 7.7–8.5 (2 H, vbs).

Anal. Calcd for $C_{21}H_{27}O_4N_7$: C, 57.13; H, 6.16; N, 22.21. Found: C, 57.02; H, 5.27; N, 22.05.

Reaction of 1-Methylpyrrole with 4-Phenyl-1,2,4-triazoline-3,5-dione. A. In 20 mL of methylene chloride was dissolved 0.875 g (5.00 mmol) of 4-phenyl-1,2,4-triazoline-3,5-dione. A solution of 0.405 g (5.00 mmol) of 1-methylpyrrole in 10 mL of methylene chloride was added all at once. The solution on mixing turned bright green, then yellow-brown, and finally red-brown all within 1 min. After standing 30 min, the precipitate was filtered and washed to give 0.651 g (60.4%) of 1-methyl-2,5-bis[1-(4-phenylurazolyl)]pyrrole, mp 200–205 °C dec. Recrystallization from dilute ethanol gave an analytical sample: ^{1}H NMR (Me_2SO-d_6, δ) 3.564 (3 H, s), 6.41 (2 H, s), 7.53 (10 H, m), 7.5 (2 H, vb); ^{13}C NMR (Me_2SO-d_6, δ) 29.6 (CH_3), 106.2 (C-3,4 of pyrrole), 122.4 (C-2,5 of pyrrole), 126.4 (*o*-C's), 128.1 (*p*-C), 128.8 (*m*-C's), 131.4 (C-1), 151.1 and 151.9 (C=O's); IR (Nujol, cm^{-1}) 3130 (b, NH), 1692, 1717, 1752 (C=O's); 838, 813, 766, 720, 688 (aromatic).

Anal. Calcd for $C_{21}H_{17}N_7O_4$: C, 58.46; H, 3.97; N, 22.73. Found: C, 58.54; H, 4.14; N, 22.70.

Examination of the residue obtained by evaporation of the red filtrate in the reaction showed it to consist of a mixture of red polymer and recovered 1-methylpyrrole in an ca. 1:1 ratio.

B. In 20 mL of methylene chloride was dissolved 0.599 g (3.42 mmol) of 4-phenyl-1,2,4-triazoline-3,5-dione. This solution was added dropwise to a solution of 0.139 g (1.781 mmol) in 20 mL of methylene chloride at −60 °C. The red color of the azo compound disappeared as fast as it was added to give a yellow-green solution. At the end of the addition, the solution was allowed to warm to room temperature. As the solution reached room temperature, it turned dark red as the polymer formed. The precipitate was filtered and washed with methylene chloride to give 0.61 g (62.7%) of 1-methyl-2,5-bis[1-(4-phenylurazolyl)]prrole.

Evaporation of the filtrate gave a red polymer, whose ^{1}H NMR ($CDCl_3$) showed broad bands at δ 3.0 (3 H, vb), 6.2 (1 H, b), 6.5 (1H, b) and 7.4 (5 H, b), indicating that the polymer is 1:1.

Reaction of 1-Methylpyrrole with 4-*n*-Butyl-1,2,4-triazoline-3,5-dione. A. The reaction was run as in A above. The reaction mixture was chilled to −10 °C and filtered and the solid washed with cold methylene chloride to give 0.601 g (61.5%) of 1-methyl-2,5-bis[1-(4-*n*-butylurazolyl)]pyrrole, mp 187–189 °C dec. Recrystallization from ethyl acetate gave an analytical sample with 1 mol of ethyl acetate of crystallization. Heating at 110 °C removed the ethyl acetate: mp 190–192 °C dec; Anal. Calcd for $C_{17}H_{25}N_7O_4$: C, 52.16 H, 6.44 N, 25.05. Found: C, 52.39; H, 6.64; N, 25.04.

^{1}H NMR (Me_2SO-d_6, δ) 0.91 (6 H, t), 1.4 (8 H, m), 3.36 (3 H, s), 3.51 (4 H, t), 6.27 (2 H, s).

B. In 20 mL of methylene chloride was dissolved 0.243 g (3.00 mmol) of *N*-methylpyrrole, and the solution was cooled to −50 °C. To this solution was added dropwise a solution of 0.465 g (3.00 mmol) of 4-*n*-butyl-1,2,4-triazoline-3,5-dione in 20 mL of methylene chloride over a period of 1 h. The solution remained yellow during the addition but turned red as the solution warmed above 0 °C. The white precipitate was filtered to give 0.135 g of 1-methyl-2,5-bis[1-(4-*n*-butylurazolyl)]pyrrole, mp 186–188 °C dec. Extraction of the filtrate with aqueous potassium hydroxide, followed by acidification with hydrochloric acid, gave an oil that eventually solidified. Filtration gave 0.387 g of a red-purple solid. It was placed in 5 mL of benzene and an additional 0.053 g of the disubstited pyrrole filtered to give a total yield of 0.188 g (32%). The benzene was evaporated and the purple residue was dissolved in hot carbon tetrachloride and treated with charcoal. Cooling to −10 °C gave 0.197 g (27%) 1-methyl-2-[1-(4-*n*-butylurazolyl)]pyrrole, mp 101–103 °C. A second recrystallization gave an analytical sample: ^{1}H NMR ($CDCl_3$, δ) 0.93 (3 H, t), 1.1–1.9 (4 H, m), 350 (3 H, s), 3.58 (2 H, t), 6.09, 6.19 (2 H, AB), 6.59 (1 H, X, J_{AB} = 4.2, J_{AX} = 3.0, J_{BX} = 2.1), 7.1–8.0 (1 H, vb). Anal. Calcd for $C_{11}H_{16}N_4O_2$: C, 55.92; H, 6.83; N, 23.71. Found: C, 55.91; H, 6.79; N, 23.66.

Reaction of 1-Ethylcarbazole with 4-Phenyl-1,2,4-triazoline-3,5-dione. In 20 mL of methylene chloride was dissolved 0.875 g (5.00 mmol) of 4-phenyl-1,2,4-triazoline-3,5-dione, and 0.487 g (2.50 mmol) of 9-ethylcarbazole was added. The solution turned dark red instantly. After 3 h, the red color was essentially gone. After an additional 3 h, the precipitate was filtered to give 0.130 g (16.2%) of 1,3,5,7-tetraoxo-2,6-diphenylperhydro-*s*-triazolo[1,2-*a*]-*s*-triazole: ^{1}H NMR(Me_2SO-d_6, δ) 7.68 (s); ^{13}C NMR (Me_2SO-d_6, δ) 126.7 (*o*-C's), 129.4 (*m*- and *p*-C's), 129.8 (C-1), 145.4 (C=O); IR (Nujol, cm^{-1}) 1751, 1783, 1795 (sh, C=O's), 1165, 1013, 745, 729, 687, 643 (aromatic).

This compound was identical with that reported by Wamhoff and Wald.[3] Its IR, ^{1}H NMR, and ^{13}C NMR spectra were identical with those of sample prepared by heating a 1:1 molar mixture of 4-phenylurazole and 4-phenyl-1,2,4-triazoline-3,5-dione in anisole as reported by Wamhoff and Wald.[3]

Evaporation of the filtrate from the above reaction gave a residue whose ^{1}H NMR ($CDCl_3$) showed broad peaks at 1.25, 4.15 and 7.13 ppm together with a trace of unreacted 9-ethylcarbazole. Consideration of the integration and the material balance suggests that the polymer contains 9-ethylcarbazole and urazole residues in a 1:2 ratio. Changing the mole ratio of the reactants from 2:1 to 1:1 to 1:2 did not change the yield of or the composition of the polymer.

Registry No. **6a**, 90432-40-9; **6b**, 90432-41-0; **7**, 32494-23-8; **8a**, 90432-42-1; **8b**, 90432-43-2; **9** (R = Ph), 4233-33-4; **9** (R = Bu), 13482-57-0; **10**, 96-54-8; **15b**, 90432-44-3; 1-methylindole, 603-76-9; 1-ethylcarbazole, 19275-57-1; indole, 120-72-9.

Studies Directed toward the Synthesis of Ionomycin(I): Synthesis of the Furanoid Fragment

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A synthesis of the tetrahydrofuranoid fragment of the calcium ion selective ionophore ionomycin is described. The synthesis utilizes geraniol acetate to establish the carbon skeleton and the Sharpless asymmetric epoxidation to introduce chirality.

The ionophores as a class of natural products have recently attracted considerable attention,[1] perhaps due to their unique property in that they serve to transport metal ions across hydrophobic biological membranes[2] and the

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