Nitrene Insertion Reactions. Part III. The Steric Effect of the *Iso*propyl and *t*-Butyl groups. 1,6 Type Cycloaddition of Tetracyanoethylene to 1*H*-Azepines (1).

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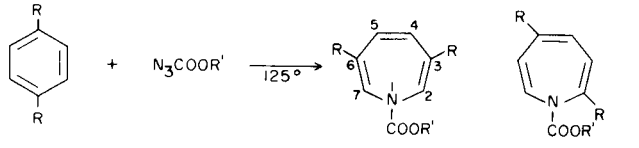
Various alkyl and aryl carboxynitrenes generated thermally from the azidoformates react with *para*-di-*t*-butylbenzene with a high degree of selectivity to yield predominantly, or exclusively, 3,6-di-*t*-butylazepine-*N*-carboxylates. 3,6-Dialkylazepines react readily with tetracyanoethylene to afford the first known TCNE-1*H*-azepine cycloadducts of the 1,6 type.

Reports to date concerning the interaction of nitrenes and aromatic compounds with the subsequent formation of azepines support the belief that nitrenes react with little discrimination (2). Thus, monoalkyl and monohalobenzenes yield mixtures of 2-, 3-, and 4-substituted azepines. Although a recent communication describes the isolation of several 2-alkylated azepines from carbethoxynitrene reaction product mixtures (1), the general synthetic usefulness of aromatic >C=C< insertion products is lost since the mixtures obtained are, in most cases, difficult, or impossible, to resolve. It is in view of these facts that we wish to report our results dealing with the reaction between nitrenes and *p*-di-*iso*propylbenzene and *p*-di-*t*-butylbenzene.

The *t*-butyl groups of *p*-di-*t*-butylbenzene (**1**) have been found to have a pronounced steric control on the course of the thermal reaction with various azidoformates such that predominantly, or exclusively, one isomeric azepine is obtained. Ethyl azidoformate, **3a**, decomposed in a tenfold molar excess of **1** at 125° without solvent to give a mixture of azepines composed of 95% of the 3,6-di-*t*-butyl isomer, **4a**, and 5% of the 2,5-di-*t*-butyl isomer, **6a**, from which pure **4a** was obtained by crystallization. The ratio of products (**4a**/**6a**) contrasts sharply with that obtained from *p*-xylene, which was reported (3) to give only 34% of the 3,6-dimethyl isomer and 66% of the 2,5-dimethyl isomer. Cyclopropylcarbinyl, *t*-butyl and *p*-methoxyphenyl azidoformates (**3b-d**) reacted similarly with **1** to produce 100% of the 3,6-di-*t*-butyl isomer, **4b-d**, in good yields of 70-85% (4). See Table II.



1. R $C(CH_3)_3$ 3a. R' C_2H_5 4. R $C(CH_3)_3$ 6. R $C(CH_3)_3$
2. R $CH(CH_3)_2$ b. R' CH_2-cyclopropyl 5. R $CH(CH_3)_2$ 7. R $CH(CH_3)_2$
c. R' $C(CH_3)_3$
d. R' p-$C_6H_4(OCH_3)$

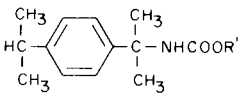
Compounds **4a-d** showed three principle absorption maxima in the ultra violet which were quite similar to those reported for 3,6-dimethyl-*N*-carbomethoxyazepine (5). See Table I. The nmr spectra displayed in addition to a singlet *t*-butyl peak and resonances expected of the ester groups, two singlets at about δ 5.9 and 6.4 assignable to the 2 and 4 azepine ring protons respectively.

TABLE I

UV Absorption Maxima in *n*-Hexane for 3,6-Di-*t*-butylazepines

R'	λ max mμ (ε)
C_2H_5	3000 (697) 2400 sh (2680) 2140 (25,800)
CH_2-cyclopropyl	3000 (690) 2400 sh (2960) 2150 (25,000)
$C(CH_3)_3$	3030 (655) 2400 (3360) 2150 (27,000)
p-$C_6H_4(OCH_3)$	3000 sh (770) 2840 (2450) 2775 (2750) 2675 (2740) 2230 (27,900) 2160 (26,400)

The azidoformates, **3a-d**, reacted similarly with *para*-di-*iso*propylbenzene (**2**) to give mixtures of azepines composed of 60-80% of the 3,6-di-*iso*propyl isomer, **5**, as determined from the integration of the vinylic region of the nmr spectrum. The yields were low (30-40%) due to the formation of urethan byproducts of structure **8**, identified by infrared (ν N-H (strong) 3360 cm^{-1}) and nmr (for R′ = Et, δ 1.58, 6H, singlet, CH_3; 2.83, 1H, septet, CH; 7.17, 4H, quartet, aromatic H) spectroscopy. The azepine



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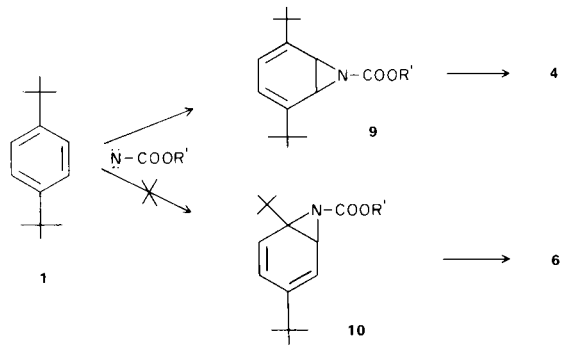
portion was, however, separable from the urethan portion by chromatography. Since the azepines, **5**, resisted crystallization, they could not be isolated from the 2,5-di*iso*propyl isomer, **7**.

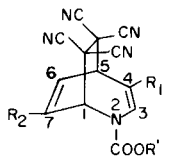
Assuming the intermediacy of nitrenes in the thermal decomposition of **3a-d** (6), the results indicate that the bulkiness of the *t*-butyl groups of **1** is sufficient to sterically prevent entry of the nitrene into the 1,2 position. Thus, the major part of the reaction can be visualized as proceeding through **9** rather than **10** (7). See Scheme I. The formation of **10** appears to become even more difficult when bulky groups are present in the ester moiety of the azidoformate. Thus, whereas 5% of the 2,5-di-*t*-butyl isomer, **6a**, was produced from ethyl azidoformate, virtually none of this isomer resulted from azidoformates, **3b-d**, in which the ester groups are larger than ethyl. Regardless of the size of the ester group, the blocking effect of the

SCHEME I



*iso*propyl group, as compared to the *t*-butyl group, in azepine formation is less pronounced.

The availability of the 60-100% isomerically pure azepines prompted a study of their behavior toward tetracyanoethylene (TCNE). The reaction between 1*H*-azepines and TCNE has gained considerable interest. Reports from several investigators (3,8) have shown that a variety of azepines undergo the usual 1,4 type Diels-Alder reaction to yield unsymmetrical adducts of structure **11**, although it was originally postulated (9) that the reaction would proceed *via* 1,6 type cycloaddition to yield symmetrical adducts of structure **12**. It is the formation of the latter 1,6 type TCNE-azepine adducts about which we now report.



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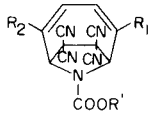
a, $R_1 = R_2 = R' = CH_3$
b, $R_1 = R_2 = CH_3$, $R' = C_2H_5$



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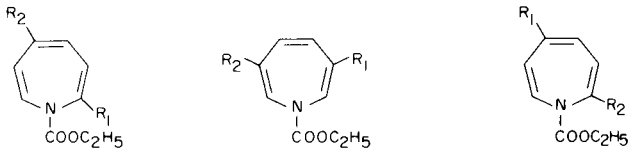
a, $R_1 = R_2 = C(CH_3)_3$, $R' = CH_2$-cyclopropyl
b, $R_1 = R_2 = CH(CH_3)_2$, $R' = C_2H_5$
c, $R_1 = R_2 = CH(CH_3)_2$, $R' = CH_2$-cyclopropyl
d, $R_1 = R_2 = CH(CH_3)_2$, $R' = C(CH_3)_3$
e, $R_1 = R_2 = CH(CH_3)_2$, $R' = p\text{-}C_6H_4OCH_3$
f, $R_1 = R_2 = CH(CH_3)_2$, $R' = o\text{-}C_6H_4OCH_3$
g, $R_1 = R_2 = CH_3$, $R' = C_2H_5$
h, $R_1 = CH_3$, $R_2 = CH(CH_3)_2$, $R' = C_2H_5$
i, $R_1 = CH_3$, $R_2 = C(CH_3)_3$, $R' = C_2H_5$
j, $R_1 = R_2 = CH_2OCH_3$, $R' = C_2H_5$

Azepines **4a** and **4c** were found to react with an equivalent amount of TCNE in benzene at room temperature to give mixtures of adducts **11** and **12** ($R_1 = R_2 = C(CH_3)_3$, $R' = C_2H_5$, $C(CH_3)_3$) whereas azepine **4b** reacted to give exclusively adduct **12a** in 63% yield. The mixtures of azepines **5a-d** and **7a-d** reacted with less than the equivalent amount of TCNE in benzene to give only adducts **12b-e**. Reaction of TCNE with azepine **4d** led only to tars and aromatic urethan.

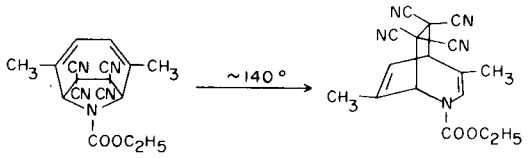
In order to examine further the behavior of TCNE toward 3,6-dialkylated azepines, mixtures of azepines **13**, **14** and **15**, of undetermined isomeric composition, were synthesized by thermolyzing ethyl azidoformate (3a) in *p*-xylene, *p*-cymene, *p*-*t*-butyltoluene and 1,4-benzenedimethanol dimethyl ether. Less than the equivalent amount of TCNE reacted with each of these mixtures (10) to give only 1,6 type adducts, **12g-j**, derived from the 3,6-dialkyl isomers, **14a-d**.



13 14 15

a, $R_1 = R_2 = CH_3$
b, $R_1 = CH_3$, $R_2 = CH(CH_3)_2$
c, $R_1 = CH_3$, $R_2 = C(CH_3)_3$
d, $R_1 = R_2 = CH_2OCH_3$

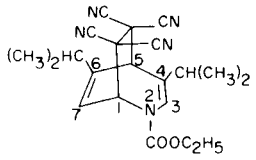
Thus, 3,6-dialkylazepines appear to be particularly reactive toward TCNE and their favored path of reaction is a 1,6 type of cycloaddition at room temperature. Under these conditions, 2,4-, 2,5-, 3,4- and 3,5-dimethyl-*N*-carbethoxyazepines have been shown to give 1,4 type adducts with TCNE (3). At a much higher temperature of 130° the reaction between TCNE and 3,6-dimethyl-*N*-carbomethoxyazepine was reported to yield the 1,4 adduct, **11a** (8a). Heating of adduct **12g** in *p*-xylene at reflux temperature gave after 4 hours an 80% yield of the 1,4 adduct, **11b**, m.p. 141-142.5°. The structure of this adduct was evident from its nmr spectrum, which was quite similar to the analogous methyl ester (8a) (δ (TMS-deuteriochloroform) 5.68, broad s, H-1; 6.69, broad s, H-3; 3.27, doublet of doublets, $J_{5,6}$ = 7.0 Hz, $J_{3,5}$ = 1.0 Hz, H-5; 6.41, doublet of triplets, $J_{6,5}$ = 7.0 Hz, $J_{6,CH_3\text{-}7}$ = 1.6 Hz, H-6). Whether, or not, the high temperature reaction of Baldwin and Smith (8a) actually proceeded through a 1,6 adduct is



12g 11b

not certain. Perhaps the 1,4 adduct derived from *N*-carbethoxyazepine, itself, (8a-c) proceeded through the 1,6 type adduct, **12** (R_1 = R_2 = H, R′ = C_2H_5), which was thermally much less stable than the dialkylated analogs, **12a-j**. In any case the 1,6 adducts of 3,6-dialkylazepines appear to be the kinetically favored products, whereas a 1,4 adduct would appear to be the thermodynamically favored product.

Steric factors do not appear to be important criteria for the isolation of 1,6 adducts (compare **12a** and **12g**). Rather the 3,6 substitution of the alkyl groups is the factor governing the cycloaddition reaction. This was further demonstrated by the isolation of adduct **16** from the reaction of TCNE with the azepine fraction obtained from **3a** and *m*-di*iso*propylbenzene. The structure was readily established by its nmr spectrum which showed a high field singlet (δ 3.30, deuteriochloroform) characteristic of the bridgehead proton, H-5 (8a).



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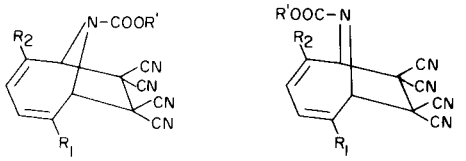
Adducts **12a-j** showed absorptions in the nmr spectrum between δ 5.0-6.3 assignable to the bridgehead and vinylic protons. The latter appeared as a sharp singlet between δ 5.9-6.3 in each adduct. The signal for the bridgehead protons at δ 5.0-5.6 varied in appearance depending on the nature of the alkyl and ester groups as illustrated in figure 1. Generally, the bulkier groups (11) caused a broadening of the signal and in some cases (**12d** and **f**) a temperature dependent doubling effect was observed. At elevated temperature (80°) a signal such as that seen for **12d** (fig. 1b) at room temperature sharpened to a somewhat broad singlet, whereas at reduced temperature (-41°) the bridgehead proton singlet of **12e** (fig. 1c) appeared doubled as that in the room temperature spectrum of **12f** (fig. 1d). This suggests the possibility that adducts, **12**, exist as conformational isomers, perhaps **17** and **18**, the rate of interconversion being dependent on the substituent groups. The nmr spectrum of **12j** (fig. 1a) would indicate that such an interconversion is rapid at room temperature.



17 18

EXPERIMENTAL (12)

Azidoformates **3b** and **3d** were synthesized from the corresponding chloroformates according to the procedure for ethyl azidoformate, **3a** (2b), except that a reaction time of 4 hours was used. The azidoformate products displayed ir ν (N_3) = 2150-2180, ν (C=O) = 1720-1740 and ν (C-O) = 1220 cm^{-1}. Cyclopropylcarbinyl and *o*- and *p*-methoxyphenyl chloroformates were synthesized by rapidly adding a carbon tetrachloride solution of the hydroxy compound to an excess of phosgene in carbon tetrachloride followed by neutralization with aqueous sodium hydroxide. These showed ir ν (C=O) = 1770-1780 and ν (C-O) = 1120-1150 cm^{-1}.

3,6-Di-*t*-butylazepine-*N*-carboxylates (**4**). General procedure.

To 150 g. (0.790 mole) of *p*-di-*t*-butylbenzene (**1**) heated to 125° in an oil bath was added 0.079 mole of the appropriate azidoformate and the mixture was heated for 2-4 hours when the evolution of nitrogen ceased. The hot reaction mixture was then poured into 1 liter of methanol in a beaker immersed in a dry ice-acetone bath and allowed to cool to about -10°. The precipitated *p*-di-*t*-butylbenzene (135-144 g.) was filtered and washed with 300 ml. of cold methanol. The methanol filtrates were combined and evaporated and the oily residue chromatographed on alumina. Hexane eluted excess **1** (1-5 g.). Hexane-benzene mixtures and finally benzene eluted the azepines as pale yellow-green oils which crystallized from hexane. See Table II.

Azepine Mixtures (**5** and **7**, **13**, **14** and **15**).

Fifteen g. of the appropriate azidoformate was added to 300-400 ml. of the dialkyl benzene heated in an oil bath at 125-130°. After

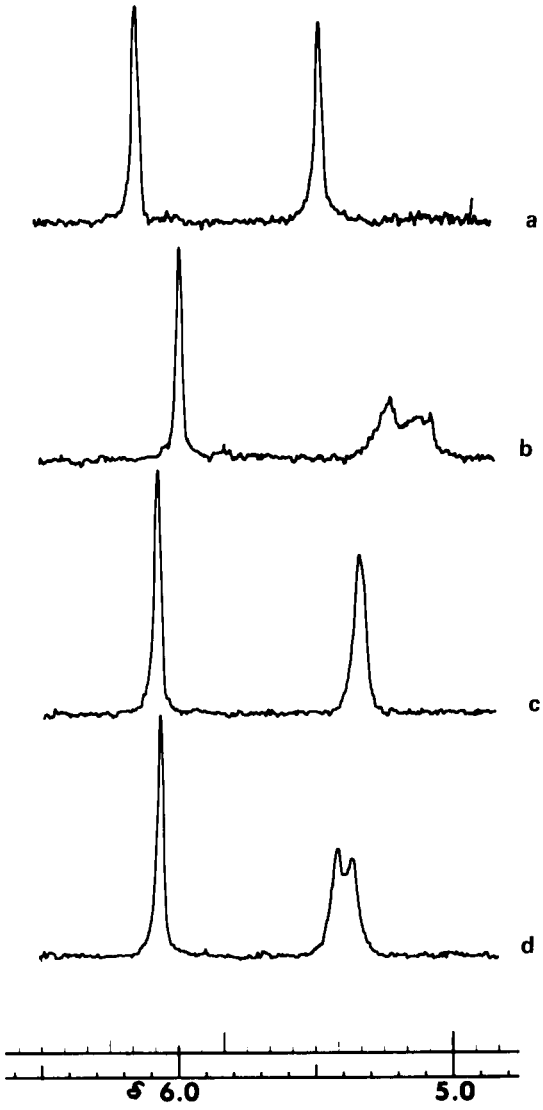


Fig. 1. 60 MHz nmr spectra of the vinylic regions of TCNE adducts a) **12j**, b) **12d**, c) **12e** and d) **12f**.

3 hours the excess dialkylbenzene was vacuum distilled and the oily residue was chromatographed on alumina. Elution with hexane removed any remaining dialkylbenzene. Benzene then eluted the azepine fractions as orange colored oils.

TCNE Adducts.

Two g. (15.6 mmoles) of TCNE was added to ten g. of the azepine mixtures in 100 ml. of benzene and the dark colored solution was stirred at room temperature for 15-24 hours. The oily residue from evaporation of the benzene was dissolved in hexane and, if necessary, a little ethyl acetate. The adduct soon began to crystallize and the solution was chilled for several days to complete crystallization. See Table III.

In the case of **12a**, 1.0 g. (7.8 mmoles) of TCNE was added to 2.4 g. (7.9 mmoles) of azepine **4b** in 50 ml. of benzene and treated as above.

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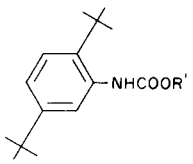
(1) For Part II in the series see J. M. Photis, *J. Heterocyclic Chem.*, **8**, 167 (1971).

(2) K. Hafner, D. Zinser and K.-L. Moritz, *Tetrahedron Letters*, 1733 (1964); (b) R. J. Cotter and W. F. Beach, *J. Org. Chem.*, **29**, 751 (1964); (c) J. E. Baldwin and R. A. Smith, *ibid.*, **32**, 3511 (1967); (d) F. D. Marsh and H. E. Simmons, *J. Am. Chem. Soc.*, 87, 3530 (1965).

(3) J. M. Photis, *J. Heterocyclic Chem.*, 7, 1249 (1970).

(4) Not all azidoformates were found to yield the corresponding azepine, **4**. For R′ = CH_3 a mixture of azepines and other products resulted; for R′ = C_6H_5, *o*-$C_6H_4OCH_3$, 2,6-$C_6H_3(OCH_3)_2$, $CH_2C_6H_5$, *n*-propyl, *iso*butyl, *sec*-butyl and $CH_2C(CH_3)_3$ only rearrangement product urethans, **i**, resulted; for R′ = $CH_2CH{:}CH_2$ and *iso*propyl the azepine, **4**, was found to readily rearrange to **i** even in the cold.



i

(5) L. A. Paquette, D. E. Kuhla, J. H. Barrett and R. J. Haluska, *J. Org. Chem.*, **34**, 2866 (1969).

TABLE II

Experimental Data for 3,6-Di-*t*-butylazepine-*N*-carboxylates

Compound	Color	% Yield (a)	m.p. °C	Analyses Calcd. %C	%H	%N	Found %C	%H	%N
4a $C_{17}H_{27}NO_2$	gr-yl	76	67-69	73.60	9.81	5.05	73.64	10.05	5.03
4b $C_{19}H_{29}NO_2$	gr-yl	69	41-43	75.20	9.63	4.62	74.87	9.94	4.60
4c $C_{19}H_{31}NO_2$	yl	85	100-102	74.71	10.23	4.59	74.82	10.65	4.65
4d $C_{22}H_{29}NO_3$	white	75	142-144	74.33	8.22	3.94	74.50	8.38	3.90

(a) Based upon *p*-di-*t*-butylbenzene consumed.

TABLE III

Experimental Data for TCNE-Azepine Cycloadducts

	Adduct	% Yield	m.p. °C	Analyses Calcd. %C	%H	%N	Found %C	%H	%N
12a	$C_{25}H_{29}N_5O_2$	63	134-136	69.58	6.77	16.23	69.75	6.80	16.37
12b	$C_{21}H_{23}N_5O_2$	82	120-122	66.82	6.14	18.56	66.74	6.20	18.63
12c	$C_{23}H_{25}N_5O_2$	81	125.5-127.5	68.46	6.25	17.36	68.28	6.26	17.44
12d	$C_{23}H_{27}N_5O_2$	67	146-149d	68.12	6.71	17.27	68.78	6.47	17.28
12e	$C_{26}H_{25}N_5O_3$	46	145-147	68.55	5.53	15.38	68.90	5.55	15.28
12f	$C_{26}H_{25}N_5O_3$	58	181-183	68.55	5.53	15.38	68.48	5.56	15.09
12g	$C_{17}H_{15}N_5O_2$	70	160-162	63.54	4.70	21.80	63.45	4.83	21.94
12h	$C_{19}H_{19}N_5O_2$	57	164-166	65.31	5.48	20.05	65.49	5.30	20.17
12i	$C_{20}H_{21}N_5O_2$	73	160-162	66.10	5.82	19.27	66.37	5.75	19.34
12j	$C_{19}H_{19}N_5O_4$	35	149-151	59.83	5.02	18.36	59.96	4.78	18.32
16	$C_{21}H_{23}N_5O_2$	35	206-208	66.82	6.14	18.56	66.58	6.17	18.69

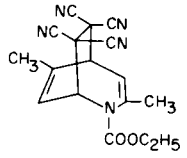
(6) Several investigators have indicated that the thermal decomposition of azidoformates preceeds through the nitrene. See (a) W. Lwowski and T. W. Mattingly, Jr., *J. Am. Chem. Soc.*, **87**, 1947 (1965); (b) L. E. Chapman and R. F. Robbins, *Chem. Ind.* (London), 1267 (1966): (c) D. S. Breslow, T. J. Prosser, A. F. Marcantonio and C. A. Genge, *J. Am. Chem. Soc.*, **89**, 2348(1967).

(7) Azanorcaradiene intermediates (**9** and **10**) have been proposed in the formation of *N*-carbethoxyazepine from benzene and *N*-carbethoxynitrene. See (a) K. Hafner and C. Konig, *Angew. Chem.*, **75**, 89 (1963); (b) W. Lwowski, T. J. Maricich and T. W. Mattingly, Jr., *J. Am. Chem. Soc.*, **85**, 1200 (1963).

(8a) J. E. Baldwin and R. A Smith, *ibid.*, **87**, 4819 (1965); (b) J. H. Van den Hende and A. S. Kende, *Chem. Commun.*, **1**, 384 (1965); (c) A. S. Kende, P. T. Izzo and J. E. Lancaster, *J. Am. Chem. Soc.*, **87**, 5044 (1965); (d) L. A. Paquette, D. E. Kuhla, J. H. Barrett and L. M. Leichter, *J. Org. Chem.*, **34**, 2888 (1969).

(9) K. Hafner, *Angew. Chem.*, **75**, 1041 (1963); *Angew. Chem. Intern. Ed. Engl.*, **3**, 165 (1964).

(10) The reaction of the mixture of azepines derived from *p*-xylene and ethyl azidoformate with an equivalent amount of TCNE at room temperature has been inferred (3) to yield a mixture of isomeric adducts **ii** and **11b**. It now appears that the reaction product was actually a mixture of adducts **ii** and **12g**.



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(11) For the purpose of comparing the *p*-methoxyphenyl with the *o*-methoxyphenyl substituent, adduct **12f** was synthesized from TCNE and the azepine fraction obtained from *o*-methoxyphenyl azidoformate and **2**.

(12) The nmr spectra of the azepines in carbon tetrachloride and the adducts in deuteriochloroform solution were recorded on a Varian A-60 spectrometer relative to TMS as internal standard. Alcoa, F-20, alumina was used without treatment for chromatography. Melting points were taken on a Thomas Hoover Melting Point Apparatus and are uncorrected. The uv spectra were recorded on a Cary model 14 spectrophotometer.