# Nitrene Insertion Reactions. Part II. The Isolation of α-Alkyl-*N*-Carbethoxyazepines.

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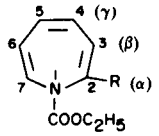
The isolation of 2,5-dimethyl-*N*-carbethoxyazepine from a mixture of isomeric azepines derived from ethyl azidoformate and *p*-xylene was recently reported (1) to have been accomplished by treating the crude mixture with refluxing ethanolic potassium hydroxide. A slight modification of this base reaction has since been found useful for the isolation of numerous isomerically pure azepines of the general structure, **1**, where R is an alkyl substituent, from mixtures containing several azepines. Thus, ethyl

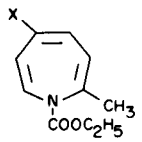



**1**

a, R = $CH_3$ d, R = $i$-$C_3H_7$
b, R = $C_2H_5$ e, R = $C(CH_3)_3$
c, R = $n$-$C_3H_7$

azidoformate decomposed in two hours in toluene (2) at reflux temperature and in ethylbenzene, *n*-propylbenzene, cumene and *t*-butylbenzene (2b) at 125° to give mixtures of azepines from which compounds **1a-e** were isolated after reacting the crude mixtures with potassium hydroxide in ethanol at room temperature. The success of the reaction can be attributed to a slower rate of hydrolysis of the α-substituted isomer as a consequence of steric hindrance about the nitrogen and ester group.

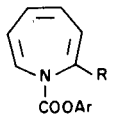
α-Alkyl azepines having additional substituents on the ring were obtainable by this technique. Ethyl azidoformate reacted at 125° with *p*-chlorotoluene and *p*-bromotoluene to give mixtures containing more than one azepine from which **2a** and **2b** were isolated. This method, although far from quantitative and limited only to α-alkylated azepines,




**2a**, X = Cl
**b**, X = Br

provides a convenient route to substituted *N*-carbethoxyazepines that might be difficult to obtain by the procedure of Paquette (3).

A further limitation was imposed by the ester moiety. The isolation of azepines of type **3**, where Ar is a phenyl group such as *o*- or *p*-$C_6H_4OCH_3$, *via* reaction with potassium hydroxide in ethanol, could not be achieved. During




**3**

the alkali treatment, these ester groups underwent transesterification to yield only the α-alkyl-*N*-carbethoxyazepine. Thus, *o*- and *p*-methoxyphenyl azidoformates (4) decomposed in refluxing *p*-xylene to give mixtures of azepines from which only 2,5-dimethyl-*N*-carbethoxyazepine (1) was isolated after reaction with potassium hydroxide.

The structure and isomeric purity of each azepine was established by nmr spectroscopy. Each monosubstituted azepine displayed complex, but similar, vinylic absorption patterns between δ 5.60-6.40. The presence of a halogen atom, as in **2b**, greatly simplified the spectrum: δ 5.60,

TABLE I

Proton nmr data
(60MHz, Carbon Tetrachloride)

| Compound | δ Alkyl substituent |
|---|---|
| **1a** | 2.06 (s) (5), $CH_3$ (6) |
| **1b** | 2.48 (q), $CH_2$; 1.00 (t), $CH_3$ |
| **1c** | 2.45 (t, br), allylic $CH_2$; 1.46 (sextet), $CH_2$; 0.90 (t), $CH_3$ |
| **1d** | 2.92 (br), CH; 1.06 (d), $CH_3$ |
| **1e** | 1.20 (s), $C(CH_3)_3$ (7) |
| **2a** | 2.05 (s) (5), $CH_3$ |
| **2b** | 2.01 (s) (5), $CH_3$ |

s = singlet; d = doublet; t = triplet; q = quartet; br = broad

TABLE II

Experimental Data

| | Compound | Anal. Calcd. %C | %H | %N | Found %C | %H | %N | Time of reaction with KOH | Yield (gms) | Column solvent |
|---|---|---|---|---|---|---|---|---|---|---|
| **1a** | $C_{10}H_{13}NO_2$ | 67.02 | 7.31 | 7.82 | 67.04 | 7.54 | 7.54 | 6-7 hours | 3.0 | $C_6H_6$ |
| **1b** | $C_{11}H_{15}NO_2$ | 68.37 | 7.82 | 7.25 | 68.38 | 7.72 | 6.90 | 6-7 hours | 3.1 | $C_6H_6$ |
| **1c** | $C_{12}H_{17}NO_2$ | 69.54 | 8.27 | 6.76 | 69.45 | 8.28 | 6.49 | 15 hours | 2.5 | $C_6H_6$ |
| **1d** | $C_{12}H_{17}NO_2$ | 69.54 | 8.27 | 6.76 | 70.04 | 8.48 | 6.65 | 15 hours | 1.9 | $C_6H_6$ |
| **1e** | $C_{13}H_{19}NO_2$ | 70.55 | 8.65 | 6.33 | 70.70 | 8.55 | 6.17 | 15 hours | 2.1 | $CHCl_3$ |
| **2a** | $C_{10}H_{12}NO_2Cl$ | 56.22 | 5.66 | 6.56 | 56.32 | 5.97 | 6.22 | 6 hours | 3.5 | $C_6H_6$ |
| | | %Cl calcd. 16.54 | | | %Cl found 15.72 | | | | | |
| **2b** | $C_{10}H_{12}NO_2Br$ | 46.53 | 4.69 | 5.43 | 46.69 | 4.72 | 5.07 | 6 hours | 0.25 | $C_6H_6$ |
| | | %Br calcd. 30.96 | | | %Br found 30.33 | | | | | |

H-3, doublet of doublets, $J_{3,4}$ = 6.0Hz, $J_{CH_3\text{-}2,3}$ = 1.4Hz; 5.86, H-6 and H-7, triplet, $J_{6,7}$ = 7.9Hz; 6.57, H-4, doublet of doublets, $J_{4,3}$ = 6.0Hz, $J_{4,6}$ = 0.9Hz. All of the mixtures showed multiple absorptions ascribable to the alkyl substituent, whereas the pure isomer showed only one signal or set of signals. See Table I.

The larger the alkyl group, the greater was the tendency for the azepine to rearrange to the aromatic urethan (8). However, the azepine was easily separated from the urethan by column chromatography.

## EXPERIMENTAL (11)

General Procedure.

Twenty-five g. of ethyl azidoformate was added to 200-300 ml. of the alkyl benzene and the solution was heated under reflux to 125° in an oil bath for two hours or until the evolution of nitrogen ceased. Vacuum distillation of the excess alkyl benzene left a viscous, oily mixture of crude azepines which was dissolved in 200 ml. of 95% ethanol. Sixty g. of potassium hydroxide was then added and the mixture was stirred at room temperature for the period of time indicated in Table II. The dark colored solution was then poured into one liter of water and extracted three times with 300 ml. portions of ether. The residue from evaporation of the dried ether extracts was chromatographed on alumina. Elution with hexane first removed any excess alkyl benzene that was carried over. The appropriate solvent (see Table II) then eluted the azepine fraction followed by phenylurethans (12) and other by-products whose composition was not investigated.

## REFERENCES

(1) "Nitrene Insertion Reactions. Part I." by J. M. Photis accepted for publication in *J. Heterocyclic Chem.*

(2a) R. J. Cotter and W. F. Beach, *J. Org. Chem.*, **29**, 751 (1964); (b) J. E. Baldwin and R. A. Smith, *ibid.*, 32, 3511 (1967).

(3) L. A. Paquette and D. E. Kuhla, *Tetrahedron Letters*, 4517 (1967); L. A. Paquette, D. E. Kuhla, J. H. Barrett and R. J. Haluska, *J. Org. Chem.*, 34, 2866 (1969).

(4) These azidoformates were synthesized from the corresponding chloroformates by stirring a carbon tetrachloride solution of the latter with a solution of sodium azide in water for 15 hours.

(5) Small long range coupling is not included.

(6) Paquette (3) has reported a chemical shift of δ 2.04 for the α-methyl group of the analogous *N*-carbomethoxyazepine.

(7) In the analysis of the nmr spectrum of the mixture of azepines obtained from *t*-butylbenzene and methyl azidoformate, Baldwin and Smith (2b) assigned two singlets to the isomer having the α-*t*-butyl group. Only one *t*-butyl singlet was observed for azepine **1e**.

(8) The acid promoted and thermal rearrangement of azepines to urethans have been studied by Hafner (9) and Paquette (10).

(9) K. Hafner, *Angew. Chem.*, 75, 1041 (1963).

(10) L. A. Paquette, D. E. Kuhla and J. H. Barrett, *J. Org. Chem.*, 34, 2879 (1969).

(11) All analytical samples were prepared by bulb to bulb vacuum distillation from an oil bath heated to 130°. Alcoa, F-20, chromatographic alumina was used without activation for chromatography. All nmr spectra in carbon tetrachloride solution were recorded on a Varian A-60 instrument relative to tetramethylsilane.

(12) *N*-Carbethoxyazepine is known to rearrange to phenylurethan when treated with base. (See T. Sasaki, *et. al.*, *J. Org. Chem.*, 35, 426 (1970)).