Cycloadditions of Azulene at High Pressure**

By Frank-Gertr Klämer*, Barbara Dogan, Wolfgang R. Roth, and Klaus Hafner

Dedicated to Professor William von E. Doering on the occasion of his 65th birthday

Reaction of dimethyl acetylenedicarboxylate 2a with azulene 1 (boiling tetralin, 207.6 °C) leads to the heptalene-dicarboxylic acid dimethyl ester 7a[12]. It was presumed that the intermediates 3a and 4a are involved. We have now established that high pressure (7 kbar) has an accelerating effect on this reaction and have also been able to isolate an intermediate from which the heptalene derivative

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1a also reacts with 2b at 7 kbar and 70 °C to afford the adduct 6b, although the reaction is very slow and the yield only moderate (ca. 2% after 66 h); neither yield nor conversion can be improved by increasing the temperature because at 150 °C the 1-azulene ester 9b is now formed through cleavage of acetylene from 6b. Thermolysis of 6b at 80 °C, both at 7 kbar and at 1 bar (126 h, 70–80% conversion in each case) leads only to 1 and 2b. In no case is the 1-heptalene ester 7b formed. These results cannot be accounted for by the reaction mechanism originally postulated. The intermediate 4a is also not observed at 60 °C[13]. Apparently, 6a is an intermediate on the route to the heptalene derivative 7a. The question of whether the reversible reaction 1 + 2 = 6 proceeds via the dipolar intermediate 3 or by concerted [4+2]-cycloaddition[14] remains open. Here, the effect of pressure is less revealing. In both cases a strongly negative volume of activation is expected[15]. Since 6a reacts 22 times faster than 6b at 80 °C, we presume that a concerted Diels-Alder reaction occurs.

The different thermal behavior of 6a and 6b suggests the diradical intermediate 12a is involved in the rearrangement 6a → 7a: 12a is transformed into the norcadiene 13a, which can readily react further to 7a via valence bond isomerization[16]. Formation of the diradical intermediate...
Isocyanates as Universal Reagents for the Formation of Derivatives for Gas Chromatographic Enantiomer Separation**

By Ingrid Benecke and Wilfried A. König*

Hitherto, the formation of volatile derivatives for the gas chromatographic separation of enantiomers on chiral stationary phases required several different reaction steps, depending on the class of substance in question. We have now achieved this aim in only one step for some important classes of compounds by using isocyanates as reagents (Scheme 1). The separation effects, as obtained by the formation of diastereomeric association complexes between the chiral sample molecules and the chiral stationary phase, are considerably increased by the carbamate-, ureido- or amide-derivatives, which are obtained on reaction with isocyanates.

In this way the eight stereoisomers of menthol could be separated as N-isopropylcarbamates. Chiral alcohols are of considerable importance in flavor and pheromone chemistry. For the first time β-hydroxy acids can now be separated as well as α-hydroxy acids. Such acids frequently occur as natural metabolites or as chiral constituents of natural products. The formation of derivatives is simple: On heating 0.1 mg of the sample for 1 h in isopropyl isocyanate and dichloromethane (1:2 v/v) the N-isopropyl-β-(N-isopropylcarbamoyl)alkane amides are readily obtained. The preparation of amides by heating carbocyclic acids and isocyanates has been known for some time but has never been used in microanalysis.

By analogy, the procedure mentioned here allows for the first time the preparation of derivatives of N-methylamino acids which are suitable for direct enantiomer separation. N-Methylamino acids frequently occur as constituents of peptide antibiotics and have gained increasing importance in peptide synthesis. Under the conditions described here the ureido derivatives are obtained in only one step. A racemization test for N-methylamino acids is of particular interest because of the strong tendency of such acids to undergo racemization during peptide coupling.[14]

Chiral amines, which could be separated as N-trifluoroacetyl derivatives only on special stationary phases, readily form N-isopropylureido derivatives even at room temperature. They are separated with unusually high separation factors. The same is true for α-branched amino acid derivatives and carboxylic acids.

![Fig. 2. Separation of racemic mixtures of 2-phenylbutyric acid 1, 5-enantiomer = 2nd peak; lactic acid 2, L-enantiomer = 2nd peak; 2-hydroxybutyric acid 3, L-enantiomer = 2nd peak; N-methylvaline 4, D-enantiomer = 2nd peak; 2-amino-6-methylheptane 5, no peak assignment; 3-hydroxybutyric acid 6, no peak assignment. Derivatives were obtained as shown in Scheme 1 by reaction with isopropyl isocyanate. Glass capillary (borosilicate glass, 40 m, 0.2 mm i.d.) coated with DE-60-L-valine-(S)-α-phenylethylamide (7), T = 190 °C (Carlo Erba Model 2101 A gas chromatograph, carrier gas: 0.7 bar H2).](image-url)

The carbamate-, ureido-, and amide-derivatives, prepared with isopropyl isocyanate as universal reagent, are stable over months in solution; no racemization during formation of derivatives has been observed so far.

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