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THE INTRAMOLECULAR CYCLIZATION
1-DIAZOETHYL 3-CYCLOHEXEN-1-YL KETONE

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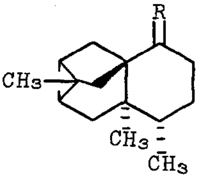
Eleven years ago, Stork and Ficini described the first example of an intramolecular cyclization of an unsaturated diazomethyl ketone.[1] Since then, numerous examples of this reaction have appeared in the literature testifying to its immense synthetic utility. Specifically, a variety of bicyclic,[2a] tricyclic,[2b,c] and tetracyclic[2d] ketones have been prepared by this method, many of which would have been unattainable by alternative routes. In addition, the preparation of a number of naturally occurring materials, such as 2-carone,[3a] 4-demethylaristolone,[3b] sesquicarene,[3c] sirenin,[3d] sabinene,[3e] thujopsene,[3f] agarospirol[3g] as well as some key synthetic intermediates related to sesqui- and diterpene total synthesis,[3h] have been reported in which the crucial step in all cases is the above-mentioned intramolecular cyclization. Normally, the reaction is catalyzed by copper powder, various copper salts or, in some cases, the reaction is photochemically induced.[4] To our knowledge, no example of this reaction has been reported in which anything but a diazomethyl ketone[1-4] or ester[5] has been employed.

The apparent difficulties involved in preparing homologues of diazomethyl ketones,[6] and, once prepared, their reluctance to readily undergo standard reactions[7] or their propensity to rearrange to α,β-unsaturated ketones[8] has probably militated against their use.

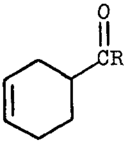
The recent structural elucidation of a unique class of sesquiterpenes, exemplified by ishwarone (1a)[9a] and ishwarane (1b),[9b] both of which



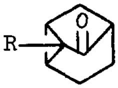
1a; R = O
1b; R = H_2

contain a 1-methyltricyclo[3.2.1.0^{2,7}]octane ring system[10] prompted us to investigate the intramolecular cyclization of an unsaturated α-diazoethyl ketone with the hope of circumventing the problems alluded to above[6-8] as well as providing a viable synthetic entry into such a tricyclic ring system.

To this end, 3-cyclohexene-1-carboxylic acid (2) was converted by standard methods[1-4] (oxalyl chloride) to the corresponding acyl chloride,



2; R = OH
3; R = Cl
4; R = C(N_2)CH_3
5; R = CH=CH_2



6; R = CH_3
7; R = H

3, which in turn was treated with an ethereal solution of diazoethane[11] at -20° for 1 hr.[12] Removal of excess diazoethane and solvent at 0° afforded the diazoketone 4 [nmr (CCl_4) 1.98 (s, 3, CH_3), 5.62 ppm (broad s, 2, HC=CH). The structure of 4 was evident from its method of synthesis, its spectral characteristics, and its conversion (γ-collidine and benzyl alcohol at 185° for 5 min) to benzyl 2-[3-cyclohexen-1-yl]propanoate.[7a] Although a variety of catalytic methods were investigated to effect the desired intramolecular cyclization, the most successful proved to be a suspension of anhyd $CuSO_4$ in cyclohexane to which was added diazoketone 4. When this mixture was heated to reflux for 15 - 18 hr, 7-methyltricyclo[$3.2.1.0^{2,7}$]octan-6-one (6) [bp 70° (2 mm); ir (film) 1715 cm^{-1} (C=O); nmr (CCl_4) 1.15 (s, 1, CH_3), 1.52 (m, 2, cyclopropyl methine), 1.93 ppm (broad m, 7, remaining H's)[13]; mass spectrum (70 eV) m/e 136 (M^+); anal. calcd for $C_9H_{12}O$: C, 79.37; H, 8.88, found C, 79.22; H, 8.88; 2,4-DNP, mp 174-175°, anal. calcd for $C_{15}H_{16}N_4O_4$: C, 56.95; H, 5.10; N, 17.71, found C, 57.09; H, 5.19; N, 17.70]. There was no spectral evidence for the formation of the isomeric α,β-unsaturated ketone 5.[8]

Studies utilizing this reaction in the preparation of naturally occurring compounds containing this tricyclic ring system are currently in progress in our laboratories.

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(12) Longer reaction times and/or higher reaction temperatures lead to undesirable by-products which were not investigated further but which presumably were largely the azine.^{6}

(13) The nmr spectrum of ketone 6 was totally consistent with the assigned structure and corresponded closely to the reported spectrum of the related demethyltricyclic ketone 7.^{2c}