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REACTION OF DICARBONYL COMPOUNDS WITH DIMETHYL 3-KETOGLUTARATE. INFLUENCE OF STERIC EFFECTS ON SUCCESS OF THE CONDENSATION

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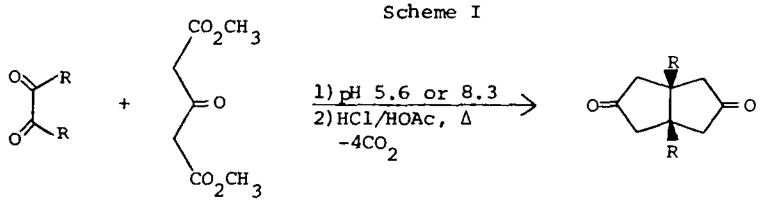
Abstract: The influence of steric factors on the synthesis of substituted bicyclo[3.3.0]-octane-3,7 diones via the condensation of 1,2-dicarbonyl compounds with dimethyl 3-ketoglutarate 2 is described.

Recently Bertz reported a new approach to synthetic analysis[1a,1b] which employs graph theory and information theory in order to evaluate alternate synthetic routes toward a common target. In this vein, the generation of molecular complexity in the polyquinane area via reaction of 1 with 2 (Scheme I) compared favorably with the formation of complex polycyclic molecules composed of six-membered rings formed by the Diels-Alder[2] reaction. This is in agreement with our earlier view on the condensation.[3]

The versatility of this reaction has been demonstrated by synthesis of several different polyquinane systems in our laboratory,[3,4a,b,c] moreover, Dauben[5a] has recently prepared isocomene via the technology described in reference 4b. In addition, Coates[5b] and Paquette[5c] have synthesized gymnomitrol by use of the method outlined in Scheme I, while, Nicolaou has prepared carboprostacycline[6] from bicyclo[3.3.0]octane-3,7-dione.[7]

Scheme I

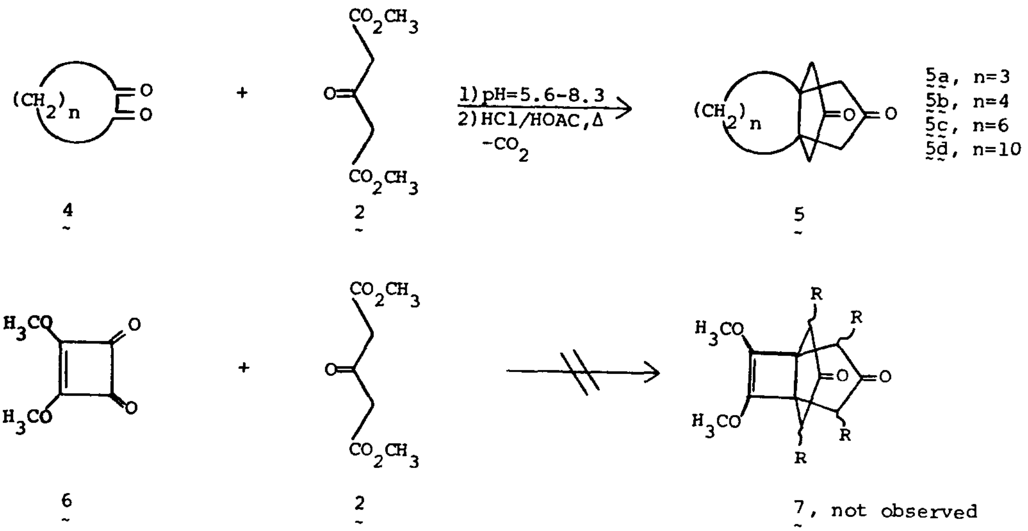


1 2 3

The interest in the reaction sequence outlined above for the synthesis of polyquinane ring systems and natural products has prompted a study of the influence of steric factors on the success or failure of this condensation. We wish to report our results in this area.

Previously, we had shown that 1,2-diones such as cyclohexanedione 4 (n=4)[4a,8a] and cyclododecanedione 4 (n=10),[8b] when reacted with 2, provided the corresponding propellanediones 5b and 5d in yields greater than 85% and 92%, respectively, as illustrated in Scheme II. In stark contrast to this, however, dimethyl squarate 6 on reaction with 2, under a variety of conditions, did not yield the 1:2 adduct 7. This is presumably due to the strain inherent in the [3.3.2] propellane system 7 for there are various equilibria involved in

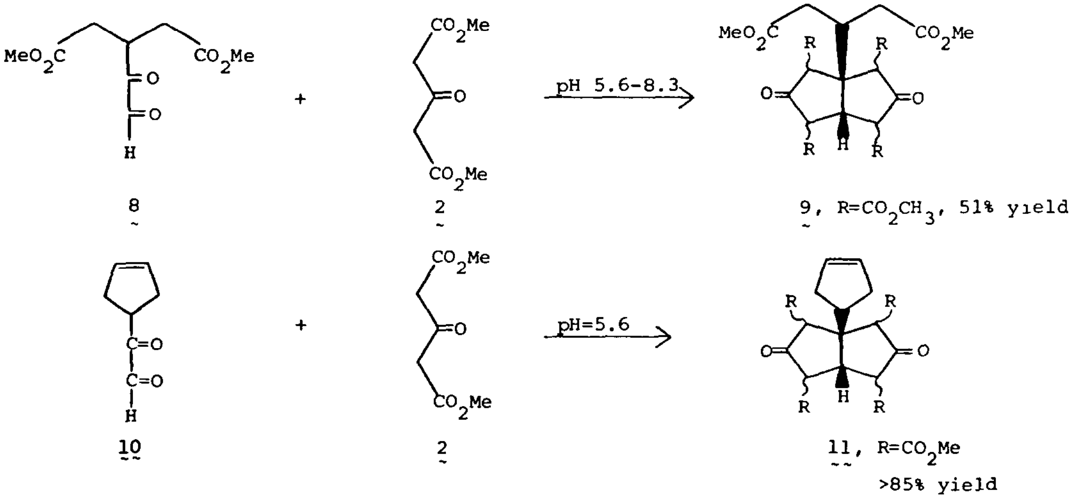
Scheme II



formation of the bicyclo[3.3.0]octanedione system which are not favored under these circumstances (see reference 9 for details). In essence, the above experiments define the limits of the condensation in terms of ring size, for alicyclic 1,2-diones of four members or less would not appear to be suitable substrates for this process.

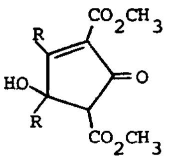
During a study in the acyclic area of steric influence on reaction progress, the 1,2-dione 8 (Scheme III) was stirred with 2; however, despite many efforts to increase the yield of 9 to better than 51%, we were never able to achieve this goal. In order to circumvent this problem, the cyclopentene substituted glyoxal 10 has been prepared and condensed with two equivalents of 2. The advantage of 10 over 8 rests on the fact that the two side chains are tied back and occupy a smaller molecular volume than their non-cyclic counterparts in 8. In fact, this sequence provided better than an 85% yield of crystalline 1:2 adduct 11,[10] moreover, additional quantities of 11 are present in the mother liquors. This example clearly illustrates the advantage of a substituted 1,2-dione in the reaction which occupies a molecular volume less than the acetic acid chains of 8. We have also recently found that a cycloheptene-substituted gly-

Scheme III

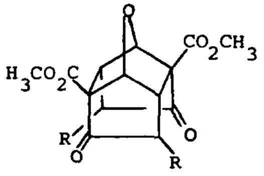


oxal undergoes the reaction, but not as rapidly, nor in as good a yield as 10.

A good deal of effort has been expended in our laboratory[9] and other laboratories[11] over the past several years in an attempt to isolate a 4-hydroxycyclopentenolone intermediate such as 12 from the condensation. In the case of benzil and phenanthrenequinone, 1:1 adducts[9] were obtained; however, in the more important alicyclic area isolation of the cage compound 13 [self-condensation product of two molecules of 12 (R=H)] by Bertz[11] has provided the only tangible proof



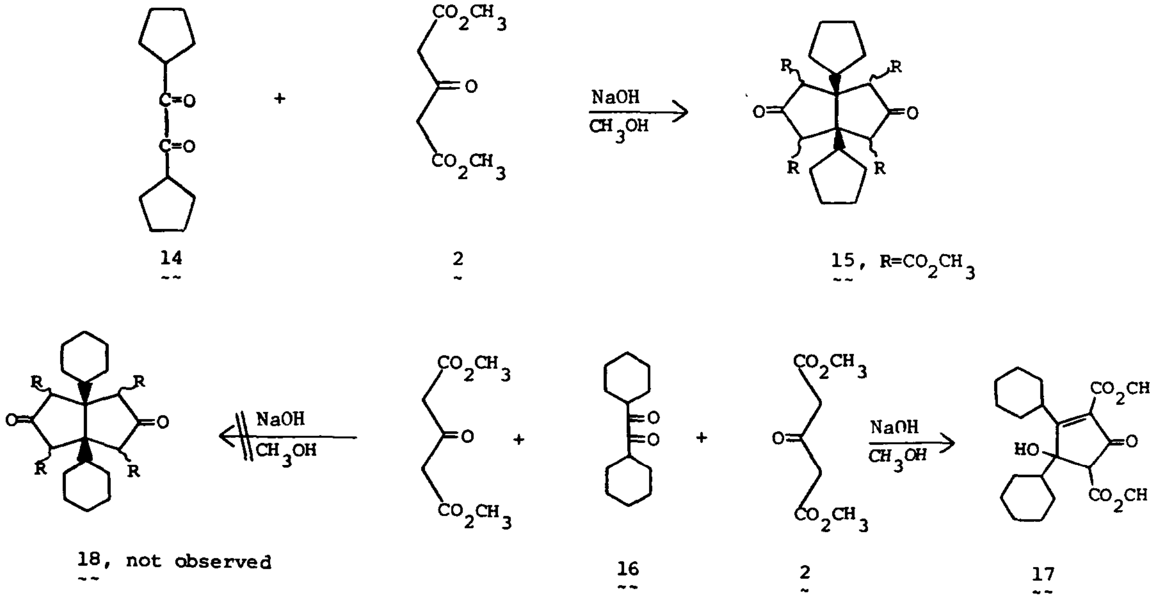
12



13, R=CO$_2$CH$_3$

that molecules such as 12 were present in the reaction. In this vein we have prepared both the bis-cyclopentyl and bis-cyclohexyl-1,2-dicarbonyl compounds 14 and 16, respectively, according to the method of Stocker.[12] When either of the 1,2-diones 14 or 16 was stirred with 2 in aqueous buffer (pH=5.6 or 8.3) most of the starting material was recovered unchanged. It was clear that diones 14 and 16 were quite hindered, therefore, vigorous conditions were required to promote the condensation. For this reason, the cyclopentane derivative 14 was stirred with two equivalents of 2 in sodium hydroxide-methanol which provided a white crystalline solid (m.p. 177-79°) on workup. The spectral data [ir(KBr) 3480, 1750(s), 1740 (s), 1712 (m), 1655(s) and 1625(m) cm^{-1}; NMR (CDCl$_3$) δ 0.80-2.40 (18H, m), 3.00-3.60 (2H, broad signal) 3.60-3.80 (13H, 4 singlets overlapping with another proton (4 x OCH$_3$); mass spectrum (C.I./CH$_4$) 507 (M+1),100)] for this material are in complete accord with the structure of the 1:2 adduct 15,

Scheme IV



illustrated in Scheme IV. When the same reaction was carried out with 16 and 2; however, an entirely different result was realized. The product of the condensation of 16 with 2 was a white crystalline solid whose properties are in accord with the structure of the 1:1 adduct 17[13] not the 1:2 adduct 18. This result was very gratifying for not only did the isolation of 17 end a long search for a hydroxycyclopentenolone in the alicyclic area, but clearly, and more importantly, the difference in size between the cyclohexane units of 16 vs. the cyclopentane units of 14 is the critical factor in predicting success or failure in the condensation. Consequently, it is felt that 1,2-dicarbonyl compounds which carry substituents that occupy a molecular volume equal to or less than a cyclopentane unit (for example 14) will be useful in the preparation of polyquinanes; however, diketones with two substituents as large as cyclohexyl (16) will not be useful substrates for this reaction.

In previous work in aqueous buffer (pH 5.6) we proposed 12 as an intermediate.[9] In agreement with this Bertz found 13 at acidic pH (~5) and formation of this product at higher pH (~6.8)[11] was suppressed; however, the system employed with 14 and 16 (sodium hydroxide, methanol) is a more vigorous reaction medium and did lead to the formation of the 1:1 adduct 17.

Since the generation of molecular complexity via reaction of 1 with 2 is such a facile process[1a,b,3], the influence of steric factors described here, on the success of the reaction, should provide a frame of reference for others to follow who wish to use the method for preparation of polyquinane systems of complex structure.

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10. 11: m.p. 144-145° (CH_3OH/H_2O) ir (KBr) 3400 (br) and 1730 cm^{-1} (enol and carbonyl bands) NMR ($CDCl_3$) δ 2.00-2.60 (4H, m), 3.40-3.90 (14H, four signals due to OCH_3 protons which overlap with two other protons) 5.73 (2H, S), 10.50 (s, broad), 11.30 (s, sharp), mass spectrum (C.I./CH_4) 437 (M+1, 100).
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13. 17: mp 58-61°C; ir (KBr), 3510 (s), 2945 (s), 2862, 1755 (s), 1735 (shoulder), 1700 (s) and 1620 cm^{-1}; NMR ($CDCl_3$) δ 0.60-2.10 (23H, broad multiplet, 2.40-2.90 (1H, m), 3.60 (1H, S), 3.70 (3H, S), 3.80 (3H, S) and 4.60 (1H, S, hydroxyl); mass spectrum (C.I./NH_3) 379 (M+1, 95%), 396 (M+18, 100%).

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