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ON THE REACTION OF CHALCONE WITH ETHYL CYANOACETATE

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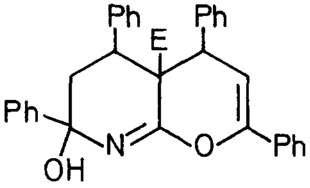
Summary: The recently reported condensation of chalcone with ethyl cyanoacetate is discussed and a cyclohexanol structure is proposed for the reaction product.

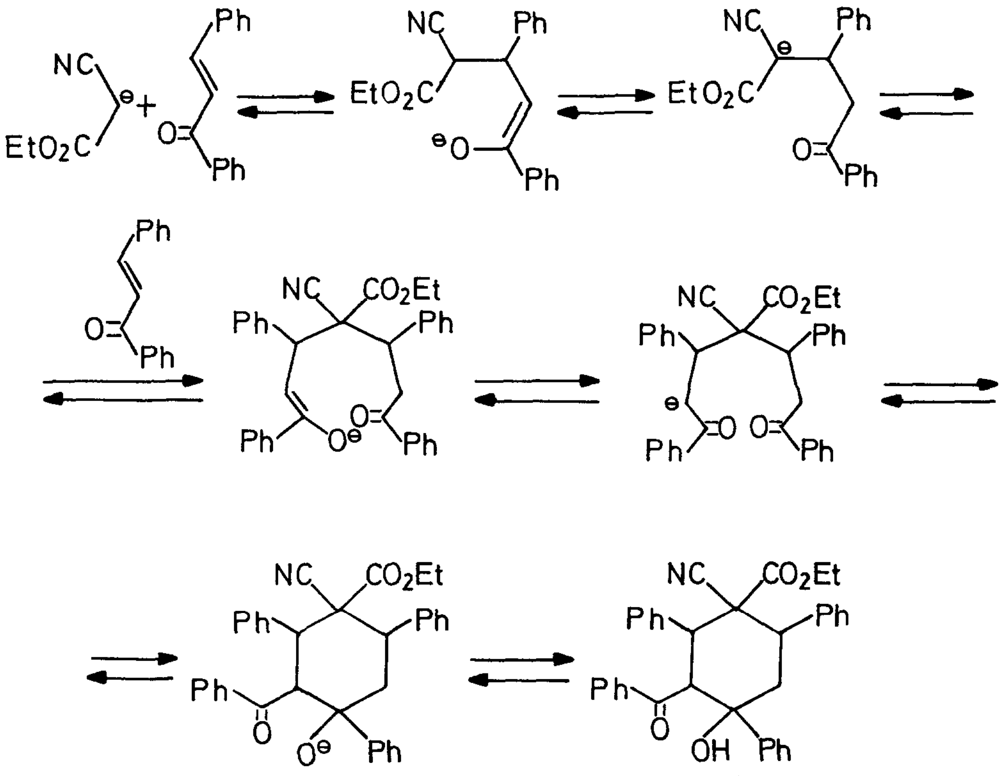
In a paper recently published in this journal[1], a structure of substituted 2,3,4,5-tetrahydro-8-oxaquinoline (1) was proposed for the products obtained from the condensation of chalcones with ethyl cyanoacetate in 2:1 molar ratio.



1, E=CO_2Et

We have also investigated this reaction with chalcone (and substituted derivatives) and we have isolated a compound with chemical and spectroscopic properties which do not agree with structure 1. The condensation was carried out by refluxing two moles of chalcone with one mole of ethyl cyanoacetate in dry ethanol, in the presence of a catalytic amount of piperidine, until TLC shows that the starting materials are exhausted (160 hours). On cooling, a crystalline solid, m. p. 198-200°C (from ethanol), precipitates from the reaction mixture in 64% yield. The microanalytical and mass spectral data are in agreement with the molecular formula $C_{35}H_{31}O_4N$. This corresponds with structure 1, with the open chain bis-adduct and also with the 2-benzoylcyclohexanol (2) structure (Scheme 1). On the basis of the data discussed below, this latter structure should be assigned to the compound.

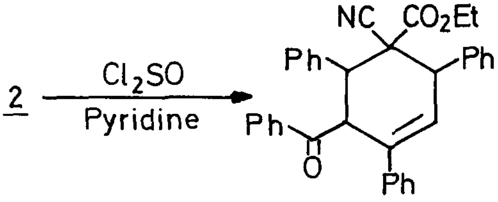
The IR spectrum (potassium bromide pellet, Perkin Elmer 580) shows, together with the ethoxycarbonyl group band (1739 cm^{-1}) and the hydroxyl band at 3300-3500 cm^{-1}, a very intense carbonyl band at 1655 cm^{-1} and a cyano stretching band at 2239 cm^{-1}, which is very weak as expected for an unconjugated nitrile[2]. This band becomes more intense in concentrated chloroform solution. The low wavenumber of the carbonyl band is attributed to the formation of an intramolecu-



Scheme 1

2

lar hydrogen bond with the hydroxyl group[3]. The fact that the position of the hydroxyl and carbonyl bands do not change with the concentration corroborates this intramolecular association. When cyclohexanol 2 is treated with thionyl chloride in pyridine, dehydration takes place. In the resulting cyclohexene (3) (vinylic hydrogen at 6.0 ppm in the ^{1}H-NMR spectrum) (Note 4), in which no hydrogen bond exists, the wavenumber of the carbonyl band increases to 1670 cm^{-1}. Such facts cannot be accounted for by structure 1.



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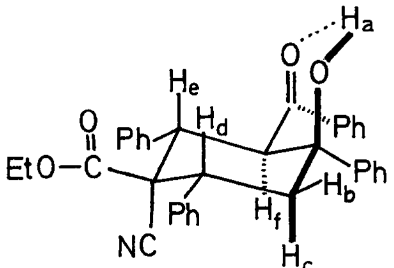
On the other hand, the ^{13}C-NMR spectrum of our compound (in DMSO-d_6 at 20 MHz) shows, besides an ethoxycarbonyl carbon at 166.80 ppm and the six aliphatic carbons of the cyclohexane ring, a characteristic singlet of the cyano carbon[5] at 116.97 ppm and a carbonyl carbon at 198.77 ppm, which is in good agreement with the reported value for a hydrogen-bonded carbonyl of an aromatic ketone[6,7].

In the ^{1}H-NMR spectrum of 2 (in deuterochloroform at 60 MHz), the ethoxycarbonyl group gives rise to a quartet (3.70 ppm) and a triplet (0.67 ppm)[8] with J=7.5 Hz and the aromatic hydrogens appear as a multiplet at 6.8-7.8 ppm. The hydroxyl group appears as a doublet (J=2 Hz) at δ_a=5.3 ppm; the CH-CH_2 moiety is a three spin AMX system corresponding to H_b, H_c and H_d at δ_b= 2.25 ppm, δ_c= 2.98 ppm and δ_d= 4.35 ppm (J_{bc}= 13 Hz, J_{bd}= 3.5 Hz, J_{cd}= 14.5 Hz and J_{ac}= 2 Hz); the CH-CH moiety appears as a two spin AB system due to H_e and H_f at δ_e=4.35 and δ_f= 4.94 ppm (J_{ef}= 12.5 Hz). The intramolecular hydrogen bonding is responsible for the rigid W geometry between H_a and H_c which makes possible the long range coupling observed between these hydrogen atoms[9].



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A closely related situation has been recently reported[10] for 3-benzoyl-2,4,6-triphenyl-4-hydroxythiane, the hydroxyl group of which is also involved in hydrogen bonding. Computer spin simulation of the ^{1}H-NMR spectrum of this compound showed the presence of long range spin coupling between the hydroxyl hydrogen and the axial methylene hydrogen, with a coupling constant of 2 Hz.

As shown in Scheme 1, the formation of cyclohexanol 2 in this reaction can be explained through a double Michael addition of ethyl cyanoacetate to two molecules of chalcone to give a bis-adduct. This 1,5-diketone undergoes an aldol-type cyclization to the cyclohexanol ring[11]. Similar reactions have been reported for the condensation of chalcones with malononitrile[11e], diethyl malonate[12] and cyanoacetamide[13].

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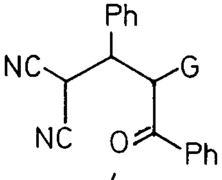
REFERENCES AND NOTES

1. E. Degny, S. Z. Zard, R. Pastor and A. Cambon, Tetrahedron Letters, 22(23), 2169 (1981).
2. L. J. Bellamy, "The Infrared Spectra of Complex Molecules", 2nd edition, Methuen & Co. Ltd. , London 1958, p. 265.
3. K. Nakanishi and P. Solomon, " Infrared Absorption Spectroscopy", 2nd edition, Holden-Day, San Francisco 1977, p. 233.
4. The unusual dehydration of 2 to a β,γ-unsaturated ketone rather than an α,β-unsaturated ketone could be accounted for by steric factors. In the α,β-unsa-

turated ketone (Dreiding models) the steric hindrance between the benzoyl group and the contiguous phenyl groups prevents the conjugation of the ethylenic double bond with either the phenyl group or the benzoyl group. However, conjugation of the double bond with the phenyl group is less hindered in the actually obtained β,γ-unsaturated compound, since the benzoyl group is now not compelled to any degree of conjugation. On the other hand, the hydrogen located in the γ position in <u>2</u> seems less hindered towards elimination than the α hydrogen.

5. E. Pretsch, T. Clerc, J. Seibl and W. Simon, "Tabellen zur Strukturaufklarung organischer Verbindungen mit spektroscopischen Methoden", Springer-Verlag, Berlin-Heildelberg-New York, 1976.
6. K.S. Dhami and J.B. Stothers, Can. J. Chem., <u>43</u>, 479 (1965)
7. E. Breitmaier and W. Voelter, "^{13}C NMR Spectroscopy", 2nd edition, Verlag-Chemie, Weinheim-New York, 1978, p. 76.
8. The equatorial position of the ethoxycarbonyl group, shielded by two phenyl groups, explains this unusually low chemical shift.
9. On addition of TFA, the hydroxyl signal dissappears from the spectrum and the Ha-Hc coupling dissappears from the multiplet at 2.98 ppm.
10. D.D. Mazza and M.G. Reinecke, J. Org. Chem., <u>46</u>, 129 (1981).
11. The alternative cyclization to structure <u>1</u> involves the nucleophilic attack of the carbonyl oxygen to the cyano group. In our previous studies on the cyclization of δ-cyanoketones to a pyran ring, we have found that this reaction requires the stabilization of the enolic form of the carbonyl group by an adequate substituent in the α position with respect to the carbonyl group. For example, with δ-cyanoketones of structure <u>4</u>, the cyclization to a pyran ring is achieved only when G=CN, CO_2Et or C_6H_5, but not when G=H as is the case of the reaction discussed in this paper.



<u>4</u>

For more details see:

a) M. Quinteiro, C. Seoane and J.L. Soto, Tetrahedron Letters, 1835 (1977)
b) M. Quinteiro, C. Seoane and J.L. Soto, J. Heterocyclic Chem. , <u>15</u>, 57 (1978)
c) M. Quinteiro, C. Seoane and J.L. Soto, Rev. Roumaine Chim., <u>24</u>, 859 (1979)
d) J.L. Soto, C. Seoane, J. A. Valdés and N. Martín, An. Quim., <u>75</u>, 152 (1979)
e) J.L. Soto, C. Seoane and J.A. Ciller, An. Quim., <u>76C</u>, 281 (1980)
f) J.L. Soto, C. Seoane, N. Martín and H. Pérez, 8th International Congress of Heterocyclic Chemistry, Graz (Austria), August 1981.
g) C. Seoane, J.L. Soto and M. Quinteiro, Heterocycles, <u>14</u>, 337 (1980)

12. A. Michael and J. Ross, J. Am. Chem. Soc., <u>55</u>, 1632 (1933)
13. J.L. Soto, C. Seoane and A.M. Mansilla, Org. Prep. and Proced., in press.

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