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METAL COMPLEXES IN ORGANIC SYNTHESIS. PREPARATION OF α-(1-ADAMANTYL)-β-DICARBONYL COMPOUNDS AND 4-(1-ADAMANTYL)-3,5-DISUBSTITUTED PYRAZOLES AND ISOXAZOLES.

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Abstract.- α-(1-Adamantyl)-β-dicarbonyl compounds are prepared by the reactions of the Co(II) complexes of β-dicarbonyl compounds with 1-bromoadamantane. This provides a route to the previously inaccessible 4-(1-adamantyl)-3,5-disubstituted pyrazoles and isoxazoles.

Introduction.-

Adamantyl substituted heterocycles have lately appeared frequently in the chemical literature (1), anticancer and antiviral properties being reported for one of them (1d). The 1-adamantyl moiety confers special and biologically interesting properties (2) to the heterocyclic molecule due to its compact structure, volume and lipophilic character.

Previously we have preliminary reported that alkylations of β-dicarbonyl compounds by activation through their cobalt(II), cobalt(III) and zinc(II) complexes offer clear advantages over the classical methods for S_N1 active halides (3,4).

It is well known that 1-halogenosubstituted bridgehead compounds like 1-bromoadamantane are very unreactive in nucleophilic substitution reactions. Different adamantyl intermediates such as ion pairs (5), radical anions (6), or simple radicals (7) have been suggested in these reactions. Although 1-bromoadamantane and 1-iodoadamantane react with nucleophiles in good yields by the $S_{RN}1$ mechanism (8), they fail to alkylate carbanionic nucleophiles such as ketone enolate anions (9). 1-Bromoadamantane α-alkylate carbonyl compounds via the corresponding silyl enol ethers in the presence of Lewis acids (10), but this procedure has not been applied to β-dicarbonyl compounds.

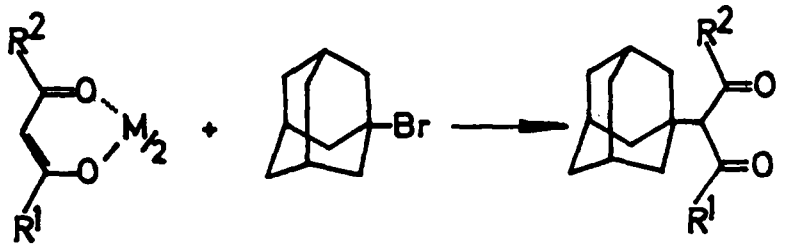
We wish to report here full details for the alkylation, in preparative useful yields, of several β-dicarbonyl compounds with 1-bromoadamantane through their Co(II) complexes. The usefulness of the obtained α-(1-adamantyl)-β-diketones, 1-5, as starting materials for 1-adamantylsubstituted heterocyclic compounds is demonstrated by the preparation of several highly crowded 4-(1-adamantyl)--3,5-disubstituted pyrazoles and isoxazoles, 6-12, accessible now through our new methodology.

Results and discussion.-

a.- Preparation of α-(1-adamantyl)-β-dicarbonyl compounds:

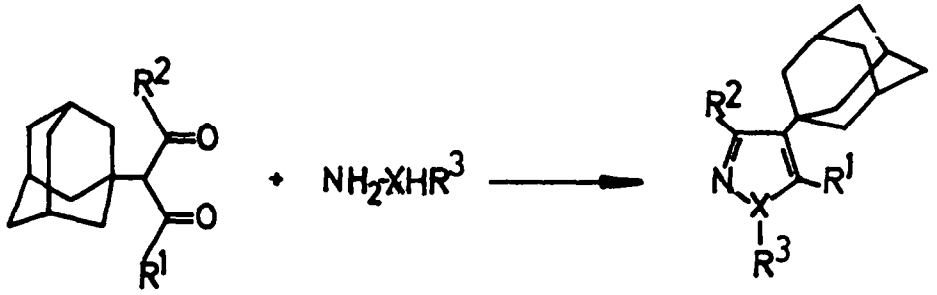
The α-(1-adamantyl)-β-dicarbonyl compounds 1-5, were prepared by reaction of the corresponding cobalt(II) β-dicarbonyl complexes with 1-bromoadamantane. The starting complexes were prepared following standard literature methods (11,12). In Table 1, the yields and physical constants of the obtained C-alkylated products are reported. The general conditions used were reflux in chlorobenzene for 24-48 h. Attempted reactions in chloroform did not work. Table 1 shows that products 1, 2 and 4 were obtained in very high yields considering the low reactivity of the alkylating agent.

Table 1. Reactions of Co(II) β-dicarbonyl complexes with 1-bromoadamantane.



	PRODUCTS				ELEMENT. ANALYS.		
	R^1	R^2	Yield	Mp°	Calc.	Found	IR C=O
1	CH_3	CH_3	81	54	C: 76.88 H: 9.46	76.55 9.76	1680(br) (KBr)
2	Ph	CH_3	89	70	C: 81.04 H: 8.16	81.07 8.32	1720, 1650 (KBr)
3	OEt	CH_3	38	oil	C: 72.69 H: 9.15	72.41 9.55	1770-1680(br) (neat)
4	Ph	Ph	80	210-1	C: 83.76 H: 7.31	83.94 7.41	1690, 1645 (KBr)
5	t-Bu	t-Bu	31	141-2	C: 79.19 H: 10.76	78.88 10.71	1710, 1670(br) (KBr)

Table 2. Preparation of five membered adamantyl substituted heterocycles



	PRODUCTS						ELEMENT. ANALYS.		U.V.
	R^1	R^2	R^3	X	Condit. (%)	Mp°	Calc.	Found	EtOH
6	CH_3	CH_3	H	N	EtOH refl., 1h. (93)	220-1	C: 78.21 H: 9.63 N: 12.16	77.89 9.82 11.99	224 (4300)
7	CH_3	Ph	H	N	EtOH refl., 1h. (92)	237-8	C: 82.15 H: 8.27 N: 9.58	82.05 8.41 9.44	230 (7900)
8	CH_3	OH	H	N	EtOH refl., 1h. (85)	294-5	C: 72.38 H: 8.68 N: 12.06	72.44 8.89 11.79	227 (4900)
9	Ph	Ph	H	N	EtOH 130°, press., 1h. (90)	250-1	C: 84.71 H: 7.39 N: 7.90	84.68 7.42 7.74	230 (13100)
10	CH_3	CH_3	Ph	N	140°, neat. 1.5h. (77)	138-9	C: 82.31 H: 8.55 N: 9.14	82.15 8.73 9.05	252 (9700)
11	Ph	Ph	Ph	N	140°, neat. 1.5h. (71)	250-1	C: 86.47 H: 7.02	86.85 6.97	250 (17100)
12	CH_3	CH_3	—	O	EtOH refl., 24h. (70)	95	C: 77.88 H: 9.15 N: 6.05	77.86 9.37 5.88	223 (3600)

The preparation of ethyl 2-(1-adamantyl)acetoacetate, 3, gave poorer results probably due to the fact that transition metal complexes of β-ketoesters are more unstable than those of β-diketones. Moreover, in the case of the product 5, strong steric hindrance is very likely to occur making this reaction more difficult.

^{1}H-NMR spectra of compounds 1-5 show only the dicarbonyl tautomers in agreement with the known fact that substitution by bulky groups in the position shifts the equilibrium towards this tautomer.

In Table 1 the infrared carbonyl absortions of products 1-5 are also reported. Two absortion bands can be clearly observed for 4 and 5, the absortion for 1 appearing as a broad band. Considering the exclusive presence of the dicarbonyl tautomer, the observation of two carbonyl bands, one of them at extraordinary low frequency, points out to some coupling or to the presence of different rotamers. Both explanations, proposed in the literature for some malonate esters (15), involve the presence of fixed conformations. We have found this phenomenon to be quite general for other heavily α-substituted pentane-2,4-diones (16), and is currently being investigated.

As previously noted, 1-bromoadamantane reacts well with nucleophiles by the $S_{RN}1$ mechanism. Even though this sort of mechanism is very unlikely in chlorobenzene (17), we have tested the effect of added galvinoxyl (powerful radical scavenger) in the reaction between cobalt(II) bis(pentane-2,4-dionato) and 1-bromoadamantane. No effect was observed suggesting that electron transfer ($S_{RN}1$) and other radical processes were not operative in our reactions (considering always that the reaction does not occur inside the solvent cage). From these data, we consider more likely a polar mechanism similar to that reported for other known reactions of cobalt(II) bis(pentano-2,4-dionato) with alkyl halides (4).

b.- Preparation of five-membered adamantyl substituted heterocycles:

The α-(1-adamantyl)-β-dicarbonyl compounds prepared were used as starting materials for a series of previously unknown 4-(1-adamantyl)-3,5-disubstituted pyrazoles. The results are summarized in Table 2. 4-(1-Adamantyl)-3,5-dimethylpyrazole, 6, 4-(1-adamantyl)-5(3)-methyl-3(5)-phenylpyrazole, 7, and 4-(1-adamantyl)-3(5)-hydroxy-5(3)-methylpyrazole, 8, were prepared from the corresponding α-(1-adamantyl)-β-dicarbonyl compounds and 80% hydrazine hydrate in refluxing ethanol. 4-(1-Adamantyl)-3,5-diphenylpyrazole, 9, needed stronger conditions and the reaction was carried out at 130° in a sealed tube. 4-(1-Adamantyl)-3,5-dimethyl-1-phenylpyrazole, 10, and 4-(1-adamantyl)-1,3,5-triphenylpyrazole, 11, were prepared from excess phenylhydrazine at 140° without solvent. The yields were good in all cases considering the steric crowding. Finally, using hydroxylamine, 4-(1-adamantyl)-3,5-dimethylisoxazole, 12, was prepared in a fair yield. Attempts to prepare 4-(1-adamantyl)--3,5-di-tert-butylpyrazole were unsuccessful in all the tested conditions, even in a sealed tube at 140-150° and buffered medium (NaAcO/AcOH). Neither the monohydrazone nor the bishydrazone could be detected, indicating that steric hindrance precluded the initial attack on the starting 5, which was always recovered unaltered.

In Table 2, the UV spectra in ethanol of all the prepared five membered heterocycles are shown. Comparison of these values with those described in the literature for other substituted pyrazoles (18) indicate that no pyrazole ring deformation exists in any case and that the phenyl groups in C-3 and C-5 are not fully conjugated with the pyrazole ring, probably due to a non planar conformation of the polycyclic system. This fact is confirmed by analysis of the ^{1}H-NMR spectra of 9 and 11. In these two products the absortion corresponding to the adamantyl protons is shifted upfield (δ 1.3-1.8) compared with those of the other products (δ 1.6-2.1), indicating that at least one of the phenyl groups at C-3 and C-5 is out of the plane of the pyrazole ring.

EXPERIMENTAL

Cobalt(II) bis(pentane-2,4-dionato) was commercially available. Cobalt(II) bis(1-phenylbutane-1,3-dionato) (11), cobalt(II) bis(1,3-diphenylpropane-1,3-dionato) (12), cobalt(II) bis(ethylacetoacetate)(13) and cobalt(II) bis(2,2,6,6-tetramethylheptane-3,5-dionato) (14) were prepared according to literature methods.

3-(1-Adamantyl)pentane-2,4-dione, 1.-
A solution of 2.00g (7.78 mmol) of cobalt(II) bis(pentane-2,4-dionato) and 3.34g (15.56 mmol) of 1-bromoadamantane in 60 ml of chlorobenzene was refluxed for 24 h. The reaction mixture was partitioned between chloroform and water. The organic layer was dried and evaporated. The resulting oil was chromatographed through a silica gel column with dichloromethane as eluent to afford 2.96g (81%) of 1, m.p. 54° (from hexane). Ir(KBr): 2900, 2840, 1680 (broad) cm^{-1}. PMR ($CDCl_3$): δ 1.5-2.1(15H), 2.13(s, 6H), 3.34(s, 1H). CMR ($CDCl_3$): δ 28.5, 37.2, 36.5, 38.2, 40.3, 78.2, 203.9. MS: m/e 234(M,6), 135(75), 92(22), 79(20), 43(100).

1-Phenyl-2-(1-adamantyl)butane-1,3-dione, 2.-
Same procedure as for 1, starting from cobalt(II) bis(1-phenylbutane-1,3-dionato). Product 2 had m.p. 70° (from hexane). Ir(KBr): 2890, 2840, 1720, 1650 cm^{-1}. PMR($CDCl_3$): δ 1.5-2.1(15H), 2.21(s, 3H), 4.38(s, 1H), 7.4-8.1(m, 5H). CMR($CDCl_3$): δ 28.7, 31.2, 36.6, 38.8, 40.6, 71.8, 92.3, 128.2, 128.6, 133.1, 138.9, 196.7, 202.9. MS: m/e 296(M,5), 135(21), 105(100), 77(69), 53(51).

Ethyl 2-(1-adamantyl)-3-oxobutanoate, 3.-
Same procedure as for 1, starting from the cobalt(II) complex of ethyl acetoacetate. Product 3 was a liquid, b.p.° 170-5 (oven temp.)/4 mmHg. Ir(film): 2900, 2840, 1770-1680(broad) cm^{-1}. PMR($CDCl_3$): δ 1.19(t, 3H), 1.5-2.1(15H), 2.15(s, 3H), 3.09(s, 1H), 4.08(q, 2H). CMR($CDCl_3$): δ 14.0, 28.5, 31.7, 36.6, 40.0, 60.5, 70.0, 168.4, 202.6. MS: m/e 264(M,7), 135(100), 91(22), 43(38).

1,3-Diphenyl-2-(1-adamantyl)propane-1,3-dione, 4.-
Same procedure as for 1, starting from the cobalt(II) complex of 1,3-diphenylpropane-1,3-dione. Product 4 had m.p. 210-1° (from methanol). Ir(KBr): 2880, 2840, 1690, 1645 cm^{-1}. PMR($CDCl_3$): δ 1.5-2.1(15H), 5.45(s, 1H), 7.3-8.1(m, 10H). CMR($CDCl_3$): δ 27.9, 36.2,37.4, 39.8, 128.0, 128.6, 133.0, 138.0, 194.6. MS: m/e 358(M,2), 105(100), 77(59).

4-(1-Adamantyl)-2,2,6,6-tetramethylheptane-3,5-dione, 5.-
Same procedure as for 1, starting from the cobalt(II) complex of 2,2,6,6-tetramethylheptane-3,5-dione. The reflux was kept in this case for 48h. Product 4 had m.p. 141-2° (from hexane). Ir(KBr): 2910, 2845, 1710, 1670 cm^{-1}. PMR($CDCl_3$): δ 1.2(s, 18H), 1.5-2.1(15H), 4.70(s, 1H). CMR($CDCl_3$): δ 27.7, 28.9, 36.5, 41.4, 44.1, 45.3, 63.4, 207.8. MS: m/e 318(M,4), 135(100), 57(46).

4-(1-Adamantyl)-3,5-dimethylpyrazole, 6.-
A mixture of 0.35g (1.30 mmol) of 1, 6 ml of ethanol and 1 ml of 80% hydrazine hydrate was kept at room temperature for 15 minutes and then refluxed for 1 hour; it was finally left overnight and poured over 50 ml of brine. The mixture was extracted with dichloromethane. The organic solution was washed, dried and evaporated, and the residue was recrystallized from chloroform-hexane to afford 0.32g (92%) of 6, m.p. 220-1°. Ir(KBr): 3500-2500(broad), 2900, 2840 cm^{-1}. PMR($CDCl_3$): δ 1.6-2.1(15H), 2.37(s, 6H). MS: m/e 231(M+1,6), 230(M,48), 173(100), 41(22).

4-(1-Adamantyl)-3(5)-methyl-5(3)-phenylpyrazole, 7.-
Same procedure as for 6, starting from 2. Product 7 had m.p. 237-8° (from chloroform-hexane). Ir(KBr): 3300-2500(broad) ,2900, 2840 cm^{-1}. PMR($CDCl_3$): δ 1.5-2.1(15H), 2.37(s, 3H), 7.30(s, 5H). MS: m/e 293(M+1,21), 292(M,70), 236(20), 235(100), 135(26), 77(31).

4-(1-Adamantyl)-3(5)-hydroxy-5(3)-methylpyrazole, 8.-
Same procedure as for 6, starting from 3. Product 8 had m.p. 294-5° (from ethanol). Ir(KBr): 3360, 3200-2400(broad), 2900, 2840 cm^{-1}. PMR(DMSO-d_6): δ 1.5-2.1(15H), 2.18(s, 3H), 3.29(broad s, 2H). MS: m/e 233(M+1,10), 232(M,35), 175(100), 135(88), 93(25), 91(24), 79(32), 77(22), 41(34).

4-(1-Adamantyl)-3,5-diphenylpyrazole, 9.-
A mixture of 0.358g (1.0 mmol) of 4, 2 ml of 80% hydrazine hydrate and 10 ml of ethanol was kept at 130° for 17 hours in a sealed tube. On cooling, a white solid separated which was characterized as 9, m.p. 250-1° (from chloroform-hexane). Ir(KBr): 3500-2600(broad), 2880, 2830 cm^{-1}. CMR(DMSO-d_6) δ :1.27-1.80(15H), 7.4(s, 10H). MS: m/e 355(M+1,26), 354(M,92), 298(28), 297(100), 77(32), 41(23).

4-(1-Adamantyl)-3,5-dimethyl-1-phenylpyrazole, 10.-
To a solution of 0.35g (1.5 mmol) of 1 in 10 ml of chloroform, 0.162g (1.5 mmol) of freshly distilled phenylhydrazine were added. The solvent was completely evaporated and the oily residue was heated at 140° for 1.5 hours. The residue was then chromatographed through a silica gel column with dichloromethane. After recrystallization from ethanol-water, 0.354g (77%) of 10 were obtained exhibiting m.p. 138-9°. Ir(KBr): 2890, 2830 cm^{-1}. PMR($CDCl_3$): δ 1.6-2.2(15H), 2.35(s, 3H), 2.45(s, 3H), 7.38(s, 5H). MS: m/e 307(M+1,17), 306(M,67), 252(22), 249(100), 212(20), 77(31).

4-(1-Adamantyl)-1,3,5-triphenylpyrazole, 11.-
Same procedure as for 10, starting from 4. Product 11 had m.p. 250-1° (from ethanol-water). Ir(KBr): 2890, 2840 cm^{-1}. PMR($CDCl_3$): δ 1.3-1.9(15H), 7.00-7.66(15H). MS: m/e 431(M+1,40), 430(M,98), 373(100), 87(44).

4-(1-Adamantyl)-3,5-dimethylisoxazole, 12.-
A solution of 0.35g (1.5 mmol) of 1, 0.11g (1.58 mmol) of hydroxylamine hydrochloride and 70mg (1.75 mmol) of NaOH in 8 ml of ethanol and 1 ml of water was heated at reflux for 2 hours. This solution was then poured into 50 ml of brine and extracted with dichloromethane. The organic layer was washed, dried and evaporated. The solid residue was recrystallized from hexane to afford 0.24g (70%) of 12, m.p. 95°. Ir(KBr): 2890, 2830 cm^{-1}. PMR($CDCl_3$): 1.5-2.2(15H), 2.37(s, 3H), 2.46(s, 3H). MS: m/e 231(M,46), 174(46), 133(25), 105(55), 91(26), 79(44), 77(46), 65(23), 55(21), 43(100), 41(35).

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