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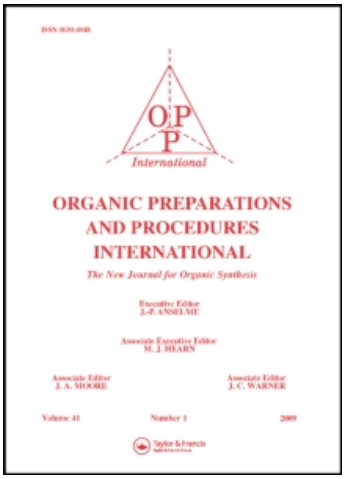

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REGIOSELECTIVE FORMATION OF β-KETOAMIDES IN THE DIBENZOCYCLOOCTANE FAMILY

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REGIOSELECTIVE FORMATION OF β-KETOAMIDES IN THE DIBENZOCYCLOOCTANE FAMILY

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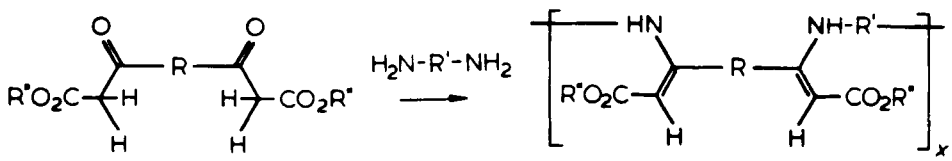
In previous work[1-5] dealing with the formation of poly(enaminoesters) by reaction of diamines with bis-β-ketoesters it was generally found that reaction occurred regioselectively at the carbonyl group of the ketone and not at the ester carbonyl group.



When we attempted to generalize this polymerization process to new monomer types such as dibenzo(a,e)cycloocten-6,12-bis(carbomethoxy)-5,11-dione (1), no poly(enaminoesters) were obtained, rather polyamides were formed.[6] To better understand these polymeric systems, we investigated the chemistry of appropriate model compounds which could not yield polymers and would therefore be readily characterized. When 11,12-dihydrodibenzo(a,e)cycloocten-6-(carbomethoxy)-5-one (3) was studied, attack by the amines used occurred only at the ester carbonyl group to give good to excellent yields of the corresponding β-ketoamides, (Fig 2, Table 1).

The high yields of β-ketoamides observed are in contrast to the behavior observed in previous work[1-5] which showed that aliphatic amines react very easily with β-ketoesters to form enaminoesters, even in the

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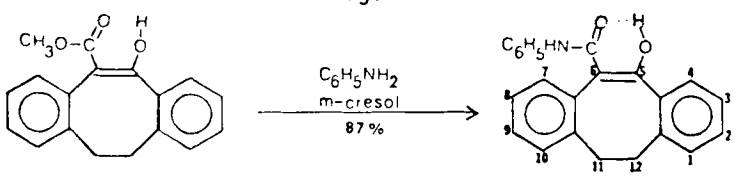
1 2

Fig. 1



3 4

Fig. 2

absence of an acid catalyst. The ketone carbonyl (or enol) groups in 1 and 3 may be sterically hindered to nucleophiles by the peri hydrogen atoms of the fused benzene rings and the transannular bridge. It is interesting to note that the β-ketoamides in Table 1 are all completely enolized as were the starting ketoesters. This result may be caused by a bulky group effect. This idea agrees with the results of Hufker[7] which show that there is a general increase in enol content as branching of the terminal alkyl groups adjacent to the ketone carbonyl group increases.

EXPERIMENTAL SECTION

All melting points are uncorrected and were determined in capillary tubes with a Hoover-Thomas Unimelt apparatus. Nuclear magnetic resonance (NMR) spectra were obtained on Varian T-60 and CFT-20 Spectrometers and are reported in δ units using tetramethylsilane as an internal standard. Infrared spectra (IR) were recorded on a Perkin-Elmer model 521 Spectrophotometer with the following band intensity notations being used: vs = very strong, s = strong, m = medium and w = weak, for known compounds only characteristic bands are given. Ultraviolet spectra (UV) were recorded on a Cary 14 spectrophotometer. Mass spectra were taken on a CEC 21-104 mass spectrometer operating at 70 ev and are reported as m/e with relative intensity (percent of base peak) in parentheses. Microanalyses were performed by Galbraith Laboratories, Knoxville, Tenn. Gas chromatography-mass spectral data (GC-mass spec) was obtained on a Varian MAT 111 instrument using an electron impact detector. A 10 foot glass column (2 mm I.D.) packed with OV-17 on 100-120 mesh Gas Chrom Q was used. The instrument was programmed from 30° to 300° at 20°/min using helium as the carrier gas. Thin layer chromatography (TLC)

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Table I. Physical Properties of N-Substituted β-Ketoamides from 3

R of RNH_2	Yield (%)	(°C) m.p.	^{13}C NMR[a] ($CDCl_3$)	λ max (log ε)	^{1}H NMR[b] $CDCl_3$	IR(KBr)[c]
			171.74			3334s
C_6H_{13}-	92	121-122	170.21	272	15.79	1615s
			104.69	(4.08)		1533s
			172.17			3320
$-CH_2CH_2CH_2-$	95	257-259	170.29	273	15.36	1610
			104.71	(4.37)	(2H)	1520
			172.28			3395
C_6H_5-	87	163-164	170.18	295	15.57	1615
			105.25	(4.20)	(1H)	1520
			172.20			3385
$-C_6H_4$-(p)	65	238-240	170.00	320	15.55	1615
			105.15	(3.53)	(2H)	1533
			172.49			3395
$-C_6H_4$-(m)	73	145-148	170.19	300	15.46	1618
			105.16	(4.50)	(2H)	1520

a)Amide carbonyl, C-5 and C-6 respectively. b)Chemical shift of chelated proton c)Amide NH, carbonyl group and aromatic unsaturation, respectively.

analyses were obtained using 50 mm x 100 mm silica gel coated glass slides which were purchased from VWR Scientific, Rochester, NY. The developed TLC plates were visualized with a USVL25 Mineralight® emitting short or long wavelength ultraviolet light (Ultraviolet Products, San Gabriel, California).

Extractions were usually completed by washing finally with a saturated sodium chloride solution, drying over anhydrous magnesium sulfate followed by vacuum filtration and evaporation of solvent under vacuum on a rotary evaporator at room temperature up to 100°.

Magnesium Methyl Carbonate Solution.-A stock solution of magnesium methyl carbonate (MMC) was prepared according to the procedure of Finkbeiner and Stiles.[8] The final solution of MMC in N,N-dimethylformamide was filtered under N_2 through Celite®. The solution was placed in 100 mL bottles, sealed with Parafilm® and stored in a refrigerator. The concentration was determined by decomposing 1 ml of the of the solution with 100 mL of standard 0.10 N HCl solution and the unreacted HCl was titrated with standard 0.10 N NaOH solution. The

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solutions so prepared were found to be approximately 5.0 molar in magnesium methyl carbonate.

Dibenzo(a,e)cycloocten-6-carboxy-5-(11H, 12H)-one.-To a 100 mL three-necked flask equipped with a mechanical stirrer and a condenser was added 1.10 g (5.0 mmol) of 11,12-dihydro-dibenzo(a,e)cycloocten-5-(6H)-one[9] and 4.0 mL of dry N,N-dimethylformamide. To this solution was added 40 mL of magnesium methyl carbonate solution (6.56 M). This clear solution was heated in an oil bath at 120° for one hour under an atmosphere of dry nitrogen. Samples analyzed by TLC on silica gel (CH_2Cl_2) at 0.5 hr and 1.0 hr showed the reaction to be completed.

Concentrated HCl (100 mL) and enough ice to bring the level to the one liter mark were added to a 2L beaker. To this mixture was added 200 mL of diethyl ether with vigorous stirring. The reaction mixture was cooled to room temperature and poured slowly into a vigorously stirred mixture of ice-HCl-diethyl ether. The solution in the beaker was poured into a separatory funnel, the ethereal layer was separated and the aqueous layer was washed once with 100 mL of diethyl ether. The ether layers were combined, returned to the separatory funnel and washed with a saturated NaCl solution until the aqueous phase was neutral to litmus paper. The ether solution was then dried ($MgSO_4$) and concentrated under vacuum while being cooled in an ice bath. The recovered solid weighed 1.21 g (91.8%), mp. 134° (dec.). TLC analysis on silica gel showed one spot when developed with CH_2Cl_2 (R_f = 0) and with MeOH (R_f = 0.77). Attempted recrystallization of the solid from EtOH gave one spot by TLC (CH_2Cl_2, R_f = 0.63 which was shown to be identical to the starting ketone. Spectral analysis of the solid isolated above showed it to be the desired compound.

^1H NMR (Acetone d_6): δ 2.33-3.33 (m, 4H, $ArCH_2CH_2$), 6.42-7.17 (m, 8H,

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ArH). The solid was treated with N,O-bis(trimethylsilyl)acetamide and the resulting solution, analyzed by GC-MS, showed four peaks: 11,12-dihydro-5-(trimethylsiloxy)-dibenzo(a,e)cyclooctene, mass spectrum m/e (rel. intensity): 294 (M^+, 12), 203 (10), 75 (31), 73 (100, Me_3Si), 45 (32); 11,12-dihydro-dibenzo(a,e)cycloocten-5(6H)-one, 222 (M^+, 100), 194 (40), 193 (42), 179 (40), 178 (45), 130 (49), 118 (38), 92 (51), 91 (50), 89 (88); 11,12-dihydro-dibenzo(a,e)-6-(trimethylilyvstnocy)-cycloocten-5-one, 222 (55), 194 (24), 193 (30), 179 (39), 178 (38), 92 (32), 90 (37), 89 (36), 73 (72, Me_3Si), 55 (39), 28 (100); and 11,12-di-11,12-dihydro-5-(trimethylsiloxy)-6-(trimethylsiylcarboxy) dibenzo(a,e) cyclooctene 410 (M^+, 4), 395 (17), 320 (20), 147 (55), 75 (14), 73 (100, Me_3Si), 45 (14).

11,12-Dihydro-dibenzo(a,e)cycloocten-6-(carbomethoxy)-5-one.- Diazomethane was prepared in special glassware with polished connections obtained from Aldrich Chemical Co. using sufficient N-methyl-N-nitroso-p-toluenesulfonamide (Diazald®) to generate ~ 48 mmols. Ethereal diazomethane was codistilled into a flask containing 8.8 g (33 mmols) of dibenzo(a,e)cycloocten-6-carboxy-5-(11H,12H)-one as a slurry in 200 mL of diethyl ether. The acid dissolved as it reacted. A permanent pale yellow color caused by excess CH_2N_2 was taken as an indication that the reaction had been completed. The solution was partially evaporated in the hood (CAUTION!) to remove excess diazomethane, and to cause precipitation of 8.8 g (95%) of a white solid, mp. 116-119° (dec).

^1H NMR($CDCl_3$): δ 2.90-3.34 (m, 4H, $ArCH_2CH_2Ar$), 3.88 (s, 3H, OCH_3), 7.20-7.67 (m, 8H, Ar-H), 13.80 (s, 1H, chelated OH); ^{13}C NMR($CDCl_3$): 173.01 (ester C=O), 172.52 (C=C-OH chelated), 139.79, 137.61, 135.31, 131.06, 129.59, 129.25, 128.88, 127.14, 125.58, 125.19 (aromatic),

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103.83 (C=C-CO_2CH_3), 51.68 (OCH_3), 33.83 and 32.53 ppm ($ArCH_2CH_2Ar$); UV max (MeOH): 271 nm (ε 8454); mass spectrum m/e (rel. intensity): 280 (M^+, 23), 248 (loss of CH_3OH, 25), 222 ($C_{16}H_{14}O$, 100), 194 (33), 193 (42), 179 (44), 178 (51), 91 (74), 90 (54).

Anal. Calcd for $C_{18}H_{16}O_3$: C, 77.14; H, 5.71. Found: C, 77.16; H, 5.80

11,12-Dihydro-5-hydroxy-6-(n-hexylcarbamoyl)-dibenzo(a,e)cyclooctene.- To a 100 mL reaction flask equipped with a mechanical stirrer, condenser, and dropping funnel was added a mixture of 1.4 g (5 mmols) of β-ketoester 3 in 10 g of m-cresol. From the dropping funnel was added a solution of 1.06 g (10.5 mmols) n-hexylamine in 5g of m-cresol. The reaction flask was immersed in an oil bath at 60°. Addition of the amine solution was carried out under a N_2 atmosphere and the resulting solution was heated at 60° for 2 hr. A distillation condenser was attached and the reaction mixture was heated to 150° while N_2 was passed over the mixture to assist in removal of the solvent. The residue obtained after the solvent was removed was dissolved in 3 mL of N-methylpyrrolidone and poured, with stirring, into 100 mL of water acidified with 1 mL of concentrated HCl. The milky solution was extracted with diethyl ether. The ether layer was washed with a saturated NaCl solution, dried ($MgSO_4$) and concentrated. Recrystallization from hexane gave 1.6 g (92%) of product, mp. 121-122°C; IR (KBr): 3334s (NH), 1615s (amide I), 1590s, 1533s (amide II) and 1275s cm^{-1} (amide III); UV λmax (MeOH): 272 nm (ε 12,022);

^1H NMR ($CDCl_3$): δ 0.7-1.83 (m, 11H, C_5H_{11}), 2.80-3.90 (m, 6H, $ArCH_2CH_2Ar$ and CH_2NH), 5.60 (broad, 1H, NH), 7.17-7.83 (ArH), 15.79 (s, 1H, chelated OH); ^{13}C NMR ($CDCl_3$): 171.74 (amide C=O), 170.21 (C-5), 141.80, 137.50, 136.47 and 134.73 (c-12a, C-4a, C-6a, C-10a), 130.60, 130.03, 129.81, 129.07, 128.07, 127.64, 126.33, 126.89, 104.69 (C-6), 39.35

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(hexyl C-10, 34.09 and 32.86 (C-11, C-12), 31.36 (hexyl C-2), 29.44 (hexyl C-3), 26.47 (hexyl C-4), 22.51 (hexyl C-5) and 13.93 ppm (hexyl C-6); mass spectrum m/e (rel. intensity): 349 (M^+, 36), 248 ($C_{17}H_{12}O_2$, M^+-$C_6H_{13}NH_2$, 100), 220 ($C_{16}H_{12}O$, 60), 204 (52), 191 (36), 115 (10), 102 (13), 91 (10), 43 (16) and 30 (83).

Anal. Calcd. for $C_{23}H_{27}NO_2$: C, 79.08; H, 7.74; N, 4.01. Found: C, 79.11; H, 8.12; N, 4.00

Bis(11,12-dihydro-5-hydroxydibenzo(a,e)cyclooctenyl-6)-1,3-propylenedicarbamide.

The β-ketoester[9] (1.4 g, 5.0 mmols) was reacted with 1,3-propanediamine (0.194 g, 2.5 mmols) in the same manner as given above. To be assured that all of the propanediamine had reacted, the reaction mixture was heated at 130° for one hour prior to purging with N_2 at 150°. The white solid was dissolved in N-methylpyrrolidone and poured into 100 mL of 0.1 N HCL. The solid was washed with ethanol and air-dried. After drying in a vacuum oven at 80°, 1.36 g (95%) of product as a white solid was obtained: mp. 257-259°C. IR (KBr): 3415w, 3320s (NH), 1610s (amide I), 1590s, 1520s (amide II), 1285s cm^{-1} (amide III); UV max (MeOH): 273 nm (ε 23,442); ^1H NMR ($CDCl_3$): δ 1.53-1.87 (m, 2H, $CH_2\underline{CH_2}CH_2$) 2.87-3.87 (m, 12H, $Ar\underline{CH_2}\underline{CH_2}Ar$ and $\underline{CH_2}NH$), 6.15 (broad, 2H, $\underline{NH}$), 7.20-7.73 (m, 16H, $Ar\underline{H}$), and 15.36 (s, 2H, chelated $O\underline{H}$); ^{13}C NMR ($CDCl_3$): 172.17 (amide C=O), 170.29 (C-5), 141.68 (C-4a), 137.55 (C-12a), 136.38 (C-6a), 134.49 (C-10a), 130.78, 129.91, 128.25, 127.59, 126.48, 125.92, 104.71 (C-6), 35.38 ($\underline{C}H_2NH$), 34.13, 32.89 (C-11, C-12), and 29.77 ppm ($CH_2\underline{C}H_2CH_2$); mass spectrum m/e (rel. intensity): 248 ($C_{17}H_{12}O_2$, M^+-$C_3H_{10}N_2$, 12), 129 (12), 111 (14), 97 (21), 85 (23), 83 (29), 71 (35), 69 (44), 57 (60), 55 (50), 44 (54), 43 (58), 40 (100), 32 (18) and 14 (17).

Anal. Calcd. for $C_{37}H_{34}O_4N_2$: C, 77.89; H, 5.96; N, 4.98. Found: C,

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77.68; H, 6.12; N, 5.16

Bis(11,12-dihydro-5-hydroxy-dibenzo(a,e)cyclooctenyl-6-1,4-phenylenedicarbamide.-The β-ketoester[9] (1.4 g, 5.0 mmols) was reacted with 1,4-phenylenediamine (0.283 g, 2.5 mmols) in the same manner given above. The solid residue remaining in the reaction flask was insoluble in 5 mL of N-methylpyrrolidone. The slurry was poured into water, filtered, and the solid was washed extensively with water. Recrystallization from EtOH gave 0.92 g (65%) of product which gave one spot by TLC on silica gel (R_f = 0.23) when developed with CH_2Cl_2, mp. 238-240°. IR (KBr): 3385s (NH), 1615s (amide I), 1587m, 1533s (amide II), 1506s and 1215m (amide III); UV λmax (MeOH): 320nm (ε 3,388); ^1H NMR ($CDCl_3$): δ 2.85 (m, 8H, $ArCH_2CH_2Ar$), 7.32-7.95 (m, 20H, ArH), and 15.55 (s, 2H, chelated OH); ^{13}C NMR ($CDCl_3$): 172.20 (amide C=O), 170.00 (C-5), 142.02 (C-1, C-4 of phenylene), 137.53, 136.26, 134.16, 133.73 (C-12a, C-4a, C-6a, C-10a), 130.65, 130.35, 129.90, 129.39, 128.66, 127.60, 126.73, 126.01, 120.88 (C-2, C-3, C-5, C-6 of phenylene), 105.15 (C-6), 34.01 and 32.93 ppm (C-11, C-12); mass spectrum m/e (rel. intensity): 248 ($C_{17}H_{12}O_2$, M^+-$C_6H_8N_2$, 1%), 220 (0.8), 97 (14), 94 (100), 85 (11), 83 (15), 71 (18), 69 (22), 57 (40), 55 (28), 43 (34), 41 (19) and 32 (14).
Anal. Calcd. for $C_{40}H_{32}O_4N_2$: C, 79.47; H, 5.30; N, 4.64. Found: C, 79.70; H, 5.30, N, 4.40

Bis(11,12-dihydro-5-hydroxydibenzo(a,e)cyclooctenyl-6)-1,3-phenylenedicarbamide.-The β-ketoester[9] (1.4 g, 5.0 mmols) was reacted with m-phenylenediamine (0.283 g, 2.5 mmols) in the same manner as given above. The solid obtained was dissolved in N-methylpyrrolidone (5 mL) and poured into 100 mL of 0.1 N HCl. The resulting precipitate was collected by filtration and air-dried. Recrystallization from 95% ethanol gave 1.10 g of product (73%), a yellow solid, mp. 145-148°.

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IR (KBr): 3395s (NH), 1618s (amide I), 1520s (amide II) and 1223 cm^{-1} (amide III); UV λmax (MeOH): 300 nm (ε 31,622) ^1H NMR($CDCl_3$): δ 2.99-3.78 (m, 8H, $ArCH_2CH_2Ar$), 7.28-7.72 (m, 20H, ArH) and 15.46 (s, 2H, chelated OH); ^{13}C NMR($CDCl_3$): 172.49 (amide C=O), 170.19 (C-5), 141.98 (C-1, C-3 of phenylene), 137.73, 137.56, 136.25, 134.05 (C-a, C-b, C-e, C-f), 130.68, 130.40, 129.87, 129.41, 128.73, 127.69, 127.56, 126.96, 126.77, 126.01, 116.68 (C-4, C-6 of phenylene), 112.50 (C-2 of phenylene), 105.16 (C-6), 33.97 and 32.94 ppm (C-11, C-12); mass spectrum m/e (rel. intensity): 248 ($C_{17}H_{12}O_2$, M^+-$C_6H_8N_2$, 45), 220 (28), 204 ($C_{16}H_{12}$, 22), 191 (35), 164 (11), 108 (33), 81 (15), 55 (15), 44 (19) and 28 (100). Anal. Calcd. for $C_{40}H_{32}O_4N_2$: C, 79.47; H, 5.30; N, 4.64. Found: C, 79.51; H, 5.43; N, 4.47

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