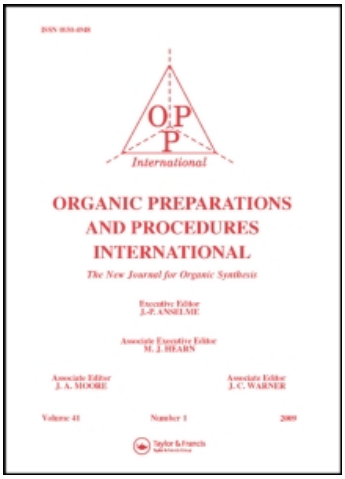

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NEW CONDENSATION PRODUCTS OF DIAMINES WITH 3-UREIDOMETHYLENECOUMARIN

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NEW CONDENSATION PRODUCTS OF DIAMINES WITH 3-UREIDOMETHYLENECOUMARIN

Submitted by (02/14/94)

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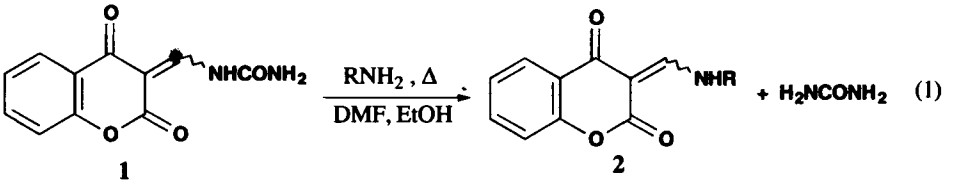
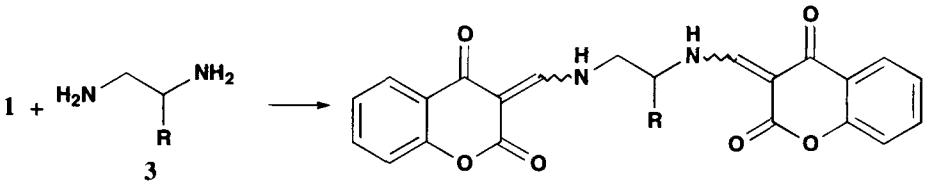
A recent publication described the facile synthesis of N-(methylene-4-oxocoumarinyl)-amines (**2**) by reaction of 3-ureidomethylenecoumarin (**1**) with a variety of substituted amines to afford a single product in good yield.[1]



The possibility that diamines might react further intermolecularly or intramolecularly [2] at either of the two carbonyl groups, prompted us to examine the interaction of diamines with **1**.

The reactions of equimolar amounts of **1** and **3** were carried out at reflux in DMF-ethanol for 3 hrs. With 1,2-diaminoethane and 1,2-diaminopropane (**3a** and **3b**), thin layer chromatography showed the formation of a single product in both cases. Their ^{1}H NMR spectra showed the presence of two

doublets of the same intensity at δ 10-12, corresponding to two exchangeable protons, the ethylenic protons of the Z- and E-isomers[3] as two doublets at δ 8-9 and signals corresponding to the expected Ar, CH_2, CH, CH_3 protons.



(2)

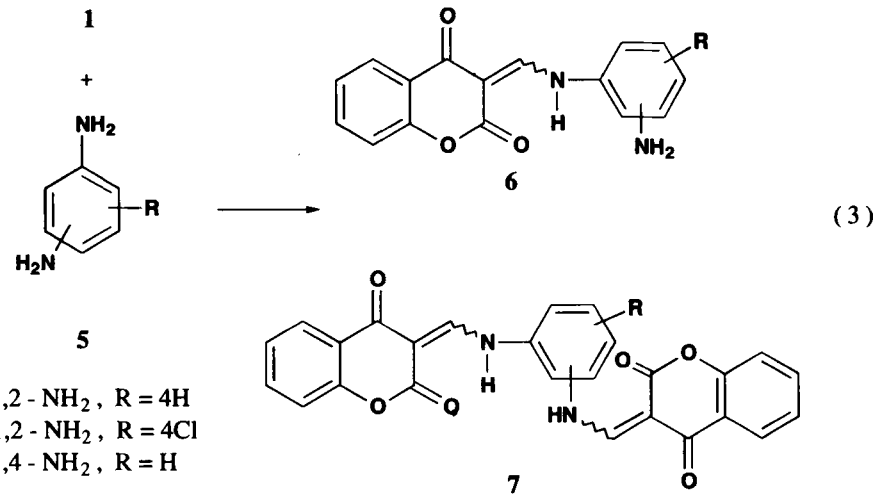
These observations indicated that an intermolecular double condensation to a *bis* N-(methylene-4-oxocoumarinyl)-1,2-diaminoalkanes (**4**) had occured. Mass spectrometry and elemental analyses provided further support. With 1,2-phenylenediamine (**5a**), **1** gave a single product. Its ^1H NMR spectrum showed two doublets at δ 8.84 and 8.95 corresponding to the ethylenic protons of the Z and E isomers, a multiplet between δ 6.90-7.31 (aromatic protons) and a singlet at δ 3.8 due to the NH_2 group (disappearance on addition of D_2O).

TABLE 1. Condensation of **1** with Diamines

Diamines	Ratio **1** to diamine	Products	mp. (°C)	Solvent	Yield (%)
3a	1:1	**4a**	340 (dec)	DMF/MeOH	45
3b	1:1	**4b**	278	DMF/MeOH	45
	2:1	**4b**			80
5a	1:1	**6a**	205 (**6a**)	$CHCl_3$/Hexane	75
	2:1	**6a+7a** (50/50)	310 (**7a**)	DMF/MeOH (**7a**)	70
5b	1:1	**6b**	248	DMF/EtOH	90
5c	1:1	**6c+7c** (70/30)	300 (**6c**, dec)		70
5c	2:1	**7c**	340 (dec)		95

This spectrum was consistent with the single condensation product N-(methylene-4-oxocoumarinyl)-1,2-phenylenediamine (**6a**); this assignment was also supported by MS and elemental analysis.

The same reaction with two equivalents of **1** led to a mixture of two compounds (**6a** and **7a**) which was separated on the basis of their different solubility in the reaction mixture. With equimolar quantities of 1,4-phenylenediamine, **1** afforded two products (**6c** and **7c**). With two equivalents of **1** and one of diamine, only the double condensation product (**7c**) was formed in almost quantitative yield (95%). This difference in reactivity of the 1, 2 and 1,4-phenylenediamines may be accounted for by the relative positions of the two amino groups on the aromatic ring, when a second molecule of **1** was reacted with the monocondensation product.

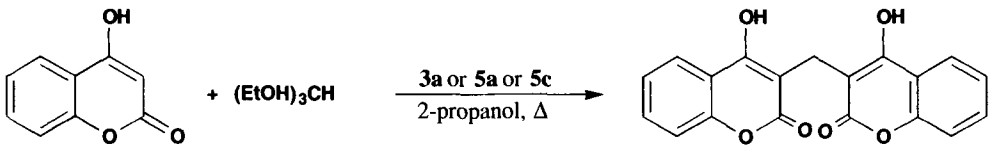


(3)

TABLE 2. Elemental Analyses and ^{1}H NMR Spectra of Products

Products	Elemental Analysis (Found)			^{1}H NMR (δ)
	C	H	N	
4a	65.05 (65.35)	3.95 (3.96)	6.85 (6.93)	3.92 (m, 4H, CH_2), 7.23-7.94 (m, 8H, Ar), 8.46-8.5 (dd, 1H, CH, Z and E), 10.38 (m, 1H, NH, Z and E) 11.58 (m, 1H, NH, Z and E)
4b	65.83 (66.02)	4.19 (4.30)	6.52 (6.70)	1.32 (d, 3H, CH_3), 3.9 (m, 2H, CH_2), 4.21 (m, 1H, CH), 7.17-7.93 (m, 8H, Ar), 8.44 (m, 2H, CH), 10.31-11.54 (m, 2H, NH)
6a	68.39 (68.57)	4.21 (4.28)	9.82 (10.00)	3.8 (s, 2H, NH_2), 6.65-7.31 (m, 4H, Ar), 7.49-8.11 (m, 4H, Ar), 8.83-8.94 (d, 1H, CH, Z and E) 13.79-14.05 (d, 1H, NH, Z and E)
7a	68.74 (69.02)	3.65 (3.53)	6.15 (6.19)	7.27-7.80 (m, 8H, Ar), 7.47-8.0 (m, 4H, Ar), 11.97-13.3 (s, 1H, 2NH)
6b	61.09 (61.04)	3.39 (3.49)	8.84 (8.90)	5.62 (s, 2H, NH_2), 6.73-8.02 (m, 7H, Ar), 8.66- 8.75 (dd, 1H, CH, Z and E), 11.55-13.35 (dd, 1H, NH, Z and E)
6c	68.31 (68.57)	4.13 (4.28)	9.75 (10.00)	3.86 (s, 2H, NH_2), 6.70-7.18 (m, 4H, Ar), 8.75-8.90 (dd, 1H, CH, Z and E), 11.97-13.74 (dd, 1H, NH, Z and E)
7c	68.89 (69.02)	3.42 (3.53)	6.09 (6.19)	7.31-8.00 (m, 12H, Ar), 8.67 (d, 2H, CH), 11.95 and 13.28 (s, 1H, 2NH)

The results of the addition of diamines in molar equivalents to 3-ureidomethylenecoumarin were thus found to depend on the nature of the diamine. We did not observe any heterocyclic compounds resulting from the further intramolecular nucleophilic attack in the single condensation product. Attempts to prepare compounds **4a**, **6**, and **7** by condensation of 4-hydroxycoumarin and diamines **3a**, **5a** and **5c** in the presence of excess of ethyl orthoformate were not useful. Only poor yields (20-25%) of **4a** and inseparable mixtures of **6a** and **7a** and of **6c** and **7c** were formed. The major product (75-80%) of these reactions was identified as dicoumarol (**8**)[4], identical in all respect (mp., sm and ^{1}H NMR) with an authentic sample[4]. In the absence of diamine, only a 5% yield of **8** was formed, the major product being unreacted 4-hydroxycoumarin. The mode of formation of **8** is not immediately evident as a reduction step must obviously be involved.



8

Since the condensation reaction of 3-ureidomethylenecoumarin with aromatic and aliphatic diamines is the only route to these new coumarinic compounds, it represents a useful synthetic method. The reactivity of the compound **6** is currently under investigation.

EXPERIMENTAL SECTION

Melting points were determined on an Electrothermal apparatus. The PMR spectra were recorded on a Bruker AC80 or 300WB spectrometer and the mass spectra were recorded on a Nermag R 1010 instrument. Elemental analysis were carried out at the Inter-University Microanalysis Center in Toulouse.

Reaction of Diamines with 3-Ureidomethylenecoumarin.- A solution of 3-ureidomethylenecoumarin **1** [5] (1g:4.4 mmoles) and diamine **3** or **5** (1 or 2 equivalents) in a mixture of DMF (20 mL) and absolute ethanol (30mL) was heated at reflux for 3 hrs with stirring. The progress of the reaction was monitored by thin layer chromatography (eluent dichloromethane/methanol, 10/1 v/v on silica gel 60 F_{254}). The precipitate formed (upon cooling to room temperature or after evaporation of solvents) was washed with methanol and recrystallized.

***bis*-[N-(Methylene-4-oxocoumarinyl)]-1,2-diaminoethane (4a)**, mp. 340° (dec., DMF/methanol); ^{1}H NMR (DMSO-d_6): δ 3.92 (m, 4H, CH_2), 7.23-7.94 (m, 8H, Ar), 8.46 and 8.5 (dd, 1H, CH, Z and E), 10.38 (m, 1H, NH, Z and E), 11.58 (m, 1H, NH, Z and E);

Anal. Calcd. for $C_{22}H_{16}N_2O_6$: C, 65.35; H, 3.96; N, 6.93. Found: C, 65.05; H, 3.95; N, 6.85

***bis*-[N-(Methylene-4-oxocoumarinyl)]-1,2-diaminopropane (4b)**, mp. 278° (DMF/methanol); ^{1}H NMR (DMSO-d_6): δ 1.32 (d, 3H, CH_3), 3.9 (m, 2H, CH_2), 4.21 (m, 1H, CH), 7.17-7.93 (m, 8H, Ar), 8.44 (m, 2H, CH), 10.31 and 11.54 (m, 2H, NH); MS m/z (relative abundance):418 (M^+, 2), 391 (3),

361 (1) 275 (9), 247 (100), 121 (3), 120 (4), 85 (29);

Anal. Calcd. for $C_{23}H_{18}N_2O_6$: C, 66.02; H, 4.30; N, 6.70. Found: C, 65.83; H, 4, 19; N, 6.52

N-(Methylene-4-oxocoumarinyl)-1,2-phenylenediamine (6a), mp. 205° (chloroform/hexane); ^{1}H NMR ($CDCl_3$): δ 3.8 (s, 2H, NH_2), 6.65-7.31 (m, 4H, Ar), 7.49-8.11 (m, 4H, Ar), 8.83-8.94 (d, 1H, CH, Z and E), 13.79-14.05 (d, 1H, NH, Z and E); MS m/z (relative abundance): 280 (M^+, 39), 279 (43), 121 (39), 120 (17), 93 (23), 92 (83), 85 (21), 83 (32), 65 (100);

Anal. Calcd. for $C_{16}H_{12}N_2O_3$: C, 68.57; H, 4.28; N, 10.00. Found: C, 68.39; H, 4.21; N, 9.82

***bis*-[N-(Methylene-4-oxocoumarinyl)]-1,2-phenylenediamine (7a)**, mp. 310° (DMF/methanol); ^{1}H NMR (DMSO-d_6): δ 7.27-7.80 (m, 8H, Ar), 7.47-8.0 (m, 4H, Ar), 11.97-13.3 (s, 1H, 2NH); MS m/z (relative abundance): 452 (M^+, 48), 121 (34), 93 (11), 92 (57), 65 (100), 43 (83);

Anal. Calcd. for $C_{26}H_{16}N_2O_6$: C, 69.02; H, 3.53; N, 6.19. Found: C, 68.74; H, 3.65; N, 6.15

N-(Methylene-4-oxocoumarinyl)-4-chloro-1,2-phenylenediamine (6b), mp.248° (DMF/ethanol); ^{1}H NMR (DMSO-d_6): δ 5.62 (s, 2H, NH_2), 6.73-8.02 (m, 7H, Ar), 8.66-8.75 (dd, 1H, CH, Z and E), 11.55-13.35 (dd, 1H, NH, Z and E); MS m/z (relative abundance): 316 (27), 314 (M^+, 78), 313 (M^+-1, 100), 269 (10), 193 (18), 153 (75), 121 (47), 93 (25), 92 (42), 83 (5), 65 (53);

Anal. Calcd. for $C_{16}H_{11}ClN_2O_3$: C, 61.04; H, 3.49; N, 8.90. Found: C, 61.09; H, 3.39; N, 8.84

N-(Methylene-4-oxocoumarinyl)-1,4-phenylenediamine (6c), mp.300° (dec.); ^{1}H NMR ($CDCl_3$): δ 3.86 (s, 2H, NH_2), 6.70-7.18 (m, 4H, Ar), 7.23-8.15 (m, 4H, Ar), 8.75-8.90 (dd, 1H, CH, Z and E), 11.97-13.74 (dd, 1H, NH, Z and E); MS m/z (relative abundance): 280 (M^+, 100), 132 (15), 121 (13), 93 (7), 92 (13), 65 (19);

Anal. Calcd. for $C_{16}H_{12}N_2O_3$: C, 68.57; H, 4.28; N, 10.00. Found: C, 68.31; H, 4.13; N, 9.75

***bis* N-(Methylene-4-oxocoumarinyl)-1,4-phenylenediamine (7c)**, mp. 340° (dec.); ^{1}H NMR (DMSO-d_6): δ 7.31-8.00 (m, 12H, Ar), 8.67 (d, 2H, CH), 11.95 and 13.28 (s, 1H, 2NH); MS m/z (relative abundance): 452 (M^+, 83), 173 (46), 121 (100), 120 (13), 93 (29), 92 (75), 83 (8), 77 (17), 73 (21), 72 (17) 71 (8), 65 (33), 43 (54);

Anal. Calcd. for $C_{26}H_{16}N_2O_6$: C, 69.02; H, 3.53; N, 6.19. Found: C, 68.89; H, 3.42; N, 6.09

Condensation of Diamines with 4-Hydroxycoumarin in the Presence of Ethyl Orthoformate. A solution of diamine **3a** and **5a** and **5c** (0.01 mole), 4-hydroxycoumarin (0.01 mole), ethyl orthoformate (0.015 mole, 50% excess) in 2-propanol (30 mL) was heated at reflux with stirring for 3 hrs. The precipitate which formed was filtered from the hot solution and identified as dicoumarol (75-80%), mp. 290° (DMF-MeOH);[6] ^{1}H NMR (DMSO-d_6): δ 3.75 (s, 2H, CH_2), 4.5 (s, very broad, OH), 7.32-7.95 (m, 8H, Ar); MS m/z (relative abundance): 354 (8.20), 339 (4.15), 338 (19.84), 337 (100), 336 (M^+, 2.05), 194 (2.09), 193 (0.68), 180 (2.43), 163 (2.10), 102 (0.74), 100 (0.64);

Anal. Calcd. for $C_{19}H_{12}O_6$: C, 67.85; H, 3.57. Found: C, 67.75; H, 3.52

Evaporation of the filtrates gave **4a** and inseparable mixtures of **6a** and **7a** and of **6c** and **7c**.

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A NOVEL SYNTHESIS OF ORGANIC DISELENIDES

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In spite of their importance as intermediates in organic synthesis, many organic diselenides have only been obtained by displacement of halides or tosylates by nucleophilic selenium species.[1] Carbonyl compounds are potentially attractive novel starting materials for such syntheses.[2] Margolis[3] and Cohen[4] found that reacting carbonyl compounds with hydrogen selenide gave diselenides in the presence of triethylamine. Lewicki[2] reported the synthesis of diselenides from aldehydes, (a) by the reaction of aldehydes with sodium hydrogen selenide in the presence of amine and (b) by the reduction of the reaction mixture with sodium borohydride. In order to avoid the use of toxic hydrogen selenide gas, to simplify the procedure and to improve the yields, we developed a facile and efficient method for the synthesis of organic diselenides.

We initially found only small amounts of organic diselenides were obtained upon reaction of aldehydes with sodium hydrogen selenide in ethanol. It was rationalized that the formation of the organic diselenide might result from the attack of the aldehyde by the minute amounts of disodium diselenide present in the solution of sodium hydrogen selenide. Since disodium diselenide already contains the selenium-selenium bond and sodium hydrogen selenide is a selective reducing agent, we used the mixture of these two species to provide the source of selenium-selenium bond efficiently and perform the subsequent reduction selectively. A solution in which disodium diselenide and sodium hydrogen selenide are generated in the desired molar ratio may be obtained by adjusting the amount of