Cross reactions of cyanoacetic acid derivatives with carbonyl compounds

3.* One-step synthesis of substituted 2-amino-5-oxo-4,5-dihydropyrano[3,2-*c*]chromenes**

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Three-component reactions of 4-hydroxycoumarin, carbonyl compounds, and malononitrile or alkyl cyanoacetates in ethanol in the presence of Et_3N as a catalyst give substituted 2-amino-5-oxo-4,5-dihydropyrano[3,2-*c*]chromenes.

Key words: malononitrile, alkyl cyanoacetates, 4-hydroxycoumarin, 2-amino-5-oxo-4,5-dihydropyrano[3,2-*c*]chromenes, spiro[indoline-3,4´]pyrano[3,2-*c*]chromenes, cross reactions, 6-amino-2,1´-bis(benzyloxycarbonyl)-5,7,7-tricyanospiro[3,7,8,8a-tetrahydro-1*H*-isoquinoline-8,4´-piperidine].

A key compound in the synthesis (Scheme 1) of warfarin (rodenticide, a blood anticoagulant) is 2-amino-3-cyano-5-oxo-4-phenyl-4,5-dihydropyrano[3,2-*c*]chromene (**3**) prepared by heating of 4-hydroxycoumarin **1** with benzylidenemalononitrile **2** in pyridine[2] or water.[3] Acid hydrolysis of substituted pyrano[3,2-*c*]chromene **3** gives compound **4**, which is used to synthesize warfarin **5**.[2—6]

2-Amino-4-aryl-3-(thiocarbamoyl, alkoxycarbonyl, or cyano)-5-oxo-4,5-dihydropyrano[3,2-*c*]chromenes were also obtained[4,7] by morpholine-catalyzed reactions of 4-hydroxycoumarin with arylidenecyanothioacetamide, alkyl arylidenecyanoacetates, or arylidenemalononitrile in hot benzene or ethanol. Despite some achievements attained in recent years in the synthesis of compounds of the type **3** with other substituents in position 4, preparation and isolation of unsaturated nitriles **2**, which are analogs of toxic agents CS,[8] substantially complicated the aforementioned synthesis (see Scheme 1). In some cases, the condensation does not yield the target unsaturated nitrile at all: in the reaction of pyridine-4-carbaldehyde with malononitrile, 1-amino-2,4,4,6,6-pentacyano-3,5-di(4-pyridyl)cyclohex-1-ene was obtained instead.[9] This

* For Part 2, see Ref. 1.

** Dedicated to Academician V. I. Minkin on the occasion of his 70th birthday.

Scheme 1

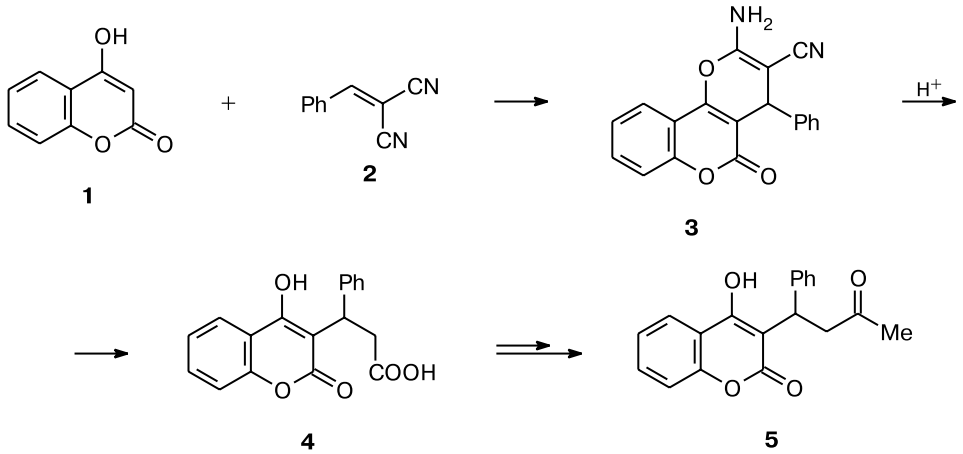

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Table 1. Physicochemical characteristics of substituted 2-amino-5-oxo-4,5-dihydropyrano[3,2-*c*]chromenes **8** and **20**

Compound	M.p. /°C	Yield (%)	Found / Calculated (%)			Molecular formula
			C	H	N	
8a	238—240 (decomp.)	78	68.32 68.14	3.21 3.49	13.04 13.24	$C_{18}H_{11}N_3O_3$
8b	188—189	67	63.87 63.96	4.66 4.60	7.19 7.10	$C_{21}H_{18}N_2O_6$
8c	190—192 (decomp.)	68	67.41 67.50	3.85 3.78	8.82 8.75	$C_{18}H_{12}N_2O_4$
8d	232—233	90	70.69 70.58	4.75 4.85	7.39 7.48	$C_{22}H_{18}N_2O_4$
8e	277—229	74	68.39 68.31	4.85 4.98	6.74 6.93	$C_{23}H_{20}N_2O_5$
8f	204—206	93	63.32 63.01	3.92 4.09	9.86 10.02	$C_{22}H_{17}N_3O_6$
8g	221—222	85	63.24 63.16	3.71 3.79	3.61 3.51	$C_{21}H_{15}F_2NO_5$
20a	>300	92	67.04 67.23	2.93 3.10	11.38 11.76	$C_{20}H_{11}N_3O_4$
20b	>300	89	67.68 67.92	3.35 3.53	11.07 11.32	$C_{21}H_{13}N_3O_4$
20c	>300	90	63.73 64.00	2.45 2.69	10.94 11.20	$C_{20}H_{10}FN_3O_4$

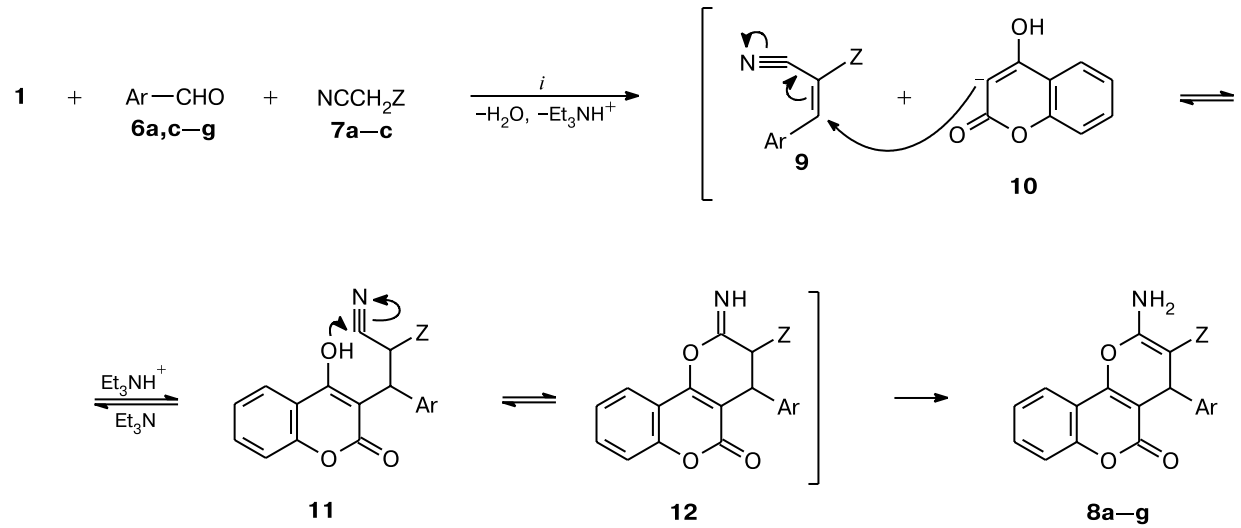
precludes the synthesis of pyrano[3,2-*c*]chromones containing the 4-pyridyl substituent in position 4.

In further investigations of cross reactions of cyanoacetic acid derivatives with carbonyl compounds[1,10] with the aim of developing one-step syntheses of functionalized heterocycles, we studied three-component reactions of 4-hydroxycoumarin, cyanoacetic acid derivatives (malononitrile and alkyl cyanoacetates), and carbonyl compounds (aromatic and heterocyclic aldehydes, cyclic aliphatic ketones, or isatin). To obtain potential biologically active compounds, we introduced into this reaction not only heterocyclic aldehydes but also alkoxy- or dialkoxybenzaldehydes, the residues of which are found in many natural physiologically active compounds.[6]

The brief heating of 4-hydroxycoumarin **1** with aldehydes **6** and cyanoacetic acid derivatives **7** in boiling ethanol in the presence of Et_3N as a catalyst gave substituted 2-amino-5-oxo-4,5-dihydropyrano[3,2-*c*]chromenes **8a,f** in high yields (67—93%). Using this method, we avoided side processes and obtained 4-(4-pyridyl)-, 4-(4-alkoxyphenyl)-, and 4-(3,4-dialkoxyphenyl)pyranochromenes **8a,b,d—f** (Table 1). Such a high regioselectivity is probably associated with the fixed sequence of reaction steps. Apparently, the initial Knoevenagel reaction of aldehyde **6** with cyanoacetic acid derivative **7** gives unsaturated nitrile **9**, which, when at the "reaction intersection", enters into the Michael reaction with coumarin anion **10**. The resulting Michael adduct **11** undergoes intramolecular cyclization into annelated iminopyran **12**. Subsequent tautomeric [1,3]sigmatropic shift gives compounds **8** (Scheme 2).

Under these conditions, the reaction sufficiently rapidly and smoothly affords target chromenes **8** in high yields; no Michael adducts **11** were detected. However, this scheme is confirmed to some degree by isolation of analogous Michael adducts (Z = $CSNH_2$) in the previ-

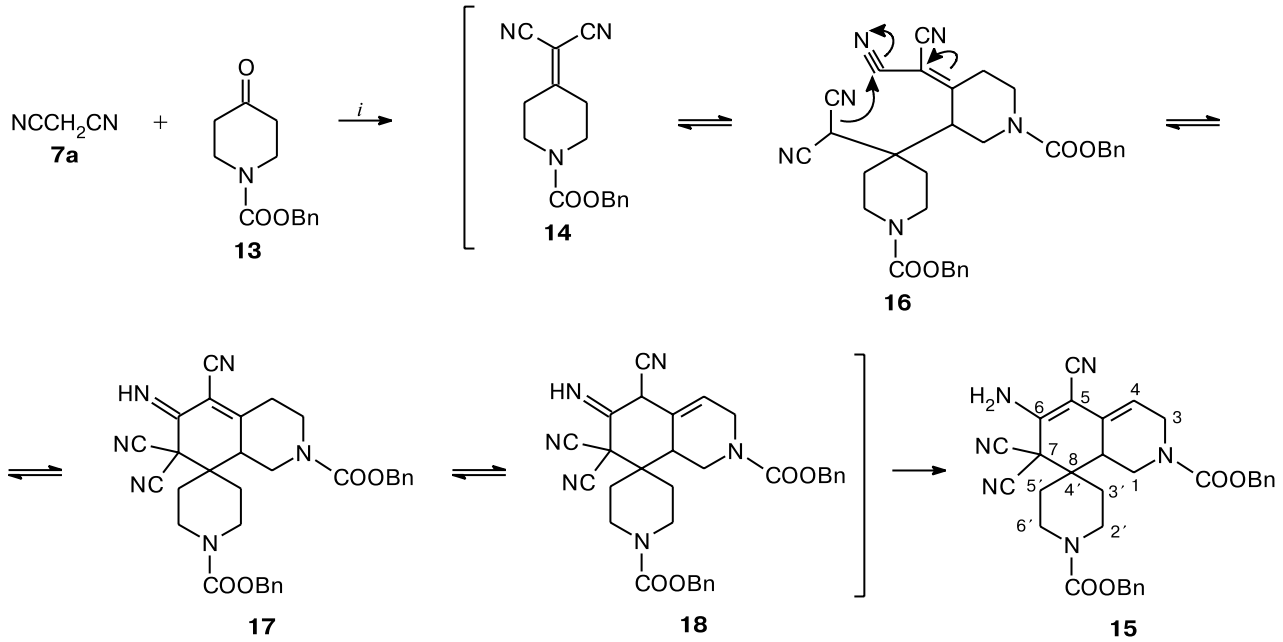
Scheme 2



Z = CN (**7a, 8a,c—f**), COOEt (**7b, 8g**), $COO(CH_2)_2OMe$ (**7c, 8b**)
6, 8: Ar = 4-Py (**a, b**), 2-(5-MeC_4H_2O) (**c**), 4-$Pr^iOC_6H_4$ (**d**), 3-MeO-4-$Pr^iOC_6H_3$ (**e**), 3-MeO-4-$(OCH_2CONH_2)C_6H_3$ (**f**), 2,4-$F_2C_6H_3$ (**g**)

Reagents and conditions: *i*. EtOH, Et_3N, Δ, 5 min.

Scheme 3



Reagents and conditions: *i*. EtOH, Et_3N, Δ.

ously studied reactions of 4-hydroxycoumarin with arylidenecyanothioacetamides.[4]

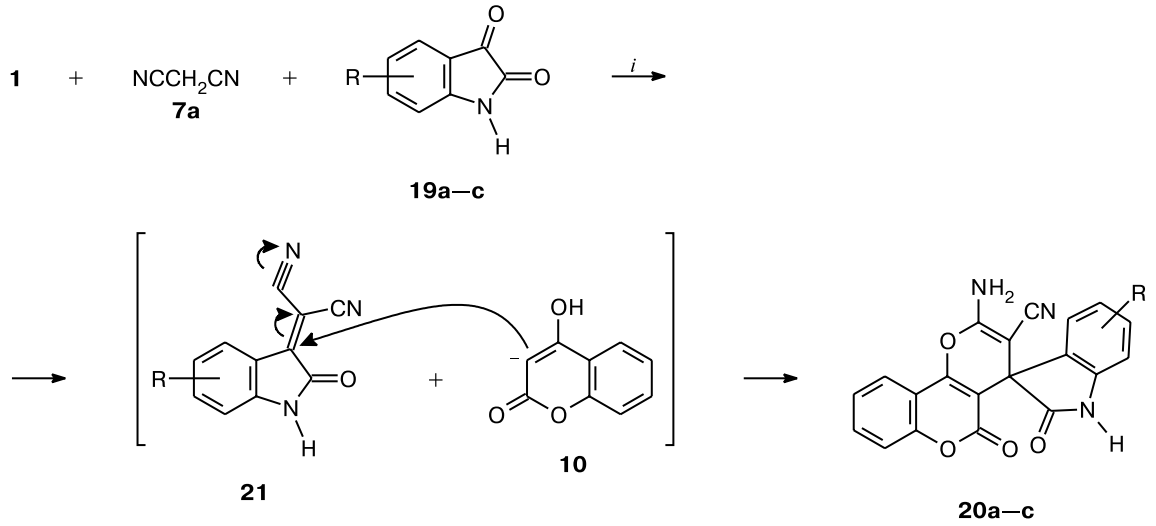
The three-component reaction between coumarin **1**, malononitrile **7a**, and 1-benzyloxycarbonylpiperidin-4-one (**13**) as the carbonyl compound follows a different pathway. Under analogous conditions (see above), malononitrile **7a** reacts with piperidin-4-one **13** to give unsaturated nitrile **14**, which dimerizes into spiroheterocycle **15** rather than reacting with coumarin **1**. The suggested scheme involves dimerization of unsaturated nitrile **14** into Michael adduct **16**, its Thorpe—Ziegler cyclization into spiroheterocycle **17**, and final tautomerization into compound **15** through intermediate **18**. Thus, coumarin **1** is out the process. Indeed, we obtained compound **15** from malononitrile **7a** and ketone **13** in ethanol in the presence of Et_3N (Scheme 3). An analogous dimerization was observed earlier in the reaction of 1-methylpiperidin-4-one with malononitrile.[10] This reaction pathway is probably due to a higher γ-CH acidity of unsaturated nitrile **14** compared to 4-hydroxycoumarin **1**.

Our assumption was confirmed by a three-component reaction with isatin **19** (containing no γ-CH acid fragment) as the carbonyl compound, which gives spiro(indoline-3,4′-pyrano[3,2-*c*]chromenes) **20** rather than dimerization products from unsaturated nitriles **21** (Scheme 4). The yields of spiro compounds **20** were high (89—92%), regardless of the type of substituent in the benzene ring of isatin **19**.

The pyranochromenes **8** and **20** obtained are air-stable colorless solid powders, which are well soluble in acetone, DMF, and DMSO. The structures of these compounds were confirmed by elemental analysis and IR and ^{1}H NMR spectroscopy (Tables 1, 2). The IR spectra of pyranochromenes **8** and **20** contain characteristic absorption bands of the enamino nitrile and enamino carbonyl fragments: $\delta(NH_2)$ 1660—1678 cm^{-1}, $\nu(NH_2)$ 3135—3378 cm^{-1}, ν(CN) 2190—2208 cm^{-1}, and ν(COOR) 1673—1696 cm^{-1}. An analogous spectral pattern was observed for 2-amino-4*H*-pyrans containing similar fragments.[1,9—12] The IR spectra of pyranochromenes **8** and **20** show a peculiar absorption band of the lactone group at 1688—1720 cm^{-1}. The ^{1}H NMR spectra of pyranochromenes **8** exhibit, apart from signals for protons of the aromatic and chromene fragments, characteristic singlets for the C(4)H and NH_2 protons at δ 4.37 to 4.90 and 7.09 to 7.85, respectively. Signals of the C(4)H group are absent from the spectra of spiroheterocycles **20**; instead, signals for the protons of the isatin fragment are present.

In conclusion, it should be noted that the cross reactions studied are based on simultaneous double generation of a nucleophile (4-hydroxycoumarin anion) and an electrophile (unsaturated nitrile) in the reaction mixture. At the "intersection point", the reaction between intermediates can give pyranochromenes **8** and **20** or isoquinoline **15**.

Scheme 4



19, 21: R = H (**a**), 7-Me (**b**), 5-F (**c**)

Reagents and conditions: *i*. EtOH, Et_3N, Δ, 10 min.

Experimental

Melting points were determined on a Kofler unit. IR spectra were recorded on Specord M-80 and Perkin—Elmer 577 instruments (pellets with KBr, 1/200). ^{1}H NMR spectra were recorded on a Bruker AC-300 spectrometer (300 MHz) in DMSO-d_6; chemical shifts were referenced to Me_4Si. Elemental analysis was performed with a Perkin—Elmer C,H,N-analyzer. The course of the reactions was monitored and the purity of the compounds obtained was checked by TLC on Silufol UV-254 plates with hexane—acetone (5 : 3) as an eluent; spots were visualized with the iodine vapor.

2-Amino-5-oxo-4,5-dihydropyrano[3,2-*c*]chromenes 8 and 20 (general procedure). A stirred mixture of 4-hydroxycoumarin **1** (1.62 g, 10 mmol), carbonyl compound **6** or **19** (10 mmol), a corresponding cyanoacetic acid derivative **7** (11 mmol), and Et_3N (0.5 mL, 0.5 mmol) in anhydrous EtOH (50 mL) was refluxed for 5 to 10 min and allowed to crystallize at 4 °C

Table 2. Spectroscopic characteristics of substituted 2-amino-5-oxo-4,5-dihydropyrano[3,2-*c*]chromenes **8** and **20**

Compound	IR, ν/cm^{-1}				^{1}H NMR (300 MHz, δ, *J*/Hz)
	δ(NH_2)	NH_2	C≡N	C=O	
8a	1673	3175, 3280, 3384	2200	1718	4.72 (s, 1 H, C(4)H); 7.25 (d, C(3)H, C(5)H, py, *J* = 5.6); 7.15 (s, 2 H, NH_2); 7.36 (d, 1 H, CH, *J* = 7.8); 7.44 (t, 1 H, CH, *J* = 7.7); 7.62 (t, 1 H, CH, *J* = 7.8); 7.96 (d, 1 H, CH, *J* = 7.7); 8.40 (d, 2 H, C(2)H, C(6)H, py, *J* = 5.6)
8b	1668	3190, 3256, 3360	—	1673, 1683	3.25 (s, 3 H, Me); 3.44, 4.09 (both m, 2 H each, CH_2); 4.73 (s, 1 H, C(4)H); 7.23 (d, 2 H, C(3)H, C(5)H, py, *J* = 5.5); 7.38 (d, 1 H, CH, *J* = 7.9); 7.44, 7.65 (both t, 1 H each, CH, *J* = 7.9); 7.85 (s, 2 H, NH_2); 7.99 (d, 1 H, CH, *J* = 7.9); 8.39 (d, 2 H, C(2)H, C(6)H, py, *J* = 5.5)
8c	1672	3187, 3288, 3376	2200	1720	2.22 (s, 3 H, Me); 4.53 (s, 1 H, C(4)H); 5.92, 6.08 (both d, 1 H each, CH, furyl, *J* = 2.2); 7.16 (s, 2 H, NH_2); 7.40 (d, 1 H, CH, *J* = 7.9); 7.42, 7.67 (both t, 1 H each, CH, *J* = 7.9); 7.92 (d, 1 H, CH, *J* = 7.9)
8d	1672	3185, 3200, 3312	2205	1712	1.28 (s, 6 H, Me_2, *J* = 5.5); 4.39 (s, 1 H, C(4)H); 4.53 (m, 1 H, CHO); 6.79 (d, 2 H, CH_{Ph}, *J* = 7.7); 7.09 (s, 2 H, NH_2); 7.16 (d, 2 H, CH_{Ph}, *J* = 7.7); 7.36 (d, 1 H, CH, *J* = 7.8); 7.41, 7.64 (both m, 1 H each, CH); 7.93 (d, 1 H, CH, *J* = 7.9)
8e	1668	3192, 2208, 3218, 3312	—	1708	1.25 (s, 6 H, Me_2, *J* = 4.9); 3.76 (s, 3 H, Me); 4.37 (s, 1 H, C(4)H); 4.44 (m, 1 H, CHO); 6.72, 6.78 (both d, 1 H each, CH_{Ph}, *J* = 8.0); 6.85 (s, 1 H, CH_{Ph}); 7.18 (s, 2 H, NH_2); 7.39 (m, 2 H, CHCH); 7.64 (m, 1 H, CH); 7.91 (d, 1 H, CH, *J* = 7.9)

(*to be continued*)

Table 2 (*continued*)

Compound	IR, ν/cm^{-1}				^{1}H NMR (300 MHz, δ, *J*/Hz)
	δ(NH_2)	NH_2	C≡N	C=O	
8f	1663	3200, 3250, 3320, 3360	2207	1707	3.77 (s, 3 H, Me); 4.37 (s, 2 H, CH_2); 4.44 (s, 1 H, C(4)H); 6.74, 6.88 (both d, 1 H each, CH_{Ph}, *J* = 7.9); 6.91 (s, 1 H, CH_{Ph}); 7.34 (br.s, 4 H, $(NH_2)_2$); 7.45 (d, 1 H, CH, *J* = 8.1); 7.48, 7.71 (both m, 1 H each, CH); 7.91 (d, 1 H, CH, *J* = 8.3)
8g	1660	3210, 3312	—	1696, 1702	1.15 (t, 3 H, Me, *J* = 7.8); 4.01 (q, 2 H, CH_2, *J* = 7.8); 4.90 (s, 1 H, C(4)H); 6.84 (m, 2 H, CH_{Ph}); 7.37 (d, 1 H, CH, *J* = 7.6); 7.43 (t, 1 H, CH, *J* = 7.6); 7.73 (s, 2 H, NH_2); 7.76 (t, 1 H, CH, *J* = 7.5); 7.99 (d, 1 H, CH, *J* = 7.5)
20a	1678	3138,* 3295, 3360	2195	1695, 1724	6.75—7.18 (m, 4 H, $(CH)_4$, isatin); 7.32 (d, 1 H, CH, *J* = 7.7); 7.42 (m, 1 H, CH); 7.48 (s, 2 H, NH_2); 7.72 (m, 1 H, CH); 7.95 (d, 1 H, CH, *J* = 7.4); 10.40 (s, 1 H, NH)
20b	1672	3140,* 3285, 3357	2192	1695, 1718	2.32 (s, 3 H, Me); 6.72—7.20 (m, 3 H, $(CH)_3$, isatin); 7.28 (d, 1 H, CH, *J* = 7.6); 7.38 (m, 1 H, CH); 7.44 (s, 2 H, NH_2); 7.75 (m, 1 H, CH); 7.98 (d, 1 H, CH, *J* = 7.3); 10.35 (s, 1 H, NH)
20c	1670	3135,* 3278, 3355	2190	1690, 1715	7.25—7.68 (m, 8 H, CH (isatin), CH (pyranochromene), *J* = 7.5); 10.35 (s, 1 H, NH)

* Overlap with ν(NH) in the isatin fragment.

for 12 h. The precipitate that formed was filtered off, washed with ethanol and hexane, and recrystallized from nitromethane to give compounds **8** and **20** (see Tables 1, 2).

6-Amino-2,1′-bis(benzyloxycarbonyl)-5,7,7-tricyanospiro[3,7,8,8a-tetrahydro-1*H*-isoquinoline-8,4′-piperidine] (15). An equimolar mixture of ketone **13** (0.47 g, 2 mmol) and malononitrile **7a** (0.13 g, 2 mmol) in anhydrous EtOH (15 mL) was stirred at 50 to 55 °C to homogenization and triethylamine (0.32 mL, 2.3 mmol) was added. The reaction mixture was refluxed for 5 min and allowed to crystallize. The precipitate that formed was filtered off, washed with ethanol and hexane, and recrystallized from nitromethane to give spiro compound **15** (0.78 g, 70%), m.p. 248—250 °C. Found (%): C, 68.16; H, 5.18; N, 14.67. $C_{32}H_{30}N_6O_4$. Calculated (%): C, 68.31; H, 5.37; N, 14.94. IR, ν/cm^{-1}: 1668 (δ(NH_2)); 1690 (CO); 2223 (CN); 3208, 3346, 3367 (NH_2). ^{1}H NMR, δ: 1.68 (m, 1 H, C(5′)H_{eq}); 1.79 (m, 1 H, C(3′)H_{eq}); 2.22 (m, 2 H, C(3′)H_{ax}, C(5′)H_{ax}); 2.67 (m, 1 H, C(8a)H); 3.08 (m, 1 H, C(1)H_{eq}); 3.36 (m, 2 H, C(1)H_{ax}, C(2′)H_{eq}); 3.76 (m, 2 H, C(2′)H_{ax}, C(6′)H_{eq}); 3.95 (m, 1 H, C(6′)H_{ax}); 4.39 (m, 2 H, C(3)H_2); 5.08 (m, 4 H, $(CH_2)_2$); 5.78 (m, 1 H, C(4)H); 7.22 (s, 2 H, NH_2); 7.32 (m, 10 H, Ph_2).

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