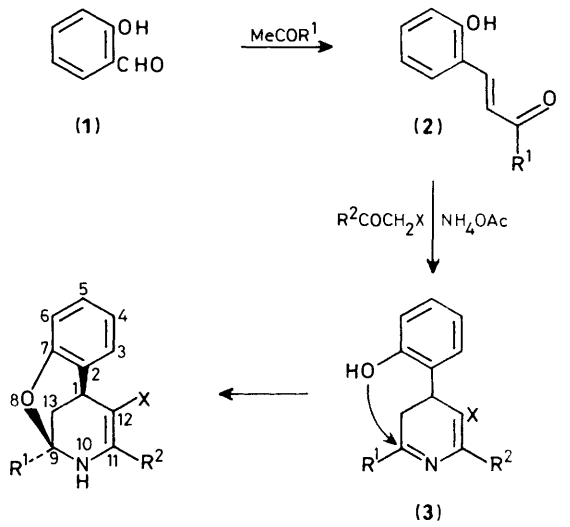
Formation of Oxygen-bridged Heterocycles in the Hantzsch Synthesis with 4-(2-Hydroxyphenyl)but-3-en-2-one

Jan Světlík *,†
Drug Research Institute, Palárikova 31, 811 04 Bratislava, Czechoslovakia
František Tureček and Vladimír Hanuš
The J. Heyrovský Institute of Physical Chemistry and Electrochemistry, Máchova 7, 121 38 Praha 2, Czechoslovakia

Condensations of 4-(2-hydroxyphenyl)but-3-2-one with methyl acetoacetate, pentane-2,4-dione, dimedone, and methyl cyanoacetate under the conditions of the Hantzsch synthesis lead to 9-methyl-8-oxa-10-azatricyclo[7.3.1.$0^{2,7}$]trideca-2,4,6,11-tetraene derivatives and related heterocycles. An analogous condensation with 2-aminopropene-1,1,3-triscarbonitrile yields stereoselectively 11-dicyanomethylene-9-methyl-8-oxa-10-azatricyclo[7.3.1.$0^{2,7}$]trideca-2,4,6-triene-12α-carbonitrile. Under suitable reaction conditions, the condensation of 4-(2-hydroxyphenyl)but-3-en-2-one with cyanamide affords various products with the 9-methyl-8-oxa-10,12-diazatricyclo[7.3.1.$0^{2,7}$]trideca-2,4,6,11-tetraene skeleton. Condensation products of salicylaldehyde with acetone, 2-aminopropene-1,1,3-triscarbonitrile, and 3-aminocrotononitrile have been identified.

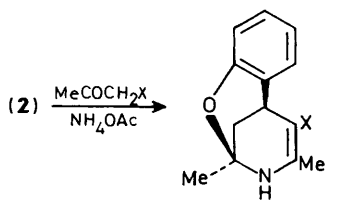
Salicylaldehyde (**1**) is a valuable bifunctional building block for the preparation of various oxygen heterocycles.[1–4] In our previous re-investigations[5] of the Hantzsch dihydropyridine synthesis[6] and related cyclocondensations[7] we found that the salicylaldehyde hydroxy group attacked intramolecularly the 2-azabutadiene moiety of the intermediate dihydropyridine (**3**) (Scheme 1) to give rise eventually to products with the 8-oxa-10-azatricyclo[7.3.1.$0^{2,7}$]trideca-2,4,6,11-tetraene skeleton.[5] Similar conformationally restricted compounds have recently been developed by a Merck group[8,9] as a tool for studying the geometrical requirements at the dihydropyridine receptor.[10,11] In the light of the growing interest in this area it appeared useful to explore further cyclocondensations of salicylaldehyde, with the aims of preparing analogous sterically constrained heterocycles and of elucidating some unclear structures published in the early literature.[12] In the present paper we report a practical one-pot synthesis of oxygen-bridged tetrahydropyridines, hexahydropyridines, and tetrahydropurimidines, related to known calcium-entry blockers.[13]



Scheme 1.

Results and Discussion

The condensation of salicylaldehyde (**1**) with acetone, ammonia, and a component possessing an active methylene group has been assumed to proceed *via* chalcone-like intermediates [(**2**), Scheme 1].[5,14] In the present work we used 4-(2-hydroxyphenyl)but-3-en-2-one[15] (**2**; R^1 = Me) directly as starting compound in order to force the subsequent heterocyclization in the desired direction. Indeed, the reaction of the enone (**2**; R^1 = Me) with methyl acetoacetate and ammonium acetate under conditions of the Hantzsch synthesis yielded the ester (**4**) in 46% yield (Scheme 2; X = CO_2Me). An analogous cyclocondensation of the butenone (**2**; R^1 = Me) with pentane-2,4-dione provided the ketone (**5**) (Scheme 2; X = COMe). Dimedone under the same conditions afforded the tetracyclic ketone (**6**) in high yield. Compound (**6**) is to our knowledge the first representative of such an oxygen-bridged octahydroquinoline system.

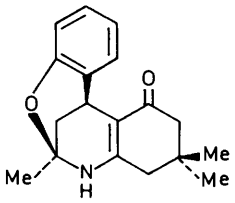


(**4**) X = CO_2Me
(**5**) X = COMe

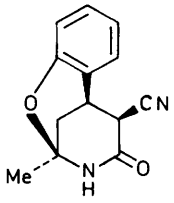
Scheme 2.

The structures for the products (**4**)—(**6**) followed from spectral data.[5] The ^{1}H n.m.r. spectra show ABX systems corresponding to the bridge methylene protons (13-H) coupled to the bridgehead methine proton (1-H). The coupling constants $J_{1,13}$ are both close to 3 Hz, indicating a synclinal orientation of the C(1)–H bond with the two C(13)–H bonds. The signals of the equatorial protons ($13_{eq.}$-H), appearing at

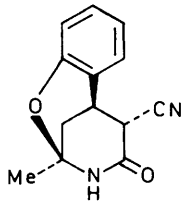
† *Present address*: Institute of Biotechnology, Slovak Technical University, Kolla'rovo na'm, 9, 812 37 Bratislava, Czechoslovakia.



(6)



(7)



(8)

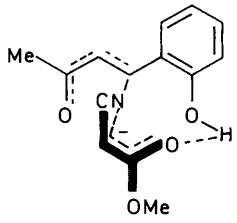
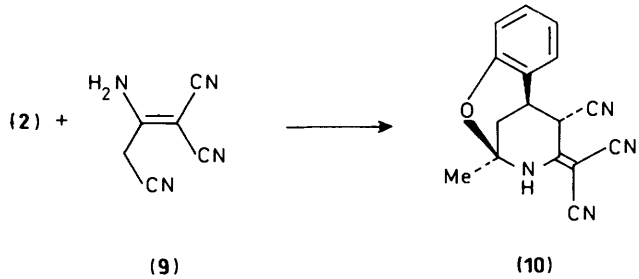


Figure 1.



(9) (10)

Scheme 3.

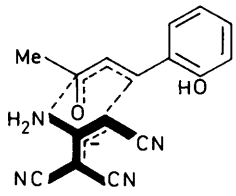
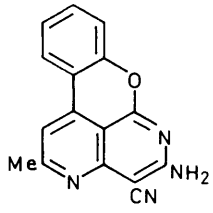
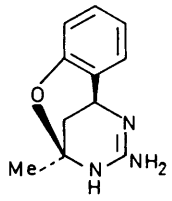


Figure 2.



(11)



(12)

lower field are split by long-range couplings with the N–H protons (confirmed by double resonance experiments). Because of bridging, the phenyl group is held pseudoaxial with respect to the tetrahydropyridine ring. Further details as to the conformation of the tetrahydropyridine ring[8,9] in the molecules (**4**)—(**6**) cannot be deduced from the ^{1}H n.m.r. spectra.

In the ^{13}C n.m.r. spectra the C-9 signals appear as singlets at δ_C 80.9—81.0. The signals of the carbon atoms of the enamino ester and enamino ketone double bonds appear as singlets at δ_C 98—111 (C-12) and 151.9—155.4 (C-11).

The i.r. spectra of the heterocycles (**4**)—(**6**) show the carbonyl stretching bands at unusually low wavenumbers (1 575—1 628 cm^{-1}).

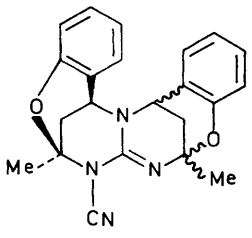
Cyclocondensation of the butenone (**2**; R^1 = Me) with methyl cyanoacetate afforded an inseparable mixture of nitriles (**7**) (85%) and (**8**) (15%) in moderate yield. The gross structural features of the products can be deduced from the ^{1}H and ^{13}C n.m.r. spectra of the mixture. The ^{13}C n.m.r. spectrum of the major isomer (**7**) shows a singlet for the nitrile group (δ_C 117.3), two doublets for C-1 and C-12 (δ_C 31.7 and 42.4, respectively), and a singlet for the quaternary C-9 (δ_C 82.8). The stereochemical assignment for the epimer (**7**) is based on the absence of long-range coupling of 12-H with $13_{eq.}$-H which suggests that the former proton is axial. The vicinal coupling constants $^3J_{1,12}$ are identical for the two isomers (J 4 Hz) and cannot be used for stereodifferentiation.

The preferential formation of the *endo*-isomer (**7**) may be due to hydrogen-bonding complexation between the methoxycarbonyl group and the phenolic hydroxy group in the transition state (Figure 1), which would favour their *cis*-arrangement in the product.

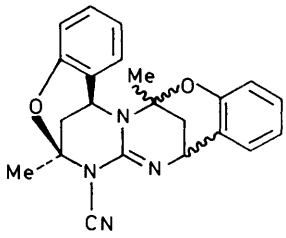
Treatment of the butenone (**2**; R^1 = Me) with 2-aminopropene-1,1,3-triscarbonitrile (**9**)[16] afforded cleanly the nitrile (**10**) in good yield (Scheme 3). The structure (**10**) was deduced from the spectral data. The ^{13}C n.m.r. spectrum showed signals of an H_2N–C=C$(CN)_2$ segment (δ_C 161.3, 52.6, 114.5, and 113.0), which closely resemble those reported for the same segment of a co-dimer of malononitrile with methyl cyanoacetate.[17] The position and configuration of the nitrile group in the hexahydropyridine ring also followed from the n.m.r. spectra. The ^{1}H-coupled ^{13}C n.m.r. spectrum of the heterocycle (**10**) showed two methine doublets at δ_C 37.3 and 30.3, corresponding to the bridgehead carbon atom (C-1) and that bearing the nitrile group (C-12). The signal of the nitrile carbon atom (δ_C 115.8) shows a coupling with 1-H, ^3J 3.5 Hz, which indicates the *exo*-configuration for the nitrile group. Consistent with this, the ^{1}H n.m.r. spectrum displays an ANXY system for the methylene protons (13-H), the bridgehead proton (1-H), and 12-H. The *endo*-orientation of 12-H follows from the small vicinal coupling constant ($J_{1,12}$ 2 Hz) and from a long-range coupling with $13_{eq.}$-H ($^4J_{12,13}$ 1 Hz).

The formation of the single stereoisomer (**10**) from (**2**) and (**9**) is remarkable, and contrasts with the formation of a mixture in the cyclocondensation of the butenone (**2**; R^1 = Me) with methyl cyanoacetate (see before). We were unable to detect an *endo*-isomer of (**10**) even in the crude reaction mixture, the ^{1}H n.m.r. spectrum of which was essentially identical with that of pure (**10**). The highly preferential formation of the α-isomer may be due to a favourable pseudo-diequatorial arrangement of the hydroxyphenyl and the cyano groups in a cyclic transition state from the condensation (Figure 2).

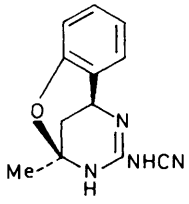
In contrast to the enone (**2**; R^1 = Me), the heterocyclization of salicylaldehyde (**1**) with acetone and malononitrile dimer (**9**) under classical Hantzsch conditions afforded a different product, identified as 5-amino-2-methyl[1]benzopyrano[4,3,2-



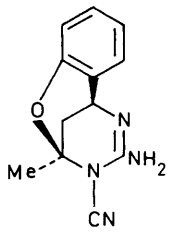
(13a)



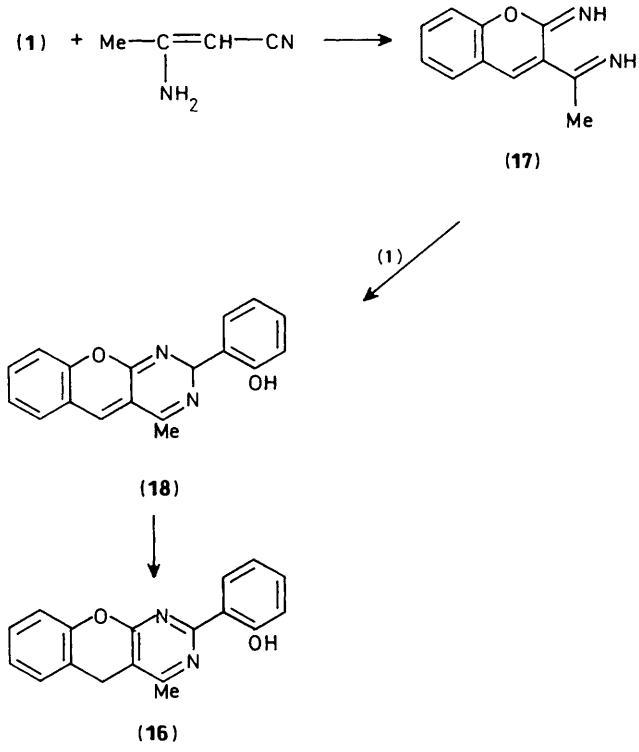
(13b)



(14)



(15)



Scheme 4.

de][1,6]naphthyridine-4-carbonitrile (**11**). In this case the salicylaldehyde hydroxy group attacked one of the nitrile groups in compound (**9**) and the intermediate dihydropyridine underwent oxidation to the fully aromatic derivative (**11**).

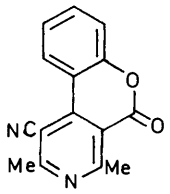
The course of the cyclocondensation of the enone (**2**; R^1 = Me) with cyanamide, another bifunctional reagent, was found to depend crucially on the reaction conditions. In the presence of ammonium acetate the cyclocondensation afforded the expected bridged tetrahydropyrimidine (**12**), easily identified through its spectra. If the butenone (**2**; R^1 = Me) was treated with cyanamide in the presence of piperidine in ethanol at 60 °C, a different condensation product (**13**) was obtained after 5 h, in low yield. A large fraction of starting material (**2**; R^1 = Me) was recovered. Prolongation of the reaction time led to another product (**14**), isolated in reasonable yield. The latter compound was independently prepared in a satisfactory yield by treating the enone (**2**; R^1 = Me) with cyanamide in 1,2-dimethoxyethane. The condensation in ethanol also afforded a minor amount of yet another compound (**15**), isolated by crystallization.

The products (**14**) and (**15**) were found to be isomers ($C_{12}H_{12}N_4O$ by high resolution mass spectroscopy) containing a bridged tetrahydropyrimidine skeleton, but differing in the position of the nitrile group. The ^1H n.m.r. spectra differ in the chemical shifts of the methyl groups [δ_H 1.69 and 1.85 for (**14**) and (**15**), respectively] and, especially, in the position of the signal of the nitrogen-bound protons [δ_H 8.58 and 5.80, respectively]. The ^{13}C n.m.r. spectra also differ significantly. The signals of the nitrile carbon atom and the central guanidine carbon atom of compound (**15**) appear at unusually high-field values (δ_C 108.6 and 150.1, respectively); those of (**14**) are unexceptional (δ_C 117.7 and 157.8, respectively). Both products (**14**) and (**15**) show narrow singlets for the nitrile carbon atoms in the proton-coupled ^{13}C n.m.r. spectra. The chemical shifts of the quaternary carbon atoms also differ, with that of (**15**) appearing at a lower field (δ_C 85.4) than that of (**14**) (δ_C 80.9). On the basis of these data, the compound showing the more shielded quaternary carbon atom and the less shielded N–H proton was assigned structure (**14**), with the nitrile group attached to the exocyclic nitrogen atom. Of two remaining possible structures for the other isomer (**15**), that with the nitrile group at N-12 was excluded because of the lack of a three-bond coupling between 1-H and the nitrile carbon atom.

A reasonable pathway to the heterocycle (**14**) would involve the formation of the pyrimidine (**15**), which then undergoes a Dimroth-type rearrangement affording the exocyclic appendage on the pivotal carbon atom. Support for the proposed mechanism was obtained by the isolation of the intermediate (**15**). Nevertheless, a direct route involving attack by cyanoguanidine (dimer of dyanamide) cannot be excluded.

The structures of the tetrahydropyrimidines (**14**) and (**15**) provided some clue to the structure of the transient product (**13**). According to its formula $C_{22}H_{20}N_4O_2$ (by high-resolution mass spectrometry) compound (**13**) consists of two butenone units condensed with two molecules of cyanamide or a molecule of cyanoguanidine. This is supported by the n.m.r. spectra, which reveal the presence of two distinct methyl groups, two sp^3 quaternary carbon atoms, two disubstituted aromatic rings, two $-CH_2-CH-$ units, one nitrile group and one sp^2 quaternary carbon atom flanked by three nitrogen atoms. In the ^{13}C n.m.r. spectrum of the doubly bridged heterocycle (**13**) the signals of C(N)(O) (δ_C 85.9), CN (δ_C 107.2), N=C(N)(N) (δ_C 152.3), and $C_{ar.}$–O (δ_C 145.3) resemble closely those in the spectrum of the pyrimidine (**15**) and suggest that the latter is incorporated as a building block in the derivative (**13**). However the further attachment of the C_{10} fragment is ambiguous and allows for four topochemical and stereochemical isomers [*syn*- or *anti*- (**13a** and **b**)], which all are compatible with the spectral data.

Finally, we examined the reaction of salicylaldehyde (**1**) with 3-aminocrotonitrile, first described more than 50 years ago.[12] The product was originally characterized by its molecular formula only ($C_{18}H_{14}N_2O_2$), which suggested a 2:1 adduct with elimination of two molecules of water. We have reproduced the original procedure (reflux in AcOH for 1 h) with a 2:1 molar ratio of salicylaldehyde (**1**) and 3-aminocrotononitrile and obtained a product (**16**) of the same formula (by high-resolution mass spectrometry) as reported.[12] The identification of compound (**16**) as 4-methyl-2-(2-hydroxyphenyl)-5*H*-[1]benzopy-



(19)

rano[2,3-*d*]pyrimidine followed unequivocally from the n.m.r. spectra. The formation of the fused pyrimidine (**16**) from salicylaldehyde (**1**) can be rationalized by a reaction sequence (Scheme 4) involving the intermediate (**17**), which undergoes condensation with another molecule of salicylaldehyde (**1**) to give compound (**18**). The latter isomerizes formally *via* a 1,5-sigmatropic hydrogen shift to give the final heterocycle (**16**).

The course of condensation of salicyladehyde (**1**) with 3-aminocrotononitrile was found to depend on the molar ratio of the components. When 2 mol. equiv. of the enaminonitrile reacted with 1 equiv. of salicylaldehyde (**1**) we obtained the substituted benzopyrano[3,4-*c*]pyridine (**19**) instead of the heterocycle (**16**). This simple preparation of compound (**19**) represents an alternative to the classical, more complicated synthetic route,[18] and is analogous to the condensation of salicylaldehyde (**1**) with methyl 3-aminocrotonate published recently.[19]

Experimental

General experimental directions are given in ref. 5.

Condensation of 4-(2-*Hydroxyphenyl*)*but*-3-*en*-2-*one* (**2**; R = Me) *with Active Methylene Compounds and Ammonium Acetate: General Procedure.*—To a stirred solution of 4-(2-hydroxyphenyl)but-3-en-2-one (1.62 g, 10 mmol) in ethanol (30 ml) were added ammonium acetate (0.85 g, 11 mmol) and the active methylene compound (10 mmol). The solution was refluxed for 3 h and then evaporated under reduced pressure. The oily residue was triturated with diethyl ether–hexane. The crystalline material obtained was filtered off, washed with diethyl ether, and recrystallized from acetone [(**4**), (**5**), and (**6**)], or ethanol [(**7**) and (**10**)]. In the case of malononitrile dimer a small amount of polymeric material was separated by suction of the warm reaction mixture and the filtrate was kept overnight at room temperature to crystallize.

Methyl 9,11-*Dimethyl*-8-*oxa*-10-*azatricyclo*[7.3.1.0^{2,7}]*trideca*-2,4,6,11-*tetraene*-12-*carboxylate* (**4**) (1.2 g, 46%) had m.p. 204—206 °C (Found: C, 69.65; H, 6.4; N, 5.5. $C_{15}H_{17}NO_3$ requires C, 69.5; H, 6.6; N, 5.4%); *m*/*z* 259 ($M^{+\bullet}$, 12%), 244 (11), 226 (6), 225 (5), 200 (7), 167 (11), 166 ($C_9H_{12}NO_2$, 100), 145 (10), 134 (7), 106 (8), 42 (12), and 39 (7); $\nu_{max.}$(KBr) 3 347 (NH), 1 628 (CO), 1 595, and 1 507 cm^{-1}; δ_H[$(CD_3)_2SO$] 1.66 (3 H, s, 9-Me), 1.77 and 1.93 (2 H, m, J_{AB} 12.6, J_{AX} 3.0, and J_{BX} 3.3 Hz, AB part of ABX; for signal A additional coupling, *J* 0.9 Hz), 2.09 (3 H, s, 11-Me), 3.61 (3 H, s, OMe), 4.04 (1 H, m, X part of ABX), 6.72 (2 H, m, ArH), 6.98 (1 H, m, ArH), 7.17 (1 H, m, ArH), and 7.68 (1 H, br s, NH); δ_C[$(CD_3)_2SO$] 19.2 (q, 11-Me), 26.4 (q, 9-Me), 29.5 (d, C-1), 31.5 (t, C-13), 50.1 (q, OMe), 80.9 (s, C-9), 98.1 (s, C-12), 115.8 (d, C-6), 119.7 (d, C-4), 126.6 (d, C-3), 128.0 (d, C-5), 128.3 (s, C-2), 151.9 (s, C-11 or C-7), 152.0 (s, C-7 or C-11), and 166.9 (s, CO).

12-*Acetyl*-9,11-*dimethyl*-8-*oxa*-10-*azatricyclo*[7.3.1.0^{2,7}]-*trideca*-2,4,6,11-*tetraene* (**5**) (870 mg, 36%), had m.p. 244—245 °C (Found: C, 74.2; H, 7.2; N, 5.5. $C_{15}H_{17}NO_2$ requires C, 74.05; H, 7.0; N, 5.8%); *m*/*z* 243 ($M^{+\bullet}$, 16%), 242 (8), 226 (31), 200 (22), 151 (11), 150 ($C_9H_{12}NO$, 100), 115 (11), 108 (9), 107 (12), 106 (7), 43 (25), 42 (21), and 39 (14); $\nu_{max.}$(KBr) 3 290 (NH), 1 570 (CO), and 1 500 cm^{-1}; δ_H[$(CD_3)_2SO$] 1.67 (3 H, s, Me), 1.72 (1 H, dd, *J* 12.7 and 2.8 Hz), 1.95 (1 H, ddd, *J* 12.7, 3.5, and 1.1 Hz), 2.12 (3 H, s, Me), 2.24 (3 H, s, Me), 4.24 (1 H, dd, *J* 3.5 and 2.8 Hz), 6.71 (2 H, m, ArH), 6.97 (1 H, ddd, *J* 7.5, 7.5, and 1.7 Hz, ArH), 7.21 (1 H, dd, *J* 7.5 and 1.7 Hz, ArH), and 7.70 (1 H, br d, *J* 1.1 Hz, NH); δ_C[$(CD_3)_2SO$] 20.9 (q), 26.5 (q), 29.5 (q), 30.5 (d), 31.7 (t), 80.8 (s), 110.9 (s), 115.9 (d), 119.9 (d), 126.6 (d), 128.2 (d), 128.3 (s), 151.90 (s), 151.93 (s), and 192.1 (s).

9,13,13-*Trimethyl*-8-*oxa*-10-*azatetracyclo*[7.7.1.0^{2,7}.0^{11,16}]-*heptadeca*-2,4,6,11(16)-*tetraen*-15-*one* (**6**) (1.64 g, 58%) and m.p. 246—247 °C (Found: C, 76.4; H, 7.2; N, 5.1. $C_{18}H_{21}NO_2$ requires C, 76.3; H, 7.5; N, 4.9%); *m*/*z* 243 ($M^{+\bullet}$, 16%), 242 (8), 226 (31), 200 (22), 151 (11), 150 ($C_9H_{12}NO$, 100), 115 (11), 108 (9), 107 (12), 106 (7), 43 (25), 42 (21), and 39 (14); $\nu_{max.}$(KBr) 3 290 (NH), 1 757 (CO), and 1 510 cm^{-1}; δ_H[$(CD_3)_2SO$] 0.75 (3 H, s, Me), 0.97 (3 H, s, Me), 1.70 (3 H, s, Me), 1.75 (1 H, dd, *J* 12.5 and 3.0 Hz), 1.99 (1 H, ddd, *J* 12.5, 3.2, and 1.0 Hz), 1.96 and 2.05 (2 H, d, *J* 16.0 Hz, AB system), 2.11, 2.18 (2 H, *J* 16.7 Hz, AB system), 4.12 (1 H, dd, *J* 3.2 and 3.0 Hz), 6.67 (1 H, dd, *J* 8.2 and 1.2 Hz, ArH), 6.68 (1 H, ddd, *J* 7.4, 7.5, and 1.3 Hz, ArH), 6.84 (1 H, ddd, *J* 8.2, 7.4, and 1.7 Hz), 7.14 (1 H, dd, *J* 7.4 and 1.5 Hz, ArH), and 7.96 (1 H, br s, NH); δ_C[$(CD_3)_2SO$] 26.1 (q), 26.4 (q), 27.6 (q), 28.1 (d), 31.7 (t), 32.2 (t), 40.4 (s), 49.9 (t), 81.0 (s), 108.6 (s), 115.5 (d), 119.5 (d), 126.2 (d), 127.91 (d), 127.94 (s), 151.8 (s), 155.4 (s), and 190.4 (s).

9-*Methyl*-11-*oxo*-8-*oxa*-10-*azatricyclo*[7.3.1.0^{2,7}]*trideca*-2,4,6-*triena*-12-*carbonitrile* [β-isomer (**7**) and α-isomer (**8**)] (730 mg, 32%) had m.p. 210 °C (decomp.) (Found: C, 68.3; H, 5.4; N, 12.45. $C_{13}H_{12}N_2O_2$ requires C, 68.4; H, 5.3; N, 12.3%); *m*/*z* 228 ($M^{+\bullet}$, 42%), 227 (24), 213 (22), 201 (9), 160 (23), 146 (21), 145 ($C_{10}H_9O$, 45), 144 (35), 135 ($C_7H_7N_2O$, 100), 118 (10), 115 (8), 107 (11), 91 (14), 57 (25), 51 (13), 42 (42), and 39 (24); $\nu_{max.}$(KBr) 3 200 (NH), 2 255 (CN), 1 670 (CO), 1 611, and 1 485 cm^{-1}; isomer (**7**) had δ_H[$(CD_3)_2SO$] 1.62 (3 H, s, Me), 2.14, 2.28 (2 H, m, J_{AB} 13.6, J_{AX} 2.1, and J_{BX} 4.5 Hz, AB part of ABX), 3.50 (1 H, m, additional coupling J_{XY} 4.0 Hz, X part of ABX), 4.53 (1 H, d, J_{XY} 4.0 Hz, 12-H), 6.82 (1 H, m, ArH), 6.96 (1 H, m, ArH), 7.26 (2 H, m, ArH), and 8.97 (integrated for 0.65 H, br s, NH); isomer (**8**) had δ_H 1.68 (3 H, s, Me), 2.16, 2.32 (2 H, J_{AX} 2.4 Hz, J_{BX} obscured, AB part of ABX), 3.59 (1 H, m, J_{XY} 4.0 Hz, X part of ABX), 4.52 (1 H, dd, J_{XY} 4.0 Hz, 12-H), 6.80 (1 H, dd, ArH), 6.93 (1 H, ddd, ArH), 7.26 (2 H, m, ArH), and 9.10 (1 H, br s, NH); isomer (**7**) had δ_C[$(CD_3)_2SO$] 26.6 (q), 31.4 (t), 31.7 (d), 42.4 (d), 82.8 (s), 117.1 (d), 117.3 (s), 120.6 (s), 120.8 (d), 129.7 (d), 130.8 (d), 151.4 (s), and 163.9 (s).

11-*Dicyanomethylene*-9-*methyl*-8-*oxa*-10-*azatricyclo*-[7.3.1.0^{2,7}]*trideca*-2,4,6-*triene*-12-*carbonitrile* (**10**) (2.0 g, 72%) had m.p. >230 °C (decomp.) (Found: C, 69.3; H, 4.15; N, 20.4. $C_{16}H_{12}N_4O$ requires C, 69.55; H, 4.4; N, 20.3%); *m*/*z* 276 ($M^{+\bullet}$, 53%), 275 (17), 261 (19), 249 (27), 183 (42), 182 (30), 156 (15), 145 ($C_{10}H_9O$, 100), 133 (18), 107 (16), 42 (22), 41 (21), and 39 (20); $\nu_{max.}$(KBr) 3 285 (NH), 2 230, 2 220 (CN), 1 610, and 1 488 cm^{-1}; δ_H[$(CD_3)_2SO$] 1.85 (3 H, s, Me), 2.24, 2.33 (2 H, m, J_{AB} 14.3, J_{AX} 4.4, and J_{BX} 2.0 Hz, AB part of ABX), 3.72 (1 H, additional coupling $J_{1,12}$ 2.0 Hz, X part of ABX), 4.47 (1 H, dd, *J* 2.0 and 1.0 Hz, 12-H), 6.83 (1 H, dd, *J* 7.0 and 1.2 Hz, ArH), 6.99 (1 H, ddd, *J* 7.0, 7.0, and 1.2 Hz, ArH), 7.25 (1 H, ddd, *J* 7.9, 7.0, and 1.9 Hz, ArH), 7.53 (1 H, dd, *J* 7.9 and 1.9 Hz, ArH), and 10.07 (1 H, br s, NH); δ_C[$(CD_3)_2SO$] 25.8 (q), 28.9 (tm), 30.3 (dm), 37.3 (dm), 52.6 (sdd, ^3J 3.3 Hz), 82.2 (sm), 113.0 (s), 114.5 (s), 115.8 (sdd, ^2J 12.5, and ^3J 3.5 Hz), 117.0 (ddd, ^1J 164, ^3J 7.5, and ^2J 3.5 Hz), 120.5 (sm), 121.9 (dd, ^1J 162 and ^3J 8.5 Hz), 130.0 (ddd, ^1J 162, ^3J 8.5, and ^2J 3.5 Hz), 130.3 (dm, ^1J 161 Hz), 150.9 (sm), and 161.3 (sdd, ^nJ 5.6, and 5.6 Hz).

Cyclocondensation of Salicylaldehyde with Compound (**9**), *Acetone, and Ammonium Acetate.*—Salicylaldehyde (1.8 ml, 16.5

mmol) was added dropwise to a stirred solution of compound (**9**) (2.2 g, 16.5 mmol), ammonium acetate (1.35 g, 17.5 mmol), and acetone (1.5 ml, 20 mmol) in ethanol (60 ml). The mixture was refluxed for 1 h, and the yellow precipitate, already formed after 30 min heating, was filtered off and washed several times with ethanol. *5-Amino-2-methyl*[1]*benzopyrano*[4,3,2-de]-[1,6]*naphthyridine-4-carbonitrile* (**11**) (2.47 g, 54%) was further crystallized from dimethyl formamide; m.p. >340 °C (decomp.) (Found: C, 70.2; H, 3.85; N, 20.5. $C_{16}H_{10}N_4O$ requires C, 70.1; H, 3.7; N 20.4%): $\nu_{max.}$(KBr) 3 440, 3 340, 3 210 (NH), 2 205 (CN), 1 630, 1 590, and 1 571 cm^{-1}; δ_H[$(CD_3)_2SO$] 2.60 (3 H, s, Me), 3.09 (1 H, br s, NH), 7.04 (1 H, br s, NH), 7.34 (1 H, m, ArH), 7.37 (1 H, m, ArH), 7.45 (1 H, s, ArH), 7.60 (1 H, m, ArH), and 8.09 (1 H, m, ArH); δ_C[$(CD_3)_2SO$] 25.5 (q), 100.4 (s), 107.9 (d), 116.2 (s), 117.0 (s), 117.9 (d), 124.5 (d), 125.3 (d), 132.9 (d), 137.4 (s), 151.9 (s), and 166.8 (s).

Condensation of 4-(2-*Hydroxyphenyl*)*but*-3-*en*-2-*one* (**2**; R^1 = Me) *with Cyanamide and Ammonium Acetate*.—A mixture of the butenone (3.24 g, 20 mmol), cyanamide (1 g, 24 mmol), and ammonium acetate (1.6 g, 21 mmol) was stirred at 60 °C for 2 h. The solvent was then removed and the residue triturated with diethyl ether. The separated crystals of 11-*amino*-9-*methyl*-8-*oxa*-10,12-*diazatricyclo*[7.3.1.0^{2,7}]*trideca*-2,4,6,11-*tetraene* (**12**) (1.4 g, 34%) were recrystallized from EtOH; m.p. 248—251 °C (Found: C, 65.2; H, 6.3; N, 20.75. $C_{11}H_{13}N_3O$ requires C, 65.0; H, 6.45; N, 20.7%); *m/z* 203 ($M^{+\bullet}$, 47%), 202 (53), 188 (26), 160 (8), 147 (14), 110 ($C_8H_5N_3$, 100), 109 (21), 60 (27), 45 (39), 43 (69), and 42 (24); $\nu_{max.}$(KBr) 3 600—2 300 (NH_2, NH), 1 670, 1 603, and 1 550 cm^{-1}; δ_H[$(CD_3)_2SO$] 1.72 (3 H, s, Me), 2.14 (2 H, m, AB part of ABX), 4.57 (1 H, t, *J* 3.0 Hz, X part of ABX), 6.82 (1 H, m, ArH), 6.91 (1 H, m, ArH), 7.21 (1 H, m, ArH), 7.23 (1 H, m, ArH), and 7.60 (3 H, br s, NH_2 and NH); δ_C[$(CD_3)_2SO$] 25.5 (q), 31.2 (t), 43.1 (d), 79.9 (s), 116.4 (d), 120.5 (d), 123.6 (s), 128.7 (d), 129.2 (d), 151.0 (s), and 154.4 (s).

Condensation of 4-(2-*Hydroxyphenyl*)*but*-3-*en*-2-*one* (**2**; R^1 = Me) *with Cyanamide*.—(*a*) A solution of the butenone (1.62 g, 10 mmol), cyanamide (0.8 g, 15 mmol), and four drops of piperidine was heated at 50—60 °C for 5 h. The solvent was removed under reduced pressure and the red oily residue chromatographed on a silica gel column. Elution with 5% MeOH in $CHCl_3$ afforded 75 mg (4%) of 1,5-*dimethyl*-6,22-*dioxa*-2,4,14-*triazahexacyclo*[13.7.1.0^{3,14}. 1^{5,13}.0^{7,12}.0^{16,21}]-*tetracosa*-3,7,9,11,16,18,20-*heptaene*-2-*carbonitrile* (**13a** or **b**), colourless needles from EtOH, m.p. 244—246 °C (Found: C, 71.1; H, 5.25; N, 15.0. $C_{22}H_{20}N_4O$ requires C, 70.95; H, 5.4; N, 15.0%); *m/z* 372 ($M^{+\bullet}$, 9%), 279 (5), 228 (3), 224 (4), 146 (12), 145 ($C_{10}H_9O$, 100), 144 (13), 135 (4), 116 (4), 115 (14), 91 (5), 51 (4), and 39 (5); $\nu_{max.}$(KBr) 2 240 (CN), 1 615, 1 604, and 1 488 cm^{-1}; δ_H[$(CD_3)_2SO$] 1.46 (3 H, s, Me), 1.52 (1 H, m, J_{AB} 13.2 and J_{BX} 3.5 Hz, B part of ABX), 2.07 (1 H, m, J_{AX} 2.5 Hz, A part of ABX), 5.05 (1 H, m, X part of ABX); 1.88 (3 H, s, Me), 2.04 (1 H, m, J_{AB} 14.2 and J_{BX} 3.0 Hz, B part of ABX), 2.39 (1 H, m, J_{AX} 3.4 Hz, A part of ABX), 4.95 (1 H, m, X part of ABX), 6.76 (1 H, dd, *J* 8.1, and 1.0 Hz, ArH), 6.88 (1 H, ddd, *J* 7.6, 7.6, and 1.2 Hz, ArH), 6.93 (1 H, dd, *J* 7.6 and 1.0 Hz, ArH), 7.05 (1 H, ddd, *J* 7.6, 7.6, and 1.2 Hz, ArH), 7.18 (1 H, ddd, *J* 8.1, 7.6, and 1.6 Hz, ArH), 7.31 (1 H, ddd, *J* 8.1, 7.6, and 1.6 Hz, ArH), 7.55 (1 H, dd, *J* 7.6, and 1.6 Hz, ArH), and 7.66 (1 H, dd, *J* 7.6 and 1.6 Hz, ArH); δ_C[$(CD_3)_2SO$] 25.2 (q), 28.5 (q), 32.0 (t), 32.7 (t), 49.2 (d), 51.5 (d), 83.1 (s), 85.9 (s), 107.2 (s), 116.5 (d), 116.8 (d), 119.8 (d), 121.9 (d), 122.3 (s), 122.8 (s), 128.1 (d), 128.3 (d), 129.3 (d), 129.9 (d), 145.3 (s), 149.7 (s), and 152.3 (s).

Further fractions contained the precursor (**2**; R^1 = Me) and a minor quantity of N^{11}-cyano-9-methyl-8-oxa-10,12-diazatricyclo[7.3.1.0^{2,7}]trideca-2,4,6,11-tetraene-11-amine (**14**).

(*b*) If the oily residue was dissolved in a mixture of diethyl ether and acetone and kept at 0 °C for 2—3 h, a crystalline solid (110 mg, 5%), 11-*amino*-9-*methyl*-8-*oxa*-10,12-*diazatricyclo*-[7.3.1.0^{2,7}]*trideca*-2,4,6,11-*tetraene*-10-*carbonitrile* (**15**), was obtained, m.p. 186—188 °C (from EtOH) (Found: C, 62.9; H, 5.05; N, 24.5. $C_{12}H_{12}N_4O$ requires C, 63.1; H, 5.3; N, 24.5%); *m/z* 228 ($M^{+\bullet}$, 36%), 227 (17), 187 (12), 147 ($C_8H_7N_2O$, 100), 145 (54), 144 (21), 115 (20), 91 (13), 67 (21), 51 (14), 43 (21), 42 (25), and 39 (18); $\nu_{max.}$(KBr) 3 440, 3 273, 3 228 (NH_2), 2 235 (CN), 1 685, 1 611, and 1 581 cm^{-1}; δ_H[$(CD_3)_2SO$] 1.85 (3 H, s, Me), 2.11, 2.20 (2 H, m, J_{AB} 13.7, J_{AX} 2.6, and J_{BX} 2.4 Hz, AB part of ABX), 4.44 (1 H, m, X part of ABX), 5.80 (2 H, br s, NH), 6.89—6.98 (2 H, m, ArH), and 7.16—7.23 (2 H, m, ArH); δ_C[$(CD_3)_2SO$] 25.4 (q), 31.5 (tm), 45.9 (dm), 85.4 (sm), 108.6 (s), 116.8 (dd, ^1J 162, and ^3J 8.2 Hz), 121.9 (dd, ^1J 162 and ^3J 7.8 Hz), 125.0 (sm), 128.9 (dd, ^1J 163 and ^3J 8.2 Hz), 129.7 (dm, ^1J 160 Hz), 144.8 (sm), and 150.1 (st, *J* 10 Hz).

(*c*) After 28 h reaction and cooling to room temperature we isolated 485 mg of compound (**14**). An additional crop (185 mg) and some starting material (**2**) were obtained chromatographically. The total amount of *compound* (**14**) was 660 mg (29%); m.p. 271—273 °C (from EtOH) (Found: C, 63.3; H, 5.05; N, 24.6%. $C_{12}H_{12}N_4O$ requires C, 63.1; H, 5.3; N, 24.5%); *m/z* 228 ($M^{+\bullet}$, 78%), 227 (67), 213 (44), 144 (16), 135 ($C_6H_7N_4$, 100), 93 (22), 91 (14), 68 (17), 65 (15), 42 (31), 41 (14), and 39 (22); $\nu_{max.}$(KBr) 2 185 (CN), 1 640, 1 588, and 1 555 cm^{-1}; δ_H-[$(CD_3)_2SO$] 1.69 (3 H, s, Me), 2.15 (2 H, d, dgenerate AB part of ABX), 4.50 (1 H, t, X part of ABX), 6.80 (1 H, dd, *J* 8.0 and 1.2 Hz, ArH), 6.91 (1 H, ddd, *J* 7.2, 7.2, and 1.1 Hz, ArH), 7.22 (2 H, m, ArH), and 8.58 (1 H, br s, NH); δ_C[$(CD_3)_2SO$] 25.8 (q), 31.2 (tm), 44.1 (dm), 80.9 (sm), 116.8 (dd, ^1J 163 and ^3J 8.8 Hz), 117.7 (s), 120.9 (dd, ^1J 163 and ^3J 7.9 Hz), 124.0 (sm), 129.4 (ddd, ^1J 163, $^{\prime\prime}J$ 8.7 and 4.3 Hz), 129.7 (ddd, ^1J 161, $^{\prime\prime}J$ 8.7 and 3.9 Hz), 151.3 (sm), and 157.8 (sd, $^{\prime\prime}J$ 6 Hz).

(*d*) A solution (25 ml) of the reactants in 1,2-dimethoxyethane, in the same ratio as under (*a*), was refluxed for 5 h. The crystals of (**14**) which separated overnight at room temperature were filtered off by suction and washed with diethyl ether (yield 840 mg). Evaporation of the filtrate followed by column chromatography using (5% MeOH in $CHCl_3$) gave compounds (**13**) (40 mg) and (**14**) (200 mg; total yield 1.04 g, 46%). Elution with acetone afforded cyanoguanidine (70 mg), m.p. 210—213 °C (lit.,[20] 208—211 °C).

Condensation of Salicylaldehyde with 3-*Aminocrotononitrile*.—(*a*) A mixture of 3-aminocrotononitrile (0.82 g, 10 mmol) and salicylaldehyde (2.2 ml, 20 mmol) in glacial acetic acid (5 ml) was refluxed for 1 h. The deep purple solution was then kept at room temperature. 2-(2-*Hydroxyphenyl*)-4-*methyl*-5H-[1]-*benzopyrano*[2,3-d]*pyrimidine* (**16**), which slowly crystallized, was filtered off, thoroughly washed with diethyl ether–EtOH, and dried (yield 670 mg, 23%); m.p. 187—190 °C (from EtOH) (Found: C, 74.3; H, 4.7; N, 9.55. $C_{18}H_{14}N_2O_2$ requires C, 74.5; H, 4.9; N, 9.65%); *m/z* 290 ($M^{+\bullet}$, 100%), 262 (4), 261 (4), 170 (13), 130 (29), 124.5 (13), and 102 (13); $\nu_{max.}$(KBr) 1 620, 1 598, 1 579, and 1 491 cm^{-1}; δ_H[$(CD_3)_2SO$] 2.50 (3 H, s, Me), 4.06 (2 H, s, 5-H), 6.91 (2 H, m, ArH), 7.17 (2 H, m, ArH), 7.32 (3 H, m, ArH), and 8.27 (1 H, dd, *J* 8.2 and 1.8 Hz, ArH); δ_C[$(CD_3)_2SO$] 20.6 (q), 23.4 (t), 109.0 (s), 116.4 (d), 117.2 (d), 117.9 (s), 118.5 (d), 119.2 (s), 124.5 (d), 128.0 (d), 128.4 (d), 129.1 (d), 132.6 (d), 149.6 (s), 159.8 (s), 161.6 (s), 162.7 (s), and 165.3 (s).

(*b*) A solution of 3-aminocrotononitrile (1.64 g, 20 mmol), and salicylaldehyde (1.1 ml, 10 mmol) in glacial acetic acid (8 ml) was stirred and refluxed for 1 h, during which time a white solid separated. Cooling precipitated 2,4-dimethyl-5-oxo-5*H*-[1]benzopyrano[3,4-*c*]pyridine-1-carbonitrile (**19**), which was filtered off and washed with EtOH (yield 1.17 g, 47%). It was further recrystallized from MeCN; m.p. 288—290 °C (lit.,[18] 281 °C); *m/z* 250 ($C_{15}H_{10}N_2O_2$, $M^{+\bullet}$, 100%), 222 (32), 193 (7),

181 (11), 153 (11), 126 (9), 77 (9), and 39 (10); $\delta_H[(CD_3)_2SO]$ 2.86 (3 H, s, Me), 3.00 (3 H, s, Me), 7.45—7.56 (2 H, m, ArH), 7.78 (1 H, ddd, *J* 8.3, 7.2, and 1.4 Hz, ArH), and 9.06 (1 H, dd, *J* 8.3 and 1.5 Hz, ArH).

References

1 J. D. Hepworth in 'Comprehensive Heterocyclic Chemistry,' eds. A. J. Boulton and A. McKillop, Pergamon, Oxford, 1984, vol. 3, pp. 782, 804, and 864.
2 G. Lamotte, P. Demerseman, and R. Royer, *Synthesis*, 1984, 1068.
3 A. Tromelin, P. Demerseman, and R. Royer, *Synthesis*, 1985, 1074.
4 R. S. Varma, M. Kadkhodayan, and G. W. Kabalka, *Synthesis*, 1986, 486.
5 J. Světlík, F. Tureček, and V. Hanuš, *J. Chem. Soc., Perkin Trans. 1*, 1987, 563.
6 K. Rajyalakshmi and V. N. Srinivasan, *J. Heterocycl. Chem.*, 1980, **17**, 1737.
7 A. Sakurai, Y. Motomura, and H. Midorikawa, *Bull. Chem. Soc. Jpn.*, 1973, **46**, 973.
8 D. A. Claremon, J. Hirshfield, P. K. Lumma, D. E. McClure, and J. P. Springer, *Synthesis*, 1986, 144.
9 D. C. Remy, S. W. King, D. Cochran, J. P. Springer, and J. Hirshfield, *J. Org. Chem.*, 1985, **50**, 4120.
10 G. D. Hartman, B. T. Phillips, and W. Halczenko, *J. Org. Chem.*, 1985, **50**, 2423.
11 G. D. Hartman, W. Halczenko, and B. T. Phillips, *J. Org. Chem.*, 1985, **50**, 2427.
12 N. Palit, *J. Indian Chem. Soc.*, 1933, **10**, 529 (*Chem. Abstr.*, 1934, **28**, 1345).
13 J. Prous, O. Blancafort, J. Castañer, M. N Serradell, and N. Mealy, *Drugs Fut.*, 1981, **6**, 427.
14 A. R. Katritzky, D. L. Osterkamp, and T. I. Yousaf, *Tetrahedron*, 1986, **42**, 5729.
15 C. D. Harries, *Ber. Dtsch. Chem. Ges.*, 1891, **24**, 3180.
16 E. C. Taylor and K. S. Hartke, *J. Am. Chem. Soc.*, 1959, **81**, 2452.
17 M. Mittelbach and H. Junek, *Liebigs Ann. Chem.*, 1986, 533.
18 A. Courts and V. Petrow, *J. Chem. Soc.*, 1952, 334.
19 C. N. O'Callaghan, *Synthesis*, 1986, 136.
20 L. A. Pinck, *Inorg. Synth.*, 1950, **3**, 43; see also 'Beilsteins Handbuch der Organischen Chemie,' 4th edn., ed. F. Richter, Springer Verlag, Berlin, 1961, vol. 3, p. 168.

Received 28*th September* 1987; *Paper* 7/1719