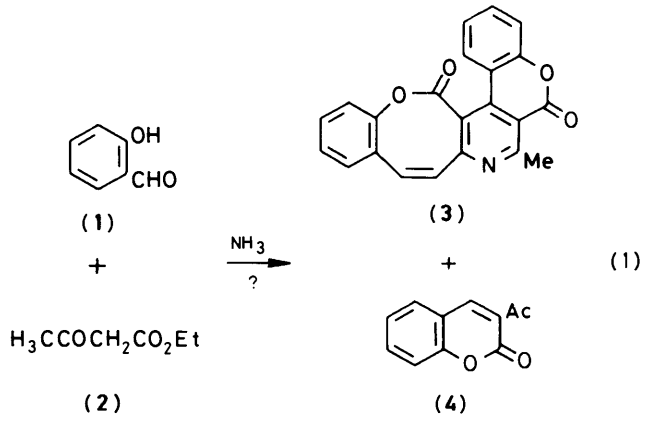
The Hantzsch Synthesis with Salicylaldehyde Revised. On the Formation of Bridged Tetrahydropyridine Derivatives

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

The Hantzsch condensation of salicylaldehyde with ethyl acetoacetate and ammonia has been re-examined. The reaction leads primarily to a 1,4-dihydropyridine intermediate which, after isomerization, undergoes a ring closure to give a bridged 1,4,5,6-tetrahydropyridine product, or is oxidized to 4-methyl-2-(2-oxo-2*H*-1-benzopyran-3-yl)[1]benzopyrano[3,4-*c*]pyridin-5-one. Bridged tetrahydropyridines with the 8-oxa-10-azatricyclo[7.3.1.$0^{2,7}$]trideca-2,4,6,11-tetraene skeleton were found in the Hantzsch-type condensation of salicylaldehyde with malononitrile, ammonium acetate, and acetone or butan-2-one. A mechanism for these reactions is discussed.

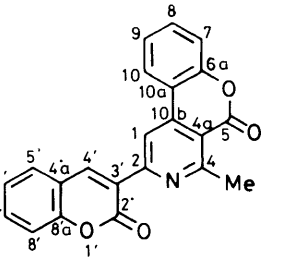
1,4-Dihydropyridine derivatives are pharmaceutically important compounds[1] which stimulate coronary vasodilatory activity.[2] A common synthetic approach to substituted 1,4-dihydropyridines makes use of the Hantzsch reaction or its modern modifications.[3] In our search for biologically active heterocyclic compounds[4] we have examined the Hantzsch condensation of salicylaldehyde (**1**) with ethyl 3-aminocrotonate, or an equivalent system consisting of ethyl acetoacetate (**2**) and ammonia. The reaction afforded a [1]benzopyrano[4,3-*d*][1]benzoxacino[4,3-*b*]pyridine derivative (**3**) [equation (1)] in low yield, besides the main product, 3-acetylcoumarin (**4**).[5] When reproducing the original synthetic procedure,[5] we obtained two products, neither of which was compatible with the postulated structures. The present paper reports on the Hantzsch condensation of salicylaldehyde (1) with some systems possessing active methyl or methylene groups, and presents evidence for the formation of a bridged tetrahydropyridine skeleton instead of the structures suggested previously.[5,6]



(1)

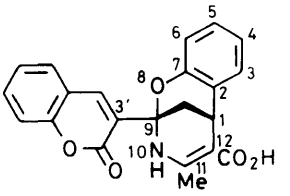
Results and Discussion

The reaction of salicylaldehyde (1) with ethyl acetoacetate (**2**) and ammonia gave in our hands two products. The first, (**5**), separated out, while the reaction mixture was being heated (3 h), as a pale yellow, highly insoluble solid which, because of its m.p. (301—302 °C), may be identical with the product previously[5] assigned structure (**3**). The second product, (**6**) [equation (2)], obtained from the mother liquor, was different from 3-acetylcoumarin (**4**), as judged by its m.p. (226—228 °C) and spectral properties. Similar results were obtained when the reaction time and the molar ratio of the reactants were varied, or when methyl acetoacetate was used instead of the ethyl analogue (**2**).



(5)

(1) + (2) $\xrightarrow{NH_3}$ + (2)



(6)

The high melting product (**5**) had the same molecular formula ($C_{22}H_{13}NO_4$ by combustion analysis and high-resolution m.s.) as had been given for compound (**3**).[5] However, the relative abundance of fragment ions in the mass spectrum was different from that reported for compound (**3**).[5] The ionized molecules $(M)^{+\cdot}$ and the $(M - CO)^{+\cdot}$ fragments represent the most abundant species in the spectrum of our product, (**5**), while fragments at *m/z* 299, 255, 243, 241, and 189 are of much lower abundance, and some even appear at different *m/z* values than previously described[5] (*m/z* 270 instead of *m/z* 271). The ^{1}H n.m.r. spectrum of compound (**5**) is clearly incompatible with structure (**3**), as it lacks signals due to the isolated AB system, and instead shows two low-field singlets at δ_H 9.21 and 9.49. The signals of the aromatic protons appear as multiplets at δ_H 7.60—

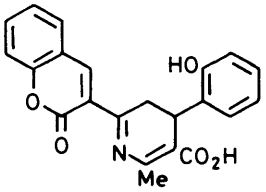
7.75 (4 H), 8.03 (3 H), and as a doublet of doublets at δ_H 8.52 (1 H). The structural assignment of compound (**5**) is based mainly on the ^{13}C n.m.r. spectrum, which shows all 22 resolved ^{13}C signals (one methyl, ten sp^2 methines, and eleven sp^2 quaternary carbons). Eight of the ten sp^2 methines belong to two *ortho*-disubstituted benzene rings originating from the salicylaldehyde units which further manifest themselves by two oxygen-bound (low field) and two carbon-bound (high field) quaternary sp^2 carbons. Of the two remaining methines, that at lower field (δ_C 149.8) corresponds to a C-4′ position of a coumarin system.[7] The presence of the latter is also substantiated by a coupling of the lowest-field ^{13}C signal of the lactone carbonyl (δ_C 162.5) with that of 4′-H, $^3J_{H,C}$ 9.5 Hz.[7] As the higher-field methine signal of a coumarin C-3′ position is absent in the spectrum of compound (**5**), while an additional singlet appears in the region of δ_C 111—117, it follows that compound (**5**) contains the coumarin unit linked *via* C-3′.

The other part of the molecule contains a tetrasubstituted pyridine nucleus (singlets at δ_C 150.4, 152.6 for C_α and C_α', 117.4 for C_β, and 147.4 for C_γ) which further shows a high-field doublet of a C_β, methine (δ_C 113.6, ^1J 172 Hz).[8] From the absence of long-range ^1H–^{13}C couplings of the latter carbon nucleus it follows that the methyl group, which is the only source of protons on the pyridine ring beside C_β', must be remote from the unsubstituted C_β' position. The second coumarin residue, which is apparent in the ^{13}C n.m.r. spectrum, must be condensed to the pyridine ring to conform to the number of rings and double bonds in the molecule. Taking into account the building blocks incorporated into compound (**5**) on the one hand, and the structural units and connectivity deduced from the n.m.r. spectra on the other, structure (**5**) appears to be the single logical candidate compatible with all spectral data.

The second product, (**6**), has the formula $C_{22}H_{17}NO_5$, indicating a structural relationship with compound (**5**). The ^1H n.m.r. spectrum exhibits a singlet for the methyl group and an ABX system in the aliphatic region, the latter corresponding to an insolated $-CH_2CH<$ subsystem ($|J_{gem}|$12.9 Hz). Furthermore, there are eight aromatic protons arranged in five multiplets, which indicate the presence of two *ortho*-condensed benzene rings, a singlet at δ_H 8.50 due to a coumarin 4′-H proton, and a temperature-dependent singlet at δ_H 8.80 which disappears upon hydrogen–deuterium exchange.

The ^{13}C n.m.r. spectrum confirms the presence of a C-3′-linked coumarin residue (δ_C 140.7 d, 118.5 s). The other part of the molecule contains the second aromatic ring which is condensed to a bicyclic, singly unsaturated system. Further substructures which can be deduced from the chemical shifts and signal multiplicities are: sp^3-C(N)(O) (δ_C 81.9 s) (ref. 9), N–C(Me)=CCO_2H (δ_C 150.0 s, 18.4 q, 101.8 s, and 171.4 s), and $-CH_2CH<$ (δ_C 30.5 t, and 29.9 d). The high-field singlet belonging to the α-carbon of the capto-dative β-enamino-carbonyl system in compound (**6**) (δ_C 101.8) resembles from the value of its chemical shift, the signals of C-3 and C-5 in 1,4-dihydropyridines.[10]

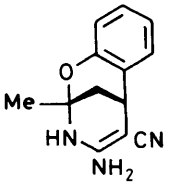
Assembly of the molecular fragments gives several isomeric structures of which only (**6**) is topologically related to (**5**) [equation (2)]. Indeed, when refluxed in acetic acid, compound (**6**) is converted into lactone (**5**) *via* opening of the oxygen ring,



(**7**)

lactonization, and aromatization of the intermediate dihydropyridine (**7**) (see Scheme).

In order to obtain support for structure (**6**) and to examine the interconversion (**6**) ⇌ (**7**), we have prepared the condensation product of salicylaldehyde (**1**) with malonitrile, acetone, and ammonium acetate for which a 3,4-dihydropyridine structure was reported.[6] In contrast to the original work,[6] in our hands the reaction reproducibly yielded two isolable products, one of which was readily identified as 2,4-diamino-5-imino-5*H*-[1]benzopyrano[3,4-*c*]pyridine-1-carbonitrile[11] (**9**) [equation (3)]. The second product, (**8**) had an identical molecular formula with the product reported in the literature,[6] while having a higher m.p. The ^1H n.m.r. spectrum of compound (**8**) shows an ABX system with coupling constants very similar to those in the spectrum of compound (**6**), and with chemical shifts nearly identical with those reported earlier for the postulated 3,4-dihydropyridine derivative.[6] In the ^{13}C n.m.r. spectrum, however, compound (**8**) lacks the signal of the quaternary imine carbon atom which would have been expected for a 3,4-dihydropyridine. An analogous compound with the 2-azabutadiene system shows a ^{13}C signal near δ_C 166,



(**8**)

(1) + $CH_2(CN)_2$ + CH_3COCH_3 $\xrightarrow{NH_4OAc}$ (8) + (9) (3)

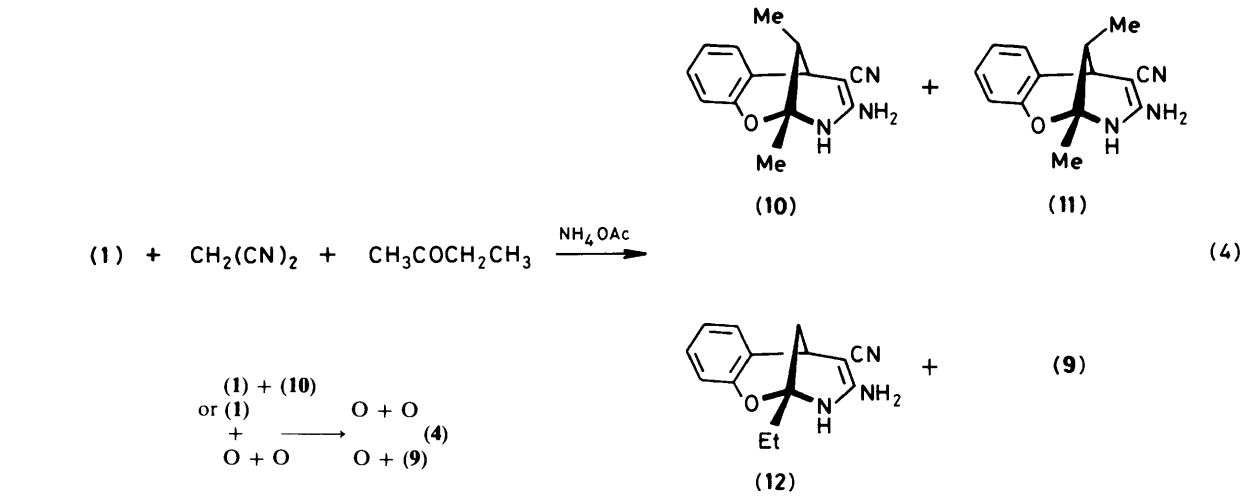
(1) + O + O ⟶ (8) + (9) (2)

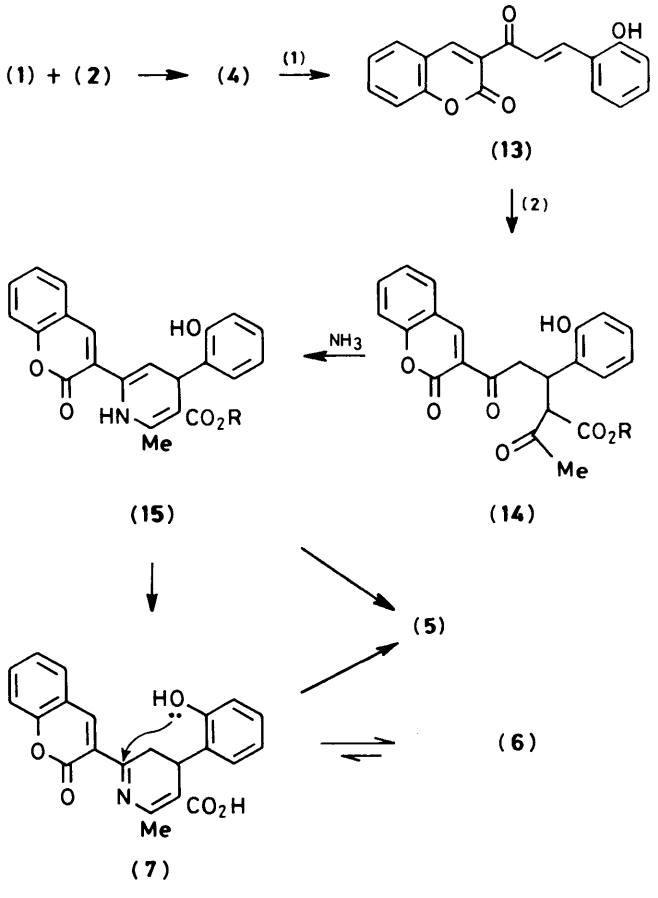
(**9**)

corresponding to the imine carbon atom.[12] By contrast, the spectrum of compound (**8**) reveals a singlet for an sp^3 carbon atom at δ_C 81.6 which is analogous to that of the C(O)(N) grouping in compound (**6**). The other signals can be assigned to an N–C(NH_2)=CCN system[13] (δ_C 155.8 s, 55.4 s, and 123.2 s), a $CH_2CH<$ fragment (δ_C 32.6 t, and 30.8 d), the methyl group (δ_C 27.2 q), and the benzene ring. All these data suggest that the postulated 3,4-dihydropyridine[6] exists as an oxygen-bridged tetrahydropyridine isomer of structure (**8**).

The condensation of compound (**1**) with malononitrile and butan-2-one afforded, besides compound (**9**), a mixture of the three isomers (**10**), (**11**), and (**12**) [equation (4)], which were not separated, but could be identified through their ^{13}C n.m.r. spectra. The configuration of the apical methyl group was not established and may be reversed in isomers (**10**) and (**11**). The formation of the 8-oxa-10-azatricyclo[7.3.1.$0^{2,7}$]trideca-2,4,6,11-tetraene skeleton in compounds (**6**), (**8**), and (**10**)—(**12**) has an analogy in the condensation of benzamidine with unsaturated ketones derived from salicylaldehyde (**1**), for which the structures of the products, 8-oxa-10,12-diazatricyclo[7.3.1.$0^{2,7}$]trideca-2,4,6,11-tetraene derivatives, was confirmed by *X*-ray analysis.[14]

Having the structures of all products established, we now return to the Hantzsch condensation leading to compounds (**5**)





Scheme.

and (**6**) (Scheme). The reaction sequence probably starts in a conventional manner with the condensation of compounds (1) and (**2**) to give 3-acetylcoumarin[15] (**4**) which then undergoes aldol condensation with a second molecule of aldehyde (**1**). The chalcone-like product (**13**) further reacts with another molecule of ester (**2**) in a Michael addition, and the resulting diketone intermediate (**14**) closes to give a 1,4-dihydropyridine ring with ammonia. Oxidation and lactone ring closure in this product (**15**) eventually give compound (**5**). In order to produce compound (**6**) the ester group must be hydrolysed and the 1,4-dihydropyridine system in compound (**15**) must isomerize to a 3,4-dihydropyridine (**7**). A driving force for the prototropic isomerization is possibly provided by the extension of the conjugated system in compound (**7**), compared with the cross-conjugated one in precursor (**15**). The final intramolecular Michael addition of the phenolic hydroxy group to the imine system can be viewed as a simultaneous 6-*exo*-trig/8-*endo*-trig process, according to Baldwin's rules.[16] The last step also takes place in the condensation of salicylaldehyde (**1**) with malononitrile, ketones, and ammonium acetate. This shows that the imino group of the intermediate 3,4-dihydropyridines is reactive enough towards intramolecular nucleophilic attack by the phenolic hydroxy group such that the reaction can proceed as a favourable ring-forming process.[16]

Experimental

Methods.—Mass spectra were recorded on a Jeol D-100 double-focusing spectrometer (75 eV; 300 μA), using a direct probe inlet. Elemental compositions of ions were measured by the peak-matching method with perfluorokerosene as an internal standard. ^{1}H and ^{13}C n.m.r. spectra were measured on a Varian XL-200 spectrometer (200.057 and 50.309 MHz for ^{1}H and ^{13}C, respectively; FT mode; 22 °C). The chemical shifts (δ) were referenced to the residual signals of the solvents used. I.r. spectra were measured on a IR-75 Zeiss (Jena) grating spectrophotometer. M.p.s (uncorrected) were determined on a Boetius micro hot-stage apparatus.

Condensation of Salicylaldehyde with Methyl Acetoacetate and Ammonia.—Salicylaldehyde (2.2 ml, 200 mmol) was added dropwise at room temperature to a stirred solution of methyl acetoacetate (2.4 ml, 20 mmol) and ammonia (3 ml of 26% solution, 42 mmol) in ethanol (7 ml). A voluminous precipitate formed immediately which later dissolved when the mixture was refluxed for 3 h. The separated solid was filtered off, washed successively with acetone, hot dimethylformamide, and EtOH, and dried *in vacuo*. 4-*Methyl*-2-(2-*oxo*-2H-1-*benzopyran*-3-*yl*)[1]*benzopyrano*[3,4-c]*pyridin*-5-*one* (**5**) (115 mg, 3%) was obtained as pale yellow needles, m.p. 301—302 °C (Found: C, 74.1; H, 3.5; N, 4.1. $C_{22}H_{13}NO_4$ requires C, 74.36; H, 3.69; N, 3.94%); *m/z* 355.0836 ($M^{+\bullet}$, 89%), 327 (100), 299 (12), 298 (5), 271 (5), 270 (10), 177.5 (12, M^{2+}), and 156 (12); $\nu_{max.}$(KBr) 1 717, 1 710 (CO), 1 637, 1 630, 1 609 (C=C), 1 487, 1 457, and 1 443 cm^{-1}; δ_H (CF_3CO_2D) 3.48 (3 H, s, Me), 7.64 (1 H, dd, *J* 8.6 and 0.8 Hz, ArH), 7.71 (3 H, m, ArH), 8.03 (3 H, m, ArH), 8.52 (1 H, dd, *J* 8.1 and 1.0 Hz, ArH), 9.21 (1 H, s, 4′-H), and 9.49 (1 H, s, 1-H); δ_C (CF_3CO_2D) 21.4 (q, Me), 111.1 (s, C-3′), 112.9 (s, C-10a), 113.6 (d, ^1J 172 Hz, C-1), 114.6 (s, C-4′a or C-4a), 116.1 (d, C-7 or C-

8'), 117.3 (d, C-8' or C-7), 117.4 (s, C-4a or C-4'a), 124.6, 126.1, 126.4, 130.0, 137.0, and 137.1 (d, C-8, -9, -10, -5', -6', and -7'), 147.4 (s, C-10b), 149.8 (d, ^1J 166 Hz, C-4'), 150.4 (s, C-2), 152.6 (s, C-4), 153.5 (s, C-8'a), 158.6 (s, C-5), 160.0 (s, C-6a), and 162.5 (d, ^3J 9.5 Hz, C-2').

11-*Methyl*-9-(2-*Oxo*-2H-1-*benzopyran*-3-*yl*)-8-*oxa*-10-*azatricyclo*[7.3.1.0^{2,7}]*trideca*-2,4,6,11-*tetraene*-12-*carboxylic acid* (**6**) (715 mg, 19%) slowly crystallized from the filtrate to give an essentially pure product, which was recrystallized from MeCN, m.p. 226—228 °C (decomp.) (Found: C, 70.2; H, 4.4; N, 3.8%; M^+, 375.1097. $C_{22}H_{17}NO_5$ requires C, 70.39; H, 4.56; N, 3.73%; *M*, 375.1107); $\nu_{max.}$(KBr) 3 427 (NH), 1 720 (CO), 1 607, 1 597, 1 573, 1 543, 1 455, 1 440, 1 393, 1 274, 1 258, 1 180, 1 100, 1 045, 1 034, and 1 023 cm^{-1}; δ_H [$(CD_3)_2SO$] 2.11 (1 H, dd, *J* 12.9 and 3.8 Hz, A part of ABX), 2.26 (3 H, s, Me), 2.85 (1 H, dd, *J* 12.9, 2.7 Hz, B part of ABX), 4.13 (1 H, dd, *J* 3.8 and 2.7 Hz, X part of ABX), 6.99 (2 H, m, ArH), 7.22 (2 H, m, ArH), 7.42 (2 H, m, ArH), 7.68 (1 H, m, ArH), 7.90 (1 H, dd, *J* 7.7 and 1.4 Hz, ArH), 8.50 (1 H, s, 4'-H), and 8.80 (1 H, br s, exchangeable, NH); δ_C [$(CD_3)_2SO$] 18.4 (q, Me), 29.9 (d, C-1), 30.5 (t, C-13), 81.9 (s, C-9), 101.8 (s, C-12), 115.8 (d, C-6 or C-8'), 117.2 (d, C-8' or C-6), 118.5 (s, C-3'), 126.3 (s, C-2 or C-4'a), 127.1 (s, C-4'a or C-2), 121.4, 124.7, 128.0, 128.3, 129.2, and 132.3 (d, C-3, -4, -5, -5', -6', and -7'), 140.7 (d, C-4'), 150.0 (s, C-11), 153.3 (s, C-7 or C-8'a), 157.9 (s, C-8'a or C-7), 169.0 (s, C-2'), and 171.4 (s, CO_2H).

Aromatization of Compound (**6**).—A solution of compound (**6**) (300 mg) in glacial acetic acid (15 ml) was refluxed for 10 h. On cooling, pale yellow crystals were obtained (80 mg, 28%) which were identical by n.m.r., i.r., m.s., and m.p. with an authentic sample of compound (**5**). The starting compound (**6**) was recovered from the filtrate.

Condensation of Compound (1) *with Malononitrile, Acetone, and Ammonium Acetate.*—A solution of malononitrile (2.2 g, 33 mmol), compound (**1**) (3.5 ml, 33 mmol), acetone (2.5 ml, 33 mmol), and ammonium acetate (2.7 g, 40 mmol) in ethanol (20 ml) was stirred and refluxed for 1 h. 2,4-*Diamino*-5-*imino*-5H-[1]*benzopyrano*[3,4-c]*pyridine*-1-*carbonitrile* (**9**), which precipitated out during the reaction, was filtered off, washed with hot EtOH, and dried (200 mg, 3%), m.p. 315—317 °C (lit.,[11] 293—295 °C); (Found: M^+, 251.0808. $C_{13}H_9N_5O$ requires *M*, 251.0807); δ_H [$(CD_3)_2SO$] 6.93 (2 H, br s, NH_2), 7.20 (1 H, dd, ArH), 7.30 (1 H, ddd, ArH), 7.58 (1 H, ddd, ArH), 7.69 (br d, *J* 4 Hz, NH), 8.35 (1 H, br s, NH), 8.83 (1 H, dd, ArH), and 10.08 (1 H, br d, *J* 4 Hz, NH); δ_C [$(CD_3)_2SO$] 70.8 (s), 92.4 (s), 116.0 (s), 116.6 (d), 119.6 (s), 123.5 (d), 125.3 (d), 132.9 (d), 152.1 (s), 155.3 (s), 160.2 (s), 161.0 (s), and 162.5 (s).

The filtrate was kept at room temperature for 2 days, during which a crystalline solid separated. It was recrystallized from EtOH to give 11-*amino*-9-*methyl*-8-*oxa*-10-*azatricyclo*-[7.3.1.0^{2,7}]*trideca*-2,4,6,11-*tetraene*-12-*carbonitrile* (**8**) (800 mg, 11%), m.p. 273—275 °C (Found: C, 68.85; H, 5.7; N, 18.35%; M^+, 227.1056. $C_{13}H_{13}N_3O$ requires C, 68.70; H, 5.77; N, 18.49%; *M*, 227.1059); $\nu_{max.}$ (KBr) 3 400, 3 333, 3 227 (NH_2, NH), 2 150 (CN), 1 647, 1 600, 1 520, 1 483, 1 455, 1 400, 1 387, 1 320, 1 252, 1 175, 1 144, 1 113, 1 077, 920, and 860 cm^{-1}; δ_H [$(CD_3)_2SO$] 1.64 (3 H, s, Me), 1.94 (1 H, m, *J* 12.7 and 3.2 Hz, A part of ABX), 1.99 (1 H, m, *J* 12.7 and 3.2 Hz, B part of ABX), 3.42 (1 H, m, *J* 3.2 and 3.2 Hz, X part of ABX), 5.31 (2 H, s, exchangeable, NH_2), 6.72 (2 H, m, ArH), 7.03 (2 H, m, ArH), and 7.16 (1 H, s, exchangeable, NH); δ_C [$(CD_3)_2SO$] 27.2 (q, Me), 30.8 (d, C-1), 32.6 (t, C-13), 55.4 (s, C-12), 81.6 (s, C-9), 116.1 (d, C-6), 120.1 (d, C-4), 123.2 (s, CN), 127.2 (d, C-3 or C-5), 127.4 (d, C-5, or C-3), 129.0 (s, C-2), 151.8 (s, C-7), and 155.8 (s, C-11).

Cyclocondensation of Compound (**1**) *with Malononitrile, Butan-2-one, and Ammonium Acetate.*—The reaction was carried out as described above, and yielded a 50:30:20 mixture of tricyclic products (**10**), (**11**), and (**12**) (7%), m.p. 253—255 °C [Found (for the mixture): C, 69.55; H, 6.4; N, 17.6%; M^+, 241.1221. Calc. for $C_{14}H_{15}N_3O$: C, 69.69; H, 6.27; N, 17.41%; *M*, 241.1215]); $\nu_{max.}$(KBr) 3 420, 3 327, 3 222 (NH_2, NH), and 2 147 cm^{-1} (CN).

anti-11-Amino-9,13-dimethyl-8-oxa-10-azatricyclo-[7.3.1.0^{2,7}]trideca-2,4,6,11-tetraene-12-carbonitrile (**10**) had δ_H [$(CD_3)_2SO$] 0.99 (3 H, d, Me), 1.55 (3 H, s, Me), 2.00 (1 H, qm, J_q 6.8 Hz, w_m 5.5 Hz), 3.09 (1 H, d, *J* 2.6 Hz), 5.32 (2 H, br s, exchangeable, NH_2), 6.73 (2 H, m, ArH), 7.00 (2 H, m, ArH), and 7.02 (1 H, br s, exchangeable, NH); δ_C [$(CD_3)_2SO$] 13.9 (q, Me), 24.7 (q, Me), 33.1 (d, C-1), 37.4 (d, C-13), 52.2 (s, C-12), 85.1 (s, C-9), 115.7 (d, C-6), 119.7 (d, C-14), 123.4 (s, CN), 126.7 (d, C-3 or C-5), 127.0 (d, C-5 or C-3), 130.5 (s, C-2), 141.4 (s, C-7), and 155.1 (s, C-11).

The *syn* isomer (**11**) had δ_H 0.86 (3 H, d, Me), 1.55 (3 H, s, Me), 1.89 (1 H, qm), 3.10 (1 H, d), 5.32 (2 H, br s, NH_2), 6.73 and 7.00 (4 H, m, C_6H_4), and 7.02 (1 H, br s, NH); δ_C 13.4 (q, Me), 24.9 (q, Me), 34.0 (d, C-1), 37.5 (d, C-13), 56.9 (s, C-12), 83.8 (s, C-9), 115.7 (d, C-6), 120.4 (d, C-4), 122.7 (s, CN), 127.0 (d, C-3 or C-5), 128.4 (d, C-5 or C-3), 126.5 (s, C-2), 151.1 (s, C-7), and 155.3 (s, C-11).

11-Amino-9-ethyl-8-oxa-10-azatricyclo[7.3.1.0^{2,7}]trideca-2,4,6,11-tetraene-12-carbonitrile (**12**) had δ_H (*inter alia*) 0.99 (3 H, t, Me), 1.90 (2 H, q, CH_2Me), 1.95 (1 H, m), 3.24 (1 H, t), and 5.32 (2 H, br s, NH_2); δ_C 7.85 (q, Me), 29.9 (t, CH_2Me), 30.6 (d, C-1), 32.4 (t, C-13), 55.6 (s, C-12), 83.7 (s, C-9), 116.0 (d, C-6), 119.9 (d, C-4), 122.9 (s, CN), 126.7 (d, C-3 or C-5), 127.2 (d, C-5 or C-3), 129.0 (s, C-2), 151.8 (s, C-7), and 156.0 (s, C-11).

References

1 D. Lednicer and L. A. Mitscher, 'The Organic Chemistry of Drug Synthesis,' Wiley, New York, 1980, vol. 2, p. 283.
2 J. Prous, P. Blancafort, J. Castañer, M. N. Serradell, and N. Mealy, *Drugs Fut.*, 1981, **6**, 427.
3 J. Kuthan and A. Kurfürst, *Ind. Eng. Chem. Prod. Res. Dev.*, 1982, **21**, 191 (*Chem. Abstr.*, 1982, **96**, 199 434*e*) D. M. Stout and A. I. Meyers, *Chem. Rev.*, 1982, **82**, 223.
4 P. Čupka and J. Světlík, *Synth. Commun.* 1986, **16**, 529.
5 K. Rajyalakshmi and V. N. Srinivasan, *J. Heterocycl. Chem.*, 1980, **17**, 1737.
6 A. Sakurai, Y. Motomura, and H. Midorikawa, *Bull. Chem. Soc. Jpn.*, 1973, **46**, 973.
7 N. J. Cussans and T. N. Huckerby, *Tetrahedron*, 1975, **31**, 2587.
8 E. Breitmeier and W. Voelter, '^{13}C NMR Spectroscopy,' Verlag Chemie, Weinheim, New York, 1978, p. 200.
9 H. O. Kalinowski, S. Berger, and S. Braun, '^{13}C-NMR Spektroskopie,' Thieme Verlag, Stuttgart, New York, 1984, pp. 314—333; C. Filliatre and C. Servens, *J. Heterocycl. Chem.*, 1985, **22**, 1009.
10 R. A. Dommisse, J. A. Lepoivre, and F. C. Alderweireldt, *Bull. Soc. Chim. Belg.*, 1977, **86**, 267.
11 A. Sakurai, Y. Motomura, and H. Midorikawa, *J. Org. Chem.*, 1972, **37**, 1523.
12 L. Fuentes, A. Lorente, and J. L. Soto, *J. Heterocycl. Chem.*, 1979, **16**, 273.
13 H. Wamhoff and H. A. Thiemig, *Chem. Ber.*, 1985, **118**, 4473.
14 A. L. Weiss and F. Frolow, *J. Org. Chem.*, 1984, **49**, 3635.
15 E. Knoevenagel, *Ber. Dtsch. Chem. Ges.*, 1898, **31**, 2585.
16 J. E. Baldwin, *J. Chem. Soc., Chem. Commun.*, 1976, 734; J. E. Baldwin, J. Cutting, W. Dupont, L. Kruse, L. Silberman, and R. C. Thomas, *ibid.*, p. 736; J. E. Baldwin, R. C. Thomas, L. I. Kruse, and L. Silberman, *J. Org. Chem.*, 1977, **42**, 3846.

Received 14*th March* 1986; *Paper* 6/511