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5*H*-Pyrrolo[1,2-*a*][3,1]benzoxazin-5-ones Reconsideration of the Double Cyclisation of *o*-Carboxyphenylglycine

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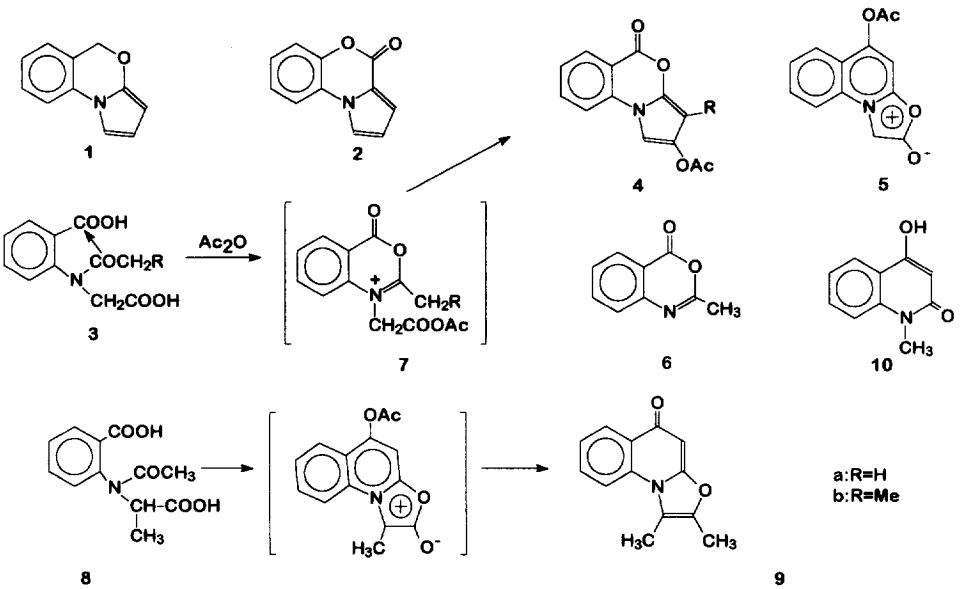
Abstract: The X-ray structure of the title reaction product is 2-acetoxy-5*H*-pyrrolo[1,2-*a*][3,1] benzoxazin-5-one (**4a**). New tautomeric forms of tetramic acid as the fixed derivatives **4** and **11** are described as well as a 1,3-dipolar cycloaddition of **4** and a reverse Diels-Alder reaction of the hydrogenated cycloadducts **15a-c** . Copyright © 1996 Published by Elsevier Science Ltd

Very little information about the heterocyclic system of 5*H*-pyrrolo[1,2-*a*][3,1]benzoxazine (**1**) can be found in the literature.[1] The unstable parent compound could not be isolated and only the related 4*H*-pyrrolo[2,1-*c*][1,4]benzoxazin-4-one (**2**) has been fully described.[2] It has been proved now by single crystal X-ray analysis (Fig. 1 and Experimental Part) that the real structure of the product of the title reaction as well as of the double cyclisation of **3a** (better yields), resulting from the action of acetic anhydride and which was previously[3] considered as the mesoionic oxazolone **5a**, is 2-acetoxy-5*H*-pyrrolo[1,2-*a*][3,1]benzoxazin-5-one (**4a**) (Chart 1).

We can reasonably assume that the first step of the cyclisation follows the course of a similar reaction, the formation of acetylanthranil (**6**) from N-acetylanthranilic acid.[4] In our case the intermediate benzoxazinonium cation **7a** cyclises further to the final product **4a**. Curiously, under the same conditions the *o*-carboxyphenylalanine (**8**) led to the 1,2-dimethyl-5*H*-oxazolo[3,2-*a*]quinolin-5-one (**9**) by the Dakin-West route which involves a mesoionic intermediate.[3] The first case implies the attack of the amidic oxygen at the benzoic carbonyl group while the second one involves attack of the activated methyl of the same acyl group. The latter case can be exemplified by the cyclisation of the *N*-methylanthranilic acid to *N*-methyl-4-hydroxycarbostyril (**10**).[5] The formation in a first step of intermediate 2,4-pyrrolidinedione or mesoionic derivatives by the same type of attacks at the glycine carbonyl group can be ruled out as they anhydrodimerise or are readily stabilised by acylation and no such compounds were identified in the reaction mixtures.[3,6]

CHART 1

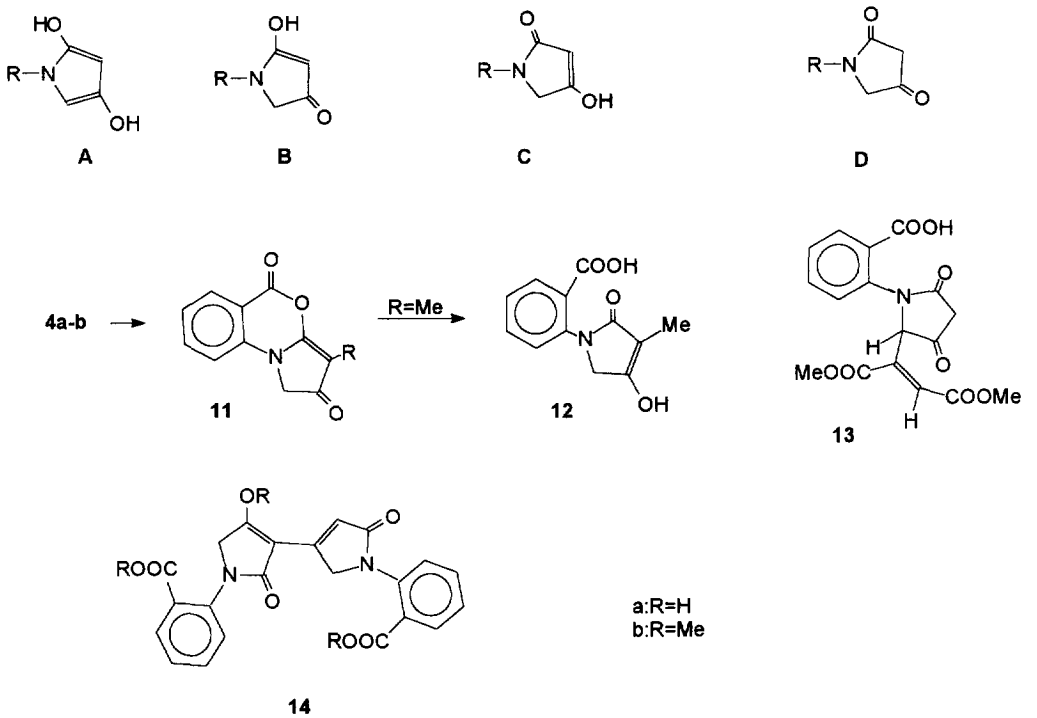


Compounds **11, 12, 13** and **14** (Chart 2) have been already described but their formerly assigned structures must now be reconsidered (Table).[3,7] They are of interest as representing with **4** the tautomers **A-D** in free state or as fixed derivatives of tetramic acid (2,4-pyrrolidinedione). The latter was synthesised in 1972 and was shown to occur in the keto and enol forms **C** and **D**.[6] The formation of the 5-hydroxy-3-pyrrolinones **11a-b** was the result of the selective hydrolysis by reflux in 96% acetic acid of the 2,4-dihydroxypyrrole derivatives **4a-b.** The 4-hydroxy-2-pyrrolinone **12** was obtained by acid or alkaline hydrolysis of **4b.** Under the same conditions **4a** led to the anhydrodimer **14a**, which on treatment with diazomethane gave the ester **14b**. The reaction closely resembles the anhydrodimerisation of tetramic acid.[6]

Pyrrolobenzoxazinones **4a-b** behave as 1,3-dipoles. For **4b**, ^{13}C-NMR (CD_3NO_2): δ = 97.3 (1-C) and 140 (3a-C) assignments being made by HETCOR and COLOC. In aprotic solvents with dimethyl acetylenedicarboxylate (DMAD) the cycloadducts **15a-c** (Chart 3) resulted by a stepwise mechanism since the intermediate diions could be trapped in protic solvents as the fumaric esters *E*-**16a-c.** The *Z*-**16** isomers could be obtained by partial cycloreversion of **15a-c** in refluxing acetic anhydride. Selective acid hydrolysis of either **15a** or *E*-**16a** in 96% acetic acid with a trace of hydrochloric acid led to the pyrrolidinedione **13**.[7]

The significant spectral data are the IR-carbonyl stretching frequencies and the ^{1}H-NMR chemical shifts of methylene groups. The former are (KBr): 1670 and 1780 (**13**),[6,8] 1785 (**11**) and 1688 cm^{-1} (**12**).[9] For the latter (δ): 4.30-4.35 (**11** and **12**; d_6-DMSO), 3.47 and 3.53 (**13**; $CDCl_3$; J_{ABX} = 21, 1.5 and 0.75 Hz; X=5-H at 6.49 ppm. No tautomeric equilibria were observed. The protons in the ethylenic side chains are at 7.04 (**13**), 7.12-7.20 (*E*-**16**) and at 6.13-6.27 (*Z*-**16**).

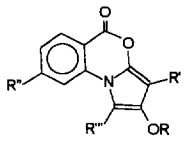
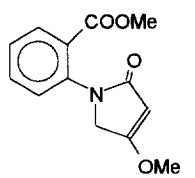
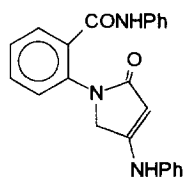
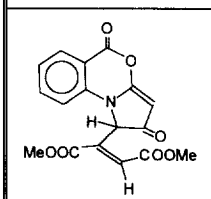
CHART 2



Selective hydrogenation of **15a-c** at room temperature with Pd/C-catalyst led to **17a-c**. For **17a** , ^{1}H-NMR ($CDCl_3$) ; δ = 2.08 (dd ; H_b), 2.80 (dd ; H_a), 5.38 (d ; H_d), 5.67 (octet; H_c); J_{ab} = 12, J_{ac} = 8, J_{bc} = 2.75 and J_{cd} = 4.25 Hz. The reaction occurs stereoselectively according to Alder's rule[10] of *exo*-addition. Evidence is furnished by the value of J_{cd} which corresponds to an *exo*-H_c[11] and by the fact that in the case of **17b** the coupling constant which implies the *endo*-H_b is lacking. Therefore an *endo-cis* configuration can be unambiguously assigned to **17b**. The hydrogenated product **17a** on mild thermolysis at 175° underwent a reverse Diels-Alder reaction with elimination of vinyl acetate and formation of the pyrrolobenzoxazinone **18.** Evidence in favour of a concerted mechanism is brought by the thermolysis of **17b** which afforded exclusively the *Z*-1-propen-1-ol acetate (**19b**) which exhibits an ethylenic *cis*-coupling of 6.8 Hz.[12] By partial hydrolysis of **18** and treatment with diazomethane the methoxy triester **20** was obtained. Attempts of decarboxylative alkaline hydrolysis of **18** led to anthranilic acid (enamine behaviour) and as expected no reaction with DMAD could be observed.

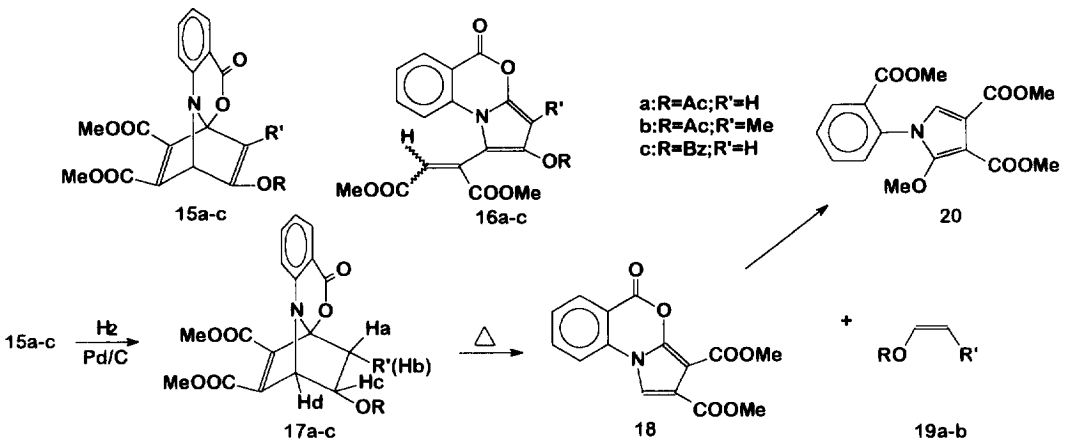
TABLE

Revised Structures of Refs. 3 and 7

Revised structures	Substituents	Erroneous structures [a]	Refs.
4a-h 	a: R=Ac;R'=R"=R"'=H b: R=Ac;R'=Me;R"=R"'=H c: R=Ts;R'=R"=R"'=H d: R=Bz;R'=R"=R"'=H e: R=Ac;R'=R"'=H;R"=PhCH$_2$O f: R=Ac;R'=R"'=H;R"=OH g: R=Ac;R'=R"=H;R"'=CF$_3$CO h: R=Ac;R'=Me;R"=H;R"'=CF$_3$CO	**5a** **5b** **7** **8** **16** **17** **23a** **23b**	3
11a-b	a: R=H b: R=Me	**6a-b**	3
12		**27a**	3
		**27b**	3
13		**6a;(V)**	7
14a-b	a: R=H b: R=Me	**28a-b**	3
		**32**	3
15a-c	a: R=Ac;R'=H b: R=Ac;R'=Me c: R=Bz;R'=H	**2a-c;(II)**	7
E-**16a-d** *Z*-**16a-c**	a: R=Ac;R'=H b: R=Ac;R'=Me c: R=Bz;R'=H d: R=Ts;R'=H	**3a-d;(*E*-III)** **4a-c;(*Z*-III)**	7
	a: R=H b: R=Me	**5a-b;(IV)**	7

[a] Roman numbers in parentheses refer to the chemical abstract of reference 7.

CHART 3



EXPERIMENTAL

Single crystal X-ray analysis of **4a.**

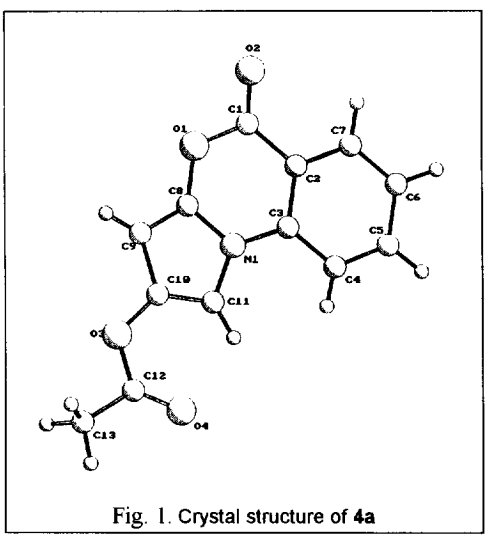


Fig. 1. Crystal structure of **4a**

The structure was solved with SHELX-86 by the direct method. Hydrogen atoms were included at the calculated position and refined isotropically. The non-hydrogen atoms were refined anisotropically. Some significant bond lengths (Å) angles in degrees and E's.d. in parentheses are as follows: O(1)-C(1) 1.371(3); O(1)-C(8) 1.373(2); O(2)-C(1) 1.203(3); N-C(3) 1.387(3); N-C(8) 1.381(3); N-C(11) 1.407(3); C(1)-C(2) 1.467(3); C(8)-C(9) 1.343(4); C(9)-C(10) 1.426(3); C(10)-C(11) 1.355(4); O(2)-C(1)-O(1) 116.4(2); O(2)-C(1)-C(2) 125.6(2); O(1)-C(1)-C(2) 118.0(2); N-C(3)-C(4) 123.3(2); N-C(3)-C(2) 117.2(2); C(8)-C(9)-C(10) 104.9(2); C(11)-C(10)-C(9) 110.4(2); C(10)-C(11)-N 106.4(2).

Further details are available from Cambridge Crystallographic Data Center.

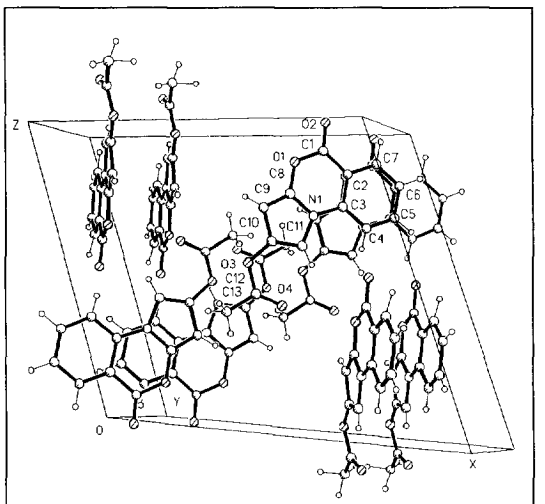


Fig.2. Crystal packing of **4a**

New compounds and reactions.

NMR spectra were recorded on Varian Gemini-300 and Varian A 60-A instruments, the chemical shifts being expressed in δ values. UV and IR spectra were measured with Specord and UR-20 (Carl Zeiss-Jena) spectrometers respectively. All mps were taken with a micro-Boetius apparatus.

Dimethyl 11-acetoxy-12-methyl-5-oxo-1,3a-ethano-5*H*-pyrrolo[1,2-*a*][3,1]benzoxazine-2,3-dicarboxylate (17b). Hydrogenation of **15b**[7] occurred catalytically at room temperature and ordinary pressure in the presence of 5% Pd/C. In 260 ml of tetrahydrofuran, 13 g of the cycloadduct **15b** were dissolved. No more hydrogen was absorbed after 5 hrs when after filtration and vacuum evaporation of the solvent a viscous residue was obtained. This readily crystallised on trituration with ethanol when 10.5 g of **17b** were obtained (yield 76 %) which after recrystallisation from ethanol had a mp of 149°.

In some experiments the hydrogenation of the double bond $\Delta^{11,12}$ could not be brought to completion. The separation of the product from the unreacted material did not succeed by the usual methods. These difficulties could be avoided by a simple procedure. The raw hydrogenation product was dissolved in 70% perchloric acid in the cold, 1:10 (w/v). By reprecipitation with ice-water and recrystallisation from ethanol a pure product was obtained with mp 150°.

Found: C 60.14; H 4.98; N 3.63. Calcd. for $C_{20}H_{19}NO_8$: C 59.85; H 4.77; N 3.49. IR (KBr): 1720 (ester CO), 1756 (δ-lactone). ^{1}H-NMR ($CDCl_3$): 1.10 (d, 3, 12-Me), 2.07 (s, 3, 11-AcO), 2.97 (split quintet, 1, Ha), 3.78 and 3.85 (ss, 6, 2- and 3-COOMe), 5.32 (d, 1, Hd), 5.67 (dd, 1, Hc), 6.84 (d, 1, 9-H), 7.08 (dt, 1, 7-H), 7.53 (dt, 1, 8-H), 8.02 (dd, 1, 6-H); $J_{Me,Ha}$= 7.5, J_{ac}= 8.5 and J_{cd}= 4.5 Hz.

Dimethyl 11-acetoxy-5-oxo-1,3a-ethano-5*H*-pyrrolo[1,2-*a*][3,1]benzoxazine-2,3-dicarboxylate (17a). Starting from **15a** the same procedure as for **17b** was followed: yield 83% and mp 135° after recrystallisation from ethanol or carbon tetrachloride.

Found: C 59.34; H 4.79; N 3.83. Calcd. for $C_{19}H_{17}NO_8$: C 58.91; H 4.42; N 3.61. IR (KBr): 1732 (ester CO), 1758 cm^{-1} (δ-lactone). ^{1}H-NMR ($CDCl_3$): 2.02 (s, 3, AcO), 3.77 and 3.88 (ss, 6, COOMe), 6.83 (d, 1, 9-H), 7.07 (t, 1, 7-H), 7.52 (t, 1, 8-H), 8.00 (d, 1, 6-H). The rest of the chemical shifts and the coupling constants are discussed in the theoretical part of the paper. ^{13}C-NMR: 20.5 ($\underline{C}H_3COO$), 37.6 (12-

CH_2), 52.5 and 52.9 (OCH_3), 62.8 (1-CH), 70.0 (11-C), 101.1 (3a-C), 114.6 (5a-C), 116.1, 122.8, 131.4 and 136.1 (aromatic CH), 134.2 (9a-C), 145.5 and 146.8 (2- and 3-C), 160.1, 162.0 and 162.6 (COOMe and CO-lactone), 170.3 (MeCOO).

Dimethyl 11-benzoyloxy-5-oxo-1,3a-ethano-5*H*-pyrrolo[1,2-*a*][3,1]benzoxazine-2,3-dicarboxylate (17c). The same method as above was used. Starting from **15c** white crystals with mp 175° (from ether) were obtained (yield 84%).

IR (KBr): 1725 (CO), 1745 (lactone). ^{1}H-NMR ($CDCl_3$): 2.25 (dd, 1, Hb), 2.97 (dd, 1, Ha), 3.52 and 3.76 (ss, 6, COOMe), 5.55 (d, 1, Hd), 5.97 (octet, 1, Hc), 6.95 (d, 1, 9-H), 7.20 (dd, 1, 7-H), 7.62 (m, 4, aromatic), 8.02 (m, 2, *o*-, *o*'-H), 8.12 (dd, 1, 6-H); J_{ab}= 12.5, J_{ac}= 8, J_{bc}= 2.5, J_{cd}= 5 Hz.

Dimethyl 5-oxo-5*H*-pyrrolo[1,2-*a*][3,1]benzoxazine-2,3-dicarboxylate (18). In a semimicro distilling flask, 2 g of **17a** were introduced and heating was gradually applied up to the melting point when decomposition occurred. Subsequently the temperature was maintained for a short time at 170-180°. A small amount of colourless liquid distilled which proved to be vinyl acetate identified by its characteristic ^{1}H-NMR spectrum. The residue was triturated with acetonitrile when 1,2 g of **18**, white crystals, were obtained (yield 75%) which after recrystallisation from nitromethane mp 241°. The same results were obtained with **17b** when the *Z*-1-propen-1-ol acetate (**19b**) was collected. Slightly higher yields were obtained by heating either of the compounds **17a-c** (4 g) in solution in 25 ml of tetralin at 180° when evolution of gas was observed. When no more decomposition occurred the solution was left to cool and white crystals of **18** separated (yields over 80%).

Found: C 59.73; H 3.73; N 4.50. Calcd. for $C_{15}H_{11}NO_6$: C 59.80; H 3.68; N 4.65. ^{1}H-NMR (d_5-Py):3.83 and 3.87 (ss, 6, COOMe), 7.40 (t, 1, 7-H), 7.82 (t, 1, 8-H), 7.99 (d, 1, 9-H), 8.24 (s, 1, 1-H), 8.26 (d, 1, 6-H), ^{13}C-NMR ($CDCl_3$ + CF_3COOH): 53.8 and 54.0 (OMe), 95.3, 111.5, 114.6 and respectively 143.1, 138.6, 135.8 (strongly polarised aromatic bonds of the enamino carbonyl moieties), 115.3, 115.9, 128.5 and 132.0 (CH-groups of the benzene nucleus), 157.4 (lactone), 166.0 and 167.1 (COOMe). IR (KBr): 1700, 1725 and 1755 cm^{-1} (CO). UV (EtOH): λ_{max} (log ε)= 296 (3.94), 256 (4.05), 221 nm (4.30).

Dimethyl 1-(2-carbomethoxyphenyl)-2-methoxy-1*H*-pyrrole-3,4-dicarboxylate (20). In 200 ml of 5% aqueous solution of NaOH, 2.3 g of **18** were introduced and the resulted suspension was stirred at room temperature for about 5 hrs when almost complete dissolution occurred. After removal by filtration of some unreacted material the resultant clear solution was brought to pH 3 with hydrochloric acid. After a short time the corresponding hydroxy acid of **18** crystallised with incipiently hydrolysed carbomethoxy groups as evidenced by ^{1}H-NMR (mp 160-162°). Without further purification it was introduced into an ethereal solution of diazomethane in excess with magnetic stirring when dissolution occurred. After removal of the solvent in vacuum the viscous residue crystallised affording 1.7 g of **20** (yield 64%), mp 94°(MeOH/CCl_4).

Found: C 58.65; H 4.99; N 4.27. Calcd. for $C_{17}H_{17}NO_7$: C 58.80; H 4.90; N 4.03. ^{1}H-NMR ($CDCl_3$): 3.83, 3.87, 3.90 and 3.97 (ss, 12, OMe), 7.12 (s, 1, 5-H), 7.43 (d, 1, 6'-H), 7.69 (t, 1, 4'-H), 7.78 (t, 1, 5'-H), 8.13 (d, 1, 3'-H).

Hydrolysis of 4a to 5*H*-pyrrolo[1,2-*a*][3,1]benzoxazine-2,5(1*H*)-dione (11a). In 15 ml of 96% acetic acid , 1 g of **4a** was dissolved and refluxed for 30 min. After removal of the acid under reduced pressure the residue was triturated with ethanol when 0.8 g of **11a** were obtained with mp 234° after recrystallisation from ethanol (yield 85%). The same results were obtained with **4b**.

Alkaline hydrolysis of 18. The partially hydrolysed product of **18** (see above) with mp 160-2° was dissolved in 17 g of 18% aqueous NaOH and refluxed for 1.5 hrs. By neutralisation of the cooled solution anthranilic acid separated quantitatively.

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