Chemistry of Heterocyclic Compounds, Vol. 30, No. 6, 1994

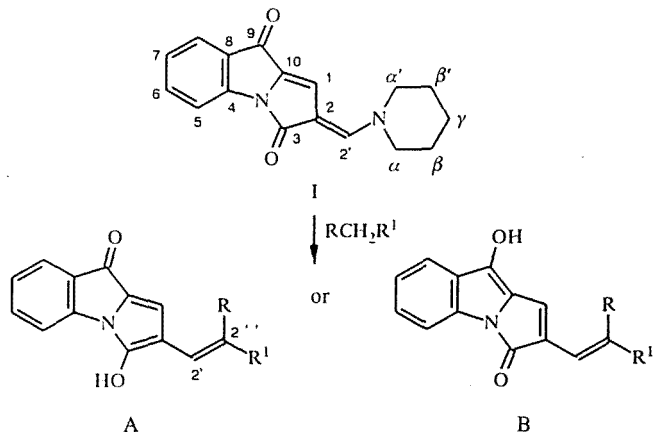
SYNTHESIS, ALKYLATION, AND STRUCTURAL STUDIES OF 2-VINYLPYRROLO[1,2-*a*]INDOLES

N. Z. Tugusheva, S. Yu. Ryabova, N. P. Solov'eva and V. G. Granik

2-Piperidinomethylene-2H-pyrrolo[1,2-a]indole-3,9-dione can readily react with substances having an active methylene unit to form piperidinium salts which are converted to 2-vinyl pyrrolo[1,2-a]indoles. They can also undergo O-methylation using dimethyl sulfate in polar and non-polar solvents to form the 9-alkoxy derivatives.

In continuation of work on the synthesis of indoles using indoxyl enamines [1-3], we have studied the reactions of 2-piperidinomethylene-2H-pyrrolo[1,2-*a*]indole-3,9-dione (I, recently synthesized by us [4]) with compounds having active methylene units. The basis for this study was previous work which had shown the possible transamination of this unusual enaminoketone and the potential synthesis of novel enamines having cardiotonic activity [5].

By treating enamine I with active methylene compounds it was possible to prepare vinyl derivatives with aromatic pyrrole (A) or indole (B) rings. It is clear that the question of the relative energies of the indicated systems cannot be decided by simple examination of their structures but needs a detailed spectroscopic study of the compounds prepared. To check the correctness of the signal assignments it was necessary to study first the starting compound I using NMR spectroscopy.



According to the PMR spectra (Table 1), I exists in $CDCl_3$ solution as a mixture of two isomers with not more than 3% of the minor isomer (D). This minor component has a lower field signal for the piperidine α,α'-CH_2 protons ($\simeq$3.65 and 4.58 ppm) and a higher field signal for 1-H (6.80 ppm) when compared with the major isomer (Table 1). In $CDCl_3-DMSO-d_6$ solution (10:1) the signals for the minor species are notably broadened and addition of a small amount of CD_3OD to the solution causes a further signal broadening and a shift towards the signals of the major isomer. In DMSO-d_6 solution I shows only one set of signals. Such a dependence of structure of I on the nature of the solvent can be explained by the presence of geometrical isomers about the enamine $C_2{=}C_{2'}$ double bond.

Center for Medicinal Chemistry, All-Russian Science Research Chemico-Pharmaceutical Institute, Moscow 119021.
Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 6, pp. 781-792, June, 1994. Original article submitted June 22, 1994.

0009-3122/94/3006-0683$12.50

TABLE 1. PMR Spectral Data for I-VI*

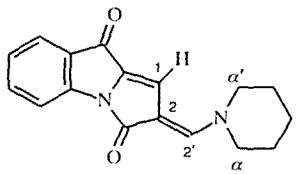
Compound	Chemical shift, δ (ppm), J_{CH} (Hz)				Solvent; NOE, %
	1-H	2'-H	R, R^1	aryl protons	
I	7,45, 7,65, 7,11, 7,66		Piperidine protons: (pm): 1,66 (m, β-,β'-H, γ-H), 3,70 (m, α-H), 3,77 (m, α'-H), 1,76 (m, β-,β'-H, γ-H), 3,59 (m, α-H), 3,63 (m, α'-CH_2)	7,15 (t), 7,50...7,70 (m), 7,18 (t), 7,53...7,87 (m)	DMSO-D_6 $CDCl_3$*2
IIa	7,50, 7,54		Piperidine protons : 1,81 (2H, m, γ-H), 2,05 (4H, m, β-,β'-H), 3,41 (2H, t, α-,α'-H), 9,16 (2H, br s, $^+NH_2$); $COOCH_2CH_3$: 1,27 (t, CH_3), 4,08 (q, CH_2)	6,94 (t), 7,28...7,44 (m)	$CDCl_3$
IIb	7,24, 7,32		Piperidine protons : 1,54 (6H, m, β, β'-H, γ-CH_2), 2,96 (4H, t, α-,α'-H), 8,20 (2H, br s, $^+NH_2$)	7,13 (t), 7,53...7,65 (m)	DMSO-D_6
IIIa	7,77, 7,88		OH*3: ~4,15; $COOCH_2CH_3$: 1,30 (t, CH_3), 4,17 (q, CH_2)	7,17 (t), 7,53...7,68 (m)	DMSO-D_6
IIIb	7,25, 7,35		OH*3: ~5,80	7,17 (t), 7,55...7,65 (m)	DMSO-D_6
IIIc	7,94, 8,23		OH*3: ~3,60; dimedone protons: 0,98 (s, 2-CH_3), 2,36 (s, 2-CH_3)	7,14 (t), 7,54...7,70 (m)	DMSO-D_6
IV	7,25, 7,33		$OCOCH_3$: 1,92	7,12 (t), 7,50...7,60 (m)	DMSO-D_6
Va	8,40*4	8,00*4	OCH_3 4,21; $COOCH_2CH_3$: 1,38 (t, CH_3), 4,35 (q, CH_2)	7,15 (t), 7,45...7,75 (m)	$CDCl_3$ NOE 25% (OCH_3, 1-H)
Vb	8,42	7,76	OCH_3 4,31	7,25 (t), 7,52...7,83 (m)	$CDCl_3$
Vc	8,44	7,88	OCH_3 4,28; $COOCH_3$ 3,85	7,24 (t), 7,55...7,65 (m)	DMSO-D_6
Vd	8,34	7,78	OCH_3 4,23; NH_2 7,70, 7,94 br s	7,20 (t), 7,40...7,65 (m)	DMSO-D_6
VIa	8,36*4	8,13*4	OCH_2CH_3: 1,64 (t, CH_3), 4,42 (q, CH_2), $COOCH_2CH_3$: 1,42 (t CH_3), 4,36 q, CH_2)	7,18 (t), 7,45...7,78 (m)	$CDCl_3$ NOE 20% (OCH_2CH_3, 1-H)
	8,37	7,87	OCH_2CH_3: 1,51 (t, CH_3), 4,53 (q, CH_2), $COOCH_2CH_3$: 1,29 (t, CH_3), 4,30 (q, CH_2)	7,19 (t), 7,40...7,70 (m)	DMSO-D_6
VIb	8,34	7,86	OCH_2CH_3: 1,51 (t, CH_3), 4,56 (q, CH_2)	7,17 (t), 7,40...7,65 (m)	DMSO-D_6 NOE 18% (OCH_2CH_3, 1-H)

*For all compounds except I their PMR spectra showed a spin–spin coupling between 1-H and 2'-H ($^4J_{12'}$ = 0.7-0.9 Hz).

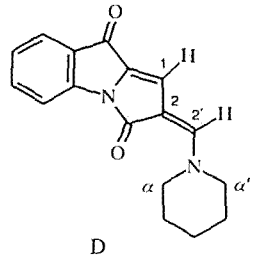
*2For I (solvent $CDCl_3$) the data in the table refer to the major isomer. The minor isomer has the following signals: 4.58, 3.65 (α,α'-H), 1.75 (β, β', γ-H), 6.80 (2'-H), 7.10 ppm (1-H).

*3The hydroxyl proton and water in DMSO-d_6 exchange with one another and therefore give an averaged signal.

Note: Footnote *4 is missing.

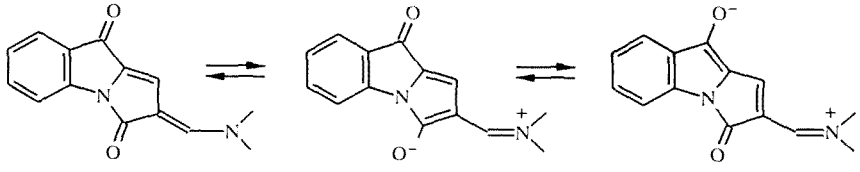


C



D

Examination of molecular models shows that isomer (C) with a transoid relationship for 1-H and 2′-H is sterically less hindered and therefore energetically more favored.



It is well known for enamines [6, 7] that they show a decrease in the double bond character via resonance leading to a lowering of the barrier to cis−trans isomerization. Moreover, an increase in solvent polarity causes an acceleration of the isomerization. Hence it is quite reasonable to propose that enamine I in $CDCl_3$ solution is a mixture of the geometrical isomers C (major) and D (minor). Isomerization is made easier by addition of polar solvents (DMSO-D_6 or CD_3OD) and in pure DMSO-D_6 (Table 1) only one set of signals is seen which correspond to the averaged state.

Assignment of structure C to the major isomer is indicated by nuclear Overhauser effect (NOE) experiments. This showed a sterically close approach to 1-H and the α-CH_2′ protons and of 2′-H and the α-CH_2 protons of the piperidine ring (NOE 18-20%) in this isomer. Protons 1-H and 2′-H and 2′-H appeared to be sterically remote from one another.

Additional structural confirmation for the isomer geometries for I came from their ^{13}C NMR spectra.

The ^{13}C NMR spectrum of I ($CDCl_3$) showed signals for both geometric isomers (Table 2) however, those for the quaternary aromatic carbon atoms of the minor isomer could not be identified due to its low concentration. In the high field region signals for the piperidine carbons in the minor isomer D are seen at 23.3 (γ-CH_2), 26.3 and 27.1 (β,β' $-CH_2$), and 52.2 and 57.0 ppm (α,α^* $-CH_2$). For the 52.2 ppm signal a direct hetero spin−spin coupling J_{CH} of 140 Hz was found. From Tables 1 and 2 the corresponding values for isomer C (48.7 ppm, 137 Hz; 56.8 ppm, 140 Hz) are virtually the same as for the minor isomer.

From an analysis of the ^{13}C NMR chemical shift values (Table 1) it is found that the 9-carbonyl signal is at 178.1 and the 3-carbonyl is at 163.1 ppm. When accumulated without proton decoupling the first signal is a slightly broadened singlet and the second a quartet (due to spin−spin coupling to 1-H and 2′-H. This large difference in carbon chemical shifts for the two carbonyl functions could then be used to determine the structures of subsequent reaction products (structure A or B).

In the first synthetic step we treated I with malononitrile or cyanoacetic ester. The reaction occurs readily, probably because of the gain in energy with pyrrole ring aromatization. The piperidinium salts of α-cyano-β-(3-hydroxy-9-oxo-pyrrolo-[1,2-*a*]indol-2-yl)acrylic ester IIa and acrylonitrile IIb were obtained in nearly quantitative yields. The IR spectra showed absorption at 3420, 3320 (NH^+), 2200 (CN), and 1690 cm^{-1} (for IIa, COOEt). PMR Spectra were in good agreement with the structures proposed (Table 1). Treatment of salt IIa with dilute HCl gave the hydroxy derivative IIIa; its analog IIIb was separated from the reaction of IIb with insufficient dimethyl sulfate (see below). These hydroxy compounds IIIa,b are quite strong organic acids (pK_a of IIIb in 50% EtOH 3.46). Ionization of these compounds means that the OH protons in an aqueous DMSO-d_6 medium exchange intermolecularly to give an averaged OH/water signal at 4.15 ppm for IIIa and 5.8 ppm for IIIb. Refluxing IIb in acetic anhydride gives the 3-acetoxy derivative IV.

The PMR spectrum of IV shows the acetoxy methyl singlet at 1.92 (3 protons), a multiplet for the benzene protons at 7.12-7.60 ppm and two singlets at 7.25 and 7.35 ppm for protons 1-H and 2′-H (Table 1). The singlets are slightly split by a mutual spin−spin coupling ($^4J_{1,2'} \approx 0.8$ Hz) showing that the protons are transoid related. A similar splitting of 1-H and 2′-H in the PMR spectra of IIa,b, IIIa,b points to the same mutual disposition of the side chain fragments about the 2′-CH=2″−CRR′ molecule relative to the plane of the tetracycle in IIa,b, IIIa,b, and IV. In all of the above PMR spectra it was not possible to assign with certainty the singlets to a specific (1-H or 2′-H) proton since their chemical shifts were so close.

TABLE 2. ^{13}C NMR Data for I, IIb, IIIa, IV, Va, and VIa*

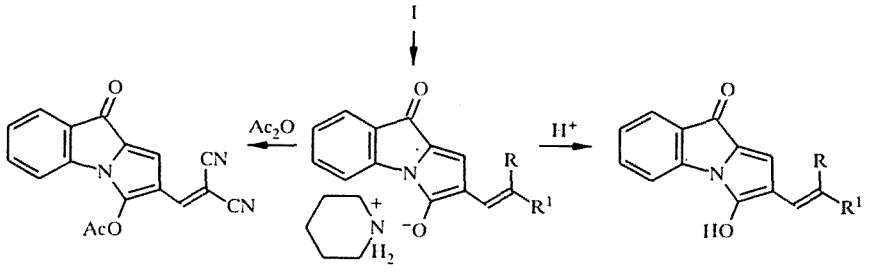
Compound	Chemical shift, δ (ppm), J_{CH} (Hz)									
	$C_{(1)}$	$C_{(2)}$	$C_{(2')}$	$C_{(2'')}$	$C_{(3)}$	$C_{(4a)}$	$C_{(8a)}$	$C_{(9)}$	$C_{(10)}$	CN
I*2	110,0 dd, $^1J_{CH}$ = 176,0, $^3J_{CH}$ = 7,6	104,9 q, $^2J_1$ = 4,7, $^2J_1$ = 1,6	148,9 dt, $^1J_{CH}$ = 167,0	–	163,1 q, Σ ^3J ~11,0	142,6 t, Σ ^3J ~7,0	129,5 q, Σ ^3J =13,4	178,1 br s	130,2 d, ^2J = 4,2	–
IIb	112,0 dd, $^1J_{CH}$ = 175,0, $^3J_{CH}$ = 7,5	113,1 q, Σ ^2J~6,0	145,3 d, $^1J_{CH}$ = 154,0	53,0 s	160,7 q, Σ ^3J ~11,0	142,0 t, Σ ^3J ~7,0	129,9 q Σ ^3J ~14,0	175,1 br s	127,8 d, ^2J = 5,1	119,0 d, $^3J_{CN}$*trans*H =12,3, 119,4 d, $^3J_{CN}$*cis*H = 6,9
IIIa	117,6 dd, $^1J_{CH}$ =175,6, $^3J_{CH}$ = 9,9	113,7 d, $^2J_1$ = 3,4	143,4 d, $^2J_{CH}$ = 154,6	82,8 s	165,2 q, Σ ^3J ~10,0	140,8 t, Σ ^3J ~7,0	129,7 q, Σ ^3J ~14,0	171,2 s	125,9 d, ^2J = 5,7	120,0 d, $^3J_{CN}$ *trans* H = 12,5
IV*3	112,0 dd, $^1J_{CH}$ = 175,2, $^3J_{CH}$ = 7,6	113,4 q, Σ ^2J ~7,0	145,5 d, $^1J_{CH}$ = 145,9	54,6 s	160,6 q, Σ ^3J ~10,0	141,8 t, Σ ^3J ~7,0	126,3 q, Σ ^3J ~14,0	175,1 s	127,7 d, ^2J = 5,1	118,9 d, $^3J_{CN}$*trans* H = 12,3, 119,2 d $^3J_{CN}$*cis*H = 7,2
Va	134,4 dd, $^1J_{CH}$ = 178,7, $^3J_{CH}$ = 7,3	120,3 q, Σ ^2J ~9,0	142,3 br s $^1J_{CH}$ = 162,8, $^3J_{CH}$ = 2,6	101,4 br s	162,1 q, Σ ^3J ~12,0	135,5 q, Σ ^3J ~6,0	126,3 q, Σ ^3J ~14,5	151,4 m, Σ ^3J ~10,0	126,0 s	116,5 d, $^3J_{CN}$*trans*H = 13,6
VIa	134,4 dd $^1J_{CH}$ = 178,5, $^3J_{CH}$ = 7,3	120,2 q, Σ ^2J ~9,0	142,3 br s $^1J_{CH}$ = 262,6, $^1J_{CH}$ = 2,2	101,1 br s	162,0 q, Σ ^3J ~12,0	135,3 q, Σ ^3J ~6,0	126,4 m, Σ ^3J ~14,5	150,6 m, Σ ^3J ~8,0	125,7 s	116,4 d, $^3J_{CN}$*trans*H = 13,7

*Solvent $CDCl_3$ for I, Va, VIa, and DMSO-d_6 for IIb, IIIa. For all of the compounds studied the chemical shifts $C_{(5)}$, $C_{(6)}$, $CC_{(7)}$, and $C_{(8)}$ have the values 113.8-135.0 ppm and $^1J_{CH}$ = 162-168 Hz; piperidine ring carbon shifts (and $^1J_{CH}$) were for I: 23.1 C γ (130.0), 25.0, 26.4 C β,β′ (127.0, 129.0), 48.7, 56.8 C α,α′ (137.0, 140.0 Hz); for IIb: 21.8 C γ (129.0), 22.5 C β,β′ (129.8), 40.2 C α,α′ (142.0); IIIa R,R′ = $COOCH_2CH_3$ 161.4 (C=O) m 14.7 (CH_2CH_3) (126.7), 60.6 (CH_2CH_3) (147.4); Va R,R′ = $COOCH_2CH_3$ 161.5 (C=O) m, 14.1 (CH_3) qt, 62.4 (CH_2) tq, OCH_3, 60.7 q; VIa R,R′ = $COOCH_2CH_3$ 161.4 (C=O) m, 14.1 (CH_3) qt, 62.3 (CH_2) tq, (OCH_2CH_3) 14.4 (CH_2) qt, 69.7 (CH_2) tq.

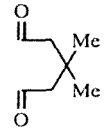
*2For I the δ ^{13}C shifts are given for the major isomer C (see text). The values for the minor isomer D are: 23.3, 26.3, 27.1, 52.2 ppm (140 Hz), 57.0, 113.2 (d), 120.5 (d), 134.3 (d), 152.0 ppm (d). The remaining signals are masked by strong peaks from isomer C.

*3Freshly prepared solution of IV showed signals for $C_{(1)}$, $C_{(2)}$, $C_{(2')}$, $C_{(3)}$ and $COCH_3$ broadened due to hydrolysis of the acetoxy group hydrolysis. Data in the Table is given for solution allowed to stand [acetic acid formed, 172.3 (C=O, q, $^2J_{CH}$ = 6.7 Hz), 21.4 ppm (CH_3, q, $^1J_{CH}$ = 128.7 Hz)].

It was expected that the O-ethyl of the COOEt group in this conformation would approach in space the cisoid related 2′-H proton. However, irradiation of these O-ethyl signals did not change the intensity of any of the aromatic singlets. This showed that proton 2′-H and the OCH_2CH_3 group were sterically remote (implying that 2′-H and the C=O of the $COOCH_2CH_3$ fragment were closely placed).



IIa, IIIa R = CN, $R^1 = CO_2Et$; IIb, IIIb R = R^1 = CN; IIc, IIIc R, R^1 =



IIId R = CN, $R^1 = CO_2Me$

Data in Table 1 shows IV and IIIb to be very similar and we propose a rapid hydrolysis of IV in wet DMSO during the process of spectrum accumulation. Experiments with a mixed sample confirm this. The PMR spectrum of IV shows a signal at 1.92 ppm which increases markedly on addition of one drop of acetic acid. The spectrum of a mixture of IV and IIIb shows one set of signals in the low field region (7.25 and 7.35 ppm for 1-H and 2′-H).

Consideration of the ^{13}C NMR data for IIb, IIIa, and IV and comparison with similar values for starting compound I allows us to resolve the structure of these products in favor of A or B. In the ^{13}C NMR spectra, assignment of protonated sp^2 hybridized carbon atoms were made based on analysis of values of direct hetero spin–spin coupling ($^1J_{CH}$). It is known that five membered aromatic rings have a value of ~170-180 Hz [8]. Hence the carbon signal having a value of 175-178 Hz was assigned to atom C-1 with a chemical shift of ~110-117.6 ppm (compounds I, IIb, IIIa, IV, Table 2). Carbon C_2, in the analyzed spectra can be assigned to the signal at 143-149 ppm with $^1J_{CH}$ ~ 146-155 Hz (IIb, IIIa, IV) and 167 Hz (I). This increase to 167 Hz is associated with the presence of the nitrogen heteroatom at $C_{2'}$. The chemical shift values for the benzene ring carbons ($C_{(4a)}$, $C_{(5)}$, $C_{(6)}$, $C_{(7)}$, $C_{(8)}$, and $C_{(8a)}$) in I, IIb, IIIa, and IV are quite close (Table 2). Both for I and for IIb, IIIa, and IV, the lowest field signal (171-175 ppm) corresponded to the carbon atom of the 9-C=O group, hence all the investigated compounds can be unambiguously assigned the structure A. It should be noted that the carbon chemical shift for C-3 in IIb, IIIa, and IV is found at ~161-165 ppm, due to the presence of two heteroatoms at C-3. The carbon signal for C-2″ in IIb, IIIa, and IV was interestingly at quite high field [53.0 (IIb), 54.6 (IV), and 82.8 ppm (IIIa)]. The chemical shifts for the CN groups of IIb, IIIa, and IV have standard values (Table 2). When acquired without proton decoupling the signal for the CN carbon was a doublet with a spin–spin coupling ($^3J_{CN,2'-H}$) identifying the orientation of the CN and 2′-H about the $C_{2'}$=$C_{2''}$ double bond (*trans* = ~12-13 Hz, *cis* = ~7 Hz).

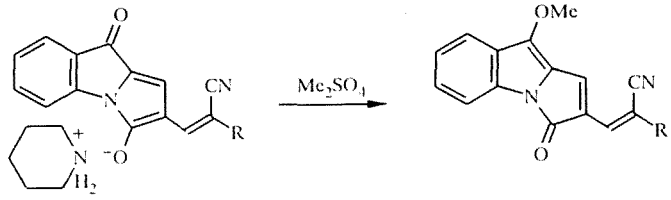
When observing the carbon spectrum of the acetoxy derivative IV, hydrolysis of the acetoxy group was observed (as in the proton spectrum). Thus the carbon signals for $C_{(1)}$, $C_{(2)}$, $C_{(2')}$, $C_{(3)}$, and $COCH_3$ were strongly broadened in the spectrum of a freshly prepared solution. The spectrum taken after 4-5 h showed signals which were then sharp and corresponded to compound IIIb and acetic acid in solution (Table 2) showing complete hydrolysis.

Reaction of enaminoketone I with dimedone occurs more slowly and could not be carried to completion even upon standing for 20 days at 20°C or 30 h at 50-70°C. Thus it was not possible to prepare the intermediate salt IIc in an analytically pure state. Acidification of IIc solution gave a low yield of the hydroxy derivative IIIc.

The PMR spectrum of the dimedone derivative IIIc confirms the proposed structure (Table 1). The 3-OH proton is evidently exchanged with the solvent water (3.60 ppm, Table 1), as was the case for IIIa,b.

The next step was a study of the methylation of salts IIa,b with dimethyl sulfate. As is apparent from the structures of IIa,b alkylation can occur both at position 3 and via transfer of the reaction center to form the 9-methoxy derivative. The location was shown using ^1H or ^{13}C NMR. The methoxy group PMR signals for Va,b occur at 4.21 and 4.31 ppm. It is obvious from Table 1 that protons 1-H and 2′-H ($^4J_{12'}$ = 0.8 Hz) are at lower field than analogous signals in the salts IIa,b (8.00 and 8.40 ppm for Va and 7.76 and 8.42 ppm for Vb, for assignment see below).

The ^{13}C NMR spectrum of Va differs significantly from both the starting compound I and the products (II-IV) (Table 2). Firstly, the spectrum of Va does not show a signal at ~170-180 ppm which characterized the 9-C=O carbon signal in I-IV. Instead, a signal is seen at 151.4 ppm which is a multiplet when accumulated without proton decoupling. Secondly, the signals for $C_{(1)}$ and $C_{(2)}$ are found at lower field than those in the spectra of I-IV. On this basis we conclude that methylation of salts IIa,b occurs at carbonyl 9 of the tricycle.



IIa-b Va-d

Va R = CO_2Et, b R = CN, c R = CO_2Me, d R = $CONH_2$

This structure for Va is in agreement with the signal at 151.4 ppm which can be assigned to atom C-9 with splitting due to interaction with the methoxy group. The 3-carbonyl signal is observed at 162.1 ppm (similar to 3-C=O in I). The nitrile carbon signal (116.5 ppm) in Va, taken with proton coupling, appears as a doublet with $^3J_{CN,2'-H}$ = 13.6 Hz corresponding to a transoid placing of the CN group and the 2'-H proton about the $C_{(2')}$=$C_{(2'')}$ bond.

For assignment of protons 1-H and 2'-H in Va the ^{13}C NMR spectra were taken using selective proton irradiation. It was shown that the splitting of the CN carbon is due to the singlet located at 8.00 ppm (i.e., 2'-H). Hence the singlet at 8.40 ppm must be 1-H. A PMR experiment on Va using NOE showed that irradiation of the methoxy signal leads to a significant (~25%) increase in the intensity of the signal for 1-H at 8.40 ppm. This clearly demonstrates the steric proximity of the OMe group and 1-H, possible only for the 9-methoxy derivative. Since the spectral characteristics of Va,b are similar, this reasoning also applies to dinitrile Vb (see Table 1).

It was also found that methylation of salts IIa,b needed an least a threefold excess of Me_2SO_4. With a one and a half fold excess of reagent the basic product is the hydroxy derivative IIIb, since methylation occurred mainly on the piperidine.

With the aim of increasing the methylation yield for IIb we studied the effect of different solvents on the course of the reaction. It was found that alkylation was very sensitive to the solvent type. In nonpolar solvent (benzene) high yields of alkylated products could not be achieved due to the low solubility of the starting compound. Hence we tried more polar solvents. Refluxing salt IIb with a threefold excess of dimethyl sulfate in methanol for 4.5 h gives a mixture of three products (Vb,c,d) which could not be separated preparatively. The structure of the alkylation products was shown by PMR spectroscopy.

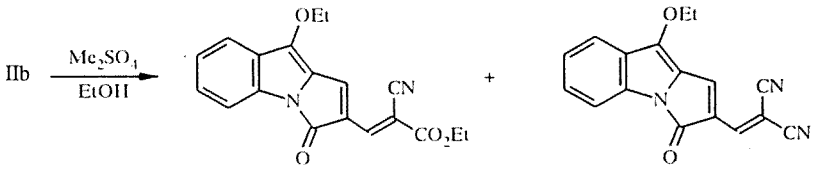
The PMR spectrum of a freshly prepared solution of the obtained mixture (DMSO-d_6 solvent) showed three groups of similar signals differing in relative intensities. For all three the mixture showed pairs of split singlets in the aromatic region at 8.41 and 7.77 (Vb), 8.44 and 7.87 (Vc), and 8.33 and 7.77 ppm (Vd). The methoxy region showed signals at 4.29 (Vb), 4.28 (Vc), and 4.24 ppm (Vd). By comparison with the OCH_3 signal in Vc, the peak at 3.85 ppm can be assigned to the $COOCH_3$ in this compound. All of the benzene protons occur in the range 6.95-7.75 ppm. A strongly broadened signal at 8.05 ppm can be assigned to one of the two protons of the $CONH_2$ group in Vd. The other mobile proton is masked by the aromatic proton multiplet. According to their relative intensities, the composition of the mixture is Vc >> Vd > Vb. PMR Spectral examination of a technical sample and of the mother liquors also showed that Vc predominated. It was found that one of the aromatic proton singlets had the same chemical shifty (~8.40 ppm) as the 1-H proton signal in Va, the structure of which has been identified above.

When the analyzed solution is allowed to stand for 7-14 days or upon heating, a change is seen in the PMR spectra. The intensity of the OCH_3 singlets fall for Vb, c and there appear and gradually increase in intensity singlets at 3.21 and 3.75 ppm. Changes also occur in the aromatic and vinyl proton region. Addition of 1-2 drops of methanol to the latter solution shows that the signal at 3.21 ppm is actually methanol which is formed in the ampul on standing or heating. Hence we propose that Vb, c undergo hydrolysis in solution to form methanol, IIIb, and its carbomethoxy analog IIId. For Vd, hydrolysis occurs much more slowly and requires prolonged heating at ~60°C (~12 h). From the above data we propose that the first step in the methylation of salt IIb with excess dimethyl sulfate in methanol gives the desired compound Vb, piperidinium metasulfate, and methylsulfuric acid. Addition of authentic Vb (obtained previously) to the obtained mixture causes an increase in the appropriate signals and proves its presence. Methylsulfuric acid catalyzes the addition of methanol to the cyano group to form the iminoether which subsequently reacts to give the carbomethoxy derivative Vc and amide Vd.

It was found for Vc,d that an NOE experiment could unambiguously prove the closeness of the 1-H OCH_3 protons which (as for Va,b) pointed to a 9-methoxy structure for Vc,d.

When the methylation of salt IIb was carried out with a large excess of alkylating agent for a long time (40 h refluxing in methanol) it was found from PMR that a mixture of three products was formed. One of these could not be identified but the other two were separated and shown to be the ester Vc and amide Vd (see Table 1). For both Vc and Vd, PMR spectra were obtained for freshly prepared solutions, solutions allowed to stand for a long time, and for solutions after prolonged heating (DMSO-d_6 solvent, heating at ~60°C for 6 and 12 h). In time, hydrolysis of the 9-methoxy group occurs to give the corresponding 9-oxo derivatives IIIb,d.

Several changes in reaction mixture composition occur when changing the medium from methanol to ethanol, the products identified by PMR spectroscopy being VIa and b.



VIa VIb

According to the PMR data, the reaction process involves methylation, transformation of CN to COOEt, and exchange of a methoxy for an ethoxy group. In DMSO-d_6, the PMR spectrum shows ethoxy proton signals (COOEt and OEt) for VIa at 1.29 ($COOCH_2\underline{CH_3}$), 4.30 ($COO\underline{CH_2}CH_3$), 1.51 ($OCH_2\underline{CH_3}$), and 4.53 ppm ($O\underline{CH_2}CH_3$) and for the OEt group of VIb at 1.51 ($OCH_2\underline{CH_3}$) and 4.56 ppm ($O\underline{CH_2}CH_3$) (full spectral data is given in Table 1). According to their relative intensities the ratio of VIa to VIb is 3:2. The assignments were proved by comparison with a mixture of the individual isomers, prepared as described in a subsequent publication. When the mixture was allowed to stand for one week (DMSO-d_6), hydrolysis of the ethoxy group occurred to give the hydroxy derivatives IIIa, b and ethanol (1.05 and 3.43 ppm). The same reaction occurred for the individual isomers in DMSO-d_6.* Attention was then turned to the similarities in the aromatic proton signals for VIa with Va and VIb with Vb (Table 1). The results of the NOE experiment (increasing intensity of the low field signal when irradiating at the frequency for the OCH_2CH_3 methylene protons by ~20% for VIa and 18% for VIb) confirmed the steric proximity of the given groups in VIa,b. Both of these cases point in favor of forming the 9-ethoxy derivative VIa, b when methylating in ethanol. Hence methylation of salt IIb in polar solvents can occur ambiguously and, more preparatively, a non polar (benzene) solvent may be used.

In summary, it is found that the tricyclic enaminocarbonyl compound I reacts readily with compounds having active methylene units to form salts II. On one hand these react smoothly to 2-vinyl pyrrolo[1,2-*a*]indoles III and on the other they undergo O-methylation with dimethyl sulfate in non polar and polar solvents. Significantly, methylation occurs not at the position of highest electron density (the 3-carbonyl oxygen) but with transfer of the reaction centre to give the 9-alkoxy derivatives V and VI. Another route to preparation of these kinds of compounds and their use in heterocyclization will be described in a subsequent publication.

EXPERIMENTAL

IR Spectra were obtained on a Perkin–Elmer 457 instrument for vaseline mulls and mass spectra on a Varian MAT-112 with direct introduction of the sample into the ion source. The ionization energy was 70 eV and the ionization chamber temperature 180°C. ^1H and ^{13}C NMR Spectra were measured on a Varian XL-200 with internal standard TMS. The reaction course and compound purities were monitored by TLC on Silufol UV-254 plates in chloroform–methanol (10:1) with UV light visualization.

Elemental analytical data agreed with that calculated.

*The hydrolysis reported above for IV and V was not observed for VIa,b in $CDCl_3$ solution.

Piperidinium Salt of Ethyl α-Cyano-β-(3-hydroxy-9-oxopyrrolo[1,2-*a*]indol-2-yl]acrylate (IIa, $C_{22}H_{23}N_3O_4$). Ethyl cyanoacetate (11.3 g, 100 mmole) and triethylamine (5 ml, 36 mmole) were added to a solution of enaminoketone I (13.7 g, 49 mmole) in DMF (300 ml) and stirred for 24 h at 20°C. DMF was evaporated, the residue washed with hexane, and treated with ether. After standing overnight at −1°C the crystalline precipitate was filtered, and washed with ether and hexane to give salt IIa (18.2 g, 95%), mp 200-201°C. IR Spectrum: 2200, 1690, 1630, 1620 cm^{-1}. M^+ 308 (85).

Piperidinium Salt of α-Cyano-β-(3-hydroxy-9-oxopyrrolo-[1,2-*a*]indol-2-yl)acrylic Acid Nitrile (IIb, $C_{20}H_{18}N_4O_2$). Malononitrile (0.24 g, 3.6 mmole) and triethylamine (0.2 ml, 1.4 mmole) were added to a solution of I (1 g, 3.6 mmole) in DMF (100 ml) and stirred for 1 h at 20°C. DMF was evaporated and the residue was triturated with either and filtered to give a crystalline precipitate (IIb, 1.2 g, 98%) with mp 200-201°C. IR Spectrum: 3420, 3320, 2200, 1600 cm^{-1}. M^+ 261 (85).

Ethyl α-Cyano-β-(3-hydroxy-9-oxopyrrolo[1,2-*a*indol-2-yl)acrylate (IIIa, $C_{17}H_{12}N_2O_4$). Salt IIa (0.5 g, 1.3 mmole) in absolute alcohol (30 ml) was treated with 1 N HCl (1 ml) and held for 12 h at 20°C. The precipitate was filtered off and washed with alcohol and ether to give IIIa (0.3 g, 77%) with mp 248-250°C. IR Spectrum: 2200, 1720, 1630, 1600 cm^{-1}. M^+ 308.

Nitrile of α-Cyano-β-(3-hydroxy-9-oxopyrrolo[1,2-*a*]indol-2-yl)acrylic Acid (IIIb, $C_{15}H_{17}N_3O_2$). A mixture of salt IIb (1.85 g, 5 mmole) and dimethyl sulfate (1.1 g, 8 mmole) in absolute benzene (100 ml) was refluxed with stirring for 15 h. After cooling, the precipitated solid was filtered, and washed with benzene to give a mixture (1.6 g) of salt IIb and compounds IIIb and Vb. The mixture was refluxed in benzene (150 ml) and the insoluble residue (1 g) filtered and recrystallized from acetonitrile to give IIIb (0.85 g, 61%) with mp > 290°C. IR Spectrum: 3400, 2200, 1590 cm^{-1}. M^+ 261.

5,5-Dimethyl-2-(3-hydroxy-9-oxopyrrolo[1,2-*a*]indol-2-yl methylene)cyclohexane-1,3-dione (IIIc, $C_{20}H_{17}NO_4$). Dimedone (0.25 g, 1.8 mmole) and triethylamine (1 ml, 7.1 mmole) were added to a solution of I (0.5 g, 1.8 mmole) in DMF (45 ml) and stirred for 9 days at 20°C. DMF was evaporated and the residue triturated with ether, dissolved in water (30 ml), and filtered from insoluble residue to give I (0.25 g). The aqueous mother liquor was acidified with 1 N HCl (1 ml) and held for 12 h at 20°C. The precipitate was filtered, washed with water, and dried to give IIIc (0.15 g). It was recrystallized from absolute alcohol to give 0.02 g (2%) with mp 250°C (decomp.). IR Spectrum: 3400, 1710, 1650, 1600 cm^{-1}. M^+ 335.

Nitrile of α-Cyano-β-(3-acetoxy-9-oxopyrrolo[1,2-*a*]indol-2-yl)acrylic Acid (IV, $C_{17}H_9N_3O_3$). A solution of IIb (0.45 g, 1.3 mmole) and acetic anhydride (5 ml) was refluxed for 1-2 min, cooled, and the precipitate filtered, washed with acetic anhydride, ether, methanol, and ether. The yield of IV was 0.33 g (85%) with mp 222°C (from acetic anhydride). IR Spectrum: 2200, 1780, and 1600 cm^{-1}. M^+ 303.

Ethyl α-Cyano-β-(3-oxo-9-methoxypyrrolo[1,2-*a*]indol-2-yl)acrylate (Va, $C_{18}H_{14}N_2O_4$). Dimethyl sulfate (2.1 g, 17 mmole) was added to a solution of IIa (2 g, 5.1 mmole) in methanol (50 ml) and refluxed with stirring. After 4 and 6 h from the beginning of the experiment a further addition of dimethyl sulfate (1 g, 0.85 mmole) was made and the solution refluxed for a further 4 h. The product was cooled and the precipitate filtered and washed with ether to give Va (0.75 g, 47%) with mp 204-206°C (from benzene). IR Spectrum: 2200, 1700, 1690, 1600 cm^{-1}. M^+ 322.

Nitrile of α-Cyano-β-(3-oxo-9-methoxypyrrolo[1,2-*a*]indol-2-yl)acrylic Acid (Vb, $C_{16}H_{19}N_3O_2$). A. The benzene mother liquors obtained after refluxing the mixture of IIb, IIIb, Vb (synthesis of IIIb) was cooled and the precipitate filtered to give Vb (0.1 g, 7%) with mp 286-288°C (from benzene). IR Spectrum: 2200, 1700, 1590 cm^{-1}. M^+ 275.

B. A mixture of IIb (0.5 g, 1.4 mmole) and dimethyl sulfate (0.26 g, 2.1 mmole) in benzene (40 ml) was refluxed with stirring for 5 h. A further 0.26 g of dimethyl sulfate was added and the refluxing continued for a further 7 h. After cooling, the precipitate was filtered and washed with benzene to give Vb (0.1 g, 25%). The melting point of a sample mixed with that prepared by method A was not depressed.

C. A. Mixture of IIb (0.5 g, 1.4 mmole) and dimethyl sulfate (0.26 g, 2.1 mmole) in methanol (40 ml) was stirred under reflux for 2 h, a further 0.26 g dimethyl sulfate added, and refluxing continued for 2 h. After cooling, the precipitate was filtered to give Vb (M^+ 275) mixed with ester Vc (M^+ 293) in the ratio Vc >> Vd > Vb according to PMR spectroscopy (Table 1).

α-Cyano-β-(3-oxo-9-methoxypyrrolo[1,2-*a*]indol-2-yl)acrylic Acid Aimde (Vd, $C_{16}H_{11}N_3O_2$). A suspension of IIb (1 g, 2.8 mmole) in methanol (70 ml) was refluxed with stirring for 42 h adding dimethyl sulfate (0.52 g, 4.2 mmole) every 7 h (six times, total of 25.2 mmole). After cooling, the precipitate was filtered and washed with methanol and acetonitrile to give a mixture of Vc,d (0.65 g) and an unidentified material with M_1^+ 308, M_2^+ 293). The mixture was refluxed in acetonitrile (200 ml) and the insoluble residue filtered and washed with chloroform to give Vd (0.02 g, 2%).

Methyl α-Cyano-β-(3-oxo-9-methoxypyrrolo[1,2-*a*]indol-2-yl)acrylate (Vc, $C_{17}H_{12}N_2O_4$). The acetonitrile mother liquors obtained after refluxing the mixture of Vc,d and unidentified material (synthesis of Vd) and separation of Vd were

evaporated. The residue was recrystallized from benzene to give a mixture of Vc and unidentified material (0.2 g) in the ratio 70:30 by PMR (see Table 1). The mixture was repeatedly recrystallized from benzene to give Vc (0.14 g, 16%) with mp 240-241°C. IR Spectrum: 2200, 1710, 1600 cm^{-1}. $M^{+\cdot}$ 308.

Ethyl α-Cyano-β-(3-oxo-9-ethoxypyrrolo[1,2-*a*]indol-2-yl)acrylate (VIa, $C_{19}H_{16}N_2O_4$). A suspension of IIa (1 g, 2.9 mmole) in absolute alcohol (50 ml) was refluxed for 42 h adding dimethyl sulfate (0.52 g, 4.2 mmole) every 14 h (3 times, 12.6 mmole in all). After cooling, the precipitate was filtered and washed with ether to give a mixture (0.65 g) of VIa, b ($M_1^{+\cdot}$ 336, $M_2^{+\cdot}$ 289). Recrystallization from benzene gave VIa (0.3 g, 31%) with mp 196-197°C. IR Spectrum: 2200, 1720, 1690, 1600 cm^{-1}. $M^{+\cdot}$ 336.

REFERENCES

1. S. Yu. Ryabova, Yu. I. Trofimkin, L. M. Alekseeva, G. A. Bogdanova, Yu. N. Sheinker, and V. G. Granik, Khim. Geterotsikl. Soedin., No. 11, 1487 (1990).
2. S. Yu. Ryabova, Yu. I. Trofimkin, L. M. Alekseeva, L. S. Khabarova, and V. G. Granik, Khim. Geterotsikl. Soedin., No. 3, 343 (1991).
3. S. Yu. Ryabova, L. M. Alekseeva, and V. G. Granik, Khim. Geterotsikl. Soedin., No. 9, 1991 (1991).
4. S. Yu. Ryabova and V. G. Granik, Mendeleev Commun., No. 2, 59 (1992).
5. S. Yu. Ryabova, N. Z. Tugusheva, N. P. Solov'eva, S. D. Yuzhakov, A. V. Denisov, and V. G. Granik, Khim.-Farm. Zh., No. 11, 21 (1993).
6. J. Shvo and H. Shanan-Atidi, J. Am. Chem. Soc., **91**, 6689 (1969).
7. N. P. Kostyuchenko, V. G. Granik, A. M. Zhidkova, and R. G. Glushkov, Khim. Geterotsikl. Soedin., No. 9, 1212 (1974).
8. P. E. Hansen, Progress in NMR Spectroscopy, **14**, 274 (1981).