3-H-PYRROLIZIN-3-ONES

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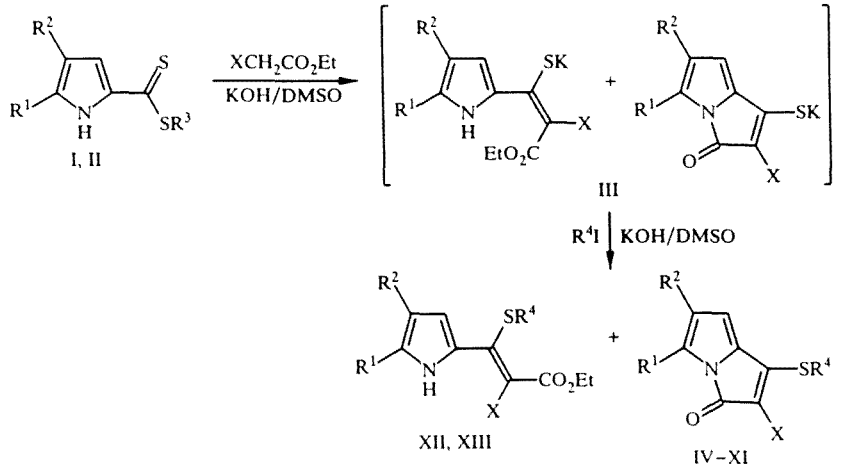
Previously unknown 1-alkylthio-3H-pyrrolizin-3-ones have been obtained by the condensation of pyrrole-2-dithiocarboxylates with CH acids containing ester groupings in the KOH–DMSO system. On treating the products with secondary amines they are readily converted into the corresponding 1-amino derivatives.

We showed previously [1] that 2-(1-alkylthio-2-cyanoethenyl)pyrroles are relatively stable in the KOH–DMSO system and in practice are not subject to the expected intramolecular annelation into 3-imino-3H-pyrrolizines.

The corresponding ethenylpyrroles with carboxylate groups, in difference to the 2-cyanoethenylpyrroles, are subject to intramolecular cyclization significantly more readily, frequently at the time of synthesis, when appropriate CH acids such as acetoacetic, malonic, and cyanoacetic esters are condensed with pyrrole-2-dithiocarboxylates in the KOH–DMSO system [2].

Scheme 1



Compound	R^1	R^2	R^3	R^4	X
I	$(CH_2)_4$		Et	—	—
II	Ph	H	Et	—	—
IV	$(CH_2)_4$		—	Et	CN
V	$(CH_2)_4$		—	Et	COMe
VI	$(CH_2)_4$		—	Et	CO_2Et
VII	$(CH_2)_4$		—	n-Bu	CO_2Et
VIII	$(CH_2)_4$		—	Allyl	CO_2Et
IX	Ph	H	—	Et	CN
X	Ph	H	—	Et	COMe
XI	Ph	H	—	Et	CO_2Et
XII	$(CH_2)_4$		—	Et	CN
XIII	Ph	H	—	Et	CN

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TABLE 1. Physicochemical Characteristics of the Synthesized Compounds

Compound	Empirical formula	mp, °C	IR spectrum, cm^{-1} (KBr)	PMR spectrum ($CDCl_3$, δ, ppm)	Yield, %
IV	$C_{14}H_{14}N_2SO$	163...164	1730 (CO), 2200 (CN)	6,25 (1H, s, H-3), 3,43 (2H, q, SCH_2), 1,48 (3H, t, CH_3), 1,74, 2,40, 2,72 (8H, m, CH_2 cyclohexane ring)	61
V	$C_{15}H_{17}NSO_2$	142...143	1700 (COMe), 1720 (CO)	6,22 (1H, s, H-3), 3,07 (2H, q, SCH_2), 2,45 (3H, s, CH_3CO), 1,40 (3H, t, Me), 1,73, 2,45, 2,73 (8H, m, CH_2 cyclohexane ring)	62
VI	$C_{16}H_{19}NSO_3$	105...106	1660 (CO_2Et), 1720 (CO)	6,26 (1H, s, H-3), 4,25 (2H, q, OCH_2), 3,17 (2H, q, SCH_2), 1,40 (3H, t, CH_3), 1,24 (3H, t, CH_3), 1,72, 2,40, 2,72 (8H, m, CH_2 cyclohexane ring)	75
VII	$C_{18}H_{23}NSO_3$	160...161	1660 (CO_2Et), 1720 (CO)	6,26 (1H, s, H-3), 4,32 (2H, q, OCH_2), 3,17 (2H, q, SCH_2), 1,36 (3H, t, $\underline{CH_3}H_2S$), 0,98 (3H, t, CH_3), 1,77, 2,43, 2,72 (8H, m, CH_2 cyclohexane ring)	59
VIII	$C_{17}H_{19}NSO_3$	139...140	1665 (CO_2Et), 1725 (CO)	6,26 (1H, s, H-3), 5,89 (1H, m, =CH), 5,43 (2H, d, =CH *-trans*), 5,30 (2H, d, =CH *-cis*), 4,30 (2H, q, OCH_2), 3,83 (2H, d, SCH_2), 1,34 (3H, t, CH_3), 1,75, 2,39, 2,74 (8H, m, CH_2 cyclohexane ring)	51
IX	$C_{16}H_{12}N_2SO$	132...133	2200 (CN), 1730 (CO)	7,38...7,82 (5H, m, Ph), 6,51 (1H, d, H-4), 6,40 (1H, d, H-3), 3,48 (2H, q, SCH_2), 1,50 (3H, t, CH_3)	62
X	$C_{17}H_{15}NSO_2$	178	1730 (CO), 1730 (CO)	7,39...7,74 (5H, m, Ph), 6,58 (1H, d, H-4), 6,38 (1H, d, H-3), 3,22 (2H, q, SCH_2), 2,46 (3H, s, CH_3CO), 1,46 (3H, t, CH_3)	48
XI	$C_{18}H_{17}NSO_3$	128	1660 (CO_2Et), 1725 (CO)	7,35...7,83 (5H, m, Ph), 6,53 (1H, d, H-4), 6,34 (1H, d, H-3), 4,32 (2H, q, OCH_2), 3,25 (2H, q, SCH_2), 1,46 (3H, t, CH_3), 1,36 (3H, t, $\underline{CH_3}CH_2$)	68
XVI	$C_{14}H_{15}N_3S$	152...153	1630 (C=N), 2195 (CN), 3250 (NH)	6,15 (1H, s, H-3), 3,31 (2H, q, SCH_2), 1,40 (3H, t, CH_3), 1,75, 2,41, 2,64 (8H, m, CH_2 cyclohexane ring)	70
XVII	$C_{17}H_{19}N_3O$	171...172	1720 (CO), 2200 (CN)	6,22 (1H, s, H-3), 1,77, 3,84 (10H, m, CH_2 piperidine ring), 1,77, 2,43, 2,77 (8H, m, CH_2 cyclohexane ring)	90
XVIII	$C_{19}H_{24}N_2O_3$	111...112	1720 (CO), 1720 (CO)	6,16 (1H, s, H-3), 4,25 (2H, q, OCH_2), 1,34 (3H, t, CH_3), 1,74, 3,71 (10H, m, CH_2 piperidine ring) , 1,74, 2,44, 2,82 (8H, m, CH_2 cyclohexane ring)	91
XIX	$C_{19}H_{17}N_3O$	186...187	1712 (CO), 2190 (CN)	7,35...7,80 (5H, m, Ph), 6,46 (1H, d, H-4), 6,40 (1H, d, H-3), 4,10, 3,80 (4H, m, NCH_2 piperidine ring) , 1,86 (6H, m, CH_2 piperidine ring)	92
XX	$C_{21}H_{22}N_2O_3$	153...154	1705 (CO), 1710 (COMe)	7,35...7,80 (5H, m, Ph), 6,46 (1H, d, H-4), 6,38 (1H, d, H-3), 3,75, 1,80 (10H, m, CH_2 piperidine ring) , 2,45 (3H, s, CH_3CO)	94
XXI	$C_{20}H_{20}N_2O_2$	152	1660 (CO_2Et), 1720 (CO)	7,35...7,80 (5H, m, Ph), 6,46 (1H, d, H-4), 6,38 (1H, d, H-3), 4,25 (2H, q, OCH_2), 3,78, 1,78 (10H, m, CH_2 piperidine ring) , 1,32 (3H, t, CH_3)	94

TABLE 2. Elemental Analysis Data for the Synthesized Compounds

Compound	Found, %				Empirical formula	Calculated, %			
	C	H	N	S		C	H	N	S
IV	64,5	5,4	10,5	12,8	$C_{14}H_{14}N_2SO$	64,8	5,5	10,3	12,4
V	64,5	5,9	5,5	11,9	$C_{15}H_{12}NSO_2$	65,5	6,2	5,1	11,6
VI	62,6	6,3	4,6	10,9	$C_{16}H_{19}NSO_3$	62,9	6,2	4,6	10,5
VII	64,2	6,8	4,2	9,8	$C_{18}H_{23}NSO_3$	64,9	6,9	4,2	9,6
VIII	64,0	5,9	4,0	10,2	$C_{17}H_{19}NSO_3$	64,4	6,0	4,4	10,1
IX	68,3	4,5	10,1	11,2	$C_{16}H_{12}N_2SO$	68,6	4,3	10,0	11,4
X	69,1	5,0	4,8	10,5	$C_{17}H_{15}NSO_2$	68,7	5,1	4,7	10,8
XI	65,7	5,0	4,3	9,6	$C_{18}H_{17}NSO_3$	66,1	5,2	4,3	9,8
XV	65,5	5,8	16,1	12,2	$C_{14}H_{15}N_3S$	65,4	4,6	16,3	12,4
XVII	73,0	6,9	14,2	—	$C_{17}H_{19}N_3O$	72,6	6,8	14,9	—
XVIII	70,3	7,1	8,6	—	$C_{19}H_{24}N_2O_3$	69,8	7,3	8,4	—
XIX	75,2	5,6	13,9	—	$C_{19}H_{17}N_3O$	74,8	5,6	14,1	—
XX	72,0	6,3	8,0	—	$C_{21}H_{22}N_2O_3$	71,5	6,4	8,2	—

The aim of the present investigation was to study the reaction mentioned, to establish the range of its applicability and selectivity, and also to synthesize new functionally substituted 3H-pyrrolizin-3-ones (Scheme 1).

The reaction was effected by heating (100-110°C, 1.5 h) pyrrole-2-dithiocarboxylates (I) and (II) with anions of CH acids, which were formed on treating (room temperature, 0.5 h) esters containing reactive methylene groups in the KOH–DMSO system. Alkylation of the intermediate thiolates with alkyl halides also occurs at room temperature.

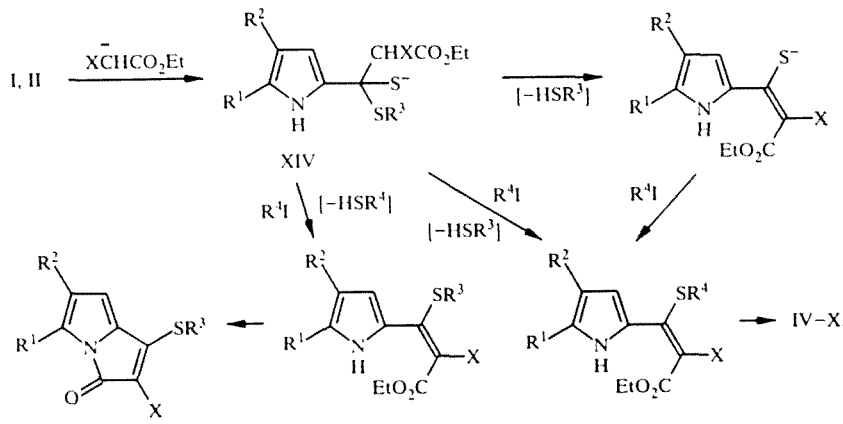
All three stages of the reaction, generation of the CH acid anion, interaction of the latter with the pyrrole-2-dithiocarboxylates (I) and (II), and alkylation of the intermediate thiolates (III), are brought about as a one-reactor process.

We reported previously in [1-3] that condensation of 4,5,6,7-tetrahydroindole-2-dithiocarboxylic acid ethyl ester (I) with cyanoacetate and subsequent ethylation with EtI gave 2-(2-carbethoxy-2-cyanoethenyl-1-ethylthio)-4,5,6,7-tetrahydroindole (XII) in addition to the corresponding 3H-pyrrolizin-3-one (IV). It was established in the course of this work that the sole product of the condensation of the pyrrole (II) under analogous conditions was the 3H-pyrrolizin-3-one (IX) (62% yield). Its linear analog (XIII) was detected in the reaction mixture only as an impurity (TLC data). Isolation and characterization of it were unsuccessful.

When condensing the pyrroles (I) and (II) with acetoacetic and malonic esters the reaction products were the corresponding 3H-pyrrolizin-3-ones (V), (VI), and (X), (XI). On studying this reaction we discovered that acetoacetic ester was very readily hydrolyzed in the KOH–DMSO system. To achieve a stable yield of 3H-pyrrolizin-3-ones with an acetyl group (V) and (X) it was necessary to use anhydrous DMSO and KOH and a 3-4 times molar excess of acetoacetic ester relative to pyrrole-2-dithiocarboxylate (I) and (II).

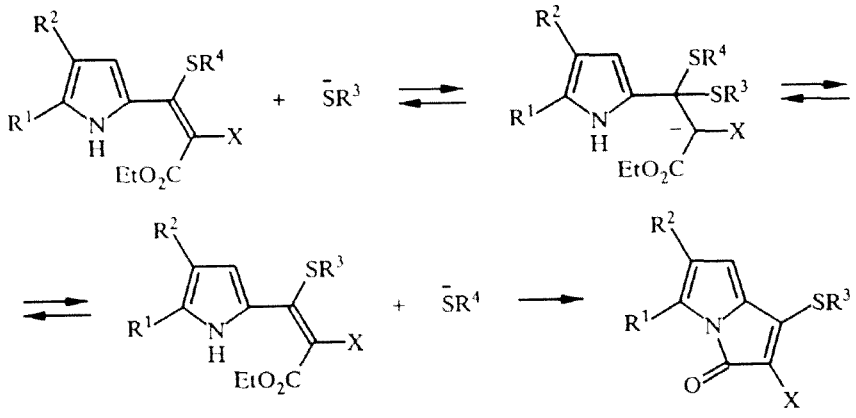
When carrying out the alkylation of the intermediate thiolates (III) with butyl and allyl iodides ($R^3 \neq R^4$), a 3H-pyrrolizin-3-one with an ethylthio group (VI) was formed in addition to the 3H-pyrrolizin-3-ones (VII) and (VIII). This may be explained by incomplete fission of ethyl mercaptan from the intermediate (XIV) in the initial stage of the condensation (Scheme 2) or by exchange between the 3H-pyrrolizin-3-ones or their linear precursors and the R^3S anions in the reaction medium (Scheme 3).

Scheme 2



Similarly, the formation of 3H-pyrrolizin-3-one (VI) may be avoided by increasing the duration of heating the reaction mixture before introducing the alkylating agent (from 1.5 to 2 h).

Scheme 3



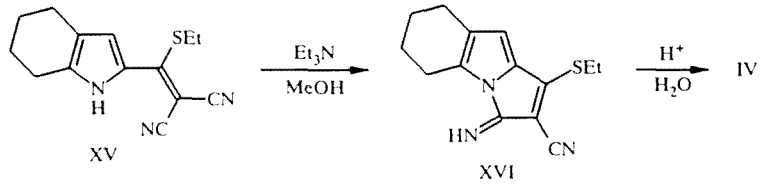
This reaction is a more convenient method of synthesizing 3H-pyrrolizin-3-ones which were obtained previously in low yield (20-30%) by the cyclization of 2-carboxy- or 2,2-dicarboxyvinylpyrroles on boiling in acetic anhydride [4, 5].

3H-Pyrrolizin-3-ones (IV)-(XI) are brightly colored (cherry, violet) crystals, the yields and physicochemical characteristics of which are given in Table 1. The structures of the compounds synthesized were reliably confirmed by data of IR and NMR spectroscopy (Table 1). There were significant differences between the ^1H NMR spectra of 2-(1-alkylthio-2-cyanoethenyl)pyrroles [1] and 3H-pyrrolizin-3-ones (IV)-(XI), which in combination confirmed the cyclic structure of the compounds obtained. For example, the 3-H proton appeared in the spectra of 2-cyanoethenylpyrroles as a doublet as a result of interaction with the NH group [1], but became a singlet in the spectra of 3H-pyrrolizin-3-ones. In addition it underwent more shielding in this case, which caused a reduction in its chemical shift of about 1 ppm. The cyclohexane ring protons at carbon atoms C^5 and C^8 formed an unresolved multiplet at 2.60-2.65 ppm in the spectra of 2-cyanoethenyl pyrroles but in the spectra of compounds (IV)-(XI) these methylene groups have different chemical shifts.

Signals for the ethylthio group (14.33 and 27.26), the pyrrole skeleton (118.33-135.82), a carbonyl group (163.37), and the pyrrolizine ring (C^1 at 160.5 and C^2 at 91.94-108.52 ppm) were present in the ^{13}C NMR spectra of the pyrrolizin-3-ones.

The absorption bands at 3255-3440 cm^{-1} (NH of pyrrole ring) and 1673 cm^{-1} (ν_{CO} of ester grouping) disappear from the IR spectra of 3H-pyrrolizin-3-ones and an absorption band appears at 1720 cm^{-1} assigned to carbonyl group vibrations. Absorption bands for ester and carbonyl groups were present in the spectra of compounds (VI) and (XI).

Scheme 4



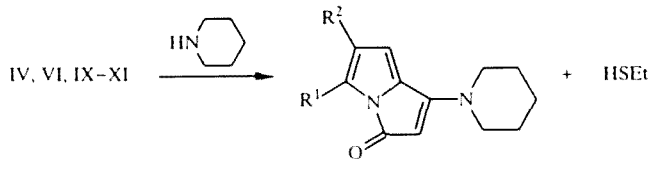
In addition, the 3H-pyrrolizin-3-one (IV) was synthesized by the acid hydrolysis of 2-cyano-1-ethylthio-3-imino-4,5,6,7-tetrahydrobenz[c]-3H-pyrrolizine (XVI), the cyclization product of the corresponding 2-cyanoethenyl-pyrrole (XV) (methanol, catalytic quantity of triethylamine) (Scheme 4). The hydrolysis occurred unusually readily. The bright orange methanolic solution of the 3-iminopyrrolizine (XVI) became violet instantaneously on adding 5% HCl solution. On diluting the solution with water the precipitated crystals had characteristics completely identical to the characteristics of compound (IV) obtained by the condensation of the pyrrole (I) with cyanoacetate.

We mentioned previously [6] that 3-imino-3H-pyrrolizines exchange the alkylthio group for an amino group on boiling in methanol for 4 h. It transpired that such an exchange takes place significantly more rapidly with 3H-pyrrolizin-3-ones

(Scheme 5). A mercaptan odor appeared instantly on mixing the reactants at room temperature, and after 15 min not even traces of the initial 3H-pyrrolizin-3-ones remained in the reaction medium.

Compounds (XVII)-(XXI) formed bright yellow crystals and their structures were confirmed by IR and NMR spectra.

Scheme 5



XVII–XXI

R	XVII	XVIII	XIX	XX	XXI
R^1	$(CH_2)_4$	$(CH_2)_4$	Ph	Ph	Ph
R^2			H	H	H
X	CN	CO_2Et	CN	COMe	CO_2Et

EXPERIMENTAL

The IR spectra of the pyrrolizinones were taken on a Specord IR 75 spectrometer in KBr disks. The ^1H NMR spectra were recorded on a Jeol FX 90 Q (100 MHz) spectrometer, solvent was $CDCl_3$, internal standard HMDS. A check on the progress of reactions and the purity of the compounds obtained was effected by thin layer chromatography on Silufol UV 254 plates in the systems ether, ether–hexane (1:1), and ether–ethanol (10:1).

The data of elemental analysis of the compounds corresponded to the calculated values.

1-Alkylthio-3H-pyrrolizin-3-ones (IV)-(XI) (general method). The reactive methylene ester (15 mmole or 30-40 mmole for acetoacetic ester), KOH (15 mmole), and DMSO (50 ml) were stirred at room temperature for 0.5 h. Pyrrole (I) or (II) (10 mmole) was then added and the mixture heated at 108-110°C for 1.5 h. After cooling the reaction mixture to room temperature, alkyl halide (15 mmole) was added, and the mixture stirred for 2 h. The reaction mixture was diluted with water and extracted with ether. After removing the ether, the residue was crystallized from ethanol and the 3H-pyrrolizin-ones obtained.

2-Cyano-1-ethylthio-3-imino-4,5,6,7-tetrahydrobenz[c]-3H-pyrrolizine (XVI). A solution of 2-(2,2-dicyanoethenyl-1-ethylthio)-4,5,6,7-tetrahydroindole (XV) in methanol (10 ml) was boiled in the presence of triethylamine (2-3 drops) for 2 h and cooled to room temperature. The precipitated solid was filtered off and washed with ether. The pyrrolizine of mp 152-153°C was obtained in 71% yield.

2-Cyano-1-ethylthio-4,5,6,7-tetrahydrobenz[c]-3H-pyrrolizin-3-one (IV). 3-Imino-3H-pyrrolizine (XVI) (0.51 g: 2 mmole) was dissolved in methanol (60 ml) and 5% HCl solution (10 ml) added. The bright orange solution immediately became violet. After 5 min it was diluted with 5 volumes of water, and violet crystals of 3H-pyrrolizin-3-one (IV) (0.44 g: 85%) of mp 162-163°C were filtered off.

1-Piperidino-3H-pyrrolizin-3-ones (XVII)-(XXI) (general method). 1-Ethylthio-3H-pyrrolizin-3-one (IV), (VI), or (IX)-(XI) (1 mmole) was dissolved in methanol (10 ml) and piperidine (2 mmole) added. The odor of mercaptan appeared straight away. After 15 min the reaction mixture was cooled and crystals of 1-piperidino-3H-pyrrolizin-3-ones (XVII)-(XXI) were filtered off (see Tables).

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