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3H-PYRROLIZIN-3-ONES

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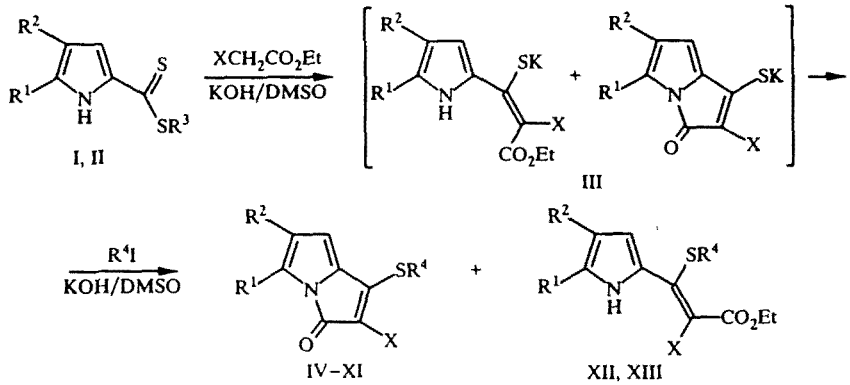
Condensation of pyrrole-2-dithiocarboxylates with CH acids containing ester groups, in the KOH–DMSO system, was used to prepare previously unknown 1-alkylthio-3H-pyrrolizin-3-ones. The latter, treated with secondary amines, are readily converted to the corresponding 1-amino derivatives.

We have shown previously [1] that 2-(1-alkylthio-2-cyanoethenyl)pyrroles are relatively stable in the KOH–DMSO system and for all practical purposes do not undergo the expected intramolecular cyclization leading to 3-imino-3H-pyrrolizines.

In contrast to 2-cyanoethenylpyrroles, the corresponding ethenylpyrroles with carboxylate groups undergo intramolecular cyclization much more readily, often during their synthesis, when the corresponding CH acids, such as acetoacetic, malonic, and cyanoacetic esters, condense with pyrrole-2-dithiocarboxylates in the KOH–DMSO system [2].

In our view, the study of this reaction and determination of its scope of applicability and selectivity are useful, since the reaction opens up the possibility of synthesizing new, functionally substituted 3H-pyrrolizin-3-ones.

Scheme 1



I R^1, R^2 = (CH$_2$)$_4$, R^3 = Et; II R^1=Ph, R^2 = H, R^3 = Et; IV R^1, R^2 = (CH$_2$)$_4$, R^4 = Et, X = CN; V R^1, R^2 = (CH$_2$)$_4$, R^4 = Et, X = COMe; VI R^1, R^2 = (CH$_2$)$_4$, R^4 = Et, X = CO$_2$Et; VII R^1, R^2 = (CH$_2$)$_4$, R^4 = Bu, X = CO$_2$Et; VIII R^1, R^2 = (CH$_2$)$_4$, R^4 = CH$_2$CH=CH$_2$, X = CO$_2$Et; IX R^1 = Ph, R^2 = H, R^4 = Et, X = CN; X R^1 = Ph, R^2 = H, R^4 = Et, X = COMe; XI R^1 = Ph, R^2 = H, R^4 = Et, X = CO$_2$Et; XII R^1, R^2 = (CH$_2$)$_4$, R^4 = Et, X= CN; XII R^1 = Ph, R^2 = H, R^4 = Et, X = CN

The reaction was carried out by heating (100-110°C, 1.5 h) pyrrole-2-dithiocarboxylates I, II with anions of CH acids, obtained from methylene-active esters by treatment with the KOH–DMSO system (room temperature, 0.5 h). Alkylation of the intermediate thiolates with alkyl halides takes place at room temperature.

All three successive reactions, i.e., formation of the CH-acid anion, reaction of the latter with pyrrole-2-dithiocarboxylate I, II, and alkylation of intermediate thiolates III, are carried out in the same reaction vessel.

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TABLE 1. Physicochemical Properties of the Synthesized Compounds

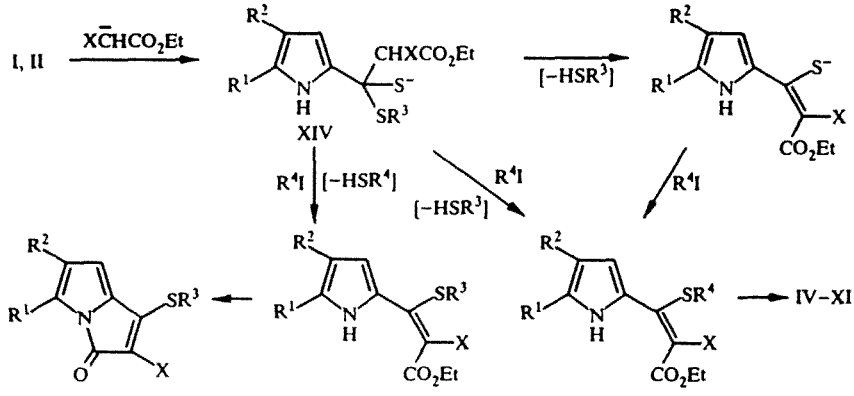
Compound	mp, °C	IR spectra, cm^{-1} (KBr)	PMR spectra ($CDCl_3$, δ, ppm)	Yield, %
IV	163...164	1730 (CO), 2200 (CN)	6,25 (1H, s, H-3), 3,43 (2H, q, SCH_2), 1,48 (3H, t, Me), 1,74, 2,40, 2,72 (8H, m, CH_2 of cyclohexane ring)	61
V	142...143	1700 (COMe), 1720 (CO)	6,22 (1H, s, H-3), 3,07 (2H, q, SCH_2), 2,45 (3H, s, CH_3CO), 1,40 (3H, t, Me), 1,73, 2,45, 2,73 (8H, m, CH_2 of cyclohexane ring)	62
VI	105...106	1660 (CO_2Et_3), 1720 (CO)	6,26 (1H, s, H-3), 4,25 (2H, q, CO_2Me), 3,17 (2H, q, SCH_2), 1,40 (3H, t, Me), 1,24 (3H, t, Me), 1,72, 2,40, 2,72 (8H, m, CH_2 of cyclohexane ring)	75
VII	160...161	1660 (CO_2Bu), 1720 (CO)	6,26 (1H, s, H-3), 4,32 (2H, q, OCH_2), 3,17 (2H, q, SCH_2), 1,36 (3H, t, $MeCH_2S$), 0,98 (3H, t, Me), 1,77, 2,43, 2,72 (8H, m, CH_2 of cyclohexane ring)	59
VIII	139...140	1665 (CO_2Allyl), 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, Me), 1,75, 2,39, 2,74 (8H, m, CH_2 of cyclohexane ring)	51
IX	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, Me)	62
X	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, MeCO), 1,46 (3H, t, CH_3)	48
XI	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, Me), 1,36 (5H, t, $MeCH_2$)	68
XV	152...153	1630 (C=N), 2195 (CN), 3250 (NH)	6,15 (1H, s, H-3), 3,31 (2H, q, CH_2), 1,40 (3H, t, Me), 1,75, 2,41, 2,64 (8H, m, CH_2 of cyclohexane ring)	70
XVII	171...172	1720 (CO), 2200 (CN)	6,22 (1H, s, H-3), 1,77, 3,84 (10H, m, CH_2 of piperidine ring), 1,77, 2,43, 2,77 (8H, m, CH_2 of cyclohexane ring)	90
XVIII	111...112	1720 (CO), 1720 (CO)	6,16 (1H, s, H-3), 4,25 (2H, q, OCH_2), 1,34 (3H, t, Me), 1,74, 3,71 (10H, m, CH_2 of piperidine ring), 1,74, 2,44, 2,82 (8H, m, CH_2 of cyclohexane ring)	91
XIX	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 of piperidine ring), 1,86 (6H, m, CH_2 of piperidine ring)	92
XX	153...154	1705 (CO), 1710 ($COCH_3$)	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 of piperidine ring), 2,45 (3H, s, CH_3CO)	94
XXI	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 of piperidine ring), 1,32 (3H, t, Me)	94

We reported previously [1-3] that condensation of ethyl 4,5,6,7-tetrahydroindole-2-dithiocarboxylate (I) with cyanoacetate followed by ethylation with EtI together with the corresponding 3H-pyrrolizin-3-one IV led to the formation of 2-(1-ethylthio-2-carbethoxy-2-cyanoethyl)-4,5,6,7-tetrahydroindole (XII). It was also found that condensation of pyrrole II under these conditions forms 3H-pyrrolizin-3-one IX as the only product of the reaction (yield, 62%). Its linear analog XIII was detected in the reaction mixture only as an impurity (based on TLC data). We were not successful in isolating and characterizing it.

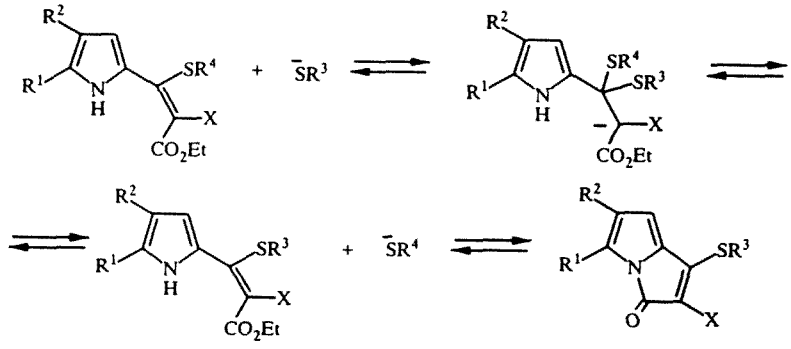
In the condesation of pyrroles I, II with acetoacetic and malonic esters, the only reaction products were the corresponding 3H-pyrrolizin-3-ones V, VI and X, XI. In studying this reaction, we found that acetoacetic ester hydrolyzes very readily in the KOH–DMSO system, and therefore, in order to obtain a steady yield of 3H-pyrrolizin-3-ones with an acetyl group, V and X, it is necessary to use dehydrated DMSO and KOH and a 3-4-fold molar excess of acetoacetic ester with respect to pyrrole-2-dithiocarboxylates I, II.

In the alkylation of intermediate thiolates III with butyl and allyl iodides ($R^3 \neq R^4$), in addition to 3H-pyrrolizin-3-ones VII, VIII, there is also formed 3H-pyrrolizin-3-one with an ethylthio group, VI, and this can also be explained by a partial splitting off of ethyl mercaptan from the intermediate XIV in the initial stage of condensation (scheme 2), or by the exchange between 3H-pyrrolizin-3-ones or their linear precursors and the reaction medium containing R^3S^- anions (scheme 3).

Scheme 2



Scheme 3



Secondary formation of 3H-pyrrolizin-3-one VI can be avoided by increasing the duration of heating of the reaction mixture (from 1.5 h to 2 h) prior to adding the alkylating agent.

Thus, this reaction constitutes a more convenient method of synthesizing 3H-pyrrolizin-3-ones, which previously were obtained in moderate yields (20-30%) by cyclization of 2-carboxy- and 2,2-dicarboxyvinylpyrroles with boiling of the latter in acetic anhydride [4, 5].

3H-Pyrrolizin-3-ones IV-XI are brightly colored (cherry, volet) crystals, the yield and physicochemical properties of which are shown in Table 1. The structure of the synthesized compounds was confirmed by data of IR and NMR spectroscopy (Table 1).

Thus, the ^1H NMR spectra of 2-(1-alkylthio-2-cyanoethenyl)pyrroles [1] and 3H-pyrrolizin-3-ones IV-XI differ considerably. For example, the H-3 proton, represented by a doublet in the spectra of 2-cyanoethylpyrroles as a result of interaction with the NH group [1], becomes a singlet in the spectra of 3H-pyrrolizin-3-ones. In addition, in this case it undergoes considerable screening, and this causes a decrease of its chemical shift by approximately 1 ppm. The protons of the cyclohexane ring at the $C_{(5)}$ and $C_{(8)}$ atoms in the spectra of 2-cyanoethenylpyrroles form an unresolved multiplet around 2.60-2.65 ppm, whereas in the spectra of compounds IV-XI these methylene groups are distinguishable.

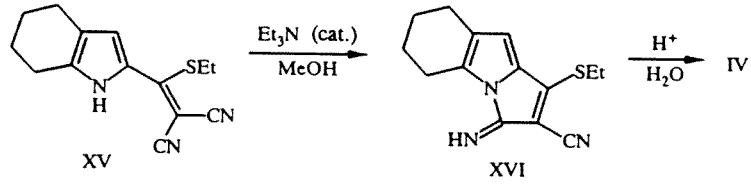
The ^{13}C NMR spectra of pyrrolizin-3-ones contain signals of the ethylthio group (14.33 and 27.26), pyrrole skeleton (118.33-135.82), carbonyl group (163.37), and pyrrolizine ring ($C_{(1)}$ — 160.5 and $C_{(2)}$ — 91.94-108.52 ppm).

In the IR spectra of 3H-pyrrolizin-3-ones, the absorption bands at 3255-3440 cm^{-1} (pyrrole-ring NH) and 1673 (ester-group ν_{CO}) disappear, and the absorption band at 1720 cm^{-1}, responsible for vibrations of the carbonyl group, appears. Com-

TABLE 2. Ultimate-Analysis Data for the Synthesized Compounds

Compound	Empirical formula	Found, % / Calculated, %			
		C	H	N	S
IV	$C_{14}H_{14}N_2SO$	64.8 64,8	5.5 5,5	10.3 10,3	12.4 12,4
V	$C_{15}H_{12}NSO_2$	64.5 64,5	5.9 6,2	5.5 5,1	11.9 11,6
VI	$C_{16}H_{19}NSO_3$	62.6 62,9	6.3 6,2	4.6 4,6	10.9 10,5
VII	$C_{18}H_{23}NSO_3$	64.2 64,9	6.8 6,9	4.2 4,2	9.8 9,6
VIII	$C_{17}H_{19}NSO_3$	64.0 64,4	5.9 6,0	4.0 4,4	10.2 10,1
IX	$C_{16}H_{12}N_2SO$	68.3 68,6	4.5 4,3	10.1 10,0	11.2 11,4
X	$C_{17}H_{15}NSO_2$	69.1 68,7	5.0 5,1	4.8 4,7	10.5 10,8
XI	$C_{18}H_{17}NSO_3$	65.7 66,1	5.0 5,2	4.3 4,3	9.6 9,8
XV	$C_{14}H_{15}N_3S$	65.5 65,4	5.8 4,6	16.1 16,3	12.2 12,4
XVII	$C_{17}H_{19}N_3O$	73.0 72,6	6.9 6,8	14.2 14,9	—
XVIII	$C_{19}H_{24}N_2O_3$	70.3 69,8	7.1 7,3	8.6 8,4	—
XIX	$C_{19}H_{17}N_3O$	75.2 74,8	5.6 5,6	13.9 14,1	—
XX	$C_{21}H_{22}N_2O_3$	72.0 71,5	6.3 6,4	8.0 8,2	—
XXI	$C_{20}H_{20}N_2O_2$	75.0 74,4	6.3 6,3	8.8 9,0	—

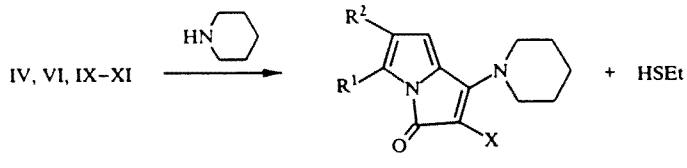
pounds VI and XI contain absorption bands of the ester and carbonyl groups. In addition, 3H-pyrrolizin-3-one IV was synthesized by acid hydrolysis of 3-imino-1-ethylthio-2-cyano-4,5,6,7-tetrahydrocyclohexa[c]-3H-pyrrolizine (XVI), the cyclization product of the corresponding 2-cyanoethenylpyrrole XV.



The hydrolysis takes place with unusual ease: the bright orange methanol solution of 3-iminopyrrolizine instantly turns violet on addition of 5% HCl solution. The crystals precipitating on dilution of the solution with water have properties that are completely identical to those of compound IV, which is obtained by condensation of pyrrole I with cyanoacetate.

We noted previously [6] that 3-imino-3H-pyrrolizines tend to exchange the alkylthio group for an amino group when boiled with ethanol for 4 h. It was found that in 3H-pyrrolizin-3-ones, such an exchange takes place much more readily: when the reactants are mixed at room temperature, a mercaptan odor is instantly perceived, and after 15 min, not even traces of the initial 3H-pyrrolizin-3-ones remain in the reaction medium.

Compounds XVII-XXI are bright yellow crystals whose structure is confirmed by IR and NMR spectra.



XVII–XXI

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

EXPERIMENTAL

The IR spectra of pyrrolizines were taken in KBr pellets with a Specord IR-75 spectrometer. The ^1H NMR spectra were recorded with a Jeol FX 90 spectrometer (100 MHz) with $CDCl_3$ as the solvent and HMDS as the internal standard. The reaction and purity of the compounds obtained were monitored by thin-layer chromatography on Silufol UV-254 plates in the systems, 1:1 ether–hexane and 10:1 ether–ethanol.

The ultimate-analysis data for the compounds correspond to the calculations (Table 2).

1-Alkyl-3H-pyrrolizin-3-ones IV-XI (standard method). At room temperature, 15 mmole of KOH, 15 mmole of methylene-active ester (acetoacetic ester is used in an amount of 30-40 mmole) and 50 ml of DMSO are stirred for 0.5 h, 10 mmole of pyrrole I or II is added, and the mixture is heated for 1.5 h at 108-110°C. After cooling, 15 mmole of alkyl halide is added, and the mixture is stirred for 2 h. The reaction mixture is diluted with water and extracted with ether. After the ether is driven off, the residue is recrystallized from ethanol, and 3H-pyrrolizin-3-ones are obtained.

3-Imino-1-ethylthio-2-cyano-4,5,6,7-tetrahydrocyclohexa[c]-3H-pyrrolizine (XVI). A solution of 0.51 g (2 mmole) of 2-(1-ethylthio-2,2-dicyanoethenyl)-4,5,6,7-tetrahydroindole (XV) in 10 ml of methanol is boiled in the presence of 2 to 3 drops of triethylamine for 2 h and cooled to room temperature. The precipitate is filtered off and washed with ether, and 0.36 g (71%) of pyrrolizine, 152-153°C, is obtained.

1-Ethylthio-2-cyano-4,5,6,7-tetrahydrocyclohex[c]-3H-pyrrolizin-3-one (IV). 3-Imino-3H-pyrrolizine XVI in an amount of 0.51 g (2 mmole) is dissolved in 60 ml of methanol, and 10 ml of a 5% HCl solution is added. The brightly colored orange solution instantly turns violet. After 5 min, it is diluted fivefold with water, and violet crystals of 3H-pyrrolizin-3-one (IV) (0.44 g, 85% yield, 162-163°C) are filtered off.

1-Piperidino-3H-pyrrolizin-3-ones XVII-XXI (standard method). 1-Ethylthio-3H-pyrrolizin-3-one IV, VI, IX-XI in an amount of 1 mmole is dissolved in 10 ml of methanol, and 2 mmole of piperidine is added. An odor of mercaptan is immediately perceived. After 15 min, the reaction mixture is cooled, and crystals of 1-piperidino-3H-pyrrolizin-3-ones XVII-XXI are filtered off (Table 1).

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