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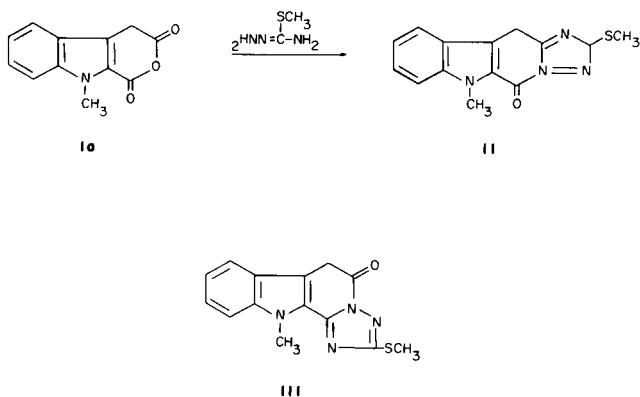
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2-Carboxy-1-alkylindole-3-acetic acid anhydrides (I) condensed with *S*-methylisothiosemicarbazide in DMF to form 5,11-dihydro-6-methyl-2-methylthioindolo[3',2':4,5]pyrido[1,2-*b*]-s-triazol-5-one (II). Compound II underwent ring opening on refluxing with sodium hydroxide solution to give IV. The anhydride I reacted with primary amines in benzene to give 2-carboxy-1-alkylindole-3-acetanilide derivatives (VI) which yielded 1-methylindole-3-acetic acid by decarboxylation followed by hydrolysis. Compound II oxidised to the diketo compound X which could be prepared by the hydrolysis of the azomethine derivative IX with acetic acid-hydrochloric acid mixture. Compound II reacted with benzyl chloride to yield the dibenzyl derivative XII, condensed with *p*-chlorobenzaldehyde to form the 11-*p*-chlorobenzylidene derivative XI and coupled with arenediazonium salt to give the 11-arylhydrazone derivatives XIII.

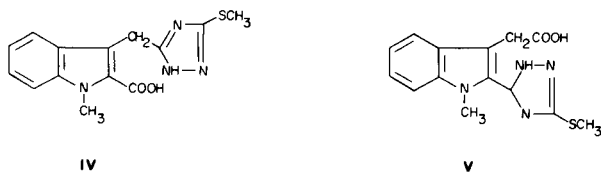
J. Heterocyclic Chem., **19**, 993 (1982).

In continuation of our interest in the condensation reactions of acid anhydrides with amines (1,2), 2-carboxy-1-methylindole-3-acetic acid anhydride (Ia) was condensed with *S*-methylisothiosemicarbazide to form 5,11-dihydro-6-methyl-2-methylthioindolo[3',2':4,5]pyrido[1,2-*b*]-s-triazol-5-one (II) or its angular isomer (III).



The condensation product II (III) is susceptible to oxidation during its crystallisation and transformed into the diketo compound (X), which was identical with that obtained by the hydrolysis of the azomethine derivative, IX as described below.

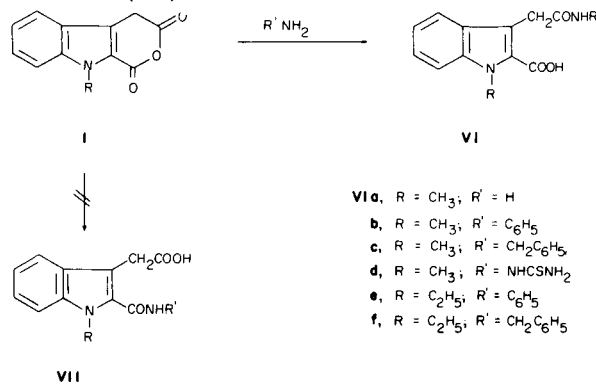
Crude II (III) undergoes ring opening in aqueous sodium hydroxide to give 3-(5-methylthio-1,2,4-triazol-3-ylmethyl)-*N*-methylindole-2-carboxylic acid (IV) or the isomer (V).



The ir spectrum of IV (V) showed bands at 3100 cm⁻¹ (broad, COOH and NH) and 1700 cm⁻¹ (COOH).

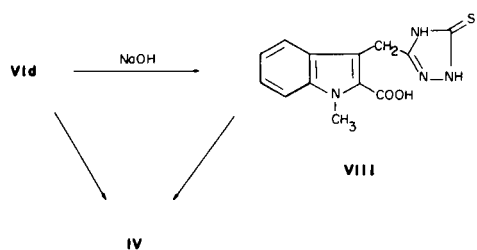
We have previously reported (3) that the reaction of the

anhydride I with amines in presence of phosphorus pentoxide in xylene resulted in the formation of arylpyrido[3,4-*b*]indole-1,3-diones. Now we have found that the reaction of I with amines in anhydrous benzene resulted in opening of the anhydride ring with the formation of 2-carboxy-1-alkylindole-3-acetanilide derivatives (VI), rather than 2-phenylcarbonyl-1-alkylindole-3-acetic acid derivatives (VII).



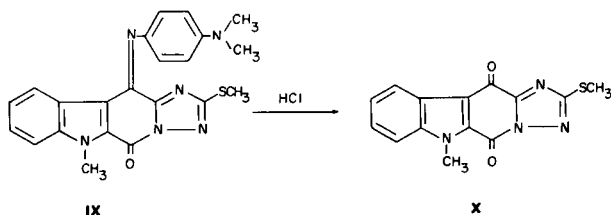
The ir spectrum of compound VIb shows a broad peak at 3290 cm⁻¹ for OH and NH groups with hydrogen bond, a peak at 1675 cm⁻¹ for COOH group and at 1655 cm⁻¹ for CONH group.

Decarboxylation of compound VIb at 250° yielded 1-methylindole-3-acetanilide (4) which was hydrolysed to 1-methylindole-3-acetic acid identical with an authentic sample (5). This confirms that the structure of the products of action of amines on the anhydride I can be correctly regarded as VI. Treatment of VIc with sodium hydroxide afforded 3-(5-thio-1,2,4-triazolin-3-ylmethyl)-*N*-methylindole-2-carboxylic acid (VIII), [the cyclisation of acylthiosemicarbazides to form triazolinethiones is reported in literature (6,7)]. The action of methyl iodide on both VIc or VIII in presence of alkali gave the *S*-methyl derivative which is identical with the hydrolysis product IV of II.

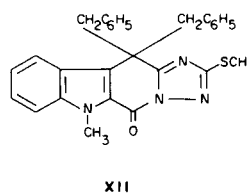
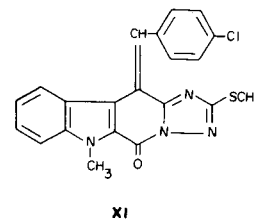


Therefore the condensation product of the anhydride I with *S*-methylisothiosemicarbazide has the linear structure II and not III.

Crude II reacted with *p*-nitrosodimethylaniline to give 11-(*p*-dimethylaminophenylimino) derivative IX. When the azomethine derivative IX was hydrolysed by acetic-hydrochloric acid, it yielded 5,11-dihydro-6-methyl-2-methylthioindolo[3',2':4,5]pyrido[1,2-*b*]-*s*-triazole-5,11-dione (X). The ir spectrum of X shows two absorptions at 1720 and 1670 cm^{-1} .



Compound II condensed with *p*-chlorobenzaldehyde in refluxing acetic acid in the presence of anhydrous sodium acetate, to yield 5,11-dihydro-11-*p*-chlorobenzylidene-6-methyl-2-methylthioindolo[3',2':4,5]pyrido[1,2-*b*]-*s*-triazol-5-one (XI). The ir spectrum of XI shows CO absorption at 1718 cm^{-1} .



The CO absorption of XII appeared at 1720 cm^{-1} which is similar to the carbonyl absorption in the *p*-chlorobenzylidene derivative XI. The absence of a shift between these two peaks reveals that there is no conjugation between the carbonyl group and the exocyclic C=C double bond in XI. Such a state of affairs is provided by the linear structure, II, since the angular structure, III, would lead to conjugation.

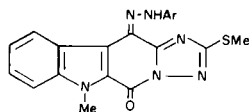
Compound II coupled with arenediazonium salts in pyridine to yield 5,11-dihydro-6-methyl-2-methylthioindolo[3',2':4,5]pyrido[1,2-*b*]-*s*-triazole-5,11-dione 11-arylhydrazones (XIII).

Table I

2-Carboxy-1-alkylindole-3-acetanilide Derivatives

Compound	Mp	Yield %	Solvent	Formula	Analysis %		
					Calcd./	Found	N
VIa	223	74	Ethanol	$\text{C}_{12}\text{H}_{12}\text{N}_2\text{O}_3$ (232.2)	62.06 61.90	5.20 5.10	12.06 12.10
VIb	212-214	95	Ethanol	$\text{C}_{18}\text{H}_{16}\text{N}_2\text{O}_3$ (308.3)	70.11 69.90	5.23 5.20	9.09 9.10
VIc	192-193	85	Aqueous Ethanol	$\text{C}_{15}\text{H}_{18}\text{N}_2\text{O}_3$ (322.4)	70.78 71.10	5.63 5.90	8.70 8.80
VId	205	71	Ethanol	$\text{C}_{13}\text{H}_{14}\text{N}_2\text{O}_3\text{S}$ (a) (306.3)	50.96 50.60	4.61 4.40	18.29 18.00
VIe	225	90	Ethanol	$\text{C}_{15}\text{H}_{18}\text{N}_2\text{O}_3$ (322.4)	70.78 70.9	5.63 5.80	8.70 8.40
VIf	125	96	Ethanol	$\text{C}_{20}\text{H}_{20}\text{N}_2\text{O}_3$ (336.4)	71.39 71.70	5.99 6.20	8.33 8.10

(a) S, Calcd.: 10.46, Found: 10.2.

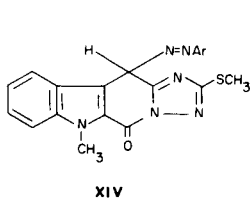


- XIIIa, Ar = C₆H₅
 b, Ar = C₆H₄Cl-p
 c, Ar = C₆H₄OCH₃-p

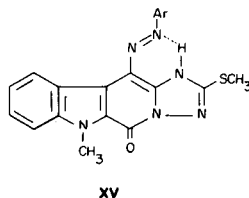
The uv spectrum of XIIIa shows a maximum band at 488 nm. Monophenylhydrazones are known to exhibit sharp absorption at wave lengths higher than 320 nm (8,9). On the other hand, azo compounds obtained from the coupling of diazonium salts with aliphatic carbon atoms absorb strongly at about 280 nm (10).

In the ir spectrum of XIIIa the carbonyl absorption appeared at 1707 cm⁻¹, which is near those of the carbonyl group of XI and XII.

These arguments reveal that the coupling products XIII exist mainly in the hydrazone form rather than other structures such as XIV and XV. These spectral data are also in favour of the linear structure II.



xiv



xv

The coupling product XIIIa was also obtained by the reaction of the dione X with phenylhydrazine.

EXPERIMENTAL

All melting points are uncorrected. The ir spectra were recorded on a Pye Unicam SP 1000 spectrophotometer, uv spectra were recorded on a Perkin-Elmer spectrophotometer model 402.

5,11-Dihydro-6-methyl-2-methylthioindolo[3',2':4,5]pyrido[1,2-b]-s-triazol-5-one (II).

A mixture of 21.5 g (0.1 mole) of 2-carboxyl-1-methylindole-3-acetic acid anhydride (I), 27.9 g (0.12 mole) of *S*-methylisothiosemicarbazide hydriodide, and 16.4 g (0.2 mole) of anhydrous fused sodium acetate in 50 ml of dry dimethylformamide was gently heated on a water bath for 2 hours and then refluxed for 30 minutes with occasional shaking. The reaction mixture was cooled and then poured into 250 ml of cold water, the greenish white precipitate formed was filtered off and washed with little ethanol to give 21.3 g (75%) of crude II, mp > 300°. Compound II was dissolved in dimethylformamide, filtered and reprecipitated with water. The precipitate obtained was filtered off, washed with ethanol and dried.

Anal. Calcd. for C₁₄H₁₂N₄OS: C, 59.14; H, 4.25; N, 19.72; S, 11.26. Found: C, 58.8; H, 4.0; N, 19.6; S, 11.0.

3-(5-Methylthio-1,2,4-triazol-3-ylmethyl)-*N*-methylindole-2-carboxylic Acid (IV).

Method A.

One g of VI_d dissolved in 50 ml of 5% sodium hydroxide, was treated with 0.5 g of methyl iodide. The mixture was refluxed for 3 hours, cooled and acidified with 10% hydrochloric acid. The solid, IV, (0.6 g, 60%) that separated was filtered off, washed with water and crystallised from aqueous ethanol as colourless crystals, mp 218°.

Anal. Calcd. for C₁₄H₁₄B₄O₂S: C, 55.60; H, 4.67; N, 18.53; S, 10.60. Found: C, 55.5; H, 5.0; N, 18.2; S, 10.4.

Method B.

One half g of VIII dissolved in 25 ml of 1% sodium hydroxide solution, was treated with 0.25 g of methyl iodide. The whole was refluxed for 2 hours and then cooled. The reaction mixture was acidified with 10% hydrochloric acid. The solid that separated was collected, washed with water and crystallised from aqueous ethanol to yield 0.35 g (70%) of IV as colourless crystals, mp and mmp with the product of method A 218°.

Method C.

A suspension of 2 g of II in 50 ml of 10% sodium hydroxide was refluxed for 3 hours and cooled. It was then acidified with 10% hydrochloric acid and the precipitate formed was filtered off, washed with water and crystallised from aqueous ethanol (charcoal) to give 1.2 g (57%) of IV as colourless crystals, mp 218°; not depressed when mixed with the compound prepared above.

2-Carboxy-1-alkylindole-3-acetanilides (VI).

A solution of 0.01 mole of I in 50 ml of dry benzene was treated with 0.011 mole of the appropriate amine and the reaction mixture was refluxed.

Table II

5,11-Dihydro-6-methyl-2-methylthioindolo[3',2':4,5]pyrido[1,2-b]-s-triazole-5,11-dione 11-Arylhydrazones (XIII)

Compound	Mp	Yield %	Solvent	Formula	C	Analysis %			
						Calcd./Found			
						H	N	S	
XIIIa	248	83	AcOH	C ₂₀ H ₁₆ N ₆ OS (388.4)	61.83	4.15	21.63	8.25	
					62.10	4.50	22.00	8.30	
XIIIb	288	85	Aqueous dioxan	C ₂₀ H ₁₃ ClN ₆ OS (a) (422.9)	56.78	3.57	19.87	7.58	
					56.8	3.50	20.10	7.80	
XIIIc	258	87	Aqueous dioxan	C ₂₁ H ₁₈ N ₆ O ₂ S (418.5)	60.27	4.33	20.08	7.66	
					60.30	4.40	20.40	7.90	

(a) Cl, Calcd.: 8.38, Found: 8.5.

ed for 1 hour. It was then cooled and the solid that separated was collected and crystallised from the proper solvent (See Table I).

2-Carboxy-1-methylindole-3-acetamide (VIa).

Dry ammonia gas was bubbled slowly through a solution of one gram of the anhydride (I) in 30 ml of anhydrous dioxan. The ammonium salt of the product VIa separated in a few minutes. After the dioxan has been saturated with ammonia, water was added to obtain a clear solution, which was then acidified with 10% hydrochloric acid solution. The resulting precipitate was collected to yield 0.8 g of VIa and then recrystallized.

1-Methylindole-3-acetanilide.

One half g of VIb was heated in a metal bath at 230° until the evolution of carbon dioxide stopped. The residue was triturated with little ethanol and the solid so obtained (0.3 g, 70%) was recrystallised from aqueous ethanol as colourless crystals, mp 117° (4).

1-Methylindole-3-acetic Acid.

A mixture of 1 g of 1-methylindole-3-acetanilide and 15 ml of 70% sulfuric acid was refluxed for 1 hour. The reaction mixture was then cooled and poured into 100 ml of cold water. The collected precipitate (0.5 g, 63%) was washed with water and recrystallised from aqueous ethanol (charcoal) as colourless crystals, mp 128°, not depressed when mixed with an authentic sample (5).

3-(5-Thioxo-1,2,4-triazolin-3-ylmethyl)-N-methylindole-2-carboxylic Acid (VIII).

A solution of 1 g of VIId in 50 ml of 5% sodium hydroxide was refluxed for 2 hours and left to cool. The solution was acidified with 10% hydrochloric acid and the white precipitate formed was collected, washed with water, and crystallised from ethylene glycol as colourless crystals, mp 272°, yield 0.6 g (70%).

Anal. Calcd. for $C_{13}H_{12}N_4O_2S$: C, 54.16; H, 4.20; N, 19.44; S, 11.12. Found: C, 54.3; H, 4.5; N, 19.5; S, 11.0.

5,11-Dihydro-6-methyl-2-methylthio-11-(p-dimethylaminophenylimino)indolo[3',2':4,5]pyrido[1,2-b]-s-triazol-5-one (IX).

p-Nitrosodimethylaniline (1.5 g, 0.01 mole) was added to a suspension of II (0.01 mole) in ethanol (100 ml) followed by one drop of piperidine and the reaction mixture was refluxed for 1 hour. The solution became violet in colour and compound IX separated and was crystallised from benzene in dark blue crystals, mp 270°, yield 65%.

Anal. Calcd. for $C_{22}H_{20}N_6O_2S$: C, 63.44; H, 4.84; N, 20.18; S, 7.70. Found: C, 63.5; H, 5.1; N, 20.4; S, 7.8.

Hydrolysis of the Azomethine Derivative IX.

Hydrochloric acid (2*N*, 5 ml) was added dropwise to a suspension of IX (1 g) in acetic acid (25 ml) and after stirring at room temperature for 15 minutes, it was warmed for 10 minutes. Water (10 ml) was added and stirring was continued for a few minutes and the precipitate was crystallised. From acetic acid to give X in 85% yield, mp 218°.

Anal. Calcd. for $C_{14}H_{10}N_4O_2S$: C, 56.37; H, 3.38; N, 18.78; S, 10.75. Found: C, 56.7; H, 3.5; N, 18.9; S, 10.8.

5,11-Dihydro-11-*p*-chlorobenzylidene-6-methyl-2-methylthioindolo[3',2':4,5]pyrido[1,2-b]-s-triazol-5-one (XI).

A mixture of 1 g of II, 2 g of anhydrous fused sodium acetate, 50 ml of acetic acid, and 0.5 g of *p*-chlorobenzaldehyde was refluxed for 2 hours. It was then cooled and the solid, XI, that separated was filtered off and recrystallised from dimethylformamide as orange crystals, mp 270°, yield 73%.

Anal. Calcd. for $C_{21}H_{15}ClN_4OS$: C, 61.97; H, 3.71; Cl, 8.71; N, 13.77; S, 7.88. Found: C, 61.6; H, 3.7; Cl, 8.9; N, 13.9; S, 8.0.

5,11-Dihydro-11,11-dibenzyl-6-methyl-2-methylthioindolo[3',2':4,5]pyrido[1,2-b]-s-triazol-5-one (XII).

A mixture of 1.4 g (1 mole) of II, 25 ml of 10% sodium carbonate solution, 10 ml of ethanol, and 1.3 g (2 moles) of benzyl chloride was refluxed for 2 hours. The reaction mixture was cooled and poured into 100 ml of cold water. The precipitate formed, XII, was collected, washed with water, and finally crystallised from ethanol (charcoal) as colourless crystals, mp 200°, yield 65%.

Anal. Calcd. for $C_{28}H_{24}N_4OS$: C, 72.38; H, 5.21; N, 12.06; S, 6.90. Found: C, 72.2; H, 5.0; N, 12.3; S, 7.0.

5,11-Dihydro-6-methyl-2-methylthioindolo[3',2':4,5]pyrido[1,2-b]-s-triazole-5,11-dione 11-Arylhydrazones (XIII).

The aromatic amine (0.01 mole) was dissolved in 3 ml of concentrated hydrochloric acid and 2 ml of water, cooled to 0° and treated with 0.7 g of sodium nitrite in 5 ml of water. The diazotised amine was gradually added with stirring to a cooled solution of 0.01 mole of II in 30 ml of pyridine. The reaction mixture was refrigerated for 1 hour and then poured into cold dilute hydrochloric acid solution. The product that separated was filtered off, washed thoroughly with water and crystallised from the proper solvent (See Table II).

Condensation of the Dione X with Phenylhydrazine.

A solution of 0.25 g of X in 25 ml of glacial acetic acid was treated with 0.1 ml of phenylhydrazine, and the reaction mixture was refluxed for 15 minutes, and cooled. The brick red crystals that separated were collected (0.22 g, 69%) and recrystallised from acetic acid, mp 248°; not depressed on admixture with XIIIa.

REFERENCES AND NOTES

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