SYNTHESIS AND PROPERTIES OF HYDROGENATED 2-ALKYLTHIO-5-OXO-3-CYANOINDENO [1, 2-b]-PYRIDINES

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Condensation of 2-arylidene-1, 3-indandiones with cyanothioacetamide in the presence of piperidine, followed by treatment with alkyl halides, has given partially hydrogenated 2-alkylthio-5-oxoindeno [1, 2-b]-pyridines, the oxidation, interconversion, and Thorpe cyclization of which to give a novel heterocyclic system, indeno [1', 2':6, 5]pyrido [2, 3-b]thiophene, have been examined.

Continuing work on the synthesis and study of 2-alkylthio-1, 4-dihydropyridines [1, 2], we have now obtained some novel hydrogenated 2-alkylthio-5-oxoindeno [1, 2-b]pyridines, and examined their interconversion and Thorpe cyclization to the novel indeno [1', 2':6, 5]pyrido-[2, 3-b]thiophene system.

Condensation of 2-arylidene-1, 3-indandiones with cyanothioacetamide in the presence of piperidine, followed by treatment with alkyl halides has given the colorless 9b-hydroxy-2-alkylthio-5-oxo-4-aryl-3-cyano-1, 4, 4a, 9b-tetrahydroindeno [1, 2-b] pyridines (I), which are unstable compounds with a tendency to lose a molecule of water. This takes place to some extent during this reaction, giving mixtures of (I) and the 5-oxo-2-alkylthio-1, 4-dihydro-indeno [1, 2-b] pyridines (II). The compounds (II) have been obtained preparatively in high yields by boiling the 9b-hydroxy-compounds (I) in acidified ethanol.

The tetrahydroindenopyridines (I) are also formed, although in slightly lower yields, by the joint condensation of 1, 3-indandione, the aromatic aldehyde, and cyanothioacetamide in the presence of piperidine as condensing agent, followed by treatment with an alkyl halide.

2-Alkylthio-5-oxo-3-cyano-1, 4-dihydroindeno [1, 2-b] pyridines (II) which contain a reactive methylene group in the 2-alkylthio substituent, readily undergo closure of the thienyl ring in basic media to give the novel heterocyclic system 3-amino-5-oxo-4-aryl-4, 10-dihydro-indeno [1', 2':6, 5] thiophene (III).

The 2-carbamoylmethylthio-5-oxo-3-cyano-1, 4-dihydroindeno [1, 2-b] pyridine (IId) is oxidized by sodium nitrite in acetic acid to the corresponding 2-carbamoylmethylthio-5-oxo-4-(p-nitrophenyl)-3-cyanoindeno [1, 2-b] pyridine (IV), which, like (II), readily cyclizes on treatment with sodium ethoxide to give high yields of 3-amino-5-oxo-4-(p-nitrophenyl)-2-carbamoylindeno-[1',2':6,5]pyrido[2,3-b]thiophene (V).

The structures of the products were confirmed by spectroscopy. The IR spectra (Table 2) of (I), (II), and (IV) showed characteristic absorption for ν_{CN} at 2182-2204 cm^{-1} and 2224 cm^{-1} respectively, and for ν_{NH}, ν_{NH_2} and ν_{OH} at 3160-3476 cm^{-1}. The absorption ν_{CO} for the 5-oxo-group in (II) and (III) was slightly less than that in the tetrahydroindenopyridines (I) and the indenopyridines (IV), which is characteristic of β-aminovinyl ketones. The IR spectra of (III) and (V) showed no ν_{CN} absorption, but new ν_{NH_2} absorption appeared.

The UV spectra (Table 2) of the tetrahydroindenopyridines (I) showed long wavelength absorption at 280-288 nm, the dihydroindenopyridines (II) at 466-474 nm, and the dihydro-indenopyridothiophenes (III) at 492-494 nm, i.e., as the extent of conjugation in the hydrogenated compounds increased, the long wavelength maximum was shifted bathochromically. The indenopyridine (IV) and the indenopyridothiophene (V) showed a long wavelength absorption maximum at 367 and 405 nm respectively, i.e., the absorption was shifted hypsochromically as compared with their dihydro-analogs, in agreement with earlier reports [3, 4].

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TABLE 1. Properties of Compounds (I-V)

Compound	mp, °C	Empirical formula	Yield, %*	
			A	B
Ia	>160**	$C_{20}H_{16}N_2O_2S$	76	
Ib	>150**	$C_{20}H_{15}N_3O_4S$	88	
Id	166...168**	$C_{21}H_{16}N_4O_5S$	73	
If	>130**	$C_{21}H_{16}N_4O_5S$		67
Ig	>160**	$C_{20}H_{15}ClN_2O_2S$	70	
IIa	176...178	$C_{20}H_{14}N_2OS$	54	
IIb	227...229	$C_{21}H_{15}N_3O_2S$	51	
IIc	318...320	$C_{20}H_{13}N_3O_3S$	70	
IId	212...214	$C_{21}H_{14}N_4O_4S$	72	
IIe	211...213	$C_{20}H_{13}N_3O_3S$		35
IIf	260...262	$C_{21}H_{14}N_4O_4S$		48
IIg	300...302	$C_{20}H_{13}ClN_2OS$	68	
IIh	232...234	$C_{21}H_{14}ClN_3O_2S$	44	
IIId	324...326	$C_{21}H_{14}N_4O_4S$	95	
IIIh	268...270	$C_{21}H_{14}ClN_3O_2S$	90	
IV	252...254	$C_{21}H_{12}H_4O_4S$	86	
V	332...334	$C_{21}H_{12}N_4O_4S$	72	

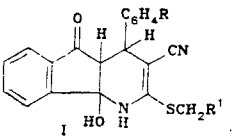
*The yield of (II) was calculated on the starting cyanothioacetamide.
**With decomposition.

TABLE 2. IR and UV Spectra of (I-V)

Compound	IR spectrum, ν, cm^{-1}			UV spectrum, λ, nm
	CO	CN	NH, NH_2, OH	
Ia	1714	2182	3258, 3305, 3350 s*	246, 288
Ib	1712	2184	3332, 3370	249, 282
Id	1677, 1720	2194	3168, 3288, 3350, 3448	247, 282
If	1671, 1725	2186	3186, 3344	248, 280
Ig	1712	2192	3306, 3366	245, 288
IIa	1674	2204	3206	254, 262, 282 s, 348, 474
IIb	1685, 1698	2201	3160, 3300, 3350	253, 264, 352, 474
IIc	1673	2203	3276	256, 262, 282 s, 338, 470
IId	1674, 1688	2200	3200, 3354, 3462	265, 276 s, 342, 472
IIe	1690	2196	3196	256, 264, 281 s., 346, 466
IIf	1667, 1693	2196	3180, 3374	255, 264, 345, 468
IIg	1682	2196	3270	254, 263, 350, 472
IIh	1675, 1688	2190	3180, 3356, 3476	254, 264, 348, 474
IIIa	1644, 1667	—	3192, 3312, 3442	239, 267, 307, 355, 492
IIIb	1628, 1673	—	3144, 3344, 3472, 3488	243, 266, 312, 365, 494
IVa	1689, 1720	2224	3160, 3440, 3475	268, 292 sh., 316, 367
V	1655, 1717	—	3166, 3270, 3322, 3460, 3482	264, 306, 335, 405 sh.

*s) strong.

TABLE 3. PMR Spectral Parameters for



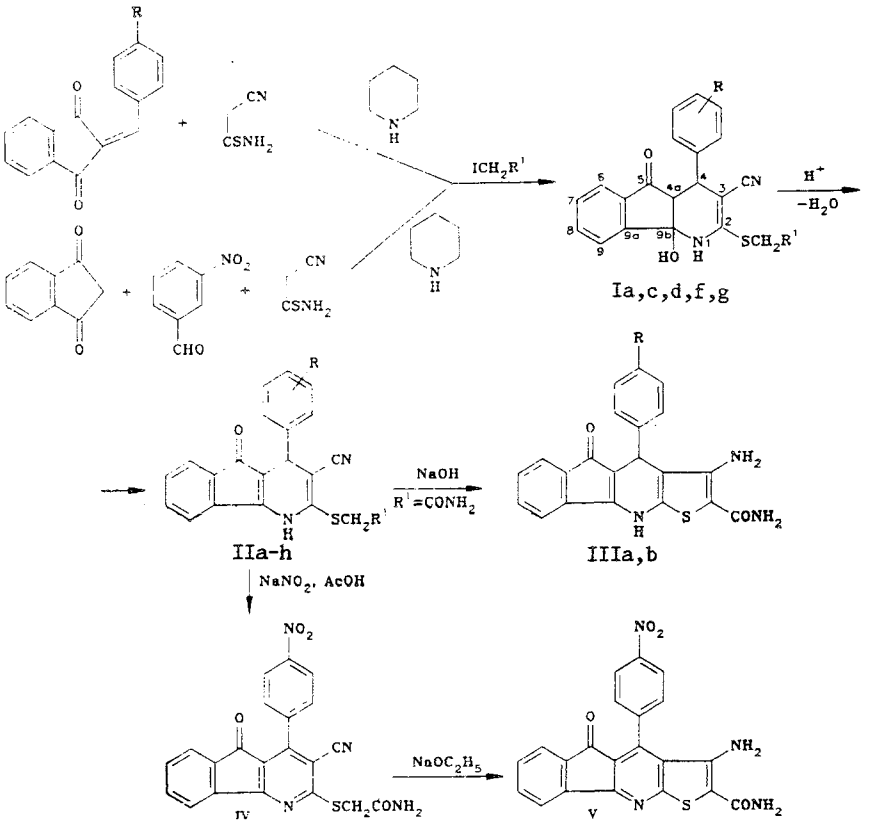
I

Compound	Chemical shifts, δ, ppm							CC, J, Hz	
	NH (s)	arom. protons (m)	6-OH (s)	4-H (d)	4a-H (d)	SCH_2R^1 (d and d)	SCH_3 (s)	H_4-H_5	$S-CH_2$
Ia	8,03	7,9...7,2	6,82	4,06	3,36	—	2,28	2,2	—
Ib*	9,22	7,9...7,3	6,98	4,10	3,36	3,54 and 3,28	—	2,2	14,4
Ic	8,06	8,3...7,6	6,92	4,23	3,47	—	2,22	2,4	—
Id*	9,38	8,3...7,8	7,10	4,29	3,47	3,58 and 3,30	—	2,2	14,4
Ie	8,10	8,4...7,6	6,98	4,26	3,50	—	2,30	2,2	—
If*	9,37	8,4...7,5	7,18	4,28	3,42	3,54 and 3,40	—	2,2	14,4
Ig	8,07	7,9...7,4	6,85	4,06	3,37	—	—	2,4	—
Ih*	9,24	7,9...7,3	6,96	4,08	3,34	3,54 and 3,28	2,2	2,2	14,4

*The signals for the $CONH_2$ protons lie beneath those for the aromatic protons.

In the PMR spectra (Table 3), the signals most characteristic of the compounds (I) were those for the 4-H and 4a-H protons, the chemical shifts of which were 4.29-4.06 and 3.47-3.36 ppm, with $^3J_{H_4,H_5}$ = 2.2-2.4 Hz, which according to Kuthan et al. [5] indicates that the 4-H and 4a-H protons are disposed trans-diequatorially, so that the 4-aryl substituent is oriented trans-axially.

In the PMR spectra of (II) and (III), the most important signals confirming the dihydro structure are those for the 4-H and N-H protons. In the case of (III), the signals for the 4-H protons are seen at 5.20-5.08 ppm, i.e. at lower field than those for (II) (4.92-4.61) as a result of an increase in the overall conjugation of the molecule in the dihydroindenopyridothiophenes (III).



I, II a,b R=H,c,d R=*p*-NO_2,e,f R=*m*-NO_2, g,h R=*p*-Cl;a,c,e,g R^1=H, b,d,e,f,h R^1=$CONH_2$; III a R=NO_2, b R=Cl

The signals for the SCH_2 protons (when R^1 = $CONH_2$) in (I) and (II) are seen as an AB quartet with $^2J_{SCH_2}$ = 14.4-15.0 Hz, showing that the CH_2 protons are nonequivalent as a result of the presence in the molecule of an asymmetric center at $C_{(4)}$.

Noteworthy is the shift to lower field of the NH protons in (I) and (IIb, d, f, h) (R^1 = $CONH_2$) as compared with (I) and (IIa, c, e, g) (R^1 = H) (Tables 3 and 4), owing to the presence of intramolecular hydrogen bonding between $N_{(1)}$–H and the amide group. This was confirmed by obtaining the IR spectra of these compounds in solution in DMSO, when ν_{CO} remained the same when the saturated solution was repeatedly diluted.

EXPERIMENTAL

IR spectra were obtained on a Perkin-Elmer 580 B (in Vaseline grease), UV spectra on a Specord UV-VIS (in ethanol), and PMR spectra on a WH 90/DS instrument (90 MHz) in DMSO-D_6, internal standard TMS. The progress of the reactions and the purity of the products were followed by TLC on Silufol UV-254 plates, eluent chloroform–hexane–acetone, 2:1:1.

The principal characteristics of the products are given in Tables 1-4.

9b-Hydroxy-2-alkylthio-5-oxo-4-aryl-3-cyano-1,4,4a,9b-tetrahydroindeno[1,2-b]-pyridines (I).

A) A mixture of 10 mmole of the 2-arylideneindan-1,3-dione and 10 mmole of cyanothioacetamide

TABLE 4. PMR Spectral Parameters for (II-V) in DMSO-D_6

Compound	Chemical shifts, δ, ppm						CC, J, Hz	
	NH (s)	arom. protons (m)	$CONH_2$ (s and s)	4-H (s)	$S-CH_2R^1$ (d and d)	SCH_3 (s)	3-NH_2 (s)	SCH_2
IIa	10,82	7,8...7,2	—	4,61	—	2,62	—	—
IIb	11,92	7,6...7,3	8,09 and 7,79	4,62	3,94 and 3,84	—	—	15,0
IIc	10,92	8,3...7,3	—	4,88	—	2,66	—	—
IId	12,04	8,3...7,3	8,08 and 7,78	4,90	3,94 and 3,84	—	—	14,4
IIe	10,95	8,2...7,2	—	4,92	—	2,65	—	—
IIf	12,10	8,2...7,2	beneath arom. protons	4,95	3,91 and 3,83	—	—	15,0
IIg	10,85	7,8...7,2	—	4,67	—	2,63	—	—
IIh	11,98	7,5...7,2	8,06 and 7,76	4,68	3,88 and 3,78	—	—	15,0
IIId	11,47	8,2...7,2	6,80	5,20	—	—	6,26	—
IIIh	11,42	7,5...7,2	6,80	5,08	—	—	6,23	—
IV	—	8,5...7,6	7,66 and 7,28	—	4,18	—	—	—
V	—	8,5...7,5	7,32	—	—	—	5,70	—

in 20-40 ml of abs. ethanol and 1.5 ml (15 mmole) of piperidine was stirred for 20-30 min at ambient temperature, then 2.5 ml (40 mmole) of methyl iodide was added, and the mixture heated on the water bath to 40-50°C for 2-3 min. After 3 h at ambient temperature, the precipitated solid was filtered off, and washed with ethanol and water to give (Ia), (Ic), and (Ig) in 70-88% yield. The product was then recrystallized from ethanol or a mixture of ethanol and DMF (3:1).

Similarly, from a mixture of 10 mmole of the 2-arylideneindan-1, 3-dione and cyanothioacetamide in 30 ml of abs. ethanol and 1.1 ml (11 mmole) of piperidine, followed by addition of 1.87 g (11 mmole) of iodiacetamide, there was obtained (Id), yield 73%, mp 166-168°C with decomp. (from ethanol–DMF, 3:1).

B. A mixture of 1.46 g (10 mmole) of 1, 3-indandione and 1.51 g (10 mmole) of m-nitrobenzaldehyde in 50 ml of ethanol and 0.5 ml of piperidine was stirred for 1-2 min at ambient temperature, 1.0 g (10 mmole) of cyanothioacetamide and 0.5 ml (5 mmole) of piperidine added, stirred for a further 30 min, and 2.04 g (12 mmole) of iodoacetamide added. The mixture was heated on a water bath to 50-60°C for 2-3 min, kept at ambient temperature for one hour, and the solid filtered off and washed with ethanol and water to give 2.92 g (67%) of (If), mp > 130°C with decomp. (from ethanol–DMF, 3:1) .

2-Alkylthio-5-oxo-4-aryl-3-cyano-1, 4-dihydroindeno [1, 2-b]pyridines (II). Ten mmole of the tetrahydroindenopyridine (I) or crude material as a mixture of (I) and (II) in 100 ml of 0.2 N HCl in ethanol was boiled for 3-5 min on the water bath, kept for one hour at ambient temperature, and the solid filtered off and washed with ethanol and water to give (II), which was recrystallized from a mixture of ethanol and DMF (3:1)-(1:1).

3-Amino-5-oxo-4-aryl-2-carbamoyl-4, 10-dihydroindeno [1', 2':6, 5] pyrido[2, 3-b] thiophenes (III). A mixture of 5 mmole of the 1, 4-dihydroindenopyridine (II) and 1.7 ml of 3 N NaOH in 50-60 ml of ethanol was boiled on the water bath for 3-5 min, kept for 30 min at ambient temperature, and neutralized with 5 ml of 1 N HCl in ethanol. The solid was filtered off, and washed with ethanol and water to give (III) in 90-95% yield, recrystallized from ethanol-DMF (1:1).

2-Carbamoylmethylthio-5-oxo-4-(p-nitrophenyl)-3-cyanoindeno [1, 2-b]-pyridine (IV). A mixture of 0.84 g (2 mmole) of the 1, 4-dihydroindenopyridine (IId) and 0.28 g (4 mmole) of sodium nitrite in 10 ml of glacial acetic acid was boiled on the water bath until oxides of nitrogen ceased to be evolved. The mixture was then kept for one hour at ambient temperature, 10 ml of ethanol added, and the solid filtered off and washed with 10 ml of water to give 0.72 g (86%) of (IV), mp 252-254°C (from ethanol–DMF, 1:1).

3-Amino-5-oxo-4-(p-nitrophenyl)-2-carbamoylindeno [1', 2':6, 5] pyrido[2, 3-b]-thiophene (V). A mixture of 0.42 g (1 mmole) of the indenopyridine (IV) and 1 ml of 1 N sodium ethoxide in 10 ml of ethanol was heated for 2-3 min on the water bath, kept for 30 min at ambient temperature, and the solid filtered off and washed with ethanol and water to give 0.3 g (72%) of (V), mp 332-334°C (from ethanol–DMF, 1:1).

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STRUCTURE OF PRODUCTS OF ADDITION OF THIOSEMICARBAZIDES AND THIOSEMICARBAZONES TO ACETYLENEDICARBOXYLIC ACID AND ITS DIMETHYL ESTER

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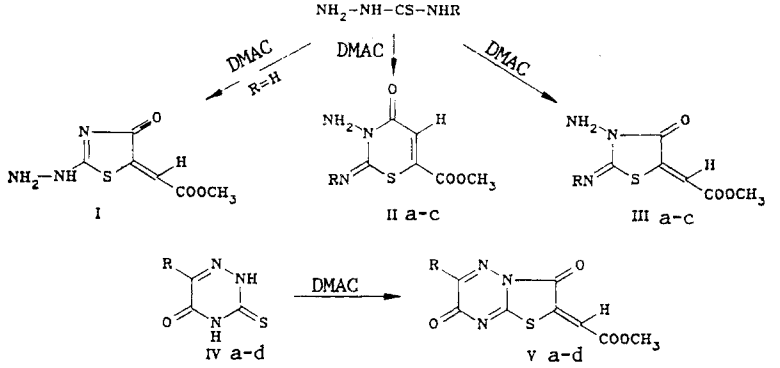
Addition of 1, 1-di-, 1, 4-di-, and 1, 1, 4-trisubstituted thiosemicarbazides to acetylenedicarboxylic acid and its dimethyl ester affords 2-hydrazono-4-oxo-1, 3-thiazolidine-$\Delta^{5,\alpha}$-acetic acids, while 4-monosubstituted thiosemicarbazides give 2-imino-3-amino-1, 3-thiazolidin-4-ones.

Addition of thiosemicarbazides to acetylenedicarboxylic acids affords a variety of heterocyclic systems, but information on their structure is contradictory.

The product of the reaction of thiosemicarbazide with dimethyl acetylene-dicarboxylate (DMAC) has been assigned [1] the 1, 3-thiazoline structure (I).

The products of the reactions of 4-monosubstituted thiosemicarbazides with DMAC have been assigned [2] the 1, 3-thiazine structure (II), although according to [3] these compounds are the 3-amino-1, 3-thiazolidin-4-ones (III). It was reported in [4] that DMAC reacts with 6-substituted-3-thioxo-5-oxo-1, 2, 4-triazines (IV) (cyclic analogs of thiosemicarbazides) to give the 1, 3-thiazolidin-4-ones (V) rather than the 1, 3-thiazines [5]. The structure of (V) was proved by ^{13}C NMR spectroscopy.



II, III a $R=CH_3$, b $R=CH_2CH=CH_2$, c $R=C_6H_5$; IV, V a $R=H$, b $R=CH_3$, c $R=C_6H_5$, d $R=C_6H_5CH_2$

It has previously been shown by X-ray diffraction examination of the thiazolidines obtained by reaction of thioureas with DMAC [6] that donor—acceptor interactions are present

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