894. *Thiophen Derivatives of Potential Biological Interest. Part III.* The Chemistry of 5-Substituted Thiophen-2-aldehydes.*

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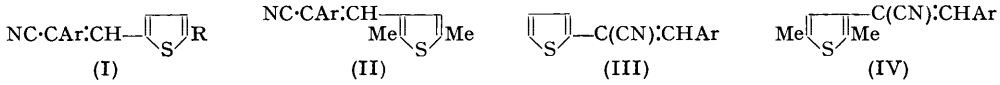
The chemistry of several 5-substituted thiophen-2-aldehydes has been investigated, chiefly with the view to preparing new compounds for biological investigation. Two series of derivatives in particular have been studied: stilbene-like substances for cancer research, and thiosemicarbazones and 4-keto-Δ^2-thiazolin-2-ylhydrazones for the testing of tuberculostatic activity.

In continuation of earlier research on the use of thiophen-aldehydes for the synthesis of stilbene-like compounds (Buu-Hoï, Hoán, and Lavit, *J.*, 1950, 2130; Buu-Hoï and Hoán, *J.*, 1951, 251), and in view of the activity of α-phenylcinnamonitriles as mitotic poisons (cf. Lettré. *Angew. Chem.*, 1947, **59**, 26), the preparation of new αβ-disubstituted acrylo-

* Part II, *J.*, 1951, 251.

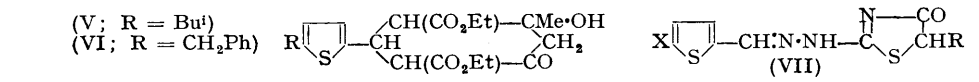
nitriles in the thiophen series is reported. These include (*a*) α-aryl-β-2-thienylacrylonitriles (as I) formed by the alkali-catalysed condensation with arylacetonitriles of thiophen-2-aldehyde or several of its 5-substituted derivatives, (*b*) α-aryl-β-3-thienylacrylonitriles (II), obtained in the same way from 2 : 5-dimethylthiophen-3-aldehyde, and (*c*) β-aryl-



(I) (II) (III) (IV)

α-2- (III) and β-aryl-α-3-thienylacrylonitriles (IV), arising similarly from the condensation of 2-thienyl- and of 2 : 5-dimethyl-3-thienyl-acetonitrile with aromatic aldehydes (see also Cagniant, *Bull. Soc. chim.*, 1949, **16**, 850).

The thiophen intermediates used were 2 : 5-dimethylthiophen-3-aldehyde, thiophen-2-aldehyde, and 5-ethyl-, 5-*iso*butyl-, 5-benzyl-, and 5-chloro-thiophen-2-aldehyde. All these were prepared in high yield from the appropriate thiophens by the *N*-methylformanilide procedure (King and Nord, *J. Org. Chem.*, 1948, **13**, 635). According to earlier findings, thiophen-2-aldehydes, in contrast with thiophen-3-aldehydes, condense readily with ethyl acetoacetate in the presence of piperidine to give *cyclo*hexane derivatives instead of the expected ethyl thenylideneacetoacetates (Buu-Hoï, Hoán, and Lavit, *loc. cit.*). In agreement, 5-*iso*butyl- and 5-benzyl-thiophen-2-aldehyde give the *cyclo*hexane esters (V) and (VI).



(V; R = Bu^i)
(VI; R = CH_2Ph) (VII)

The nitriles (I), (II), (III), and (IV) (see Tables 1 and 2) crystallise well and give halochromic colours with sulphuric acid; those bearing halogen atoms were of special interest to us as potential inhibitors of œstrogens, and as liver-poisons.

The tuberculostatic activity of thiosemicarbazide (Jouin and Buu-Hoï, *Ann. Inst. Pasteur*, 1946, **72**, 580) and of its reaction products with various aldehydes and ketones (Domagk, Behnisch, Mietzsch, and Schmidt, *Naturwiss.*, 1946, **33**, 315; Hoggarth, Martin, Storey, and Young, *Brit. J. Pharmacol.*, 1949, **4**, 248; Donovick, Pausy, Stryker, and Bernstein, *J. Bacteriol.*, 1950, **59**, 667) led us to prepare, for bacteriological testing, the thiosemicarbazones of thiophen-2-aldehyde and its 5-substituted derivatives, which were found to be highly active *in vitro* against *Mycobacterium tuberculosis* var. *bovis* (Welsch, Buu-Hoï, Dechamps, Hoán, Le Bihan, and Binon, *Compt. rend.*, 1951, **232**, 1608). *cyclo*-Condensation of these thiosemicarbazones with various α-halogenated fatty acids in the presence of sodium acetate (Chabrier *et al.*, *Bull. Soc. chim.*, 1947, **14**, 797; 1950, **17**, 48; cf. also Wilson *et al.*, *J.*, 1922, **121**, 876; 1923, **123**, 799; 1926, 253) led easily to a series of 4-keto-Δ^2-thiazolin-2-ylhydrazones (VII) of the thiophen-2-aldehydes quoted above (see Table 3); these were less toxic, but also far less tuberculostatic, than the parent thiosemicarbazones.

These biological studies, including the animal tests, will be reported in full elsewhere.

Experimental

Preparation of Intermediates.—Thiophen-2-aldehyde, 5-ethyl- and 5-chloro-thiophen-2-aldehyde, and 2 : 5-dimethylthiophen-3-aldehyde were prepared according to King and Nord, and Buu-Hoï, Hoán, and Lavit (*locc. cit.*). The arylacetonitriles were prepared by treatment of the corresponding substituted arylmethyl chlorides or bromides with sodium cyanide in acetone.

5-iso*Butylthiophen-2-aldehyde.* To a stirred mixture of 2-*iso*butylthiophen (40 g.) (b. p. 174—176°; best prepared by Huang-Minlon's modification of the Wolff–Kishner reduction of 2-*iso*butyrylthiophen; *J. Amer. Chem. Soc.*, 1946, **68**, 2486) and *N*-methylformanilide (50 g.) under reflux, phosphorus oxychloride (50 g.) was added in small portions; after the spontaneous reaction had subsided, the mixture was heated for 2 hours on a boiling-water bath, cooled, treated with a concentrated aqueous sodium acetate, and steam-distilled, giving the *aldehyde* (37 g.) as a colourless oil, b. p. 133°/20 mm., of unpleasant odour, becoming green on exposure to air (Found : C, 64·2; H, 7·1. $C_9H_{12}OS$ requires C, 64·3; H, 7·1%). The *thiosemicarbazone*,

made in ethanol, crystallised from that solvent as almost colourless needles, m. p. 152° (Found: C, 49·7; H, 6·4. $C_{10}H_{15}N_3S_2$ requires C, 49·8; H, 6·2%).

5-Benzylthiophen-2-aldehyde. 2-Benzylthiophen (60 g.) was treated as above with *N*-methylformanilide (60 g.) and phosphorus oxychloride (60 g.); after removal by steam of *N*-methylaniline and excess of 5-benzylthiophen, the sparingly volatile 5-benzylthiophen-2-aldehyde was extracted with chloroform. The extract obtained was washed with dilute hydrochloric

TABLE 1. *Acrylonitriles* (I) *and* (II).

Ar	R	M. p.	Formula	Found, % C	Found, % H	Reqd., % C	Reqd., % H
Type (I).							
p-C_6H_4Cl	H	124°	$C_{13}H_8NSCl$	63·2	3·6	63·5	3·3
p-C_6H_4F	,,	94	$C_{13}H_8NSF$	68·0	3·6	68·1	3·5
p-C_6H_4Br	,,	118	$C_{13}H_8NSBr$	53·5	2·8	53·8	2·8
p-C_6H_4I	,,	112	$C_{13}H_8NSI$	46·0	2·2	46·3	2·4
β-$C_{10}H_7$	,,	127	$C_{17}H_{11}NS$	78·0	4·5	78·2	4·2
p-C_6H_4F	Et	90	$C_{15}H_{12}NSF$	70·1	5·0	70·0	4·7
p-C_6H_4Cl	,,	121	$C_{15}H_{12}NSCl$	65·9	4·1	65·8	4·4
p-C_6N_4Br	,,	120	$C_{15}H_{12}NSBr$	56·4	4·0	56·6	3·8
p-C_6H_4I	,,	128	$C_{15}H_{12}NSI$	49·6	3·2	49·3	3·3
p-C_6H_4Me	,,	87	$C_{16}H_{15}NS$	76·2	5·8	75·9	5·9
p-$NO_2{\cdot}C_6H_4$	,,	173	$C_{15}H_{12}O_2N_2S$	63·2	4·4	63·4	4·2
Ph	Bu^i	53	$C_{17}H_{17}NS$	76·6	6·6	76·4	6·4
p-C_6H_4F	,,	86	$C_{17}H_{16}NSF$	71·4	5·4	71·6	5·6
p-C_6H_4Cl	,,	96	$C_{17}H_{16}NSCl$	67·3	5·2	67·7	5·0
p-C_6H_4Br	,,	88	$C_{17}H_{16}NSBr$	58·8	4·4	59·0	4·6
p-C_6H_4I	,,	89	$C_{17}H_{16}NSI$	51·6	4·0	51·9	4·1
p-$MeO{\cdot}C_6H_4$	,,	63	$C_{18}H_{19}ONS$	72·4	6·7	72·7	6·4
p-$HO{\cdot}C_6H_4$	,,	128	$C_{17}H_{17}ONS$	71·7	6·3	72·1	6·0
p-$NO_2{\cdot}C_6H_4$	,,	159	$C_{17}H_{16}O_2N_2S$	65·1	5·0	65·4	5·1
β-$C_{10}H_7$	,,	110	$C_{21}H_{19}NS$	79·3	6·2	79·5	6·0
Ph	CH_2Ph	95	$C_{20}H_{15}NS$	79·4	5·3	79·7	5·0
2-Thienyl	,,	119	$C_{18}H_{13}NS_2$	70·1	4·3	70·4	4·2
p-C_6H_4Me	,,	110	$C_{21}H_{17}NS$	80·2	5·5	80·0	5·4
p-C_6H_4F	,,	102	$C_{20}H_{14}NSF$	75·0	4·4	75·2	4·4
p-C_6H_4Cl	,,	105	$C_{20}H_{14}NSCl$	71·1	4·5	71·5	4·2
p-C_6H_4Br	,,	132	$C_{20}H_{14}NSBr$	62·9	3·8	63·2	3·7
p-C_6H_4I	,,	142	$C_{20}H_{14}NSI$	56·0	3·5	56·2	3·3
p-$MeO{\cdot}C_6H_4$	,,	106	$C_{21}H_{17}ONS$	75·7	5·4	76·1	5·1
p-$NO_2{\cdot}C_6H_4$	,,	152	$C_{20}H_{14}O_2N_2S$	69·2	4·3	69·4	4·0
β-$C_{10}H_7$	,,	131	$C_{24}H_{17}NS$	82·0	4·6	82·1	4·8
p-C_6H_4Cl	Cl	177	$C_{13}H_7NSCl_2$	55·4	2·2	55·7	2·5
p-C_6H_4Br	,,	171	$C_{13}H_7NSClBr$	47·7	2·0	48·1	2·2
p-C_6H_4I	,,	167	$C_{13}H_7NSClI$	41·9	2·2	42·0	1·9
Type (II).							
p-C_6H_4F		98	$C_{15}H_{12}NSF$	70·3	4·5	70·0	4·7
p-C_6H_4Cl		147	$C_{15}H_{12}NSCl$	65·4	4·2	65·8	4·4
p-C_6H_4Br		157	$C_{15}H_{12}NSBr$	56·3	3·6	56·6	3·8
p-C_6H_4I		146	$C_{15}H_{12}NSI$	49·0	3·2	49·3	3·3
β-$C_{10}H_7$		131	$C_{19}H_{15}NS$	78·6	5·4	78·9	5·2

TABLE 2. *Acrylonitriles* (III) *and* (IV).

Ar	M. p.	Formula	Found, % C	Found, % H	Reqd., % C	Reqd., % H
Type (III).						
p-C_6H_4F [a]	77°	$C_{13}H_8NSF$	67·9	3·4	68·1	3·5
3 : 4 : 1-$C_6H_3Cl_2$ [b]	119	$C_{13}H_7NSCl_2$	55·5	2·3	55·7	2·5
2 : 4 : 1-$C_6H_3Cl_2$ [b]	150	$C_{13}H_7NSCl_2$	55·5	2·2	,,	,,
α-$C_{10}H_7$ [c]	110	$C_{17}H_{11}NS$	78·3	4·4	78·2	4·2
β-$C_{10}H_7$ [a]	115	$C_{17}H_{11}NS$	78·0	4·5	,,	,,
5-Acenaphthyl [c]	143	$C_{19}H_{13}NS$	79·1	4·6	79·4	4·5
Type (IV).						
p-C_6H_4F [a]	85	$C_{15}H_{12}NSF$	70·1	5·0	70·0	4·7
p-C_6H_4Cl [a]	106	$C_{15}H_{12}NSCl$	65·5	4·2	65·8	4·4
α-$C_{10}H_7$ [d]	100	$C_{19}H_{15}NS$	79·0	5·5	78·9	5·2
β-$C_{10}H_7$ [a]	102	$C_{19}H_{15}NS$	79·2	5·5	,,	,,
3-Pyrenyl [c]	182	$C_{25}H_{17}NS$	82·3	4·5	82·6	4·7

Colours with sulphuric acid : [a] red; [b] yellow-green; [c] blue; [d] violet.

TABLE 3. 4-*Keto*-Δ^2-*thiazolin*-2-*ylhydrazones* (VII).

X	R	M. p.	Formula	Found, % C	Found, % H	Reqd., % C	Reqd., % H
H	H	248°	$C_8H_7ON_3S_2$	42·4	3·0	42·7	3·1
,,	Et	215	$C_{10}H_{11}ON_3S_2$	47·1	4·0	47·4	4·3
,,	Pr^i	207	$C_{11}H_{13}ON_3S_2$	49·1	4·7	49·4	4·9
,,	Pr^n	208	$C_{11}H_{13}ON_3S_2$	49·2	4·6	,,	,,
,,	Bu^n	209	$C_{12}H_{15}ON_3S_2$	51·0	5·1	51·2	5·3
,,	*iso*-C_5H_{11}	202	$C_{13}H_{17}ON_3S_2$	52·6	5·7	52·9	5·8
,,	*n*-C_5H_{11}	191	$C_{13}H_{17}ON_3S_2$	52·5	5·8	52·9	5·8
,,	*n*-$C_{14}H_{29}$	131	$C_{22}H_{35}ON_3S_2$	62·4	8·5	62·7	8·3
,,	*n*-$C_{16}H_{33}$	120	$C_{24}H_{39}ON_3S_2$	64·3	8·5	64·1	8·7
Cl	H	280	$C_8H_6ON_3S_2Cl$	37·0	2·3	36·9	2·3
,,	Et	220	$C_{10}H_{10}ON_3S_2Cl$	41·4	3·6	41·7	3·5
,,	Pr^i	226	$C_{11}H_{12}ON_3S_2Cl$	43·4	4·2	43·7	4·0
,,	Pr^n	219	$C_{11}H_{12}ON_3S_2Cl$	43·6	3·9	,,	,,
,,	*n*-C_5H_{11}	197	$C_{13}H_{16}ON_3S_2Cl$	47·0	4·6	47·3	4·8
,,	*n*-$C_{14}H_{29}$	168	$C_{22}H_{34}ON_3S_2Cl$	57·6	7·6	57·9	7·5
,,	*n*-$C_{16}H_{33}$	159	$C_{24}H_{38}ON_3S_2Cl$	59·4	8·1	59·5	7·9
Bu^i	H	216	$C_{12}H_{15}ON_3S_2$	50·9	5·1	51·2	5·3
,,	Et	162	$C_{14}H_{19}ON_3S_2$	54·1	6·2	54·4	6·1
,,	Pr^i	169	$C_{15}H_{21}ON_3S_2$	55·6	6·3	55·7	6·5
,,	Pr^n	167	$C_{15}H_{21}ON_3S_2$	55·4	6·4	,,	,,
,,	*n*-C_5H_{11}	160	$C_{17}H_{25}ON_3S_2$	57·9	7·2	58·1	7·1
,,	*n*-$C_{14}H_{29}$	133	$C_{26}H_{43}ON_3S_2$	65·5	9·2	65·4	9·0
,,	*n*-$C_{16}H_{33}$	115	$C_{28}H_{47}ON_3S_2$	66·6	9·5	66·5	9·3
CH_2Ph	H	235	$C_{15}H_{13}ON_3S_2$	56·7	4·1	57·1	4·1
,,	Et	189	$C_{17}H_{17}ON_3S_2$	59·2	4·9	59·5	5·0
,,	C_5H_{11}	188	$C_{20}H_{23}ON_3S_2$	62·0	6·3	62·3	6·0
,,	*n*-$C_{14}H_{29}$	148	$C_{29}H_{41}ON_3S_2$	67·8	8·2	68·1	8·0
,,	*n*-$C_{16}H_{33}$	143	$C_{31}H_{45}ON_3S$	68·8	8·3	69·0	8·3
Et	*n*-C_5H_{11}	167	$C_{15}H_{21}ON_3S_2$	55·9	6·3	55·7	6·5

acid, then with water, and dried (Na_2SO_4), the solvent removed, and the residue vacuum-distilled, yielding the *aldehyde* (30 g.) as a pale yellow oil, b. p. 195°/13 mm. (Found : C, 71·0; H, 5·0. $C_{12}H_{10}OS$ requires C, 71·3; H, 5·0%). The *thiosemicarbazone* formed from acetic acid yellowish needles, m. p. 175° (decomp.) (Found : N, 15·0. $C_{13}H_{13}N_3S_2$ requires N, 15·3%).

Ethyl 2-(5-iso*Butyl*-2-*thienyl*)-4-*hydroxy*-6-*keto*-4-*methyl*cyclo*hexane*-1 : 3-*dicarboxylate* (V).—A mixture of 5-*iso*butylthiophen-2-aldehyde (2 g.) and ethyl acetoacetate (1·5 g.) was cooled in ice, and 5 drops of piperidine were added. After 24 hours at room temperature, the solid cyclic *ester* had formed; it crystallised from ether–ligroin (b. p. 100—120°) as colourless needles, m. p. 96°, giving an orange-yellow colour with sulphuric acid (Found : C, 61·1; H, 7·3. $C_{21}H_{30}O_6S$ requires C, 61·5; H, 7·3%).

Ethyl 2-(5-*benzyl*-2-*thienyl*)-4-*hydroxy*-6-*keto*-4-*methyl*cyclo*hexane*-1 : 3-*dicarboxylate* (VI), similarly prepared, formed from ether colourless prisms, m. p. 145°, giving a red colour with sulphuric acid (Found : C, 64·6; H, 6·3. $C_{24}H_{28}O_6S$ requires C, 64·9; H, 6·3%).

Preparation of Acrylonitriles.—The *nitriles* (Tables 1 and 2) were prepared by shaking a solution of the aldehyde and arylacetonitrile in warm ethanol with a few drops of 30% aqueous potassium hydroxide. The substance precipitated was washed with water, and recrystallised from ethanol; in the case of *p*-nitrophenylacetonitrile, piperidine was used in place of potassium hydroxide. β-(5-*iso*Butyl-2-thienyl)-α-*p*-hydroxyphenylacrylonitrile was prepared by demethylation of the corresponding methyl ether with pyridine hydrochloride. With sulphuric acid, the acrylonitriles from thiophen-2-aldehyde gave a red or violet colour, those from 5-substituted thiophen-2-aldehydes gave a green or brown colour, those from the 5-benzyl aldehyde a red or brown-red colour, and those from the 5-chloro-aldehyde a yellow colour, becoming green on heating of the mixture; β-(2 : 5-dimethyl-3-thienyl)-α-2-naphthylacrylonitrile gave a violet colour.

Preparation of 4-*Keto*-Δ^2-*thiazolin*-2-*ylhydrazones.*—A suspension of the appropriate thiosemicarbazone (1 mol.) with chloroacetic acid or the appropriate α-bromo-acid in acetic acid or ethanol, was refluxed for 5 hours in the presence of sodium acetate; the precipitated *hydrazones* (Table 3) were recrystallised from acetic acid or ethanol. 5-*Chlorothiophen*-2-*aldehyde thiosemicarbazone* formed from ethanol colourless prisms, m. p. 163° (Found : C, 32·4; H, 2·8. $C_6H_6N_3S_2Cl$ requires C, 32·7; H, 2·7%).

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