Tetrahedron. Vol. 25, pp. 389 to 395. Pergamon Press 1969. Printed in Great Britain

SYNTHESIS OF ISOTHIAZOLES

THE TRANSFORMATION OF ISOXAZOLES INTO ISOTHIAZOLES

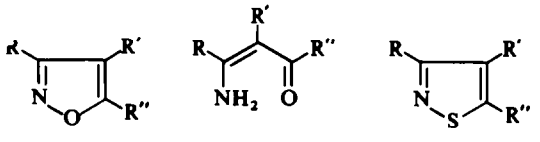
D. N. McGREGOR, U. CORBIN, J. E. SWIGOR and L. C. CHENEY

Research Division, Bristol Laboratories, Division of Bristol-Myers Company, Syracuse, New York 13201

(*Received in USA* 27 *May* 1968; *Received in the UK for publication* 19 *August* 1968)

Abstract—A method has been devised whereby a substituted isoxazole (I) can be efficiently converted to an isothiazole (III) with a similar substitution pattern. The isoxazole ring is opened by reduction with Raney nickel, and the resulting enamino ketone (II) is treated with phosphorus pentasulfide and chloranil to give the corresponding isothiazole derivative. Thus, by taking advantage of the relatively numerous and reliable routes available for the preparation of variously substituted isoxazoles, it is now possible to obtain readily many isothiazole derivatives which were previously available only with great difficulty.

ACTIVE investigation of the chemistry of the isothiazole ring system and its derivatives, apart from the benzisothiazoles, has come only in recent years.[1] During this time, a number of routes have been devised for the preparation of variously substituted isothiazoles, notably the oxidative cyclization of imino thioamides of Adams and Slack[2] and Goerdeler,[3] and of imino thioketones of Crenshaw,[4] the treatment of olefins with sulfur dioxide and ammonia according to Hubenett,[1b] the Wille[5] sequence starting with an acetylenic aldehyde or ketone, the dithiolium salt method of Leaver and Robertson,[6] the Williams mercapto nitrile route,[7] and a number of others.[8]



I II III

	R	*R′*	*R″*
a	C_6H_5	CO_2H	CH_3
b	C_6H_5	$CO_2C_2H_5$	CH_3
c	2,6-$Cl_2C_6H_3$	H	CH_3
d	2,6-$Cl_2C_6H_3$	CN	CH_3
e	2,6-$Cl_2C_6H_3$	CO_2H	CH_3
f	2,6-$Cl_2C_6H_3$	CO_2CH_3	CH_3
g	2,6-$Cl_2C_6H_3$	$CONH_2$	CH_3
h	2,6-$Cl_2C_6H_3$	$CSNH_2$	CH_3
i	2-furyl	CO_2H	CH_3
j	2-furyl	$CO_2C_2H_5$	CH_3
k	CH_3	CO_2H	C_6H_5
m	CH_3	CO_2CH_3	C_6H_5
n	CH_3	CO_2H	CH_3
o	CH_3	CO_2CH_3	CH_3

We now wish to report a general synthesis of isothiazoles which employs an isoxazole of the corresponding substitution pattern as the precursor. The sequence consists of the reductive ring opening of the isoxazole, I, to the enamino ketone, II, followed by treatment with phosphorus pentasulfide and an oxidizing agent to give the isothiazole, III.

The availability of the isoxazole precursors (I) will depend upon the substitution pattern desired. Unlike the isothiazoles, the isoxazoles have been studied extensively for many years,[9] and a number of fairly general synthetic schemes are available. More recent work, in addition to clearing some of the confusion which existed in the older literature,[10] has confirmed the utility of these schemes in the preparation of a wide range of variously substituted isoxazoles.[11, 12]

The reductive ring-opening of isoxazoles of the type I to an enamino ketone of the type II has been known for some time[13] and has been shown to apply to isoxazoles with a wide range of substitution patterns.[14] In our experience, the reduction proceeded cleanly and selectively with commercial Raney nickel and the products, which are shown in the enamino ketone tautomeric form,* showed a considerable stability to hydrolytic and cleavage conditions.

Table 1. Enanino ketones (II)

Compound	M.p. °C	Yield, %	Formula	Analysis					
				Required, %			Found, %		
				C	H	N	C	H	N
IIb	81–82	54[b]	$C_{13}H_{15}NO_3$	66·93	6·48	6·00	66·79	6·57	6·02
IIc	167	88[a]	$C_{10}H_9Cl_2NO$	52·49	3·92	6·09	52·53	4·02	5·96
IId	231–232	44[c]	$C_{11}H_8Cl_2N_2O$	51·79	3·16	10·98	51·57	3·19	10·85
IIe	145–147	38[a]	$C_{11}H_9Cl_2NO_3$	48·18	3·31	5·11	48·30	3·29	4·93
IIf	155–156·5	60[d]	$C_{12}H_{11}Cl_2NO_3$	50·02	3·85	4·86	50·12	3·86	4·78
IIg	226–228	69[e]	$C_{11}H_{10}Cl_2N_2O_2$	48·37	3·69	10·26	48·40	3·88	10·26
IIj	58	90[b]	$C_{11}H_{13}NO_4$	59·30	5·88	6·28	59·22	5·89	6·22
IIm	83–84	53[c]	$C_{12}H_{13}NO_3$	65·74	5·98	6·39	65·42	6·00	6·48
IIo	97	80[b]	$C_7H_{11}NO_3$	53·51	7·12	8·91	53·43	7·01	9·02

[a] Recrystallized from acetone–water.
[b] Recrystallized from Skellysolve B.
[c] Recrystallized from ethyl acetate–Skellysolve B.
[d] Recrystallized from toluene.
[e] Recrystallized from 2-propanol–water.

* The other tautomeric form, the imino enol, cannot be excluded. In the cases of II where R′ = CO_2Me and R″ = Me, these protons were usually seen in the NMR ($CDCl_3$) as singlets at about δ 3·3 and δ 2·3 respectively. Some preparations contained small (< 10%) amounts of a component in which these peaks came at δ 2·15 and δ 3·8, while the Me of IIg always appeared as two peaks at δ 1·5 and δ 2·2 (in DMSO-d_6) It was felt that these apparent mixtures could be ascribed to differences in hydrogen bonding. In the case of IIo, the Me peaks came at δ 3·75, δ 2·27 and δ 2·23. For IIm, the Me's appeared as double peaks at δ 3·39 and δ 3·27, and δ 2·29 and δ 2·03; this may represent a mixture of tautomeric forms. The IR spectra were consistent with a conjugated CO at ca. 1700 cm^{-1} and a hydrogen bonded CO at ca. 1600 cm^{-1}.

Table 1 lists the physical data for some of the enamino ketones prepared during these studies. It is noteworthy that other investigators have also recognized the synthetic utility of a readily available enamino ketone system.[14,15]

The conversion of the enamino ketones to isothiazoles was approached from the point of view of an initial conversion of the ketone to a thioketone and then, in an oxidation step, closure of the ring. Many of the known methods for converting ketones to thioketones[16] were tried.* In most cases, either no reaction was obtained, or the enamino ketone was degraded in some specific† or non-specific way. It was found, however, that phosphorus pentasulfide‡ in conjunction with an oxidizing agent was successful in effecting the desired conversion to the isothiazole. A limited attempt was made to find the optimum reaction conditions, with the following results: (a) Two molar equivalents of fresh phosphorus pentasulfide are preferred. Lower yields were obtained with one equivalent; three equivalents gave the same yields as two (Table 2,

TABLE 2. PREPARATION OF THE ISOTHIAZOLE ESTER IIIf

No.	Moles P_2S_5	Moles chloranil	Moles S	Time, min	Yield, %
1	0·03[a]	—	0·03[a]	10	38
2	0·03[a]	—	0·03	30	37
3	0·03[a]	—	0·03	30[c]	37
4	0·03[b]	—	0·03	15	43
5	0·03[a]	0·01	—	15	53
6	0·03[b]	0·01	—	15	61
7	0·02[b]	0·01	—	15	61
8	0·01[b]	0·01	—	15	50
9	0·03[b]	0·02	—	15	37
10	0·03[a]	[d]	—	15	33

[a] Old P_2S_5 used.
[b] Fresh P_2S_5 used.
[c] Run at 100° instead of reflux.
[d] 0·01 mole of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone.

Nos. 6–8). Assuming two "available" atoms of sulfur per mole of P_2S_5, this corresponds to a 4-fold excess; (b) Using IIf as a standard substrate, one equivalent of chloranil was the best oxidizing system found. This was superior to two equivalents of chloranil, one equivalent of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, three equivalents of sulfur, or subsequent treatment with iodine. Of considerable interest was the observation that, when no additional oxidizing agent was added, an appreciable amount of isothiazole was still obtained; (c) Toluene, which seemed to combine favorable solvent properties, inertness, and reflux temperature, was used as the reaction medium. The reaction failed in refluxing pyridine; (d) Time and temperature for the reaction have depended on the substrate. In most cases, refluxing in toluene for 15 min has

* During the exploratory phases of this investigation, IIb was used as substrate, and reaction mixtures were analysed for the presence of IIIb by GLPC.

† For example, IIf, on treatment with HCl and H_2S in alcohol solution, was deacetylated to the β-aminocinnamate derivative.

‡ In this report, the common term "phosphorus pentasulfide" and the formula P_2S_5 for molar calculations have been used, even though the molecular formula has been shown to be P_4S_{10}.[17]

been adequate. In the case of IId, however, almost three hours under reflux were required. Lowering the reaction temperature to 100° did not affect the yield (Table 2, Nos. 2 and 3). In one of the attempts to convert IIe to IIIe, a reaction was run for one week at 25° using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone as the oxidant, and a small yield of IIIc was obtained. Thus, it would appear that the temperature of the reaction could be lowered considerably as long as the time was increased sufficiently. This may be important when attempting to apply the method to sensitive systems.

From the examples described here, some indication of the scope and limitations of the thiation and ring closure reaction can be obtained: (a) Substituents in the 1-position of II (R) have been alkyl and aryl; (b) In the 3-position of II (R″), alkyl and aryl groups have also been successful; (c) In the 2-position of II (R′), hydrogen, cyano, carboxamide (or thiocarboxamide), carbomethoxy, and carbethoxy have been successful; (d) Some substituents have not been stable under the conditions of this method. A carboxylic acid group in the 2-position was lost by decarboxylation (IIe yields IIIc). The carboxamide group in the 2-position (IIg) suffered both dehydration to the nitrile (IIId) and thiation to the thioamide (IIIh); the possible side product, 5-amino-3-(2,6-dichlorophenyl)-4-thioacetylisothiazole, was not found. It is noteworthy that esters and sensitive heterocycles such as furan are stable.

The work-up of these reaction mixtures was conveniently carried out by filtration, replacement of the solvent with benzene and passage through a column of alumina. This procedure removed most of the colored contaminants produced during the reaction.

Table 3 lists the physical data for some of the isothiazoles obtained by these methods. These have, in general, shown the properties expected of compounds of this type.*

Table 3. Isothiazoles (III)

Compound	M.p. °C	Formula	Analysis					
			Required, %			Found, %		
			C	H	N	C	H	N
IIIa	153–155[a]	$C_{11}H_9NO_2S$	60·40	4·14	6·40	60·22	4·24	6·52
IIIc	67	$C_{10}H_7Cl_2NS$	49·20	2·88	5·73	48·94	2·88	5·54
IIId	120–122[b]	$C_{11}H_6Cl_2N_2S$	49·08	2·24	10·41	48·69	2·28	10·14
IIIe	215[c]	$C_{11}H_7Cl_2NO_2S$	46·82	2·43	4·84	46·54	2·45	4·72
IIIf	82–85	$C_{12}H_9Cl_2NO_2S$	47·70	3·00	4·64	47·85	3·05	4·46
IIIh	221–224	$C_{11}H_8Cl_2N_2S_2$	43·56	2·65	9·24	43·56	3·07	9·36
IIIi	168	$C_9H_7NO_3S$	51·75	3·41	6·70	51·57	3·34	6·66
IIIk	186–187[d]	$C_{11}H_9NO_2S$	60·25	4·14	6·39	60·27	4·34	6·33
IIIn	180–200 subl.[e]	$C_6H_7NO_2S$	45·85	4·47	8·92	44·93	4·63	8·81
IIIo	32	$C_7H_9NO_2S$	49·15	5·29	8·19	49·06	5·50	8·03

[a] Lit.[4] m.p. 151–153°.
[b] Lit.[4] m.p. 125–126°.
[c] Lit.[4] m.p. 213·5–215°.
[d] Lit. m.p. 186–188°, M. S. Grant, D. L. Pain and R. Slack, *J. Chem. Soc.* 3842 (1965).
[e] Lit. m.p. 184–189°, M. P. L. Caton, D. H. Jones, R. Slack and K. R. H. Wooldridge, *Ibid.* 446 (1964).

* In the cases of III where R″ = Me, these protons are seen in the NMR as a singlet at δ 2·65–2·85. For IIIn, the ring Me's come at δ 2·62 and δ 2·73; for IIIo, at δ 2·59 and δ 2·70. The ring hydrogen in IIIc comes at δ 7·00.

EXPERIMENTAL

M.ps are uncorrected. IR spectra were obtained on a Beckman IR-9 spectrophotometer as KBr disks. NMR spectra were obtained on a Varian A-60 spectrometer in $CDCl_3$ containing sufficient DMSO-d_6 to effect solubility (unless otherwise specified). Peak positions are reported in ppm (δ) relative to internal TMS. GLPC was carried out with an F and M Model 500 gas chromatograph, equipped with a thermal conductivity detector and a mixed column of 10 parts of Carbowax 20M-terephthalic acid, 9 parts of diethylene glycol succinate, and 1 part of SE-30 on Gas Chrom Z.

P_2S_5 and chloranil were practical grades from Eastman. Raney Ni was Grace No. 38 Raney Active Nickel Catalyst in water and was used without washing. Alumina chromatography was carried out on Merck reagent aluminum oxide. Skellysolve B is a petroleum solvent, essentially n-hexane, b.p. 60–68°.

Starting isoxazoles. The isoxazoles Ia,[10] Ib,[10] Ie,[11e], If,[11e]Ig,[11e] Ii,[11b], Ik,[10] and In[18] are described in the literature. The acids Ii, Ik, and In were converted to their methyl esters (Ij, Im, and Io respectively) either via the acid chloride (in the case of Ii) or with MeOH–H_2SO_4. In most cases, these esters were used directly for subsequent reactions after their structure and purity were confirmed by infrared and/or NMR spectra.

4-Cyano-3-(2,6,dichlorophenyl)-5-methylisoxazole (Id). A mixture of 26 g (0·096 mole) of Ig, 36 ml (0·26 mole) of Et_3N, and 200 ml of $POCl_3$ was refluxed for 2 hr. After removal of the volatile components of the reaction mixture under reduced press, the residue was dissolved in $CHCl_3$ and added to ice. The aqueous layer was made basic with Na_2CO_3, and the layers were separated. The organic layer was washed with water, dried over $MgSO_4$, then concentrated under reduced press to a solid. Recrystallization from 2-propanol–water gave 19·4 g (80%) of crystals, m.p. 99–100°. (Found: C, 52·03; H, 2·54; N, 10·81. $C_{11}H_6Cl_2N_2O$ requires: C, 52·19; H, 2·19; N, 11·07%).

General procedures for the reductive ring-opening of the isoxazole derivatives (I). The isoxazole derivative was dissolved in sufficient MeOH or EtOH to form approximately a 10% soln. Raney Ni (about 60 g per mole of substrate) was then added, and the reduction was carried out at 50 psig in a Parr apparatus. When one equivalent of H_2 had been absorbed, the reduction was stopped, and the catalyst was removed by filtration through diatomaceous earth. The solvent was removed from the filtrate under reduced press leaving a residue which, upon slurrying with Skellysolve B, usually crystallized spontaneously and could be recrystallized as indicated in Table 1. In most cases, recrystallization did not appear necessary for synthetic purposes.

In the cases of the isoxazolecarboxylic acids, the reduction solvent was water containing an equivalent of NaOH, and the products were isolated by acidification after removal of the catalyst. The reduction of Ia led to a mixture of IIa and the decarboxylated product. Reduction of Ie led to the relatively stable acid IIe led to the relatively stable acid IIe which could be decarboxylated to IIc by heating at 164° for 5 min.

3-(2,6-Dichlorophenyl)-5-methyl-4-isothiazolecarboxylic acid (IIIe) *and the methyl ester* (IIIf). *Iodine oxidant.* To 23·2 g (0·18 mole) of IIf in 400 ml toluene was added 53·3 g (0·24 mole) P_2S_5, and the mixture was refluxed with efficient stirring for 30 min. After cooling to 25°, the mixture was filtered and the filtrate was concentrated under reduced press to 34·6 g of a red-brown oil. A 2·0-g sample (5·8%) of this oil was removed for further study (see *No added oxidant*). The remainder was treated with 400 ml benzene, filtered, and 11·0 g (0·08 mole) of K_2CO_3 and a soln of 20·3 g (0·08 mole) I_2 in 50 ml benzene was added. After stirring 55 min at 25°, the reaction mixture was washed with 200 ml 10% $NaHSO_3$ aq, dried over $MgSO_4$, then concentrated under reduced press to 20·2 g of a brown oil which spontaneously crystallized. This was purified by passage over a 3·5- × 17-cm column of alumina in benzene soln, followed by recrystallization from MeOH–water to yield 10·1 g (42%) of crystals. A soln of this ester in a mixture of 108 ml MeOH and 54 ml water containing 2·56 g NaOH was refluxed for 2 hr. After cooling to 25°, the MeOH was largely removed under reduced press and the aqueous residue was washed with 20 ml EtOAc, then acidified with 65 ml 1N HCl. The ppt was removed by filtration, washed with water and dried to give 5·75 g crystalline IIIe, m.p. 215°. An additional 2·85 g was obtained from the EtOAc extract, giving a hydrolysis yield of 91% and an overall yield of 38%.

No added oxidant. The 2·0-g sample from *iodine oxidant* was purified by chromatography on a 2- × 11 cm column of alumina. Eluates of benzene, benzene-EtOAc, EtOAc, and acetone were combined and concentrated under reduced press to a crystalline residue. This was recrystallized from MeOH–water to yield 0·403 g (30% yield from the starting amino ketone) of crystalline IIIf, m.p. 82–85°.

Sulfur oxidant. To 2·88 g (0·01 mole) of IIf in 50 ml toluene was added 0·96 g (0·03 mole) S, 2 g sand and 6·66 g (0·03 mole) P_2S_5, and the mixture was refluxed with efficient stirring for 30 min. After cooling to 25°, the mixture was filtered and the toluene was removed under reduced press. The residue was taken up to 75 ml benzene, filtered, and placed on a 2- × 14-cm column of alumina. The benzene eluate was collected

and the solvent removed under reduced press. The residue was treated with 30 ml MeOH, filtered (S), and concentrated under reduced press to 1·5 g of a crystalline residue. This material was dissolved in a mixture of 2 ml MeOH and 10 ml water containing 0·55 g NaOH. After reflux for 2 hr the MeOH was removed under reduced press, 5 ml water was added and the soln was washed with 15- and 10-ml portions EtOAc. Acidification with 15 ml 1N HCl gave a ppt which was removed by filtration, washed with water, and dried to yield 1·29 g (45% overall) crystals of IIIe, m.p. 208–210°.

Chloranil oxidant. To 2·88 g (0·01 mole) of IIf in 50 ml toluene was added 2·45 g (0·01 mole) chloranil, then 6·66 g (0·03 mole) P_2S_5 and, with efficient stirring, the mixture was refluxed for 15 min in an oil bath held at 120°. After cooling to 25°, the mixture was filtered and the filtrate was concentrated under reduced press to a mixture of oil and solid. This residue was treated with 50 ml benzene, filtered, and concentrated under reduced press to a volume of about 20 ml. This soln was placed on a 1- × 29-cm column of alumina and eluted with 250 ml benzene. The eluate was concentrated under reduced press to a solid which, on crystallization from MeOH–water, yielded 1·6 g (53%) of IIIf, m.p. 81–84°.

Modification of conditions. Using a standard work-up procedure, various sets of conditions for this reaction were evaluated (Table 3). A mixture of 2·88 g (0·01 mole) of IIf, 50 ml toluene, and the other reactants was refluxed with stirring as outlined on Table 3. The reacted mixture, after cooling to about 25° and stirring for 30 min, was filtered and the toluene was removed under reduced press. The residue was taken up to 75 ml of benzene, filtered and concentrated to a volume of 20 ml, which was placed on a 1- × 29-cm column of alumina and eluted with 250 ml benzene. The solvent was removed from the eluate under reduced press and the residue was crystallized from 20 ml MeOH and 60 ml water.

5-Methyl-3-phenyl-4-isothiazolecarboxylic acid (IIIa). IIb (2·33 g, 0·01 mole), 6·66 g P_2S_5, 2·45 g (0·01 mole) chloranil, 50 ml toluene, and a reflux time of 15 min gave 1·3 g of IIIb as an oil. Basic hydrolysis (as in IIIf to IIIe) and recrystallization of the acid from toluene afforded 0·70 g of IIIa in 33% overall yield.

3-(2-Furyl)-5-methyl-4-isothiazolecarboxylic acid (IIIi). A mixture of 7·0 g (0·031 mole) of IIj, 20 g (0·109 mole) P_2S_5, 7·55 g (0·031 mole) chloranil and 150 ml toluene (20-min reflux period) gave, after two recrystallizations of the product from EtOH–water, 2·15 g (34%) of IIIj. Basic hydrolysis afforded 1·85 g (92%) of IIIi. Recrystallization from toluene gave an analytical sample.

In another run, Ii was converted via the methyl ester to IIIi in 11% overall yield.

3,5-Dimethyl-4-isothiazolecarboxylic acid (IIIn) *and methyl ester* (IIIo). A mixture of 4·0 g (0·025 mole) of IIo, 16·6 g (0·075 mole) P_2S_5, 6·1 g (0·025 mole) chloranil, and 100 ml toluene was refluxed with vigorous stirring for 10 min. The alumina column was eluted with 1:1 benzene–EtOAc to give 1·25 g (30%) of IIIo, m.p. 32°. Recrystallization Skelly-solve B gave an analytical sample, m.p. 32°. Basic hydrolysis of 0·5 g of IIIo afforded 0·4 g of IIIn, m.p. 180–200° with sublimation.

3-(2,6-Dichlorophenyl)-5-methylisothiazole (IIIc). A mixture of 2·3 g (0·01 mole) of IIc, 6·66 g (0·03 mole) P_2S_5, 0·92 g (0·03 mole) S and 50 ml toluene gave 1·25 g (51%) crystalline IIIc. Recrystallization from MeOH–water gave an analytical sample, m.p. 67°.

A mixture of 2·74 g (0·01 mole) of IIe, 6·66 g (0·03 mole) P_2S_5, 2·45 g (0·01 mole) chloranil and 50 ml toluene was refluxed for 10 min. The mixture was cooled, filtered, and the solvent was removed under reduced press. The residue was taken up in 50 ml benzene, filtered, and extracted with 50 ml 2% NaOH. No carboxylic acid could be isolated from this basic extract. The benzene layer yielded 0·6 g (25%) of IIIc.

Various attempts were made to obtain IIIe by this route, using reaction conditions which were milder with respect to time and temperature, but only IIIc was isolated.

4-Cyano-3-(2,6-dichlorophenyl)-5-methylisothiazole (IIId). A mixture of 3·0 g (0·012 mole) of IId, 8 g (0·036 mole) P_2S_5, 1·15 g (0·036 mole) S and 80 ml toluene was refluxed for 3 hr (note that, after 30 min reflux, no isothiazole and a 57% recovery of starting material was obtained). The mixture was filtered while hot, then cooled in ice and filtered again. The toluene was removed under reduced press, and the residue was taken up in EtOAc, filtered, then concentrated under reduced press to a solid. Two recrystallizations of this solid from 95% EtOH yielded 1·05 g (33%) of crystals, m.p. 120–122°.

Attempted preparation of 3-(2,6-dichlorophenyl)-5-methyl-4-isothiazolecarboxamide (IIIg). A mixture of 8·19 g (0·03 mole) of IIg, 20 g (0·09 mole) P_2S_5, 2·88 g (0·09 mole) S, and 150 ml toluene was refluxed for 30 min. After cooling to about 25°, the mixture was filtered, and the toluene was removed under reduced press from the filtrate. The residue was dissolved in about 100 ml of EtOAc, filtered, concentrated to a volume of about 30 ml, filtered again, then concentrated to an oil. When subjected to alumina chromatography, this oil gave 1·6 g of IIId (eluted with benzene) and 1·6 g of IIIh, m.p. 221–224° (eluted with 1:1 benzene–EtOAc). Acid hydrolysis of both IIId and IIIh gave the carboxylic acid, IIIe.

3-Methyl-5-phenyl-4-isothiazolecarboxylic acid (IIIk). A mixture of 6·3 g (0·029 mole) of IIm, 20 g (0·09

mole) P_2S_5, 7·5 g (0·03 mole) chloranil and 120 ml toluene gave 2·05 g of IIIm as an oil. Basic hydrolysis followed by recrystallization from toluene gave 1·3 g (21% overall) of IIIk.

Acknowledgements—The authors are grateful to Mr. W. F. Minor and his associates for the preparation of some of the intermediates; to Messrs. D. F. Whitehead and A. Vulcano for infrared and NMR spectra; to Mr. R. M. Downing and his associates for elemental analyses; to Mr. H. D. Taylor and his associates for the vapor phase chromatographic studies; and to Miss Carol Botteron for technical assistance.

REFERENCES

For recent reviews; [a] R. Slack and K. R. H. Wooldridge, *Advances in Heterocyclic Chemistry* (Edited by A. R. Katritzky) Vol. 4, p. 107. Academic Press, New York, N.Y. (1965);
[b] F. Hubenett, F. H. Flock, W. Hansel, H. Heinze and H. Hofmann, *Angew. Chem. (Intern. Ed. Engl.)*, **2**, 714 (1963).
For refs to recent work;
[c] A. Holland, R. Slack, T. F. Warren and D. Buttimore, *J. Chem. Soc.* 7277 (1965);
[d] J. Goerdeler and U. Keuser, *Chem. Ber.* **97**, 3106 (1964).

[2] A. Adams and R. Slack, *J. Chem. Soc.* 3061 (1959).

[3] J. Goerdeler, *Angew. Chem. (Intern. Ed. Engl.)* **2**, 693 (1963).

[4] R. R. Crenshaw, J. M. Essery and A. T. Jeffries, *J. Org. Chem.* **32**, 3132 (1967).

[5] F. Wille, L. Capeller and A. Steiner, *Angew. Chem. (Intern. Ed. Engl.)* **1**, 335 (1962); R. Raap, *Canad. J. Chem.* **44**, 1324 (1966).

[6] D. Leaver, D. M. McKinnon and W. A. H. Robertson, *J. Chem. Soc.* 32 (1965); R. A. Olofson, J. M. Landesberg, R. O. Berry, D. Leaver, W. A. H. Robertson and D. M. McKinnon, *Tetrahedron* **22**, 2119 (1966).

[7] R. P. Williams, U.S. Pat. 3,285,930 (1966); *Chem. Abstr.* **66**, 2742 (1967).

[8] K. Gewald, *J. Prakt. Chem.* **31**, 214 (1966); W. D. Crow and N. J. Leonard, *Tetrahedron Letters* No. 23, 1477 (1964); M. Davis, G. Snowling and R. W. Winch, *J. Chem. Soc.* 124 (1967).

[9] For reviews: [a] R. A. Barnes, *Heterocyclic Compounds* (Edited by R. C. Elderfield), Vol. 5, p. 452. Wiley New York, N.Y. (1957);
[b] A. Quilico, *The Chemistry of Heterocyclic Compounds* (Edited by A. Weissberger) Vol. 17; p. 1. Wiley, New York, N.Y. (1962);
[c] N. K. Kochetkov and S. D. Sokolov, *Advances in Heterocyclic Chemistry* (Edited by A. R. Katritzky) Vol. 2; p. 365. Academic Press, New York, N.Y. (1963).

[10] A. E. Hydorn, F. A. McGinn, J. R. Moetz, and J. Schwartz, *J. Org. Chem.* **27**, 4305 (1962).

[11] [a] J. C. Hanson, A. A. W. Long, J. H. C. Nayler, and E. R. Stove, *J. Chem. Soc.* 5976 (1965);
[b] F. P. Doyle, J. C. Hanson, A. A. W. Long, and J. H. C. Nayler, *Ibid.* 5845 (1963);
[c] F. P. Doyle, J. C. Hanson, A. A. W. Long, J. H. C. Nayler, and E. R. Stove, *Ibid.* 5838 (1963).

[12] G. Stork and J. E. McMurry, *J. Am. Chem. Soc.* **89**, 5461 (1967).

[13] L. Claisen, *Chem. Ber.* **24**, 3900 (1891).

[14] G. Stagno d'Alcontres, *Gazz. Chim. Ital.* **80**, 441 (1950); G. Shaw and G. Sugoudz, *J. Chem. Soc.* 665 (1954); G. Casnati, A. Quilico, A. Ricca and P. Vita Finzi, *Tetrahedron Letters* No. 2, 233 (1966).

[15] G. Stork, S. Danishefsky and M. Ohashi, *J. Am. Chem. Soc.* **89**, 5459 (1967); M. Ohashi, H. Kamachi, H. Kakisawa, and G. Stork, *Ibid.* **89**, 5460 (1967); G. Stork and J. E. McMurry, *Ibid.* **89**, 5463 (1967); *Ibid.* **89**, 5464 (1967).

[16] E. E. Reid, *Organic Chemistry of Bivalent Sulfur*, Vol. 3; p. 148. Chemical Publishing, New York, N.Y. (1960); E. Campaigne, *Chem. Rev.* **39**, 1 (1946).

[17] A. Vos and E. H. Wiebenga, *Acta Cryst.*, **8**, 217 (1955).

[18] L. Claisen, *Ann. Chem.* **277**, 174 (1893).