[Chem. Pharm. Bull.
31(10)3424—3445(1983)]

Studies on the Synthesis and Analgesic and Anti-inflammatory Activities of 2-Thiazolylamino- and 2-Thiazolyloxy-arylacetic Acid Derivatives

RYOZO MAEDA,* EIICHI OHSUGI, TOSHIHIRO FUJIOKA, and KATSUMI HIROSE

Shionogi Research Laboratories, Shionogi & Co., Ltd., 5–12–4, Sagisu, Fukushima-ku, Osaka 553, Japan

(Received February 7, 1983)

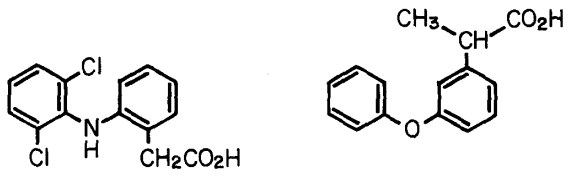
A series of 2-thiazolylamino-, 2-thiazolyloxy- and 2-thiazolylthio-arylacetic acid derivatives was prepared by condensation of thioamides with halo-acetals according to Hantzsch's method, and thioamides having the α-methylarylacetic acid moiety were conveniently obtained from halo-aromatic nitro compounds by a combination of known methods.

In the model reaction of *O*-phenyl thiocarbamate (XVIII) with chloro-diethylacetal, isolation of intermediates such as acyclic halo-compound (XIX) and 4-ethoxy-2-phenoxy-2-thiazoline (XX) clarified the reaction path for the formation of 2-phenoxythiazole (XXI).

The analgesic and anti-inflammatory effects of the compounds studied were evaluated by using the acetic acid-induced writhing method in mice and the rat carrageenin paw edema method, respectively. 2-[4-(2-Thiazolyloxy)phenyl]propionic acid (XIVa) had the most favorable therapeutic ratio between activity and toxicity (in mice).

Keywords——Hantzsch thiazole synthesis; *N*-arylthiourea; *O*-aryl thiocarbamate; *S*-aryl dithiocarbamate; reaction path; anti-inflammatory activity; analgesic activity; structure–activity relationship; preliminary selection; acute toxicity

A number of aryl and heteroaromatic alkanoic acids are well known as nonsteroidal anti-inflammatory agents. Among them, 2-(2,6-dichloroanilino)phenylacetic acid (diclofenac) and 2-(3-phenoxyphenyl)propionic acid (phenoprofen) have been used clinically as safer drugs than indomethacin to treat gastrointestinal lesions.



diclofenac phenoprofen

Fig. 1

Our research on the synthesis and cleavage reaction of phenoxyheteroaryl compounds[1] prompted us to synthesize 2-thiazolylamino-, 2-thiazolyloxy- and 2-thiazolylthio-arylacetic acid derivatives and test them for analgesic and anti-inflammatory effects. This paper describes their synthesis by effective methods and their analgesic and anti-inflammatory activities.

Synthesis

The simplest method[2] for synthesizing 2-arylamino- and 2-aryloxy-thiazoles involves

condensation of 2-halothiazoles with either arylamines or phenols. In trying to prepare analogues of *para*-substituted arylacetic acid derivatives,[3] we found that the condensation reaction does not proceed smoothly under mild conditions even in the presence of cupric oxide catalyst and some compounds are obtained only in low yield. This result led us to adopt the procedure of the Hantzsch thiazole synthesis.

Of a variety of compounds corresponding to arylic acetic acid derivatives of arylamines, *N*-methylarylamines, phenolic compounds, and thiophenols, most having the α-methylacetic acid moiety, were prepared by the routes shown in Charts 1 and 2.

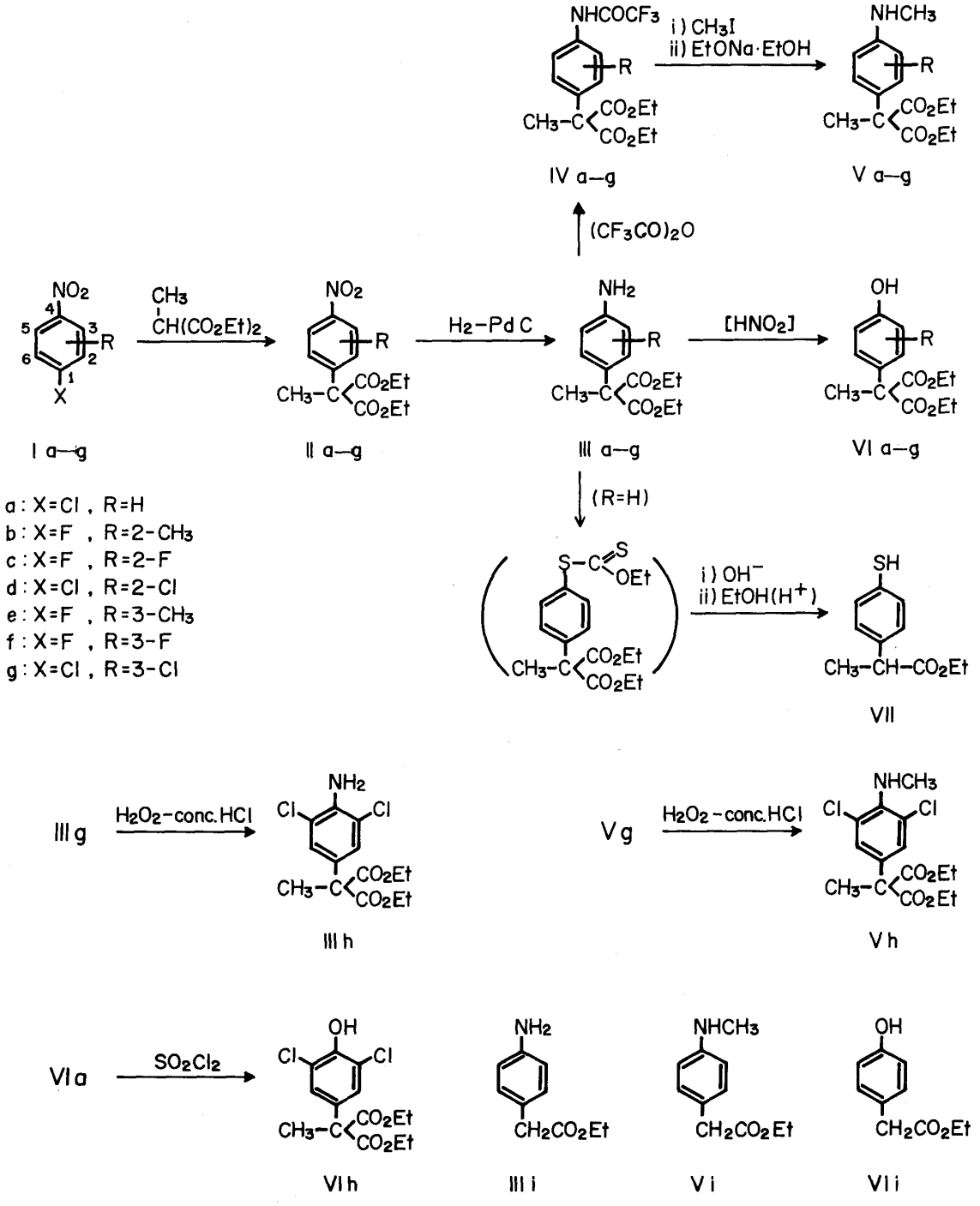


Chart 1

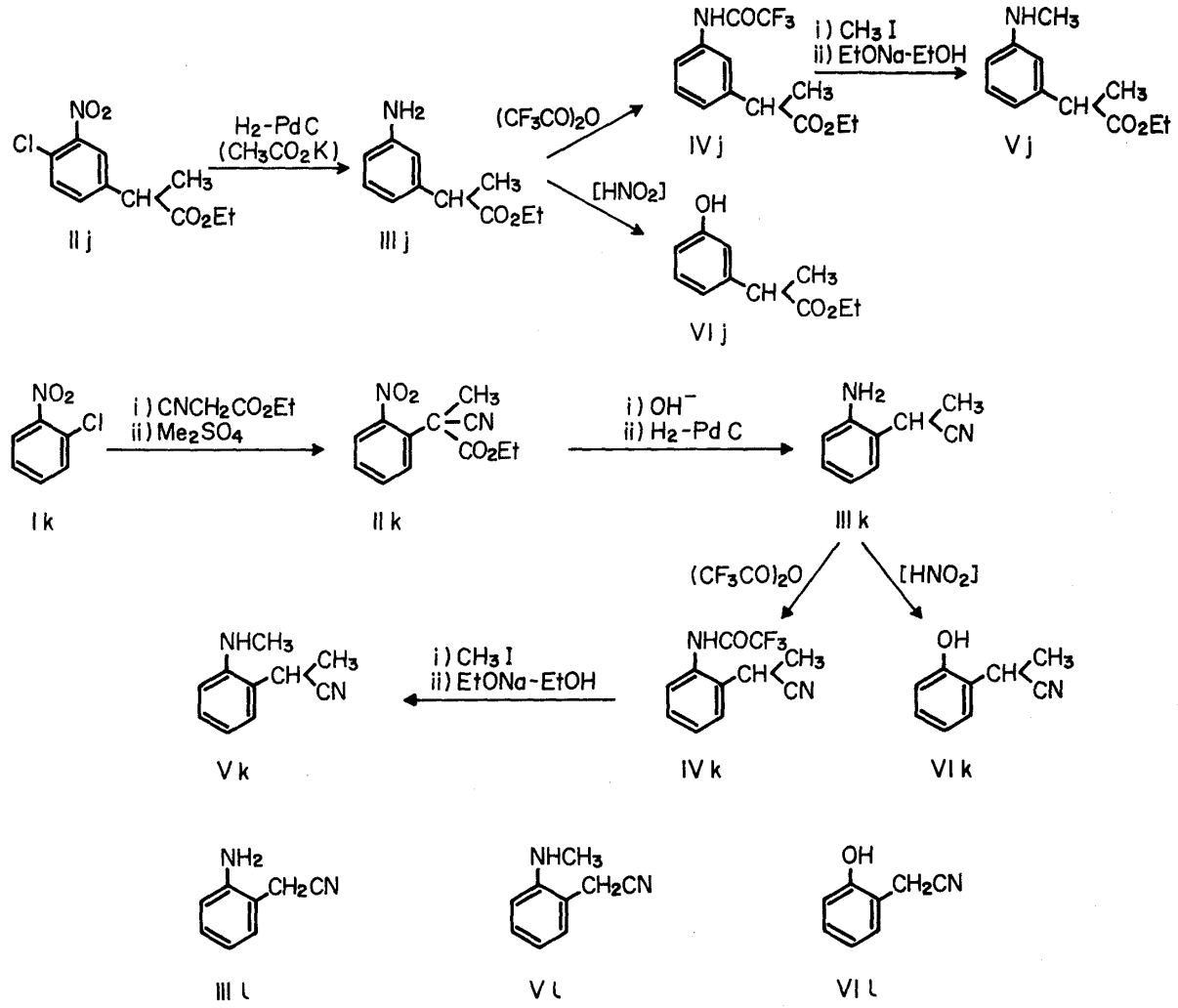


Chart 2

In these preparations, *para*-amino isomers (IIIa—g) were obtained in 50—80% yields from the corresponding Ia—g *via* IIa—g by condensation with diethyl methylmalonate followed by catalytic hydrogenation according to Carney *et al.*[4] or Dumaitre *et al.*[5] Compound IIIh was conveniently prepared from IIIg by the action of 30% H_2O_2 in conc. HCl according to Saikel's method[6] in nearly quantitative yield. In preparing the *meta*-amino isomer, catalytic hydrogenation of IIj[7] in the presence of potassium acetate gave IIIj in 90% yield. To avoid the intermolecular cyclization of the *ortho*-amino isomer to form the γ-lactam compound, the cyano derivative (IIIk) was prepared from Ik through multi-step reactions including condensation with ethyl cyanoacetate, methylation, hydrolysis, decarboxylation and catalytic hydrogenation *via* IIk; the yield of IIIk was 47%. On the other hand, IIIi, l having the acetic acid moiety were readily prepared from commercially available 4-aminophenylacetic acid and 2-nitrophenylacetonitrile, respectively.

In the transformation of these amino compounds (IIIa—l) to *N*-methyl derivatives (Va—l), the *N*-monomethylation of IIIa—g, i—l *via* IVa—g, i—l using Johnstone's process[8] gave Va—g, i—l in about 90% yield, and Vh was prepared directly from Vg in 96% yield as described for IIIh.

For the phenolic compounds (VIa—l), IIIa—e, i—l was converted to the corresponding diazonium salts in aq. H_2SO_4, and these were thermally decomposed as described by Wilds and Biggerstaff,[9] providing Va—e, i—l in 50—80% yields. Conversion of IIIf, g, having a

halogen atom at the *ortho* position to the amino group, was carried out by aryl radical oxidation *via* formation of the corresponding diazonium ions as described by Cohen *et al.*,[10] providing VIf, g in 40—50% yields. Compound VIh, having two chlorine atoms, was prepared conveniently from VIa in 87% yield by chlorination with SO_2Cl_2 according to Tarbell's method.[11] To prepare the thiophenolic compound (VII), the diazonium solution obtained from IIIa was treated with potassium xanthogenate. This gave the xanthate, which was converted into VII by alkaline hydrolysis followed by esterification according to Wilson's method[12] in 36% yield based on IIIa. The arylamino-, *N*-methylarylamino-, phenolic and thiophenolic compounds (IIIa—l, Va—l, VIa—l and VII, respectively) were converted into the corresponding 2-thiazolyl derivatives as shown in Chart 3.

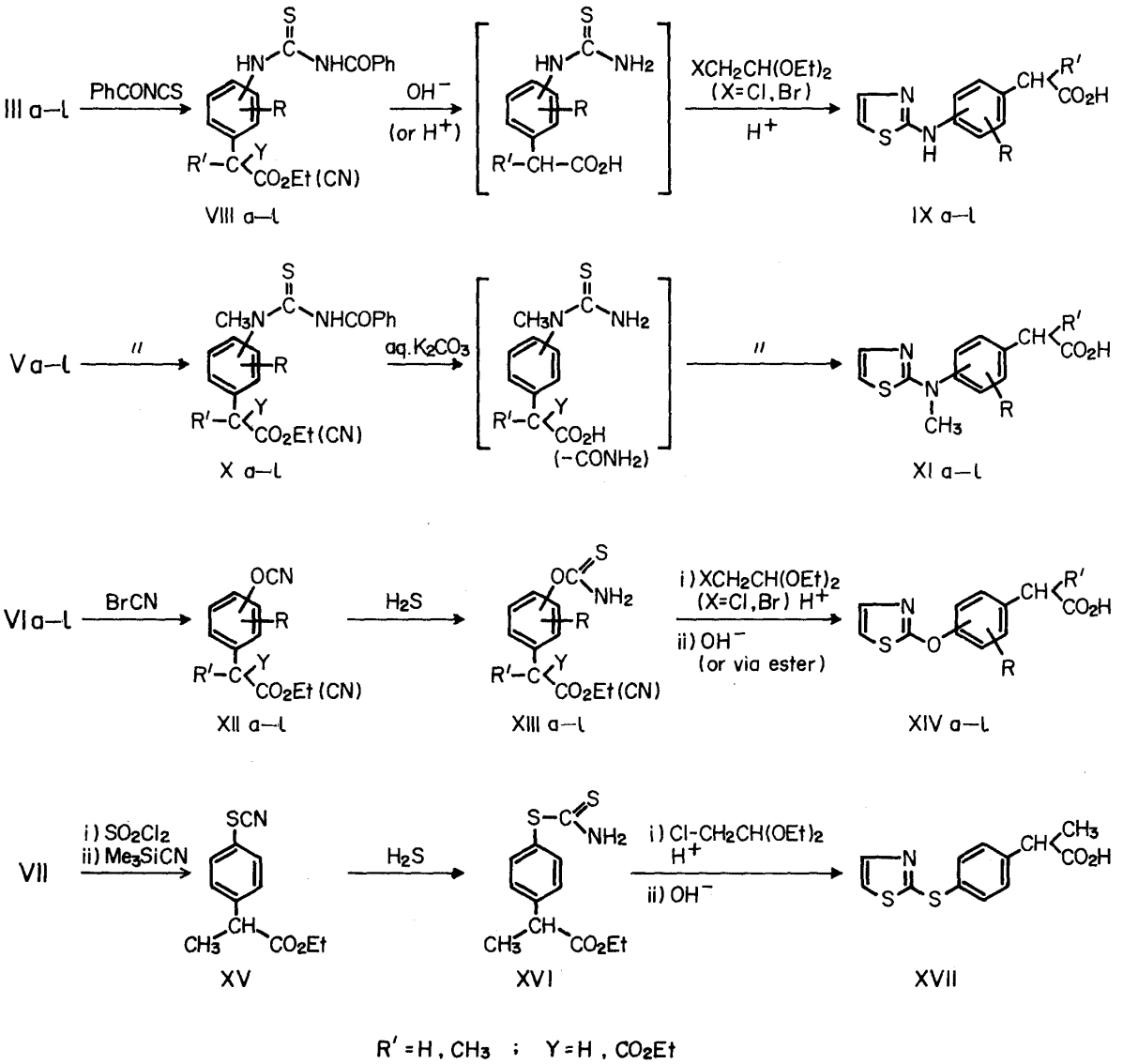
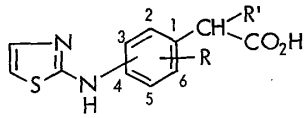


Chart 3

With these 2-thiazolylamino derivatives (IXa—l), we tried to obtain the corresponding *N*-arylthioureas as key intermediates for Hantzsch thiazole synthesis by the direct action of IIIa with NH_4SCN as proposed by Kurzer[13] or Sawhney *et al.*[14] However, the reaction was unsatisfactory even in the presence of excess reagent, and the expected compounds were obtained in low yield. Thus, IIIa—l were converted into thioureas *via* the intermediates VIIIa—l, which were hydrolyzed with alkali or acid according to the usual methods[15,16] for

TABLE I.



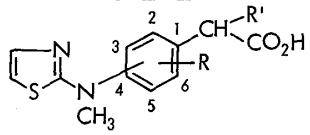
Comp. No.	Position	R	R′	mp (°C)	Recryst. solvent	Yield[a] (%)	Formula	Analysis (%) Calcd (Found) C	H	N	S	Anti-infl. activity ED_{30} (mg/kg)	Analgesic activity acetic acid writhing ED_{50} (mg/kg)
IXa	4	H	CH_3	176—177	MeOH	72	$C_{12}H_{12}N_2O_2S$	58.04 (58.19	4.87 4.83	11.28 11.36	12.91 12.76)	1.9	3.5
IXb	4	2-CH_3	CH_3	160—161.5	AcOEt	73	$C_{13}H_{14}N_2O_2S$	59.52 (59.33	5.38 5.47	10.68 10.62	12.22 12.16)	1.1	>50.0
IXc	4	2-F	CH_3	190—191.5	EtOH	77	$C_{12}H_{11}FN_2O_2S$	54.12 (54.06	4.16 4.40	10.52 10.46	12.04 12.07)	2.3	23.9
IXd	4	2-Cl	CH_3	174—175	AcOEt	58	$C_{12}H_{11}ClN_2O_2S$	50.97 (51.26	3.92 3.97	9.91 9.81	11.34 11.25)	1.6	>50.0
IXe	4	3-CH_3	CH_3	143—144	AcOEt	57	$C_{13}H_{14}N_2O_2S$	59.52 (59.58	5.38 5.38	10.68 10.40	12.22 12.00)	9.3	>40.0
IXf	4	3-F	CH_3	162—163	AcOEt	75	$C_{12}H_{11}FN_2O_2S$	54.12 (54.10	4.16 4.43	10.52 10.50	12.04 12.15)	0.63	24.3
IXg	4	3-Cl	CH_3	144—145	AcOEt	63	$C_{12}H_{11}ClN_2O_2S$	50.97 (50.99	3.92 4.03	9.91 9.80	11.34 11.43)	1.1	23.8
IXh	4	3,5-di-Cl	CH_3	176—178	AcOEt	69	$C_{12}H_{10}Cl_2N_2O_2S$	45.44 (45.50	3.18 3.03	8.83 8.96	10.11 10.30)	3.6	34.2
IXi	4	H	H	195—197	Me_2CO	72	$C_{11}H_{10}N_2O_2S$	56.40 (56.23	4.30 4.35	11.96 12.12	13.68 13.79)	>20	>50.0
IXj	3	H	CH_3	153.5—154.5	MeOH	81	$C_{12}H_{12}N_2O_2S$	58.04 (58.27	4.87 4.81	11.28 11.37	12.91 12.99)	>20	>40.0
IXk	2	H	CH_3	119—120	MeOH	10	$C_{12}H_{12}N_2O_2S$	58.04 (57.80	4.87 4.64	11.28 11.35	12.91 13.20)	>20	>40.0
IXl	2	H	H	145—147	MeOH	25	$C_{11}H_{10}N_2O_2S$	56.40 (56.47	4.30 4.15	11.96 11.93	13.68 13.79)	18.6	>40.0
												0.8	7.4
												1.9	25.9

Indomethacin

Diclofenac-Na

a) Yield from the corresponding III.

TABLE II.



Comp. No.	Position	R	R′	mp (°C)	Recryst. solvent	Yield[a] (%)	Formula	Analysis (%) Calcd (Found) C	H	N	S	Anti-infl. activity ED_{30} (mg/kg)	Analgesic activity acetic acid writhing ED_{50} (mg/kg)
XIa	4	H	CH_3	123—124	Et_2O	69	$C_{13}H_{14}N_2O_2S$	59.52 (59.27	5.38 5.49	10.68 10.42	12.22 12.32)	3.6	41.0
XIb	4	2-CH_3	CH_3	165—166	AcOEt	71	$C_{14}H_{16}N_2O_2S$	60.84 (60.96	5.84 5.91	10.14 10.20	11.60 11.57)	2.6	40.7
XIc	4	2-F	CH_3	111—112.5	Et_2O–Hexane	68	$C_{13}H_{13}FN_2O_2S$	55.70 (55.60	4.67 4.60	10.00 9.99	11.44 11.54)	3.1	32.9
XId	4	2-Cl	CH_3	141—142	AcOEt–Hexane	66	$C_{13}H_{13}ClN_2O_2S$	52.61 (52.64	4.42 4.39	9.44 9.51	10.80 10.76)	11.5	32.5
XIe	4	3-CH_3	CH_3	104—105	Et_2O–Hexane	75	$C_{14}H_{16}N_2O_2S$	60.84 (60.93	5.84 5.83	10.14 10.06	11.60 11.59)	10.5	>40.0
XIf	4	3-F	CH_3	98—100	AcOEt–Hexane	72	$C_{13}H_{13}FN_2O_2S$	55.70 (55.82	4.67 4.95	10.00 10.17	11.44 11.54)	1.7	22.0
XIg	4	3-Cl	CH_3	91—92	Hexane	75	$C_{13}H_{13}ClN_2O_2S$	52.61 (52.43	4.42 4.20	9.44 9.42	10.80 10.85)	4.0	28.5
XIh	4	3,5-di-Cl	CH_3	180—181	Et_2O	78	$C_{13}H_{12}Cl_2N_2O_2S$	47.13 (47.17	3.65 3.71	8.46 8.46	9.68 9.78)	1.9	29.5
XIi	4	H	H	203—204	MeOH	82	$C_{12}H_{12}N_2O_2S$	58.04 (57.95	4.87 4.99	11.28 11.29	12.91 12.90)	9.8	>50.0
XIj	3	CH_3	CH_3	124—125	AcOEt	69	$C_{13}H_{14}N_2O_2S$	59.52 (59.71	5.38 5.28	10.68 10.68	12.22 12.35)	>20	>40.0
XIk	2	CH_3	CH_3	173—174	Et_2O–Hexane	52	$C_{13}H_{14}N_2O_2S$	59.52 (59.58	5.38 5.40	10.68 10.71	12.22 12.25)	>20	>40.0
XIl	2	H	H	165—167	MeOH	59	$C_{12}H_{12}N_2O_2S$	58.04 (57.87	4.87 4.61	11.28 11.10	12.91 13.01)	>20	>40.0
										Indomethacin		0.8	7.4
										Diclofenac-Na		1.9	25.9

a) Yield from the corresponding V.

preparing *N*-phenylthiourea. Although the expected *N*-arylthiourea compounds could not be separated from a small amount of benzoic acid in our experiments, treatment of the crude products with halo-diethylacetal in the presence of an acid catalyst gave the desired 2-thiazolylaminoarylacetic acid compounds (IXa—l). Data for compounds IXa—l are listed in Table I.

Based on our success in preparing 2-thiazolylamino compounds, we also converted the *N*-methyl derivatives (Va—l) into *N*-methyl-*N*-thiazol-2-ylaminoarylacetic acid compounds (XIa—l) *via* Xa—l. Data for compounds XIa—l are listed in Table II.

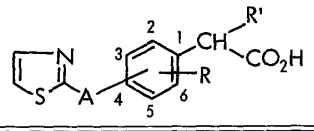
On the basis of the 2-aryloxythiazole synthesis by Hantzsch's method, the preliminary conversion of the phenolic compounds (VIa—l) into the corresponding *O*-aryl thiocarbamates (XIIIa—l) was achieved by treatment with cyanogen bromide in the presence of triethylamine according to Vowinkel's method[17] to yield cyanates (XIIa—l), which were treated with H_2S in the presence of triethylamine according to Grigat's method[18] to provide XIIIa—l in 65—95% yield based on VIa—l.

Although no precedent for Hantzsch thiazole synthesis was found in the literature in the case of *O*-aryl thiocarbamates, the treatment of XIIIa—l with halo-diethylacetal in acetic acid in the presence of a catalytic amount of *p*-toluenesulfonic acid gave the expected 2-thiazolyloxy derivatives in generally good yields except for a di-chloro compound (yield, 16%). The nuclear magnetic resonance (NMR) spectra ($CDCl_3$) of these products all showed an olefinic doublet ($J=3.7$ Hz) proton signal in the region of 6.72—6.88 (δ), assignable to the thiazole-C_5 proton. The thiazole-C_4 proton was included among the aromatic protons or appeared as a doublet ($J=3.7$ Hz) in the region of 7.18—7.23 (δ). The products were converted either directly by the action of aq. alkali for ester compounds, or indirectly by initially transforming the cyano group into an ester group followed by alkaline hydrolysis, to the desired 2-thiazolyloxyarylacetic acid compounds (XIVa—l). Similar conversion of the thiophenolic compound (VII) into the *S*-aryl dithiocarbamate compound (XVI) was carried out by chlorination with SO_2Cl_2 followed by cyanation with trimethylsilyl cyanide according to Harpp's method[19] to yield the thiocyanate XV as an intermediate; this was treated with H_2S to obtain XVI in 50% yield. Cyclization of XVI with chloro-diethylacetal followed by alkaline hydrolysis gave 2-[4-(2-thiazolylthio)phenyl]propionic acid (XVII) as in the case of XIIIa—l. Data for compounds XIVa—l and XVII are listed in Table III.

To elucidate the reaction path for thiazole synthesis, a model experiment on *O*-phenyl thiocarbamate (XVIII)[18] was conducted by treating chloro-diethylacetal with Et_2O–acetic acid (4 : 1) in the presence of *p*-toluenesulfonic acid as catalyst at room temperature (Chart 4).

The prepack high performance liquid chromatography (HPLC) of the crude product obtained by careful treatment of the reaction mixture with K_2CO_3 gave an unstable oily halo-compound (XIX), which was indicated to be the *N*-substituted acyclic intermediate by the following results. The infrared (IR) spectrum (CCl_4) showed an imino band (3370 cm^{-1}) and a thioureido band (1470 cm^{-1}). The NMR spectrum (CCl_4) displayed signals due to one methine proton (5.80 δ, m), four partly accumulated methylene protons (3.68—3.50 δ, m), three methyl protons (1.25 δ, t, $J=7.0$ Hz), and also five aromatic protons together with one imino proton. Although XIX changed easily into a mixture of XX and XXI, even ice-cooling, with removal of HCl and immediate treatment with K_2CO_3 in acetonitrile gave only XX which showed the formula $C_{11}H_{13}NO_2S$ upon elemental analysis. The IR spectrum (CCl_4) of XX exhibited a characteristic absorption at 1625 cm^{-1} due to the C=N stretching band, and the NMR spectrum (CCl_4) revealed signals due to one methine proton (5.47 δ, m), four partly accumulated methylene protons (3.93—3.13 δ, m), three methyl protons (1.17 δ, t, $J=$ 7.0 Hz), and also five aromatic protons. While further study is necessary to confirm the structure of XX, our spectral results compare well with those of the 5-ethoxy-isomer (XXIII), which was prepared from α-isothiocyano-diethylacetal[20] and phenol *via* XXII by a com-

TABLE III.



Comp. No.	Position	A	R	R′	mp (°C)	Recryst. solvent	Yield[a] (%)	Formula	Analysis (%) Calcd (Found) C	H	N	S	Anti-infl. activity ED_{30} (mg/kg)	Analgesic activity acetic acid writhing ED_{50} (mg/kg)
XIVa	4	O	H	CH_3	121—122	Dichloroethane	74	$C_{12}H_{11}NO_3S$	57.81 (57.60	4.45 4.44	5.62 5.50	12.86 12.98)	4.1	10.9
XIVb	4	O	2-CH_3	CH_3	120—121	AcOEt–Hexane	64	$C_{13}H_{13}NO_3S$	59.30 (59.21	4.98 5.02	5.32 5.35	12.18 11.97)	3.7	>50.0
XIVc	4	O	2-F	CH_3	74—75	AcOEt–Hexane	58	$C_{12}H_{10}FNO_3S$	53.92 (53.93	3.77 3.80	5.24 5.09	12.00 12.22)	5.4	25.6
XIVd	4	O	2-Cl	CH_3	86—87	C_6H_6–Hexane	53	$C_{12}H_{10}ClNO_3S$	50.80 (51.04	3.55 3.60	4.94 4.94	11.30 11.50)	10.5	>50.0
XIVe	4	O	3-CH_3	CH_3	93—94	Et_2O–Hexane	71	$C_{13}H_{13}NO_3S$	59.30 (59.60	4.98 4.94	5.32 5.53	12.18 12.05)	8.8	>40.0
XIVf	4	O	3-F	CH_3	107—108	Et_2O–Hexane	37	$C_{12}H_{10}FNO_3S$	53.92 (54.01	3.77 4.04	5.24 5.02	12.00 12.28)	0.83	21.4
XIVg	4	O	3-Cl	CH_3	115—116	Et_2O–Hexane	62	$C_{12}H_{10}ClNO_3S$	50.80 (51.08	3.55 3.33	4.94 4.75	11.30 11.25)	8.6	>50.0
XIVh	4	O	3,5-di-Cl	CH_3	136.5—137.5	Et_2O–Hexane	9	$C_{12}H_9Cl_2NO_3S$	45.30 (45.50	2.85 2.90	4.40 4.38	10.08 10.19)	10.3	>40.0
XIVi	4	O	H	H	152—153	Dichloroethane	56	$C_{11}H_9NO_3S$	56.16 (56.19	3.86 3.81	5.95 5.85	13.63 13.75)	>20	>50.0
XIVj	3	O	H	CH_3	88—89	Et_2O–Hexane	48	$C_{12}H_{11}NO_3S$	57.81 (57.88	4.45 4.44	5.62 5.77	12.86 12.92)	10.8	>50.0
XIVk	2	O	H	CH_3	81—82	Iso-Pr_2O	30	$C_{12}H_{11}NO_3S$	57.81 (57.81	4.45 4.38	5.62 5.54	12.86 12.79)	>20	>40.0
XIVl	2	O	H	H	134.5—135.5	Dichloroethane	34	$C_{11}H_9NO_3S$	56.16 (56.15	3.86 3.89	5.95 5.89	13.63 13.75)	>20	>40.0
XVII	4	S	H	CH_3	85—87	Et_2O–Hexane	37	$C_{12}H_{11}NO_2S_2$	54.34 (54.20	4.18 4.25	5.28 5.24	24.13 24.13)	2.3	31.1
									Indomethacin				0.8	7.4
									Phenoprofen-Ca				12.0	86.0

a) Yield from the corresponding VI or VII.

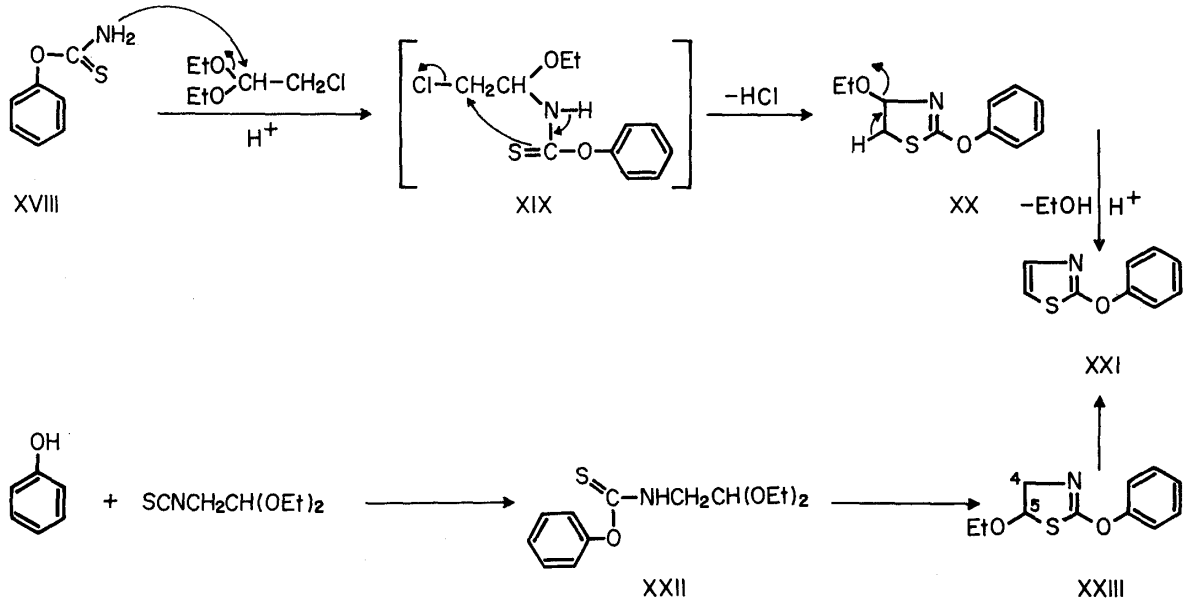


Chart 4

bination of Bost's[21] and Lawson's[22] methods. The IR spectrum (CCl_4) of XXIII showed the C=N absorption band at 1643 cm^{-1}, and the NMR spectrum (CCl_4) displayed signals due to one C_5 proton (5.50 δ, m) and two C_4 protons (4.23—3.77 δ, m), which could be discriminated from the methylene protons (3.37—3.00 δ, m) of the ethoxy group. Also found were three methyl protons (1.17 δ, t, J=7.0 Hz) together with five aromatic protons. Moreover, the subsequent removal of EtOH from XX proceeded smoothly in the presence of a catalytic amount of *p*-toluenesulfonic acid to give XXI in nearly quantitative yield. However, the same treatment of XXIII did not change its hemiacetalic nature. Thus, XXIII was converted into authentic XXI in nearly quantitative yield by heating with a large amount of either conc. H_2SO_4 or polyphosphoric acid. This product was used for the identification with a sample obtained from XX.

On the basis of these observations, it may safely be assumed that the reaction path for thiazole synthesis (preparation of IXa—l, XIa—l, XIVa—l and XVII) is similar to that in the formation of XXI from XVIII.

Pharmacology and Discussion

The anti-inflammatory activities of these thiazole compounds (IXa—l, XIa—l, XIVa—l and XVII) were examined by means of the rat carrageenin paw edema assay method as described by Winter *et al.*[23] The results, expressed as the dosage which inhibited 30% of the edema (ED_{30}), were calculated by regression analysis for significant effects. Representative ED_{30} values were used to elucidate relative potency in comparison with that of either diclofenac-Na or phenoprofen-Ca after considering the structural correlations between thiazolylamino and thiazolyloxy compounds in order to examine the structure–activity relationships. Indomethacin was included in some of the assays for comparison.

2-[4-(2-Thiazolylamino)phenyl]propionic acid (IXa), a *para* isomer, showed activity comparable to that of diclofenac-Na whereas the corresponding *meta* and *ortho* isomers (IXj and k, respectively) displayed no significant activity. Similar examination of structure–activity correlations for parent acetic acid analogues showed less good discrimination between *para* and *ortho* isomers (IXi and l, respectively), because both compounds showed weak activity. Among a variety of substituents on the benzene ring of IXa, a methyl group at the 2-position

or a halogen atom (including fluorine and chlorine) at the 2- or 3-position showed either an increase or retention of the original activity, and 3-halo compounds (IXf, g), which were nearly comparable in activity to indomethacin, were more active than the corresponding 2-halo compounds (IXc, d) in the two cases where direct comparison was possible. However, the placement of either a methyl group at the 3-position or two chloro atoms at the 3,5-positions decreased the activity.

To examine various substituted methyl compounds, the activities of *N*-methyl derivatives (XIa—l) were compared with those of IXa—l. We found that placement of the methyl group at the bridged nitrogen resulted in structure–activity correlations similar to those found in the examination of IXa—l, and most compounds showed relatively lower activity. There were three exceptions; the 3,5-dichloro compound (XIh) showed strong activity (comparable to that of diclofenac-Na), and XId and XIi showed weak activity due to either marked reduction or slight improvement of the original activity.

Examination of the thiazolyloxy compounds (XIVa—l) showed that 2-[4-(2-thiazolyloxy)phenyl]propionic acid (XIVa), a *para* isomer, had stronger activity than the corresponding *meta* isomer (XIVj), which was comparable in activity to phenoprofen-Ca, while the corresponding *ortho* isomer (XIVk) showed no significant activity. Similar comparisons for XIVi and XIVk could not be done because of their negligible activity. Among the substituted derivatives of XIVa, the 3-fluoro compound (XIVf) showed increased activity (comparable to that of indomethacin), while most compounds having a methyl group or one or two halogen atoms at a suitable position, such as IXb—h (except IXf), displayed no significant improvement of the original activity. Moreover, the thiazolylthio compound (XVII) having a thioether bridge instead of an ether bridge showed slightly increased activity.

The analgesic activity of these compounds was tested by the acetic acid-induced writhing method in mice as described by Kostar *et al.*,[24] and the ED_{50} values of the active compounds were determined by regression analysis. Representative ED_{50} values were used to elucidate the relative potency with reference to that of either diclofenac-Na or indomethacin.

Experimental results on the IXa—l, XIa—l and XIVa—l (XVII) series showed that several compounds having strong anti-inflammatory activity displayed analgesic activity which was either superior or nearly comparable to that of diclofenac-Na, as shown in Tables I—III. Among them, the original compounds (IXa and XIVa, respectively) in the two series showed optimum activity superior or nearly comparable to that of indomethacin. These observations justified with our preliminary selection of IXa and XIVa as analgesic agents possessing anti-inflammatory activity.

The selected compounds were next tested for acute toxicity in mice (*p.o.*), and the results, expressed as LD_{50} values, were calculated by the Probit method.[25] Direct comparison of IXa and XIVa showed that IXa is more active with an LD_{50} of 98.3 mg/kg, and XIVa is slightly less potent with an LD_{50} of 660.1 mg/kg. As XIVa is a reasonably potent analgesic and anti-inflammatory agent, having a favorable therapeutic ratio, it was selected for further study. This compound, 48-0156-S, is now under clinical trial.

Experimental

All melting and boiling points are uncorrected. The extracted organic solutions were dried over $MgSO_4$ and concentrated by evaporation under reduced pressure. IR spectra were recorded with a Jasco DS-403G or a Hitachi 215 grating infrared spectrometer. NMR spectra were measured with a Varian T-60 (60 MHz) or EM 360 L (60 MHz) spectrometer using tetramethylsilane as an internal standard. The following abbreviations are used: singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), broad (br) and shoulder (sh).

Compound III——Diethyl 4-aminophenyl-methylmalonate (IIIa) and diethyl (4-amino-3-chlorophenyl)-methylmalonate (IIIg) were synthesized from the corresponding Ia, g *via* IIa, g after Carney *et al.*[4] and Dumaitre *et al.*[5] Condensation of Ia—g with diethyl methylmalonate gave IIa—g, and catalytic hydrogenation of IIa—g

yielded oily IIIa—g.

Diethyl (4-Amino-3,5-dichlorophenyl)methylmalonate (IIIh)——IIIg (39.0 g) in 240 ml of conc. HCl and 390 ml of benzene was treated dropwise with 13.2 ml of 37% H_2O_2 over 20 min at 10 °C, with vigorous stirring. After being stirred for 2 h at room temperature, the reaction mixture was diluted with 200 ml of water, and the separated organic layer was washed with aq. $NaHCO_3$. Evaporation of the solvent gave 41.7 g (96%) of IIIh, which was used for the next step without further purification. A small sample showed bp 165—167 °C (1 mmHg). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3500, 3390 (NH_2); 1730 (C=O). NMR ($CDCl_3$) δ: 7.22 (2H, aromatic-H), 4.55—3.90 (br, 2H, NH_2), 4.20 (q, J=7.0 Hz, 4H, $-\underline{CH_2}-CH_3 \times 2$), 1.78 (s, 3H, $\equiv C-CH_3$), 1.25 (t, J=7.0 Hz, $-CH_2\underline{CH_3} \times 2$).

Ethyl 2-(3-Aminophenyl)propionate (IIIj)——A solution of 12.9 g of IIj[7] in 130 ml of EtOH was hydrogenated overnight over 1.3 g of 5% Pd-C catalyst in the presence of 5.4 g of potassium acetate at room temperature. The residue obtained after removal of the catalyst and solvent was treated with dil. HCl and washed with Et_2O. The aqueous solution was made alkaline with $NaHCO_3$ and then extracted with Et_2O. Evaporation of Et_2O gave 8.7 g (90%) of IIIj, which was used for the next step without further purification. A small sample showed bp 133—135 °C (2 mmHg). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3450, 3360 (NH_2), 1720 (C=O).

2-(2-Aminophenyl)propionitrile (IIIk)——A solution of 70.0 g of 2-chloronitrobenzene (Ik) in 15 ml of abs. dimethylformamide (DMF) was added to a stirred suspension of ethyl cyanoacetate-sodium [prepared from 100.5 g of ethyl cyanoacetate and 21.4 g of NaH in 250 ml of abs. DMF], and stirring under nitrogen was continued at 44—47 °C for 24 h. After ice-cooling, 240 ml of 10% HCl was added to liberate the product, which was extracted with benzene. Removal of volatile components from the benzene solution under reduced pressure gave 98.6 g of arylcyanoacetate compound, which was used for the next reaction without further purification. For spectral analysis, a small sample was purified by HPLC. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 2240 (CN), 1760 (C=O), 1530 (NO_2). NMR (CCl_4) δ: 8.25—7.43 (4H, aromatic-H), 5.63 (s, 1H, $\equiv CH-$), 4.30 (q, J=8.0 Hz, 2H, $-\underline{CH_2}-CH_3$), 1.53 (t, J=8.0 Hz, 3H, $-CH_2-\underline{CH_3}$). A solution of 63.7 g of dimethyl sulfate in 60 ml of acetone was added dropwise to a vigorously stirred solution of the above product (98.5 g) in 430 ml of acetone containing 81.4 g of K_2CO_3 powder, and the whole was then refluxed for 5 h. Filtration to remove the precipitate followed by evaporation of the solvent together with excess reagent gave an oily material, which was treated with 100 ml of hexane to separate 94.2 g of crystals, from which 70.0 g (63.4%) of IIk was obtained by column chromatography on 94 g of silica gel with benzene as the eluting solvent followed by recrystallization from isopropanol, mp 66.5—67 °C. *Anal.* Calcd for $C_{12}H_{12}N_4O_4$: C, 58.06; H, 4.88; N, 11.28. Found: C, 58.27; H, 4.84; N, 11.24. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 2230 (CN), 1760, 1750 (C=O), 1530 (NO_2). NMR (CCl_4) δ: 8.17—7.30 (4H, aromatic-H), 4.28 (q, J=7.0 Hz, 2H, $-\underline{CH_2}-CH_3$), 2.08 (s, 3H, $\equiv C-CH_3$), 1.32 (t, J=7.0 Hz, 3H, $-CH_2-\underline{CH_3}$). A solution of 46.0 g of IIk in 1150 ml of 7.3% aq. EtOH was refluxed in the presence of 38.4 g of K_2CO_3 under nitrogen for 18 h, and EtOH was then evaporated off. After treatment of the residual mixture with benzene, the separated benzene solution was chromatographed on 31 g of silica gel and eluted with benzene to yield 29.8 g of the de-ethoxycarbonyl product, from which 27.1 g (82.9%) of pure compound was obtained by recrystallization from Et_2O–hexane, mp 45—46 °C. *Anal.* Calcd for $C_9H_8N_2O_2$: C, 61.36; H, 4.58; N, 15.90. Found: C, 61.41; H, 4.49; N, 15.90. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 2240 (CN), 1520 (NO_2). NMR (CCl_4) δ: 8.07—7.30 (4H, aromatic-H), 4.72 (q, J=7.0 Hz, 1H, $>\underline{CH}-CH_3$), 1.70 (d, J=7.0 Hz, 3H, $>CH-\underline{CH_3}$). A solution of 20.8 g of the de-ethoxycarbonyl compound in 210 ml of EtOH was hydrogenated over 2.1 g of 5% Pd-C catalyst, and the reaction mixture was worked up as usual to yield 15.5 g (89.8%) of oily IIIk, which was used for the next step without further purification. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3460, 3380 (NH_2), 2230 (CN).

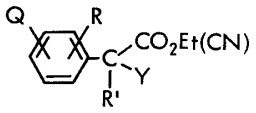
Data for compounds IIb—f and IIIb—f and l are listed in Table IV.

Compound V: Diethyl (4-Methylaminophenyl)methylmalonate (Va)——A solution of 18.4 g of IIIa in 90 ml of CH_2Cl_2 was treated with 16.0 g of trifluoroacetic anhydride under stirring at room temperature for 1 h. The residue after evaporation of the solvent was dissolved in Et_2O, and the solution was washed successively with 10% HCl, satd. $NaHCO_3$ and satd. brine. Evaporation of the Et_2O gave 23.6 g (94.5%) of IVa. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3440, 3340 (NH), 1735 (C=O). A stirred solution of IVa in 118 ml of abs. DMF containing 10.0 g of K_2CO_3 powder was treated with 11.2 g of CH_3I under nitrogen at room temperature for 3 h. The residual product obtained through filtration followed by evaporation of the solvent was taken up with Et_2O and the solution was washed with 10% HCl. The oily product (24.1 g) obtained from the ether solution was saponified with a solution of NaOEt [prepared from 1.6 g of metallic sodium and 120 ml of abs. EtOH] under stirring at room temperature for 0.5 h. Acetic acid was added to decompose the excess reagent and EtOH was then evaporated off. The resulting basic material was taken up with Et_2O and the ether solution was treated with 10% HCl. The aqueous solution was made alkaline with $NaHCO_3$, and back-extraction with Et_2O gave 17.5 g (90.5% based on IIIa) of oily Va, which was used for the next step without further purification. A small sample showed bp 147—149 °C (1 mmHg). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3420 (NH), 1725 (C=O). NMR ($CDCl_3$) δ: 7.20, 6.55 (4H, aromatic-H), 4.22 (q, J=7.0 Hz, 4H, $-\underline{CH_2}-CH_3 \times 2$), 3.17 (1H, NH), 2.82 (s, 3H, NCH_3), 1.82 (s, 3H, $\equiv C-CH_3$), 1.25 (t, J=7.0 Hz, 6H, $-CH_2-\underline{CH_3} \times 2$).

Compounds Vb—g, i and j were prepared in the same manner.

Diethyl (3,5-Dichloro-4-methylaminophenyl)methylmalonate (Vh)——Vg (20.0 g) in 200 ml of conc. HCl and 200 ml of benzene was treated dropwise with 6.2 ml of 37% H_2O_2 under ice-cooling, with vigorous stirring, and the stirring was continued for 1 h at room temperature. The reaction mixture was worked up as described for the

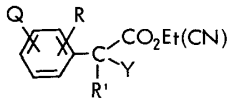
TABLE IV.



Y=H, CO_2Et Q=NO_2 (compound II) NH_2 (compound III)

Compound II					Compound III					
Comp. No.	bp (°C)	Yield[a] (%)	IR $\nu_{max}^{CCl_4}$ cm^{-1} (C=O)	(NO₂)	Comp. No.	bp or mp (Recryst. solvent) (°C)	Yield[b] (%)	IR $\nu_{max}^{CCl_4}$ cm^{-1} (NH_2)	(C=O or C≡N)	NMR in $CDCl_3$ (δ)
IIb	160—165 (0.2 mmHg)	60	1730, 1740 (sh)	1520	IIIb	164—166 (0.2 mmHg)	87	3460, 3380	1730	6.98—6.23 (m, 3H), 4.20 (q, J=7.0 Hz, 4H), 3.58 (br, 2H), 2.17 (s, 3H), 1.82 (s, 3H), 1.23 (t, J=7.0 Hz, 6H)
IIc	133—138 (0.2 mmHg)	91	1730, 1745 (sh)	1525	IIIc	163—166 (0.2 mmHg)	98	3500, 3410	1735	7.13—6.23 (m, 3H), 4.23 (q, J=7.0 Hz, 4H), 3.78 (br, 2H), 1.80 (s, 3H), 1.25 (t, J=7.0 Hz, 6H)
IId	165—170 (0.5 mmHg)	73	1750, 1730 (sh)	1525	IIId	164—167 (0.2 mmHg)	93	3480, 3400	1740 1725 (sh)	7.03—6.37 (m, 3H), 4.23 (q, J=7.0 Hz, 4H), 3.80 (br, 2H), 1.87 (s, 3H), 1.27 (t, J=7.0 Hz, 6H)
IIe	135—138 (0.15 mmHg)	56	1753	1520	IIIe	153—155 (0.2 mmHg)	93	3450, 3370	1725	6.98—6.30 (m, 3H), 4.13 (q, J=7.0 Hz, 4H), 3.40 (br, 2H), 2.05 (s, 3H), 1.70 (s, 3H), 1.20 (t, J=7.0 Hz, 6H)
IIf	165—170 (0.5 mmHg)	61	1735	1525	IIIf	158—160 (0.2 mmHg)	85	3500, 3410	1730	7.57—6.52 (m, 3H), 4.20 (q, J=7.0 Hz, 4H), 3.73 (br, 2H), 1.80 (s, 3H), 1.25 (t, J=7.0 Hz, 6H)
					IIIl	mp 70—71 (Et_2O–Hexane)	79	3460, 3390	2250	7.40—6.63 (m, 4H), 3.67 (br) and 3.53 (s) (4H)

IIb—f and IIIb—f and l: Structural analogues of the corresponding IX (Table I).
a) Yield from the corresponding I. *b*) Yield from the corresponding II.

TABLE V.  Q=NHCOCF$_3$ (compound IV), NHCH$_3$ (compound V); Y=H, CO$_2$Et

Compound IV					Compound V					
Comp. No.	mp (°C) (Recryst. solvent)	Yield[a] (%)	IR $\nu_{max}^{CCl_4}$ cm^{-1} (NH)	IR $\nu_{max}^{CCl_4}$ cm^{-1} (C=O or C≡N)	Comp. No.	Yield[a] (%)	bp or mp (°C) (Recryst. solvent)	IR $\nu_{max}^{CCl_4}$ cm^{-1} (NH)	IR $\nu_{max}^{CCl_4}$ cm^{-1} (C=O or C≡N)	NMR in CCl_4 (δ)
IVb	Oil	100	3430 3320	1740	Vb	90	174—175 (0.2 mmHg)	3430	1725	7.37—6.22 (m, 3H), 4.22 (q, J=7.0 Hz, 4H), 3.67 (br, 1H), 2.78 (s, 3H), 2.22 (s, 3H), 1.83 (s, 3H), 1.25 (t, J=7.0 Hz, 6H)
IVc	Oil	100	3440 3320	1735 1710	Vc	88	Oil[c]	3460	1735	7.13—6.07 (m, 3H), 4.22 (q, J=7.0 Hz, 4H), 3.85 (br, 1H), 2.78 (s, 3H), 1.80 (s, 3H), 1.25 (t, J=7.0 Hz, 6H)
IVd	Oil	98	3440	1740	Vd	93	140—143 (0.1 mmHg)	3430	1730	6.96—6.33 (m, 3H), 4.30 (q, J=7.0 Hz, 4H), 3.52 (br, 1H), 2.82 (s, 3H), 1.88 (s, 3H), 1.27 (t, J=7.0 Hz, 6H)
IVe	Oil	100	3430 3310	1725	Ve	90	Oil[c]	3440	1720	7.20—6.47 (m, 3H), 4.17 (q, J=7.0 Hz, 4H), 3.48 (br, 1H), 2.85 (s, 3H), 2.10 (s, 3H), 1.82 (s, 3H), 1.23 (t, J=7.0 Hz, 6H)
IVf	Oil	89	3420	1740	Vf	87	129—132 (0.1 mmHg)	3440	1730	7.33—6.47 (m, 3H), 4.22 (q, J=7.0 Hz, 4H), 3.53 (br, 1H), 2.87 (s, 3H), 1.87 (s, 3H), 1.27 (t, J=7.0 Hz, 6H)
IVg	Oil	99	3380	1730	Vg	90	Oil[c]	3420	1725	7.17—6.58 (m, 4H), 4.22 (q, J=7.0 Hz, 4H), 2.88 (s, 3H), 1.80 (s, 3H), 1.23 (t, J=7.0 Hz, 6H)
IVi	121—122 (Et_2O–Hexane)	97	3380	1730[b]	Vi	88	113—115 (1 mmHg)	3420	1725	7.08—6.55 (dd, 4H), 4.13 (q, J=7.0 Hz, 2H), 3.48 (s, 2H), 3.10 (br, 1H), 2.80 (s, 3H), 1.22 (t, J=7.0 Hz, 3H)
IVj	Oil	100	3400 3370	1720	Vj	92	129—130 (1 mmHg)	3430	1725	7.27—6.37 (m, 4H), 4.12 (q, J=7.0 Hz, 2H), 3.80—3.13 (m, 3H), 2.80 (s, 3H), 1.20 (t, J=7.0 Hz, 3H)
IVl	115—115.5 (Et_2O–Hexane)	99	3400 3260	2250[b]	Vl	88	75—75.5 (Et_2O–Hexane)	3430	2250	7.40—6.60 (m, 4H), 3.47 (s-like, 3H), 2.87 (s, 3H)

IVb—g, i, j and l and Vb—g, i, j and l: Structural analogues of the corresponding XI (Table II).
a) See the corresponding footnote in Table I. *b*) Measured in Nujol. *c*) Not distillation.

preparation of IIIh to yield 21.4 g (96.4%) of Vh, mp 34—36 °C. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3400 (NH), 1730 (C=O). NMR ($CDCl_3$) δ: 7.20 (2H, aromatic-H), 4.27 (q, J=7.0 Hz, 4H, $-\underline{CH_2}-CH_3 \times 2$), 3.80 (br, 1H, NH), 3.03 (s, 3H, NCH_3), 1.25 (t, J=7.0 Hz, 6H, $-CH_2-\underline{CH_3} \times 2$), 1.80 (s, 3H, $\equiv C-CH_3$).

2-(2-Methylaminophenyl)propionitrile (Vk)——A solution of 13.0 g of IIIk in 20 ml of CH_2Cl_2 was treated with 20.5 g of trifluoroacetic anhydride in the same manner as described for the preparation of IVa to yield 21.5 g (99.3%) of IVk. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3400, 3270 (NH), 2240 (CN), 1740 (C=O). A solution of 10.6 g of IVk in 54 ml of abs. DMF was treated with 8.7 g of CH_3I in the presence of 7.0 g of Na_2CO_3 powder under stirring at room temperature for 2.5 h. Usual work-up of the reaction mixture by successive filtration, evaporation and extraction as described above gave 11.0 g of an oily product. This product was dissolved in a mixture of 56 ml of benzene, 28 ml of DMF and 28 ml of water, and the solution was treated with 144 ml of 4.8% aq. NaOH under stirring at 8 °C for 1 h. The benzene layer was separated, and the mother liquor was extracted repeatedly with benzene. The basic material obtained from the combined benzene solution was worked up as described for the preparation of Va to yield 5.4 g (78.5% based on IIIk) of oily Vk. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3440 (NH), 2230 (CN). NMR (CCl_4) δ: 7.27—6.53 (4H, aromatic-H), *ca.* 3.78 (m, 2H, NH and $>\underline{CH}-CH_3$), 2.85 (s, 3H, NCH_3), 1.58 (d, J=8.0 Hz, 3H, $>CH-\underline{CH_3}$).

Compound Vl was prepared in the same manner. Data for compounds IVb—g, i, j and l and Vb—g, i, j and l are listed in Table V.

Compound VI: Diethyl (4-Hydroxyphenyl)methylmalonate (VIa)——A solution of 7.8 g of $NaNO_2$ in 20 ml of water was added portionwise to a stirred solution containing 29.4 g of IIIa in 370 ml of 7.3% H_2SO_4 over 2 h under nitrogen at 0 °C. After the resulting solution had been stirred for an additional 30 min, 0.6 g of urea was added to decompose the excess reagent, and the resulting diazonium bisulfate solution was then refluxed in the presence of 200 ml of toluene for 15 min with vigorous stirring. After cooling, the separated toluene layer was fractionally distilled to yield 24.0 g (81.3%) of VIa, bp 163 °C (1 mmHg). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3640, 3460 (br) (OH), 1735 (C=O). *Anal.* Calcd for $C_{14}H_{18}O_5$: C, 63.15; H, 6.81; O, 30.04. Found: C, 62.93; H, 6.76; O, 29.82.

Compounds VIb—e and i—l were prepared in the same manner.

Diethyl (3-Chloro-4-hydroxyphenyl)methylmalonate (VIg)——A solution containing 10.0 g of IIIg in 100 ml of 20% H_2SO_4 was treated with a solution of 2.4 g of $NaNO_2$ in 20 ml of water as described above. A mixture of the resulting diazonium bisulfate solution, 100 ml of benzene and a solution of 397.5 g of $Cu(NO_3)_2 \cdot 3H_2O$ in 700 ml of water was vigorously stirred in the presence of 4.5 g of Cu_2O at room temperature for 15 min. After removal of precipitates through filtration, the separated benzene layer was fractionally distilled to yield 4.8 g (47%) of VIg, bp 143—145 °C (1 mmHg). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3540 (OH), 1735 (C=O). *Anal.* Calcd for $C_{14}H_{17}ClO_5$: C, 55.91; H, 5.70; Cl, 11.79. Found: C, 55.99; H, 5.81; Cl, 11.97.

Compound VIf was prepared in the same manner.

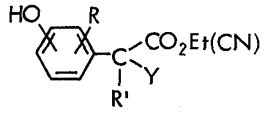
Diethyl (3,5-Dichloro-4-hydroxyphenyl)methylmalonate (VIh)——A solution of 6.4 g of VIa in 8.2 g of freshly distilled sulfuryl chloride was heated at 50—55 °C for 1 h. After cooling, the reaction mixture was poured onto ice water and extracted with benzene. The benzene solution was washed with aq. $NaHCO_3$, and the solvent was evaporated off. Crystallization of the oily product with Et_2O–hexane gave 7.0 g (86.8%) of VIh, mp 93—94 °C. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3560 (OH), 1740 (C=O). *Anal.* Calcd for $C_{14}H_{16}Cl_2O_5$: C, 50.16; H, 4.81; Cl, 21.16. Found: C, 50.06; H, 4.85; Cl, 20.89.

Data for compounds VIb—f and i—l are listed in Table VI.

Ethyl 2-(4-Mercaptophenyl)propionate (VII)——A solution of diazonium chloride [prepared from 15.9 g of IIIa in 20 ml of 20% HCl] was added dropwise to a solution of 14.0 g of potassium xanthogenate in 18 ml of water over 1 h under stirring at 40—50 °C. After cooling, the reaction mixture was made alkaline with NaOH and then extracted with Et_2O. The product (xanthate) obtained from the ether solution was saponified with 14 g of KOH pellets using 60 ml of EtOH as a solvent at 90—100 °C for 7 h. The residue after evaporation of the EtOH was treated with dil. HCl to adjust the pH to 3 and then extracted with Et_2O. The acidic material from the ether solution was dissolved in abs. EtOH, and the solution was refluxed in the presence of a catalytic amount of conc. H_2SO_4 for 8 h. The oily product obtained in a usual manner was distilled to yield 4.6 g (36%) of VII, bp 117 °C (3 mmHg). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 2570 (SH), 1735 (C=O).

Compound IX: 2-[4-(2-Thiazolylamino)phenyl]propionic Acid (IXa)——A solution of benzoylisothiocyanate[15,16] prepared from 7.9 g of benzoyl chloride and 4.9 g of NH_4SCN in 40 ml of acetone was treated with a solution of 14.2 g of IIIa in 35 ml of acetone under stirring at room temperature for 1 h. The residue after evaporation of the solvent was triturated with 50% aq. EtOH to dissolve the inorganic material, and the separated material was recrystallized from EtOH to give 19.7 g (85.6%) of VIIIa, mp 79—80 °C. *Anal.* Calcd for $C_{22}H_{24}N_2O_5S$: C, 61.66; H, 5.65; N, 6.54; S, 7.48. Found: C, 61.64; H, 5.65; N, 6.50; S, 7.51. IR ν_{max}^{Nujol} cm^{-1}: 3350 (NH), 1720 (C=O), 1670 (CON). A mixture of 19.6 g of VIIIa and 200 ml of 10% NaOH was stirred at 98 °C for 10 min. After cooling, the alkaline solution was acidified with dil. HCl and then concentrated under reduced pressure to separate 23.9 g of crude thiourea compound. The resulting product was heated with a mixture of 7.7 g of chloro-diethylacetal, 9.1 ml of 20% HCl and 120 ml of 50% aq. isopropanol under stirring at 90—93 °C for 4 h, then the aqueous solvent was evaporated off. The residual hydrochloride was diluted with 15% HCl and washed with Et_2O to remove a small amount of benzoic acid. The acidic solution was adjusted to pH 4 with $NaHCO_3$, and the separated crystalline substance was recrystallized from MeOH

TABLE VI.



compound VI

Y=H, CO_2Et

Compound VI

Comp. No.	bp or mp (Recryst. solvent) (°C)	Yield[a] (%)	Formula	Analysis (%) Calcd (Found) C	H	N or halogen	IR $\nu_{max}^{CCl_4}$ cm^{-1} (OH)	(C=O or C≡N)
VIb	152—154 (0.1 mmHg)	82	$C_{15}H_{20}O_5$	64.27 (64.31	7.19 7.08)		3580 3430 (br)	1730
VIc	148—151 (0.12 mmHg)	50	$C_{14}H_{17}FO_5$	59.15 (59.28	6.03 6.00	6.68 6.55)	3580 3420 (br)	1735
VId	90 (Et_2O–Hexane)	66	$C_{14}H_{17}ClO_5$	55.91 (56.00	5.70 5.73	11.79 11.85)	3600 3400	1740 1705 (sh)
VIe	150—153 (0.12 mmHg)	82	$C_{15}H_{20}O_5$	64.27 (64.21	7.19 7.15)		3575 3300	1720
VIf	137—139 (0.15 mmHg)	40	$C_{14}H_{17}FO_5$	59.15 (59.20	6.03 5.99	6.68 6.71)	3600 3250	1735
VIi	126—129 (2 mmHg)	77	[b]				3600 3430	1735
VIj	137—139 (1 mmHg)	81	$C_{11}H_{14}O_3$	68.02 (68.11	7.27 7.36)		3570 3280	1730 (sh) 1710
VIk	73—74.5 (Et_2O)	50	C_9H_9NO	73.45 (73.51	6.16 6.25	9.52 9.61)	3600 3370	2230
VIl	118—119 (Benzene)	64	C_8H_7NO	72.16 (72.06	5.30 5.35	10.52 10.71)	3570 3300	2240

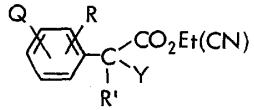
VIb—f and i—l: Structural analogues of the corresponding XIV (Table III).
a) See the corresponding footnote in Table I. *b*) Not analyzed.

to give 9.6 g (72.3% based on IIIa) of IXa, mp 176—177 °C. IR ν_{max}^{Nujol} cm^{-1}: 3250, 3200 (NH), 2440 (br), 1689 (CO_2H).

Compounds IXb—h and IXj were prepared in the same manner.

4-(2-Thiazolylamino)phenylacetic Acid (IXi)——A mixture of 7.9 g of crude thiourea compound [obtained from 5.0 g of IIIi *via* VIIIi as described above], 4.2 g of chloro-diethylacetal and 0.08 g of *p*-toluenesulfonic acid in 70 ml of acetic acid was heated under stirring at 90—95 °C for 4 h. The residual product obtained after evaporation of the solvent was treated with 15% HCl, and the acidic solution was worked up as described for the preparation of IXa to yield a crystalline material, from which 4.6 g (72.4% based on IIIi) of IXi was obtained by recrystallization from acetone, mp 195—197 °C. IR ν_{max}^{Nujol} cm^{-1}: 3260, 3200 (NH), 2360 (br), 1677 (CO_2H).

2-[2-(2-Thiazolylamino)phenyl]propionic Acid (IXk)——A solution of 8.0 g of VIIIk (mp 164—167 °C) obtained from 4.0 g of IIIk in 80 ml of dioxane together with 52.8 ml of 15% HCl was refluxed under stirring overnight. The residue from evaporation of the aqueous solvent was treated with aq. $NaHCO_3$ and then washed with $CHCl_3$. The alkaline solution was acidified to pH 3 with conc. HCl, and then concentrated to separate 5.2 g of crude thiourea compound. A solution of the resulting product in 20 ml of 50% aq. isopropanol together with 2 ml of 20% HCl was refluxed in the presence of 5.1 g of bromo-diethylacetal for 2.5 h, and the aqueous solvent was then evaporated off. The residual product was diluted with 50 ml of 10% HCl and washed with Et_2O to remove benzoic acid. After being made alkaline with $NaHCO_3$, the aqueous solution was treated with $CHCl_3$ to isolate a syrup from which 1.0 g (16.8% based on IIIk) of amide compound was obtained by crystallization from Et_2O–hexane, mp 69—70 °C. IR ν_{max}^{Nujol} cm^{-1}: 1730, 1710 (C=O). *Anal.* Calcd for $C_{12}H_{10}N_2OS$: C, 62.58; H, 4.38; N, 12.17; S, 13.92. Found: C, 62.65; H, 4.19; N, 12.10; S, 14.13. The remaining alkaline solution was acidified to pH 4 with dil. HCl and then extracted with Et_2O. The product from the ether solution was recrystallized from MeOH to yield 0.6 g (9.5% based on IIIk) of

TABLE VII.  Q=–NHCSNHCOPh (compound VIII)

Y=H, CO_2Et

Compound VIII											Compound IX[b]		
Comp. No.	mp (Recryst. from EtOH) (°C)	Yield[a] (%)	Formula	Analysis (%) Calcd (Found)				IR ν_{max}^{Nujol} cm^{-1}			Comp. No.	IR ν_{max}^{Nujol} cm^{-1}	
				C	H	N	S	(NH)	(C=O or C≡N)	(CON)		(NH)	(C=O)
VIIIb	107—108	87	$C_{23}H_{26}N_2O_5S$	62.42 (62.18	5.92 5.81	6.33 6.47	7.25 7.14)	3310	1735 1705 (sh)	1665	IXb	3250	1680
VIIIc	99—100	94	$C_{22}H_{23}FN_2O_5S$	59.18 (59.32	5.19 5.23	6.27 6.31	7.18 7.30)	3350	1705	1670	IXc	3270 3210	1690
VIIId	100—101	85	$C_{22}H_{23}ClN_2O_5S$	57.07 (57.15	5.01 5.13	6.05 6.00	6.93 6.73)	3350	1735 1710 (sh)	1670	IXd	3200	1690
VIIIe	103—104	89	$C_{23}H_{26}N_2O_5S$	62.42 (62.65	5.92 6.10	6.33 6.21	7.25 7.04)	3250	1755 (sh) 1725	1670	IXe	3210 3100	1685
VIIIf	100—101	92	$C_{22}H_{23}FN_2O_5S$	59.18 (59.28	5.19 5.33	6.27 6.01	7.18 7.31)	3310	1730	1670	IXf	3200	1690
VIIIg	113—114	84	$C_{22}H_{23}ClN_2O_5S$	57.07 (57.35	5.01 4.76	6.05 6.01	6.93 6.98)	3350	1730 (sh) 1720	1670	IXg	3200	1690
VIIIh	144—145	87	$C_{22}H_{22}Cl_2N_2O_5S$	53.12 (53.09	4.46 4.42	5.63 5.77	6.45 6.44)	3350	1735 1720 (sh)	1670	IXh	3200	1700
VIIIi	140—141	93	$C_{18}H_{18}N_2O_3S$	63.14 (63.28	5.30 5.21	8.18 8.01	9.36 9.22)	3410 3150 (sh)	1725	1650	IXi	3260 3200	1677
VIIIj	81—82	92	$C_{19}H_{20}N_2O_3S$	64.02 (63.91	5.66 5.54	7.86 7.96	9.00 8.86)	3360	1725	1670	IXj	3270 3220	1680
VIIIk	164—167	95	$C_{17}H_{15}N_3OS$	65.99 (66.13	4.89 4.96	13.58 13.44	10.36 10.25)	3175	2240	1680	IXk	3210	1664
VIIIl	135—136	98	$C_{16}H_{13}N_3OS$	65.01 (65.12	4.44 4.38	14.23 14.41	10.86 10.75)	3280 3100	2230	1660	IXl	3160	1690

VIIIb—l: Structural analogues of the corresponding IX (Table I).
a) See the corresponding footnote in Table I. *b*) See Table I.

IXk, mp 119—120 °C. IR ν_{max}^{Nujol} cm^{-1}: 3210 (NH), 2460 (br), 1664 (CO_2H).

Compound IXl was prepared in the same manner. Data for compounds VIIIb—l and IXb—l are listed in Table VII.

Compound XI: 2-[3,5-Dichloro-4-(*N*-methyl-*N*-thiazol-2-ylamino)phenyl]propionic Acid (XIh)——A solution of benzoylisothiocyanate[15,16] [prepared from 4.1 g of benzoyl chloride and 2.3 g of NH_4SCN in 64 ml of acetone] was treated with 6.4 g of Vh under stirring at room temperature for 1 h. The residue after evaporation of the solvent was treated with benzene and then washed with 10% HCl. The benzene layer was diluted with hexane to about three times the original volume and then chromatographed on 19 g of silica gel with hexane as the eluting solvent. After removal of excess reagent, further elution with benzene gave 9.3 g (98.9%) of oily Xh. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3480, 3400, 3270 (NH), 1730, 1710 (C=O). A solution of Xh in 93 ml of 50% aq. MeOH was refluxed in the presence of 2.8 g of K_2CO_3 under stirring for 9 h. The syrup obtained after evaporation of the MeOH was made acidic with dil. HCl and then washed with Et_2O, and the acid solution was evaporated to dryness under reduced pressure. The resulting material was triturated with acetone to separate the inorganic component, and the acetone solution was concentrated to give 7.3 g of crude methylthiourea compound. A solution of the compound in 73 ml of 30% aq. isopropanol was heated with 3.4 g of chloro-diethylacetal in the presence of 1.5 ml of 20% HCl under stirring at 90—95 °C for 6 h. The reaction mixture was worked up as described for the preparation of IXa to give a crystalline material, from which 4.7 g (78% based on Vh) of XIh was obtained by recrystallization from Et_2O, mp 180—181 °C. IR ν_{max}^{Nujol} cm^{-1}: 2560 (br), 2475 (br), 1713 (CO_2H).

Compounds XIa—g and XIi—j were prepared in the same manner.

2-[2-(*N*-Methyl-*N*-thiazol-2-ylamino)phenyl]propionic Acid (XIk)——A solution of 8.1 g of crude methylthiourea compound [obtained from 6.0 g of Vk *via* Xk as described above] in 45 ml of acetic acid was heated with 6.8 g of bromo-diethylacetal in the presence of 0.1 g of *p*-toluenesulfonic acid under stirring at 90—92 °C for 8 h. After evaporation of the solvent together with excess reagent, the residual product was heated with 100 ml of 10% HCl at 90—92 °C for 3 h to complete hydrolysis of the cyano group. The resulting solution was worked up as described for the preparation of IXa to give a crystalline substance from which 4.2 g (51.8% based on Vk) of XIk was obtained by recrystallization from Et_2O–hexane, mp 173—174 °C. IR ν_{max}^{Nujol} cm^{-1}: 2640 (br), 1713 (CO_2H).

Compound XIl was prepared in the same manner. Data for compounds Xa—g, and i—l and XIa—g and i—l are listed in Table VIII.

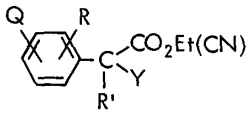
Compound XIV: 2-[4-(2-Thiazolyloxy)phenyl]propionic Acid (XIVa)——A solution of 5.0 g of VIa and 1.9 g of triethylamine in 70 ml of abs. Et_2O was added portionwise to a solution of 2.2 g of cyanogen bromide in 40 ml of abs. Et_2O over 20 min under stirring at −10 °C, and the stirring was continued for 1 h. After removal of a small amount of precipitate by filtration, evaporation of the solvent gave 5.5 g (quantitative yield) of XIIa. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 2270 (sh), 2255, 2230 (sh) (CN), 1735 (C=O). H_2S was bubbled through a solution of XIIa in 150 ml of abs. Et_2O for 50 min in the presence of a catalytic amount of triethylamine under stirring at room temperature, and the solvent was then evaporated off. The residual product was treated with hexane to separate 5.8 g (94.9%) of XIIIa, mp 65—69 °C. Recrystallization of the product from $CHCl_3$–hexane raised the melting point to 78—82 °C. *Anal.* Calcd for $C_{15}H_{19}NO_5S$: C, 55.37; H, 5.89; N, 4.31; S, 9.86. Found: C, 55.51; H, 5.92; N, 4.13; S, 9.57. IR ν_{max}^{Nujol} cm^{-1}: 3350, 3270, 3170 (NH_2), 1760 (sh), 1725 (C=O). A solution of 4.0 g of XIIIa, 2.3 g of chlorodiethylacetal and 0.04 g of *p*-toluenesulfonic acid in 20 ml of acetic acid was heated under stirring at 90—95 °C for 1.5 h. After evaporation of the solvent, the oily product was taken up with benzene and the solution was washed with 1 N NaOH. The benzene solution was chromatographed on 10 g of silica gel and eluted with benzene to give 3.6 g (85.3%) of oily thiazolyloxy compound. NMR ($CDCl_3$) δ: 7.62—7.18 (m, 5H, aromatic-H and thiazole-C_4–H), 6.85 (d, J=3.7 Hz, 1H, thiazole-C_5–H), 4.25 (q, J=7.0 Hz, 4H, $-\underline{CH_2}-CH_3 \times 2$), 1.87 (s, 3H, $\equiv C-CH_3$), 1.25 (t, J=7.0 Hz, 6H, $-CH_2-\underline{CH_3} \times 2$). A solution of this compound and 1.6 g of K_2CO_3 in 36 ml of 50% aq. MeOH was refluxed overnight under stirring, then the MeOH was evaporated off. After being washed with CH_2Cl_2, the resulting aqueous solution was brought to pH 4 with 10% HCl, and the separated crystalline material was recrystallized from dichloroethane to yield 2.5 g (74.1% based on VIa) of XIVa, mp 121—122 °C. IR ν_{max}^{Nujol} cm^{-1}: 2520 (br), 1715 (CO_2H).

Compounds XIVb—j were similarly prepared but with a slightly modified hydrolysis procedure in the last step as described below.

2-[2-(2-Thiazolyloxy)phenyl]propionic Acid (XIVk)——A solution of 5.3 g of XIIIk [mp 87—88 °C; obtained from 4.6 g of VIk as described above], 4.7 g of chloro-diethylacetal and 0.09 g of *p*-toluenesulfonic acid in 53 ml of acetic acid was heated under stirring at 90—95 °C for 1.5 h. The oily product (4.4 g) obtained after evaporation of the solvent followed by chromatographic separation with benzene as the eluting solvent was dissolved in 45 ml of abs. MeOH, and gaseous HCl was bubbled through the methanolic solution over a 3 h period at 55 °C. After the saturated solution had been kept standing overnight at room temperature, the solvent was evaporated off, and the residual ester was hydrolyzed with a mixture of 40 ml of 5% aq. NaOH and 40 ml of MeOH at 40 °C for 3 h. The resulting alkaline solution was worked up as described for the preparation of XIVa to provide a crystalline material from which 2.4 g (29.6% based on VIk) of XIVk was obtained by recrystallization from isopropyl ether, mp 81—82 °C. IR ν_{max}^{Nujol} cm^{-1}: 2665 (br), 2530 (br), 1710 (CO_2H).

Compound XIVl was prepared in the same manner. Data for compounds XIIb—j and l and XIIIb—j and l are

TABLE VIII.



Y=H, CO_2Et Q=–N(CH3)CSNHCOPh (compound X)

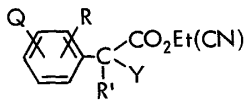
Compound X					Compound XI[b]	
Comp. No.	mp (Recryst. solvent) (°C)	Yield[a] (%)	IR $\nu_{max}^{CHCl_3}$ cm^{-1} (NH)	IR $\nu_{max}^{CHCl_3}$ cm^{-1} (C=O, C≡N)	Comp. No.	IR ν_{max}^{Nujol} cm^{-1} (CO_2H)
Xa	Oil	98	3380	1725 1705	XIa	2500 (br), 1700
Xb	Oil	96	3380	1725 1705	XIb	2500 (br), 1700
Xc	Oil	96	3380	1725 1700	XIc	2500 (br), 1700
Xd	Oil	93	3380	1740 1720 1700	XId	2500 (br), 1695
Xe	Oil	97	3345	1720 1695	XIe	2450 (br), 1700
Xf	Oil	97	3310	1740 1715 (sh) 1700	XIf	2500 (br), 1720
Xg	Oil	99	3380	1720 1700	XIg	2450 (br), 1710
Xi	Oil	97	3260	1725 1670	XIi	2500 (br), 1715
Xj	139—140 ($CHCl_3$–Hexane)	94	3320	1730 1685	XIj	2450 (br), 1710
Xk	71—73 (Et_2O–Hexane)	70	3360	2225 1695	XIk	2640 (br), 1713
Xl	151—152 (EtOH)	92	3400	2230 1680	XIl	2500 (br), 1700

Xa—g and i—l: Structural analogues of the corresponding XI (Table II).
a) See the corresponding footnote in Table II. *b*) See Table II.

listed in Tables IX and X.

2-[4-(2-Thiazolylthio)phenyl]propionic Acid (XVII)——A solution of 4.1 g of SO_2Cl_2 in 63 ml of CCl_4 was added dropwise over 1 h to a solution of 6.3 g of VII in 63 ml of CCl_4 containing a catalytic amount of triethylamine under stirring at −10——15 °C, and the stirring was continued for 30 min. The residue (7.4 g) obtained after evaporation of the solvent was dissolved in 30 ml of acetonitrile, and the solution was treated with a solution of 3.2 g of trimethylsilyl cyanide in 30 ml of CCl_4 under stirring at room temperature for 1 h. Evaporation of the solvent gave 6.9 g (97.4% based on VII) of oily thiocyanate (XV). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 2160 (CN), 1735 (C=O). H_2S was bubbled for 1 h through a solution of XV in 70 ml of abs. Et_2O containing 0.2 g of triethylamine under stirring at 10—20 °C. The residue after evaporation of the solvent was chromatographed on 15 g of silica gel and eluted with benzene to separate 5.3 g (66.8%) of a dithiocarbamate (XVI), mp 55—60 °C. Purification through preparative HPLC on a Lobar column (type B) with benzene–AcOEt (10:1) as the eluting solvent followed by recrystallization from Et_2O–hexane raised the melting point to 68—69 °C. *Anal.* Calcd for $C_{12}H_{15}NO_2S_2$: C, 53.50; H, 5.61; N, 5.20; S, 23.81. Found: C, 53.75; H, 5.61; N, 5.13; S, 23.56. IR ν_{max}^{Nujol} cm^{-1}: 3375, 3240, 3175 (NH_2), 1735 (C=O). A solution of 3.6 g of XVI in 25 ml of acetic acid was treated with 2.0 g of chloro-diethylacetal in the presence of 0.04 g of *p*-toluenesulfonic acid under

TABLE IX.



Y=H, CO_2Et

Q=–OCN (compound XII)
–$OCSNH_2$ (compound XIII)

Compound XII				Compound XIII										
Comp. No.	Yield[a] (%)	IR $\nu_{max}^{CCl_4}$ cm^{-1} (C≡N)	(C=O)	Comp. No.	mp (°C)	Recryst. solvent	Yield[a] (%)	Formula	Analysis (%) Calcd (Found) C	H	N	S	IR ν_{max}^{Nujol} cm^{-1} (NH_2)	(C=O or C≡N)
XIIb	100	2270 2250 2220	1725	XIIIb	96—97	Isopropyl-ether–Hexane	82	$C_{16}H_{21}NO_5S$	56.62 (56.41	6.24 6.21	4.13 4.36	9.45 9.57)	3410, 3240 3380 (sh), 3160	1740 1720 (sh)
XIIc	100	2260 2230	1735 1745 (sh)	XIIIc	90—91	Et_2O–Hexane	85	$C_{15}H_{18}FNO_5S$	52.47 (52.58	5.28 5.31	4.08 4.21	9.34 9.17)	3330, 3280 3170	1735 1715 (sh)
XIId	97	2280 2240	1740	XIIId	89—90	Et_2O–Hexane	88	$C_{15}H_{18}ClNO_5S$	50.07 (49.88	5.04 4.83	3.89 3.79	8.91 9.18)	3330, 3280, 3160	1740
XIIe	100	2260 2240 2220	1725	XIIIe	103—105	Et_2O–Hexane	92	$C_{16}H_{21}NO_5S$	56.62 (56.35	6.24 6.25	4.13 4.43	9.45 9.68)	3360, 3270, 3170	1715

XIIf	100	2260 1740		XIIIf	83—84	Et_2O–Hexane	47	$C_{15}H_{18}FNO_5S$	52.47 (52.65	5.28 5.46	4.08 4.12	9.34 9.49)	3440, 3380 3190	1735
XIIg	100	2280 2250 2200 1730		XIIIg	98—100	Et_2O–Hexane	91	$C_{15}H_{18}ClNO_2S$	50.07 (50.21	5.04 4.93	3.89 3.98	8.91 9.05)	3370, 3275, 3180	1720
XIIh	100	2250 2200 1735		XIIIh	Unstable oil		65	[b]					3500, 3370, 3330	1735[d]
XIIi	100	2270 2250 2230 1735		XIIIi	114—117	Et_2O–Hexane	93	$C_{11}H_{13}NO_3S \cdot 1/4C_6H_{14}$	57.56 (57.35	6.37 6.06	5.37 5.26	12.29 12.11)	3330, 3255, 3150	1735
XIIj	98	2270 2250 2230 1735		XIIIj	Oil[c]		87	$C_{12}H_{15}NO_3S$	56.89 (56.60	5.97 6.14	5.53 5.31	12.66 12.53)	3500, 3480, 3170	1725[d]
XIIk	99	2270 2250 2210		XIIIk	87—88	$CHCl_3$	81	$C_{10}H_{10}N_2O_2S$	58.23 (58.10	4.89 4.73	13.58 13.62	15.55 15.48)	3425, 3290, 3170	2240
XIIl	100	2270 2250 2230		XIIIl	130—132.5	$CHCl_3$	74	$C_9H_8N_2O_2S$	56.23 (56.32	4.17 3.97	16.68 16.63	14.57 14.74)	3330, 3275, 3170	2240

XIIb—l, XIIIb—l and thiazolyloxy crop b—l: Structural analogues of the corresponding XVI (Table III).
a) See the corresponding footnote in Table I. *b*) Not analyzed.
c) Purified by HPLC (Lobon column type B) benzene–AcOEt (9 : 1). *d*) Measured in $CHCl_3$.

TABLE X. 2-Thiazolyloxyarylacetic Acid Derivatives

Thiazolyloxy compounds		Compound XIV[b]	
Yield[a] (%)	NMR in $CDCl_3$ (δ)	Comp. No.	IR ν_{max}^{Nujol} cm^{-1} (CO_2H)
b 88	7.32—7.03 (m, 4H), 6.80 (d, J=3.7 Hz, 1H), 4.25 (q, J=7.0 Hz, 4H), 2.28 (s, 3H), 1.87 (s, 3H), 1.27 (t, J=7.0 Hz, 6H)	XIVb	2500 (br), 1692
c 87	7.38—6.87 (m, 4H), 6.82 (d, J=3.7 Hz, 1H), 4.23 (q, J=7.0 Hz, 4H), 1.85 (s, 3H), 1.27 (t, J=7.0 Hz, 6H)	XIVc	2500 (br), 1705
d 85	7.58—7.25 (m, 3H), 7.18 (d, J=3.7 Hz, 1H), 6.85 (d, J=3.7 Hz, 1H), 4.22 (q, J=7.0 Hz, 4H), 1.85 (s, 3H), 1.25 (t, J=7.0 Hz, 6H)	XIVd	2550 (br), 1700
e 89	7.43—6.83 (m, 4H), 6.77 (d, J=3.7 Hz, 1H), 4.27 (q, J=7.0 Hz, 4H), 2.27 (s, 3H), 1.87 (s, 3H), 1.25 (t, J=7.0 Hz, 6H)	XIVe	2520 (br), 1725
f 88	7.53—7.18 (m, 4H), 6.83 (d, J=3.7 Hz, 1H), 4.27 (q, J=7.0 Hz, 4H), 1.85 (s, 3H), 1.25 (t, J=7.0 Hz, 6H)	XIVf	2550 (br), 1708
g 80	7.63—7.25 (m, 3H), 7.18 (d, J=3.7 Hz, 1H), 6.72 (d, J=3.7 Hz, 1H), 4.23 (q, J=7.0 Hz, 4H), 1.87 (s, 3H), 1.27 (t, J=7.0 Hz, 6H)	XIVg	2500 (br), 1705
h 16	7.50 (s, 2H), 7.23 (d, J=3.7 Hz, 1H), 6.88 (d, J=3.7 Hz, 1H), 4.27 (q, J=7.0 Hz, 4H), 1.85 (s, 3H), 1.27 (t, J=7.0 Hz, 6H)	XIVh	2500 (br), 1725
i 66	7.50—7.08 (m, 5H), 6.78 (d, J=3.7 Hz, 1H), 4.12 (q, J=7.0 Hz, 2H), 3.58 (s, 2H), 1.23 (t, J=7.0 Hz, 3H)	XIVi	2520 (br), 1720
j 67	7.57—7.02 (m, 5H), 6.80 (d, J=3.7 Hz, 1H), 4.10 (q, J=7.0 Hz, 2H), 3.70 (q, J=7.0 Hz, 1H), 1.47 (d, J=7.0 Hz, 3H), 1.18 (t, J=7.0 Hz, 3H)	XIVj	2500 (br), 1710
k 75	7.40—7.18 (m, 5H), 6.87 (d, J=3.7 Hz, 1H), 4.22 (q, J=7.0 Hz, 1H), 1.60 (d, J=7.0 Hz, 3H)	XIVk	2665 (br), 1710 2530 (br)
l 68	7.67—7.20 (m, 5H), 6.87 (d, J=3.7 Hz, 1H), 3.80 (s, 2H)	XIVl	2550 (br), 1722

a) Yield from the corresponding XIII. *b*) See Table III.

stirring at 90—95 °C for 2 h. The thiazolylthio compound obtained after evaporation of the solvent followed by chromatographic separation of the residue on 7 g of silica gel with benzene as the eluting solvent was treated with a mixture of 14 ml of 20% aq. KOH and 14 ml of EtOH at room temperature for 2 h. The resulting alkaline solution was worked up as described for the preparation of XIVa to separate a crystalline material from which 2.0 g (36.6% based on VII) of XVII was obtained by recrystallization from Et_2O–hexane, mp 85—87 °C. IR ν_{max}^{Nujol} cm^{-1}: 2535 (br), 1715 (CO_2H).

2-Phenoxythiazole (XXI) from Isothiocyano-diethylacetal[20]——A mixture of 53.7 g of phenol and 10.0 g of isothiocyano-diethylacetal was stirred in the presence of 6.1 g of triethylamine at room temperature for 3 d. The reaction mixture was diluted with benzene and then washed with 1 N HCl. The residue after evaporation of the solvent together with excess reagent was treated with hexane to separate 11.3 g of a crystalline product. This product was purified by preparative HPLC on a Lobar column (size C) with $CHCl_3$–AcOEt (10 : 1) as the eluting solvent followed by recrystallization from isopropanol–Et_2O to give 9.2 g (60%) of XXII, mp 85—86 °C. *Anal.* Calcd for $C_{13}H_{19}NO_3S$: C, 57.97; H, 7.11; N, 5.20; S, 11.90. Found: C, 57.84; H, 7.13; N, 5.20; S, 11.94. IR ν_{max}^{Nujol} cm^{-1}: 3230 (NH). NMR ($CDCl_3$) δ: 7.38—6.95 (m, 6H, aromatic-H and NH), 4.70 (t, J=5.0 Hz, , 1H, –CH<), 3.92—3.42 (m, 6H, $-CH_2-\times 3$), 1.25 (t, J=7.0 Hz, 6H, $-CH_2-\underline{CH_3}\times 2$). A mixture of 5.0 g of XXII and 8.0 g of *p*-toluenesulfonic acid was stirred in 100 ml of abs. Et_2O under ice-cooling for 2 h. After removal of the solvent by decantation, the syrup was made alkaline with 10% NaOH and then extracted with benzene. The oily product from the benzene solution was purified through preparative HPLC using the same system as described above to yield 3.5 g (83%) of XXIII. A solution of 3.0 g of XXIII in 6 ml of conc. H_2SO_4 was heated at 97—100 °C under stirring for 3 h, and then cooled. The resulting solution was poured onto ice water, the aqueous solution was made alkaline with NaOH and then extracted with benzene. Evaporation of the benzene layer gave 2.3 g (97%) of XXI, which showed bp 84—85 °C (1 mmHg). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1508, 1460 (thiazole). NMR ($CDCl_3$) δ: 7.37 (5H, benzene ring-H), 7.10 (d, J=3.7 Hz, 1H, thiazole-C_4–H), 6.70 (d, J=3.7 Hz, 1H, thiazole-C_5–H).

2-Phenoxythiazole (XXI) from *O*-Phenyl Thiocarbamate (XVIII)[18]——A solution of 0.90 g of XVIII, 0.70 g of chlorodiethylacetal and 0.005 g of *p*-toluenesulfonic acid in 4.5 ml of acetic acid–Et_2O (1 : 4) was treated under stirring at room temperature for 3 d. The resulting solution was diluted with Et_2O and then made alkaline with K_2CO_3 (powder) under ice-cooling. The crude product obtained after removal of the precipitate by filtration, followed by evaporation of the solvent, was worked up by preparative HPLC on a Lobar column (type B) with benzene–AcOEt (12 : 1) as the eluting solvent to separate 0.30 g (19.4%) of unstable halo-compound (XIX), which was used immediately for the next reaction. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3370 (NH), 1470 (–N=C=S). NMR (CCl_4) δ: 7.53—6.87 (m, 6H, aromatic-H and NH), 5.80 (m, 1H, –CH=), 3.68—3.50 (m, 4H, $-CH_2-$), 1.25 (t, J=7.0 Hz, 3H, $-CH_2-\underline{CH_3}$). A mixture of 0.20 g of XIX and 0.17 g of K_2CO_3 (powder) was stirred in 2 ml of acetonitrile at room temperature for 3 h. After removal of the precipitate and solvent, the oily material was purified through preparative HPLC using the same system as described above to give 0.15 g (87.2%) of XX. *Anal.* Calcd for $C_{11}H_{13}NO_2S$: C, 59.17; H, 5.87; N, 6.27; S, 14.36. Found: C, 59.24; H, 5.97; N, 6.03; S, 14.29. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1625 (C=N). NMR (CCl_4) δ: 7.53—6.93 (m, 5H, aromatic-H), 5.47 (m, 1H, =CH–), 3.93—3.13 (m, 4H, $-CH_2-\times 2$), 1.17 (t, J=7.0 Hz, 3H, $-CH_2-\underline{CH_3}$). A solution of 0.50 g of XX in 5 ml of DMF was heated in the presence of a catalytic amount of *p*-toluenesulfonic acid at 125—130 °C for 10 min. The residue after evaporation of the solvent was treated with benzene and aq. NaOH. The benzene solution was chromatographed on 2 g of silica gel with benzene as the eluting solvent to yield 0.38 g (96%) of XXI. The IR and NMR spectra were identical with those of authentic XXI prepared in the above experiment.

References

1) Y. Sawa, J. Irisawa, and R. Maeda, Ger. Offen. 2030981 (1971) [*Chem. Abstr.*, **75**, 5491*u* (1971)]. U.S. Patent 3707470 (1972).
2) J. M. Sprague and A. H. Land, "Heterocyclic Compounds," Vol. V, ed. by R. C. Elderfield, John Wiley and Sons, Inc., New York, 1957, p. 484.
3) R. Maeda and K. Hirose, Ger. Offen. 2450617 (1975) [*Chem. Abstr.*, **83**, 79232*x* (1975)]. U.S. Patent 4025528 (1977).
4) R. W. J. Carney, J. J. Chart, R. Goldstein, N. Howie, and J. Wojtkunski, *Experientia*, **29**, 938 (1973).
5) B. Dumaitre, A. Fouquet, C. Perrin, P. J. Cornu, A. Boucherle, C. Plotka, G. Domage, and G. Streichenberger, *Eur. J. Med. Chem.*, **14**, 207 (1979).
6) M. K. Saikel, "Organic Syntheses," Coll. Vol. III, ed. by E. C. Horning, John Wiley and Sons, Inc., New York, 1955, p. 262.
7) H. Miyamatsu, S. Ueno, M. shimizu, J. Hosono, M. Tomari, K. Seida, T. Suzuki, and J. Wada, *J. Med. Chem.*, **17**, 491 (1974).
8) R. A. W. Johnstone, D. W. Payling, and C. Thomas, *J. Chem. Soc.* (*C*), **1969**, 2223.
9) A. L. Wilds and W. R. Biggerstaff, *J. Am. Chem. Soc.*, **67**, 789 (1945).
10) T. Cohen, A. G. Dielz, Jr., and J. R. Miser, *J. Org. Chem.*, **42**, 2053 (1977).
11) D. S. Tarbell, J. W. Wilson, and P. E. Fanta, "Organic Syntheses," Coll. Vol. III, ed. by E. C. Horning, John Wiley and Sons, Inc., New York, 1955, p. 267.
12) H. F. Wilson and D. S. Tarbell, *J. Am. Chem. Soc.*, **72**, 5203 (1950). (D. S. Tarbell and D. K. Fukushima, "Organic Syntheses," Coll. Vol. III, ed. by E. C. Horning, John Wiley and Sons, Inc., New York, 1955, p. 809.)
13) F. Kurzer, "Organic Syntheses," Coll. Vol. IV, ed. by N. Rabjohn, John Wiley and Sons, Inc., New York, 1963, p. 180.
14) S. N. Sawhney, S. K. Arova, J. V. Singh, O. P. Bansal, and S. P. Singh, *Indian J. Chem.*, **16B**, 605 (1978).
15) I. B. Douglass and F. B. Dains, *J. Am. Chem. Soc.*, **56**, 1408 (1934).
16) R. L. Frank and P. V. Smith, "Organic Syntheses," Coll. Vol. III, ed. by E. C. Horning, John Wiley and Sons, Inc., New York, 1955, p. 735.
17) E. Vowinkel and H. J. Baese, *Chem. Ber.*, **107**, 1213 (1974).
18) E. Grigat and R. Pütter, *Chem. Ber.*, **97**, 3022 (1964).
19) D. N. Harpp, B. T. Friedlander, and R. A. Smith, *Synthesis*, **1979**, 181.
20) J. C. Jochims and A. Seeliger, *Angew. Chem. Int. Ed. Engl.*, **6**, 174 (1967).
21) R. W. Bost and E. R. Andrews, *J. Am. Chem. Soc.*, **65**, 900 (1943).
22) A. Lawson and C. E. Searle, *J. Chem. Soc.*, **1957**, 1956.
23) C. A. Winter, E. A. Rsiley, and G. W. Nuss, *Proc. Soc. Exp. Biol. Med.*, **111**, 544 (1962).
24) R. Kostar, M. Anderson, and E. J. Dobber, *Fed. Proc.*, **22**, 248 (1963).
25) C. I. Bliss, *Quart. J. Year Book Pharm.*, **11**, 192 (1938).