[CONTRIBUTION FROM THE WELLCOME RESEARCH LABORATORIES]

Hantzsch's Pyridine Synthesis

BY ARTHUR P. PHILLIPS

The Hantzsch pyridine synthesis[1] has been run using cinchoninaldehyde,[2] *m*-nitrobenzaldehyde, *p*-dimethylamino- and *p*-diethylaminobenzaldehydes as the aromatic aldehydic reactants, and with a variety of alkyl acetoacetates as the ester components. The first products obtained by this synthesis were all of the normal dihydropyridine type, and manifested weak analgesic and curare-like activities in laboratory animals.

A series of quaternary salts has been prepared from each of the original basic Hantzsch products (including the *m*-aminophenyl ones obtained by reduction of the *m*-nitrophenyl derivatives) by the addition of alkyl halides to the quinoline (or aminophenyl) nitrogen, (the dihydropyridine nitrogen being relatively non-basic[1,3]) hoping in this way to attain products with increased water solubility and enhanced curariform activity. The correlation of curare-like activity with quaternary ammonium salt structure represents one of the oldest and best examples of a relationship between chemical constitution and physiological action.

Many of the quaternary ammonium iodides were very sparingly soluble in water and some of the more active substances were converted to different salts, chlorides and ethanesulfonates, by reaction with the appropriate silver salts. The chlorides so obtained were not significantly more soluble in water than the iodides, but the ethanesulfonates were very readily soluble.

The chlorides, obtained from analytically pure iodides with silver chloride, after careful purification by repeated recrystallizations gave consistently low analyses for carbon, though the hydrogen, nitrogen and chloride results agreed well with the calculated figures.

Attempts at catalytic hydrogenations of I, Table I, with the object of reducing the dihydropyridine ring to a piperidine ring, using either palladium charcoal or Adams catalyst and hydrogen at three atm. overpressure, and temperatures from 30–70°, gave back only the unchanged starting material.

The pronounced steric hindrance to be expected in the quinoline dihydropyridine I, Table I, was confirmed by the almost complete lack of hydrolysis of the carbethoxy groups during prolonged refluxing with either aqueous or alcoholic alkali. Furthermore, treatment of the diethyl ester, I, Table I, with excess methanol containing hydrogen chloride gave no evidence of ester interchange. Resistance to saponification in this type of compound was reported by Hantzsch[1] in his original studies, and is surprising only because the true pyridine derivatives, resulting on mild oxidation of the dihydropyridines, are smoothly saponified by alcoholic alkali, even though steric effects of a similar order of magnitude should prevail here, too.

It is felt that the physiological activity observed in this series may be related to the particular steric structure involved here. Because of the saturated nature of the 4-carbon of the dihydropyridine ring to which the quinoline ring is attached the quinoline and dihydropyridine rings will be non-coaxial. Because of the substitution *ortho* to the 4-position of the pyridine ring of quinoline and the *di-ortho* substitution with respect to the 4-position of the dihydropyridine nucleus (by carbethoxy groups buttressed by methyl groups) free rotation about the quinoline-dihydropyridine juncture would be restricted to a marked degree (as in various *ortho*-substituted biphenyls) and the two rings would be distorted still further from anything approaching coplanarity by rotation of one ring about its not quite coaxial axis to the extent of approximately 90°. This property of non-coplanarity of rings is a feature held in common with morphine.

The *m*-nitrophenyl derivatives were reduced rapidly by Adams catalyst and hydrogen to the free primary aminophenyl compounds. The aminophenyldihydropyridines on treatment with excess alkyl iodide (methyl or ethyl) in the presence of potassium carbonate, to neutralize the hydrogen iodide formed, gave in nearly all cases the quaternary ammonium salt directly. In one case alkylation of the aminophenyl with ethyl iodide gave as the principal product the tertiary amine, the diethylaminophenyl compound VIII, Table II, which was then purified and subsequently converted to quaternary salts IX and XI, Table II, with methyl iodide and ethyl iodide in separate experiments.

The aminophenyl dihydropyridine V, Table II (R = C_2H_5) when heated for some time with acetonylacetone gave the 4-(3′-(2″,5″-dimethylpyrryl-1″)-phenyl) dihydropyridine XII, Table II.

Reaction of the *p*-dimethylaminophenyl compounds with a series of alkyl (methyl through *n*-butyl) iodides gave excellent yields of the corresponding quaternary salts. With the *p*-diethylaminophenyl series, as might be expected, the alkyl iodides above methyl iodide reacted very much more slowly, if at all, because of enhanced steric hindrance. Yields with these higher iodides were usually much poorer and in certain

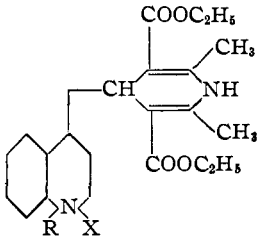
(1) Hantzsch, *Ann.*, **215**, 1 (1882), and many papers thereafter.

(2) (a) Phillips and Randall, U. S. Patent 2,359,329; (b) Heilbron, *et al.*, *J. Chem. Soc.*, 413 (1943).

(3) Hantzsch, *Ber.*, **18**, 2579 (1885).

TABLE I

COMPOUNDS DERIVED FROM THE HANTZSCH PYRIDINE SYNTHESIS USING CINCHONINALDEHYDE



Compd.	R X	Yield, %	M. p., °C.[a]	Crystn. solvent[b]	Analyses, % Calcd. C	Calcd. H	Found C	Found H
I	None	60	203–204	A	69.47	6.37	69.44	6.65
II	HCl	60	273	A	63.31	6.04	63.47	6.29
III	None[c]	100	122–123	H	69.86	5.86	69.86	5.87
IV	None[d]	65	234–235	Æ. H	68.14	5.74	68.13	5.79
V	CH_3I	92	248–249	M. E.	52.85	5.21	52.75	5.12
VI	C_2H_5I	71	248–250 (dec.)	M. E.	53.71[e]	5.45	53.42	5.46
VII	$C_6H_5CH_2Cl$	77	245	M. E.	63.68	6.18	68.30	5.98
VIII	$C_6H_5CH_2OSO_2C_2H_5 \cdot H_2O$	93	155–156	AqAcE	62.18	6.40	62.90	6.44
IX	$BrCH_2COOC_2H_5$	73	206–207	A. E.	57.01	5.70	57.19	5.78

[a] All melting points are uncorrected. [b] A = ethanol; Æ = ethyl acetate; Aq = water; Ac = acetone; E = ether; H = hexane; M = methanol. [c] True pyridine structure obtained by nitric oxidation of I. [d] Dimethyl ester. [e] Calcd.: I, 23.69. Found: I, 23.68.

cases some side-product of the original tertiary amine hydroiodide resulted.

Curare-like action seems to be enhanced, within these series, by accumulation of large alkyl groups both on the quaternary nitrogen and in the ester positions. Interest in these types of compounds has diminished with the noting of undesirable side effects during clinical trials, and with the advent of new and more potent drugs in the fields for which these were being evaluated.

Experimental

Most of these compounds were made by more or less uniform procedures. Thus experimental details are supplied for only one representative of a particular type of compound, while pertinent data for all are included in Tables I–III.

Part I (Table I)

Preparation of the Dihydropyridine, I.—(A) One mol of cinchoninaldehyde and two mols of acetoacetic ester were dissolved in an equal volume of ethyl alcohol. Two mols of concentrated aqueous ammonia were added and the mixture was heated for two hours on the steam-bath. Cooling of the reaction mixture gave I, yield 60%. (B) Alternatively two mols of β-aminocrotonic ester could be used in place of the acetoacetic ester and ammonia of (A); or (C). One mol of acetoacetic ester and one mol of β-aminocrotonic ester could be used with the cinchoninaldehyde. Yields by routes (B) or (C) were never as good as by route (A).

Oxidation of I to the True Pyridine, III.—One mol of I warmed with an excess of 3–6 *N* nitric acid gave a rapid solution of the originally suspended solid accompanied by evolution of oxides of nitrogen. When reaction was complete, in less than an hour, the mixture was cooled and basified with aqueous alkali precipitating the base III in quantitative yield.

Preparation of the Quaternary Salts.—In general one mol of I was dissolved in a little ethanol and heated several hours in presence of excess of the alkyl halide. Finally, the mixture was cooled and the product precipitated with ethyl acetate or ether.

Details concerning individual compounds are included in Table I.

Part II (Table II)

Preparation of the *m*-Nitrophenyl Compound, XIII.—A mixture of 16 g. of *m*-nitrobenzaldehyde, 34 cc. of *n*-butyl acetoacetate, 60 cc. of ethanol, and 10 cc. of concentrated aqueous ammonia was heated for three hours on the steam-bath, allowing alcohol to evaporate. Chilling and scratching converted the originally viscous oil to yellow crystals, yield 29 g. (68%). After recrystallization from benzene–hexane the yellow needles melted at 109–110°.

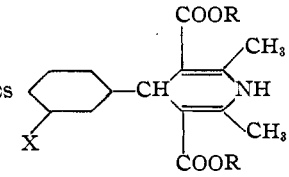
Hydrogenation of the Nitrophenyl Compound, XIII, to the Amino Compound, XIV.—A suspension of 8 g. of the nitro compound XIII in 50 cc. of methanol was hydrogenated in the presence of platinic oxide at room temperature and one to three atmospheres of hydrogen overpressure. Reduction was rapid, and the calculated amount of hydrogen was absorbed within an hour. After removal of the platinum by filtration, the methanol was evaporated to a small volume. All attempts to obtain this particular aminophenyl derivative crystalline, either as the base, the hydrochloride, oxalate or picrate failed. Thus it never was analyzed or characterized as such, but samples of the viscous, oily base were used directly for alkylations. Alkylations with methyl or ethyl iodides gave essentially quantitative yields of the corresponding quaternary ammonium salts, verifying in this way both the purity and identity of the otherwise uncharacterized oil.

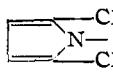
Preparation of the Quaternary Salt, XV, from XIV.—A sample of unpurified base XIV from the preceding experiment, 6 g., dissolved in 100 cc. of benzene, plus 10 cc. of methyl iodide was combined with a concentrated solution of 15 g. of potassium carbonate in 40 cc. of water. The mixture was refluxed on a steam-bath for ten hours. A third oily layer formed, during the reaction, insoluble in either benzene or the carbonate solution. Cooling and scratching converted this oily precipitate to a mass of white crystals; yield 8.3 g. (95%). After washing with water and recrystallization from methanol–ether these crystals melted at 178–179°.

Preparation of the *m*-Pyrrylphenyl Compound, XII.—A mixture of 3.3 g. of the aminophenyldihydropyridine V, 1.3 g. of acetonylacetone and 20 cc. of ethanol was heated

TABLE II

m-SUBSTITUTED PHENYL DIHYDROPYRIDINES



Compd.	X	Yield, %	M. p., °C.[a]	Crystn. solvent[b]	Analyses, % Calcd. C	Calcd. H	Found C	Found H
			A, Methyl esters, R = CH_3					
I	NO_2–	75	209–210	M	58.94	5.23	59.06	5.04
II	NH_2–	90	218–219	M. B. H.	64.52	6.39	64.53	6.67
III	$(CH_3)_3NI$–	83	205–208	M. E.	49.36	5.59	49.56	5.80
					I, 26.12		26.01	
			B, Ethyl esters, R = C_2H_5					
IV	NO_2–[c]	86	164–165	A. Aq				
V	NH_2–	98	151–153	A. Aq	66.28	7.03	66.22	7.38
VI	$(CH_3)_3NI$–	90	173–174	A. E.	51.36	6.08	51.26	6.36
VII	$(CH_3)_3NCl$–[d]	95	186–187	M. E.	62.44	7.39	61.80	7.23
					Cl, 8.40	N, 6.62	8.31	6.60
VIII	$(C_2H_5)_2N$–	54	162–163	M	69.00	8.06	69.12	7.82
IX	$(C_2H_5)_2(CH_3)NI$–	90	165–166	A. E.	53.11	6.51	53.33	6.52
X	$(C_2H_5)_2(CH_3)N$–$OSO_2C_2H_5$–[d]	80	164–165	A. E.	59.51	7.69	59.51	7.41
XI	$(C_2H_5)_3NI$–	50	162–163	Aq	53.93	6.71	53.80	6.52
				A. E.	I, 22.83		22.85	
XII		60	164–165	A	71.06	7.15	71.34	7.05
			C, Butyl esters, R = C_4H_9-*n*					
XIII	NO_2–	68	109–110	B. H.	64.16	7.02	63.85	6.98
XIV	NH_2–[e]	95						
XV	$(CH_3)_3NI$–	95	178–179	M. E.	54.71	6.89	54.73	6.76
XVI	$(CH_3)_3$–N–$OSO_2C_2H_5$–[d]	90	Gray crystals, oils out, no analysis					
XVII	$(C_2H_5)_3$–NI–	65	182–183	A. E.	56.83	7.41	56.74	7.30
XVIII	$(C_2H_5)_3$–N–$OSO_2C_2H_5$–[d]	100	125–126	Ac. E.	62.58	8.48	62.44	8.48

[a] All melting points are uncorrected. [b] A = ethanol; Ac = acetone; Aq = water; B = benzene; E = ether; H = Skelly B; M = methanol. [c] Known compound; Lepetit, *Ber.*, 20, 1338 (1887); German Patent 42,295, *Friedl.*, 1, 195. [d] This salt obtained from the iodide and the appropriate silver salt as described in Part II (see ref. 1). [e] Not analyzed; see experimental part for details.

for sixteen hours on the steam-bath, allowing solvent to evaporate. The crystalline residue after recrystallization from ethanol gave 2.5 g. (60%) of white crystals melting at 164–165°.

Other experimental details are to be found in Table II.

Part III (Table III)

Preparation of 2,6-Dimethyl-3,5-dicarbomethoxy-4-(4′-dimethylaminophenyl)-1,4-dihydropyridine (Compound II, Table III).—A mixture of 30 g. (1 mol) of *p*-dimethylaminobenzaldehyde, 50 g. (2.2 mols) of methyl acetoacetate, 20 cc. (excess) of concentrated aqueous ammonium hydroxide, and 60 cc. of methanol was allowed to stand one hour at room temperature. Next in a closed bottle, wired tight, the reaction mixture was heated for seven hours in a steam-bath. After cooling, scratching gave a yellow crystalline product. The yield was 30 g. (43%) of yellow crystals from methanol, m. p. 193–194°. Evaporation of the methanol mother liquors gave 12 g. more of product melting at 192°; total yield 42 g. (61%).

Preparation of the *n*-Butyl Iodide Adduct of II (Compound VI).—A suspension of 6 g. of the above tertiary base (II) in 10 cc. of methanol and 6 cc. of *n*-butyl iodide was refluxed on a steam-bath for sixty-four hours. The crystalline product, 10 g. (100%), was precipitated from the reaction mixture by addition of excess ether, and scratching to induce crystallization. After recrystallization from methanol–ether mixtures it melted at 186–187°.

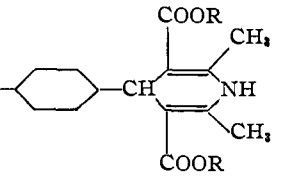
Preparation of the Chloride, VII, from the Iodide, VI.—A solution of 4 g. of the iodide (VI) in 200 cc. of methanol was digested for two hours on a steam-bath with 6 g. of freshly prepared silver chloride (washed well previously first with water, then with methanol). The mixture of insoluble silver chloride and silver iodide was then filtered off and the clear methanol filtrate was concentrated to about 20 cc. Addition of excess ether, with scratching, gave a white crystalline precipitate, 3 g. (94%) which after recrystallization from methanol–ether melted at 198–199°.

Preparation of the Ethanesulfonate, XXI, from the Iodide, XX.—Exactly equimolecular quantities of the quaternary iodide (XX) and silver ethanesulfonate were dissolved separately in methanol and the clear solutions were mixed. After digesting the mixture for about an hour on the steam-bath the precipitated silver iodide was removed by filtration and the clear filtrate was concentrated by evaporation. The quaternary ethanesulfonate was recovered by precipitation with ether, and was purified by recrystallization from ethanol–ether.

Preparation of the Oxidized, True Pyridine Compound, XIX.—The dihydropyridine quaternary salt, compound XVIII, 1.5 g. was heated for one hour on the steam-bath with 8 *N* nitric acid. Copious fumes of oxides of nitrogen

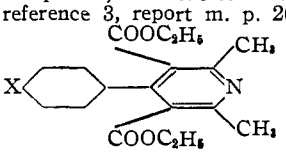
TABLE III

p-AMINOPHENYLDIHYDROPYRIDINES



Compd.	X	Yield, %	M. p., °C.[a]	Crystn. solvent[b]	Analyses, % Calcd. C	Calcd. H	Found C	Found H
			A, Methyl esters, R = CH_3					
I	H–	63	197–198	M	67.73	6.37	67.90	6.27
II	$(CH_3)_2N$–	61	193–194	B. H. or M. Aq.	66.24	7.03	66.11	6.89
III	$(CH_3)_3$–NI–	95	Starts 172–173	M. E.	49.36	5.59	48.75	5.82
			Final 202–203		I, 26.12	N, 5.76	26.03	5.55
IV	$(CH_3)_2(C_2H_5)$NI–	100	194–195	M. E.	50.38	5.84	50.10	5.70
					I, 25.39	N, 5.60	25.39	5.47
V	$(CH_3)_2(n\text{-}C_3H_7)$–NI–	100	196–197	M. E.	51.36	6.08	51.23	5.92
					I, 24.70		24.61	
VI	$(CH_3)_2(n\text{-}C_4H_9)$–NI–	100	186–187	M. E.	52.24	6.30	52.17	6.05
VII	$(CH_3)_2(n\text{-}C_4H_9)$–NCl–	94	198–199	M. E.	Cl, 8.13	N, 6.41	7.94	6.44
VIII	$(C_2H_5)_2N$–	53	209–210	M	67.71	7.58	67.94	7.29
IX	$(C_2H_5)_2$(H)NI–	40[c]	240–241	M	50.38	5.82	50.29	5.79
X	$(C_2H_5)_2(CH_3)$–NI–	100	193–194	M. E.	51.36	6.08	51.44	6.11
					I, 24.70		24.67	
XI	$(C_2H_5)_2(CH_3)$–NCl–	93	210–211	M. E. or Aq.	Cl, 8.40	N, 6.62	7.99	6.47
XII	$(C_2H_5)_3$NI–	60	235 (dec.)	M	52.24	6.30	51.61	6.08
					I, 24.04		23.92	
XIII	$(C_2H_5)_2(n\text{-}C_3H_7)$NI–	50[c]	167–168	M. E.	I, 23.42		23.25	
			B, Ethyl esters, R = C_2H_5					
XIV	$(CH_3)_3$–N–[d]	53	158.5–159.5	M				
XV	$(CH_3)_2$(H)NCl[e]	85	204–205	M. E.	61.66	7.14	61.21	7.01
					N, 6.85		6.68	
XVI	$(CH_3)_3$–NI–[f]	100	174–175	M. Æ. E.	51.36	6.08	51.61	6.01
				A. E.				
XVII	$(CH_3)_2(C_2H_5)$NI–	95	166–167	M. E.	I, 24.04		23.95	
XVIII	$(CH_3)_2(n\text{-}C_3H_7)$NI–	90	182–183	M. E.	53.11	6.51	53.08	6.52
					I, 23.42		23.54	
XIX	$(CH_3)_2(n\text{-}C_3H_7)$NI[g]	80	177–178	A. E.	53.30	6.16	53.73	6.03
XX	$(CH_3)_2(n\text{-}C_4H_9)$NI–	72	174–175	M. E.	53.93	6.71	53.70	6.35
					I, 22.83		22.80	
XXI	$(CH_3)_2(n\text{-}C_4H_9)$N–$C_2H_5SO_2O$–	60	205–210	A. E.	60.19	7.86	60.59	7.88
XXII	$(C_2H_5)_2N$–	50	158–159	M. Aq.	68.95	8.07	68.96	7.92
XXIII	$(C_2H_5)_2(CH_3)$NI–	100	127–128	M. Æ. E.	53.11	6.51	53.46	6.44
XXIV	$(C_2H_5)_3$NI–	93	174–175	M. Æ. E.	53.93	6.71	53.56	6.80

[a] All melting points are uncorrected. [b] A = ethanol; Æ = ethyl acetate; Aq = water; B = benzene; E = ether; H = Skelly B; M = methanol. [c] Based on tertiary amine used; recovered 75% of unused tertiary amine [d] Known, compound; see ref. 3 of text. [e] Isolated from the reaction of compound XIV with benzyl chloride. Hinkel and Cremer, reference 3, report m. p. 201° for this. [f] Hinkel and Cremer report m. p. 182–183°. [g] True pyridine structure



were evolved, and free iodine was liberated and steam distilled or sublimed out of the reaction mixture. The product, presumably the quaternary nitrate of the true pyridine structure, was isolated by reconversion to the iodide. The aqueous acid reaction mixture was basified to *p*H 8 with 40% aqueous potassium hydroxide, and 4 g. of potassium iodide was added precipitating the quaternary iodide. After purification by crystallization from water, then from ethanol–ether the yield of white crystals was 1.2 g. (80%), m. p. 177–178°.

The success of this nitric acid oxidation of the dihydro to the true pyridine structure gives evidence of stabilization of the molecule in the quaternary salt from. Hinkel and Cremer[4] reported that the tertiary amino derivative, compound XIV, could not be oxidized by nitrous fumes to the corresponding tertiary aminophenyl true pyridine, for under these conditions they observed decomposition of the molecule to form *p*-nitrosodimethylaniline nitrate.

(4) Hinkel and Cremer, *J. Chem. Soc.*, **117**, 137 (1920).

Acknowledgment.—The author is indebted to Mr. Samuel W. Blackman for the microanalytical results reported here.

Summary

A series of quaternary ammonium salts has been made for examination as potential curare substitutes. These were all derived from the Hantzsch pyridine synthesis employing aromatic aldehydes containing basic salt-forming groups or containing other substituents readily convertible to salt-forming groups.

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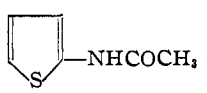
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

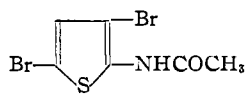
The 2-Aminothiazoles

BY CHARLES D. HURD AND H. L. WEHRMEISTER[1]

Some relationships were developed in the thiophene series, in particular with aceto-2-thiophenamide (I) and its derivatives, which were of an unexpected nature.[2] The 3,5-dibromo derivative (II), for example, underwent nitration to yield the same 3,5-dinitro derivative that was obtained by nitration of I. This substitution



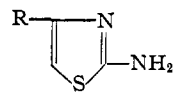
I



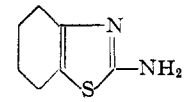
II

of bromine atoms by nitro groups is most unusual. Then again, II was found to couple readily with *p*-nitrobenzenediazonium chloride to form a dye with replacement of the 5-bromo group by azo. Coupling of I even occurred while the solution was strongly acidic. It is remarkable, as a matter of fact, that either I or II should yield azo dyes, since an amine group (not amide) is usually required to activate an aromatic molecule sufficiently for coupling.

The study of substitution reactions of amino and acetamido heterocyclic compounds now has been extended to the thiazoles. The 4-methyl- and 4-phenyl-2-aminothiazoles (III) were prepared by the reaction of thiourea with either the chloro ketone ($RCOCH_2Cl$) or with a mixture of the ketone ($RCOCH_3$) and iodine.[3] A similar procedure, using cyclohexanone, thiourea and iodine, was developed for the preparation of 2-amino-4,5,6,7-tetrahydrobenzothiazole (IV). The preparation of IV from 2-chlorocyclohexanone has been reported.[4]

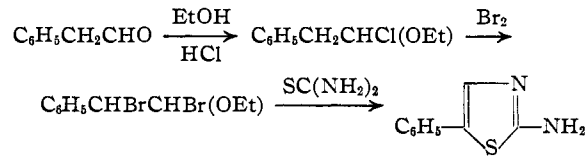


III



IV

5-Phenyl-2-aminothiazole was prepared from phenylacetaldehyde as outlined



The conventional procedure in the first step is to add the hydrogen chloride gas slowly with as little agitation as possible to avoid mixing of the water layer (formed in the reaction) with the organic layer. In the present work emulsions always were encountered, probably because of nearly identical densities of the two phases. Very dark products resulted. Some investigators[5] have designed special apparatus to perform this type of reaction so as to avoid the difficulty mentioned. In the present work, the addition of anhydrous sodium sulfate to the reaction mixture was found to be a simple solution to the problem. With this modification light colored products were obtained even when hydrogen chloride was introduced rapidly and with stirring.

Nitration of 2-acetamidothiazole is known[6] to yield 5-nitro-2-acetamidothiazole. The same compound was obtained in the present study by nitration of 5-bromo-2-acetamidothiazole, thus demonstrating that replacement of halogen does occur in the thiazole as in the thiophene series. Since the structure of the 5-bromo-2-acetamidothiazole is known,[7] the replacement reaction serves to establish the structure of the nitro compound as 5-nitro-2-acetamidothiazole.

Monomercuration of 2-acetamidothiazole occurred in position 5 with mercuric chloride in water, whereas 4,5-dimercuration took place with mercuric acetate in acetic acid. The position of the chloromercuri group in the first of these compounds (V) was established by cleavage with bromine to the known 5-bromo-2-acetamidothiazole. Conversion of V into 5-iodo-2-acetamidothiazole by reaction with iodine also proceeded

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