[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF KANSAS]

The Synthesis of Heterocyclic Compounds by Means of Isothiourea Ethers

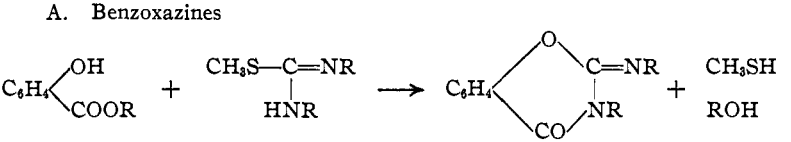
BY J. F. DECK AND F. B. DAINS

While the ureas[1,2,3] and thioureas[4,5] have served in many instances in the synthesis of heterocyclic rings, the use of the thio ethers $CH_3S-C(=NR\,(H))-NHR\,(H)$ has been very limited. Wheeler and Johnson[6] and their students have employed methyl isothiourea in the synthesis of pyrimidines, and in one instance a substituted quinazoline,[7] but only in this latter case did ring closure involve loss of the CH_3S- grouping.

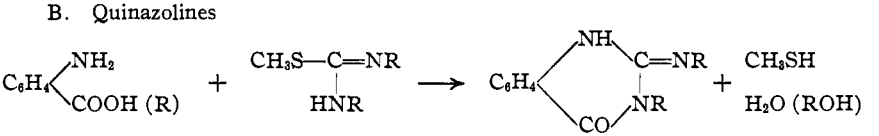
A thiourea of the type $RN{=}C{-}(SCH_3)NHR$ contains two points of attack; (a) the SCH_3- group can be eliminated as mercaptan on fusion with an amino group or in some cases hydroxyl, (b) the hydrogen of the NHR group can be replaced by an acyl group or the whole grouping split off an amine.

In consequence of this reactivity, a study has been made of the action of these thiourea ethers on *o*-substituted benzenes and on phenylaminoacetic acid, which contain amino, hydroxyl and carboxyl groups. The main types of reactants and the resulting products are briefly outlined as follows

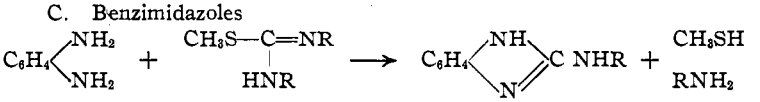
A. Benzoxazines



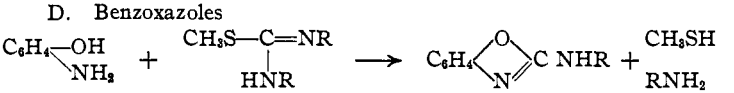
B. Quinazolines



C. Benzimidazoles

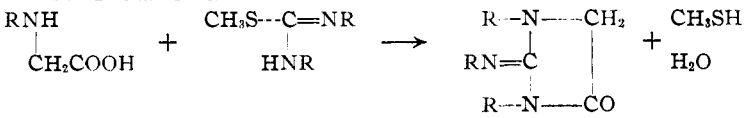


D. Benzoxazoles



(1) Will, *Ber.*, **14**, 1490 (1881).
(2) Will, *ibid.*, **15**, 338 (1882).
(3) Gabriel and Posner, *ibid.*, **28**, 1029 (1895).
(4) Johnson and Hill, *Am. Chem. J.*, **45**, 356 (1911).
(5) Biltz, *Ann.*, **339**, 265 (1905).
(6) Wheeler and Merriam, *Am. Chem. J.*, **29**, 418 (1903).
(7) Wheeler, Johnson and McFarland, THIS JOURNAL, **25**, 797 (1903).

E. Imidazolones



Experimental

Preparation of the Methyl Isothiourea Ethers.—Excellent yields (80–90%) of the thio ethers were obtained as follows: thiocarbanilide (450 g.) was dissolved in as little acetone as possible. An equimolecular quantity (250 g.) of dimethyl sulfate was added slowly to the cooled solution with constant shaking. The mixture was then refluxed for three hours and the acetone removed by distillation. The heavy oil was taken up in iced water, filtered and the base precipitated with dilute sodium carbonate. In the case of di-*p*-bromo- (I) and the *m*-nitro-diphenyl thiourea (II), the free base separated and not the salt[8] as with the di-*m*-tolyl- (III), the monobromo-diphenyl- (IV) and *α*-methyl-*β*-phenyl thioureas (V).[9]

Synthesis of Benzoxazines.—The fusion of salicylic acid with methyl isodiphenylthiourea or methyl isodi-*o*-tolyl thiourea gave only mercaptans, unchanged acid and diphenyl or di-tolylurea, due evidently to the splitting off of water and its action on the isothioureas at 180°.

$\overline{C_6H_4OC(NC_6H_5)NC_6H_5CO}$, **2-Phenylimino-3-phenyl-1,3,4-benzoxazine-4-one** (VI).—Methyl salicylate and the diphenyl thio ether were heated at 180° until the evolution of mercaptan ceased. From the melt was isolated a little carbanilide and the benzoxazine. The white needles from chloroform melted at 157–158°. On hydrolysis it gave carbanilide and salicylic acid. Salol[10] which gave a 68% yield of the benzoxazine was used in the later syntheses since the phenol liberated was far less reactive with the thio ether at the temperatures employed, than the methanol. Direct experiment showed that phenol and the methyl ether at temperatures from 180–220° liberated only traces of mercaptan, the reactants being recovered unchanged. The di-*o*-tolyl-benzoxazine was formed when the methyl isothiodi-*o*-tolylurea and phenyl salicylate were heated at 195° for ten hours (VII).

3-*o*-Tolyl-1,3,4-benzoxazine-2,4-dione (VIII) $\overline{C_6H_4OCONC_7H_7CO}$.—A mixture of the benzoxazine (VII) (2 g.), concentrated hydrochloric acid (1 cc.) and alcohol (50 cc.) was refluxed for four hours. From the neutralized solution after evaporation of the alcohol were isolated *o*-toluidine and the diketo compound.

2-Phenylimino-3-*p*-bromophenyl-1,3,4-benzoxazine-4-one (XI).—This compound resulted when salol was fused with the methyl thio ether of *p*-bromodiphenylurea. The experiment was carried out in order to determine the effect of the substituted bromine on the relative positions of the phenyl and monobromophenyl groups in the benzoxazine ring. The oily product finally crystallized in needles from dilute alcohol (m. p. 135–136°). That the benzoxazine (XI) had the above structure was shown by the fact that on hydrolysis with dilute acid, it gave aniline and 3-*p*-bromophenyl-1,3,4-benzoxazine-2,4-dione (XII) which melted at 214° and contained bromine.

Phenyl Salicylate and the Methyl Thioether of Monophenylurea.—Fusion at 180° or boiling in xylene solution gave the same results. The benzene or xylene solution was extracted with sodium hydroxide (10%). When the alkaline solution was acidified,

(8) The salt of monophenyl thiourea ether was precipitated as a white crystalline solid in the warm acetone solution, melting at 141–142°. The constitution of this salt was determined as $C_6H_5NHC(SCH_3)NHCH_3HSO_4$ by analysis. N calcd. for $C_9H_{14}N_2O_4S_2$: 10.08; N found, 10.10.

(9) The perchlorate salt melted at 114°.

(10) Titherly, *J. Chem. Soc.*, **97**, 208 (1910).

a white solid, soluble also in sodium carbonate, was obtained, which proved to be 2-phenylimino-1,3,4-benzoxazine-4-one, $C_6H_4OC(NC_6H_5)NHCO$ (XIII). The crystals from alcohol melted at 189°. When boiled for four hours with sulfuric acid (40%) it gave aniline and the 1,3,4-benzoxazine-2,4-dione (m. p. 224°).[11] This product was identical with the di-one made by heating salicylic acid and urea at 220° for five hours. The original benzene solution after extraction with alkali contained a residue from which nothing definite could be isolated.

Synthesis of Quinazolines.—2-Phenylimino-3-phenyl-4-keto-tetrahydroquinazoline (m. p. 163°) $C_6H_4NHC(NC_6H_5)NC_6H_5CO$ (XIV). The reaction product obtained by boiling anthranilic acid and methyl isodiphenylthiourea in xylene or fusion at 170–180° for three hours, was repeatedly extracted with hot dilute hydrochloric acid. The acid solution contained a little aniline and a solid precipitated by alkali which was found to be the above quinazoline. McCoy[12] had previously synthesized this compound by the interaction of benzene, carbodiphenylimide hydrochloride and aluminum chloride. This quinazoline was obtained almost exclusively from methyl anthranilate in boiling nitrobenzene.

3-Phenyl-2,4-diketo-tetrahydroquinazoline (XV).—The residue insoluble in acid from the original fusion mixture was extracted with hot dilute alkali and filtered. Neutralization gave the diketo compound (m. p. 271°) which was evidently formed by the action of water, in fusing at 180°, on the original diphenylquinazoline. Following McCoy's procedure, hydrolysis of the diphenylquinazoline (XIV) with dilute hydrochloric acid at 180° gave aniline and this same diketo derivative,[13,14] thus proving the constitution.

1-Methyl-2,4-diketo-3-phenylquinazoline (XVI).—This product resulted when N-methylanthranilic acid and the methyl thio ether were heated at 185°. Mercaptan was liberated and a little aniline distilled over. The residue contained carbanilide and diketo compound (m. p. 224–225°) due to hydrolysis at the elevated temperature. The compound has been described previously by Fortmann and McCoy[15,16] who obtained melting points of 238 and 223°, respectively.

Tolyl Derivatives.—The fusion of anthranilic acid or its ester or the N-methyl acid with the methyl ethers of di-*o*- and di-*p*-tolylthiourea gave analogous results. Usually a little di-tolylurea was formed (XVII)–(XXI).

2-Phenylimino-4-keto-tetrahydroquinazoline (m. p. 256°).—Anthranilic acid and the methyl ether of monophenylthiourea ether were heated alone and in boiling xylene with the evolution of mercaptan, water and ammonia. The residue was a mixture, partly soluble in acid and in alkali from which no pure compound could be isolated. Wheeler and McFarland[17] had obtained the quinazoline (m. p. 256°) by the fusion of the above reactants, and for the purpose of comparison it was synthesized as follows. Douglass[18] obtained from benzoyl mustard oil and anthranilic acid, the benzoyl thiourea, $C_6H_5CONHCSNHC_6H_4COOH$. Boiling this thiourea with sodium hydroxide (10%) for five minutes closed the ring with loss of benzoic acid. Subsequent methylation gave 2-thio-methyl-4-keto-quinazoline. This heated with aniline at 110° yielded the 2-phenyl-tetrahydroquinazoline (256°) (XXII), which proved to be different from any of the products we had isolated.

(11) Einhorn and Mettler, *Ber.*, **35**, 3647 (1902).
(12) McCoy, *Am. Chem. J.*, **21**, 131 (1899).
(13) McCoy, *Ber.*, **30**, 1687 (1897); Pawlewski, *ibid.*, **38**, 131 (1905).
(14) Busch, *J. prakt. Chem.*, [2] **51**, 257 (1895); Stewart, *ibid.*, **49**, 318 (1893).
(15) Fortman, *ibid.*, [2] **55**, 130 (1899).
(16) McCoy, *Am. Chem. J.*, **21**, 131 (1899).
(17) Wheeler, McFarland and Johnson, THIS JOURNAL, **25**, 797 (1903).
(18) Douglass, unpublished thesis, University of Kansas.

Synthesis of Benzimidazoles. 2-Anilino-benzimidazole, $\overline{C_6H_4NHC(NHC_6H_5)N}$ **(XXIII).**—The reaction between *o*-phenylenediamine and methyl isodiphenylthiourea took place smoothly at 145° with the separation of mercaptan and aniline and was completed after three hours. The product which was weakly basic (the hydrochloride melted at 151–152°) was decolorized with charcoal in an alcohol solution and later recrystallized from benzene (m. p. 188°). It was identical with the imidazolone obtained by Keller[19] from carbodiimide and the diamine. The corresponding tolylamino-benzimidazoles were obtained from the methyl thio ethers of di-*p*- and di-*o*-tolylureas (XXIV)–(XXV).

Synthesis of Benzoxazoles. 1-Anilinobenzoxazoles, $\overline{C_6H_4OC(NHC_6H_5)N}$ **(XXVI).**—Methyl pseudo diphenylthiourea and *o*-aminophenol were heated at 170° for two hours with the evolution of mercaptan and traces of water and aniline. The reaction product was dissolved in hydrochloric acid (5%) at 65–70° with constant agitation. On cooling a heavy white precipitate settled out. This crystallized from alcohol melted at 170° and proved to be the above benzoxazole which Kalchoff[20] had obtained by fusing 1-mercapto-benzoxazole with aniline. The original hydrochloric acid solution on neutralization gave the same benzoxazole, thus showing that it was a weak base.

The same base (170°) was also formed when the aminophenol was heated with (a) the methyl ether of monophenyl thiourea and (b) the methyl ether of α-methyl-β-phenylthiourea, ammonia and methylamine being eliminated, respectively.

The corresponding tolyl amino benzoxazoles were obtained from the methyl thio ethers of di-*p*- and di-*m*-tolylureas (XXVII)–(XXVIII).

The constitution of these 1-aryl-aminobenzoxazoles was further proved by Kalchoff's synthesis. When 1-mercapto-benzoxazole was heated at 180° with aniline, *p*- and *m*-toluidine, compounds were obtained identical in all respects with the ones described.

Reactions with Substituted Aminophenols.—The methyl ethers were heated with 4-chloro- and 4-nitro-2-aminophenol in order to ascertain whether the presence of chlorine or a nitro group in the ring would affect the reaction in any way. No difficulty occurred and the 4-chloro and 4-nitro-1-aryl aminobenzoxazoles (XXIX)–(XXXIV) were obtained in good yields. It was noted however that the nitroaminophenol reacted more easily than the other aminophenols and its derivatives were best crystallized from glacial acetic acid.

Proof of Structure of the Chloro and Nitro Benzoxazoles: 4-Chloro-mercapto-benzoxazole, $\overline{ClC_6H_3OCSNH}$ **(XXXV).**—A mixture of the chloraminophenol (50 g.), alcohol (300 cc.) and carbon disulfide (100 g.) was refluxed for thirty-six hours. The mercapto benzoxazole which separated out melted at 261–262°, after recrystallization from glacial acetic acid.

4-Nitro-1-mercaptobenzoxazole $NO_2\overline{C_6H_3OCSNH}$ **(XXXVI).**—Nitroaminophenol (20 g.), pyridine (5 cc.) and carbon disulfide (50 cc.) were heated for twenty hours at 60°, using a mercury seal. The product was distilled with steam taking care to remove all traces of pyridine, which hindered crystallization. The residue from acetic acid melted at 235–238°, the use of pyridine[21] was necessary since without it no reaction occurred. When the chloro or nitro-mercaptobenzoxazole was heated with the various aryl amines, the same aryl-aminobenzoxazole was obtained as by the previous procedure (XXIX–XXIV). Some difficulty was experienced in purifying the nitro compounds, due possibly to the reducing action of hydrogen sulfide on the nitro group.

Reactions with *o*-Dihydroxybenzene.—Catechol and the methyl thio ether were

(19) Keller, *Ber.*, **24**, 2498 (1891).

(20) Kalchoff, *ibid.*, **16**, 1825 (1883).

(21) Fry, THIS JOURNAL, **35**, 1545 (1913).

heated for six hours at 180°. Mercaptan was liberated but no ortho condensation product was formed. The only products isolated were diphenylurea and triphenylguanidine which was identified by analysis and comparison with a known specimen. This was the only instance in which this guanidine was found. The results were evidently due to loss of water from the catechol, and its action on the thiourea yielding carbanilide and aniline which in turn with the unchanged methyl ether gave the guanidine.

Synthesis of Imidazolones: $C_6H_5\overline{NC(NC_6H_5)NC_6H_5CH_2}CO$ **1,3-Diphenyl-2-phenylimino-5-imidazolone, (XXXVII).**—The ethyl ester of phenylglycine was fused with the methyl thio ether at 180–200° until the evolution of mercaptan ceased, and the melt taken up in benzene. Treatment with alkali removed only traces of acidic material, while extraction with dilute hydrochloric acid dissolved the imidazolone, which was precipitated with alkali. The base after crystallization from dilute alcohol melted at 150–151°. Its constitution was proved by the fact that on hydrolysis with boiling hydrochloric acid (20%), aniline and the well-known diphenylhydantoin (m. p. 138.5°) (XXXVIII) were formed. This same diphenylhydantoin was found in the benzene solution from which the imidazolone (XXXVII) had been removed, a result due to partial hydrolysis in the original fusion.

4-*m*-Nitrobenzal-triphenylimidazolone.—The presence of a reactive methylene group was shown by its condensation with *m*-nitrobenzaldehyde on heating with sodium acetate and acetic acid. The yellow benzal derivative was difficulty soluble and melted at 169–170° (XXXIX).

The following cases (Table XL–XLVII) have shown that this method of synthesis of imidazolones was of general applicability.

Reactions of Phenylaminoethanol.—Molar quantities of the ethanol and the methyl thio ether were heated in boiling xylene. Methyl mercaptan was readily evolved but the reaction products consisted only of diphenyl piperazine and carbanilide. The aminol simply condensed to the piperazine while the water formed reacted with the thiourea. Similar results were obtained with methyl pseudo di-*p*-tolylthiourea.

TABLE I

Text no.	Compound	Formula	M. p., °C.	Nitrogen, % Calcd.	Found
I	Methyl isodi-*p*-bromo-diphenylthiourea	$C_{14}H_{12}Br_2N_2S$	129	7.00	6.68
II	Methyl iso-*m*-nitro-diphenylthiourea	$C_{14}H_{13}N_3O_2S$	87–89	14.60	14.80
III	Methyl iso-di-*m*-tolylthiourea	$C_{16}H_{18}N_2S$	97.5	10.37	10.54
IV	Methyl iso-monobromo-diphenylthiourea	$C_{14}H_{13}BrN_2S$	79–80	8.75	8.40
V	Thio-Methyl ether of methyl phenyl urea	$C_9H_{12}N_2S$	58–59	15.55	15.22
	Perchlorate salt of V	$C_9H_{12}B_2S\cdot ClO_4$	114	10.00	9.93
VI	2-Phenylimino-3-phenyl-1,3,4-benzoxazine-4-one	$C_{20}H_{14}N_2O_2$	157–158	8.92	9.05
VII	2-*o*-Tolylimino-3-*o*-tolyl-1,3,4-benzoxazine-4-one	$C_{22}H_{18}N_2O_2$	114	8.18	8.24
VIII	3-*o*-Tolyl-1,3,4-benzoxazine-2,4-dione	$C_{15}H_{11}NO_3$	129–130	5.53	5.62
IX	2-*p*-Tolylimino-3-*p*-tolyl-1,3,4-benzoxazine-4-one[a]	$C_{22}H_{18}N_2O_2$	163–164	8.18	8.01
X	3-*p*-Tolyl-1,3,4-benzoxazine-2,4-dione[b]	$C_{15}H_{11}NO_3$	221	5.53	5.41
XI	2-Phenylimino-3-bromophenyl-1 3,4-benzoxazine-4-one	$C_{20}H_{13}BrN_2O_2$	135–136	7.12	6.64
XII	3-*p*-Bromophenyl-1,3,4-benzoxazine-2,4-dione	$C_{14}H_8BrNO_3$	214	4.40	4.83
XIII	2-Phenyl-1,3,4-benzoxazine-4-one	$C_{14}H_{10}N_2O_2$	189	11.76	11.75
XIV	2-Phenylimino-3-phenyl-4-ketotetrahydroquinazoline	$C_{20}H_{16}N_3O$	163	13.41	13.19
XV	3-Phenyl-2,4-diketo-tetrahydroquinazoline	$C_{20}H_{10}N_2O_2$	271	11.76	11.72
XVI	1-Methyl-3-phenyl-2-keto-tetrahydroquinazoline	$C_{15}H_{12}N_2O_2$	224.5	11.11	10.98
XVII	2-*p*-Tolylimino-3-*p*-tolyl-4-ketotetrahydroquinazoline	$C_{22}H_{19}N_3O$	149	12.32	12.08
XVIII	3-*p*-Tolyl-2,4-diketo-tetrahydroquinazoline[c]	$C_{16}H_{12}N_2O_2$	273	11.11	11.25
XIX	1-Methyl-2-keto-3-*p*-tolyl-4-ketotetrahydroquinazoline	$C_{16}H_{14}N_2O_2$	190	10.52	10.47
XX	2-*o*-Tolylimino-3-*o*-tolyl-4-ketotetrahydroquinazoline	$C_{22}H_{19}N_3O$	157–159	12.32	11.96

TABLE I (*Concluded*)

Text no.	Compound	Formula	M. p., °C.	Nitrogen, % Calcd.	Found
XXI	3-*o*-Tolyl-2,4-diketo-tetrahydroquinazoline[d]	$C_{15}H_{12}N_2O_2$	238–239	11.11	11.32
XXII	2-Phenylimino-4-keto-tetrahydroquinazoline	$C_{14}H_{11}N_3O$	256	17.71	17.80
XXIII	2-Anilinobenzimidazole	$C_{13}H_{11}N_3$	188	20.10	19.97
XXIV	2-*p*-Tolylaminobenzimidazole[e]	$C_{14}H_{13}N_3$	207	18.83	18.62
XXV	2-*o*-Tolylaminobenzimidazole[e]	$C_{14}H_{13}N_3$	182	18.83	18.84
XXVI	1-Anilino-benzoxazole	$C_{13}H_{10}N_2O$	170	13.33	13.01
XXVII	1-*p*-Tolylaminobenzoxazole	$C_{14}H_{12}N_2O$	178	12.50	12.29
XXVIII	1-*m*-Tolylaminobenzoxazole	$C_{14}H_{12}N_2O$	146	12.50	12.50
XXIX	4-Chloro-1-phenylaminobenzoxazole	$C_{13}H_9ClN_2O$	199	11.45	11.21
XXX	4-Chloro-1-*p*-tolylaminobenzoxazole	$C_{14}H_{11}ClN_2O$	204.5	10.81	10.54
XXXI	4-Nitro-1-phenylaminobenzoxazole	$C_{13}H_9N_3O_3$	235	16.47	16.62
XXXII	4-Nitro-1-*p*-tolylaminobenzoxazole	$C_{14}H_{11}N_3O_3$	222–224	15.61	15.65
XXXIII	4-Nitro-1-*o*-tolylaminobenzoxazole	$C_{14}H_{11}N_3O_3$	173–174	15.61	15.23
XXXIV	4-Nitro-1-*m*-tolylaminobenzoxazole	$C_{14}H_{11}N_3O_3$	207	15.61	15.27
XXXV	4-Chloro-1-mercaptobenzoxazole	C_7H_4ClNOS	262	7.56	7.50
XXXVI	4-Nitro-1-mercaptobenzoxazole	$C_7H_4N_2O_2S$	235–238	14.28	14.09
XXXVII	1,3-Diphenyl-3-phenylimino-5-imidazolone	$C_{21}H_{17}N_3O$	150–151	12.81	12.84
XXXVIII	1,3-Diphenyl-2-keto-5-imidazolone	$C_{15}H_{12}N_2O_2$	138.5	11.11	10.99
XXXIX	1,3-Diphenyl-3-phenylimino-4-*m*-nitrobenzal-5-imidazolone	$C_{28}H_{20}N_4O_4$	170	12.10	11.82
XL	1-Phenyl-2-*p*-tolylimino-3-*p*-tolyl-5-imidazolone[f]	$C_{22}H_{21}N_3O$	158	11.84	11.55
XLI	1-*p*-Tolyl-2-keto-3-phenyl-5-imidazolone[g]	$C_{16}H_{14}N_2O_2$	153	10.52	10.34
XLII	*m*-Nitrobenzal derivative of XL	$C_{30}H_{24}N_4O_3$	156	11.48	11.22
XLIII	1-*o*-Tolyl-2-*o*-tolylimino-3-phenyl-5-imidazolone[h]	$C_{23}H_{21}N_3O_4$	130	11.84	11.88
XLIV	1-*o*-Tolyl-2-keto-3-phenyl-5-imidazolone[i]	$C_{16}H_{14}N_2O_2$	126	10.52	10.48
XLV	1-Phenyl-2-phenylimino-3-*p*-tolyl-5-imidazolone[j]	$C_{22}H_{19}N_3O$	126	12.31	12.33
XLVI	1-Phenyl-2-keto-3-*p*-tolyl-5-imidazolone[k]	$C_{16}H_{14}N_2O_2$	155	10.52	10.62
XLVII	1-Phenyl-2-phenylimino-3-*p*-tolyl-4-*m*-nitrobenzal-5-imidazolone	$C_{29}H_{22}N_4O_3$	176	11.81	11.56

[a] From salol and methyl isodi-*p*-tolylthiourea at 180°.

[b] From the hydrolysis of IX with dilute hydrochloric acid.

[c] From the original reaction product and the hydrolysis of XVII.

[d] McCoy, *Am. Chem. J.*, **21**, 131 (1899).

[e] From *o*-phenylenediamine and the methyl thio ethers of *o*- and *p*-di-tolylthiourea, besides toluidine. The hydrochloride of XXIV melted at 174° and of XXV at 89–90°.

[f] From ethyl phenylaminoacetate and methyl isothio-di-*p*-tolylurea.

[g] From the hydrolysis of XL, and the original reaction mixture.

[h] From the glycine and methyl isothio-di-*o*-tolylurea.

[i] From the original reaction mixture and the hydrolysis of XLIII.

[j] From the ethyl ester of *p*-tolylglycine and the methyl thio ether.

[k] From the reaction product in XLV.

Summary

The methyl ethers of the substituted thioureas gave fused heterocyclic rings with *o*-substituted benzenes. The following types were synthesized: benzoxazines from esters of salicylic acid, quinazolines from anthranilic acid, benzimidazoles from *o*-phenylenediamine, benzoxazoles from *o*-aminophenols, imidazolones from aryl glycines. Catechol and phenylaminoethanol gave no fused ring derivatives. The thioureas were easily methylated using methyl sulfate in acetone solution and then neutralizing the salts formed with dilute sodium carbonate.

LAWRENCE, KANSAS RECEIVED AUGUST 17, 1933
PUBLISHED DECEMBER 14, 1933