As illustrated below, Rule I is useful for estimating the relative oximation rates of the various class members.

Every alkanone (except 2-propanone, 2-butanone, and 3-pentanone) may be assigned to one of the 25 classes listed in Table I. According to Rule I the oximation rate of a given alkanone would be the same or lower than the rate of the first member of the class to which it has been assigned. The reactivity of a given class would therefore be defined if class members of increasing branching were prepared and tested until an alkanone of low reactivity was found. This was easily and completely realized for classes A_{11}, A_{12}, B_5, C_4, C_5, E, and F and partially realized for classes A_9, A_{10}, B_2–B_4, C_1–C_3, and D. The alkanones nones in class B_1 roughly parallel the corresponding members of class B_2 (Rule III-D). The remaining classes A_1–A_8 are generally very reactive and therefore represent the greatest area of uncertainty.

Experimental

Unless otherwise indicated in Table I the ketones were prepared by the following methods.

Method A. A Grignard reagent was treated with an aldehyde and the resulting carbinol oxidized to the ketone according to the procedure of Sandborn (*8*).

Method B. A Grignard reagent was converted into the cadmium dialkyl and treated with an acid chloride according to the procedure of Cason and Prout (*3*).

Method C. An acid chloride was treated with a Grignard reagent and anhydrous ferric chloride catalyst according to the procedure of Cason and Kraus (*2*).

The intermediates were prepared by the methods indicated in the footnotes to Table I. The malonic ester syntheses and Reformatsky reaction sequences were performed according to the procedures previously described (*5*).

Analysis and rate determinations. The carbonyl percentages of new compounds and the 50% oximation times were determined by the methods previously described (*5*). An independent redetermination of the $t_{50\%}$ of 37 ketones gave an average precision of 3.1%.

Literature Cited

(1) Brandstrom, A., *Acta Chem. Scand.*, **13**, 611 (1959).
(2) Cason, J., Kraus, K. W., *J. Org. Chem.*, **26**, 1768 (1961).
(3) Cason, J., Prout, F. S., "Organic Syntheses," E. C. Horning, Ed., Collect. Vol III, p 601, Wiley, New York, N.Y., 1955.
(4) Homeyer, A. H., Whitmore, F. C., Wallingford, V. H., *J. Amer. Chem. Soc.*, **55**, 4209 (1933).
(5) Kletzke, P. G., *J. Org. Chem.*, **29**, 1363 (1964).
(6) Mosher, W. A., Cox, J. C., Jr., *J. Amer. Chem. Soc.*, **72**, 3701 (1950).
(7) Prout, F. C., *ibid.*, **74**, 5915 (1952).
(8) Sandborn, L. T., "Organic Syntheses," A. H. Blatt, Ed., Collect. Vol I, 2nd ed., p 340, Wiley, New York, N.Y., 1941.
(9) Sauer, J. C., "Organic Syntheses," N. Rabjohn, Ed., Collect Vol. IV, p 560, Wiley, New York, N.Y., 1963.

Received for review June 2, 1971. Resubmitted June 7, 1972. Accepted August 24, 1972.

Preparation and Spectral Characterization of Substituted 2-Aminothiazoles

George Y. Sarkis[1] and Subhi Al-Azawe

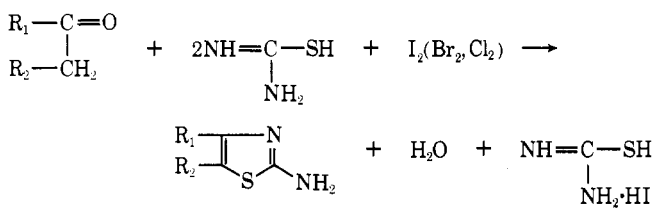
Department of Chemistry, College of Science, University of Baghdad, Baghdad, Adhamiya, Iraq

Ten 2-aminothiazole derivatives have been synthesized by the direct interaction of thiourea with a series of ketones in the presence of oxidizing agents (I_2, Br_2, Cl_2). α-Haloketones were also condensed with thiourea; the products were identical with those prepared by the direct method. The uv, ir, and nmr data for the synthesized 2-aminothiazoles are presented.

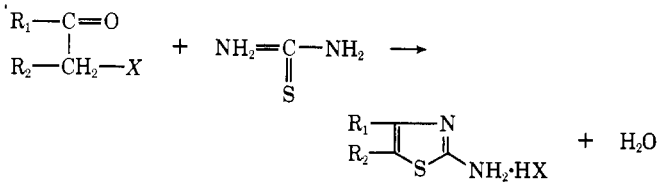
Ten 2-aminothiazoles were prepared by the method of Dodson et al. (*2–5*), by the interaction of 2 moles of thiourea and 1 mole of a ketone having a methyl or a methylene group adjacent to the carbonyl group in the presence of oxidizing agents (I_2, Br_2, Cl_2) (Method A). α-Haloketones (Table I) were also allowed to react with thiourea (*1, 6, 7*) (Method B); the products were identical with those prepared by the direct method. The structure and physical properties of the synthesized 2-aminothiazoles are given in Table II.

An examination of Table II reveals that Method A for the synthesis of 2-aminothiazoles gives excellent yield (60–90%), and can be carried out in a much shorter time than Method B. Furthermore, attempts to condense camphor with thiourea using bromine, iodine, or sulfuryl chloride as oxidizing agents, or to condense 3-bromocamphor with thiourea in alcoholic solutions were unsuccessful even on prolonged heating. This may be due to the great strain present in such bicyclic systems. It was also found during the present investigation that the condensation of cyclopentanone with thiourea, using different oxidizing agents and its corresponding α-bromoderivative with thiourea, could not be achieved. The condensation of some aliphatic ketones such as isobutyl methylketone, *n*-butyl methylketone, and mesityl oxide with thiourea using iodine or sulfuryl chloride were not successful. Sulfuryl chloride showed a violent reaction with the ketones used, and therefore it was added dropwise with cooling. Uv, ir, and nmr data for 2-aminothiazoles are given in Tables III and IV.

Method A



Method B

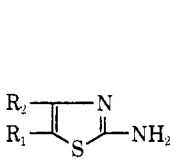


[1] Present address, Department of Chemistry, McGill University, Montreal, Que., Canada. To whom correspondence should be addressed.

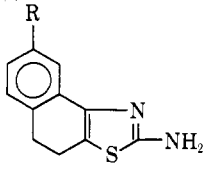
Table I. Physical Properties of α-Haloketones

α-Haloketone	Mp, °C or bp/mm Hg	Solvent of crystallization	Yield %	Reaction medium	Reaction temp
p-Hydroxyphenacyl bromide	130	Benzene	70	Chloroform	20
p-Nitrophenacyl bromide	98	Ligroin (120°)	88	Acetic acid	25
3-Bromoacetylacetone	96/13 mm	Ethanol	80	Ethanol	25
5-Bromoacetylindane	58–59	Benzene/ligroin	70	Chloroform	25
3-Bromoacetylindole	230	Methanol	50	Methanol	25
4-Bromoacetylpyridine·HBr	198–200	Acetic acid	70	Acetic acid	25
2-Bromocyclohexanone	83/6 mm	Acetic acid	70	Acetic acid	50
2-Bromo-1-tetralone	37–38	Ligroin (40–60)	75	Ether	25
2-Bromo-7-nitro-1-tetralone	68–70	Ligroin (40–60)	50	Chloroform	25
2-Bromoacetylfluorene	144–145	Ethanol	70	Ether	0
Ethyl-3-bromoacetoacetate	98/16 mm	Ethanol	75	Ethanol	10
3-Chloroacetylacetone	56/28 mm	Benzene	70	Benzene	25

Table II. Physical Properties of Substituted 2-Aminothiazoles[a]



I, free base



II, free base

	Molecular formula	R_1 (or R)	R_2	Mp, °C	% Yield Method A using I_2	% Yield Method A using Br_2	% Yield Method B using α-halo-ketone	Derivatives (mp, °C) Acetyl	Picrate	HBr salt
I_a	$C_{12}H_{12}N_2S$	5-indanyl	H	131–132	65	60	65	248–250	218–220	
I_b	$C_{11}H_9N_3S$	3-indolyl	H	168–170	70	68	60	198–190		
I_c	$C_8H_7N_3S$	4-pyridyl	H	271–272	68	60	55	332–334	262–264	
I_d	$C_9H_7N_3O_2S$	$C_6H_4NO_2(p)$	H	292–294	85	70	95	316–318		
I_e	$C_9H_8N_2OS$	$C_6H_4OH(p)$	H	198–200	65	65	55			206
I_f	$C_6H_8N_2OS$	CH_3	$COCH_3$	140–141	85	65	85			248
I_g	$C_7H_{10}N_2S$	R_1,R_2—$(CH_2)_4$—		87–88	90	75	91			244
I_h	$C_{16}H_{12}N_2S$	2-fluorenyl	H	268–269	85	71	82	303–304		264
II_a	$C_{11}H_{10}N_2S$	H	...	262–264	70	61	44			265
II_b	$C_{11}H_9N_3O_2S$	NO_2	...	245–246	64	60	40	338–340	234–236	

[a]Elemental analysis (C, H, N, S) in agreement with theoretical values were obtained and submitted for review.

The uv absorption spectra of most of the compounds studied exhibited marked bathochromic shifts in comparison with 2-aminothiazole *(8–10)*. Compounds possessing electron-withdrawing substituents in the benzene ring exhibited hypsochromic shifts. The uv absorption spectra of 2-aminothiazoles could not distinguish the tautomeric state of these compounds.

The ir absorption spectra of 2-aminothiazoles showed an NH_2 group at 3400–3450 cm^{-1} due to the NH stretching vibration. The region 1650–1590 cm^{-1} was assigned for the amino group deformation vibration. The weak =C—H stretching vibration of the aromatic ring in most of the compounds studied was hidden by the Nujol band. Nearly all compounds examined possessed one band in the 1634–1570 cm^{-1} region, and one or two sharp bands in the 1538–1493 cm^{-1} region. These regions are typical of the thiazole structure *(11)*.

The chemical shifts and coupling constants in the nmr spectra of 2-aminothiazoles are summarized in Table IV. The assignments were as follows: In I_f, two singlets were observed at 7.67 and 7.57 τ for the two methyl groups. The singlet at 7.67 τ was assigned to the methyl group, and the one at 7.57 τ to the acetyl group. A singlet at 6.17 τ integrating for two protons was assigned to the amino group. In I_f', the hydrobromide salt of I_f, the introduction of a positive charge on the amino nitrogen, shifted the methyl signal to lower fields. This supports the assignment of the resonance signal at 7.67 τ in I_f to the methyl protons. One important feature to notice is that the amino group protons in all the heterocycles studied appeared at lower fields than in I_f. This large downfield shift was attributed to the presence of electron-withdrawing substituents at position 4 of the ring. The aromatic protons appeared as complex patterns and could not be analyzed easily. The center of the complex band was taken as the chemical shift of the aromatic protons.

Experimental

Melting points were taken by a Kofler Hot Bench and are uncorrected. Elemental analyses were performed by Alfred Bernhardt's Laboratories, Ruhr, Germany. Ultraviolet absorption spectra were recorded by a Unicam SP800B uv spectrophotometer. Infrared spectra were recorded by a Perkin-Elmer Model 137B infracord spectrophotometer as Nujol mulls. Nuclear magnetic resonance spectra were measured on a Varian A60A spectrometer as solutions in deuterated dimethylsulfoxide (DMSO-d_6), or trifluoroacetic acid (TFA) with tetramethylsilane (TMS) as the internal reference. All τ-values are correct to 0.01 τ unit.

General method for preparation of α-bromoketones. The ketone (0.1 mole) in a suitable solvent was treated with bromine (0.11 mole). The mixture was continuously stirred at the specified temperature (Table I) for ½ hr and allowed to warm to room temperature. Excess sol-

Table III. Infrared and Ultraviolet Spectral Data For 2-Aminothiazoles[a]

	νNH_2, cm^{-1}	$\nu C{=}C$, $C{=}N$, cm^{-1}	$\nu C{-}H$ in-plane deformation, cm^{-1}	$\nu C{-}H$ out-of-plane deformation, cm^{-1}	λmax, nm ($\log\epsilon$)
I_a	3400	1610s, 1520s, 1310s	1200m, 1144m, 1117m, 1030s	890m, 875m, 860m, 825m, 815m, 722s, 695m	205(4.43); 233(4.22); 275(3.92)
I_b	3450	1650s, 1585m, 1525s, 1363s, 1317m	1242s, 1225w, 1130m, 1125m, 1100s	890w, 825s, 760m, 750w, 735s, 692m	203(4.02); 227(4.39); 383(3.52)
I_c	3400	1670s, 1615s, 1550s, 1375m, 1350s, 1317w	1225w, 1210m, 1138m, 1062m, 1050s, 1000s	845w, 833s, 745w, 712s, 695m, 675m	202(4.05); 230(4.26); 302(3.75)
I_d	3450	1650s, 1605s, 1550m, 1535m, 1375m, 1325s	1217m, 1117m, 1040m	855w, 845s, 725s, 690w	203(4.06); 218(3.98); 235(3.36); 345(2.98)
I_f	3400	1680s, 1625s, 1360w, 1325s,	1112m, 1035w, 985s, 920m,	820m, 770m, 730m	201(3.52); 223(3.86); 310(4.03)
I_f'[b]		1650s, 1335w, 1292s	1075m, 1025m, 975m	810m, 720m, 680w	
I_g'[b]		1650s, 1343m	1225w, 1224m, 1165w, 1105w	895s, 770m, 725m, 700m	202(2.96); 220(3.20); 262(3.95)
I_h'[b]		1650s, 1600w	1218m, 1165w	935m, 805w, 755m, 735m	
I_h	3400	1700s, 1650s, 1540m, 1308m	1100m, 1165w	925m, 775w, 735s, 725w, 695w	
II_a	3400	1620s, 1545m, 1525m, 1345s, 1305w	1065w, 1040m, 915s	875m, 870w, 770s, 745m, 725m, 690w	
II_b	3450	1650s, 1605s, 1550m, 1520s, 1385s	1195m, 1120w, 1063m, 1020w, 950m	910s, 845m, 830s, 775w, 745s, 720m, 690w	201(4.02); 223(4.25); 268(4.27)

[a] s = strong, m = medium, w = weak, EtOH = absolute ethanol. [b] I_f', I_g', and I_h' refer to hydrobromides.

Table IV. Nmr Data For 2-Aminothiazoles[a]

	Solvent	Aliphatic-H	Aromatic H[b]	NH_2 or NH_3^+[b]	H-5	J_{ab},[c] Hz	J_{bc},[d] Hz	J_{ac},[d] Hz
I_a	DMSO	6.93m, 7.55m	2.25d, 2.47d, 2.58d	4.05b	2.65s	8.7	2	
	$CDCl_3$	7.02m, 7.85m	2.3d, 2.6d, 2.68d	4.75b	3.26	9.0	2	
I_c	DMSO		1.28d, 2.13d	2.70s	2.53s	6.0		
I_d	DMSO		1.5d, 1.85d	4.06b	2.28s	9.0		
I_f	DMSO	7.67s, CH_3 7.57s, $COCH_3$		6.17b	2.53s			
I_f'	DMSO	7.47, CH_3 7.40, $COCH_3$		0.33b				
I_g'	DMSO	7.5m, 8.24m		0.60b				
I_h	DMSO	6.0, CH_2	2.5m	2.9s	2.10s			
I_h'	DMSO	6.0, CH_2	1.85m, 1.95m	0.33b	1.93s			
II_b	DMSO	6.96m, 6.63m	2.44d, 1.87dd, 1.6d	2.80b		8.0	2.5	0.70
	TFA	6.95m, 6.61	2.26d, 1.53dd, 1.42d	1.40b		8.0	3.0	0.70

[a] Compounds not mentioned in this table were insoluble in the solvents employed. [b] s = singlet, d = doublet, dd = double doublet, m = multiplet, b = broad, [c] J_{ab} = coupling constant in all AB systems. [d] J_{ac} and J_{bc} are coupling constants in all ABC systems. (J_{ab}, J_{bc}, and J_{ac} are from first-order analysis of aromatic protons. Chemical shifts are given in τ-units.

vent was distilled off under reduced pressure. Recrystallization of the crude product gave pure α-bromoketone. When oily products were obtained, extraction with ether was necessary. After removal of the ether, the oily products were distilled under vacuum. Condition of the reaction, yields, and physical properties of α-haloketones are listed in Table I.

General procedure for preparation of substituted 2-aminothiazoles. *Method A.* The halogen (0.2 mole) was added to a mixture of the ketone (0.2 mole) and thiourea (0.4 mole). When iodine was used, it was added all at once, but bromine was added dropwise. The reaction mixture was heated in a steam bath for ½ hr, diluted with water, and heated until the solid dissolved. The free sulfur was filtered off, the solution was cooled and made alkaline with concentrated ammonia solution. Recrystallization of the crude product gave the pure 2-aminothiazole derivative.

Method B. Thiourea (0.2 mole) in ethanol (50 ml) was added to the α-haloketone (0.2 mole) in ethanol (50 ml). The reaction mixture was refluxed for 4 hr. Excess alcohol was removed, the solution cooled and filtered. Recrystallization of the product gave pure 2-aminothiazole derivatives. Conditions of the reaction, yields and physi-

cal properties of the synthesized 2-aminothiazoles are summarized in Table II. Some derivatives of 2-aminothiazoles were prepared by the method of Shriner et al. *(12)* and are listed in Table II.

Literature Cited

(1) Badger, G. M., "The Chemistry of Heterocyclic Compounds," pp 207, 209, Academic Press, New York, N. Y., 1961.
(2) Dodson, R. M., *J. Amer. Chem. Soc.*, **67**, 2242 (1945).
(3) Dodson, R. M., *ibid.*, **66**, 871 (1946).
(4) Dodson, R. M., *ibid.*, **69**, 1813 (1947).
(5) Dodson, R. M., *ibid.*, **72**, 3722 (1950).
(6) Hantzsch, H., *Ann.*, **249**, 1, 31 (1888).
(7) Hantzsch, H., *Ann.*, **250**, 257, 281 (1889).
(8) Mijovic, M. P., Waker, J., *J. Chem. Soc.*, 3381 (1961).
(9) Modena, G., Risaliti, A., *Bull. Sci. Fac. Chim. Ind.* Bolgara, 11 (1953).
(10) Okamiya, J., *J. Chem. Soc.* (Japan), 80 (1959).
(11) Randall, H. M., Fowler, R. B., Fuson, N., Dangle, J. R., "Infrared Determinations of Organic Structures," Van Nostrand, New York, N. Y., 1950.
(12) Shriner, R. L., Fuson, R. C., Curtin, D. Y., "Systematic Identification of Organic Compounds," pp 226, 229, Wiley, New York, N. Y., 1956.

Received for review February 16, 1972. Accepted October 10, 1972. Research was supported by the University of Baghdad.

Synthesis and Spectral Data For Quinoxaline Derivatives

George Y. Sarkis[1] and Subhi Al-Azawe
Department of Chemistry, College of Science, University of Baghdad, Baghdad Adhamiya-Iraq

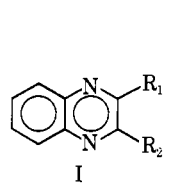
Thirteen quinoxaline derivatives were synthesized by the interaction of *o*-phenylenediamine with either α-bromoketones or the glyoxal derivatives of the corresponding methylketones. The uv, ir, and nmr spectral data for the quinoxaline derivatives obtained are presented.

Thirteen quinoxaline derivatives were prepared by the interaction of *o*-phenylenediamine with either α-bromoketones (Method A) *(3, 10, 11)*, or the glyoxal derivatives of the corresponding methylketones (Method B) *(6)*. The α-bromoketones used were: 2-bromoacetylfluorene, *p*-hydroxyphenacylbromide, *p*-nitrophenacylbromide, 2-bromo-1-tetralone, 3-bromoacetoacetic ester, 5-bromoacetylindane, 3-bromoacetylindol, and 2-bromo-7-nitro-1-tetralone. The ketones used in Method B were: *p*-hydroxyacetophenone, 7-nitro-1-tetralone, 2-acetylthiophene, 2-acetylfuran, and α-, β-, and γ-acetylpyridines. The structure and physical properties of the synthesized quinoxalines are given in Table I. The uv, ir, and nmr spectral data are presented in Tables II and III.

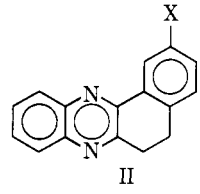
Dihydroquinoxaline, which is the primary condensation product, is so readily oxidized to the corresponding quinoxaline that it is not isolated under the standard conditions *(7)*. In Method B, the ketones were oxidized to the corresponding glyoxal derivative with selenium dioxide in dioxane solution. It was not attempted in this study to

[1]Present address; Department of Chemistry, McGill University, Montreal 101, Que., Canada. To whom correspondence should be addressed.

Table I. Physical Properties of Quinoxaline Derivatives[a]



I



II

	Molecular formula	R_1 (or X)	R_2	Mp, °C	% Yield Method A	% Yield Method B	Ref. time	Crystn solvent	4-N-oxide mp, °C (crystn solvent)
I_a	$C_{21}H_{14}N_2$	2-fluorenyl	H	200–201[b]	75		5	Ethanol	
I_b	$C_{14}H_{10}N_2O$	C_6H_4·OH(p)	H	209–210[c]	68	73	2	Benzene	234–235 (Benzene)
I_c	$C_{14}H_{19}N_3O_2$	C_6H_4·NO_2(p)	H	189–190[d]	60		4	Ligroin (bp 120)	267–268 (Acetic acid)
I_d	$C_{12}H_{12}N_2O_2$	CH_3	CO_2Et	70–71[e]	25		8	Water	
I_e	$C_{17}H_{14}N_2$	5-Indanyl	H	116–117	50		4	Methanol	
I_f	$C_{16}H_{11}N_3$	3-Indolyl	H	208–209[f]	60		4	Acetic acid	
I_g	$C_{12}H_8N_2S$	2-Thienyl	H	120–121[g]	55	65	5	Methanol	
I_h	$C_{13}H_9N_3$	α-Pyridyl	H	113–114[h]		60	5	Methanol	
I_i	$C_{13}H_9N_3$	β-Pyridyl	H	243–244		55	5	Methanol	
I_j	$C_{13}H_9N_3$	γ-Pyridyl	H	255–256		45	6	Methanol	
I_k	$C_{12}H_8N_2O$	2-Furyl	H	101–102[i]		72	5	Methanol–water	
II_a	$C_{16}H_{12}N_2$	H	...	152–153[j]	55		4	Ligroin (bp 40–60)	
II_b	$C_{16}H_{11}N_3O_2$	NO_2	...	300–301	65	75	2	Acetic acid	

[a] Elemental analyses (C,H,N) in agreement with theoretical values were obtained and submitted for review. [b] Ref. 9. mp 193°C. [c] Ref. 8. mp 204°C. [d] Ref. 3. 4. mp 187–188°C. [e] Ref. 1. mp 73°C. [f] Ref. 14. mp 202–203. [g] Ref. 5. mp 117–119°C. [h] Ref. 16. mp 112–114°C. [i] Ref. 6. mp 101°C. [j] Ref. 13. 152.5°C.