of them depending in a different manner on *p*H, concentration, temperature, mode of denaturation, and on other factors. It is not surprising, therefore, that different over-all orders of kinetics result when different properties of the protein are used as criteria of denaturation.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, BROOKLYN COLLEGE]

Preparation of Secondary and Tertiary 2-Thiazolylamines

BY IRVING ALLAN KAYE AND CHESTER L. PARRIS[1]

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Basically mono- or disubstituted derivatives of 2-aminothiazole were prepared by condensation of an appropriately substituted thiourea with dimethylchloroacetal. The reaction of 2-bromothiazole with either a primary or secondary amine was a less satisfactory method for the preparation of these compounds.

In a recent patent[2] there appeared a description of a method for the preparation, in low yield, of N,N-dimethyl-N′-benzyl-N′-(2-thiazolyl)-ethylenediamine (I). Since compounds of this type are of interest as chemotherapeutic agents, an investigation of some methods for the preparation of secondary and tertiary 2-thiazolylamines was initiated.

Sondern and Breivogel[2] prepared the diamine (I) by refluxing a mixture of 2-bromothiazole and N,N-dimethyl-N′-benzylethylenediamine in pyridine. Although we were unable to effect an improvement in their yield of this compound, a similar reaction (Method B) with 2-diethylaminoethylamine afforded a 60% yield of N,N-diethyl-N′-(2-thiazolyl)-ethylenediamine.[3] When the reaction was conducted in a high-boiling hydrocarbon rather than pyridine, yields fell off considerably. For instance, benzylamine and 2-bromothiazole in either cumene or xylene gave only a 9.5% yield of 2-benzylaminothiazole. Under the same conditions, dibenzylamine gave only tars from which none of the desired product could be isolated. This method suffers from the disadvantage that the elevated temperatures necessary for reaction are accompanied by extensive decomposition of the reaction mixture. The preparation of 2-bromothiazole is also rather lengthy and troublesome, especially when large amounts are required.[4]

A few 2-thiazolyl tertiary amines, containing substituents on either or both the nuclear carbons, have been prepared (in unstated yield) by condensing N,N-disubstituted thioureas with α-haloketones.[5a–e] Replacement of the latter by dimethyl chloroacetal (Method A) offered a route which was superior to Method B for the preparation of both N-mono- and N-disubstituted 2-aminothiazoles. The intermediate unsymmetrically disubstituted thioureas were prepared by treatment of the corresponding cyanamides with hydrogen sulfide in ammoniacal methanol.[6] N-Monosubstituted thioureas were obtained from isothiocyanates by reaction with aqueous ammonia.[7]

The reductive alkylation of 2-aminothiazole with benzaldehyde in formic acid gave intractable tars and none of the expected 2-benzylaminothiazole. Similar results were obtained by refluxing a solution of the pre-formed Schiff base (2-benzylideneaminothiazole) in formic acid.[8]

One of the products, N,N-diethyl-N′-benzyl-N′-(2-thiazolyl)-ethylenediamine, tested for antihistaminic activity on the isolated guinea pig ileum strip, showed 1.5% of the activity of Pyribenzamine.[9] This compound has recently been reported[10] as a solid melting at 121–122°. Since our product is a liquid at room temperature, a property shared by other compounds of this type,[11] and was prepared by a method which should yield compounds of unequivocal structure, it would appear that the procedure of Fox and Wenner,[10] involving a catalytic reductive alkylation, gave some other substance. N,N-Dimethyl-N′-benzyl-N′-(2-thiazolyl)-ethylenediamine (I), previously patented as an antihistaminic,[2] was 20% as active as Pyribenzamine.[12] Against acetylcholine, this compound (I) had 0.15% of the activity of atropine.[12]

(1) From a thesis submitted by Chester L. Parris to the Graduate Faculty of Brooklyn College, June, 1951, in partial fulfillment of the requirements for the Master of Arts degree.

(2) C. W. Sondern and P. J. Breivogel, U. S. Patent 2,440,703, May 4, 1948.

(3) One compound of this type, 2[(4-diethylamino-1-methyl-butyl)-amino]-thiazole, was prepared in 18% yield in similar fashion by J. N. Ashley and J. F. Grove, *J. Chem. Soc.*, 768 (1945).

(4) K. Ganapathi and A. Venkataraman, *Proc. Indian Acad. Sci.*, **22A**, 362 (1945); *C. A.*, **40**, 4059 (1946).

(5) (a) R. H. Wiley, D. C. England and L. C. Behr, "Organic Reactions," vol. VI, John Wiley and Sons, Inc., New York, N. Y., 1951, pp. 400–402; (b) G. Marchesini, *Gazz. chim. ital.*, **24**, 65 (1894); (c) F. A. Eberly and F. B. Dains, *Univ. Kansas Sci. Bull.*, **24**, 45 (1936); *C. A.*, **32**, 3398 (1938); (d) E. Ochiai and K. Kokeguti, *J. Pharm. Soc. Japan*, **60**, 271 (1940); *C. A.*, **35**, 458 (1941); (e) L. L. Bambas, U. S. Patent 2,389,126, November 20, 1945.

(6) O. Wallach, *Ber.*, **32**, 1872 (1899), prepared N,N-dibenzylthiourea, m.p. 139–140°, in this fashion. His dibenzylcyanamide, prepared from dibenzylamine and cyanogen bromide, was collected at 145–148° (10 mm.), m.p. 54°.

(7) A. W. Hofmann, *ibid.*, **1**, 201 (1868).

(8) I. A. Kaye and I. C. Kogon, *Rec. trav. chim.*, **71**, in press (1952).

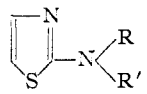
(9) Pyribenzamine is the trade mark for N,N-dimethyl-N′-benzyl-N′-(2-pyridyl)-ethylenediamine monohydrochloride, Ciba Pharmaceutical Products, Inc.

(10) H. H. Fox and W. Wenner, *J. Org. Chem.*, **16**, 225 (1951).

(11) C. P. Huttrer, *Enzymologia*, **12**, 278 (1948).

(12) This information on the pharmacological activities was kindly offered by Dr. Harold Blumberg and Mr. Eric Meyer of Endo Products, Inc.

TABLE I

2-AMINOTHIAZOLES OF FORMULA 

R	R'	Method	B.p., °C.	Mm.	Yield, %	M.p., °C.	Formula	Nitrogen analyses, % Calcd.	Found
C_2H_5	H	A			70[a]	49-50[b]	$C_5H_8N_2S$	21.86	21.49
						182-183[c]	$C_5H_8N_2S \cdot C_6H_3N_3O_7$[c]	19.60	19.62
$C_6H_5CH_2$	H	A			94[a]	126-127.5[d]	$C_{10}H_{10}N_2S$	14.72	14.55
$(C_2H_5)_2NCH_2CH_2$	H	B	112-115	0.4	60[e]	181.5-182.5[d,f]	$C_9H_{17}N_3S \cdot 2HCl$	26.05[g]	25.78[g]
C_2H_5	$C_6H_5CH_2$	A	119-122	.10	28[e]	153.5-154[c]	$C_{12}H_{14}N_2S$	12.84	12.53
							$C_{12}H_{14}N_2S \cdot C_6H_3N_3O_7$	15.65	15.35
$C_6H_5CH_2$	$C_6H_5CH_2$	A	116-120	.05	57[e]	167-167.5[d,f]	$C_{17}H_{16}N_2S$	9.99	9.81
							$C_{17}H_{16}N_2S \cdot HCl$	11.19[g]	11.13[g]
$(CH_3)_2NCH_2CH_2$	$C_6H_5CH_2$	B	118-125	.04	34[e]	158.5-159.5[d,h]	$C_{14}H_{19}N_3S$	16.07	15.72
							$C_{14}H_{19}N_3S \cdot H_2C_2O_4$	11.96	11.89
$(C_2H_5)_2NCH_2CH_2$	$C_6H_5CH_2$	A	135-139	.09	45[i]	147.5-148.5[d,h]	$C_{16}H_{23}N_3S$	14.52	14.41
							$C_{16}H_{23}N_3S \cdot H_2C_2O_4$	11.07	10.98

[a] Crude product. [b] Recrystallized twice from hexane. [c] Picrate, recrystallized from acetone. [d] Recrystallized from isopropyl alcohol. [e] Yield of distillate. [f] Hydrochloride. [g] Chloride analysis. [h] Oxalate. [i] Since the intermediate thiourea was not isolated, the yield is based on the weight of benzyl-(2-diethylaminoethyl)-cyanamide.

Experimental[13]

Intermediates.—2-Bromothiazole, b.p. 82-85° (32 mm.), was obtained in 67% yield by the method of Ganapathi and Venkataraman.[4] Benzylidene ethylamine, b.p. 128-129° (95 mm.), prepared in 93% yield by the method of Campbell, *et al.*,[14] upon reduction in the presence of palladium–charcoal, gave a 94% yield of N-ethylbenzylamine, b.p. 124-125° (82 mm.).[15] Benzyl isothiocyanate,[7] b.p. 105-107° (3 mm.), and ethyl isothiocyanate,[16] b.p. 60-70° (120 mm.), were obtained in 91 and 89% yield, respectively, by the method of Moore and Crossley.[17] N-Benzoyl-N'-benzylthiourea, prepared by the method of Frank and Smith[18] in 71% yield, melted at 124-124.5° after recrystallization from isopropyl alcohol. The melting point has been reported as 145°.[19]

Anal. Calcd. for $C_{15}H_{14}N_2OS$: N, 10.37. Found: N, 10.30.

Alkaline cleavage of the benzoyl group[18] gave N-benzylthiourea[20] in 92% yield. This product was obtained in similar yield by treatment of benzyl isothiocyanate with aqueous ammonia. In this way N-ethylthiourea[7] was obtained in 70% yield from ethyl isothiocyanate.

N-Benzoyl-N',N'-dibenzylthiourea.—A 79.5% yield, m.p. 132-141°, was obtained by the method of Frank and Smith.[18] After three recrystallizations from isopropyl alcohol the compound melted at 142-143°.

Anal. Calcd. for $C_{22}H_{20}N_2OS$: N, 7.77. Found: N, 7.71.

The benzoyl group resisted alkaline hydrolysis.[18]

Benzyl-(2-diethylaminoethyl)-cyanamide.—A solution of 82.5 g. (0.4 mole) of N,N-diethyl-N'-benzylethylenediamine[21] in 100 ml. of dry benzene was added dropwise, with stirring and cooling, to 21.2 g. (0.2 mole) of cyanogen bromide[22] dissolved in 100 ml. of the same solvent. After addition was complete, the clear solution was heated on a steam-bath for 4 hours, cooled and treated with 20 g. of sodium hydroxide dissolved in 150 ml. of water. After thorough shaking, the aqueous layer was separated and extracted twice with 50-ml. portions of benzene. The combined benzene extracts were distilled at atmospheric pressure to remove solvent. A colorless liquid, weighing 41.3 g. (89%), was collected at 179-180° (5 mm.) after 37.1 g. of the excess starting diamine had been recovered at 128-134° (5 mm.).

Anal. Calcd. for $C_{14}H_{21}N_3$: N, 18.17. Found: N, 17.98.

Ethylbenzylcyanamide[23] and dibenzylcyanamide[6] were similarly prepared except for the fact that the hydrobromides of the excess starting amines, which precipitated during the reaction, were removed by filtration at the end of the 4-hour reflux period. The filtrates, after removal of the benzene, were distilled *in vacuo*. A 95% yield of ethylbenzylcyanamide was isolated, b.p. 157-158° (12 mm.), while dibenzylcyanamide, b.p. 180-185° (3 mm.), m.p. 60-62° was formed in quantitative yield. The latter was also obtained in 60% yield from calcium cyanamide and benzyl chloride.[24]

N,N-Disubstituted Thioureas. N-Ethyl-N-benzylthiourea.—Gaseous ammonia and hydrogen sulfide were passed, at a lively rate, into a solution of 17.6 g. (0.11 mole) of ethylbenzylcyanamide in 125 ml. of methanol, previously saturated with ammonia. The temperature of the solution wss maintained below 35° during this reaction. After one hour, the passage of ammonia was discontinued; the hydrogen sulfide flow was stopped one hour later. Upon adding ice and water, a white precipitate appeared which was removed by filtration, washed with water and air-dried. The product, weighing 15.8 g. (74%), melted at 113-115°. A sample, recrystallized twice from isopropyl alcohol, melted at 122.5-123.5°.

Anal. Calcd. for $C_{10}H_{14}N_2S$: N, 14.42. Found: N, 14.48.

N,N-Dibenzylthiourea[6] was prepared in 73% yield by this method. Benzyl-(2-diethylaminoethyl)-cyanamide, treated similarly, gave a light green oil which was cyclized without purification to N,N-diethyl-N'-benzyl-N'-(2-thiazolyl)-ethylenediamine.

2-Benzylaminothiazole.[25] **Method A.**—A mixture of 74.8 g. (0.45 mole) of N-benzylthiourea, 67.3 g. (0.54 mole) of dimethyl chloroacetal[26a] and 250 ml. of water formed an orange-red solution after heating on a steam-bath for 18 hours. About one liter of water was added followed by sufficient aqueous sodium hydroxide to make the mixture alkaline. The resulting light tan precipitate was collected by filtration, washed with water and dried at 80° to constant weight. The crude amine, weighing 80.0 g. (93%), melted at 117-124°. After three recrystallizations from

(13) Melting points are corrected; boiling points are not.

(14) K. N. Campbell, C. H. Helbing, M. P. Florkowski and B. K. Campbell, THIS JOURNAL, **70**, 3868 (1948).

(15) P. C. Young and R. Robertson, *J. Chem. Soc.*, 271 (1933).

(16) M. Berthelot, *Compt. rend.*, **130**, 441 (1900).

(17) M. L. Moore and F. S. Crossley in *Org. Syntheses*, **21**, 81 (1941).

(18) R. L. Frank and P. V. Smith, *ibid.*, **28**, 89 (1948).

(19) P. Miquel, *Ann. chim. phys.*, [5] **11**, 310 (1877).

(20) A. E. Dixon, *J. Chem. Soc.*, **59**, 551 (1889).

(21) I. A. Kaye and C. L. Parris, *J. Org. Chem.*, **16**, 1859 (1951).

(22) W. W. Hartman and E. E. Dreger in "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 150.

(23) J. von Braun and A. Freidsam, *Ber.*, **63B**, 2407 (1930).

(24) E. B. Vliet in "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1941, p. 203. Samples of calcium cyanamide and dibenzylamine were generously supplied by the American Cyanamid Co. and the Heyden Chemical Corp., respectively.

(25) The preparation of this compound has not been described previously although the amine has been used in a study of the effect of 2-aminothiazoles on the thyroid gland by D. Bovet, J. Bablet and J. Fournel, *Ann. inst. Pasteur*, **72**, 105 (1946); *C. A.*, **41**, 5633 (1947).

(26) Samples were kindly donated by (a) the General Aniline and Film Corp. and (b) Sharples Chemicals, Inc.

isopropyl alcohol the compound melted at 126–127.5°. Other thiazoles, prepared by this procedure, are listed in Table I.

From 16.4 g. (0.1 mole) of 2-bromothiazole[4] and 21.4 g. (0.2 mole) of benzylamine[26b] in 75 ml. of either cumene or xylene, refluxed for 72 hours and isolated by a modification of Method B, there was obtained 1.8 g. (9.5%) of 2-benzylaminothiazole, m.p. 117–121°. The compound, recrystallized three times from isopropyl alcohol, melted at 127.5–128.5° and showed no depression in melting point when mixed with product obtained by Method A.

N,N-Diethyl-N'-(2-thiazolyl)-ethylenediamine.[10] Method B.—A solution of 8.2 g. (0.05 mole) of 2-bromothiazole and 11.6 g. (0.10 mole) of 2-diethylaminoethylamine in 12 g. of pyridine was refluxed for 3.5 hours. After cooling to room temperature, 100 ml. of water was added. The mixture was saturated with potassium carbonate and then extracted several times with ether. The combined ether extracts were dried over anhydrous potassium carbonate and the solvent removed. Distillation of the residue *in vacuo* gave 6.0 g. (60%) of a light yellow oil, b.p. 112–115° (0.4 mm.).

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BROOKLYN 10, NEW YORK

[CONTRIBUTION FROM DEPARTMENT OF CHEMISTRY, COLLEGE OF LIBERAL ARTS AND SCIENCES, TEMPLE UNIVERSITY]

A New Approach to 3-Indolecarboxaldehyde

BY FLOYD T. TYSON AND JOHN T. SHAW

The number of steps required in heretofore published syntheses of 3-indolecarboxaldehyde led to a search for a shorter method involving more readily available materials. Investigation of this problem has yielded two new methods: one method involves the use of carbon monoxide at elevated pressures with a salt of indole, and the second method is a modification of the N-methylformanilide synthesis. Of particular import is the possible applicability of the pressure reaction to other compounds of reactivity comparable to indole.

In the former preparations of 3-indolecarboxaldehyde, the reactivity of the 3-position in indole has been evidenced by the variety of methods used to place the formyl group in this position, one of the most recent being the N-methylformanilide[1] synthesis. Other well-known reactions have been used to accomplish this end: the Reimer–Tiemann[2] reaction, a modified Gattermann[3] aldehyde synthesis, a modified Claisen[4] reaction and the Grignard reaction.[5] The preparation of 3-indolecarboxylic acid by a reaction between indolemagnesium iodide and carbon dioxide[6] suggested that possibly the metal salts of indole might be sufficiently reactive with carbon monoxide under suitable conditions to yield the desired aldehyde.

An appropriate solvent for the reaction was found to be commercial dimethylformamide, although pyridine or excess indole can be used, but with decreased yields. The influence of various reaction conditions may be summarized as follows: Over the pressure and temperature ranges investigated, 47 to 480 atmospheres and 25 to 200°, respectively, the optimum conditions were found to be 480 atmospheres at 135 to 150° for a bomb of total void 120 ml., half-full of liquid reactants. The yield of aldehyde was 57%, based upon the potassium salt of indole. Using the optimum conditions cited above, potassium indole gave 24% higher yield than sodium indole, and 48% higher than lithium indole. This latter result might have been expected as the increase in atomic weight of the metal would tend to make the nitrogen metal bond more ionic and increase the tendency toward desirable electronic shifts. Use of indole or indolemagnesium bromide, the latter in diethyl ether, gave negative results. The presence of a slight amount of excess potassium amide or the use of very dry dimethylformamide, was found to influence the yield favorably. It was found that there was no correlation between pressure drop of carbon monoxide and the amount of aldehyde formed, the latter always being less than the equivalent amount of carbon monoxide consumed. In the absence of carbon monoxide there was no yield of aldehyde, all other conditions of the reaction being identical. The synthesis may prove to be applicable to other compounds of reactivity comparable to indole such as pyrrole, imidazole and pyrazole, since the metallic salts of these compounds are known, the anions of which like that of indole, are thought to be stabilized by resonance.

Since 3-indolecarboxaldehyde is appreciably soluble in dimethylformamide or aqueous solutions thereof, it is removed from the reaction mixture either by refluxing with sodium hydroxide or by distillation under reduced pressure. In both syntheses the 3-indolecarboxaldehyde was converted to the 3-indolalacetophenone[7] for identification purposes.

Experimental

3-Indolecarboxaldehyde Preparation by Reaction of Potassium Indole with Carbon Monoxide.—An Aminco autoclave, #406-35BX3, of 120 ml. void, fabricated with 18-8 stainless steel, with heater and shaker was used for the pressure reactions with carbon monoxide. Into a 3-necked 100-ml. flask, fitted with a suitable mineral oil trap and containing 50 ml. of liquid ammonia with a 2″ suspended iron nail, was added 4.0 g. (0.103 mole) of potassium. After completion of reaction which was evidenced by disappearance of the blue color of the potassium solution, 11.7 g. (0.10 mole) of indole was added. The excess ammonia was removed by evaporation and the remaining potassium indole heated to about 170° for 0.25 hour. (Potassium hydroxide[8] could have been used to prepare potassium indole also.) The flask was allowed to cool to room temperature under dry nitrogen after which 45 ml. of anhydrous dimethylformamide, dried by boiling with calcium hydride, was added.

(1) A. C. Shabica, E. E. Howe, J. B. Ziegler and M. Tishler, THIS JOURNAL, **68**, 1156 (1946).

(2) A. Ellinger, *Ber.*, **39**, 2515 (1906).

(3) W. J. Boyd and W. Robson, *Biochem. J.*, **29**, 555 (1935).

(4) J. Elks, D. F. Elliot and B. A. Hems, *J. Chem. Soc.*, 629 (1944).

(5) Dow Chemical Co., British Patent 618,638, Feb. 24, 1949 (*C. A.*, **43**, 5806 (1949)).

(6) R. Majima, *Ber.*, **55**, 3865 (1922).

(7) R. B. Van Order and H. G. Lindwall, *J. Org. Chem.*, **10**, 128 (1945).

(8) R. Weissgerber, *Ber.*, **43**, 3520 (1910).