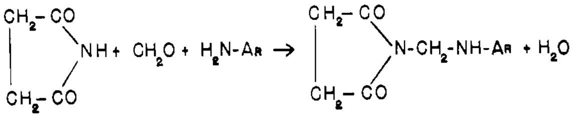
Identification of Amines: Succinimidomethyl Derivatives of Primary Amines

MELDRUM B. WINSTEAD, KAY V. ANTHONY, LINDA LIDDICK THOMAS,
ROBERT G. STRACHAN, and HAROLD J. RICHWINE
Department of Chemistry, Bucknell University, Lewisburg, Pa.

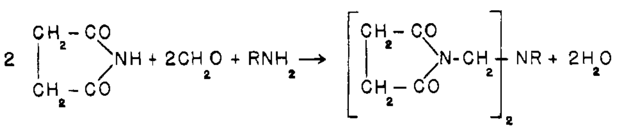
EARLIER STUDIES in this laboratory have shown that the preparation of *N*-(arylaminomethyl)-, *N*-(alkylarylaminomethyl)-, and *N*-(dialkylaminomethyl)phthalimides by the condensation of primary or secondary aromatic amines or secondary aliphatic amines with formaldehyde and phthalimide is a general reaction that is particularly useful for the identification of primary and secondary amines (*3*, *6*). It has also been shown that primary aliphatic amines will condense with two equivalents each of phthalimide and formaldehyde to yield *N,N'*-[(alkylimino)-dimethylene]diphthalimide derivatives (*3*). This reaction has now been extended to include the preparation of some *N*-(arylaminomethyl)succinimide derivatives by the condenation of primary aromatic amines with formaldehyde and succinimide.



Such compounds are useful for the characterization of primary aromatic amines since they are readily prepared and have sharp melting points. A survey of the literature has revealed that only *N*-(morpholinomethyl) succinimide has been prepared by this method (*4*). However, *N*-(piperidinomethyl)succinimide has been prepared by the reaction of *N*-hydroxymethylsuccinimide with piperidine (*1*).

A possible mechanism of this reaction involves the initial formation of *N*-hydroxymethylsuccinimide which subsequently reacts with the aromatic amine. Thus in one experiment *N*-hydroxymethylsuccinimide reacted with aniline to produce *N*-(anilinomethyl)succinimide, identical in every respect to that made by condensing succinimide and formaldehyde with aniline. Alternately, the formaldehyde may react initially with the aromatic amine to form the *N*-hydroxymethyl intermediate which would subsequently react with succinimide to form the desired derivative (*5*).

The condensation of primary aliphatic amines with formaldehyde and succinimide results in the formation of *N,N'*-[(alkylimino)dimethylene]disuccinimide derivatives (or bis-(succinimidomethyl)alkylamines).



Thus this reaction differs markedly from that observed with primary aromatic amines. A similar condensation reaction between phthalimide, formaldehyde and primary aliphatic amines was reported earlier (*3*), and the results are also in harmony with the observations of Haworth and coworkers (*2*).

Table I lists 22 *N*-(arylaminomethyl)succinimides, and Table II lists 11 *N,N'*-[(alkylimino)dimethylene]disuccinimides (or bis-succinimidomethyl)alkylamines).

EXPERIMENTAL

N-(Arylaminomethyl)succinimide Derivatives. Three grams (0.03 mole) of succinimide was dissolved in 35 ml. of 95% ethanol. Two ml. of 37% formaldehyde was added and reflux was begun. Next, 0.032 mole of the primary aromatic amine was added, and the alcoholic solution was refluxed for 1 hour (or longer, if so indicated in Table I). In a few cases the derivative began to separate from the boiling solution shortly after reflux was begun. Whenever this occurred reflux was continued for only 5 minutes longer, then the solution was cooled, and the product collected.

The reaction mixture was thoroughly chilled, and the product was filtered and dried. One or two recrystallizations from 95% ethanol solvent (unless indicated otherwise in Table I) resulted in a pure derivative.

N,N'-[(alkylimino)dimethylene]disuccinimides. Three grams (0.03 mole) of succinimide was suspended in 5–10 ml. of 95% ethanol; 2 ml. of 37% formaldehyde was added and the solution was warmed until homogenous. Next, 0.016 mole of the primary aliphatic amine was added, and the alcoholic solution was refluxed gently for approximately 30 minutes. The reaction mixture was then thoroughly chilled overnight or longer with occasional scratching in order to obtain crystals. A portion of the solution was allowed to evaporate occasionally before crystallization occurred. The solution was then filtered, the precipitate dried, then recrystallized from a small quantity of 95% ethanol until the bis(succinimidomethyl)alkylamine derivative had a constant melting point.

N-Hydroxymethylsuccinimide. This compound was prepared by adding succinimide to boiling 37% formaldehyde containing a small amount of potassium carbonate, according to the method described by Cherbuliez and Sulzer (*1*). M.p., 64–6°; reported m.p., 66°.

N-(Anilinomethyl)succinimide. In addition to being prepared by refluxing succinimide and 37% formaldehyde with aniline in 95% ethanol, this compound was also prepared by refluxing equimolar quantities of *N*-hydroxymethylsuccinimide and aniline in 95% ethanol solvent for 1 hour, cooling, and recrystallizing from 95% ethanol. M.p., 171–2°. Mixed melting point and infrared spectral analysis showed this compound to be identical to that obtained by the general method of preparation of *N*-(arylaminomethyl)-succinimides.

Table I. *N*-(Arylaminomethyl)succinimide Derivatives[a, b]

Amine	M.p., ° C.	Yield, %	Formula	Nitrogen, % Calcd.	Nitrogen, % Found
p-Aminoacetophenone[c]	203–205	72	$C_{13}H_{14}N_2O_3$	11.37	11.36
p-Aminobenzoic acid[d]	224–225	60	$C_{12}H_{12}N_2O_4$	11.29	11.32
3-Aminoquinoline	190–191	42	$C_{14}H_{13}N_3O_2$	16.45	16.38
Aniline[c]	173–174	86	$C_{11}H_{12}N_2O_2$	13.71	13.53
p-Anisidine	113–114.5	65	$C_{12}H_{14}N_2O_3$	11.95	11.68
m-Bromoaniline	155–156	65	$C_{11}H_{11}BrN_2O_2$	9.89	9.85
p-Bromoaniline[e]	151–152	76	$C_{11}H_{11}BrN_2O_2$	9.89	10.07
2-Bromo-4-methylaniline	113–113.5	57	$C_{12}H_{13}BrN_2O_2$	9.43	9.58
m-Chloraniline	159–161	70	$C_{11}H_{11}ClN_2O_2$	11.73	11.73
o-Chloroaniline	94–95	30	$C_{11}H_{11}ClN_2O_2$	11.73	11.64
p-Chloroaniline	151–153	87	$C_{11}H_{11}ClN_2O_2$	11.73	11.67
3-Chloro-2-methylaniline[f, g]	123–125	76	$C_{12}H_{13}ClN_2O_2$	11.08	10.92
2,4-Dimethylaniline[f]	119–120	24	$C_{13}H_{16}N_2O_2$	12.06	12.11
2,5-Dimethylaniline[f, h]	112–113	55	$C_{13}H_{16}N_2O_2$	12.06	12.06
Ethyl *p*-aminobenzoate	140–142.5	72	$C_{14}H_{16}N_2O_4$	10.14	9.91
Ethyl anthranilate[g]	128.5–130	56	$C_{14}H_{16}N_2O_4$	10.14	9.74
N-Methyl-*p*-Toluidine[i]	124–125	62	$C_{13}H_{16}N_2O_2$	12.06	12.21
o-Phenetidine	112–113	64	$C_{13}H_{16}N_2O_3$	11.28	11.16
p-Phenetidine[j]	121.5–122	76	$C_{13}H_{16}N_2O_3$	11.28	11.11
m-Toluidine	128–129	74	$C_{12}H_{14}N_2O_2$	12.84	12.51
o-Toluidine	129–130	90	$C_{12}H_{14}N_2O_2$	12.84	12.87
p-Toluidine	140(145–146)	70	$C_{12}H_{14}N_2O_2$	12.84	12.92

[a] Hellmann and Loschmann reported m.p. 111° for *N*-morpholinomethyl succinimide (*4*). [b] Cherbuliez and Sulzer reported m.p. 106–7° for *N*-piperidinomethylsuccinimide (*1*). [c] Derivative precipitates out during reflux. [d] Derivative recrystallized from dioxane. [e] *o*-Bromoaniline produced an oil. [f] Reaction mixture refluxed 2 hours. [g] Derivative recrystallized from 2-hexanol. [h] 2,6-Dimethylaniline produced an oil. [i] Derivatives of other alkylarylamines were oils. [j] *m*-Phenetidine produced an oil.

Table II. *N,N'*-[(Alkylimino)dimethylene]disuccinimides

Amine	M.p., ° C.	Yield, %	Formula	Nitrogen, % Calcd.	Nitrogen, % Found
Allylamine	96–98	20	$C_{13}H_{17}N_3O_4$	15.04	14.87
Isoamylamine	94–95	31	$C_{15}H_{23}N_3O_4$	13.58	13.59
Benzylamine	134.5–135.5	40	$C_{17}H_{19}N_3O_4$	12.75	12.85
n-Butylamine	119–120	48	$C_{14}H_{21}N_3O_4$	14.23	14.06
Isobutylamine	98–99	45	$C_{14}H_{21}N_3O_4$	14.23	14.43
sec-Butylamine	109–110	15	$C_{14}H_{21}N_3O_4$	14.23	14.19
Cyclohexylamine	169–170	32	$C_{16}H_{23}N_3O_4$	13.08	13.09
Ethylamine	147–148	31	$C_{12}H_{17}N_3O_4$	15.72	15.85
n-Hexylamine	90–91	42	$C_{16}H_{25}N_3O_4$	13.00	13.05
3-Methoxypropylamine	93–95	34	$C_{14}H_{21}N_3O_5$	13.50	13.53
n-Propylamine	96–97	44	$C_{13}H_{19}N_3O_4$	14.94	15.22

ACKNOWLEDGMENT

The authors thank Karl Klose, Constance Glascock Foster, Elizabeth Landis, and Dale L. Halleran for their contributions to this study.

LITERATURE CITED

(1) Cherbuliez, E., Sulzer, G., *Helv. Chim. Acta* **8**, 568–9 (1925).

(2) Haworth, R.D., Peacock, D.H., Smith, W.R., MacGillivray, R., *J. Chem. Soc.* **1952**, p. 2972.

(3) Heine, H.W., Winstead, M.B., Blair, R.P., *J. Am. Chem. Soc.* **78**, 672 (1956).

(4) Hellman, H., Loschmann, I., *Ber.* **87**, 1684–90 (1954).

(5) Weaver, W.I., Simons, J.K., Baldwin, W.E., *J. Am. Chem. Soc.* **66**, 222 (1944).

(6) Winstead, M.B., Heine, H.W., *Ibid.*, **77**, 1913 (1955).

RECEIVED for review November 9, 1961. Accepted February 13, 1962.