was dissolved in benzene, Celite added, and the solution filtered. The benzene was removed *in vacuo* and the colorless residue recrystallized from a 1:1 benzene–hexane mixture; yield 10.5 g. (73%), m.p. (dec.) 184°.

The silver salt was allowed to react with iodine at 130° under reduced pressure.[7] Two cuts were obtained on distillation; 0.5 g., b.p. 58–59°, containing combined iodine by qualitative analysis, and 3.5 g., b.p. 98–100°. The latter did not contain iodine. Its molecular weight (Dumas) was estimated as about 440.

Pyrolysis of $(CF_3)_2NCF_2COONa$.—Sixteen grams of the dry sodium salt was heated, reaction occurring at about 230°. Two cuts were obtained on distillation of the 11 g. of crude product. Fraction I, 4.5 g., b.p. 23°, mol. wt. 251–258, consisted mainly of the acid fluoride $(CF_3)_2NCF_2COF$, b.p. 25°, mol. wt. 249. It was identified further by conversion to the methyl ester, b.p. 88–89°, $n^{25}D$ 1.2974, mol. wt. 255. Known values for $(CF_3)_2NCF_2COOCH_3$ are b.p. 90°, $n^{25}D$ 1.2930, mol. wt. 261. Infrared spectra were identical. Fraction II, 4.0 g., b.p. 105–108°, reacted only partially with methanol to give a product not identical with the methyl ester of $(CF_3)_2NCF_2COOH$. A gas chromatogram showed the presence of four main components and numerous other traces.

All infrared spectra were taken on a Perkin–Elmer double beam instrument, using a 5-cm. gas phase cell whenever possible. The gas chromatograms were made on a Perkin–Elmer Fractometer, using a 2 meter × 1/4" o.d. column. Good resolution generally was obtained with Celite packing coating with the ethyl ester of Kel-F acid 8114.

Acknowledgments.—The authors are greatly indebted to Prof. H. S. Gutowsky of the University of Illinois for his nuclear magnetic resonance studies, and to Prof. T. M. Reed of this University for his aid in obtaining and interpreting the gas chromatograms.

GAINESVILLE, FLORIDA

(7) G. H. Crawford and J. H. Simons, THIS JOURNAL, **75**, 5737 (1953).

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF NOVOCOL CHEMICAL MFG. CO., INC.]

N-(Substituted Aminoacyl)-chloroanilines

BY ELIAS EPSTEIN AND DANIEL KAMINSKY

RECEIVED NOVEMBER 21, 1957

N-(Substituted aminoacetyl)- and propionylanilines of *m*-chloroaniline, methylcholoroanilines and alkoxychloroanilines were prepared. When screened on laboratory animals, several of these compounds had a high anesthetic efficiency (ratio of potency to toxicity) and low irritation warranting additional investigation.

Although N-(substituted aminoacyl)-anilines were prepared as early as 1891,[1] Einhorn[2] was the first in 1898 to recognize their ability to produce a local anesthetic effect. These early compounds were too irritating for clinical use. It was not till 1946 when Lofgren[3] prepared α-diethylamino-2,6-dimethylacetanilide (lidocaine) that an anesthetic of this structure was used clinically to any extent.

The clinical effectiveness of a chloro substituted anilide, *n*-butylamino-2-chloro-6-methylacetanilide (Hostocain), was first described by Harnisch.[4] Since then several chloroanilides have been reported.[5–9]

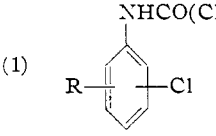
In our continuing investigation on new local anesthetics, we have prepared N-substituted aminoacetyl- and propionylanilines where the phenyl group was substituted as follows: 3-chloro, 2-methyl-3-chloro, 2-methyl-4-chloro, 2-methyl-5-chloro, 2-methyl-6-chloro, 3-chloro-4-methyl and 3-chloro-6-alkoxy.

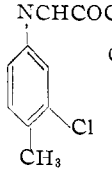
The general method used for the preparation of these compounds consisted of treating a chloroacyl chloride with a substituted aniline and condensing the resulting anilide with a primary or secondary amine. Table I lists the substituted chloroacyl anilines with their melting points and analyses. Table II lists the melting points, molecular weight determinations and analyses of the N-(substituted aminoacyl) substituted aniline hydrochlorides.

(1) W. Majert, British Patent 5,269 (1891).
(2) A. Einhorn, German Patent 106,502 (1898).
(3) N. Lofgren, *Arkiv Kemi, Mineral. Geol.*, **A22**, No. 18 (1946).
(4) H. Harnisch, *Deut. zahnärztl. Z.*, **22**, 1224 (1953).
(5) D. Beke, K. Lempert and L. Gyermek, *Acta Chim. Acad. Sci. Hung.*, **5**, 143 (1954).
(6) British Patent (a) 726,080 (1955); (b) 759,744 (1956).
(7) Swiss Patents 306,512-3 (1955); 311,578, 311,585-6, 311,588, 311,590-6 (1956).
(8) A. E. Wilder Smith and E. Hofstetter, *Helv. Chim. Acta.*, **38**, 1085 (1955).
(9) U. S. Patent 2,801,247 (1957).

TABLE I

ω-CHLOROACYLCHLOROANILINES

(1) 

R	Cl position	n	M.p., °C.	Formula	Chlorine, % Calcd.	Found
H	3	1	100–101[a]	$C_8H_7ONCl_2$	34.76	34.21
H	3	2	81–83	$C_9H_9ONCl_2$	32.53	32.38
2-CH_3	3	1	134–136	$C_9H_9ONCl_2$	32.53	32.07
2-CH_3	4	1	130–131[b]	$C_9H_9ONCl_2$	32.53	32.21
2-CH_3	4	2	128–129	$C_{10}H_{11}ONCl_2$	30.57	30.14
2-CH_3	5	1	139–141	$C_9H_9ONCl_2$	32.53	32.73
2-CH_3	6	1	142–143[c]	$C_9H_9ONCl_2$	32.53	32.32
4-CH_3	3	1	94–95	$C_9H_9ONCl_2$	32.53	32.47
4-CH_3	3	2	116–117	$C_{10}H_{11}ONCl_2$	30.57	30.19
2-OCH_3	5	1	105–107	$C_9H_9O_2NCl_2$	30.34	30.60
2-OC_4H_9	5	1	91–93	$C_{12}H_{15}O_2NCl_2$	25.72	25.91
(2) 			109–111	$C_{10}H_{11}ONCl_2$	30.57	30.61

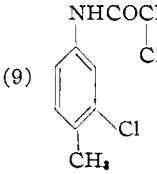
[a] Reported[5] m.p. 100–101°. [b] Reported[5] m.p. 128–129°. [c] Reported[6a] m.p. 140–141°.

TABLE II

N-(SUBSTITUTED AMINOACYL)-CHLOROANILINE HYDROCHLORIDES, $RNHCO(CH_2)_nR'$

R′	n	M.p., °C., HCl	Formula	Ionic chlorine, % Calcd.	Ionic chlorine, % Found	Mol. wt.[e] Calcd.	Mol. wt.[e] Found
		(1) R = 3-chlorophenyl					
$NHCH_3$	1	212–214	$C_9H_{12}ON_2Cl_2$	15.11	15.01	235	237
NHC_2H_5	1	221–224	$C_{10}H_{14}ON_2Cl_2$	14.26	14.38	249	245
NHC_3H_7	1	235–237	$C_{11}H_{16}ON_2Cl_2$	13.50	13.32	263	258
NHC_4H_9(iso)	1	243–246	$C_{12}H_{18}ON_2Cl_2$	12.82	12.91	277	274
NHC_4H_9(iso)	2	219–221	$C_{13}H_{20}ON_2Cl_2$	12.20	12.10	291	288
$NHCH(CH_3)C_5H_{11}$(*n*)	1	234–237	$C_{15}H_{24}ON_2Cl_2$	11.13	11.01	319	314
$N(C_2H_5)_2$	1	219–221[a]	$C_{12}H_{18}ON_2Cl_2$	12.82	12.74	277	280
$N(C_2H_5)_2$	2	127–129	$C_{13}H_{20}ON_2Cl_2$	12.20	12.01	291	296
$NH(CH_2)_3OCH_3$	1	220–222	$C_{13}H_{20}O_2N_2Cl_2$	12.12	12.14	293	290
$N(C_2H_4OH)C_5H_{11}$(*n*)	1	231–234	$C_{15}H_{24}O_2N_2Cl_2$	10.60	10.39	335	328
Piperidino	1	215–218	$C_{13}H_{18}ON_2Cl_2$	12.26	12.03	289	282
Cyclohexylamino	1	301–302	$C_{14}H_{20}ON_2Cl_2$	11.71	11.58	303	302
Morpholino	1	215–217	$C_{12}H_{16}O_2N_2Cl_2$	12.20	12.01	291	297
Morpholino	2	203–204	$C_{13}H_{18}O_2N_2Cl_2$	11.64	11.59	305	301
2,6-Dimethylmorpholino	1	243–245	$C_{14}H_{20}O_2N_2Cl_2$	11.13	10.91	319	316
2,6-Dimethylanilino	1	238–241	$C_{16}H_{18}ON_2Cl_2$	10.54	10.48	337	331
		(2) R = 2-methyl-3-chlorophenyl					
NHC_2H_5	1	258–260	$C_{11}H_{16}ON_2Cl_2$	13.50	13.61	263	261
NHC_4H_9(iso)	1	240–242	$C_{13}H_{20}ON_2Cl_2$	12.20	12.02	291	294
$N(C_2H_5)_2$	1	145–147	$C_{13}H_{20}ON_2Cl_2$	12.20	11.99	291	289
Morpholino	1	201–203	$C_{13}H_{18}O_2N_2Cl_2$	11.64	11.49	305	301
		(3) R = 2-methyl-4-chlorophenyl					
NHC_3H_7	2	213–215	$C_{13}H_{20}ON_2Cl_2$	12.20	12.00	291	287
NHC_4H_9	2	229–231	$C_{14}H_{22}ON_2Cl_2$	11.64	11.47	305	307
NHC_4H_9(iso)	1	232–234	$C_{13}H_{20}ON_2Cl_2$	12.20	12.00	291	296
NHC_4H_9(iso)	2	214–216	$C_{14}H_{22}ON_2Cl_2$	11.64	11.52	305	301
$N(C_2H_5)_2$	2	131–133	$C_{14}H_{22}ON_2Cl_2$	11.64	11.53	305	306
Morpholino	1	259–262	$C_{13}H_{18}O_2N_2Cl_2$	11.64	11.52	305	309
Morpholino	2	226–228	$C_{14}H_{20}O_2N_2Cl_2$	11.13	10.97	319	316
		(4) R = 2-methyl-5-chlorophenyl					
NHC_2H_5	1	262–265	$C_{11}H_{16}ON_2Cl_2$	13.50	13.29	263	261
NHC_4H_9(iso)	1	214–216	$C_{13}H_{20}ON_2Cl_2$	12.20	12.14	291	294
$NH(CH_2)_3OCH_3$	1	221–224	$C_{14}H_{20}O_2N_2Cl_2$	11.55	11.46	307	301
$N(C_2H_5)_2$	1	152–154	$C_{13}H_{20}ON_2Cl_2$	12.20	11.97	291	287
Morpholino	1	205–207	$C_{13}H_{18}O_2N_2Cl_2$	11.64	11.71	305	303
		(5) R = 2-methyl-6-chlorophenyl					
NHC_4H_9	1	236–239[b]	$C_{13}H_{20}ON_2Cl_2$	12.20	12.09	291	290
NHC_4H_9(*tert.*)	1	263–265	$C_{13}H_{20}ON_2Cl_2$	12.20	12.02	291	293
$N(C_2H_5)_2$	1	153–155[c]	$C_{13}H_{20}ON_2Cl_2$	12.20	11.99	291	286
Morpholino	1	223–226[d]	$C_{13}H_{18}O_2N_2Cl_2$	11.64	11.49	305	303
		(6) R = 4-methyl-3-chlorophenyl					
NHC_3H_7	1	251–253	$C_{12}H_{18}ON_2Cl_2$	12.82	12.74	277	271
NHC_3H_7	2	218–221	$C_{13}H_{20}ON_2Cl_2$	12.20	12.29	291	292
NHC_4H_9(iso)	1	265–267	$C_{13}H_{20}ON_2Cl_2$	12.20	12.01	291	290
NHC_4H_9(iso)	2	175–177	$C_{14}H_{22}ON_2Cl_2$	11.64	11.48	305	303
$N(C_2H_5)_2$	1	180–182	$C_{13}H_{20}ON_2Cl_2$	12.20	12.14	291	296
$N(C_2H_5)_2$	2	147–149	$C_{14}H_{22}ON_2Cl_2$	11.64	11.75	305	308
Cyclohexylamino	1	309–312	$C_{15}H_{22}ON_2Cl_2$	11.20	11.16	317	312
Morpholino	1	209–210	$C_{13}H_{18}O_2N_2Cl_2$	11.64	11.67	305	307
		(7) R = 2-methoxy-5-chlorophenyl					
NHC_4H_9(iso)	1	197–198	$C_{13}H_{20}O_2N_2Cl_2$	11.55	11.50	307	308
$N(C_2H_5)_2$	1	184–186	$C_{13}H_{20}O_2N_2Cl_2$	11.55	11.48	307	305
Morpholino	1	205–208	$C_{13}H_{18}O_3N_2Cl_2$	11.06	10.89	321	320
		(8) R = 2-*n*-butoxy-5-chlorophenyl					
$N(C_2H_5)_2$	1	133–135	$C_{16}H_{26}O_2N_2Cl_2$	10.17	10.26	349	342
Morpholino	1	173–176	$C_{16}H_{24}O_3N_2Cl_2$	9.78	9.60	363	358

TABLE II (*Continued*)

R′	*n*	M.p., °C., HCl	Formula	Ionic chlorine, % Calcd.	Found	Mol. wt.[e] Calcd.	Found
(9) 							
NHC_4H_9(iso)		239–241	$C_{14}H_{22}ON_2Cl_2$	11.64	11.43	305	301
$N(C_2H_5)_2$		117–120	$C_{14}H_{22}ON_2Cl_2$	11.64	11.55	305	300
Morpholino		207–209	$C_{14}H_{20}O_2N_2Cl_2$	11.13	10.97	319	312

[a] Reported[5] m.p. 219–221°. [b] Reported[6a] m.p. 231–233°. [c] Reported[6a] m.p. 154–155°. [d] Reported[6a] m.p. 210.5–213.5°. [e] Determined by titration with standard base.

Pharmacology

A pharmacological screening of these compounds for local anesthetic efficiency was conducted. The toxicities were determined intraperitoneally and subcutaneously on white mice. The potency was determined by three methods: application to the rabbit cornea, blocking the sciatic nerve of the intact guinea pig, and by the use of the wheal test on the guinea pig back. Evidence of irritation was checked after topical application to the rabbit eye and on intradermal injection in the rabbit using an intravenous injection of trypan blue as an indicator. These procedures have been previously described.[10]

The relative anesthetic efficiency is defined as the ratio of the relative potency to the relative toxicity. The relative potency as determined *via* the guinea pig wheal test is preferred as it gives a closer correlation to clinical findings with known anesthetics.[11] The intraperitoneal toxicity on white mice was used as it represents a mean value between the rapidly absorbed intravenous and slowly absorbed subcutaneous injections.

The toxicities of most of these compounds were lower than that of procaine hydrochloride. The potency and irritation were generally higher. A few compounds of note were α-isobutylamino-3-chloro-4-methylacetanilide hydrochloride and β-diethylamino-3-chloropropionanilide hydrochloride with an anesthetic efficiency of three and four, respectively, (procaine hydrochloride assigned a value of one) with little or no irritation noted.

Detailed pharmacological and clinical studies of these compounds will be published elsewhere.

Experimental

The *m*-chloroaniline, the chlorotoluidines and 2-methoxy-5-chloroaniline were obtained from commercial sources. The 2-butoxy-5-chloroaniline was prepared by alkylating 2-nitro-4-chlorophenol with butyl bromide and potassium carbonate in an anhydrous solvent. The resulting ether was reduced with iron to the substituted aniline. The general method described in the literature[12] for the alkylation of nitrophenol gave a zero yield of the desired product. This method, when modified by using ethylene glycol monomethyl ether (methyl Cellosolve) as the solvent, was found to give excellent yields, 96% of the theoretical.

The ω-chloroacylanilines were prepared by condensing the chloroacyl chloride with the substituted aniline. This method is essentially that of Jacobs and Heidelberger[13] as modified and described in our previous paper.[14] The anesthetic compounds were prepared by treating the chloroacylanilines with two to three moles of the amine. The anesthetic compounds were isolated as their hydrochloride salts and purified by recrystallization from isopropyl alcohol or isopropyl alcohol–water mixtures.

Preparation of 2-*n*-Butoxy-5-chloro-nitrobenzene.—A mixture of 17.3 g. (0.1 mole) of 2-nitro-4-chlorophenol, 8.4 g. (0.06 mole) of anhydrous potassium carbonate, 20.6 g. (0.15 mole) of *n*-butyl bromide and 300 ml. of ethylene glycol monomethyl ether (methyl Cellosolve) was refluxed vigorously for two hours. An additional 5.6 g. (0.04 mole) of anhydrous potassium carbonate and 13.7 g. (0.1 mole) *n*-butyl bromide were added and the mixture refluxed for an additional six hours. After cooling, the mixture was filtered and the filter cake washed with 100 ml. of ether. The solvent in the combined filtrates was removed by vacuum distillation at 100° and 15 mm. pressure. The residue was dissolved in 200 ml. of ether and washed successively with two 100-ml. portions of 5% sodium hydroxide solution and two 200-ml. portions of water. After drying over anhydrous sodium sulfate, the ether solution was distilled to yield a fraction boiling at 102–106° at 30 μ. The yield of 2-*n*-butoxy-5-chloronitrobenzene was 22 g. (96%) as a light yellow oil.

Anal. Calcd. for $C_{10}H_{12}O_3NCl$: Cl, 15.44. Found: Cl, 15.09.

2-*n*-Butoxy-5-chloroaniline Hydrochloride.—To 18.3 g. (0.08 mole) of 2-*n*-butoxy-5-chloronitrobenzene suspended in 250 ml. of 80% isopropyl alcohol was added one ml. of concentrated hydrochloric acid. Forty-four grams (0.8 mole) of iron powder was added in small portions over a period of one hour with stirring at 70°. The mixture was then stirred at this temperature for an additional two hours and filtered while hot through a Filter-Gel bed. The alcohol was evaporated under reduced pressure and to the residue was added 5 g. of citric acid, 1 g. of sodium hydrosulfite and 100 ml. of 5% ammonium hydroxide. The mixture was extracted with three 100-ml. portions of ether. The extract was washed twice with water and dried over anhydrous sodium sulfate. After treating with activated carbon, the ether solution was acidified with anhydrous hydrochloric acid to yield 13.9 g. of slightly colored crystals. The crude material was recrystallized from an isopropyl alcohol–ether mixture to yield 12.6 g. (67%) of 2-*n*-butoxy-5-chloroaniline hydrochloride as white crystals, m.p. 151–153°.

α-Chloro-2-butoxy-5-chloroacetanilide.—To 23.7 g. (0.1 mole) of 2-*n*-butoxy-5-chloroaniline hydrochloride in 150 ml. of glacial acetic acid was added all at once with vigorous stirring 12.5 g. (0.11 mole) of chloroacetyl chloride. The mixture was stirred for one hour and 150 g. of sodium acetate in 500 ml. of water was added. Stirring was continued for an additional hour and the mixture was filtered. The crude product was recrystallized from 50% isopropyl alcohol to yield 19.6 g. (71%) of α-chloro-2-butoxy-5-chloroacetanilide as white crystals, m.p. 91–93°.

α-Morpholino-2-butoxy-5-chloroacetanilide Hydrochloride.—A mixture of 6.9 g. (0.025 mole) of α-chloro-2-bu-

(10) E. Epstein, M. Meyer and H. Ginsberg, *Current Res. Anes. & Analg.*, **34**, 171 (1954).

(11) To be published.

(12) "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p. 140.

(13) W. A. Jacobs and M. Heidelberger, *J. Biol. Chem.*, **21**, 139 (1915).

(14) E. Epstein and D. Kaminsky, THIS JOURNAL, **79**, 5814 (1957).

toxy-5-chloroacetanilide and 8.7 g. (0.1 mole) of morpholine was heated on a steam-bath for two hours. The excess morpholine was removed by vacuum distillation and the residue was taken up in 250 ml. of ether. The extract was washed twice with water and dried over anhydrous sodium sulfate. The ether solution, after treating with activated carbon, was acidified with anhydrous hydrochloric acid to yield a yellow oil. The oil was dissolved in 20 ml. of 50% isopropyl alcohol, treated with activated carbon and then made alkaline with 100 ml. of 2% ammonium hydroxide to yield 7.2 g. (89%) of α-morpholino-2-butoxy-5-chloroacetanilide as white crystals, m.p. 116–118°. The hydrochloride salt was prepared by acidifying the base in ether solution with anhydrous hydrochloric acid and recrystallizing from an isopropyl alcohol–ether mixture, m.p. 173–176°, as white crystals.

Acknowledgment.—We are indebted to Ann Hartman for assistance in the pharmacological screening of these compounds.

BROOKLYN 7, N. Y.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, STATE UNIVERSITY OF IOWA]

The Reactions of Methylhydrazine and *unsym*-Dimethylhydrazine with Esters and Anhydrides of Carboxylic Acids; the Application of Paper Chromatography to Problems in Synthetic Organic Chemistry

BY RICHARD L. HINMAN AND DAVID FULTON

RECEIVED JUNE 28, 1957

The reactions of methylhydrazine and *unsym*-dimethylhydrazine with several simple esters have been examined. The reactions of methylhydrazine with acetic, propionic, and benzoic anhydrides also are described. The reactions of methylhydrazine were followed and the products in part identified by the use of paper chromatographic techniques. The following conclusions have been reached. (1) The reaction of an *anhydride* and an aqueous solution of methylhydrazine (1:1 mole ratio) yields mainly the 1-acyl-1-methylhydrazine, and can be used for the preparation of the latter. (2) The reaction of an *ester* and methylhydrazine yields mainly the 1-acyl-2-methylhydrazine, together with a small percentage of the unsymmetrical isomer. (3) As the size of the acyl group of an *ester* is increased, the percentage of 1-acyl-1-methylhydrazine decreases and the over-all rate of reaction decreases. This effect was not observed with anhydrides. (4) As the hydrazine molecule is more heavily substituted, the rate of reaction with *esters* decreases; the relative reactivities are $NH_2NH_2 > CH_3NHNH_2 > (CH_3)_2NNH_2$. *unsym*-Dimethylhydrazine did not react with simple esters larger than formates. (5) 1-Acyl-1-methylhydrazines generally had larger R_f values than 1-acyl-2-methylhydrazines in the solvent system: water, acetic acid and *n*-butyl or isoamyl alcohol. (6) The 1-acyl-2-methylhydrazines are low-melting solids; the 1-acyl-1-methylhydrazines are liquids at room temperature.

Although the formation of acid hydrazides by the reactions of hydrazine with esters of carboxylic acids is well known, the reactions of esters with alkyl and aryl derivatives of hydrazine have rarely been recorded. In the older literature the reactions of alkylhydrazines with esters are limited to a few reactions with ethyl oxalate.[1] More recently it has been observed that 1,1-dimethylhydrazine and methyl formate yield 1-formyl-2,2-dimethylhydrazine, while 1-formyl-1,2,2-trimethylhydrazine is obtained from the reaction of trimethylhydrazine and methyl formate.[2] Methyl isonicotinate and methylhydrazine yield 1-isonicotinyl-2-methylhydrazine.[3] On the other hand, methyl benzoate does not react with 1,1-dimethylhydrazine at atmospheric pressure.[4a] Compounds of the latter type do react easily with ethyl oxalate, acid anhydrides, cyanate and phenyl isothiocyanate to give characteristic derivatives.[4a,b]

The purpose of the present research was to examine more fully the acylation of methylhydrazine and *unsym*-dimethylhydrazine, especially by esters, and to compare the behavior of these alkylhydrazines to that of hydrazine itself.

Acylation of Methylhydrazine.—The monoacylation of methylhydrazine is complicated by the presence of two nitrogens which can undergo acylation. Considering the electron-donating character of the methyl group, acylation might be expected to occur more readily at the methyl-bearing nitrogen. Previously reported experiments support this hypothesis. Thus, methylhydrazine and benzoic anhydride yield 1-benzoyl-1-methylhydrazine.[1b] With potassium cyanate in acidic media 2-methylsemicarbazide is formed.[1b] Ethyl isocyanate and methyl isothiocyanate yield 2-methyl-4-ethylsemicarbazide and 2,4-dimethylthiosemicarbazide, respectively.[5a] Similar results have been observed with other monoalkylhydrazines,[5b] whereas acylation of arylhydrazines takes place at the $-NH_2$ group.[5c] The reactions of monoalkylhydrazines with ethyl oxalate are anomalous in that attack occurs on the unsubstituted nitrogen.[1]

In the work described here, the products from the reactions of esters with methylhydrazine were low-melting solids, which could not be purified by crystallization, and which underwent further reaction when distilled (see below). They rapidly turned yellow when exposed to air. Molecular formulas were determined from those of phenylthiosemicarbazides and other derivatives. Despite the described preference of the acylating agent for the alkylated nitrogen, it was soon evident that both of the isomeric monoacylmethylhydrazines were formed in reactions with esters (equation 1). Since separation and purification of the products could not be effected by the usual techniques,

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(2) R. T. Beltrami and E. R. Bissell, THIS JOURNAL, **78**, 2468 (1956).

(3) H. H. Fox and J. T. Gibas, *J. Org. Chem.*, **18**, 994 (1953).

(4) (a) R. L. Hinman, THIS JOURNAL, **78**, 1645 (1956); (b) H. Zimmer, L. F. Audrieth and M. Zimmer, *Ber.*, **89**, 1116 (1956).

(5) (a) M. Busch, E. Opfermann and H. Walther, *ibid.*, **37**, 2318 (1904); (b) M. Busch and R. Schmidt, *J. prakt. Chem.*, **130**, 342 (1931); (c) see for example E. Fischer, *Ann.*, **190**, 67 (1878).