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

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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 $NH_2NH_2 > CH_3NH\text{-}NH_2 > (CH_3)_2NNH_2$. *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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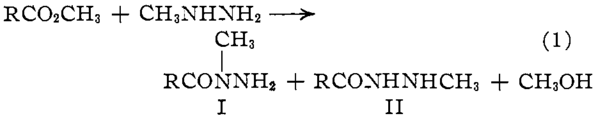
[1] (a) G. v. Brüning, *Ann.*, **253**, 13 (1889); (b) A. Michaelis and E. Hadanck, *Ber.*, **41**, 3285 (1908); (c) E. Fischer and H. Troschke, *Ann.*, **199**, 297 (1879); (d) A. Renouf, *Ber.*, **13**, 2172 (1880); (e) A. P. N. Franchimont and H. V. Erp, *Rec. trav. chim.*, **14**, 303 (1895).

[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).

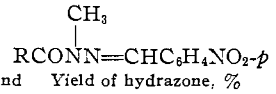


$$RCO_2CH_3 + CH_3NHNH_2 \longrightarrow \underset{I}{RCO\overset{CH_3}{\overset{|}{N}}NH_2} + \underset{II}{RCONHNHCH_3} + CH_3OH \qquad (1)$$

methods were needed for the identification of each isomer in the presence of the other. In the initial stages of the work the 1-acyl-1-methylhydrazines were identified by conversion to hydrazones of *p*-nitrobenzaldehyde. Although some hydrazone was obtained from each reaction product of an ester and methylhydrazine, the yields were low, and decreased with increasing size of the acyl group of the ester (Table I).

TABLE I

YIELDS OF 1-ACYL-1-METHYLHYDRAZONES OF *p*-NITROBENZALDEHYDE[a]



$RCO\overset{CH_3}{\overset{|}{N}}N{=}CHC_6H_4NO_2\text{-}p$

Reacn. prod. from methylhydrazine and	Yield of hydrazone, %
Methyl acetate	20-23[b]
Methyl propionate	11-13[b]
Methyl isobutyrate	Trace
Methyl benzoate	5
Acetic anhydride	63[c]
Propionic anhydride	55[c]
Benzoic anhydride	80-83[c]

[a] For properties of hydrazones see Table IV. [b] Yield based on unrecrystallized product, melting 5-10° low. [c] Yield based on twice recrystallized product.

Hydrogenolysis of the nitrogen–nitrogen bond with Raney nickel[6a,b] also was used to identify the reaction products. A 15% yield of isobutyramide was obtained from the crude reaction products of methyl isobutyrate and methylhydrazine, showing that some acylation of the $-NH_2$ group had taken place. Similar treatment of the crude products from the methyl benzoate reaction gave 15–20% yields of benzamide. Hydrogenolysis of the products of the methyl acetate and methyl propionate reactions was not attempted, since the N-methyl amides are liquids and would be difficult to distinguish from mixtures of amides which might be formed.

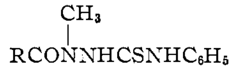
In one case a 1-acyl-2-methylhydrazine was isolated in the pure state by precipitating the hydrochloride from a chloroform solution of the products of the methyl benzoate–methylhydrazine reaction. Treatment of the hydrochloride with base gave a crystalline solid to which the structure of 1-benzoyl-2-methylhydrazine[7] was assigned on the basis of its elementary analysis, its failure to form hydrazones with various aromatic aldehydes, and its cleavage to benzamide by refluxing with Raney nickel in ethanol. The reaction of methyl benzoate and methylhydrazine, and the methods of isolation and identification of the two chief products are summarized in equation 2 (see p. 1897).

Attempts to precipitate salts of the symmetrical isomers from the chloroform solutions of the products of the methyl acetate and methyl propionate reactions, using either hydrogen chloride or sulfuric acid, were unsuccessful. No solid precipitated when hydrogen chloride was passed into a chloroform solution of what was mainly 1-benzoyl-1-methylhydrazine, prepared as described below.

These experiments established that both acylmethylhydrazines were formed in the reactions of methylhydrazine and the various esters used.

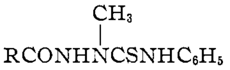
The reactions of anhydrides with methylhydrazine were carried out by dropping the anhydride into an aqueous solution of methylhydrazine, a method used previously for the reaction of benzoic anhydride and methylhydrazine.[1b] Acetic, propionic and benzoic anhydrides were used in these experiments. In each case the product was a colorless oil which, unlike the products from the ester reactions, did not crystallize even when cooled in a Dry Ice mixture. The yields of hydrazones from these products were consistently greater than 50% (Table I). The reaction of an anhydride and methylhydrazine therefore yields the 1-acyl-1-methylhydrazine as the primary product. Although the presence of the 1-acyl-2-methyl isomer was suspected, it could not be detected by the standard organic techniques described above.

In addition to the preparation of hydrazone derivatives, an additional derivative of each reaction mixture was made by treatment with phenyl isothiocyanate. It was assumed that when the reaction product consisted of a mixture of acylmethylhydrazines, the isolated phenylisothiosemicarbazide was derived from the major component of the mixture. Thus, when the 1-acyl-1-methylhydrazine (I) was the chief component of a reaction mixture, a phenylthiosemicarbazide of type III would be isolated, while type IV would be isolated from a mixture in which the 1-acyl-2-methy isomer II predominates. In every case the phenylthiosemicarbazide prepared from the products of an ester reaction was different from that obtained from the products of the reaction of the corresponding anhydride (see Table V). Moreover the phenylthiosemicarbazides derived from the products of the ester reactions exhibited the common characteristic of melting without decomposition, whereas those derived from the anhydride reactions without exception melted with evolution of a gas, resolidified, and finally decomposed at a much higher temperature. Since the derivative (IV, R = C_6H_5) prepared from an authentic sample of 1-benzoyl-2-methylhydrazine melts without decomposition, it must be concluded that decomposition with formation of a high-melting solid is characteristic of compounds of formula III.[8]



$RCO\overset{CH_3}{\overset{|}{N}}NHCSNHC_6H_5$

III



$RCONH\overset{CH_3}{\overset{|}{N}}CSNHC_6H_5$

IV

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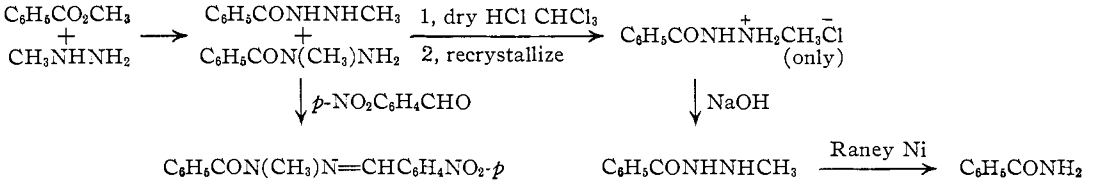
(6) (a) C. Ainsworth, THIS JOURNAL, **78**, 1635 (1956); (b) R. L. Hinman, *J. Org. Chem.*, **22**, 148 (1957).

(7) It should be noted that despite the low yield (20–30%) the reaction of methylhydrazine and methyl benzoate is the only useful method for preparing 1-benzoyl-2-methylhydrazine. Attempts to reduce 1-benzoyl-2-methylenehydrazine were unsuccessful (see Experimental).

(8) The phenylthiosemicarbazide (IV, R = C_6H_5) prepared from pure 1-benzoyl-2-methylhydrazine melted without decomposition at 159–160°. The isomer (III, R = C_6H_5), prepared from 1-benzoyl-1-methylhydrazine (the principal product from the anhydride reaction), melted with evolution of a gas at 153–155°, resolidified at 158–160° and remelted at 286–288° dec. The gas, which appeared to be hydrogen sulfide, was evolved from the propionyl derivative even in hot solvents used in recrystallization and the effect was more pronounced in hydroxylic solvents. The nature of the high-melting solids is now under investigation.



$$\begin{tikzcd}
\begin{matrix} C_6H_5CO_2CH_3 \\ + \\ CH_3NHNH_2 \end{matrix} \arrow[r] & \begin{matrix} C_6H_5CONHNHCH_3 \\ + \\ C_6H_5CON(CH_3)NH_2 \end{matrix} \arrow[r, "\text{1, dry HCl CHCl}_3", "\text{2, recrystallize}"'] \arrow[d, "p\text{-}NO_2C_6H_4CHO"] & \begin{matrix} C_6H_5CONH\overset{+}{N}H_2CH_3\overset{-}{Cl} \\ \text{(only)} \end{matrix} \arrow[d, "NaOH"] & \\
& C_6H_5CON(CH_3)N{=}CHC_6H_4NO_2\text{-}p & C_6H_5CONHNHCH_3 \arrow[r, "\text{Raney Ni}"] & C_6H_5CONH_2
\end{tikzcd} \qquad (2)$$

These results also support the earlier conclusions that the reaction of an ester with methylhydrazine yields II as the chief product, whereas I is the main product from the reaction of an anhydride and methylhydrazine.

The nature of the principal product from each type of reaction is also indicated by the fact that products from the ester reactions crystallize at room temperature, or when chilled, whereas those from the reactions with anhydrides remain liquid even at the temperature of Dry Ice. A search of the literature has revealed that symmetrical isomers, containing the –CONH– group, generally have higher melting points than the unsymmetrical isomers. The fact that the chromatograms of the anhydride reactions show the presence of one principal product, while the products from the ester reactions are much less pure, lends added significance to this point, since it is the latter which crystallize.[9]

When taken together these results led to the tentative conclusions that the reaction of an *ester* with methylhydrazine yields a mixture of 1-acyl-1-methylhydrazine and 1-acyl-2-methylhydrazine in which the latter predominates. The reaction of an *anhydride* with methylhydrazine yields the 1-acyl-1-methylhydrazine as the main product; the 1-acyl-2-methylhydrazine, if present, could not be detected.

This rather vague picture of the acylations of methylhydrazine was brought into sharp focus by the use of paper chromatography. Each reaction mixture was chromatographed on paper and the acylhydrazines (and residual methylhydrazine) were detected by spraying with an ethanolic solution of *p*-dimethylaminobenzaldehyde hydrochloride.[10] Products from the *ester* reactions were revealed as two spots. The larger spot was the one of lower R_f. The products from the *anhydride* reactions were also revealed as two spots with the same R_f values as those from the ester reactions, but the larger spot was always the one of *higher* R_f. The spots from the ester reactions showed the same behavior under white and ultraviolet lights as the spots from the corresponding anhydride reactions. The same two products, presumably the 1-acyl-1-methylhydrazine and the 1-acyl-2-methylhydrazine, must therefore be formed in *both* types of reactions.

On the basis of the yields of hydrazones the spot of higher R_f must be due to the unsymmetrical acylmethylhydrazine, which is the major product from an anhydride reaction (and therefore gives the larger spot), but the minor product from an ester reaction (thus giving the smaller spot).[11] The spot of lower R_f is then due to the presence of the 1-acyl-2-methylhydrazine. Convincing proof of the last point was afforded by chromatography of the products of the reactions of methylhydrazine with methyl benzoate and with benzoic anhydride, side-by-side with a sample of pure 1-benzoyl-2-methylhydrazine, prepared as described above. The single spot from the latter compound had the same R_f as the *lower* spots from the products of the reaction mixtures. Moreover the three spots showed the same characteristics under white and ultraviolet lights. This was the only direct proof obtained for the presence of the 1-acyl-2-methylhydrazine as a product of the anhydride–methylhydrazine reaction.

Further support for the attributions of the spots was obtained in a number of ways. When the products (two spots on the usual chromatogram) from the reaction of methyl isobutyrate and methylhydrazine were treated with an excess of *p*-nitrobenzaldehyde, and the reaction mixture was then swamped with water to precipitate both hydrazone and excess aldehyde, the chromatogram of the filtrate showed only the spot of lower R_f. This result also was obtained with the products of the reaction of methyl propionate and methylhydrazine. The spot of higher R_f must therefore be due to the 1-acyl-1-methylhydrazine.

The same conclusion can be reached from the theory of paper chromatography. It is generally true that the more soluble a substance is in the mobile phase of the chromatogram, the larger will be its R_f value.[12] Substitution of an alkyl group for hydrogen in the peptide group of an acylhydrazine is generally accompanied by decreased association with water and increased solubility in organic solvents.[13] Since the organic phase is the mobile one in the chromatograms used here, the 1,1-disubstituted isomer would be expected to have the larger R_f.

From all this evidence it can be deduced that the reaction of an *anhydride* with an aqueous solution of methylhydrazine yields mainly the 1-acyl-1-methylhydrazine, together with a trace of the 1-acyl-2-methyl isomer. This reaction should prove generally useful for preparing the unsymmetrical isomers in a fairly pure state. The reaction of an *ester* with methylhydrazine yields predominantly the 1-acyl-2-methylhydrazine, along

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[9] 1-Acetyl-1-methylhydrazine has been reported as a solid, m.p. 98°, prepared by methylation of the potassium salt of biacetyl monoacetylhydrazone, followed by hydrolysis (O. Diels and A. V. Dorp, *Ber.*, **36**, 3189 (1903)). In the light of the above discussion this result seems unlikely.

[10] R. L. Hinman, *Anal. Chim. Acta*, **15**, No. 2, 125 (1956).

[11] Since the two spots on a given chromatogram exhibit different behavior under white and ultraviolet lights (see Experimental), a precise determination of the relative quantities of materials present could not be made. However, the differences in sizes of the spots were sufficiently great to permit identification of the spots as due to major and minor products and to enable one to make a very rough estimate of the proportions of isomers in a reaction mixture.

[12] R. J. Block, E. L. Durrum and C. Zweig, "A Manual of Paper Chromatography and Paper Electrophoresis," Academic Press, Inc., New York, N. Y., 1955, pp. 5, 16, 37, 78.

[13] H. T. Hayes and L. Hunter, *J. Chem. Soc.*, 332 (1940).

with a smaller but substantial amount of the 1,1-disubstituted isomer.

An explanation for the different reaction routes of esters and anhydrides was sought in the markedly different experimental conditions. The conditions were reversed and the reaction of acetic anhydride and methylhydrazine was carried out in benzene solution, while the reaction with methyl acetate was effected in water. When the reaction mixtures were examined by the paper chromatographic techniques described above, little or no change was observed in the relative quantities of the two products from each reaction. The explanation for the different behavior of anhydrides and esters therefore must be sought elsewhere.

Steric effects play an important role in the reactions of esters and methylhydrazine. From the yields of hydrazones (Table I) it can be inferred that the proportion of unsymmetrical isomer decreases as the acyl group of the ester increases in size. This effect was most pronounced with methyl isobutyrate. The amount of hydrazone obtained in this case was so small that it had to be identified by its ultraviolet absorption spectrum (Table IV). It seems likely that monoalkylhydrazines bearing larger alkyl groups than methyl will undergo acylation by esters to an even greater extent on the unsubstituted nitrogen. No such effect was observed in the reactions of methylhydrazine with anhydrides.

In the light of these results the formation of symmetrically substituted oxalic acid hydrazides from the reaction of monoalkylhydrazines and esters of oxalic acid[1] are just further examples of the tendency of esters to attack the unsubstituted amino group. The steric effect noticed with the other esters is probably especially strong in the case of oxalates. Folpmer's work[14] is especially interesting in this regard. He found that the reaction of oxalyl chloride and methylhydrazine yields a mixture of oxal-bis-α-methylhydrazide ($NH_2N(CH_3)COCON(CH_3)NH_2$) and oxal-bis-β-methylhydrazide, in which the α-isomer is the major constituent. The formation of 1-isonicotinyl-2-methylhydrazine from the reaction of methylhydrazine and methyl isonicotinate[3] is also in accord with the observations made in this study. It seems likely that other acylating agents used in the past to prepare one isomer[1,5] may actually give rise to mixtures of products. This point is now being investigated with the aid of the paper chromatographic techniques developed in this study.

As would be expected, a steric effect also determined the rate of reaction of each ester with methylhydrazine. A rough idea of the relative rates was obtained in two different ways. At least one example of each reaction was followed by periodically removing aliquots of the reaction mixture and applying them to a paper strip. After development of the chromatogram in the usual way the degree of completion of the reaction could be inferred from the rate of disappearance of the spot due to methylhydrazine, and the growth of the spots corresponding to the acylmethylhydrazines. From these chromatograms it was found that the rate of reaction diminishes in passing from methyl acetate to methyl isobutyrate, with methyl propionate and methyl benzoate occupying intermediate positions. Although the ester was always present in excess, in no case was the methylhydrazine completely consumed within 24 hr.

Similar conclusions were drawn from the second method of estimating the rate: isolation of the mixture of products by distillation. These results are summarized in Table II. Although the products distilled over a narrow range, no separation could be effected, as shown by chromatographic examination of the distillates. That some rearrangement occurred during distillation is revealed by the appearance of a second major spot on chromatograms of the products that had shown only one major spot before distillation.[15]

TABLE II

COMPARISON OF TIME OF REACTION *vs.* TOTAL YIELD OF ACYLMETHYLHYDRAZINES FROM THE REACTIONS OF METHYLHYDRAZINE AND METHYL ESTERS OF CARBOXYLIC ACIDS

Methyl	Moles of ester/mole of methylhydrazine	Reaction time, hr.	B.p., °C. (mm.) of distillate	Yield of distillate, %
Acetate	2.1	2	118–120 (24)	33
	2	30	.....	70
Propionate	2	2	.....	9
	2	10	97–98 (6)	55
Isobutyrate	2	10	.....	6
	1	20	92–94 (4)	23

For preparative purposes the minimum reaction time should probably be 24 hr. for the smaller esters, and longer for larger ones. The reactions of anhydrides and methylhydrazine seem to be complete by the time the addition of anhydride has been completed.

Acylation of *unsym*-Dimethylhydrazine.—*unsym*-Dimethylhydrazine reacted cleanly with ethyl formate as it does with the methyl ester.[2] After 2 hr. at the reflux temperature and 48 hr. at room temperature 1-formyl-2,2-dimethylhydrazine was obtained from a solution of the two reactants in 95% ethanol. Ethyl acetate, on the other hand, did not react with *unsym*-dimethylhydrazine in six hours at the reflux temperature, nor was any product obtained when the experiment was repeated with 95% ethanol as the solvent, or with a catalytic quantity of hydrochloric or phosphoric acid added to the solvent. Varying the ratio of hydrazine to ester from 2:1 to 1:2 had no effect. Neither methyl nor ethyl acetate yielded any non-volatile material after standing for 72 hr. with an equal weight of *unsym*-dimethylhydrazine, conditions under which methyl formate readily reacts.[2] Methyl benzoate did not react in 22 hr. at the reflux temperature, nor under the various conditions used in the experiments with ethyl acetate.

In view of these results it seems unlikely that *unsym*-dimethylhydrazine will react with simple esters of acids higher than formic unless more drastic conditions (pressure, etc.) are employed. In this connection 1-benzoyl-2,2-dimethylhydrazine

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[14] T. Folpmers, *Rec. trav. chim.*, **34**, 34 (1915).

[15] 1-Benzoyl-1-methylhydrazine is converted to 1,2-dibenzoylmethylhydrazine and methylhydrazine on attempted distillation; ref. 1b.

was obtained in 20% yield from an experiment in which the *unsym*-dimethylhydrazine was stirred with sodium hydride for two hours before addition of methyl benzoate in an effort to form Me_2NNH^- which would undoubtedly be highly reactive.

In addition to the reactions of esters with *unsym*-dimethylhydrazine, formylation with chloral hydrate[16] was investigated. From the reaction of an aqueous solution of these substances at room temperature a white solid was isolated, probably $(CH_3)_2NNHCHOHCCl_3$. This substance, which melted at 80–83°, was too unstable to characterize. On standing, both the solid and its aqueous solution underwent rapid decomposition to tarry materials. Chloral and hydrazine hydrate in aqueous solution underwent an uncontrollable exothermic reaction, leaving only a tarry residue.[17] Since hydrazine and its alkyl derivatives are bifunctional, as is chloral, polymerization probably takes place.

From the experiments with methylhydrazine and with *unsym*-dimethylhydrazine it can be concluded that the order of reactivity with respect to the formation of acylhydrazines from esters is: $NH_2NH_2 > CH_3NHNH_2 > (CH_3)_2NNH_2$. This is also the order which would be expected on the basis of the steric effects. Considering only steric requirements, hydrazine, methylhydrazine and *unsym*-dimethylhydrazine can be compared to methylamine, ethylamine and isopropylamine, respectively. The relative order of rates of the reactions of the amines with esters have been shown to be that given here for their hydrazine analogs.[18] In addition, the statistical effect of the two amino groups should enhance the reactivity of hydrazine itself.

Experimental[19]

Reactions of *unsym*-Dimethylhydrazine with Esters.—These reactions were carried out under the conditions described in the Discussion. At the end of the allotted reaction time the unchanged reactants and solvents, if any, were distilled at aspirator pressure. The absence of material which was non-volatile under these conditions was taken as evidence that no reaction had occurred. Only the reaction of *unsym*-dimethylhydrazine and ethyl formate yielded a product, which was characterized as the known[2] 1-formyl-2,2-dimethylhydrazine.

Reactions of Methylhydrazine with Esters.—These reactions were carried out by refluxing a mixture of the ester and methylhydrazine, with subsequent removing of volatile materials by distillation under reduced pressure. The reaction times and yields of products are summarized in Table II. The paper chromatographic examination of the reaction mixtures was carried out as described below. The properties of the derivatives of the products are given in Tables IV and V.

The reaction of methyl benzoate and methylhydrazine was examined somewhat more carefully than the others. Increasing the mole ratio of ester to hydrazine from 1:1 to 2:1 was accompanied by a fourfold increase in yield. Other variations in the reaction conditions, such as the use of methanol as a solvent, phosphoric acid as a catalyst, or the addition of ethylene glycol, which catalyzes the reactions of ammonia with esters,[20] had a negligible effect.

The procedure for the reaction of methylhydrazine and methyl benzoate is described in detail, since it differs considerably from the general procedure.

1-Benzoyl-2-methylhydrazine Hydrochloride.—To a solution of 45.4 g. (0.33 mole) of methyl benzoate in 20 ml. of 95% ethanol, 15.4 g. (0.33 mole) of methylhydrazine was added. After the mixture had refluxed for two hours,[21] the unchanged methylhydrazine and the solvent were distilled under reduced pressure into cold ethanolic sulfuric acid, whereupon methylhydrazine hydrosulfate precipitated and was collected on a filter. The recovered methylhydrazine hydrosulfate represented 50% (25.4 g.) of the initial methylhydrazine charge. After one recrystallization a sample melted at 143–144° (reported m.p.[22] 142°). The residue from the distillation was acidified with dilute hydrochloric acid and extracted with ether. The water layer was then made basic with dilute sodium hydroxide and extracted with chloroform. Dry hydrogen chloride was passed through the chloroform solution which had been dried over magnesium sulfate. The white, water-soluble crystals which precipitated were collected on a filter, giving 5.0 g. (8%) of 1-benzoyl-2-methylhydrazine hydrochloride. Two recrystallizations from absolute ethanol gave white needles, m.p. 209–210°. Two additional recrystallizations from the same solvent provided an analytical sample, m.p. 210–210.5°.

TABLE III

R_f VALUES OF PRODUCTS FROM THE REACTIONS OF METHYLHYDRAZINE AND RCO_2CH_3[a]

R	R_f,[b,c] upper layer Solvent system i-$C_5H_{11}OH$, CH_3CO_2H, H_2O (10:1.5:10)	Solvent system n-C_4H_9OH, CH_3CO_2H, H_2O (4:1:5)
CH_3–	0.55(s), 0.72(w)	0.61(s), 0.76(w)
C_2H_5–	.67(s), .79(w)	.71(s), .81(w)
$(CH_3)_2CH$–	.76(s), .88(w)	.82(s), .88(w)
C_6H_5–	.82(s), .93(s)	....

[a] Products from anhydride reactions gave similar pairs of spots with the relative strengths reversed. [b] Chromatograms developed by the ascending technique at 28–30°; point of application 1.5 cm. from lower edge of strip. For other details of technique see ref. 10. [c] s = strong, w = weak.

Anal. Calcd. for $C_8H_{11}N_2OCl$: C, 51.50; H, 5.94; N, 15.01. Found: C, 51.50; H, 5.91; N, 14.86.

An aqueous solution of the hydrochloride did not react with ethanolic solutions of benzaldehyde, *p*-nitrobenzaldehyde or *p*-anisaldehyde.

Isolation of 1-Benzoyl-2-methylhydrazine.—An aqueous solution of 4 g. of 1-benzoyl-2-methylhydrazine hydrochloride which previously had been purified by four recrystallizations from absolute ethanol, was made basic with 20% sodium hydroxide and extracted with four 10-ml. portions of chloroform. The chloroform extract was concentrated to about one-eighth the original volume and petroleum ether (b.p. 60–70°) was added to the boiling solution until it became turbid. Cooling this solution in an ice-bath caused the separation of white needles, which were collected on a filter. The 1-benzoyl-2-methylhydrazine, after two recrystallizations from a mixture of 4 parts petroleum ether and 1 part chloroform, melted at 83–85°. The recovered 1-benzoyl-2-methylhydrazine (1.1 g.) represented a 34% conversion from the hydrochloride. Only a small amount (0.1 g.) could be recovered from the recrystallization liquors. An analytical sample, m.p. 86–88°, was prepared by three further recrystallizations from the same solvents.

Anal. Calcd. for $C_8H_{10}N_2O$: C, 63.78; H, 6.62; N, 18.68. Found: C, 63.66; H, 6.43; N, 18.94.

When a 1-g. sample of the product was subjected to Ainsworth's method[6a] for hydrogenolysis with Raney nickel, a basic gas was evolved and a white solid was isolated. The latter, m.p. 126–128°, did not depress the m.p. of an authentic specimen of benzamide.

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[16] F. F. Blicke and Chi-Jung Lu, THIS JOURNAL, **74**, 3933 (1952).

[17] It has been reported that chloral and hydrazine in water yield $Cl_3CCHOHNHNH_2$, which decomposes to a tar on standing: G. Knopper, *Monatsh.*, **32**, 768 (1911); *cf.* R. Stollé and Fr. Helwerth, *J. prakt. Chem.*, **88**, 315 (1913).

[18] E. M. Arnett, J. G. Miller and A. R. Day, THIS JOURNAL, **72**, 5635 (1950).

[19] Melting points and boiling points are uncorrected.

[20] M. Gordon, J. G. Miller and A. R. Day, THIS JOURNAL, **71**, 1245 (1949).

[21] Chromatographic examination of later experiments showed that the reaction was far from complete after two hours and that 24 hours would be a more satisfactory reaction time.

[22] J. Thiele, *Ber.*, **42**, 2575 (1909).

TABLE IV

PROPERTIES OF *p*-NITROBENZALDEHYDEHYDRAZONES: $RCON(CH_3)N{=}CHC_6H_4NO_2\text{-}p$

R[a]	M.p., °C.	U.v. absorption[b] 95% EtOH λ_{max}	a_M	Concn., mole/l.	Formula	Calcd. C	H	N	Found C	H	N
CH_3–	187–188	230	6000	7.2×10^{-5}	$C_{10}H_{11}N_3O_3$	54.35	5.04	19.00	54.06	4.94	18.86
		327	11500								
C_2H_5–	208–209	232	5700	1.0×10^{-4}	$C_{11}H_{13}N_3O_3$	55.92	5.54	17.80	56.01	5.18	17.76
		328	11200								
C_6H_5–	172–173	225	8100	6.4×10^{-5}	$C_{15}H_{13}N_3O_3$	63.59	4.63	14.84	63.91	4.20	14.57
		330	9100								
$(CH_3)_2CH$–	128–130	234	. . .	. . . .	. . . .	. . .	. .	. . .	. . .	. .	. . .
		332	. . .								

[a] Recrystallized from ethanol–water mixtures. [b] Determined with a Cary model 11 recording spectrophotometer, equipped with 1-cm. quartz cells.

TABLE V

PROPERTIES OF PHENYLTHIOSEMICARBAZIDES DERIVED FROM ACYLMETHYLHYDRAZINES: $RCO\overset{R'}{N}{-}\overset{R''}{N}CSNHC_6H_5$

R	Product[a] R′	R″	M.p., °C.	Formula	Calcd. C	H	N	Found C	H	N
CH_3	H	CH_3[b]	154–154.5	$C_{10}H_{13}N_3OS$	53.85	5.88	18.80	53.65	5.64	18.96
C_2H_5	H	CH_3[b]	144–144.5	$C_{11}H_{15}N_3OS$	55.67	6.37	17.71	55.96	6.53	17.91
$(CH_3)_2CH$	H	CH_3[b]	174.5–175	$C_{12}H_{17}N_3OS$	57.40	6.83	. . .	57.43	6.87	. . .
C_6H_5	H	CH_3[c]	159–160[e]	$C_{15}H_{15}N_3OS$	63.20	5.29	14.73	63.42	5.21	14.88
CH_3	CH_3	H[d]	163–164 d.	$C_{10}H_{13}N_3OS$	53.85	5.88	18.80	54.04	5.92	19.47
C_2H_5	CH_3	H[d]	170–172 d.	$C_{11}H_{15}N_3OS$	55.67	6.37	17.71	55.50	6.28	17.39
C_6H_5	CH_3	H[d]	153–155 d.[e]	$C_{15}H_{15}N_3OS$	63.20	5.29	14.73	63.52	5.28	14.49

[a] All recrystallized once from a chloroform–hexane mixture and then twice from ethanol–water mixtures, with the exception of 1-propionyl-1-methyl-4-phenylthiosemicarbazide which lost H_2S in hot ethanol, and was therefore recrystallized twice from an ethyl acetate–benzene mixture. [b] Structure based on assumption that the isolated thiosemicarbazide is derived from the major component of mixture of products from reaction of methylhydrazine and an *ester*. [c] Prepared from pure 1-benzoyl-2-methylhydrazine of known structure (see Discussion). [d] Same assumption as *b*, but prepared from products of anhydride and methylhydrazine. [e] Mixed m.p. with the isomeric thiosemicarbazide: 141–152° dec.

Attempted Synthesis of 1-Benzoyl-2-methylhydrazine by Hydrogenation of 1-Benzoyl-2-methylenehydrazine.—1-Benzoyl-2-methylenehydrazine[23] did not take up hydrogen during 18 hours under 2 atm. of hydrogen at 50–70° using a platinum oxide catalyst. The starting material also was recovered from an attempted reduction with lithium aluminum hydride in tetrahydrofuran, using a 100% excess of hydride and the Soxhlet technique.

Reactions of Methylhydrazine with Anhydrides.—These reactions were carried out by a modification of the method of Michaelis and Hadanck.[1b] The anhydride was added in small portions to a stirred 30% solution of methylhydrazine in water. The temperature of the reaction was kept below 20° during the addition, but was allowed to come to room temperature during a 15-minute period of stirring after the addition had been completed. The volatile materials were removed by distillation under reduced pressure, the last traces being entrained by the addition of benzene and then ligroin or ether. *p*-Nitrobenzaldehyde hydrazones and phenyl thiosemicarbazides were prepared directly from the residual oils. The properties of these derivatives are given in Tables IV and V, respectively.

Paper Chromatography.—The paper chromatographic examination of the products from the reactions of methylhydrazine with esters and anhydrides was carried out by methods described in a previous publication.[10] After each reaction the volatile materials usually were removed by distillation under reduced pressure and a sample of the residual oil was chromatographed on paper, using the ascending technique at 28–30°. In some cases, particularly when the course of a reaction was being followed, the volatile materials were not removed first. The solvent systems are given in Table III. The dry chromatogram was sprayed with an ethanolic solution of *p*-dimethylaminobenzaldehyde hydrochloride and dried in the usual way.[10]

Products from the *ester* reactions were revealed as two yellow or orange spots, which fluoresced strongly under an ultraviolet lamp. The larger spot was the one of lower R_f. The products from the *anhydride* reactions also were revealed as two spots, but only the lower one, which was usually yellow or orange, was visible in white light. The larger spot was the one of higher R_f; it appeared as a dark spot under an ultraviolet lamp.[24] The two spots from the anhydride reaction had the same R_f values as the spots from the ester reactions. Furthermore, when the material from the ester reaction was reduced to the minimum necessary for detection on the chromatogram, the upper spot no longer fluoresced; it appeared as a dark spot under an ultraviolet lamp. When coloration of the upper spot occurred, it was probably due to overloading and incomplete separation which was difficult to avoid. The spots therefore apparently are due to the same compounds, whether from the ester reaction or from the anhydride reaction.

The R_f values of spots from representative experiments are listed in Table III. The R_f values increase as the hydrocarbon residues increase in size, in accord with the effect generally observed.[25]

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[23] R. L. Hinman, THIS JOURNAL, **79**, 414 (1957).

[24] The spot of higher R_f could be detected also by exposing the dry chromatogram to hydrazine vapors for about 2 hr. The spot then appeared white against an orange background, which probably is due to the formation of *p*-dimethylaminobenzaldehyde azine.

[25] Reference 12, pp. 12–16, 108, 121, 159.