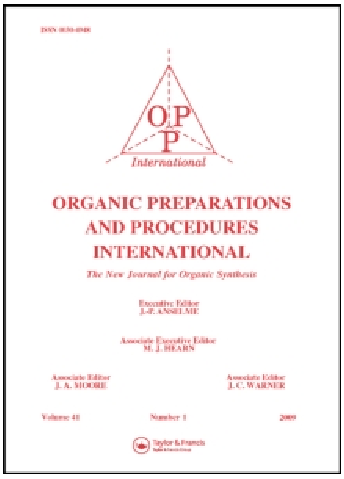

Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

THE TWENTY METHYL- AND ETHYL-SUBSTITUTED HYDRAZINES

F. E. Condon[a]; D. C. Thakkar[a]; Tamara Briks Goldstein[a]
[a] Department of Chemistry, The City College of the City University of New York, New York, NY

To cite this Article Condon, F. E. , Thakkar, D. C. and Goldstein, Tamara Briks(1973) 'THE TWENTY METHYL- AND ETHYL-SUBSTITUTED HYDRAZINES', Organic Preparations and Procedures International, 5: 5, 233 — 244
To link to this Article: DOI: 10.1080/00304947309356848
URL: http://dx.doi.org/10.1080/00304947309356848

ORGANIC PREPARATIONS AND PROCEDURES INT. 5(5), 233-244 (1973)

THE TWENTY METHYL- AND ETHYL-SUBSTITUTED HYDRAZINES

F. E. Condon*, D. C. Thakkar, and Tamara Briks Goldstein
Department of Chemistry, The City College of the
City University of New York, New York, N. Y. 10031

There are 20 conceivable methyl- and ethyl-substituted hydrazines; and at the time this work was begun, all but five of them had been prepared and described in the literature. Only three: methylhydrazine, 1,1-dimethylhydrazine, and 1,2-dimethylhydrazine are available commercially. The other 17, including five new ones, have recently been prepared in this laboratory for measurement of their pK_a's, heats of solution and neutralization, and other properties, as part of a study of the influence of hydration on base strength.[1]

In this communication are described the five methyl- and ethyl-substituted hydrazines previously unknown and five other new hydrazine derivatives obtained as intermediates in their synthesis. Reactions used in the synthesis of all 17 of the methyl- and ethyl-substituted hydrazines not commercially available are outlined; and literature references are given where detailed procedures for their synthesis can be found.

The routes used in the synthesis of 17 methyl- and ethyl-substituted hydrazines are shown in Chart I, where each hydrazine is identified by a simple four-digit code number.

CHART I

SUMMARY OF REACTIONS USED IN SYNTHESES OF METHYL- AND ETHYL-SUBSTITUTED HYDRAZINES

Code No.	
1110	$\mathrm{Me_2NNH_2 \xrightarrow{CH_2O} Me_2NN{=}CH_2 \xrightarrow{LiAlH_4} Me_2NNHMe\ (\underline{1110}) \xrightarrow{EtOCHO}}$
1111	$\mathrm{Me_2NNMeCHO \xrightarrow{LiAlH_4} Me_2NNMe_2\ (\underline{1111})}$
2111	$\mathrm{\underline{1110} \xrightarrow{Ac_2O} Me_2NN(Ac)Me \xrightarrow{LiAlH_4} Me_2NNEtMe\ (\underline{2111})}$
2000	$\mathrm{EtNHCONHEt \xrightarrow{NaNO_2,\ HCl} EtN(NO)CONHEt \xrightarrow{Zn,\ HOAc}}$
	$\mathrm{EtN(NH_2)CONHEt \xrightarrow{H_2O,\ HCl} EtNHNH_2.2HCl \xrightarrow{NaOH} EtNHNH_2\ (\underline{2000})}$
2010	$\mathrm{MeNHNH_2 \xrightarrow{Ac_2O} MeNAcNH_2 \xrightarrow{CH_3CHO} MeNAcN{=}CHCH_3 \xrightarrow{NaBH_4,\ EtOH}}$
	$\mathrm{MeN(Ac)NHEt \xrightarrow{H_2O,\ HCl} MeNHNHEt.2HCl \xrightarrow{NaOH} MeNHNHEt\ (\underline{2010})}$
2020	$\mathrm{NH_2NH_2 \xrightarrow{CH_3CHO} CH_3CH{=}N{-}N{=}CHCH_3 \xrightarrow{LiAlH_4} EtNHNHEt\ (\underline{2020})}$
2011	$\mathrm{Me_2NNH_2 \xrightarrow{CH_3CHO} Me_2NN{=}CHCH_3 \xrightarrow{LiAlH_4} Me_2NNHEt\ (\underline{2011}) \xrightarrow{Ac_2O}}$
2211	$\mathrm{Me_2NN(Ac)Et \xrightarrow{LiAlH_4} Me_2NNEt_2\ (\underline{2211})}$
2100	$\mathrm{EtNH_2 \xrightarrow{C_6H_5CHO} PhCH{=}NEt \xrightarrow{Me_2SO_4} PhCH{=}N(Me)Et^{+}MeSO_4^{-} \xrightarrow{H_2O}}$
	$\mathrm{EtMeNH_2^{+}MeSO_4^{-} \xrightarrow{NaNO_2} EtMeNNO \xrightarrow{Zn,\ HOAc} EtMeNNH_2\ (\underline{2100})}$
2110	$\mathrm{\underline{2100} \xrightarrow{CH_2O} EtMeNN{=}CH_2 \xrightarrow{LiAlH_4} EtMeNNHMe\ (\underline{2110}) \xrightarrow{Ac_2O}}$
2121	$\mathrm{EtMeNN(Ac)Me \xrightarrow{LiAlH_4} EtMeNNEtMe\ (\underline{2121})}$
2120	$\mathrm{EtMeNN{=}CH_2 \xrightarrow{CH_3MgI} EtMeNNHEt\ (\underline{2120})}$
2200	$\mathrm{Et_2NH \xrightarrow{NaNO_2,\ HCl} Et_2NNO \xrightarrow{Zn,\ HOAc} Et_2NNH_2\ (\underline{2200}) \xrightarrow{CH_2O}}$
2210	$\mathrm{Et_2NN{=}CH_2 \xrightarrow{LiAlH_4} Et_2NNHMe\ (\underline{2210}) \xrightarrow{Ac_2O}}$
2221	$\mathrm{Et_2NN(Ac)Me \xrightarrow{LiAlH_4} Et_2NNEtMe\ (\underline{2221})}$
2220	$\mathrm{Et_2NN{=}CH_2 \xrightarrow{CH_3MgI} Et_2NNHEt\ (\underline{2220}) \xrightarrow{Ac_2O}}$
2222	$\mathrm{Et_2NN(Ac)Et \xrightarrow{LiAlH_4} Et_2NNEt_2\ (\underline{2222})}$

The digits give the number of carbons in the alkyl groups replacing hydrogen, first on N_1, then on N_2. As a rule, and in accordance with rules of organic nomenclature (alphabetical order and lowest number rules), a hydrazine is coded preferentially by as large a number as possible. For example, $EtMeNNH_2$ = 2100 (preferred) = 1200 = 0021 = 0012.

Some of the intermediates, including five new hydrazine derivatives, are described in Table 1; the five new polyalkylhydrazines prepared in this work are listed in Table 2 and analytical data are given in Table 3.

In general, synthetic routes were chosen so as to minimize the chance of contamination of the desired hydrazine with other members of the set. In each case, we feel the route shown in Chart I is the most convenient and practical with respect to availability of starting material, ease and safety of operation, and yield and purity of the desired hydrazine.

Some of these hydrazines have been previously prepared by alkylation of hydrazine or an alkylhydrazine with an alkyl halide or sulfate.[2-5] Such routes were avoided in this work because of the possibility of producing another alkyl derivative in addition to the one wanted, but having a similar boiling point. Such routes may be practical, however, if the desired hydrazine forms a solid dihydrochloride that can be purified by recrystallization, such as ethylhydrazine.[2,6]

Lithium aluminum hydride reduction of acylhydrazines, used for production of the six tetraalkylhydrazines in the set, always gave also some trialkylhydrazine as a result of N-acyl bond cleavage.[7-9] The trialkylhydrazine impurity was readily

TABLE 1

PHYSICAL PROPERTIES OF INTERMEDIATES[a]

Name and Formula	B.p.[b] °C/torr	Density, 25° gm/cm^3	N. m. r. spectrum δ, ppm from TMS (CCl_4)
1-Formyl-1,2,2-trimethylhydrazine[c] $\mathrm{Me_2NN(Me)CHO}$	68/14	0.9535	
1-Acetyl-1,2,2-trimethylhydrazine[d] $\mathrm{Me_2NN(Ac)Me}$	80/21	0.9249	
1-Acetyl-1-ethyl-2,2-dimethylhydrazine $\mathrm{Me_2NN(Ac)Et}$	85/20	0.9218	3.27 (q, 2H, J = 6.9 Hz) 2.52 (s, 6H) 1.99 (s, 3H) 1.16 (t, 3H, J = 6.9 Hz)
1-Acetyl-1-methyl-2,2-diethylhydrazine[d] $\mathrm{Et_2NN(Ac)Me}$	105/25	0.9183	
Formaldehyde ethylmethylhydrazone $\mathrm{EtMeNN{=}CH_2}$	92/750	---	6.04 (d, 1H, J = 12.8 Hz) 5.82 (d, 1H, J = 12.8 Hz) 3.19 (q, 2H, J = 7.1 Hz) 2.61 (s, 3H) 1.06 (t, 3H, J = 7.1 Hz)
1-Formyl-1,2-diethyl-2-methylhydrazine $\mathrm{EtMeNN(Et)CHO}$	95/16	0.929	8.07 (s, 1H) 3.26 (q, 2H, J = 7.1 Hz) 2.71 (q, 2H, J = 7.1 Hz) 2.61 (s, 3H) 1.20 (t, 3H, J = 7.1 Hz) 1.01 (t, 3H, J = 7.1 Hz)
1-Acetyl-2-ethyl-1,2-dimethylhydrazine $\mathrm{EtMeNN(Ac)Me}$	91/20	---	2.72 (s, 3H) 2.65 (q, 2H, J = 7.3 Hz) 2.49 (s, 3H) 2.03 (s, 3H) 1.00 (t, 3H, J = 7.3 Hz)
1-Acetyl-1,2,2-triethylhydrazine $\mathrm{Et_2NN(Ac)Et}$	96/15	---	3.21 (q, 2H, J = 7.0 Hz) 2.71 (q, 4H, J = 7.1 Hz) 2.00 (s, 3H) 1.15 (t, 3H, J = 7.0 Hz) 1.02 (t, 6H, J = 7.1 Hz)

---

[a] All were colorless liquids. Satisfactory elemental analyses were obtained for all new compounds. (See Table 3.)

[b] Mid-point of narrow range. [c] Reference 23. [d] Reference 20.

eliminated, however, by acetylation with acetic anhydride to an acetyltrialkylhydrazine, from which the tetraalkylhydrazine could be separated cleanly by fractional distillation.

TABLE 2

NEW POLYALKYLHYDRAZINES[a]

Hydrazine	B. p., °C/torr	N. m. r. spectrum[b] δ, ppm from TMS (CCl_4)
1-Ethyl-1,2-dimethyl- EtMeNNHMe (2110)	79/750	2.47 (s, 3H) 2.41 (s, 3H) 2.32 (q, 2H, J = 7.1 Hz) 1.02 (t, 3H, J = 7.1 Hz)
1-Ethyl-1,2,2-trimethyl- $EtMeNNMe_2$ (2111)	95/750	2.39 (q, 2H, J = 7.1 Hz) 2.22 (s, 6H) 2.16 (s, 3H) 1.00 (t, 3H, J = 7.1 Hz)
1,2-Diethyl-1-methyl- EtMeNNHEt (2120)	97/750	2.70 (q, 2H, J = 7.1 Hz) 2.40 (q, 2H, J = 7.1 Hz) 2.32 (s, 3H) 1.02 (t, 3H, J = 7.1 Hz) 1.00 (t, 3H, J = 7.1 Hz)
1,1-Diethyl-2,2-dimethyl Et_2NNMe_2 (2211)	110/750	2.38 (q, 4H, J = 7.1 Hz) 2.25 (s, 6H) 1.00 (t, 6H, J = 7.1 Hz)
1,1,2-Triethyl-2-methyl- $Et_2NNEtMe$ (2221)	68/100	2.44 (q, 2H, J = 7.1 Hz) 2.40 (q, 4H, J = 7.1 Hz) 2.18 (s, 3H) 1.00 (2t, 9H, J = 7.1 Hz)

---

a. All were colorless liquids and gave satisfactory elemental analyses. (See Table 3.)

b. Excepting the N-H proton signal, broad and variable in position.

EXPERIMENTAL

Methylhydrazine (1000) and 1,1-dimethylhydrazine (1100) were purchased from Matheson, Coleman, and Bell, Inc. 1,2-Dimethylhydrazine (1010) was generated from its dihydrochloride purchased from Aldrich Chemical Co.[10]

TABLE 3

ANALYTICAL DATA

Compound	Formula		Analysis, % Calcd.	Analysis, % Found
1-Acetyl-1-ethyl-2,2-dimethylhydrazine	$C_6H_{14}N_2O$	C	55.32	54.84
		H	10.84	10.88
Formaldehyde ethylmethylhydrazone	$C_4H_{10}N_2$	C	55.78	56.15
		H	11.70	11.96
1-Formyl-1,2-diethyl-2-methylhydrazine	$C_6H_{14}N_2O$	C	55.32	54.91
		H	10.84	10.54
1-Acetyl-2-ethyl-1,2-dimethylhydrazine	$C_6H_{14}N_2O$	C	55.32	55.20
		H	10.84	10.74
1-Acetyl-1,2,2-triethylhydrazine	$C_8H_{18}N_2O$	C	60.73	60.97
		H	11.47	11.29
1-Ethyl-1,2-dimethylhydrazine	$C_4H_{12}N_2$	C	54.50	54.67
		H	13.73	13.88
1-Ethyl-1,2,2-trimethylhydrazine	$C_5H_{14}N_2$	C	58.78	58.57
		H	13.81	13.62
1,2-Diethyl-1-methylhydrazine	$C_5H_{14}N_2$	C	58.78	59.04
		H	13.81	13.72
1,1-Diethyl-2,2-dimethylhydrazine	$C_6H_{16}N_2$	C	62.01	62.30
		H	13.88	14.01
1,1,2-Triethyl-2-methylhydrazine	$C_7H_{18}N_2$	C	64.56	64.62
		H	13.93	13.73

Syntheses of the following have been described where indicated: Ethylhydrazine (2000),[6] 1-ethyl-1-methylhydrazine (2100),[11] and 1-ethyl-2-methylhydrazine (2010).[12] 1,1-Diethylhydrazine (2200)[13,14] was prepared by reduction of diethylnitrosamine[14] with zinc and acetic acid, essentially as described in the literature.[15]

Syntheses Involving Lithium Aluminum Hydride Reduction of Hydrazones. Trimethylhydrazine (1110),[16] 2-ethyl-1,1-dimethylhydrazine (2011),[9,17,18] 1,2-diethylhydrazine (2020),[19] 1-ethyl-1,2-dimethylhydrazine (2110) (Table 2), and 1,1-diethyl-2-methylhydrazine (2210)[20] were prepared by lithium aluminum hydride reduction of the appropriate hydrazones (Chart I). Formaldehyde dimethylhydrazone,[16] acetaldehyde dimethylhydrazone,[17] ethylidene azine,[19] formaldehyde ethylmethylhydrazone (Table 1), and formaldehyde diethylhydrazone,[20,21] were prepared by standard procedures. Freshly distilled acetaldehyde was used where needed, so as to avoid the presence of paraldehyde, which would have made troublesome the purification of the hydrazones and the hydrazines derived from them. Each hydrazone was dried ultimately by distillation from calcium hydride before reduction with lithium aluminum hydride.

The reduction of formaldehyde ethylmethylhydrazone is typical of the procedure used. A 1-l. three-necked flask was fitted with a sealed stirrer with Teflon paddle, a dropping funnel and a reflux condenser protected from atmospheric moisture by a KOH-filled guard tube. The flask was charged with 100 gm (a large excess over that theoretically required) of a 19% solution of lithium aluminum hydride in ether, supplied by Foote Mineral Co., Exton, Pa. A solution of 50 gm (0.58 mole) of formaldehyde ethylmethylhydrazone in 100 ml of anhydrous ether was added dropwise with stirring and cooling and maintaining a gentle reflux. The mixture was heated under reflux with stirring for two hours and allowed to stand overnite.

Before hydrolysis, a sample of the supernatant ether solution was taken for examination by n.m.r. spectroscopy for the presence of unreacted hydrazone, easily detectable by its methylenic proton signal. If unreacted hydrazone was present, more lithium aluminum hydride was added; and heating was continued until hydrazone was no longer detectable. The mixture was then readied for hydrolysis.

A series of traps, one cooled with ice, a second with solid CO_2-toluene, was attached to the end of the reflux condenser. The reaction flask was cooled in ice; and a cooled solution of 100 gm of sodium hydroxide in 125 ml of water was added dropwise, cautiously and extremely slowly at first, when the reaction is very exothermic. After about half of the sodium hydroxide solution had been added, a viscous, heavy precipitate made stirring difficult; and it was necessary to turn the stirrer shaft by hand for a time. With continued addition of the sodium hydroxide solution, however, the mixture became fluid and mechanical stirring could be resumed. The reflux condenser was rearranged for downward distillation, the series of cold traps being retained beyond the receiver for distillate. Stirring was continued while the reaction mixture was distilled until a vapor temperature about 100° was reached, distillation had slowed, and the distillate appeared to be largely water. The several distillates, including those from the cold traps, were separately concentrated by distillation through a 20 x 1-cm column packed with glass helices for removal of the ether. The concentrated residues from these distillations were combined and distilled. A fraction boiling at 77-81° was nearly pure 1-ethyl-1,2-dimethylhydrazine, with traces of water and ether detectable by n.m.r. spectroscopy. Yield 26.5 gm (52%).

Syntheses Involving Lithium Aluminum Hydride Reduction of Acylhydrazines.[9,22] Lithium aluminum hydride reduction of acylhydrazines was used only for the synthesis of tetraalkylhydrazines: tetramethylhydrazine (1111),[23] 1-ethyl-1,2,2-trimethylhydrazine (2111) (Table 2), 1,2-diethyl-1,2-dimethylhydrazine (2121),[9] 1,1-diethyl-2,2-dimethylhydrazine (2211) (Table 2), 1,1,2-triethyl-2-methylhydrazine (2221) (Table 2), and tetraethylhydrazine (2222).[17,21] In each case, the product was found by n.m.r. spectroscopy to be contaminated with trialkylhydrazine produced by cleavage of the N-acyl bond.[7-9] This was removed by acetylation with acetic anhydride to an acetyltrialkylhydrazine, which could be separated cleanly from the inert tetraalkylhydrazine by fractional distillation.

1-Formyl-1,2,2-trimethylhydrazine was prepared as described in the literature.[23] 1-Formyl-1,2-diethyl-2-methylhydrazine (Table 1) was prepared similarly from 1,2-diethyl-1-methylhydrazine. The acetyltrialkylhydrazines described in Table 1 were prepared by acetylation of the appropriate trialkylhydrazine with acetic anhydride in ethereal solution. Byproduct acetic acid was removed by treatment with 40%

aqueous sodium hydroxide; and the desired product was extracted into ether. The ethereal solution was dried with anhydrous potassium carbonate and the product recovered by distillation.

The procedures for lithium aluminum hydride reduction of acylhydrazines and workup of the reaction mixtures were essentially as described above for hydrazones; and the acetylation of the products for removal of contaminating trialkylhydrazines was done as described above for the preparation of acetyltrialkylhydrazines.

Grignard Syntheses. *1,2-Diethyl-1-methylhydrazine* (*2120*) (Table 2) and *triethylhydrazine* (*2220*)[3, 21] were prepared by way of addition of methylmagnesium iodide to the appropriate formaldehyde dialkylhydrazone. The preparation of *2120* is typical. In a 1-l. three-necked flask equipped with stirrer, dropping funnel, and reflux condenser, the Grignard reagent was prepared in the usual manner from 12 gm of magnesium, 80 gm of freshly distilled methyl iodide, and 300 ml of ether. A solution of 41 gm (0.48 mole) of formaldehyde ethylmethylhydrazone in 50 ml of ether was added dropwise with

---

CAUTION! In the course of extraction of these products into ether, a common occurrence after the second or third extraction was a rapid crystallization of sodium acetate trihydrate from a super-saturated solution, with evolution of heat and consequent buildup of ether vapor pressure within the separatory funnel, with attendant dangers of ejection of the glass stopper, eruption of contents into the face of the operator, and loss of material.

stirring and cooling in an ice bath. The mixture was refluxed three hours. It was then added in small portions with the aid of a Pasteur pipet to 100 gm of ice contained in a 600 ml beaker and cooled in an ice bath. As extraction with ether was ineffective for removal of the product from the gelatinous emulsion that formed, it was returned to the three-necked flask with the aid of a little water; and 120 gm of sodium hydroxide was mixed in with stirring and cooling. The mixture was then distilled as described above under "Lithium Aluminum Hydride Reduction of Hydrazones." The distillate, containing much ether, was dried with solid sodium hydroxide and distilled through a 20 x 1-cm column packed with glass helices. There was obtained 20 gm (41%) of 1,2-diethyl-1-methylhydrazine distilling at 96-98°.

Attempted syntheses of 2-ethyl-1,1-dimethylhydrazine by way of addition of methylmagnesium iodide to formaldehyde dimethylhydrazone failed because of inexplicable uncontrollable exothermic decomposition which set in during the hydrolysis step.

REFERENCES

1. F. E. Condon, J. Amer. Chem. Soc., <u>87</u>, 4491 (1965).
2. R. D. Brown and R. A. Kearley, ibid., <u>72</u>, 2762 (1950).
3. O. Westphal, Ber., <u>74</u>, 759 (1941).
4. A. N. Kost and R. S. Sagitullin, Zh. Obshch. Khim., <u>33</u>, 867 (1963); Chem. Abstr., <u>59</u>, 8724 (1964).
5. H. H. Stroh and H. G. Scharnow, Chem. Ber., <u>98</u>, 1588 (1965).

6. F. E. Condon and D. C. Thakkar, OPPI, 5, 219 (1973).

7. R. F. Nystrom and W. G. Brown, J. Amer. Chem. Soc., 70, 3738 (1948).

8. V. M. Micovic and M. L. Mihailovic, J. Org. Chem., 18, 1190 (1953).

9. R. L. Hinman, J. Amer. Chem. Soc., 78, 1645 (1956).

10. G. Davies and K. Kustin, J. Phys. Chem., 73, 2248 (1969).

11. F. E. Condon and D. G. Shapiro, OPPI, 5, 225 (1973).

12. F. E. Condon, J. Org. Chem., 37, 3615 (1972).

13. E. Fischer, Ann. Chem., 199, 308 (1879).

14. B. V. Joffe, Zhur. Obshchei Khim., 28, 1296 (1958); Chem. Abstr., 52, 19907 (1958).

15. H. H. Hatt, in "Organic Syntheses," Coll. Vol. II, Wiley, New York, N. Y., 1943, p. 211.

16. J. B. Class, J. G. Aston, and T. S. Oakwood, J. Amer. Chem. Soc., 75, 2937 (1953).

17. F. Klages, G. Nober, F. Kircher, and M. Bock, Ann. Chem., 547, 1 (1941).

18. B. V. Joffe and L. E. Poroshin, Zhur. Obshchei Khim., 29, 3154 (1959); Chem. Abstr., 54, 11975 (1960).

19. R. Renaud and L. C. Leitch, Can. J. Chem., 32, 545 (1954).

20. G. Zinner, W. Kliegel, W. Ritter and H. Böhlke, Chem. Ber., 99, 1678 (1966).

21. O. Westphal and M. Eucken, Ber., 76, 1137 (1943).

22. L. Spialter, D. H. O'Brien, G. L. Untereiner, and W. A. Rush, J. Org. Chem., 30, 3278 (1965).

23. R. T. Beltrami and E. R. Bissell, J. Amer. Chem. Soc., 78, 2467 (1956).

(Received June 12, 1973; in revised form, August 13, 1973)