N-Methyltriazolinedione Addition to 1. Reaction of MTAD (630 mg, 4.57 mmol) with isodicyclopentadiene (740 mg, 5.60 mmol) in 15 mL of ethyl acetate at -35 °C as before gave 1.2 g (88%) of **14** as transparent prisms: mp 129 °C dec; IR (CCl_4) 2960, 1785, 1728, 1448, 1182, 1010 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.00 (dd, J = 2.0, 1.5 Hz, 2 H), 2.98 (m, 2 H), 2.88 (s, 3 H), 2.47-0.92 (m, 8 H); ^{13}C NMR ($CDCl_3$) 161.3 (s), 151.0 (s), 64.7 (d), 55.4 (t), 54.9 (t), 41.3 (d), 25.7 25.4 ppm; mass spectrum, m/e calcd 245.1164, obsd 245.1170.

Anal. Calcd for $C_{13}H_{15}N_3O_2$: C, 63.66; H, 6.16. Found: C, 63.63; H, 6.17.

Catalytic Hydrogenation of 9 to 14. A 14-mg sample of platinum oxide in 1 mL of ethyl acetate was prehydrogenated, and the slurry was cooled to -20 °C. A solution of **9** (105 mg, 0.43 mmol) in 4 mL of ethyl acetate was introduced, and hydrogenation was resumed until ca. 9 mL of hydrogen was taken up. The mixture was filtered through Celite, and the filtrate was evaporated to give 103 mg (97%) of **14** whose spectra were superimposable upon those of the substance prepared above.

Diimide Reduction of 14. Following the standard procedure, 1.5 g (6.12 mmol) of **14** in 45 mL of ethanol was reduced with 4.3 g (134 mmol) of hydrazine and 6.2 mL of hydrogen peroxide. Workup gave 235 mg (15.6%) of **11**, a colorless solid: mp 157-158 °C (from ethyl acetate-hexane); ^1H NMR ($CDCl_3$) δ 4.45 (pseudo s, 2 H), 3.03 (s, 3 H), 2.52-137 (series of m, 12 H); ^{13}C NMR ($CDCl_3$) 158.2 (s), 60.4 (d), 47.8 (d), 42.3 (t), 39.4 (d), 35.7 (t), 25.6 (q), 24.3 (t) ppm; mass spectrum, m/e calcd 247.1321, obsd 247.1327.

Anal. Calcd for $C_{13}H_{17}N_3O_2$: C, 63.14; H, 6.93. Found: C, 63.02; H, 6.98.

***syn*-4,5-Diazatetracyclo[6.2.1.1^{3,6}.0^{2,7}]dodec-4-ene (15).** A solution of sodium hydroxide (0.8 g, 20 mmol) and **11** (420 mg, 1.70 mmol) in 40 mL of isopropyl alcohol was heated at reflux for 4 h, cooled in ice, and acidified with 6 mL of 3 N hydrochloric acid. The mixture was added to 300 mL of water containing 12 g of cupric chloride, and stirring was maintained for 2 h. Ammonium hydroxide was added until a deep blue color persited, and 400 mL of a 1:1 pentane-ether mixture was added. After thorough shaking, the organic phase was separated, washed with water and brine, and dried. Solvent evaporation furnished 175 mg (63.5%) of **15** as a colorless waxy solid which was sublimed 70 °C (0.4 torr): mp 101-102 °C; IR (CCl_4) 2990, 2950, 2875, 1480, 1450, 1250 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.87 (m, 2 H), 2.20 (m, 2 H), 1.67-0.85 (series of m, 10 H); ^{13}C NMR ($CDCl_3$) 76.6 (d), 45.0 (t), 40.7 (d), 37.9 (d), 34.4 (t), 24.4 (t) ppm; mass spectrum, m/e calcd 134.1095, obsd 134.1099 ($M^+ - N_2$).

Anal. Calcd for $C_{10}H_{14}N_2$: C, 74.03; H, 8.70. Found: C, 74.08; H, 8.63.

***endo,anti*-Tetracyclo[5.2.1.0^{2,6}.0^{3,5}]decane (16).** A solution of **15** (85 mg, 0.52 mmol) in 12 mL of acetone was irradiated at 3500 Å in a Rayonet reactor for 2 h. The solvent was carefully evaporated, and the residue was passed through a short column of alumina (pentane elution). Pentane was removed by distillation to leave 41 mg (59%) of **16** as a colorless mobile oil: ^1H NMR ($CDCl_3$) δ 2.38-0.95 (series of m, 13 H), 0.75 (m, 1 H); ^{13}C ($CDCl_3$) 45.1, 40.9, 38.1, 24.65, 18.7, 18.3 ppm.

Acknowledgment. The authors are grateful to the National Cancer Institute for financial support (Grant CA-12115) and to Professor J. E. Baldwin for making available to us copies of the ^1H NMR spectra of **16**.

Registry No. **1**, 6675-72-5; **2**, 6675-71-4; **3**, 73321-24-1; **4**, 74987-28-3; **5**, 74987-29-4; **6**, 74987-30-7; **7**, 74987-31-8; **8**, 74998-57-5; **9**, 73321-36-5; **10**, 74987-32-9; **11**, 74987-33-0; **12**, 75023-44-8; **13**, 74987-34-1; **13**·picrate salt, 74987-35-2; **14**, 73321-35-4; **15**, 74987-36-3; **16**, 53862-36-5; MTAD, 13274-43-6.

Supplementary Material Available: Table I, final atomic parameters for **4**; Table II, final anisotropic thermal parameters for **4**; Table III, bond lengths in **4**; Table IV, bond angles in **4** (4 pages). Ordering information is given on any current masthead page.

Palladium-Catalyzed Triethylammonium Formate Reductions. 4.[1] Reduction of Acetylenes to Cis Monoenes and Hydrogenolysis of Tertiary Allylic Amines

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Eight phenyl-conjugated and double bond conjugated acetylenes were reduced with triethylammonium formate and a palladium on carbon catalyst. Cis olefins were obtained in good yields in five examples. 4-Nitrodiphenylacetylene gave only 4-aminodibenzyl and (*Z*)-methyl non-2-en-4-ynoate gave mainly the *E,Z* dienoate. 1-Phenyl-3-methylbut-3-en-1-yne gave the cis diene initially, but it isomerized partially under the reaction conditions. Five tertiary allylic amines were shown to undergo hydrogenolysis with the same reducing agent and catalyst to give mixtures of two isomeric olefins in moderate to good yields.

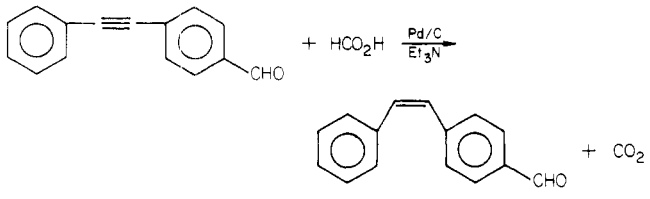
Palladium-catalyzed triethylammonium formate reduction of aromatic halides,[2] mono-[2] and dinitro[1] compounds, α,β-unsaturated carbonyl compounds,[3] conjugated dienes,[3] and acetylenes[3] has been reported. Only three simple acetylenes were studied previously, diphenylacetylene, 3-hexyne, and 1-hexyne.[3] We thought it would be useful to investigate the selective reduction of more complex acetylenes and to better define the usefulness of this reaction. Since a major advantage of the reduction with triethylammonium formate over reduction with hydrogen is the ease of precisely measuring the amount of reductant needed, we have looked for other types of compounds which may be selectively reduced, as well as the acetylenes, to find possible new applications for this reagent. With this in mind, we investigated hydrogenolysis of benzylic and allylic oxygen and nitrogen derivatives. Useful reductions were obtained with tertiary allylic amines. This reduction has proved to be useful for selectively removing morpholino and piperidino groups from the tertiary amines obtained in the recently discovered palladium-catalyzed reaction of vinylic halides with olefins and morpholine or piperidine.[4]

(1) Paper III in the series: J. R. Weir and R. F. Heck, *J. Org. Chem.*, companion paper in this issue.
(2) N. A. Cortese and R. F. Heck, *J. Org. Chem.*, **42**, 3491 (1977).
(3) N. A. Cortese and R. F. Heck, *J. Org. Chem.*, **43**, 3985 (1978).
(4) B. A. Patel and R. F. Heck, *J. Org. Chem.*, **43**, 3898 (1978).

0022-3263/80/1945-4926$01.00/0

Results and Discussion

Acetylene Reductions Eight acetylenic compounds of diverse structures were reduced. The acetylenes were all prepared by the palladium-catalyzed condensation of organic halides with monosubstituted acetylenes.[5] Selective reductions were attempted in all cases. The cis olefins were obtained in moderate to good yields in five cases and nonselective reduction occurred in three cases. The results are summarized in Table I. Reactions were usually carried out with a 3–14% excess of 97% formic acid and an excess of triethylamine over the equivalent amount relative to the formic acid. The exact amount of amine used is not critical. We generally used a 2–3 molar excess or more with the very reactive enynoates. Most often 1 mol % palladium based upon the acetylene was used in the form of 10% palladium on carbon as the catalyst. Normally, the reductions were more selective at room temperature than at higher temperature with the first example, 1-phenyl-1-hexyne being an exception. The reduction of this compound was more selective at the reflux temperature of the reaction mixture (about 90 °C) where 48% (*Z*)-1-phenyl-1-hexene and 12% 1-phenylhexane were obtained. The low yield is due to a competing palladium-catalyzed polymerization of the acetylene which destroys part of the starting acetylene. Catalytic reduction of 1-phenyl-1-hexyne with hydrogen and 1 mol % 10% palladium on carbon in methanol solution at room temperature and 1 atm of pressure also was very selective in forming only the cis olefin, but the amount of polymer formed under the milder reaction conditions was less (ca. 20%) than that in the formic acid reduction (~40%). The formic acid reduction of 4-(phenylethynyl)benzaldehyde was more selective at 25 °C where a 58% yield of (*Z*)-4-styrylbenzaldehyde was obtained. Again, no other product except polymer was produced.



58%

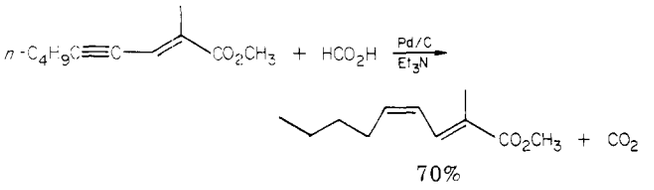
4-Nitrophenylacetylene, on the other hand, could not be reduced selectively under any conditions and only 4-aminobenzyl could be found as a product. With an excess of reducing agent this product could be obtained in 71% yield. 1-Phenyl-3-methylbut-3-en-1-yne apparently was reduced to the cis diene, but the diene underwent partial isomerization to the trans isomer under all conditions we tried. Catalytic reduction of this compound with hydrogen in methanol solution with 1 mol % 10% palladium on carbon at room temperature with 1 atm of pressure was more selective: about a 10:1 ratio of *Z*:*E* diene products was obtained. The higher selectivity of the hydrogen reduction probably is mainly a result of the lower reaction temperature rather than the different reducing agent. (*E*)-Methyl 5-phenyl-2-methylpent-2-en-4-ynoate, reduced easily to the cis dienoate in good yield (84%). The open-chain compound, (*E*)-methyl 2-methylnon-2-en-4-ynoate reduced to the *E*,*Z*-dienoate in 70% yield at 75 °C. However, the reduction was less selective when the 2-methyl group was absent. (*E*)-Methyl non-2-en-4-ynoate reduced slowly at 25 °C when a large excess of amine was used to improve the selectivity. The compound was not

(5) H. A. Dieck and R. F. Heck, *J. Organometl. Chem.*, **93**, 259 (1975).

Table I. Triethylammonium Formate Reductions of Acetylenic Compounds

compd	mol of formic acid / mol of compd	catalyst	mol of Et_3N / mol of formic acid	conditions	products (% yield)
$C_6H_5C{\equiv}C(CH_2)_3CH_3$	1.13	1 mol % 10% Pd/C	2.71	24 h, reflux	(Z)-$C_6H_5CH{=}CH(CH_2)_3CH_3$ (48), $C_6H_5(CH_2)_3CH_3$ (12)
4-$OCHC_6H_4C{\equiv}CC_6H_5$	2.10	1 mol % 10% Pd/C	6.77	24 h, 25 °C	(Z)-$OCHC_6H_4CH{=}CHC_6H_5$ (58)
4-$O_2NC_6H_4C{\equiv}CC_6H_5$	5.23	1 mol % 10% Pd/C	1.63	18 h, reflux	4-$H_2NC_6H_4(CH_2)_2C_6H_5$ (71)
4-$O_2NC_6H_4C{\equiv}CC_6H_5$	5.23	1 mol % 10% Pd/C	2.72	24 h, 25 °C	4-$H_2NC_6H_4(CH_2)_2C_6H_5$ (68)
$C_6H_5C{\equiv}CC(CH_3){=}CH_2$	4.20	1 mol % 10% Pd/C	1.36	72 h, 75 °C	(Z)-$C_6H_5CH{=}CHC(CH_3){=}CH_2$ (24), (E)-$C_6H_5CH{=}CHC(CH_3){=}CH_2$ (49)[a]
(*E*)-$C_6H_5C{=}CCH{=}C(CH_3)CO_2CH_3$	1.00	1 mol % 10% Pd/C	2.72	10 h, 100 °C	(*E*,*Z*)-$C_6H_5CH{=}CHCH{=}C(CH_3)CO_2CH_3$ (84)[c]
(*E*)-$C_6H_{11}C{=}CCH{=}C(CH_3)CO_2CH_3$	1.05	1 mol % 10% Pd/C	2.72	10 h, 100 °C	(*E*,*Z*)-$C_6H_{11}CH{=}CHCH{=}C(CH_3)CO_2CH_3$ (63)[c]
(*E*-*n*-$C_4H_9C{=}CCH{=}C(CH_3)CO_2CH_3$	1.10	1 mol % 10% Pd/C	2.90	48 h, 75 °C	(*E*,*Z*)-*n*-$C_4H_9CH{=}CHCH{=}C(CH_3)CO_2CH_3$ (70)[d]
(*E*)-*n*-$C_4H_9C{=}CCH{=}CHCO_2CH_3$	1.03	10 mol % 10% Pd/C	11.17	48 h, 25 °C	*n*-$C_8H_{17}CO_2CH_3$ (23),[e] (*E*)-*n*-$C_6H_{13}CH{=}CHCO_2CH_3$ (14),[e] (*E*,*Z*)-*n*-$C_4H_9CH{=}CHCH{=}CHCO_2CH_3$ (63)[e]
(*E*)-*n*-$C_4H_9C{=}CCH{=}CHCO_2CH_3$	1.03	10 mol % 5% Pd/$CaCO_3$	6.75	72 h, 25 °C	*n*-$C_8H_{17}CO_2CH_3$ (24),[f] (*E*)-*n*-$C_6H_{13}CH{=}CHCO_2CH_3$ (20),[f] (*E*,*Z*)-*n*-$C_4H_9CH{=}CHCH{=}CHCO_2CH_3$ (59)[f]
(*Z*)-*n*-$C_4H_9C{=}CCH{=}CHCO_2CH_3$	1.14	10 mol % 10% Pd/C	10.83	48 h, 25 °C	*n*-$C_8H_{17}CO_2CH_3$ (41), (*Z*,*Z*)-$C_4H_9CH{=}CHCH{=}CHCO_2CH_3$ (5), (*Z*,*E*)-$C_4H_9CH{=}CHCH{=}CHCO_2CH_3$ (54)
(*Z*)-*n*-$C_4H_9C{=}CCH{=}CHCO_2CH_3$	1.14	10 mol % 5% Pd/$CaCO_3$	6.75	72 h, 25 °C	*n*-$C_8H_{17}CO_2CH_3$ (24), (*Z*)-*n*-$C_6H_{13}CH{=}CHCO_2CH_3$ (22), (*Z*,*E*)-*n*-$C_4H_9CH{=}CHCH{=}CHCO_2CH_3$ (30)

[a] *E* isomer appears to be coming from isomerization of the *Z* isomer under the reaction conditions. About 20% unreacted acetylene was present at the end of the reaction. The yields reported are corrected for unreacted acetylene. [b] Reaction carried out in a capped tube. [c] GLC yield. [d] 25% starting material was unreacted. [e] 30% starting material was unreacted. [f] 54% starting material was unreacted.



selectively reduced at higher temperatures. Therefore, 10 mol % catalyst was used at 25 °C and even after 48 h only 70% reduction had occurred. At this time, the selectivity was reasonable for this type compound and a mixture of 63% *E,Z*-dienoate, 14% *E* 2-enoate, annd 23% methyl nonanoate was produced. The same reduction was carried out with 10 mole % 5% palladium on calcium carbonate as catalyst with very similar results. The related *Z* ester, (*Z*)-methyl non-2-en-4-ynoate, could not be reduced selectively under any conditions tried. The same conditions that were used for the *E* ester gave little or none of the *Z,Z* dienoate and the major product was the *Z,E* isomer. Catalytic reductions of these *E* and *Z* esters in methanol solution with hydrogen at 25 °C and 1 atm with 5% palladium on calcium carbonate gave similar mixtures of reduction products although these reductions were much faster. It can be concluded that the formic acid–triethylamine partial reduction of acetylenes is a useful method for the synthesis of cis olefins in many instances. The method appears to be comparable with hydrogen reductions as far as selectivity is concerned, and although slower, it is more convenient to carry out and has fewer safety problems.

Allylic Amine Reductions. Five tertiary allylic amines, prepared in connection with other studies,[6,7] were reduced with the triethylammonium formate reagent with 1 mol % 10% palladium on carbon as the catalyst. The results are summarized in Table II. The amount of formic acid required for these reductions is between 1 and 2 equiv per mole of allylic amine, depending upon whether or not the secondary amine liberated in the reduction forms the *N*-formyl derivative under the reaction conditions. If the formylation is complete, then 2 equiv are theoretically required. We have found that the isolated double bonds in the reduction (hydrogenolysis) products reduce further only very slowly under our conditions. Therefore, we have generally employed 3–5 mol of formic acid per mole of amine to achieve faster reduction. The yield of saturated products was not appreciably changed by using the excess formic acid. The major yield losses were due to the formation of nonvolatile products.

Unfortunately, all of the reductions gave mixtures of two isomeric olefins arising from both direct reduction of the amine carbon atom and addition of hydrogen to the more distant carbon of the double bond with double bond migration and loss of the amine group. Probably, the mixture of olefins results because a π-allylic palladium hydride species is an intermediate in the reduction.

Both (*E*)-5-morpholino- and 5-piperidino-3-hexenal dimethyl acetals reduce in 18 h at 100 °C to give about 60–70% of a mixture of (*Z*)-3- and 4-hexenal dimethyl acetals and about 10% of hexanal dimethyl acetal. It was difficult to obtain accurate analyses since these products were not separable by GLC and analyses had to be made by proton and carbon NMR. It appeared that the two olefins were present in about a 40–60 ratio, but we do not know which was the major isomer. The addition of 8 mol % of triphenylphosphine to the reaction with the piper-

Table II. Triethylammonium Formate Hydrogenolysis of Tertiary Amines

compd[a]	mol of formic acid / mol of compd	catalyst	mol of Et$_3$N / mol of formic acid	conditions	products (% yield)
(*E*)-MCH(CH$_3$)CH=CHCH$_2$CH(OCH$_3$)$_2$	3.23	1 mol % 10% Pd/C	1.32	18 h, 100 °C	(*Z*)-3- and 4-hexenal dimethyl acetal (61), hexanal dimethyl acetal (11)
(*E*)-P*CH(CH$_3$)CH=CHCH$_2$CH(OCH$_3$)$_2$	3.16	1 mol % 10% Pd/C	1.32	18 h, 100 °C	(*Z*)-3- and 4-hexenal dimethyl acetal (67), hexanal dimethyl acetal (19)
(*E*)-P*CH(CH$_3$)CH=CHCH$_2$CH(OCH$_3$)$_2$	3.22	1 mol % 10% Pd/C + 8 mol % P(C$_6$H$_5$)$_3$	1.32	18 h, 100 °C	(*Z*)-3- and 4-hexenal dimethyl acetal (93), hexanal dimethyl acetal (7)
(*E*)-(CH$_3$P*)$^+$CH(CH$_3$)CH=CHCH$_2$CH(OCH$_3$)$_2$I$^-$	3.28	1 mol % 10% Pd/C	1.32	13 h, 100 °C	(*Z*)-3- and 4-hexenal dimethyl acetal (63), hexanal dimethyl acetal (5)
(*E*)-P*CH$_2$C(CH$_3$)=CHCH$_2$C(CH$_3$)$_2$OH	4.31	1 mol % 10% Pd/C	1.32	18 h, 100 °C	(CH$_3$)$_2$C=CHCH$_2$C(CH$_3$)$_2$OH (59), CH$_2$=C(CH$_3$)CH$_2$CH$_2$C(CH$_3$)$_2$OH (3)
(*E*)-P*CH$_2$C(CH$_3$)=CHCH$_2$C$_6$H$_5$	2.12	1 mol % 10% Pd/C	1.32	72 h, 25 °C	(CH$_3$)$_2$C=CHCH$_2$C$_6$H$_5$ (60), CH$_2$=C(CH$_3$)(CH$_2$)$_2$C$_6$H$_5$ (8), (CH$_3$)$_2$CH(CH$_2$)$_2$-C$_6$H$_5$ (22)
(*E*)-P*C(CH$_3$)$_2$CH=CHCH$_2$CH(OCH$_3$)$_2$	3.30	1 mol % 10% Pd/C	1.29	48 h, 100 °C	(CH$_3$)$_2$C=CH(CH$_2$)$_2$CH(OCH$_3$)$_2$ (31), (CH$_3$)$_2$CHCH=CHCH$_2$CH(OCH$_3$)$_2$ (31)

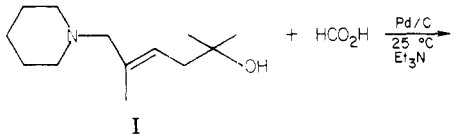
[a] MH = morpholine, P*H = piperidine.

(6) B. A. Patel, J. E. Dickerson, and R. F. Heck, *J. Org. Chem.*, **43**, 5018 (1978).
(7) B. A. Patel, L. Kao, D. Bender, and R. F. Heck, unpublished work.

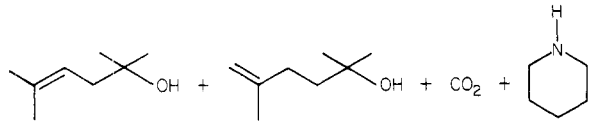
idino compound caused a significant increase in the olefin yield to 93%, with only 7% of hexanal dimethyl acetal also being formed.

The quaternary salt of the above piperidino complex with methyl iodide was reduced under similar conditions, but the products and yields were the same as those with the free amine.

The amine I could be reduced quite selectively to one olefin at 25 °C. The most substituted olefin was isolated

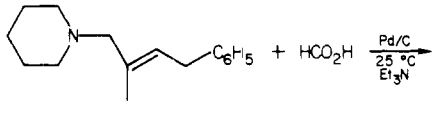


I

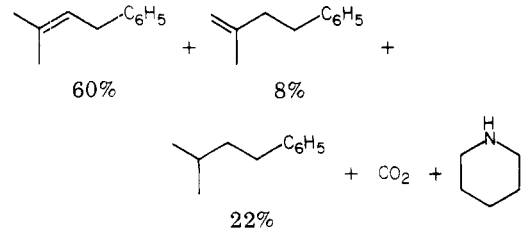


59% 3%

in 59% yield along with only 3% of the terminal olefin. The structurally similar amine II did not reduce as selectively under the same conditions. The internal olefin was still the major product, 60%, but 8% of the terminal olefin and 20% of the saturated hydrocarbon were also produced.

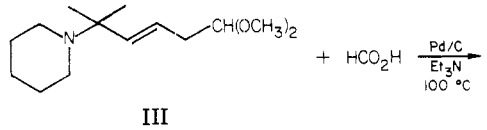


II

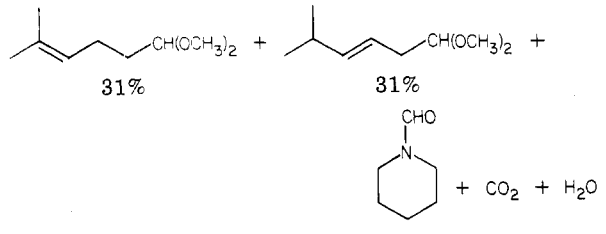


60% 8% 22%

Finally, the *N-tert*-alkylpiperidino compound III was reduced. It is interesting that this highly hindered amine reduced and that it produced a 1:1 mixture of the two isomeric olefins in 62% yield.



III

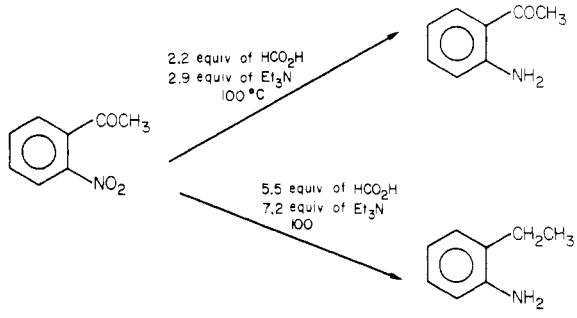


31% 31%

These few examples illustrate the facile hydrogenolysis of allylic piperidino and morpholino groups with triethylammonium formate and a palladium catalyst. The usefulness of the reaction is limited in unsymmetrical cases, however, because mixtures of isomeric olefins are produced.

We looked briefly at the reduction of a secondary allylic amine, diallylamine, and found that it reduced fairly easily also, forming mainly *N*-allylformamide.

Other Hydrogenolysis Reactions. We also have looked at the hydrogenolysis of benzyl alcohol, benzaldehyde, 2- and 4-nitroacetophenones, 2- and 4-nitrobenzaldehydes, and *N,N*-dimethylbenzylamine with triethylammonium formates, using palladium on charcoal as catalyst at 100 °C. Benzyl alcohol and *N,N*-dimethylbenzylamine both reduced very slowly to toluene, but the reactions did not appear to be very useful because they were so slow. Benzaldehyde reduced very slowly also to a mixture of benzyl alcohol and toluene. The 2- and 4-nitroacetophenones could be selectively reduced to aminoacetophenones, both in about 70% yield (based on the limiting reagent, formic acid) in 18 h at 100 °C. Further reduction of the ortho compound was achieved with more reductant to form 2-ethylaniline in 51% yield. The 2- and 4-nitrobenzaldehydes gave mainly polymer when reduced under similar conditions.



Experimental Section

The physical properties, and NMR and mass spectral data for the compounds prepared in this study are given in Table IV (see note at the end of the paper regarding supplementary material).

Materials. Formic acid, 97%, and triethylamine were used as received from Aldrich. The 10% palladium on carbon and the 5% palladium on calcium carbonate were products of Matheson, Coleman and Bell. 1-Phenyl-1-hexyne, 4-(phenylethynyl)benzaldehyde, and 1-phenyl-3-methylbut-3-en-1-yne were prepared as reported previously.[5] (*E*)-2-Methyl-1-piperidino-4-phenyl-2-butene also was prepared by a published procedure.[6]

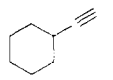
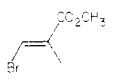
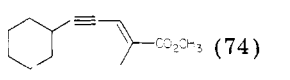
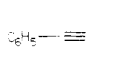
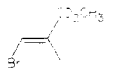
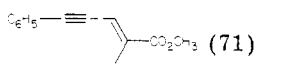
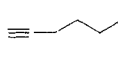
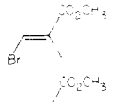
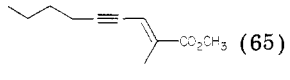
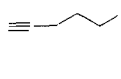
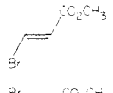
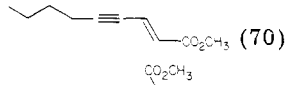
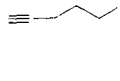
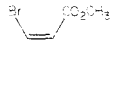
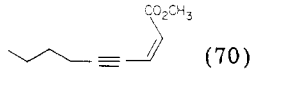
4-Nitrodiphenylacetylene.[8] In a 500-mL three-necked flask were placed 20.2 g (100 mmol) of *p*-bromonitrobenzene, 16.5 mL (15.3 g, 150 mmol) of phenylacetylene, 0.028 g (0.12 mmol) of palladium acetate, 0.066 g (0.25 mmol) of triphenylphosphine, 200 mL of triethylamine, and a magnetic stirring bar. The flask was fitted with a condenser. Nitrogen was passed through a T-tube attached to a bubbler and the top of the condenser. Stirring was begun and the solution was heated in an oil bath at 100 °C for 75 min. A spontaneous reaction set in after a few minutes, as evidence by vigorous boiling. The reaction slowly subsided as it neared completion.

The reaction mixture was allowed to cool to room temperature and 420 mL of 2 N HCl was added slowly. The insoluble product was collected by filtration and dried in a vacuum desiccator overnight. The product was then sublimed at 115 °C at 2–3 mm (about 10 h are required). The sublimed material was recrystallized from about 525 mL of ethanol and 210 mL of water. The hot solution was allowed to slowly cool at room temperature and then refrigerated at 5 °C. The pale yellow needles were collected by filtration and dried in a vacuum desiccator. The yield of 4-nitrodiphenylacetylene was 19.2 g (86%), mp 118.5–120.0 °C (lit. mp 119–120 °C).[9]

General Procedure for Preparation of Enynoate Esters. The procedure is a modification of that described by Dieck and Heck.[5] A mixture of 50 mmol of the required bromo ester, 62.5 mmol of the necessary monosubstituted acetylene, 0.50 mmol of palladium acetate (Matthey Bishop, Inc.), 1.00 mmol of triphenylphosphine and 40 mL of triethylamine was stirred at room temperature under a nitrogen atmosphere for 24 h. A large

(8) This procedure was developed by R. S. Artz in these laboratories.
(9) R. E. Sioda, D. O. Cowan, and W. S. Kaski, *J. Am. Chem. Soc.*, **89**, 230 (1967).

Table III. Enynoate Esters Prepared

substrate	organic halide	product (% yield)
		 (74)
		 (71)
		 (65)
		 (70)
		 (70)

amount of triethylammonium bromide crystallized from the red-orange solution during this time. The product was isolated by adding about 50 mL of water to dissolve the salt and extracting the product with two 50-mL portions of ether. The combined extracts were dried over magnesium sulfate and concentrated under reduced pressure. The products were distilled or in one case ((*E*)-methyl 2-methyl-5-phenylpent-2-en-4-ynoate) sublimed under reduced pressure from the residues. Yields and reactants are given in Table III. The NMR spectra and properties of the products are given in Table IV (see paragraph at the end of this article for information about supplementary material). The (*E*)-methyl 3-bromo-2-methylpropenoate required was prepared as previously described.[10] The preparation of the (*E*)- and (*Z*)-methyl 3-bromopropenoates is described below.

(*Z*)-Methyl 3-Bromopropenate. (*Z*)-3-Bromopropenoic acid was prepared by a modification of the method of Kurtz.[11] Propiolic acid (35.5 g, 0.507 mol) was added dropwise in 1 h to a stirred solution of 4.54 g (0.032 mol) of cuprous bromide in 90 mL of 48% aqueous hydrobromic acid (0.795 mol) cooled to 2 to 4 °C in an ice bath. The reaction mixture was stored overnight at −10 °C. The mixture was then warmed to room temperature and the product was extracted with several portions of ether. After the solution was dried it was concentrated and the product crystallized from the solution. The solid acid, mp 60.5–62 °C, was obtained in 82% yield.

The ester was prepared in 87% yield from the acid by esterification with methanol with sulfuric acid as catalyst, bp 61.5–63 °C (10 mm).

(*E*)-Methyl 3-Bromopropenoate. Propiolic acid (18.6 g, 0.265 mol) was added dropwise to 100 mL of 48% aqueous hydrobromic acid (0.883 mol) and the solution was boiled under a reflux condenser for 1.5 h. When the solution was cooled in an ice bath, the acid crystallized from solution. It was collected by filtration and air-dried. There was obtained 33.4 g (83%) of the *E* acid, mp 117.5–118.5 °C (lit.[12] 121 °C). The methyl ester was prepared as with the *Z* acid above. A 53% yield was obtained, bp 48–50 °C (10 mm).

Allylic Amines. The five allylic amines employed in this study were prepared by the method described previously,[4] using other olefinic reactants as necessary in place of the 1-hexene in the previous examples.

The reaction with (*Z*)-1-bromo-1-propene, acrolein dimethyl acetal, and morpholine in 48 h at 100 °C gave a 42% yield of (*E*)-5-morpholino-3-hexenal dimethyl acetal, bp 145–147 °C (10 mm). The related 5-piperidino product was prepared the same way, substituting piperidine for morpholine. This reaction was complete in 18 h at 100 °C. The products consisted of 17% hexadienal dimethyl acetals (isomeric mixture), bp 68–70 °C (10 mm), and 58% of (*E*)-5-piperidino-3-hexenal dimethyl acetal, bp 133 °C (10 mm).

A similar reaction of 2-bromo-1-propene with 2-methyl-3-buten-3-ol and piperidine gave as products 25% (*E*)-2,5-dimethyl-3,5-hexadien-2-ol, bp 78–80 °C (10 mm), and 34% 2,5-dimethyl-6-piperidino-4-hexen-2-ol, bp 132–135 °C (10 mm).

The preparation of (*E*)-2-methyl-1-piperidino-4-phenyl-2-butene was described previously.[6]

A reaction of 2-methyl-1-bromo-1-propene with acrolein dimethyl acetyl and piperidine gave the fifth allylic amine, (*E*)-5-methyl-5-piperidino-3-hexenal dimethyl acetal, in 37% yield, bp 130–132 °C (10 mm), along with 55% of a mixture of two isomeric 5-methylhexadiene dimethyl acetals, bp 80 °C (10 mm). The mixture contained approximately equal amounts of the 5-methyl-2,4-hexadienal acetal and the 3,5-dienal acetal.

(*E*)-*N*-Methyl-5-piperidino-3-hexenal Dimethyl Acetal. A solution of the tertiary amine (2.32 g, 10 mmol) in 30 mL of ether was reacted with 0.7 mL (11.2 mmol) of methyl iodide for 18 h at room temperature. The colorless crystalline product, mp 49–53 °C, was obtained in 61% yield.

General Procedure for Reducing Acetylenes and Allylic Amines. Reductions in an Open System. In a one-necked round-bottom flask of appropriate size equipped with a reflux condenser and calcium chloride filled drying tube were placed the substrate, catalyst, and triethylamine. The mixture was stirred magnetically and 97% formic acid was added slowly at room temperature. The reaction was allowed to proceed at the desired temperature until GLC analysis showed that all of the substrate had been reduced or no further reduction was taking place. Products, when isolated from the reaction mixtures, were obtained by filtering the catalyst from the reaction solution and washing the solid twice with ether. The extracts and ether washings were combined, washed with distilled water, and dried over magnesium sulfate. After removal of ether and triethylamine in vacuo, the products were either distilled or in one case sublimed from the residue.

Reductions in Closed Systems. The reactants were combined as above but placed in a heavy-walled Pyrex tube or bottle. A magnetic stirring bar was added and the solution was stirred while the formic acid was added. The tube or bottle was then capped and heated at the required temperature until GLC analysis indicated the absence of starting material or until the reaction stopped. The products were isolated as in the first procedure.

Reduction of 2- and 4-Nitroacetophenone. The same general procedure for the reduction of acetylenes and allylic amines in closed systems was used for 2- and 4-nitroacetophenones. We used 2.2 equiv of formic acid and 2.9 equiv of triethylamine to reduce the compounds to the amino ketones at 100 °C while 5.5 equiv of formic acid and 7.2 equiv of triethylamine were used to make the *o*-ethylaniline. Products were isolated by adding ether (25 mL) to the reaction mixtures and filtering the solution from the catalyst. The filtrates were extracted twice (2 × 25 mL) with 3 M aqueous hydrochloric acid. After the acid extracts were combined, excess sodium bicarbonate was added to liberate the amines. This aqueous amine solution was extracted twice (2 × 25 mL) with ether and the extracts were combined and dried over magnesium sulfate. The amine products were obtained in the following yields by removal of the ether and remaining triethylamine in vacuo: 2-aminoacetophenone (71%) [NMR δ_{Me_4Si} 2.43 (s, 3 H), 6.57 (m, 4 H), 7.12 (m, 1 H), 7.60 (dd, 1 H); identical with Sadtler 4987], 4-aminoacetophenone (68%) [NMR δ_{Me_4Si} 2.51 (s, 3 H), 4.29 (s, 2 H), 6.72 (d, 2 H), 7.84 (d, 2 H); identical with Sadtler 242], 2-ethylaniline (51%) [NMR δ_{Me_4Si} 1.20 (t, 3 H), 2.44 (q, 2 H), 3.37 (s, 2 H), 6.83 (m, 4 H); identical with Sadtler 111].

Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for the support of the research.

Registry No. 1-Phenyl-1-hexyne, 1129-65-3; 4-(phenylethynyl)benzaldehyde, 57341-98-7; 1-nitro-4-(phenylethynyl)benzene, 1942-30-9; (3-methyl-3-buten-1-ynyl)benzene, 1463-04-3; methyl (*E*)-2-methyl-5-phenyl-2-penten-4-ynoate, 20414-97-5; methyl (*E*)-5-cyclohexyl-2-methyl-2-penten-4-ynoate, 75066-85-2; methyl (*E*)-2-methyl-2-nonen-4-ynoate, 65960-09-0; methyl (*E*)-2-nonen-4-ynoate, 75066-86-3; methyl (*Z*)-2-nonen-4-ynoate, 75066-87-4; (*Z*)-1-hexenylbenzene, 15325-54-9; hexylbenzene, 1077-16-3; (*Z*)-4-(2-phenylethenyl)benzaldehyde, 71093-80-6; 4-(2-phenylethyl)benzenamine, 13024-49-2; (*Z*)-(3-methyl-1,3-butadienyl)benzene, 75066-88-5; (*E*)-

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(12) K. Alder, F. Brockhagen, C. Kaiser, and W. Roth, *Justus Liebigs Ann. Chem.*, **593**, 1 (1955).

(3-methyl-1,3-butadienyl)benzene, 68036-69-1; methyl (*E,Z*)-2-methyl-5-phenyl-2,4-pentadienoate, 20414-96-4; methyl (*E,Z*)-5-cyclohexyl-2-methyl-2,4-pentadienoate, 75066-89-6; methyl (*E,Z*)-2-methyl-2,4-nonadienoate, 75066-90-9; methyl nonanoate, 1731-84-6; methyl (*E*)-2-nonenoate, 14952-06-8; methyl (*E,Z*)-2,4-nonadienoate, 39924-44-2; methyl (*Z,Z*)-2,4-nonadienoate, 75066-91-0; methyl (*Z,E*)-2,4-nonadienoate, 75066-92-1; methyl (*Z*)-2-nonenoate, 68872-72-0; (*E*)-1,1-dimethoxy-5-morpholino-3-hexene, 75066-93-2; (*E*)-1,1-dimethyoxy-5-piperidino-3-hexene, 75066-94-3; (*E*)-1,1-dimethoxy-5-(*N*-methylpiperidinium)-3-hexene I^-, 75066-95-4; (*E*)-2,5-dimethyl-6-piperidino-4-hexen-2-ol, 75066-96-5; (*E*)-2-methyl-1-piperidino-4-phenyl-2-butene, 74312-51-9; (*E*)-1,1-dimethoxy-5-methyl-5-piperidino-3-hexene, 75066-97-6; (*Z*)-6,6-dimethoxy-2-hexene, 75066-98-7; (*Z*)-1,1-dimethoxy-3-hexene, 55444-65-0; 1,1-dimethoxyhexane, 1599-47-9; 2,5-dimethyl-4-hexen-2-ol, 14908-27-1; 2,5-dimethyl-5-hexen-2-ol, 75066-99-8; (3-methyl-2-butenyl)benzene, 4489-84-3; (3-methyl-3-butenyl)benzene, 6683-51-8; (3-methylbutyl)benzene, 2049-94-7; 6,6-dimethoxy-2-methyl-2-hexene, 2006-05-5; 1,1-dimethoxy-5-methyl-3-hexene, 75067-00-4; ethynylcyclohexane, 931-48-6; ethynylbenzene, 536-74-3; 1-hexyne, 693-02-7; methyl (*E*)-3-bromo-2-methylpropenoate, 40053-01-8; methyl (*E*)-3-bromo-2-propenoate, 6213-87-2; methyl (*Z*)-3-bromo-2-propenoate, 6214-22-8; *p*-bromonitrobenzene, 586-78-7; (*Z*)-3-bromopropenoic acid, 1609-92-3; propiolic acid, 471-25-0; (*E*)-3-bromopropenoic acid, 6213-89-4; (*Z*)-1-bromo-1-propene, 590-13-6; acrolein dimethyl acetal, 6044-68-4; morpholine, 110-91-8; piperidine, 110-89-4; 2-bromo-1-propene, 557-93-7; 2-methyl-3-buten-2-ol, 115-18-4; (*E*)-2,5-dimethyl-3,5-hexadien-2-ol, 75082-96-1; 2-methyl-1-bromo-1-propene, 3017-69-4; 5-methyl-2,4-hexadienal acetal, 75067-01-5; 5-methyl-3,5-hexadiene acetal, 75067-02-6; 2-nitroacetophenone, 577-59-3; 4-nitroacetophenone, 100-19-6; 2-aminoacetophenone, 551-93-9; 4-aminoacetophenone, 99-92-3; palladium, 7440-05-3; triethylammonium formate, 585-29-5.

Supplementary Material Available: Table IV containing physical properties and NMR and mass spectral data for the compounds prepared in this study (7 pages). Ordering information is given on any current masthead page.

Alicyclic Nitrosamines and Nitrosamino Acids as Transnitrosating Agents

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Many alicyclic nitrosamines act as nitrosating agents under mild conditions (pH 1–3, in the presence of nucleophilic catalysts such as thiocyanate). All nitrosopiperazines, nitrosomorpholines, and nitrosamino acids tested were found to act as nitrosating agents, and certain nitrosopiperidines also showed this capability. Acyclic nitrosamines are far less reactive than functionally similar cyclic compounds.

Introduction

Secondary and tertiary amines react with nitrite under mildly acidic conditions to form *N*-nitroso compounds. Carcinogenic nitrosamines can be formed by the reaction of dietary or endogenous nitrite with ingested amines, and this has, in fact, been demonstrated in laboratory animals.[1,2] However, nitrosation in vivo is not the only possible source of nitroso compounds. We have shown that many aliphatic nitroso compounds are capable of acting as nitrosating agents of naturally occurring amines under conditions similar to those found in the rat or human stomach (pH 1.7–3.6 with thiocyanate or other nucleophiles as catalyst).[3] While it has long been known that certain aromatic *N*-nitroso compounds are excellent transnitrosating agents,[4,5] the generality of this reaction has not been realized previously. In this paper we report the behavior of several widely varying classes of alicyclic nitrosamines as nitrosating agents. Included are certain derivatives of natural products such as nitrosoproline and nitrosopipecolic acid previously thought biologically innocuous but now shown to have potentially hazardous roles in the formation of carcinogenic nitrosamines.

Results and Discussion

Many nitrosamines are capable of acting as nitrosating agents at pH's of 1–3 in the presence of a nucleophilic catalyst.[3,6] The reaction, or transnitrosation, may be represented by eq 1–4.

$$R_2NNO + H^+ \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} R_2\overset{+}{N}HNO \quad (1)$$

$$R_2\overset{+}{N}HNO + {}^-SCN \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} R_2NH + NOSCN \quad (2)$$

$$NOSCN + R_2'NH \underset{k_{-3}}{\overset{k_3}{\rightleftharpoons}} R_2'NNO + SCN^- \quad (3)$$

$$NOSCN + Z \rightarrow \text{unstable product} \rightarrow N_2, \text{ etc.} \quad (4)$$

$$Z = HSO_3NH_2,\ NaN_3,\ NH_2CONH_2, \text{ etc.}$$

The reactions shown in eq 1–3 are all reversible, and the extent of reaction observed will depend on the relative rates k_{-3} vs. k_{-2}. The reaction shown in eq 4 is a special case in which the nitroso recipient forms an unstable nitroso compound which rapidly decomposes to give nitrogen (N_2), thus rendering the sequence irreversible.[7,8] Such reactions are referred to as denitrosations, and they provide a convenient method for studying the reaction sequence shown in eq 1 and 2 without complications from reversibility.

We have previously shown[6,21] that transnitrosation by aliphatic nitrosamines occurs in acidic aqueous solutions with nucleophile catalysis and no direct and/or uncatalyzed reaction occurs. A steady-state concentration of NOSCN[21] can be monitored throughout the course of the reaction. In effect, a transnitrosation by an aliphatic nitrosamine may be considered as a nitrosation reaction in

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