[Chem. Pharm. Bull. 20(10)2112—2116(1972)]

UDC 547.291.04 : 542.941 : 547.271'233.04

Formic Acid Reduction. XIII.[1] Formate Reaction of the Compounds possessing the Carbon Bound to Both Oxygen and Nitrogen

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(Received January 26, 1972)

There has been introduced a new type of formic acid reduction of the compounds in which both amine nitrogen and ether oxygen are bound to the same carbon. With series of N-(α-butoxybenzyl)dialkylamines, N-(butoxymethyl)dialkylamines and 3-methyloxazolidines, the reaction was normally carried out on heating with distillable formate, TMAF given by $5HCO_2H \cdot 2N(CH_3)_3$, to give tertiary amines, resulting in reductive fission at the carbon–oxygen bond. Mode of the reduction was clarified by the technique of using deuterated formic acids, in which formyl hydrogen of formic acid is transferred to the carbon of the carbon-oxygen bond. On the basis of this result a possible mechanism is described.

In development of the constant boiling liquids of the formates composed of formic acid and trialkylamine as reducing agents, reductive fission of the carbon-amide nitrogen bond of N-(dialkylaminomethyl)amides has been generally realized[3] on heating with the liquid formate, TMAF.[4] In the present investigation a series of the compounds possessing the carbon bound to both oxygen and nitrogen were allowed to react with TMAF. Our objective was to know site of the possible reductive fission of this type of the compounds, which might occur at the carbon–oxygen or the carbon–nitrogen bond.

The open-chain compounds possessing the carbon bound to both oxygen and nitrogen, which are available synthetically, have been known as N,O-benzylidene- and N,O-methylene compounds. N,O-Alkylidene compounds can also be available as cyclic compounds such as oxazolidine derivatives.

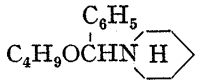
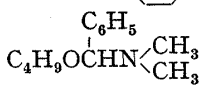
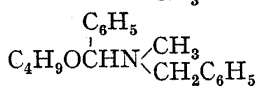
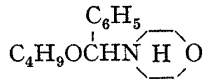
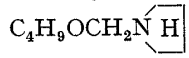
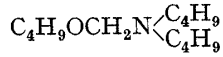
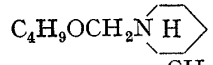
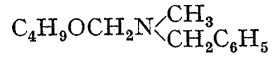
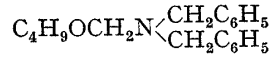
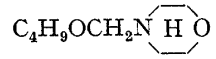
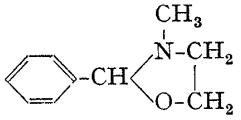
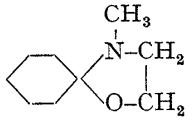
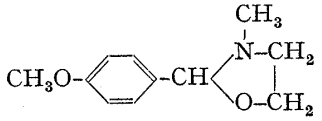
Reductive fission at the carbon–oxygen bond was seen by carrying out the reaction with the representative N-(α-butoxybenzyl)dimethylamine. When heated this compound together with TMAF, considerable emission of carbon dioxide was observed at 85—90°. Treatment of the reaction mixture gave N-benzyldimethylamnie in 88% yield and the other fission species, butanol containing its formate, was detected by gas chromatographic method.

$$C_6H_5CH\begin{matrix}\nearrow N(CH_3)_2 \\ \searrow OC_4H_9\end{matrix} + HCO_2H \text{ (TMAF)} \longrightarrow C_6H_5CH_2N(CH_3)_2 + C_4H_9OH + CO_2$$

With series of N-(α-butoxybenzyl)dialkylamines, N-(butoxymethyl)dialkylamines and 3-methyloxazolidines, results of the experiments are summarized in Table I. The reactions smoothly proceeded at moderate temperature with emission of carbon dioxide. In the runs with the former two series of the compounds the amine products were only isolated and in the runs with 3-methyloxazolidines hydrolyses of the direct products, which were composed of the ethanolamines and their formic acid esters, were necessary to give the sole amine products, the ethanolamines. As shown in Table I, their yields were excellent in most runs.

1) Part XII: M. Sekiya and K. Suzuki, *Chem. Pharm. Bull.* (Tokyo), **20**, 343 (1972).
2) Location: *2-2-1 Oshika, Shizuoka.*
3) M. Sekiya and K. Ito, *Chem. Pharm. Bull.* (Tokyo), **12**, 677 (1964).
4) The constant boiling liquid, bp 90° (15 mmHg), composed of trimethylamine and formic acid, which may be given by $5HCO_2H \cdot 2N(CH_3)_3$.[3]

Table I. TMAF Reduction of N,O-Alkylidene Compounds

Substrate	Reaction temp.[a] (°C)	Reaction time (min)	Yield[b] (%)
N,O-Benzylidene compounds[c]			
	80—83	60	93
	85—90	80	88
	81—83	60	82
	78—80	60	90
N,O-Methylene compounds[d]			
	41—45	40	97
	80—82	30	96
	40—43	50	98
	78—80	25	90
	80—82	25	95
	49—52	35	92
Oxazolidine compounds[c]			
	84—86	40	85
	93—95	50	84
	83—84	60	87

a) Temperature maintained while considerable amount of CO_2 was emitted.
b) Yield based on the tertiary amine product actually isolated.
c) substrate: TMAF (as HCO_2H)=1:20
d) substrate: TMAF (as HCO_2H)=1:10

Thus, it was generally realized that the reductive fission of the carbon–oxygen bond of the compound, in which the ether oxygen and the amine nitrogen are bound to the same carbon, is effected on heating with the reagent, TMAF. Because of ease of the preparation of the substrate compounds this formic acid reduction appeared to provide a convenient method for preparation of the tertiary amine like those described.

In our interest to speculate on a mechanism of this formic acid reduction, incorporation mode of the two different hydrogens of formic acid into the product was then investigated by the use of the formate reagent composed of deuterated formic acid. Since in the reaction the liquid formate, TEAF,[5] could be used in place of TMAF, this investigation was conducted by the use of the deuterated TEAF composed of formic-*d* acid (DCO_2H) and formic

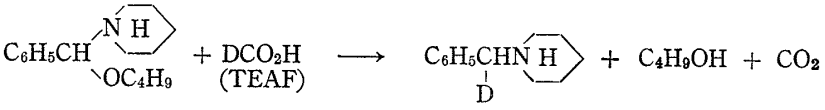
5) The constant boiling liquid, bp 95° (15 mmHg), composed of triethylamine and formic acid, which may be given by $5HCO_2H \cdot 2N(C_2H_5)_3$, K. Ito, *Yakugaku Zasshi*, **86**, 1166 (1966).

acid-*d* (HCO_2D). Selected 1-(α-butoxybenzyl)piperidine as a model substrate, the reactions of this compound with the two deuterated TEAF were carried out and deuterated positions and deuterium contents in the amine products were determined from their nuclear magnetic resonance (NMR) and mass spectra.

Since in the NMR spectrum of 1-benzylpiperidine in deuterochloroform the methylene protons appeared as singlet at τ 6.56, contents of the protons of the amine products at this position were measured in comparison of their peak areas with the phenyl and piperidino proton peak areas which appeared as singlet at τ 2.74 and as multiplets at τ 7.42—7.84 and 8.19—8.81, respectively. The product obtained from the reaction with the TEAF composed of formic-*d* acid showed 48% absence of the proton peak areas in comparison with that of the non-deuterated 1-benzylpiperidine, which indicates deuterium substitution of one proton of the methylene. On the other hand NMR spectrum of the product obtained from the reaction with the TEAF composed of formic acid-*d* showed no deuterium substitution, being well consistent with that of the non-deuterated sample.

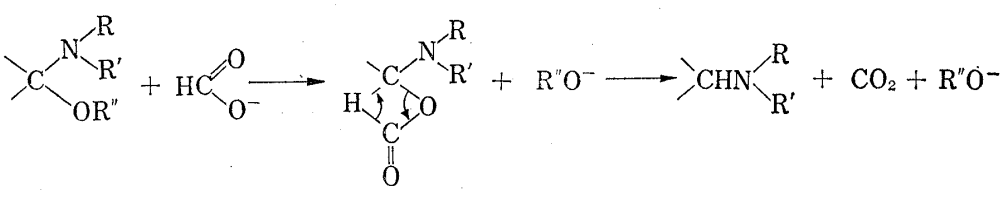
In order to obtain confidence of the above results, mass spectra of the two products obtained from the reactions with the two deuterated TEAF were also examined. The molecular ion and the principal fragments observed in the mass spectrum of 1-benzylpiperidine appeared at *m/e* 175 (M^+), 98 ($M^+-C_6H_5$), and 91 ($M^+-C_5H_{10}N$). Inspection at these peaks was made with the products. All these peaks in the product obtained from the reaction with TEAF composed of formic-*d* acid shifted to the peaks of one unit higher *m/e* values, indicating the presence of the 1-benzylpiperidine monodeuterated at the methylene. Content of this deuterated product was calculated from the heights of these peaks to be 94% in average. On the other hand, the product obtained from the reaction with TEAF composed of formic acid-*d* exhibited the mass spectrum well consistent with that of non-deuterated 1-benzylpiperidine.

From the above results obtained by NMR and mass spectral measurements, mode of the reaction with the TEAF composed of formic-*d* acid can be expressed by the following equation.



Therefore, it can be generally said that in the formic acid reduction of the compounds which possess the nitrogen and the oxygen bound to the same carbon, the formyl hydrogen of formic acid is transferred to the benzylidene carbon and acid hydrogen of formic acid to the oxygen.

Referring to the several papers,[6] the formic acid reduction has been recognized as hydride transfer of the formyl hydrogen of formic acid. When we speculate the mechanism it is then considered that such substrate compound, which is susceptible to nucleophilic attack at the carbon bound to oxygen first suffers nucleophilic substitution by attack of formate ion and the unstable ester-like intermediate undergoes rapid decarboxylation to give the amine product.



6) R. Stewart, *Can. J. Chem.*, **35**, 766 (1957); R.G.R. Bacon and J. Kochling, *J. Chem. Soc.*, **1964**, 5609; R. Grinter and S.F. Mason, *Trans. Faraday Soc.*, **60**, 889 (1964).

Experimental

TMAF Reduction of N-(α-Butoxybenzyl)dialkylamines General Procedure——The following four N-(α-butoxybenzyl)dialkylamines shown with their boiling points and refractive indexes were prepared according to the previously reported method[7] and were used as substrates for TMAF reduction: 1-(α-butoxybenzyl)piperidine,[7] bp 114—116° (0.5 mmHg), n_D^{26} 1.5051; N-(α-butoxybenzyl)dimethylamine,[7] bp 109—110° (1 mmHg), n_D^{19} 1.4856; N-(α-butoxybenzyl)-N-methylbenzylamine,[8] bp 125—126° (0.01 mmHg), n_D^{28} 1.5312; 4-(α-butoxybenzyl)morpholine,[7] bp 154—155° (0.5 mmHg), n_D^{14} 1.5011.

A mixture of 0.05 mole of the substrate and 69.6 g of TMAF (1.0 mole as HCO_2H) was stirred and heated at the requisite temperature while considerable CO_2 emission was observed. By means of passing a constant stream of air free from CO_2, emission of CO_2 was checked by $Ba(OH)_2$ solution. The reaction temperature and period for each run are recorded in Table I. After subsidence of CO_2 emission, the reaction solution was diluted with H_2O and saturated with KOH on cool. The liberated oily layer combined with benzene extract was dried. The benzene solution was evaporated and the residue was subjected to distillation under reduced pressure to give the tertiary amine product. In most runs this amine product was inevitably contaminated with very small amount of N-formyl secondary amine. This was removed by introduction of dry HCl into the benzene solution, where the amine product was precipitated as hydrochloride. After filtration, if necessary, treatment of this hydrochloride with $NaHCO_3$ gave the amine product in high purity. Yields of tertiary amine products obtained for each run are recorded in Table I. These products, which are listed in the following, were identified by noting exact correspondence of their infrared (IR) spectra with those of authentic samples.

1-Benzylpiperidine, bp 115—116° (13 mmHg), n_D^{27} 1.5218, hydrochloride, mp 173—175°; N-benzyldimethylamine, bp 82.5° (35 mmHg), n_D^{19} 1.5035; N-methyldibenzylamine, bp 120—126° (0.2 mmHg), n_D^{16} 1.5624, hydrochloride, mp 195—198°; 4-benzylmorpholine, bp 130—137° (21 mmHg), n_D^{29} 1.5251.

TMAF Reduction of N-(Butoxymethyl)dialkylamines General Procedure——The following six N-(butoxymethyl)dialkylamines shown with their boiling points and refractive indexes were prepared according to the method reported previously[9] and were used as substrates for the TMAF reduction: 1-(butoxymethyl)-pyrrolidine,[10] bp 84—85° (18 mmHg), n_D^{19} 1.4543; N-(butoxymethyl)dibutylamine,[11] bp 118—120° (15 mmHg), n_D^{19} 1.4310; 1-(butoxymethyl)piperidine,[9] bp 98—99° (19 mmHg), n_D^{12} 1.4495; N-(butoxymethyl)-N-methylbenzylamine, bp 135—137° (18 mmHg), n_D^{12} 1.4910. *Anal.* Calcd. for $C_{13}H_{21}ON$: C, 75.31; H, 10.21; N, 6.76. Found: C, 74.98; H, 10.13; N, 6.91; N-(butoxymethyl)dibenzylamine, bp 159—161° (0.1 mmHg), n_D^{19} 1.5409. *Anal.* Calcd. for $C_{19}H_{25}ON$: C, 80.52; H, 8.89; N, 4.94. Found: C, 80.51; H, 8.74; N, 4.93; 4-(butoxymethyl)morpholine,[12] bp 109—110° (20 mmHg), n_D^{19} 1.4594.

A mixture of 0.075 mole of the substrate and 52.5 g of TMAF (0.75 mole as HCO_2H) were allowed to react by the same manner as described in the runs with N-(α-butoxybenzyl)dialkylamines. The reaction temperature and period are recorded in Table I. The reaction mixture was diluted with H_2O and saturated with KOH on cool. The liberated oil was extracted with ether. The etheral extract was dried over K_2CO_3 and the tertiary amine product was isolated by the following manner. In the runs with 1-(butoxymethyl)-pyrrolidine, 1-(butoxymethyl)piperidine and 4-(butoxymethyl)morpholine, the volatile tertiary amine products were obtained as their picrates by usual treatment. In the runs with N-(butoxymethyl)dibutylamine, N-(butoxymethyl)-N-methylbenzylamine and N-(butoxymethyl)dibenzylamine, the tertiary amine products were contaminated with butanol, which was removed as its sodium salt by addition of metallic sodium to the etheral solution under refluxing. After evaporation of the etheral solution, the residue was distilled under reduced pressure to give the amine product. Yields for each run are recorded in Table I. The tertiary amine products and their picrates, which are listed in the following, were identified by noting exact correspondence of their IR spectra with those of authentic samples and no depression of their melting points by admixture with authentic picrates.

1-Methylpyrrolidine, picrate, mp 223—225°; N-methyldibutylamine, bp 161—162°, n_D^{19} 1.4220; 1-methylpiperidine, picrate, mp 219—221°; N-benzyldimethylamine, bp 82—83° (35 mmHg), n_D^{19} 1.5009; N-methyldibenzylamine, bp 124—125° (3 mmHg), n_D^{19} 1.5589; 4-methylmorpholine, picrate, mp 222—225°.

TMAF Reduction of 3-Methyloxazolidines General Procedure——The following three 2-substituted 3-methyloxazolidines were prepared according to the method reported by Bergmann, *et al.*[13] and were used as substrates for the TMAF reduction: 3-methyl-2-phenyloxazolidine,[13] bp 122—123° (22 mmHg), n_D^{19} 1.5275; 4-methyl-1-oxa-4-azaspiro[4,5]decane,[13] bp 95—97° (24 mmHg), n_D^{19} 1.4767; 2-(*p*-methoxyphenyl)-

7) A.T. Stewart and C.R. Hauser, *J. Am. Chem. Soc.*, **77**, 1098 (1955).
8) N. Sakura, K. Ito and M. Sekiya, *Chem. Pharm. Bull.* (Tokyo), **20**, 1156 (1972).
9) G.M. Robinson and R. Robinson, *J. Chem. Soc.*, **123**, 532 (1923).
10) J. Ficini and H. Normant, *Bull. Soc. Chim. France*, **1957**, 1454.
11) T.D. Stewart and W.E. Bradley, *J. Am. Chem. Soc.*, **54**, 4172 (1932).
12) A.F. Isbell and D.W. Hood, *J. Chem. Eng. Data*, **7**, **Pt 2**, 575 (1962).

3-methyloxazolidine,[13] bp 114—118° (2 mmHg), n_D^{12} 1.5350.

A mixture of 0.05 mole of the substrate and 69.6 g of TMAF (1.0 mole as HCO_2H) were allowed to react by the same manner as described for the runs with N-(α-butoxybenzyl)dialkylamines. The reaction temperature and period for each run are recorded in Table I. The oily amine residue was obtained by treatment of the reaction mixture with KOH and by successive extraction with ether. Since in the preliminary test the presence of 2-dialkylaminoethyl formate along with the desired 2-dialkylaminoethanol product was confirmed, the residue was hydrolyzed on heating with 18 ml of 50% KOH for 2 hr and the liberated oily layer was extracted with ether. After dried over $MgSO_4$ the etheral solution was concentrated and the residue was distilled under reduced pressure, where 2-dialkylaminoethanol was obtained as product. These products are listed in the following and their yields are recorded in Table I.

3-Methyl-2-phenyloxazolidine: 2-(N-Methylbenzylamino)ethanol,[14] bp 146—147° (27 mmHg), n_D^{19} 1.5264. The xanthate test was positive. *Anal.* Calcd. for $C_{10}H_{15}ON$: C, 72.69; H, 9.15; N, 8.48. Found: C, 73.08; H, 8.86; N, 8.00. IR spectrum showed exact correspondence with that of authentic sample.

4-Methyl-1-oxa-4-azaspiro[4,5]decane: 2-(N-Methylcyclohexylamino)ethanol,[15] bp 109—110° (12 mmHg), n_D^{19} 1.4831. The xanthate test was positive. *Anal.* Calcd. for $C_9H_{19}ON$: C, 68.74; H, 12.18; N, 8.91. Found: C, 68.71; H, 11.94; N, 8.60.

2-(*p*-Methoxyphenyl)-3-methyloxazolidine: 2-(*N*-Methyl-*p*-methoxybenzylamino)ethanol, bp 136—140° (3.5 mmHg), n_D^{12} 1.5340. The xanthate test was positive. *Anal.* Calcd. for $C_{11}H_{17}O_2N$: C, 67.66; H, 8.78; N, 7.17. Found: C, 67.43; H, 8.77; N, 7.14.

TEAF Composed of Formic-*d* Acid ($5DCO_2H \cdot 2NEt_3$)——A mixture of 31.8 g (0.66 mole) of formic acid-d_2 (DCO_2D), deuterated grade min. 99%, which was purchased at E. Merck AG Darmstadt, 53.6 g of triethylamine and 36.0 g of distilled water was heated at 70—80° for 30 hr. The resulting mixture was subjected to distillation under reduced pressure to afford a formate distillate. This distillate was twice processed by the treatments where the distillate was heated with distilled water at 70—80° for 30 hr and subjected to distillation under reduced pressure. The formate distillate obtained was dried over anhydrous magnesium sulfate and carefully distilled to give a liquid of bp 98° (18 mmHg). NMR (in 20% $CDCl_3$ solution) τ: 8.70 (18H, t, J=7.4 cps, CH_3), 6.84 (12H, q, J=7.4 cps, CH_2), −1.32 (5H, s, OH). By comparison of the peak area of the hydroxyl proton with the other peaks, this material was shown to be nearly pure.

TEAF Composed of Formic Acid-*d* ($5HCO_2D \cdot 2NEt_3$)——A mixture of 10.4 g (0.12 mole based on HCO_2H) of TEAF and 60.0 g (3.0 mole) of deuterium oxide, deuterated grade 99.75%, which was purchased at E. Merck AG Darmstadt, was heated at 70—80° for 30 hr. The resulting liquid was subjected to distillation under reduced pressure. The formate fraction was twice treated with deuterium oxide by the same procedure as described above. The formate liquid was dried over anhydrous magnesium sulfate and carefully distilled to give a liquid of bp 98° (18 mmHg). NMR (in 25% $CDCl_3$ solution) τ: 8.73 (18H, t, J=7.4 cps, CH_3), 6.88 (12H, q, J=7.4 cps, CH_2), 1.69 (5H, s, =CH-). By comparison of the peak areas of the formyl proton with the other peaks, this material was shown to be nearly pure.

Reduction of 1-(α-Butoxybenzyl)piperidine with TEAF Composed of Deuterated Formic Acid——Reductions of 1-(α-butoxybenzyl)piperidine with TEAF composed of deuterated formic acid were carried out by the same manner as described for the reduction with non-deuterated TMAF. The following are the spectral data[16] of the amine product obtained.

Product obtained by the reduction with TEAF composed of formic acid-*d*: NMR (in 25% $CDCl_3$ solution) τ: 2.74 (5H, s, C_6H_5), 6.55 (2H, s, CH_2), 7.40—7.80 and 8.17—8.80 (10H, unresolved m, NC_5H_{10}). Mass Spectrum (80 e/V) *m/e* (relative intensity): 175 (53, M^+), 174 (59, M^+-1), 98 (66, $M^+-C_6H_5$), 91 (100, $M^+-C_5H_{10}N$), 84 (55, $C_5H_{10}N^+$). These NMR and mass spectra were identical with those of authentic 1-benzylpiperidine.

Product obtained by the reduction with TEAF composed of formic-*d* acid: NMR (in 25% $CDCl_3$ solution) τ: 2.75 (5H, s, C_6H_5), 6.60 (1H, t, J=1.8 cps, -CHD-), 7.34—7.82 and 8.22—8.75 (10H, unresolved m, NC_5H_{10}). Mass Spectrum (80 e/V) *m/e* (relative intensity): 176 (50, M^+), 175 (56, M^+-1), 99 (73, $M^+-C_6H_5$), 92 (100, $M^+-C_5H_{10}N$), 84 (59, $C_5H_{10}N^+$). These NMR and mass spectra are well interpreted to fit the structure of the 1-benzylpiperidine monodeuterated at the methylene.

Acknowledgement The authors are indebted to the members of the Analytical Center of this college for elemental analyses and for NMR and mass spectral measurements.

13) E.D. Bergmann, E. Zimkin and S. Pinchas, *Rec. Trav. Chim.*, **71**, 237 (1952).
14) A.R. Surrey, A.J. Olivet and J.O. Hoppe, *J. Am. Chem. Soc.*, **76**, 4920 (1954).
15) E.M. Hancock, E.M. Hardy, D. Heyl, M.E. Wright and A.C. Cope, *J. Am. Chem. Soc.*, **66**, 1747 (1944).
16) NMR spectra were taken at 60 Mc with a JEOL JNM-60-H spectrometer using TMS as the internal standard. Mass spectra were determined on a Hitachi RMS-4 spectrometer.