**Periodate oxidation of V (Table II)**——The procedures are similar with that employed in the oxidation of III.

**Methyl 3-O-Methyl-$\Delta^2$-D-glucuronate (VIII)**——III (387 mg.) was dissolved in MeOH (20 ml.) and the resulting solution was cooled to $-10°$ in an ice-salt bath. To this solution was added an etheric solution of diazomethane. When evolution of nitrogen ceased and the solution colored yellow, the reaction mixture was evaporated to a crystalline solid which was recrystallized from acetone, giving 112 mg. of pure VIII, m.p. 158~160° (decomp.), IR $cm^{-1}$ : $\nu_{C=O}$ 1754, $\delta_{C-H}$ 1440 (methyl ester at C-6); $\nu_{C=C}$ 1623 $cm^{-1}$ (厂) Rf 0.60. in paper chromatography using *n*-BuOH-EtOH-$H_2O$ (2:1:1) as a solvent (*Anal.* Calcd. for $C_8H_{12}O_7$ : C, 43.64; H, 5.49. Found : C, 43.50; H, 5.50). VIII is soluble in water, methanol, ethanol and sparingly soluble in ether.

**Periodate Oxidation of VIII (Table IV)**——The procedures are similar with that employed in the oxidation of III. In order to hydrolyse the formate ester, 50% $H_2SO_4$ (3 ml.) was added to 50 ml. of the oxidation mixture and the resulting solution was heated under reflux for 10 min. Formic acid liberated was estimated the same way with that used in above described determination of volatile acid.

**Polarography of 3-Ketoglucuronic Acid**——A Yanagimoto Polarograph Model PB-4 was used. The electrolytic cell and the bridges were essentially the same with that employed by Tamura and Nagano.[14] The cell was thermostated in the range of $25 \pm 0.1°$. The pH was maintained at 2.5 by use of McIlvain buffer. 3-Ketoglucuronic acid gave oxidation wave at $E_{1/2} = +0.153$ V (*vs.* S.C.E.). Wave heights are as shown in Fig. 1. L-Ascorbic acid afforded oxidation wave at $+0.175$ V (*vs.* S.C.E.) and the wave height was $i_d = 9.35$ μA at the concentration of $1.70 \times 10^{-3}$ mol./L.

The authors express their gratitude to Dr. Y. Hirasaka, Chugai Pharmaceutical Co., Ltd. for his useful suggestions and to Mr. K. Yamamoto, of the Company for his skilful assistance. Thanks are also due to the same Company for the supply of the materials.

## Summary

Periodate oxidation of 3-ketoglucuronic acid indicated the presence of hemiacetal ring structure and in consequence the uronic acid was assigned as 3-keto-D-glucopyranuronic acid (III), which on treatment with cation resin in methanol gave methyl furanoside (V). Enolization of 3-ketoglucuronic acid between C-2 and C-3 was confirmed by conversion of the keto-acid into the corresponding enol ether, namely methyl 3-O-methyl-D-glucopyranoenediol-(2,3)-uronate (VIII). Equilibrium between keto- and enol-form of this keto-sugar in an aqueous solution was, however, found to be inclined predominantly to the keto-form (III) by means of polarography.

14) Z. Tamura, K. Nagano : This Bulletin, **11**, 793 (1963).

(Received January 26, 1966)

[Chem. Pharm. Bull. 14(9) 996~1006(1966)]

*UDC 547.582.4.04 : 542.941.7*

## 137. Minoru Sekiya and Keiichi Ito : Reaction of Amide Homologs. XIII.*1 Catalytic Hydrogenolysis of N-Acylaminomethyl and N-Arylsulfonamidomethyl Compounds.

(*Shizuoka College of Pharmacy**2)

It has been established in a recent paper[1] that formic acid reduction of N-amidomethyl compound attached to aliphatic or aromatic secondary amine introduces reductive fission at the methylene carbon bond connecting to the amido nitrogen resulting in the formation of N-methylated amine and amide.

*1 Part XII : This Bulletin, **12**, 674 (1964).

*2 Oshika, Shizuoka (関屋 実, 伊藤敬一).

1) M. Sekiya, K. Ito : This Bulletin, **12**, 677 (1964).

$$RCON(\overset{|}{C})-CH_2-N\langle \xrightarrow[\text{reduction}]{\text{formic acid}} RCONH + CH_3N\langle$$

In replacement of formic acid reduction by catalytic reduction, a few examples of hydrogenolyses of N-amidomethyl compounds, *i.e.*, N-(dimethylaminomethyl)benzamide and N-(piperidinomethyl)benzamide, with Raney nickel catalyst under high hydrogen pressure were provided earlier in this laboratory,[2] in which the carbon bonds connecting to the amide nitrogens were severed in the same way as in the formic acid reduction. In addition, the similar mode of hydrogenolysis has also been reported[3] for N-(morpholinomethyl)urea in its catalytic reduction with platinum catalyst. Moreover, other closely related hydrogenolysis can be found for some compounds of 1-amidoarylmethylene type. It has also been shown in this laboratory that the reduction of N-$\alpha$-acetamidobenzyl compound attached to aliphatic secondary amine with Raney nickel under high hydrogen pressure yields N-benzyl substituted secondary amine and acetamide,[2] and the selective reduction of N-arylmethylene-1-formamido-1-arylmethylamine with palladium-on-charcoal catalyst yields N-arylmethylene-1-arylmethylamine and formamide.[4] These facts show reductive fission of the carbon bond connecting to the amide nitrogen which bears formal resemblance to the hydrogenolysis of N-amidomethyl compound.

In view of these scattered reports on such a type of hydrogenolysis, it seemed desirable to study nature of the hydrogenolysis and to make extensive studies for general application. Investigation in these respects was undertaken using a series of N-acylaminomethyl compounds and additionally N-arylsulfonamidomethyl compounds, not only under the hydrogenolytic conditions with Raney nickel catalyst under high hydrogen pressure, but also, in some cases, under the conditions with palladium-on-charcoal catalyst under ordinary hydrogen pressure.

## Result and Discussion

**Effect of Reaction Solvent and Catalyst**——This was undertaken in an effort to determine in quantitative manner effects of reaction solvent and catalyst on the rate of catalytic hydrogenolysis of N-amidomethyl compound. As a model compound N-(piperidinomethyl)benzamide was chosen and some preliminary runs were made on

Table I. Effect of Variables on the Rate of Hydrogenolysis


| Substrate (mole) | Raney Ni (g.) | Initial $H_2$ pressure ($kg./cm^2$) | Reaction temp. (°C) | Initial rate (mole/min.) |
|---|---|---|---|---|
| 0.035 | 0.5 | 70 | 110 | $6.0\times10^{-2}$ |
| 0.035 | 0.5 | 35 | 110 | $2.8\times10^{-2}$ |
| 0.035 | 1.5 | 70 | 110 | $17.7\times10^{-2}$ |
| 0.07 | 1.5 | 70 | 110 | $19.1\times10^{-2}$ |
| 0.07 | 1.5 | 70 | 80 | $3.1\times10^{-2}$ |

In each run, 80 ml. of EtOH was employed as the reaction solvent.

2) M. Sekiya, K. Ito: This Bulletin, **11**, 892 (1963).
3) W. J. Weaver, J. K. Simons, W. E. Baldwin: J. Am. Chem. Soc., **66**, 222 (1944).
4) M. Sekiya, T. Oishi: This Bulletin, **7**, 468, 855 (1959).

hydrogenolysis of its ethanol solution over Raney nickel catalyst with the view to determine the effect of certain variables on the rate of the hydrogenolysis. As the results are shown in Table I, it was demonstrated that the rate of the reaction was first order with respect to the hydrogen pressure, zero order with respect to concentration of the substrate, and directly proportional to the amount of the catalyst used. Similar observation has previously been reported[5] in kinetic studies of liquid phase catalytic hydrogenation of certain carbon-carbon unsaturated compounds. The apparent activation energy of 16.3 kcal./mole, which is calculated from the initial rate values at 80° and 110°, is enough high to realize that the rate determining step is not the activating step of hydrogen transfer to the catalyst but usual chemical reaction step on the surface of the catalyst.

Then, if the amount of catalyst is constant, the pressure change should follow the equation

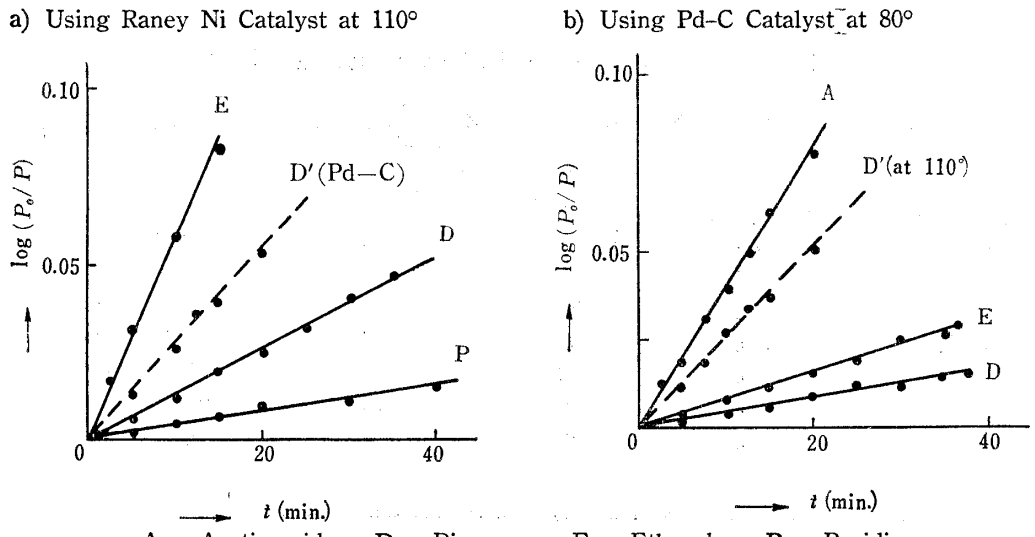
$$-dP/dt=kP \qquad (1)$$

where $P$ represents total pressure and $t$ represents time. So the integrated form of equation (1) is given

$$\log(P_0/P)=kt/2.303 \qquad (2)$$

where $P_0$ represents the initial pressure. Then a plot of log $P_0/P$ against time is expected to result in a straight line and the value of $k$ can be calculated from the slope of the line thus obtained.

Some runs under the settled condition were made to determine the effect of variation of solvent and of catalyst on rate. Acetic acid, ethanol, dioxane, and pyridine were employed as the hydrogenolysis solvent and Raney nickel and palladium-on-charcoal as the catalyst. The catalyst-solvent combinations were as follows: Raney nickel ——ethanol, dioxane, pyridine; palladium-on-charcoal——acetic acid, ethanol, dioxane. The combinations, Raney nickel——acetic acid and palladium-on-charcoal——pyridine, were avoided because of the fear of poisoning of the catalyst in the former and of hydrogenation of pyridine in the latter. For every run, the hydrogenolysis was shown to proceed almost quantitatively leading to the formation of 1-methylpiperidine and benzamide, but the rate was varied widely with nature of the catalyst and the solvent employed. Fig. 1 shows the hydrogenolysis plots of log $(P_0/P)$ against $t$.

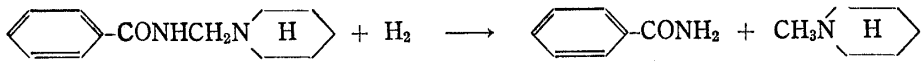



A : Acetic acid D : Dioxane E : Ethanol P : Pyridine

Fig. 1. Solvent Effect on the Rate of Catalytic Hydrogenolysis under High Hydrogen Pressure

5) H. A. Smith, D. M. Alderman, F. W. Nadig: J. Am. Chem. Soc., **67**, 272 (1945).

Table II. Relative Rate of Catalytic Hydrogenolysis under High Hydrogen Pressure



| Catalyst | Solvent | Reaction temp. (°C) | Relative rate |
|---|---|---|---|
| Raney Ni | ethanol | 110 | 1000 |
| 〃 | dioxane | 110 | 227 |
| 〃 | pyridine | 110 | 67 |
| Pd-C | acetic acid | 80 | 1000 |
| 〃 | ethanol | 80 | 199 |
| 〃 | dioxane | 80 | 126 |
| Pd-C | dioxane | 110 | 1000 |
| Raney Ni | 〃 | 110 | 56 |

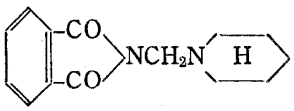
For each run, 0.07 mole of the substrate was hydrogenolyzed in 80 ml. of solvent emproying Raney Ni catalyst (1.5 g. as 50% alloy) or Pd-C catalyst (1.5 g. containing 0.15 g. of Pd) under 70 kg./cm² of initial $H_2$ pressure.

As can be seen from Fig. 1, a fair straight line was obtained in each run, indicating that the hydrogenolysis proceeds in accordance with the first order equation (1). Particularly for slower runs, falling off of the rate was noted as the hydrogenolysis proceeded. That this is thought to be due to catalyst poisoning and not to deviation from zero order was shown by means of experiments employing different initial concentration of the substrate. This observation has been also known in usual hydrogenation process.

Table II shows the relative rate calculated from the slope of the line given in Fig. 1. It is apparent from Table II that the rate increases with respect to the solvent in the order of pyridine, dioxane, ethanol, and acetic acid irrespective of the catalyst employed. That is, the hydrogenolysis rate is markedly affected by the nature of the solvent and is said to increase with the acidity of the solvent. As for the catalyst, it can also be seen from the runs in dioxane in Table II that palladium-on-charcoal is more active than Raney nickel under the same condition.

An attempt to carry out palladium-on-charcoal hydrogenolysis with N-(piperidinomethyl)benzamide in the conditions under ordinary hydrogen pressure at ordinary temperature was unsuccessful, however, with the other substrates such as N-(piperidinomethyl)succinimide and -phthalimide, the hydrogenolyses were found to proceed with considerable rapidity. Under such a constant hydrogen pressure zero order of the

Table III. Solvent Effect on the Rate of Catalytic Hydrogenolysis under Ordinary Hydrogen Pressure at Room Temperature over Palladium-on-charcoal Catalyst

| Substrate | Solvent | Relative rate |
|---|---|---|
|  | AcOH | 100 |
| 〃 | EtOH | 73 |
|  | AcOH | 100 |
| 〃 | EtOH | 74 |

In each run, 0.01 mole of substrate was hydrogenolyzed in 60 ml. of EtOH or AcOH employing Pd-C catalyst (0.5 g. containing 0.05 g. of Pd) under ordinary $H_2$ pressure and at room temperature.

rate only with respect to the substrate was readily demonstrated. Solvent effect on the rate was also determined by comparison between ethanol and acetic acid and increase of the rate was observed more with the latter than with the former as shown in Table Ⅲ.

**Hydrogenolysis Method and Scope**——With a large number of N-acylaminomethyl and N-arylsulfonamidomethyl compounds, hydrogenolyses were carried out under settled conditions by two means of using Raney nickel and palladium-on-charcoal as catalyst. With the former ethanolic solutions of the substrates were submitted to hydrogenation at elevated temperature under high hydrogen pressure and with the latter at ordinary temperature under ordinary pressure. Conditions and results were indicated in Table Ⅳ for hydrogenolyses with Raney nickel catalyst, and in Table Ⅴ for those with palladium-on-charcoal catalyst. As can be seen in the Tables, in every run in which hydrogen uptake was observed, hydrogenolysis at methylene-amido bond proceeded almost quantitatively to give amide and N-methylated amine, the latter of which was isolated as picrate and identified.

As noted in the preceding section, under high hydrogen pressure and at elevated temperature palladium-on-charcoal catalyst was shown in the hydrogenolysis of N-(piperidinomethyl)benzamide to be more active than Raney nickel catalyst, however, under ordinary pressure and at ordinary temperature, the scope of the hydrogenolysis was limited. As shown in Table Ⅴ, no hydrogenolysis occurred with N-(piperidinomethyl) benzamide and N-(anilinomethyl)phthalimide. The compounds, which suffered hydrogenolysis, can be said to be those, which show rather rapid velocity in the hydrogenolysis conditions with Raney nickel catalyst.

In addition to the experiments shown in the Tables, several N,N′-methylenebisamides such as N,N′-methylenebisbenzamide, N,N′-methylenebisacetamide, N-(benzamidomethyl)benzenesulfonamide, and N-(phthalimidomethyl)acetamide, which are regarded as those of special type of N-amidomethyl compounds, were also tested for hydrogenolysis, but these compounds were shown to resist under any conditions. Furthermore, it must also be noted that O-acylaminomethyl compounds such as N-(phenethyloxymethyl)phthalimide and N-(methoxymethyl)benzamide were resisted to hydrogenolysis, no reaction taking place even under severe conditions. Though the hydrogenolysis of N-hydroxymethylbenzamide was previously reported[2], this seems rather questionable because of the lack of how the hydroxymethyl grouping behaves.

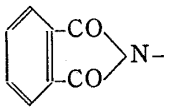
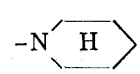
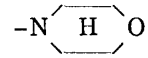
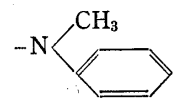
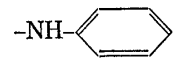
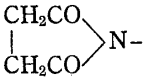
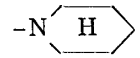
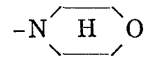
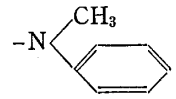
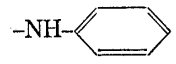
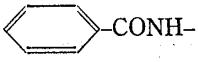
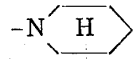
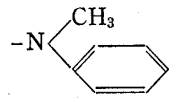
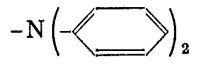
**Effect of Variation in Structure**——The hydrogenolysis data with numerous N-amidomethyl compounds with wide variation in their amido and amine groupings shown in Table Ⅳ and Ⅴ also drew some understanding for effect of variation in structure on reactivity. Qualtitatively, relative reactivities among the substrates can be deduced by comparison of the reaction times and temperatures required for the complete hydrogenolyses.

In Table Ⅳa are assembled the results on the Raney nickel hydrogenolyses of N-phthalimidomethyl, N-succinimidomethyl, and N-benzamidomethyl analogs attached to a variety of amines, together with the pKa values of the amine fragments which have been found in the literatures. With respect to their amine residues of the substrates, the relative reactivities can roughly be seen from Table Ⅳa to increase in the rising order for pKa values of the amine fragments, when contribution of other factors are considered not to be concerned so much with. Thus, it can be said that the reactivity depends on electron density at the amine nitrogen, increasing in its rising order. Negative results for hydrogenolyses of N,N′-methylenebisamides and O-acylaminomethyl compounds mentioned in the preceding section are also consistent with this respect. Lack of arrangement for N-arylsulfonamidomethyl analog was due to difficulties on preparing that with variation in its amine residue. As shown in Table Ⅴ palladium-

Table Ⅳ. Catalytic Hydrogenolysis[a] of N-Amidomethyl Compounds under High Hydrogen Pressure over Raney Nickel Catalyst

$$X\text{-}CH_2\text{-}Y + 2H \longrightarrow XH + CH_3Y$$

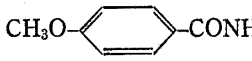
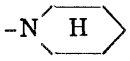
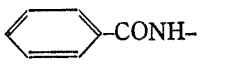
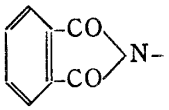
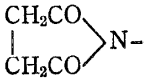
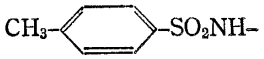
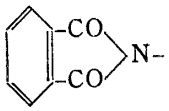
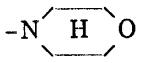
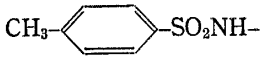
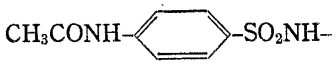
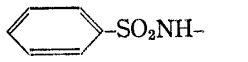
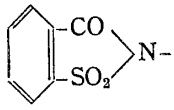
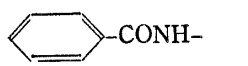
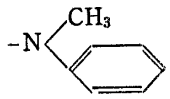
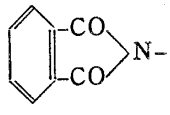
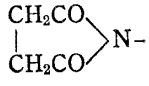
Table Ⅳa. Effect of Variation in Amine Substituent

| Compound No. | Substituent X | Substituent Y | Reaction temp. (°C) | Reaction time (min.) | Hydrogenolysis (%)[b] | pKa of YH |
|---|---|---|---|---|---|---|
| 1) With N-(phthalimidomethyl)amines | | | | | | |
| Ⅰ |  |  | 80~85 | 60 | 99 | 11.22[6] |
| Ⅱ | 〃 |  | 80~85 | 90 | 98 | 8.36[7] |
| Ⅲ | 〃 |  | 80~85 | 180 | 99 | 4.85[8] |
| Ⅳ | 〃 |  | 80~85 | 210 | 95 | 4.62[8] |
| 2) With N-(succinimidomethyl)amines | | | | | | |
| Ⅴ |  |  | 80~85 | 20 | 97 | 11.22[6] |
| Ⅵ | 〃 |  | 80~85 | 40 | 96 | 8.36[7] |
| Ⅶ | 〃 |  | 80~85 | 100 | 94 | 4.85[8] |
| Ⅷ | 〃 |  | 80~85 | 120 | 94 | 4.62[8] |
| 3) With N-(benzamidomethyl)amines | | | | | | |
| Ⅸ |  |  | 80~85 | 150 | 98 | 11.22[6] |
| Ⅹ | 〃 |  | 120~125 | 240 | 95 | 4.85[8] |
| Ⅺ | 〃 |  | 130~140 | — | 0[c] | 0.78[9] |

*a*) Substrate: 0.05 mole of N-amidomethyl compound; Solvent: 70 ml. of EtOH; Catalyst: 1 g. of Raney Ni as 50% alloy; Initial hydrogen pressure: 100 kg./cm² at room temperature.
*b*) Percentages are based on yields of both products.
*c*) Increased catalyst amount promoted the hydrogenolysis. Substrate: 0.025 mole; EtOH: 35 ml.; Raney Ni: 3 g. as 50% alloy; Reaction temp.: 92~97°; Reaction time: 240 min.; % of hydrogenolysis: 96.

6) S. Searles, M. Tamres, F. Block, L. Quarterman: J. Am. Chem. Soc., **78**, 4917 (1956).
7) H. K. Hall, Jr.: *Ibid.*, **78**, 2570 (1956).
8) N. F. Hall, M. R. Sprinkle: *Ibid.*, **54**, 3469 (1932).
9) M. A. Paul, F. A. Long: Chem. Rev., **57**, 9 (1957).

Table Ⅳb. Effect of Variation in Amido Substituent

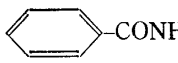
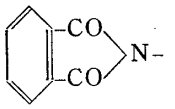
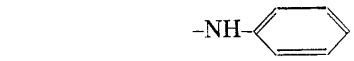
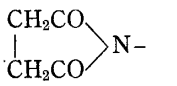
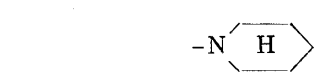
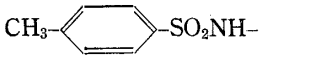
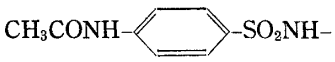
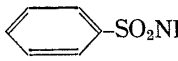
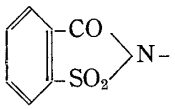
| Compound No. | Substituent X | Substituent Y | Reaction temp. (℃) | Reaction time (min.) | Hydrogenolysis (%)[b] | pKa of XH |
|---|---|---|---|---|---|---|
| 1) With N-(piperidinomethyl)amides | | | | | | |
| Ⅻ |  |  | 80～85 | 180 | 96 | 12.64[10] |
| Ⅸ |  | 〃 | 80～85 | 150 | 98 | 12.39[10] |
| Ⅰ |  | 〃 | 80～85 | 60 | 99 | 9.90[11] |
| Ⅴ |  | 〃 | 80～85 | 20 | 97 | 9.62[12] |
| ⅩⅢ |  | 〃 | 70～75 | 10 | 95 | 10.17[13] |
| 2) With N-(morpholinomethyl)amides | | | | | | |
| Ⅱ |  |  | 80～85 | 150 | 98 | 9.90[11] |
| XIV |  | 〃 | 70～75 | 15 | 94 | 10.17[13] |
| XV |  | 〃 | 70～75 | 10 | 94 | 10.02[13] |
| XVI |  | 〃 | 70～75 | 10 | 95 | 10.00[13] |
| XVII |  | 〃 | 60～65 | 5 | 98 | 2.42[14] |
| 3) With N-(N-methylanilinomethyl)amides | | | | | | |
| X |  |  | 120～125 | 240 | 95 | 12.39[10] |
| Ⅲ |  | 〃 | 80～85 | 180 | 99 | 9.90[11] |
| Ⅶ |  | 〃 | 80～85 | 100 | 94 | 9.62[12] |

b) Percentages are based on yields of both products.

10) J. T. Edward, S. C. R. Meacock : J. Chem. Soc., **1957**, 2000.
11) C. R. Guerillot : Compt. rend., **240**, 1107 (1955).
12) H. F. Walton, A. A. Schilt : J. Am. Chem. Soc., **74**, 4995 (1952).
13) A. V. Willi : Helv. Chim. Acta, **39**, 48 (1956).
14) A. Hantzsch, E. Vögeln : Chem. Ber., **34**, 3141 (1901).

Table V. Catalytic Hydrogenolysis[a] of N-Amidomethyl Compounds under Ordinary Hydrogen Pressure over Palladium-on-charcoal Catalyst

$$X\text{-}CH_2\text{-}Y + 2H \longrightarrow XH + CH_3Y$$

| Compound No. | Substituent X | Substituent Y | Reaction time (min.) | Hydrogenolysis (%)[b] | pKa of XH[d] |
|---|---|---|---|---|---|
| IX |  |  | — | 0[c] | 12.39 |
| I |  | 〃 | 450 | 99 | 9.90 |
| IV | 〃 |  | — | 0[c] | 9.96 |
| V |  |  | 150 | 95 | 9.62 |
| XIV |  |  | 60 | 96 | 10.17 |
| XV |  | 〃 | 50 | 94 | 10.02 |
| XVI |  | 〃 | 50 | 95 | 10.00 |
| XVII |  | 〃 | 30 | 92 | 2.42 |

*a*) Substrate: 0.01 mole of N-amidomethyl compound; Solvent: 60 ml. of EtOH; Catalyst: Pd-C catalyst (0.5 g. containing 0.05 g. of Pd).
*b*) Percentages are based on product isolation.
*c*) Resulted in recovery of the starting material.
*d*) See references given in Table IV.

on-charcoal hydrogenolysis under ordinary pressure was adopted only for the substrates attached to the aliphatic secondary amines which are relatively strong base. This may be reasonable for the milder conditions and is also consistent with the above respect.

Results listed in Table IVb for Raney nickel hydrogenolysis and in Table V for palladium-on-charcoal hydrogenolysis also reveals the relative reactivities among the substrates with respect to their amide residues. These were assembled the results with the substrates of varing amidomethyl groupings attached to some standard amines together with the previously reported pKa values of the amide fragment. When the substrates were divided into acylamino and arylsulfonamido analogs, in each analog the relative reactivities with respect to the amide residue were also qualitatively realized to increase in descending order for pKa values of the amide fragments for Raney nickel hydrogenolysis and also for palladium-on-charcoal hydrogenolysis, though for the latter the scope was inevitably less limited. It is apparent that this order is much the same with the descending order of electron density of the amido nitrogen. As also observed from Table IV, arylsulfonamido analogs are markedly more reactive than acylamino analogs, however there is recognized no consistent relationship between the reactivities and the pKa values throughout both of the amide residues. This appears probable to be due to that contribution of the steric influence for absorbing figure on catalyst, well known as a factor to affect reactivity for hydrogenation, would be much different between the arylsulfonamido and the acylamino group.

In summary, the above studies can be said to lead qualitative introduction for effect of variation in the structure of the substrate on reactivity, which is indicated

into two features that the hydrogenolysis is more facilitated (1) with increase of electron density at the amine nitrogen and (2) with the decrease of that at each acylamino and arylsulfonamido nitrogen. It should be noted that these features bear nearly close resemblance to that of the formic acid reduction of the same N-amidomethyl compounds reported previously.[1] We hope further studies will aid in the development for the mechanistic relationship between them.

In view of ease of preparation of N-amidomethyl compounds from amine, amide, and formaldehyde, the facility of the hydrogenolysis suggests certain advantages for its use in N-methylation of amines. With understanding the selectivity of catalyst, conditions, and amide residue of the N-amidomethyl compound, the methods would appear to be quite general and capable of extension to many other amines. Advantages of the methods are high yields of N-methylated amines with recovery of amide and certainty on N-methylation.

## Experimental

### Preparation of N-Amidomethyl Compound

Among N-amidomethyl compounds used as the substrate for the present work, those which have not been known previously, or of which the preparation could not have been given in detail, were prepared as follows.

**N-(N-Methylanilinomethyl)succinimide (VII)**——Into 30 ml. of EtOH 9.9 g. of succinimide, 9 ml. of 37% $CH_2O$, and 11.7 g. of N-methylaniline were dissolved and the solution was refluxed for 1 hr. The reaction solution was concentrated under reduced pressure and the residual crystals were collected, washed with petr.-ether, and dried. Recrystallization from MeOH afforded needles, m.p. 87~88°. Yield, 20.5 g. (94%). *Anal.* Calcd. for $C_{12}H_{14}O_2N_2$: C, 66.03; H, 6.47; N, 12.84. Found: C, 66.26; H, 6.44; N, 12.73.

**N-(Anilinomethyl)succinimide (VIII)**——Into 100 ml. of EtOH 12 g. of succinimide, 10 ml. of 37% $CH_2O$, and 12 g. of aniline were dissolved and the solution was refluxed for 20 min. whereupon crystalline solid began to separate out in the hot solution. After cool, the deposited crystals were collected and recrystallized from EtOH to give needles, m.p. 172~173° (lit.,[15] m.p. 173~174°). Yield, 23.0 g. (93%). *Anal.* Calcd. for $C_{11}H_{12}O_2N_2$: C, 64.69; H, 5.92; N, 13.72. Found: C, 64.89; H, 5.97; N, 13.46.

**N-(N-Methylanilinomethyl)benzamide (X)**——Into 200 ml. of toluene 26.1 g. of N-(dimethylaminomethyl)-benzamide and 16.0 g. of N-methylaniline were dissolved. The solution was refluxed for 12 hr., while $N_2$ gas was introduced to remove $Me_2NH$ as it was formed. The reaction solution was concentrated under reduced pressure and the residual crystals were recrystallized from benzene to prisms, m.p. 138~139°, weighing 29 g. (81% yield). *Anal.* Calcd. for $C_{15}H_{16}ON_2$: C, 74.97; H, 6.71; N, 11.66. Found: C, 75.14; H, 6.78; N, 11.52.

**N-(Diphenylaminomethyl)benzamide (XI)**——Into 60 ml. of toluene 25.5 g. of N-(dimethylaminomethyl)-benzamide and 25.4 g. of diphenylamine were dissolved and the solution was refluxed for 24 hr. with the introduction of $N_2$ gas. The reaction solution was concentrated under reduced pressure. The residue was washed with dry ether to give crystalline solid which was recrystallized from benzene to prisms, m.p. 113~114°, weighing 26 g. (60% yield). *Anal.* Calcd. for $C_{20}H_{18}ON_4$: C, 79.44; H, 6.00; N, 9.27. Found: C, 79.15; H, 6.11; N, 9.18.

**N-(Piperidinomethyl)-*p*-methoxybenzamide (XII)**——A solution of 22.7 g. of *p*-methoxybenzamide, 13.5 ml. of 37% $CH_2O$, and 15.3 g. of piperidine dissolved in 100 ml. of EtOH was refluxed for 6 hr. and the reaction solution was treated in the same manner as described in VII. Prisms from benzene, m.p. 130~132° (lit.,[16] m.p. 137°). Yield, 36.1 g. (97%). *Anal.* Calcd. for $C_{14}H_{20}O_2N_2$: C, 67.71; H, 8.12; N, 11.28. Found: C, 67.89; H, 8.20; N, 11.57.

**N-(Piperidinomethyl)-*p*-toluenesulfonamide (XIII)**——A solution of 51.3 g. of *p*-toluenesulfonamide, 24.6 ml. of 37% $CH_2O$, and 25.5 g. of piperidine dissolved in 200 ml. of EtOH was refluxed for 30 min. and the reaction solution was treated in the same manner as described in VII. Needles from EtOH, m.p. 88~90°. Yield, 75 g. (93%). *Anal.* Calcd. for $C_{13}H_{20}O_2N_2S$: C, 58.17; H, 7.51; N, 10.44. Found: C, 57.97; H, 7.55; N, 10.55.

**$N^4$-Acetyl-$N^1$-(morpholinomethyl)sulfanilamide (XV)**——A solution of 25.8 g. of $N^4$-acetylsulfanilamide, 12 ml. of 37% $CH_2O$, and 13.1 g. of morpholine dissolved in 70 ml. of EtOH was refluxed for 2 hr. and the reaction solution was treated in the same manner as described in VII. Prisms from EtOH, m.p. 113~115°

15) M. B. Winstead, K. V. Anthony, L. L. Thomas, R. G. Strachan, H. J. Reichwine: C. A., **58**, 6722 (1963).
16) S. Foldeak, B. Matkovics, J. Porszasz: C. A., **59**, 561 (1963).

(decomp.). Yield, 36 g. (96%). *Anal.* Calcd. for $C_{13}H_{19}O_4N_3S$: C, 49.83; H, 6.11; N, 13.41. Found: C, 49.46; H, 6.41; N, 12.95.

**Hydrogenolysis Method**

The following materials, which were purified as showing the following melting points, were employed as substrate for the present work: N-(Piperidinomethyl)phthalimide[17] (I, m.p. 118~120°), N-(morpholinomethyl)phthalimide[18] (II, m.p. 118~119°), N-(N-methylanilinomethyl)phthalimide[17] (III, m.p. 92~93°), N-(anilinomethyl)phthalimide[19] (IV, m.p. 145~146°), N-(piperidinomethyl)succinimide[20] (V, m.p. 107~108°), N-(morpholinomethyl)succinimide[18] (VI, m.p. 110~111°), N-(N-methylanilinomethyl)succinimide (VII, m.p. 87~88°), N-(anilinomethyl)succinimide[15] (VIII, m.p. 172~173°), N-(piperidinomethyl)benzamide[21] (IX, m.p. 129~130°), N-(N-methylanilinomethyl)benzamide (X, m.p. 138~139°), N-(diphenylaminomethyl)benzamide (XI, m.p. 113~114°), N-(piperidinomethyl)-*p*-methoxybenzamide[16] (XII, m.p. 130~132°), N-(piperidinomethyl)-*p*-toluenesulfonamide (XIII, m.p. 88~90°), N-(morpholinomethyl)-*p*-toluenesulfonamide[3] (XIV, m.p. 108~110°), $N^4$-acetyl-$N^1$-(morpholinomethyl)sulfanilamide (XV, m.p. 113~115° (decomp.)), N-(morpholinomethyl)benzenesulfonamide[22] (XVI, m.p. 78~80°), N-(morpholinomethyl)saccharin[23] (XVII, m.p. 144~146°).

Both Raney nickel and palladium-on-charcoal catalysts were prepared freshly for each run by the usual methods, the procedures of which were consistent throughout all the runs.

Every run under high pressure, shown in Table I, II, and IV, was carried out in an autoclave having a capacity of 175 ml. which was equipped with the Bourdon type of pressure gauge. After introduction of a mixture of the substrate, the solvent, and the Raney nickel or the palladium-on-charcoal, the autoclave was alternately filled and evacuated three times with hydrogen, then brought to the initial pressure at room temperature. The whole was preheated and then constant shaking was started at the requisite temperature. The rate of the hydrogenolysis, which was desired for kinetic studies, was followed by the rate of the pressure drop. After the pressure drop was nearly ceased (the period up to this time is written as the reaction time in Table IV), shaking and heating were continued for further 30 min. Amount of the pressure drop was almost theoretical in every run.

Every run under ordinary pressure, shown in Table III and V, was carried out at room temperature in an usual hydrogenation flask fitted with a magnetic stirrer. After introduction of the materials and removal of air by hydrogen flow, hydrogenolysis was worked up as usual. The rate of the hydrogenolysis was followed by the rate of the uptake of hydrogen, the whole amount of which was almost theoretical.

**General Procedures for Isolation of Hydrogenolysis Products**

Every hydrogenolysis gave the two products, N-methylated amine and amide, the former was generally isolated as its picrate. Each yield of those was at least 93% for theoretical amount. Procedures for the isolation of the products are described below.

Most of the runs for the hydrogenolysis (all runs in Table I, IV, and V, and some runs in Table II and III), where EtOH was employed as solvent, were processed generally as in the following. The reaction mixture was filtered to remove the catalyst. In the runs with the substrates of the phthalimido analogs a part of phthalimide product which deposited in the reaction mixture was obtained along with the catalyst. Solvent, EtOH, was distilled off from the filtrate under reduced pressure, whereupon the volatile aliphatic amine product was vaporized along with EtOH. To remove the amine completely, alternate addition of $H_2O$ followed by steam distillation was necessary, particularly for the aromatic amine product. The distillate was treated with alcoholic picric acid solution as usual. The amine product was obtained as its picrate and weighed. The amide product was obtained as crystalline residue on the foregoing concentration of the reaction solution.

In the two runs using dioxane as solvent, shown in Table II, the procedures were the same as described above.

An exception to the above procedures for the hydrogenolysis in EtOH solvent was the run with XVII in which the resulting residue on the concentration of the reaction solution formed a salt of saccharin with 4-methylmorpholine product. For that, the aqueous solution of the concentration residue was acidified with 10% HCl, whereupon saccharin deposited, and, after filtration, 4-methylmorpholine hydrochloride was obtained by concentration of the filtrate and weighed. This was also converted to picrate by treatment with sodium picrate.

In a few runs for kinetic studies (Table II and III), where AcOH was employed as solvent, the resulting residue on concentration of the reaction solution formed AcOH salt. Accordingly, the aqueous solution of the residue was basified with aqueous NaOH and then concentrated under reduced pressure. 1-Methylpiperidine was obtained by treatment of the distillate containing the amine with alcoholic picric acid solution and the amide

17) H. W. Heine, M. B. Winstead, R. P. Blairs: J. Am. Chem. Soc., **78**, 672 (1956).
18) H. Hellmann, I. Löschmann: Chem. Ber., **87**, 1688 (1954).
19) M. B. Winstead, H. W. Heine: J. Am. Chem Soc., **77**, 1913 (1955).
20) J. R. Feldman, E. C. Wagner: J. Org. Chem., **7**, 45 (1942).
21) A. Einhorn: Ann., **343**, 207 (1905).
22) H. Hellmann, K. Teichmann: Chem. Ber., **91**, 2432 (1958).
23) H. Zinner, U. Zelck, G. Rembarz: J. prak. Chem., **8**, 150 (1959).

product (benzamide or phthalimide) was obtained on washing the residue with $H_2O$. Only in the run with V, as succinimide is soluble in $H_2O$, this amide was obtained on extracting the residue with ether before basification.

In the run with IX using pyridine as solvent, shown in Table II, concentration of the reaction solution gave a distillate of a mixture of 1-methylpiperidine product and pyridine, and a crystalline residue of benzamide. Successful separation of the former is as follows. The mixture was neutralized with aqueous HCl and then an excess of aqueous NaOH was added to the solution in small portions. After every addition, the solution was submitted to steam distillation and each distillate was separately collected and checked. On this alternate partial basification followed by distillation, pyridine was first distilled and then 1-methylpiperidine was followed. The latter was converted to its picrate and weighed.

**Identification of Hydrogenolysis Products**

Every amide product was identified by comparison of IR spectra and mixed melting point test with authentic sample. The amine products were generally identified as their picrates with an exception of N-methyldiphenylamine, identification of which was made as its $ZnCl_2 \cdot HCl$ salt. The following are physical and analytical data for the picrates and the others.

**1-Methylpiperidine**——Picrate: m.p. 222~223°. *Anal.* Calcd. for $C_{12}H_{16}O_7N_4$: C, 43.90; H, 4.91; N, 17.07. Found: C, 43.78; H, 5.01; N, 17.02.

**4-Methylmorpholine**——Picrate: m.p. 224~225°. *Anal.* Calcd. for $C_{11}H_{14}O_8N_4$: C, 40.00; H, 4.27; N, 16.97. Found: C, 39.90; H, 4.25; N, 16.84. HCl salt: m.p. 201~204°.

**N-Methylaniline**——Picrate: m.p. 133~135°. *Anal.* Calcd. for $C_{13}H_{12}O_7N_4$: C, 46.43; H, 3.60; N, 16.66. Found: C, 46.39; H, 3.61; N, 16.61.

**N,N-Dimethylaniline**——Picrate: m.p. 157~159°. *Anal.* Calcd. for $C_{14}H_{14}O_7N_4$: C, 48.00; H, 4.03; N, 16.00. Found: C, 48.09; H, 3.97; N, 15.88.

**N-Methyldiphenylamine**——b.$p_2$ 109~111°. *Anal.* Calcd. for $C_{13}H_{13}N$: C, 85.20; H, 7.15; N, 7.64. Found: C, 85.18; H, 7.22; N, 7.61. $ZnCl_2 \cdot HCl$ salt: m.p. 185~186°.

The authors are indebted to Mrs. Y. Yanagiya and to Mr. K. Narita for the elementary analyses.

## Summary

Hydrogenolysis of N-acylaminomethyl and additionally N-arylsulfonamidomethyl compounds attached to a variety of amines, not only under conditions with Raney nickel catalyst under high hydrogen pressure, but also, in some cases, under those with palladium-on-charcoal catalyst under ordinary hydrogen pressure, was investigated in a view of the factors affecting the rate. Solvent and variation in the structure were recognized to be major rate-determining factors. Comparison of the rates of a large number of the compounds indicates that the hydrogenolysis is more facilitated with increase of electron density at amine nitrogen and decrease of that at each acylamino and sulfonamido nitrogen. The reaction scope was established and the application in N-methylation of amine was generalized.

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