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170. **Minoru Sekiya and Keiichi Ito**: Reaction of Amide Homologs. XXI.[*1] N-Monomethylation of Aromatic Primary Amines. A Method through the Formation of N-Succinimidomethyl Compound.

(*Shizuoka College of Pharmacy*[*2])

A convenient N-monomethylation method of aromatic primary amines was established. N-Succinimidomethyl compounds attached to a variety of aromatic primary amines were prepared and subjected to catalytic hydrogenolysis affording the N-monomethylated aromatic primary amines in excellent yields. For more practical use a modified direct procedure without isolating the N-(arylaminomethyl)succinimide was also successfully performed.

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It has been generalized[1,2] that the catalytic hydrogenolysis of a variety of N-amidomethyl compounds introduces reductive fission at the methylene carbon bond connecting to the amide nitrogen, affording N-methylated amine and amide in fair yield,

$$\text{RCO}\overset{|}{\text{N}}\text{-CH}_2\text{-N}\langle + \text{H}_2 \longrightarrow \text{RCO}\overset{|}{\text{N}}\text{H} + \text{CH}_3\text{N}\langle$$

and a practical way for N-methylation of various amines has opened through this method. Among the studies on this area, the useful N-monomethylation of aromatic primary amines, which has been performed[3] through hydrogenolysis of N-phthalimidomethyl compound, seems worthy of particular mention. In continuation of this work, the present paper deals with the hydrogenolysis of N-succinimidomethyl compounds which was found to be also practical for N-monomethylation of aromatic primary amines as well as that of the N-phthalimidomethyl compounds.

Available N-amidomethyl compound of aromatic primary amine has been known to be limited to only N-phthalimidomethyl and N-succinimidomethyl compounds. As to the latter, Winstead, *et al.*[4] have lately reported the preparation of the several analogs. While a pattern of the hydrogenolysis has been indicated with N-(anilinomethyl)succinimide in the previous paper[2], we undertook extension of this hydrogenolysis to various analogous compounds for general application of the N-monomethylation.

As substrates for the hydrogenolysis nine N-(arylaminomethyl)succinimides, listed in Table Ⅲ, were easily prepared on heating equimolar mixture of succinimide, formaldehyde and aromatic primary amine in ethanol by the method similar to that for N-phthalimidomethyl analogs. Among nine compounds, ethyl *p*-N-(succinimidomethyl)aminobenzoate, N,N-dimethyl-N′-succinimidomethyl-*p*-phenylenediamine, *p*-N-(succinimidomethyl)aminophenol, and *o*-(anisidinomethyl)succinimide have not been described previously.

In brief the general procedure for catalytic hydrogenolysis of these N-succinimidomethyl compounds was that each of the N-succinimidomethyl compound dissolved in ethanol was hydrogenated over Raney nickel catalyst under high hydrogen pressure at requisite temperature. The N-methylated amine product was obtained from the concentration residue of the reaction solution by extraction, being separated from succinimide.

[*1] Part XX: This Bulletin, **15**, 833 (1967).

[*2] Oshika, Shizuoka (関屋 実, 伊藤敬一).

1) M. Sekiya, K. Ito: This Bulletin, **11**, 892 (1963).

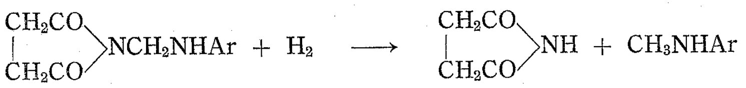
2) *Idem*: *Ibid.*, **14**, 996 (1966).

3) *Idem*: *Ibid.*, **14**, 1007 (1966).

4) M.B. Winstead, K.V. Anthony, L.L. Thomas, R.G. Strachan, H.J. Reichwine: C.A., **58**, 6722 (1963).

As shown in Table I, excellent yields of N-methylated amine products were shown in all runs with good recovery of succinimide.

Table I. Catalytic Hydrogenolysis[a] of N-(Arylaminomethyl)succinimide



$$\left.\begin{matrix}CH_2CO\\ |\\ CH_2CO\end{matrix}\right\rangle NCH_2NHAr + H_2 \longrightarrow \left.\begin{matrix}CH_2CO\\ |\\ CH_2CO\end{matrix}\right\rangle NH + CH_3NHAr$$

Run No.	Ar	Hydrogenolysis temp. (°C)	Hydrogenolysis time (min.)	Product CH_3NHAr	Yield[b] (%)
1	p-$(CH_3)_2NC_6H_4$-	65～70	100	p-$(CH_3)_2NC_6H_4NHCH_3$	96
2	p-$CH_3OC_6H_4$-	65～70	100	p-$CH_3OC_6H_4NHCH_3$	93
3	o-$CH_3OC_6H_4$-	65～70	120	o-$CH_3OC_6H_4NHCH_3$	90
4	p-HOC_6H_4-	70～75	110	p-$HOC_6H_4NHCH_3$	91
5	p-$CH_3C_6H_4$-	75～80	100	p-$CH_3C_6H_4NHCH_3$	90
6	o-$CH_3C_6H_4$-	75～80	120	o-$CH_3C_6H_4NHCH_3$	92
7	m-$CH_3C_6H_4$-	75～80	120	m-$CH_3C_6H_4NHCH_3$	91
8	p-$C_2H_5OCOC_6H_4$-	120～125	200	p-$C_2H_5OCOC_6H_4NHCH_3$	96
9	p-$HOCOC_6H_4$-	130～135	180	p-$HOCOC_6H_4NHCH_3$	97

a) General hydrogenolysis procedure is given in Experimental.
b) Based on product isolation.

From view of the reaction temperatures and times observed for the hydrogenolyses, reactivities of N-succinimidomethyl analogs for the hydrogenolysis are considered to be similar to those of the previously reported N-phthalimidomethyl analogs. And with respect to aromatic amine the relative reactivities were also seen qualitatively to be consistent with the previously established rationale that the reactivity increases in the rising order of the basicity of the amine residue of the compound.

In consideration of facility of the formation of N-succinimidomethyl compounds from aromatic primary amine, succinimide, and formaldehyde, the modified direct procedure without isolation of the N-(arylaminomethyl)succinimide was also examined as like as previously reported for N-phthalimidomethyl analogs and was found to be similarly advantageous for practical N-monomethylation of aromatic primary amines. In this modification, a mixture of equimolar amount of aromatic primary amine, succinimide, and formaldehyde dissolved in ethanol was refluxed for 30 min. and then, without isolation of N-(arylaminomethyl)succinimide from the reaction solution, the whole was directly subjected to catalytic hydrogenation over Raney nickel catalyst under high

Table II. N-Monomethylation[a] of Aromatic Primary Amine

Run No.	Starting aromatic compound	Hydrogenolysis temp. (°C)	Hydrogenolysis time (min.)	Product	Yield[c] (%)
1	p-$CH_3OC_6H_4NH_2$	65～70	100	p-$CH_3OC_6H_4NHCH_3$	91
2	p-$HOC_6H_4NO_2$[b]	70～75	130	p-$HOC_6H_4NHCH_3$	89
3	p-$CH_3C_6H_4NH_2$	75～80	110	p-$CH_3C_6H_4NHCH_3$	89
4	o-$CH_3C_6H_4NH_2$	75～80	120	o-$CH_3C_6H_4NHCH_3$	92
5	m-$CH_3C_6H_4NH_2$	75～80	120	m-$CH_3C_6H_4NHCH_3$	90
6	$C_6H_5NH_2$	80～85	140	$C_6H_5NHCH_3$	85
7	p-$C_2H_5OCOC_6H_4NH_2$	125～130	200	p-$C_2H_5OCOC_6H_4NHCH_3$	90

a) General procedure is given in Experimental.
b) This starting nitro-compound was prereduced to amino-compound by catalytic hydrogenation and the hydrogenation mixture was directly processed as in the other runs.
c) Based on product isolation.

hydrogen pressure at elevated temperature. By this modified procedure excellent yields of the N-monomethylated amine products were obtained in all runs, as shown in Table II. Particularly in the procedure for run 2 in Table II, was used *p*-nitrophenol as a starting material, which was prereduced to *p*-aminophenol in ethanol over Raney nickel catalyst under high hydrogen pressure and then followed by the foresaid general procedure in the same autoclave by addition of succinimide and formaldehyde.

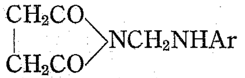
After the above results, the method through the N-succinimidomethyl compound can be said to be practically useful for N-monomethylation of various aromatic primary amines as well as the previously reported method through N-phthalimidomethyl compound with definite advantages; excellent yields are obtainable, the reagents are readily available, and the product isolation is simple.

Experimental

General Procedure for Preparation of N-(Arylaminomethyl)succinimide——N-Succinimidomethyl compounds of aromatic primary amines were prepared as in the following according to a method similar to that previously reported2) for N-(anilinomethyl)succinimide.

Aromatic primary amine (0.1 mole), succinimide, and CH_2O as 37% aqueous solution in equimolar proportion were dissolved in 100 ml. of EtOH and the solution was refluxed for 30 min. After cool, the reaction solution was concentrated under reduced pressure, whereupon almost pure crystals were obtained and weighed. To obtain analytically pure material the products were once recrystallized. Appearances, melting points, yields, and analytical data are listed in Table III.

Table III. N-(Arylaminomethyl)succinimide



$$\begin{array}{l} CH_2CO \\ | \\ CH_2CO \end{array} \Big> NCH_2NHAr$$

Ar	Yield (%)	Appearance (Recryst. solvt.)	m.p. (°C)	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
p-$C_2H_5OCOC_6H_4$-	85	leaves (EtOH)	148	$C_{14}H_{16}O_4N_2$	60.86	5.84	10.14	60.61	5.84	10.35
p-$HOCOC_6H_4$-	82	needles (dioxane)	222 (decomp.)a)	$C_{12}H_{12}O_4N_2$	58.06	4.87	11.29	57.61	5.04	10.98
p-$(CH_3)_2NC_6H_4$-	89	needles (EtOH)	147	$C_{13}H_{17}O_2N_3$	63.14	6.94	16.99	63.22	7.07	17.08
p-HOC_6H_4-	90	plates (EtOH)	153~154	$C_{11}H_{12}O_3N_2$	59.99	5.49	12.72	59.92	5.58	12.89
p-$CH_3OC_6H_4$-	88	needles (EtOH)	118~119b)	$C_{12}H_{14}O_3N_2$	61.52	6.02	11.96	61.50	6.05	12.16
o-$CH_3OC_6H_4$-	94	needles (EtOH)	34~36	$C_{12}H_{14}O_3N_2$	61.52	6.02	11.96	61.61	6.22	11.78
p-$CH_3C_6H_4$-	95	needles (EtOH)	142c)	$C_{12}H_{14}O_2N_2$	66.03	6.47	12.84	66.15	6.53	12.86
o-$CH_3C_6H_5$-	96	prisms (EtOH)	127~128d)	$C_{12}H_{14}O_2N_2$	66.03	6.47	12.84	66.25	6.64	12.96
m-$CH_3C_6H_4$-	75	prisms (EtOH)	130~132e)	$C_{12}H_{14}O_2N_2$	66.03	6.47	12.84	65.79	6.49	12.95

a) lit.4) m.p. 224~225°. decomp.=decomposition.
b) lit.4) m.p. 113~114.5°.
c) lit.4) m.p. 140°. 145~146°.
d) lit.4) m.p. 129~130°.
e) lit.4) m.p. 128~130°.

General Procedure for Catalytic Hydrogenolysis of N-(Arylaminomethyl)succinimide——In an autoclave having a capacity of 175 ml., 0.05 mole of N-(arylaminomethyl)succinimide, 70 ml. of EtOH, and Raney nickel catalyst freshly prepared as usual from 1 g. of 50% alloy were placed. Under 80 kg./cm² of initial hydrogen pressure at room temperature the whole was heated and then constant shaking was started at the requisite temperature and, after drop of hydrogen pressure was nearly ceased (the period up to this time is written as the hydrogenolysis time in Table I), shaking and heating were continued for further 30 min. Amount of the pressure drop was almost theoretical in every run.

Modified Procedure for N-Monomethylation of Aromatic Primary Amine——In all runs except run 2 in Table II, aromatic primary amine (0.05 mole), succinimide, and CH_2O as 37% aqueous solution in equimolar proportion were dissolved in 70 ml. of EtOH and the solution was refluxed for 20 min. Then the whole was transferred into an autoclave and Raney nickel catalyst prepared from 1 g. of 50% alloy was added. The hydrogenation was carried out in the same manner as described in the above method.

Procedure for run 2 in Table II, in which nitro-compound was used as the starting material, was as follows. In an autoclave a solution of 0.05 mole of *p*-nitrophenol dissolved in 70 ml. of EtOH was hydrogenated at 80~84° over Raney nickel catalyst, prepared from 1 g. of 50% alloy, under 100 kg./cm^2 of initial hydrogen pressure. After uptake of hydrogen each 0.05 mole of succinimide and CH_2O as 37% aqueous solution was added to the hydrogenation mixture and then the whole was again processed by nearly the same procedure as described above.

General Procedure for Product Isolation——The hydrogenolysis mixture was filtered to remove the catalyst and the filtrate was treated as in the following.

In all runs except for run 1 and 4 in Table I and run 2 in Table II, the filtrate was concentrated under reduced pressure and the residue was thoroughly extracted with hot petr.-ether when succinimide remained unextracted. After removal of petr.-ether from the extracts, distillation of the residue under reduced pressure (run 2, 3, 5, 6, 7 in Table I and run 1, 3, 4, 5, 6 in Table II) or recrystallization of the residual crystals (run 8 and 9 in Table I and run 7 in Table II) gave the N-methylated amine product, which was identified by analysis and measurement of its infrared spectrum.

In run 1 and 4 in Table I and run 2 in Table II, in which the products were sensitive in the air, the filtrate of the reaction mixture was acidified with a slight excess of *N* HCl (run 1 in Table I) or *N* H_2SO_4 (run 4 in Table I and run 2 in Table II) and then concentrated to dryness under reduced pressure. The residue was thoroughly extracted with hot dry benzene to remove succinimide. The N-methylated amine hydrochloride and the sulfate were obtained from the extraction residues.

The followings are the identifications of the amine products obtained.

N,N,N′-Trimethyl-*p*-phenylenediamine: Dihydrochloride: plates from MeOH, m.p. 220~221°(decomp.). *Anal.* Calcd. for $C_9H_{16}N_2Cl_2$: C, 48.44; H, 7.23; N, 13.79. Found: C, 48.15; H, 7.01; N, 13.80.

N-Methyl-*p*-anisidine: B.p$_{13}$ 118~119°, n_D^{17} 1.5605. *Anal.* Calcd. for $C_8H_{11}ON$: C, 70.04; H, 8.08; N, 10.21. Found: C, 70.42; H, 8.31; N, 9.92. Hydrochloride: needles from EtOH, m.p. 119~120°.

N-Methyl-*o*-anisidine: B.p$_{19}$ 120~122°, n_D^{17} 1.5588. *Anal.* Calcd. for $C_8H_{11}ON$: C, 70.04; H, 8.08; N, 10.21. Found: C, 70.33; H, 8.10; N, 10.16. Hydrochloride: prisms from EtOH, m.p. 110~112°.

p-Methylaminophenol: Sulfate: prisms from EtOH, m.p. 253~256°(decomp.). *Anal.* Calcd. for $C_{14}H_{20}O_6N_2S$: C, 48.82; H, 5.85; N, 8.14. Found: C, 48.91; H, 5.88; N, 8.07.

N-Methyl-*p*-toluidine: B.p$_{19}$ 98~99°, n_D^{17} 1.5542. *Anal.* Calcd. for $C_8H_{11}N$: C, 79.29; H, 9.15; N, 11.56. Found: C, 79.61; H, 9.33; N, 11.52. Hydrochloride: leaflets from EtOH, m.p. 115~116°.

N-Methyl-*o*-toluidine: B.p$_{30}$ 100~104°, n_D^{14} 1.5650. *Anal.* Calcd. for $C_8H_{11}N$: C, 79.29; H, 9.15; N, 11.56. Found: C, 79.19; H, 9.23; N, 11.60. Hydrochloride: needles from EtOH, m.p. 108~110°.

N-Methyl-*m*-toluidine: B.p$_{13}$ 90~92°, n_D^{17} 1.5595. *Anal.* Calcd. for $C_8H_{11}N$: C, 79.29; H, 9.15; N, 11.56. Found: C, 79.20; H, 9.18; N, 11.88. Hydrochloride: prisms from EtOH, m.p. 110~112°.

N-Methylaniline: B.p$_{15}$ 78~79°, n_D^{17} 1.5730. *Anal.* Calcd. for C_7H_9N: C, 78.46; H, 8.47; N, 13.07. Found: C, 78.23; H, 8.55; N, 12.90. Hydrochloride: needles from EtOH, m.p. 121~122°.

Ethyl *p*-methylaminobenzoate: Prisms from petr.-ether, m.p. 59~62°. *Anal.* Calcd. for $C_{10}H_{13}O_2N$: C, 67.02; H, 7.31; N, 7.82. Found: C, 67.02; H, 7.24; N, 8.10.

p-Methylaminobenzoic acid: Needles from benzene, m.p. 153~155°. *Anal.* Calcd. for $C_8H_9O_2N$: C, 63.56; H, 6.00; N, 9.27. Found: C, 63.26; H, 5.71; N, 9.51.

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