2. The kinetics of the hydrolysis of 2-naphthyl β-D-glucofuranosiduronic acid by β-glucuronidase were investigated. The pH optimum of the β-D-glucofuranosiduronic acid is 5.0 in phosphate-citrate buffer at 38°. The reaction velocity is constant with time. The Michaelis-Menten constant is $1.75\times10^{-2}M$. The kinetics of the hydrolysis of 2-naphthyl β-D-glucopyranosiduronic acid by the enzyme were also investigated. The pH optimum is 4.7. The Michaelis-Menten constant is $1.3\times10^{-3}M$.

3. In view of the above facts, it was concluded that β-D-glucofuranosiduronic acids could be a substrate for β-glucuronidase.

(Received December 18, 1963)

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Chem. Pharm. Bull.
12 (6) 674 ~ 677

*UDC 547.582.4.07*

## 95. **Minoru Sekiya, Keiichi Ito, and Minako Saito**: Reaction of Amide Homologs. XII.*[1] Reaction of N-Arylmethylene-1-acylamino-1-arylmethylamine with Active Methylene Compound.

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

1-Acylaminoarylmethylations of ethyl malonate were found to proceed with some N-arylmethylene-1-acylamino-1-arylmethylamines reported by Sekiya, *et al.*[1,2] by the action of alkaline catalyst. In the present paper we wish to report this reaction and related studies. Previously, there were some reports[3,4] in which 1-acylaminoarylmethylation of active methylene compound is effected in some cases only by treatment with N,N′-arylmethylenebisamide or a mixture of an aromatic aldehyde and acetamide in acetic anhydride.

The following N-arylmethylene-1-acylamino-1-arylmethylamines were used for the reaction: N-Benzylidene-α-acetamidobenzylamine, N-(4-methoxybenzylidene)-α-acetamido-4-methoxybenzylamine and formamido homolog, N-(3,4-methylenedioxybenzylidene)-α-acetamido-3,4-methylenedioxybenzylamine and formamido homolog. Among these compounds the latter two 3,4-methylenedioxybenzylidene derivatives have not been described previously. Both the compounds were prepared by the reaction of 3,4:3′,4′:3″,4″-tris(methylenedioxy)hydrobenzamide with acetamide or formamide according to the previously reported method.[2]

The N-arylmethylene-1-acylamino-1-arylmethylamines reacted with active methylene compound such as ethyl malonate, ethyl cyanoacetate, phenylacetonitrile, and malononitrile. The general procedure for carring out the reaction is to reflux a toluene solution of an active methylene compound and N-arylmethylene-1-acylamino-1-arylmethylamine with suspended sodium hydroxide powder. All reactions examined of N-arylmethylene-1-acylamino-1-arylmethylamines with ethyl malonate proceeded smoothly yielding diethyl (α-acylaminobenzyl)malonate effecting the replacement of the

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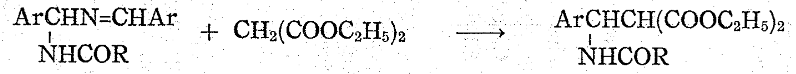
Table I. 1-Acylaminoarylmethylation of Ethyl Malonate with N-Arylmethylene-1-acylamino-1-arylmethylamine

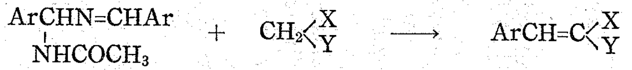


$$\underset{\text{NHCOR}}{\text{ArCHN=CHAr}} + \text{CH}_2(\text{COOC}_2\text{H}_5)_2 \longrightarrow \underset{\text{NHCOR}}{\text{ArCHCH(COOC}_2\text{H}_5)_2}$$

| Substituent | | Product | | | | | Analysis (%) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | Calcd. | | | Found | | |
| Ar | R | Yield (%) | Appearance (recryst. solvt.) | b.p. (°C) (mm. Hg) | m.p. (°C) | Formula | C | H | N | C | H | N |
| Phenyl | $CH_3$ | 27 | prisms (AcOEt) | 172～179 (0.05) | 82～85[a] | $C_{16}H_{21}O_5N$ | 62.52 | 6.88 | 4.56 | 62.65 | 6.88 | 4.84 |
| 4-Methoxyphenyl | 〃 | 51 | leaflets (toluene) | — | 97～98[b] | $C_{17}H_{23}O_6N$ | 60.52 | 6.87 | 4.15 | 60.88 | 6.66 | 4.30 |
| 4-Methoxyphenyl | H | 23 | prisms (ligroin) | 160～168 (0.02) | 88～90 | $C_{16}H_{21}O_6N$[d] | 59.43 | 6.55 | 4.33 | 59.95 | 6.55 | 4.25 |
| 3,4-Methylenedioxyphenyl | $CH_3$ | 40 | leaflets (AcOEt) | — | 95～96[c] | $C_{17}H_{21}O_7N$ | 58.11 | 6.02 | 3.99 | 58.31 | 6.29 | 4.21 |
| 3,4-Methylenedioxyphenyl | H | 36 | prisms (benzene-petr. ether) | — | 91～93 | $C_{16}H_{19}O_7N$[e] | 56.97 | 5.68 | 4.15 | 56.71 | 5.32 | 4.44 |

a) lit.[4] m.p. 85°, m.p.[5] 81～82°. b) lit.[4] m.p. 95°. c) lit.[4] m.p. 95°. d) IR $\nu_{\max}^{\text{KBr}}$ cm$^{-1}$: 3296 (NH), 1730, 1248 (COO), 1655, 1528 (CONH). e) IR $\nu_{\max}^{\text{KBr}}$ cm$^{-1}$: 3390 (NH), 1735, 1245 (COO), 1665, 1530 (CONH).

Table II. Formation of Arylmethylene Derivatives by the Reaction of N-Arylmethylene-1-acylamino-1-arylmethylamine



$$\underset{\text{NHCOCH}_3}{\text{ArCHN=CHAr}} + \text{CH}_2\!\left\langle\begin{smallmatrix}\text{X}\\\text{Y}\end{smallmatrix}\right. \longrightarrow \text{ArCH=C}\!\left\langle\begin{smallmatrix}\text{X}\\\text{Y}\end{smallmatrix}\right.$$

| Substituent | | | Product | | | | | Analysis (%) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | Calcd. | | | Found | | |
| Ar | X | Y | Yield (%) | Appearance (recryst. solvt.) | b.p. (°C) (mm. Hg) | m.p. (°C) | Formula | C | H | N | C | H | N |
| Phenyl | CN | $COOC_2H_5$ | 68 | prisms (EtOH) | 132～140 (0.05) | 48～50[a] | $C_{12}H_{11}O_2N$ | 71.62 | 5.51 | 6.96 | 71.33 | 5.67 | 7.10 |
| Phenyl | 〃 | $C_6H_5$ | 37 | plates (EtOH) | 148～156 (0.035) | 83～85[b] | $C_{15}H_{11}N$ | 87.77 | 5.40 | 6.82 | 87.92 | 5.23 | 6.61 |
| Phenyl | 〃 | CN | 97 | plates (AcOEt) | 120～128 (0.6) | 81～83[c] | $C_{10}H_6N_2$ | 77.90 | 3.92 | 18.17 | 77.81 | 3.91 | 17.75 |
| 4-Methoxyphenyl | 〃 | $COOC_2H_5$ | 97 | plates (EtOH) | — | 83～84[d] | $C_{13}H_{13}O_3N$ | 67.52 | 5.67 | 6.06 | 67.35 | 6.09 | 6.22 |
| 4-Methoxyphenyl | 〃 | $C_6H_5$ | 42 | 〃 | 178～185 (0.35) | 95～97[e] | $C_{16}H_{13}ON$ | 81.68 | 5.57 | 5.95 | 81.32 | 5.54 | 6.25 |
| 3,4-Methylenedioxyphenyl | 〃 | $COOC_2H_5$ | 95 | leaflets (EtOH) | — | 107～108[f] | $C_{13}H_{11}O_4N$ | 63.67 | 4.52 | 5.71 | 63.62 | 4.72 | 5.82 |

a) lit.[6] m.p. 50°. b) lit.[7] m.p. 86°. c) lit.[8] m.p. 87°. d) lit.[9] m.p. 85°. e) lit.[10] m.p. 93°. f) lit.[11] m.p. 106°.

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active hydrogen by 1-acylaminoarylmethyl group, excepting the reaction with N-benzylidene-α-formamidobenzylamine in which the corresponding product could not be isolated. These experiments are summarized in Table I showing that N-arylmethylene-1-acylamino-1-arylmethylamines generally give higher yields than its formamido homolog. Among the products indicated in Table I, both diethyl(α-formamido-4-methoxybenzyl)malonate and diethyl(α-formamido-3,4-methylenedioxybenzyl)malonate have not been reported previously.

Besides, various other active methylene compounds all reacted resulting in the formation of arylmethylene derivatives, as shown in Table II. It is thought in these cases that 1-acetamidoarylmethyl compounds conceived as a reaction intermediate are easier in elimination of acetamide in which sodium hydroxide would act as an alkaline catalyst. Under the condition where piperidine was used as a reaction solvent, the reaction between ethyl malonate and N-benzylidene-α-acetamidobenzylamine resulted also in the formation of ethyl benzylidenemalonate.

However, no reaction occurred, using ethyl ethylmalonate or ethyl ethylcyanoacetate as the active methylene compound. Presumably this is due to steric hindrance.

## Experimental

**N-(3,4-Methylenedioxybenzylidene)-α-acetamido-3,4-methylenedioxybenzylamine**——A mixture of 13.0 g. of 3,4:3′,4′:3″,4″-tris(methylenedioxy)hydrobenzamide and 52.3 g. of $AcNH_2$ was heated on a boiling water bath for 3.5 hr. with constant stirring. After cooling, the reaction mixture was washed with cold $H_2O$ to remove excess of $AcNH_2$, then washed well with dry $Et_2O$. The crude crystals obtained were recrystallized from EtOH to needles, m.p. 142~143°. Yield, 6.4 g. (42%). *Anal.* Calcd. for $C_{18}H_{16}O_5N_2$: C, 63.52; H, 4.74; N, 8.23. Found: C, 63.31; H, 4.79; N, 8.33. IR $\nu_{max}^{KBr}$ $cm^{-1}$: 3346 (NH), 1640, 1510 (CONH), 1257, 1035 ($Et_2O$).

**N-(3,4-Methylenedioxybenzylidene)-α-formamido-3,4-methylenedioxybenzylamine**——A mixture of 43.5 g. of 3,4:3′4′:3″,4″-tris(methylenedioxy)hydrobenzamide and 112.5 g. of $HCONH_2$ was heated on a boiling water bath for 6 hr. with constant stirring. The reaction solution was concentrated under reduced pressure to remove excess of $HCONH_2$. The crystalline residue was recrystallized from EtOH to needles, m.p. 119~120°. Yield, 38.5 g. (85%). *Anal.* Calcd. for $C_{17}H_{14}O_5N_2$: C, 62.57; H, 4.32; N, 8.59. Found: C, 62.56; H, 4.30; N, 8.38. IR $\nu_{max}^{KBr}$ $cm^{-1}$: 3336 (NH), 1657, 1537 (CONH), 1630 (C=N), 1244, 1040 ($Et_2O$).

**General Procedure for the Reaction with Active Methylene Compound**——To a solution of 0.03 mole of N-arylmethylene-1-acylamino-1-arylmethylamine and 0.045 mole of active methylene compound dissolved in 40 ml. of anhyd. toluene, 0.3 g. of powdered NaOH was added. The mixture was refluxed for 4 hr. with constant stirring. After cooling, the reaction mixture was filtered. To completely remove NaOH, a quantity of $Al_2O_3$ was added, the mixture stirred and filtered. The filtrate was concentrated under reduced pressure. In some cases, the products were isolated as crystals from the residue. In other cases, the residue were distilled in high vacuum whereupon the products were obtained as solid distillates. The isolation of diethyl(α-formamido-3,4-methylenedioxybenzyl)malonate employed chromatography over silica gel, in which this substance dissolved in benzene was absorbed on silica gel and then eluted with EtOH.

**Reaction of N-Benzylidene-α-acetamidobenzylamine with Ethyl Malonate in Piperidine**——A mixture of 20.0 g. of N-benzylidene-α-acetamidobenzylamine, 12.8 g. of ethyl malonate, and 3.4 g. of piperidine was heated on a boiling water bath for 4 hr. with constant stirring. The reaction mixture was concentrated under reduced pressure and the residual oil distilled in vacuum affording ethyl benzylidenemalonate, b.p$_{0.2}$ 100~105°. Yield, 12.0 g. (60%). *Anal.* Calcd. for $C_{14}H_{16}O_4$: C, 67.73; H, 6.50. Found: C, 67.72; H, 6.59.

This substance was catalytically hydrogenated to ethyl benzylmalonate and then, by treatment with $EtOH-NH_3$, was converted to benzylmalonamide, m.p. 225°, which showed no melting point depression on admixture with an authentic sample. *Anal.* Calcd. for $C_9H_{10}O_2N_2$: C, 60.66; H, 5.66; N, 15.72. Found: C, 60.58; H, 5.70; N, 15.88.

The authors are grateful to Prof. Emeritus M. Ishidate of the University of Tokyo for his kind encouragement during the course of this work. The authors are also indebted to Miss Y. Saito and Mr. K. Narita for the elementary analyses.

## Summary

1-Acylaminoarylmethylation of ethyl malonate was effected in several cases by interaction of N-arylmethylene-1-acylamino-1-arylmethylamine in refluxing toluene solution with suspended sodium hydroxide powder. Ethyl cyanoacetate, phenylacetonitrile and malononitrile formed arylmethylene derivatives under the same condition as with ethyl malonate.

(Received November 13, 1963)

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〔Chem. Pharm. Bull.
12 (6) 677 ~ 682〕

UDC 547.291.07

# 96. **Minoru Sekiya and Keiichi Ito**: Reduction with Formic Acid. I. Reduction of N-Acylaminomethyl and N-Sulfonamidomethyl Compound.

(*Shizuoka College of Pharmacy**1)

Previously,1) the catalytic reduction of N-acylaminomethyl compounds was shown in some examples to result in a reductive fission of the carbon bond connecting to amide nitrogen. Lately, a similar mode of the reduction was also found to occur in formic acid reduction.

$$\mathrm{RCO\overset{|}{N}\text{-}CH_2\text{-}N\langle} \xrightarrow{\mathrm{HCOOH}} \mathrm{RCO\overset{|}{N}H} + \mathrm{CH_3N\langle}$$

On formic acid reduction of compound of alkylidenediamine type there have been some reports indicating the reductive fission of the carbon-nitrogen bond, in which reductions of 1,1′-benzylidenedipiperidine,2) 1,1′-methylenedipiperidine,3) and N,N,N′,N′-tetrabenzylmethylenediamine3) were examined, however, no report has been made in the case of monoacylated alkylidenediamine. The present paper reports the studies on the formic acid reduction reaction with a series of N-acylaminomethyl and N-sulfonamidomethyl compounds, which have been developed in this laboratory.

In this work the trimethylammonium formate, which was previously reported4) to be constant-boiling liquid salt given by $5HCOOH \cdot 2N(CH_3)_3$, was employed as a reducing agent. Though there was another paper5) in which salt of formic acid with aliphatic tertiary amine was reported to be a 2:1 addition product, the above composition of trimethylammonium formate was reaffirmed by analyses and the same 5:2 proportion of formic acid and tertiary amine was also analyzed correctly with the salts of 1-methylpiperidine and of 4-methylmorpholine, which were shown to be constant-boiling liquid of $b.p_{20}$ 100.5° and of $b.p_{20}$ $89\sim90°$ respectively. On the use of trimethylammonium formate as a reducing agent, its constant high boiling point and very weak acidity appeared to

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