flocculent impurity that appeared was removed by centrifugation and the supernatant was kept in a refrigerator overnight to separate yellow microcrystals; yield, 12 mg. The sample for analysis was dried over P_2O_5 *in vacuo* for 5 hr. *Anal.* Calcd. for $C_{17}H_{20}O_{12}N_4Na_2P_2 \cdot 4H_2O$ (Sodium riboflavin diphosphate) : N, 8.58; P, 9.51. Found : N, 8.32; P, 9.75.

Summary

The alcoholysis reaction of catechol cyclic phosphate (CCP) (I) with polyols reported in the preceding paper was applied to phosphorylation of riboflavin. The latter was phosphorylated to give a mixture of riboflavin 5′-phosphate (FMP) (Vc) and riboflavin 4′,5′-cyclic phosphate in a yield of 75～78%. After acid hydrolysis the pure riboflavin 5′-phosphate was obtained by zone electrophoresis without any loss of the product during isolation.

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87. **Minoru Sekiya and Toshio Oishi** : Reactions of Amide Homologs. I. Reaction between Azomethines and Amides.

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In an earlier paper[1] dealing with the reaction between azomethines and formamide, it was shown that a reductive cleavage occurred in azomethines by reaction with formamide to afford N-alkylformamide.

$$R\text{-}CH{=}N\text{-}R' + 3\,HCONH_2 + H_2O \longrightarrow R\text{-}CH_2\text{-}NHCHO + R'\text{-}NHCHO + CO_2 + NH_3$$

(Compound $(R\text{-}CH_2)_2N\text{-}CHO$ was also produced in a side reaction)

In this reaction a portion of formamide served as a reducing agent, so that the reaction temperature is high. When the same reagents, azomethine and formamide, were allowed to react at a low temperature (about 95°) at which formamide could not act as a reducing agent, a new reaction was found to occur. This reaction which may be represented by the following equation will be discussed below.

$$2\,Ar\text{-}CH{=}N\text{-}R + 3\,R'CONH_2 \longrightarrow Ar\text{-}\underset{\displaystyle NHCOR'}{\underset{|}{CH}}\text{-}N{=}CH\text{-}Ar + 2\,R\text{-}NHCOR' + NH_3$$

The main product of this reaction was a compound of a new type, which may be termed N-arylmethylene-1-acylamino-1-arylmethylamine.

Several reactions were carried out using azomethines such as N-arylmethylenealkylamines, i.e. N-benzylidenemethylamine, N-benzylideneëthylamine, N-(*p*-chlorobenzylidene)methylamine, and N-anisylidenemethylamine.*2 In the reaction not only formamide but acetamide could also be used as a reactant, but was less reactive.

The reaction between N-benzylidenemethylamine (I) and formamide is first discussed below from the viewpoints both of confirmation of structure of the main product and of the nature of the reaction. A mixture of (I) and formamide (molar ratio, 1:3) was heated on a boiling water bath with occasional shaking. From the evaporation residue, colorless prisms of m.p. 124～125° (II) were obtained, which were analysed to give the molecular formula of $C_{15}H_{14}ON_2$. When (II) was hydrolysed with 10% phosphoric acid, 2 moles of benzaldehyde proved as its phenylhydrazone, 2 moles of ammonia, and some formic acid,

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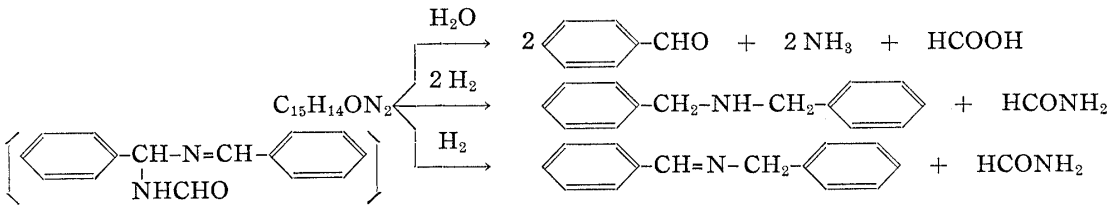
1) M. Sekiya, T. Fujita : Yakugaku Zasshi, **71**, 942(1951).

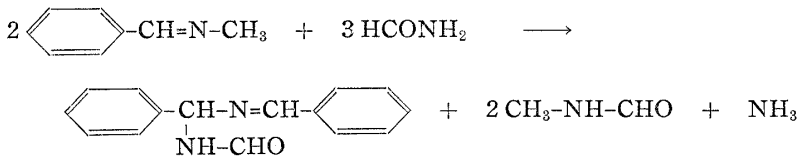
*2 Anisyl=*p*-methoxybenzyl; anisylidene=*p*-methoxybenzylidene

identified as its *p*-phenylphenacyl formate, were obtained. By catalytic reduction under a high pressure of hydrogen, using Raney nickel as a catalyst, (II) gave dibenzylamine and formamide, absorbing 2 moles of hydrogen. When the catalytic reduction under ordinary pressure of hydrogen using palladium-carbon catalyst was stopped after absorption of 1 mole of hydrogen, N-benzylidenebenzylamine, identified as its dibromide, and formamide were proved to be the products.



Considering the above facts, the structure of (II) would be indicated by N-benzylidene-α-formamidobenzylamine. Moreover, its structure was confirmed by spectroscopic method. Ultraviolet spectrum of (II) was compared with that of N-benzylidenebenzylamine. If (II) had the structure of N-benzylidene-α-formamidobenzylamine, its spectrum would not deviate markedly from that of N-benzylidenebenzylamine. Both absorption curves were almost identical to each other and exhibited characteristic peak at 248 mμ, thus indicating (II) to be the compound proposed above.

It became clear that interaction of (I) with formamide gave N-benzylidene-α-formamidobenzylamine (II), with the yield of 59% of the theoretical, and excess of the reactants was recovered. On the other hand, it was shown that in this reaction N-methylformamide was also produced simultaneously, which was proved in the distillate obtained by concentration of the reaction solution. Considering this fact and evolution of ammonia during the course of this reaction, the reaction may be represented as follows :



In the hope of increasing the yield of (II), an attempt was made to carry out the reaction under longer reaction time but was unsatisfactory. It was shown that side reactions took place simultaneously to afford 2,4,6-triphenyl-1,3,5-triazine, m.p. 235°, and N-benzylidenebenzamidine, m.p. 173~175°.

In order to pursue the reaction further, azomethines of N-arylmethylenealkylamine type such as N-benzylideneëthylamine (III), N-(*p*-chlorobenzylidene)methylamine (IV), and N-anisylidenemethylamine (V) were used as reactants instead of N-benzylidenemethylamine. It was shown that these azomethines reacted with formamide in essentially identical ways. (III) reacted in the same way as (I) to give (II). (IV) reacted to give N-(*p*-chlorobenzylidene)-α-formamido-*p*-chlorobenzylamine (VI), m.p. 150~151°, in 54% yield. (V) reacted to give N-anisylidene-α-formamidoanisylamine (VII), m.p. 154~155°, yield 49%, and producing anisylidenediformamide as a by-product. (VI) and (VII) were not previously reported, and were identified by elementary analyses and qualitative methods.

Further, instead of formamide, acetamide was allowed to react with (I). In this case, the compound of the same type, N-benzylidene-α-acetamidobenzylamine (VIII), was also obtained in 57% yield when the reaction time was prolonged to about three times that of formamide. Therefore, acetamide was distinctly less reactive than formamide.

The foregoing data are summarized in Table I.

Table I.

Azomethine	Amide	Reaction time (hr.)	Product	m.p. (°C)	Yield (%)
N-Benzylidenemethylamine	Formamide	3	N-Benzylidene-α-formamidobenzylamine	123~125	59
N-Benzylideneëthylamine	Formamide	3	N-Benzylidene-α-formamidobenzylamine		43
N-Benzylidenemethylamine	Acetamide	3 10	N-Benzylidene-α-acetamidobenzylamine	133~134	32 57
N-(*p*-Chlorobenzylidene)-methylamine	Formamide	3	N-(*p*-Chlorobenzylidene)-α-formamido-*p*-chlorobenzylamine	150~151	54
N-Anisylidenemethylamine	Formamide	3 10	N-Anisylidene-α-formamidoanisylamine	154~155	49 77

The authors are indebted to Miss Y. Saito for the elemental analyses.

Experimental

N-Benzylidene-α-formamidobenzylamine (II) (Reaction of N-Benzylidenemethylamine (I) with Formamide)—a) To 13.5 g. (0.3 mole) of formamide, 11.9 g. (0.1 mole) of (I) was added and the whole was heated for 3 hr. on a boiling water bath with occasional shaking, when evolution of NH_3 was observed. The resultant solution was concentrated on a water bath under a reduced pressure. By treating the distillate, some N-benzylidenemethylamine was recovered and a considerable amount of N-methylformamide was proved in it. The syrupy residue soon crystallized, and the product was collected, washed with a small amount of EtOH, and dried. Yield, 7 g. (59%). Plates (from EtOH), m.p. 123~125°. *Anal.* Calcd. for $C_{15}H_{14}ON_2$: C, 75.60; H, 5.92; N, 11.76. Found: C, 75.44; H, 5.77; N, 12.04. UV λ_{max}^{EtOH}: 248 mμ (log ε 4.37).

b) A mixture of 60 g. (0.5 mole) of (I) and 68 g. (1.5 moles) of formamide was treated as in the case of (a) except that 15 hr. was spent for the reaction. The syrupy evaporation residue solidified after standing for 3 days in a refrigerator. The crude product was collected and fractional recrystallisation from EtOH afforded 3 kinds of crystals. The easily soluble portion showed m.p. 123~124°, undepressed by admixture with (II). The sparingly soluble portion, m.p. 173~175°, was shown to be identical with N-benzylidenebenzamidine. This gave a hydrochloride of m.p. 275° and was hydrolyzed with dil. H_2SO_4 to BzH, BzOH, and NH_3. *Anal.* Calcd. for $C_{14}H_{12}N_2$: C, 80.74; H, 5.81; N, 13.45. Found: C, 80.60; H, 5.59; N, 13.56.

The most sparingly soluble portion crystallized from benzene to needles, m.p. 235°, which was shown to be 2,4,6-triphenyl-1,3,5-triazine by its failure to depress the m.p. of an authentic sample. *Anal.* Calcd. for $C_{21}H_{15}N_3$: C, 81.53; H, 4.89; N, 13.58. Found: C, 81.27; H, 4.87; N, 13.69.

Reaction of N-Benzylideneëthylamine (III) with Formamide—A mixture of 6.7 g. (0.05 mole) of (III) and 6.8 g. (0.15 mole) of formamide was treated as in the case of (a). (II) was obtained in a yield of 2.6 g. (43%) and showed no depression of m.p. on admixture with (II) obtained in (a).

Hydrolysis of N-Benzylidene-α-formamidobenzylamine (II)—To 75 cc. of 10% H_3PO_4, 12 g. of (II) was added and the mixture was refluxed for 30 min., giving an oily layer. The oily layer was distilled with steam and the distillate neutralized with dil. NaOH was redistilled. This distillate was added to phenylhydrazine in the presence of a little amount of AcOH to give a phenylhydrazone, which was shown to be benzaldehyde phenylhydrazone by its failure to depress the m.p. of an authentic sample. Its yield was 16.6 g. which corresponded to 84% as 2 moles for 1 mole of (II). The crystals separated from the neutralized residue was dissolved in water and treated with *p*-phenylphenacyl bromide in the usual manner to give *p*-phenylphenacyl formate, m.p. 73~74°, undepressed on admixture with an authentic sample. *Anal.* Calcd. for $C_{15}H_{12}O_3$: C, 74.99; H, 5.03. Found: C, 74.69; H, 4.99.

The residual solution from the foregoing steam distillation was added with NaOH solution and evaporated, when NH_3 vaporized. The vapor was introduced into a suitable amount of standard H_2SO_4 solution through a condenser. According to the usual manner, excess H_2SO_4 was titrated with standard NaOH solution and the consumption of the NaOH solution was recalculated to the amount of NH_3. The calculated amount corresponded to 88% as 2 moles of NH_3.

Catalytic Reduction of N-Benzylidene-α-formamidobenzylamine (II) under a High Pressure—A solution of 10 g. of (II) in 120 cc. of EtOH was mixed with Raney Ni catalyst (2 g. as 50% alloy) in an autoclave. At the initial H_2 pressure of 100 atm. the mixture was heated with constant shaking. The absorption started at 60° and was completed in about 45 min. at a final temperature of 80°, 2 moles of H_2 for 1 mole of (II) being taken up. The reaction mixture was filtered to remove the catalyst and the filtrate was evaporated. To the residue a suitable amount of water was added and extracted with benzene. After removal of benzene, the residue was distilled under a reduced pres-

sure and a distillate of $b.p_{2\sim3}$ 100~112° was obtained. This compound was shown to be identical with dibenzylamine, for the m.p. of this derivative of N-phenyl-N',N'-dibenzylthiourea was not depressed by admixture with an authentic sample. Yield, 6.5 g. (79%).

The aqueous layer was concentrated and the residue was distilled under a reduced pressure. The distillate of $b.p_5$ 84~88° was shown to be identical with formamide by its behavior of being hydrolyzed to HCOOH and NH_3. Yield, 1.6 g. (84%).

Catalytic Reduction of N-Benzylidene-α-formamidobenzylamine (II) under Ordinary Pressure—Six g. of (II) dissolved in 25 cc. of EtOH was reduced catalytically with 1 g. of 10% Pd-C at room temperature under ordinary pressure and absorbed 1 mole of H_2 for 1 mole of (II) in about 12 min., when the absorbtion slowed and then stopped. After filtration of the catalyst, the solution was evaporated. The heterogeneous residue was added to a suitable amount of water and extracted with benzene. By the usual treatment of the aqueous layer the presence of formamide was proved in it. The benzene layer was dried, evaporated, and the residue was distilled under a reduced pressure to give 4 g. of oil, $b.p_4$ 147~150°. This was hydrolyzed with 5% HCl to give benzylamine hydrochloride and benzaldehyde, and, when added to Br_2 in Et_2O, gave an orange precipitate of m.p. 139~140°, which was shown to be N-benzylidenebenzylamine dibromide by its failure to depress the m.p. of an authentic sample. From these facts the above product was found to be identical with N-benzylidenebenzylamine.

N-Benzylidene-α-acetamidobenzylamine (VIII) (Reaction of N-Benzylidenemethylamine (I) with Acetamide)—To 17.7 g. (0.3 mole) of acetamide 12 g. (0.1 mole) of (I) was added and the whole was heated for 10 hr. on a boiling water bath, when evolution of NH_3 was observed. The resultant solution was concentrated on a water bath under a reduced pressure. The residue soon crystallized and was dissolved in benzene to remove undissolved acetamide. After evaporation of benzene a crystalline substance was obtained. Yield, 7.15 g. (57%). Prisms (from EtOH), m.p. 133~134°. *Anal.* Calcd. for $C_{16}H_{16}ON_2$: C, 6.16; H, 6.39; N, 11.10. Found : C, 76.34; H. 6.33; N, 11.07.

N-(p-Chlorobenzylidene)-α-formamido-p-chlorobenzylamine (VI) (Reaction of N-(p-Chlorobenzylidene)methylamine (IV) with Formamide)—To 4.5 g. (0.1 mole) of formamide 5 g. (0.033 mole) of (IV) was added and the whole was heated for 3 hr. on a boiling water bath. The solution was concentrated under a reduced pressure. After standing overnight the residue crystallized. Yield, 2.7 g. (54%). Needles (from EtOH), m.p. 150~151°. *Anal.* Calcd. for $C_{15}H_{12}ON_2Cl_2$: C, 58.64; H, 3.96; N, 9.12. Found : C, 58.16; H, 4.02; N, 8.92.

N-Anisylidene-α-formamidoanisylamine (VII) (Reaction of N-Anisylidenemethylamine (V) with Formamide)—A mixture of 7 g. (0.15 mole) of formamide and 7.5 g. (0.05 mole) of (V) was heated for 3 hr. on a boiling water bath. The solution was concentrated under a reduced pressure. The syrupy residue was crystallized from a small amount of benzene. The crystalline substance was submitted to chromatography through an alumina column, developing with benzene, and plates, m.p. 154~155°, were obtained from the initial eluate. Yield, 3.68 g. (49%). *Anal.* Calcd. for $C_{17}H_{18}O_3N_2$: C, 68.44; H, 6.08; N, 9.39. Fonud : C, 68.37; H, 6.08; N, 9.70.

When the column was finally washed with EtOH, needles fo m.p. 170~171° were obtained, which were shown to be anisylidenediformamide by admixture with an authentic sample. *Anal.* Calcd. for $C_{10}H_{12}O_3N_2$: C, 57.68; H, 5.81; N, 13.46. Found : C, 57.58; H, 5.75; N, 13.40.

Summary

1) By the reaction between N-benzylidenemethylamine and formamide, a compound of new benzylidenediamine type, namely N-benzylidene-α-formamidobenzylamine, was obtained as the main product. Hydrolysis, catalytic reduction under a high pressure, and selective catalytic reduction of this product were examined and its ultraviolet spectrum was shown, by which its structure was confirmed.

2) N-Arylmethylene-alkylamines such as N-benzylideneëthylamine, N-(p-chlorobenzylidene)methylamine, and N-anisylidenemethylamine reacted in the same way with formamide to afford N-arylmethylene-1-formamido-1-arylmethylamines as in the reaction between N-benzylidenemethylamine and formamide. Moreover, N-benzylidenemethylamine and acetamide reacted similarly, affording N-benzylidene-α-acetamidobenzylamine.

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