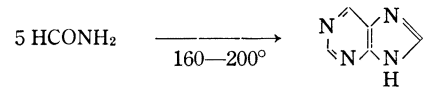
[Chem. Pharm. Bull. 20(3) 623—624 (1972)] UDC 547.857.057 : 547.298.1.04

A One-step Synthesis of Purine Ring from Formamide

There have been numerous investigations on the synthesis of purine ring which is the base component of nucleic acids, major methods of the purine synthesis being as follows: (a) Cyclization of 4,5-diaminopyrimidine with anhydrous formic acid in the carbon monoxide atmosphere;[1] (b) Reaction of tris(formylamino)methane with phthalimidacetonitrile at high temperature;[2] (c) Reaction of aminoacetonitrile with formamide;[3] (d) Reaction of formamide and glycine or glycineamide with phosphorus oxychloride in a sealed tube.[4] These synthetic methods have various handicaps such as the low yield of product and complex procedures.

Now we have found a new method for the synthesis of purine from formamide solely by heating without any other reagent or at high pressure. By this new procedure, purine can be obtained easily and in a good yield as compared with known processes mentioned above. Heating of formamide between 160° and 200° affords purine as follow:



The reaction was carried out in an open vessel with a condenser for 10—30 hr.

For example, 45 g of formamide was heated for 28 hr in an oil bath at 170—190°. After removing excess of formamide (32.1 g) by vacuum distillation, the residue was refluxed with methanol. The methanol solution was filtered, the solvent was removed from the filtrate by vacuum distillation, and 4.93 g of almost pure purine was obtained (71% calculated from formamide consumed). Recrystallization from acetone afforded purine as colorless crystals of mp 218°. *Anal.* Calcd. for $C_5H_4N_4$: C, 49.99; H, 3.36; N, 46.65. Found: C, 50.43; H, 3.40; N, 46.66. IR ν_{max}^{KBr} cm^{-1}: 1618, 1403, 1278, 909. Table I shows several examples of the reaction conditions.

TABLE I. Example of Synthesis of Purine from Formamide

Expt. No.	Condition: Reaction time (hr)	Condition: Reaction temp. (°C)	Recovered $HCONH_2$ (%)	Yield of purine: a (%)	Yield of purine: b (%)	
1	10	160	100	—	—	
2	10	150—160	100	—	—	in sealed tube
3	29	180—200	71	49	14.4	in sealed tube
4	28	170—190	71	71	20.5	

a: Yield calculated from formamide consumed in the reaction.
b: Yield from formamide used as starting material.

The yield seems to considerably depend on the reaction temperature. A reaction below 160° does not produce purine, even in a sealed tube. Furthermore, addition of molecular sieve (type 4A) or sulfuric acid as desiccant to the reaction system effects no remarkable improvement in the yield. The reaction temperature above 200° and prolonged heating seems to

1) O. Isay, *Chem. Ber.*, **39**, 251 (1906).
2) H. Bredereck, F. Effenberger, and G. Rainer, *Angew. Chem.*, **73**, 63 (1961).
3) H. Bredereck, F. Effenberger, G. Rainer, and H.P. Schosser, *Ann.*, **659**, 133 (1962).
4) K. Morita, S. Kobayashi, H. Shimazu, and M. Ochiai, Abstracts of Papers, the Second Symposium on Heterocyclic Chemistry, Japan, Nagasaki, November, 1969, p. 87.

result in decomposition of the product. Two or three intermediates, whose structures have not been determined yet, have been obtained. The mechanism of this reaction is now under investigation.

Faculty of Pharmaceutical Sciences,
University of Tokyo
Hongo, Bunkyo-ku, Tokyo

HIROSHI YAMADA
TOSHIHIKO OKAMOTO

Received October 14, 1971

[Chem. Pharm. Bull. 20(3) 624—625 (1972)]

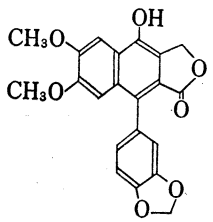
UDC 547.651.1.057 : 581.192

Biogenetic-Type Transformation of α-[α-(Hydroxymethyl)-3,4-dimethoxystyryl]-3,4-methylenedioxycinnamic Acid γ-Lactone into Diphyllin

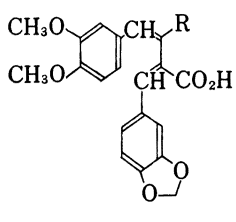
In the preceding paper,[1] we have described the structure and synthesis of diphyllin (I). Recently, Lin, *et al.*[2] have reported that taiwanin A coexisted together with taiwanin C and E in a plant and that an acetone solution of taiwanin A, after standing in the light, gave taiwanin C and E. Accordingly, we assumed that dibenzylidenebutyrolactone derivatives[2,3] could be a biogenetic precursor[4] of 1-aryl-4-hydroxy-2,3-naphthalide type lignans.[5]

In this communication, we wish to report the biogenetic-type transformation of α-[α-(hydroxymethyl)-3,4-dimethoxystyryl]-3,4-methylenedioxycinnamic acid γ-lactone (IV)[6] into diphyllin (I) *via* photosensitized oxygenation.[7]

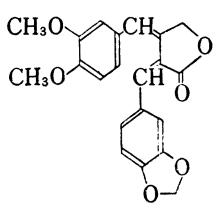
The Stobbe condensation of veratrole with diethyl piperonylidenesuccinate[8] gave the half ester (II)[6] (77%), IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1685, 1705, which was reduced on lithium aluminum diethoxyhydride[9] to give the alcohol (III)[6] (44%), IR ν_{max}^{Nujol} cm^{-1}: 3370, 1685, and subsequent treatment with *p*-toluenesulfonic acid gave the lactone (IV)[6] IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1750. A solution of the lactone (IV)[6] and Rose Bengal in acetone, through which dry oxygen was bubbled,



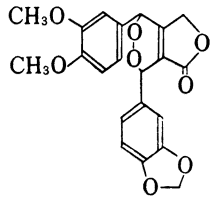
I



II : R=$CO_2C_2H_5$
III : R=CH_2OH



IV



V

1) Z. Horii, K. Ohkawa, S. Kim, and T. Momose, *Chem. Pharm. Bull.* (Tokyo), **19**, 535 (1971).
2) Y.-T. Lin, T.-B. Lo, K.-T. Wang, and B. Weinstein, *Tetrahedron Letters*, **1967**, 849.
3) B.F. MacDonald and G.M. Barton, *Can. J. Chem.*, **48**, 3144 (1970); A.W. Schrecker and J.L. Hartwell, *J. Am. Chem. Soc.*, **76**, 4896 (1954).
4) J.H. Richards and J.B. Hendrickson, "The Biosynthesis of Steroids, Terpenes, and Acetogenins," Benjamin, New York, 1964, p. 34.
5) H. Kofod and C. Jørgensen, *Acta Chem. Scand.*, **8**, 1296 (1954); H. MacLean and B.F. MacDonald, *Can. J. Chem.*, **47**, 457 (1969).
6) Each product is a mixture of the geometrical isomers.
7) D.R. Kearns and A.U. Khan, *Photochemistry and Photobiology*, **10**, 193 (1969).
8) D.C. Ayres, B.G. Carpenter, and R.C. Denney, *J. Chem. Soc.*, **1965**, 3578.
9) P.M. McCurry Jr., *Tetrahedron Letters*, **1971**, 1845.