ACTA CHEMICA SCANDINAVICA 8 (1954) 390—392

Note on the Preparation of γ-Pyridone

BØRGE BAK and DANIEL CHRISTENSEN

Chemical Laboratory of the University of Copenhagen, Copenhagen, Denmark

König and Greiner's method for the preparation of γ-pyridone from pyridine was thoroughly checked. It is superior to the method by Robinson and Thornley both with regard to time spent and amount of material used. A procedure giving analytically pure γ-pyridone in a 20 per cent yield from pyridine is described. Unsuccessful attempts to prepare the intermediate N-(4-pyridyl)-pyridinium chloride hydrochloride in a state of high purity are reported.

In connection with the preparation of 4-deutero-pyridine (I) some 4-substituted pyridine derivative had to be produced. Since (I) may be prepared from 4-chloro-pyridine which can be made from γ-pyridone (II) [1] a laboratory method for the preparation of (II) was looked for.

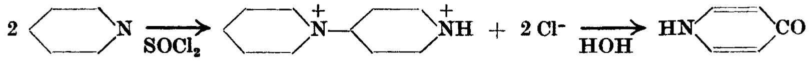
EXPERIMENTAL PART

1°. Robinson and Thornley's method[2] (compare King and Ware[3])

Chelidonic acid was satisfactorily prepared according to "Organic Synthesis"[4]. Its conversion to chelidamic acid[3] was likewise successful. 60 g chelidamic acid heated to 260° C gave 30 g white, but impure γ-pyridone (m.p. 122—5° C). The purification of γ-pyridone so produced has not been described. By conversion to hydrate, extraction of the hydrate with hot chloroform a.s.o. as described under 3°, 10 g γ-pyridone of highest quality (m.p. 150—1° C) and an additional quantity of 5—6 g impure compound (m.p. 140—43° C) was obtained. Total yield: 50 % based on chelidamic acid. King and Ware[3] reported a 95 % yield but gave no criterion of the purity. If this series of preparations is started from 430 g diethyl oxalate and acetone, 20—30 g γ-pyridone can be prepared in 5 working-days.

2°. König and Greiner's method[5]

The route to γ-pyridone found by König and Greiner is as follows:



(III) (II)

First, it was attempted to prepare *pure* N-(4-pyridyl)-pyridinium chloride hydrochloride (III) in satisfactory yield. All the attempts were fruitless. The amount of crystalline material collected according to König and Greiner definitely increased without change in quality by letting pyridine react at room temperature with thionyl chloride for three days instead of boiling the mixture for a shorter period. Well-dried pyridine was applied in all experiments but aside from this the use of high-grade pyridine and thionyl chloride had almost no effect on the yield. In a typical example, 165 g pyridine gave 145 g impure (III), dried *in vacuo* over conc. sulfuric acid. The chlorine equivalent weight of the light-brown product was 123—5 (theory: 114.6). It decomposed on heating. When 144 g of this crude product was dissolved in hydrochloric acid and treated for one hour on a steam bath with active carbon, 108 g of almost white, crystalline material (IV) was obtained after evaporation of the water and addition of alcohol as described by König and Greiner. By this procedure the chlorine equivalent weight was improved to 116—8 but still no real melting point was found contrary to the findings of König and Greiner. The crystals, heated in a stream of nitrogen, began to decompose at 170—80° forming a liquid and a white solid which were both deposited on the cold parts of the flask, and leaving a coloured solid on the hot bottom (the heating was carried out by immersing the flask in an oil-bath). Not even a trace of HCl was hereby liberated.

We were never able to obtain the two modifications of (III), mentioned by König and Greiner, neither were we able to prepare crystals with a satisfactory content of C, N, and H as reported by König and Greiner. (Found for (IV): C 49.4; N 12.3; H 4.8. Calc. for $C_{10}H_{10}N_2Cl_2$ (229.2): C 52.4; N 12.2; H 4.4). The ultraviolet absorption spectrum had two pronounced peaks at 2 330 and 2 640 Å. At these wave-lengths an aqueous solution of (IV), containing 0.01003 g per litre, had the optical density 0.327 and 0.288, respectively. (Cell-length 10 mm).

In a series of attempts to purify (IV) the chlorine equivalent weight, the C, N, and H contents and the ultraviolet absorption spectrum were constantly checked but no method giving rise to obvious improvements was found (recrystallization from methanol; ethanol; a mixture of ethanol and conc. hydrochloric acid; precipitation from methanolic solutions by ethyl ether; repeated treatments with hydrochloric acid and active carbon). Therefore, it is irrational to try to purify (IV) by any of these methods. In connection with the preparation of pyridone König and Greiner themselves recommend to omit isolation of purified (III) but their paper leaves the impression that this is a matter of convenience and not a matter of rational method.

König and Greiner report that an aqueous solution of crude (III) can be hydrolyzed to yield 70 g crude γ-pyridone. The result of their subsequent purification processes was not reported. After several experiments the procedure given under 3° was adopted for laboratory preparation of γ-pyridone.

3°. Laboratory preparation of γ-pyridone from pyridine

300 ml thionyl chloride (technical grade) was added drop by drop at room temperature to 170 ml pyridine (dry) placed in a 1 l three-necked flask with separatory funnel (for $SOCl_2$), thermometer, and an exit calcium chloride tube. The addition of the acid chloride was regulated so that the temperature was kept below 50° C. After 72 hours at room temperature during which the reaction mixture slowly turned brown, the excess thionyl chloride was evaporated *in vacuo*, the reaction flask being immersed in a water bath which was gradually heated from 50—100° in the course of 1—2 hours. The solid contents of the flask was afterwards cooled to 0° C and a freshly prepared mixture of 170 ml abs. alcohol and 17 ml conc. hydrochloric acid (0°) was added. The crystals were carefully crushed and the whole mixture left at 0° C for 30 minutes. Then the crystals were separated by suction on a sintered glass-filter and afterwards washed three times with 50 ml of the above-mentioned mixture of alcohol and conc. hydrochloric acid. The last traces of alcohol were removed by washing with dry ether and subsequent suction. The yield was 145 g crude (III), dried *in vacuo* over conc. sulfuric acid.

The whole quantity was dissolved in 250 ml water and the solution filtered through paper on a Büchner-funnel. The filtrate was heated on a steam-bath for 1 hour with 20 g active carbon and afterwards filtered through filter-paper on a Büchner-funnel. The almost colourless solution was now boiled for 72 hours in a round-bottomed flask with reflux condenser. After neutralization of the acid formed (by means of approximately 85 g anhydrous sodium carbonate) *all* the water was removed by destillation *in vacuo*. To help remove the water completely and to loosen the crystalline mixture from the flask 500 ml dry chloroform was added and afterwards again removed by destillation *in vacuo*. It was now generally easy to get the solid material out of the flask. In an extraction apparatus γ-pyridone was now separated from inorganic material by boiling dry chloroform. The extraction lasted 24 hours. After cooling of the resulting, brown chloroform solution (300 ml) crude γ-pyridone was precipitated by addition of an excess of ethyl ether. After drying *in vacuo* over conc. sulfuric acid the product so obtained weighed 30 g (m. p. 133–40° C).

Purification of this quantity was accomplished by dissolving in 300 ml dry chloroform, filtering, and boiling the filtrate placed in a round-bottomed flask together with 90 % of the water necessary for the formation of the hydrate (5 g). On cooling, the hydrate crystallizes out *very* readily (which is not the case with γ-pyridone itself). In the chloroform the coloured impurities concentrate. The chloroform solution is removed by decantation, fresh chloroform is added to the hydrate and the mixture is again boiled, shaken and cooled, after which the chloroform is decanted. By sufficient repetition of this procedure (3–4 times further) the colourless hydrate of γ-pyridone is obtained. This is very easily reconverted to γ-pyridone by heating in a flask, immersed in boiling water and constantly being evacuated by the water aspirator. The almost colourless γ-pyridone so obtained weighs 20 g, representing a 20 % yield based on pyridine. Depending on the extent to which the hydrate has been purified the melting point lies at 147–151° C. (Analysis found: C 63.16; N 14.71; H 5.50. Calc. for C_5H_5NO: C 63.15; N 14.73; H 5.30.)

The saturated solution of γ-pyridone in chloroform contains 4 g per 100 ml solution at 20° C, 12–13 g at 61° C. In spite of this fact we have been unable to use recrystallization from chloroform as a purification procedure because of the pronounced tendency of γ-pyridone to form super-saturated solutions.

REFERENCES

1. Wibaut, J. P. and Broekmann, F. W. *Rec. trav. chim.* **58** (1939) 885.
2. Robinson, R. and Thornley, S. *J. Chem. Soc.* **1924** 2169.
3. King, H., and Ware, L. L. *J. Chem. Soc.* **1939** 873.
4. *Org. Synthesis*, Collective Vol. II (1944) 126.
5. König, E. and Greiner, H. *Ber.* **64** (1931) 1049.

Received December 21, 1953.