[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY]

THE BENZOYLATION OF 2-AMINOPYRIDINE[1]

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During studies (1) on the Beckmann rearrangement of the oximes of 2-benzoylpyridine, necessity arose for the characterization of 2-(benzoylamino)pyridine. Although this compound has been previously reported by five different laboratories, the record disclosed a distressing lack of accord.

2-(Benzoylamino)pyridine was first reported (2) from 2-aminopyridine by reaction with benzoyl chloride and aqueous alkali and next (3) by reaction with benzoic anhydride. The compound was claimed to melt at 165° (2, 3), to form a picrate salt, m.p. 146° (2) and both the supposed benzoyl derivative and its salt gave, respectively, appropriate analyses (2). Despite the concordance of these results both reports were completely erroneous.

Subsequent studies by Tschitschibabin and Bylinkin (4), completely confirmed by Wibaut and Dingemanse (5), utilized both methods but obtained 2-(benzoylamino)pyridine of m.p. 87° and 2-(dibenzoylamino)pyridine of m.p. 166–167°. The latter was readily hydrolyzed with dilute sodium carbonate to the former.

This apparent resolution of the earlier errors was soon complicated by a German patent (6) which claimed that 2-aminopyridine with benzoic anhydride gave 2-(dibenzoylamino)pyridine, m.p. 94–95°, and by a report (7) that carbodi-(2-pyridyl)imide with benzoic acid gave 2-(benzoylamino)pyridine, m.p. 80°. Still later 2-aminopyridinium benzoate was reported (8) as melting 145–146°.

By Schotten-Baumann benzoylation of 2-aminopyridine we have obtained 2-(dibenzoylamino)pyridine, m.p. 167.5–169° uncor., confirming the Russian (4) and Dutch (5) reports. Hydrolysis with alcoholic sodium carbonate yielded 2-(benzoylamino)pyridine as earlier reported (4) but this product melted sharply at 82–83° uncor., and no higher value has ever been obtained for it in our work. This same 2-(benzoylamino)pyridine was also obtained (1) by Beckmann rearrangement of *syn*-phenyl 2-pyridyl ketoxime using thionyl chloride.

Contrary to the earlier reports (3, 4, 5), the reaction of 2-aminopyridine with benzoic anhydride gave in our hands 2-aminopyridinium benzoate, m.p. 145–146° uncor. [recorded (8) 145–146°], and the benzoate salt of 2-(benzoylamino)-pyridine, m.p. 93.5–94.5° previously described (6) as 2-(dibenzoylamino)pyridine. Both these salts titrated sharply with alkali, giving appropriate neutralization equivalents, while the true 2-(dibenzoylamino)pyridine did not titrate with alkali at all. The identity of the 2-(benzoylamino)pyridinium benzoate, m.p. 93.5–94.5° was further confirmed by isolation of both components and by repreparation from them.

[1] This paper is constructed from part of a dissertation submitted by Henry C. Walter to the Faculty of the Massachusetts Institute of Technology in September, 1946, in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

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The picrate salt of 2-(benzoylamino)pyridine was reported by the Russian (4) laboratory as melting at 193°, but by Zetsche (7) and Marckwald (2) at 146°. The picrate prepared from our 2-(benzoylamino)pyridine first melted 156–157° uncor., but after recrystallization changed to 196–198° uncor.

EXPERIMENTAL

2-(Dibenzoylamino)pyridine. 2-Aminopyridine (0.94 g. = 0.01 mole) was shaken at room temperature with benzoyl chloride (3.6 g. = 0.025 mole) and excess aqueous 10% sodium hydroxide solution. After disappearance of the odor of acyl halide the crude product amounted to 2.79 g. (92.5% yield). Several recrystallizations from ethanol yielded white needles, m.p. 167.5–169° uncor.

Anal. Calc'd for $C_{19}H_{14}N_2O_2$: N, 9.27. Found: N, 9.34, 9.38.

2-(Benzoylamino)pyridine. A sample of the above N,N-(dibenzoyl)-2-aminopyridine refluxed for thirty minutes with dilute ethanol containing a little sodium carbonate completely dissolved. On cooling, the solution deposited white needles (m.p. 81–83° uncor.) which on further recrystallization melted at 82–83° uncor.

Anal. Calc'd for $C_{12}H_{10}N_2O$: N, 14.14. Found: N, 14.1, 14.2.

The compound is appreciably soluble in aqueous alkali, from which it is precipitated by acetic acid. With ethanolic picric acid it yields a picrate salt, yellow needles from ethanol, m.p. 196–198° uncor.

2-(Benzoylamino)pyridinium chloride. A solution of 2-(benzoylamino)pyridine (1.5 g.) in dry ether (50 ml.) was treated with hydrogen chloride gas. The salt (1.61 g. = 91% yield) precipitated as fine white needles, m.p. 181–185° uncor. After several recrystallizations by precipitation from absolute ethanol by addition of dry ether, the salt melted 190.5–192.5° uncor. after sintering at 185–190°. The compound is readily soluble in water but insoluble in ether.

Anal. Calc'd for $C_{12}H_{11}ClN_2O$ (*i.e.*, $C_{12}H_{10}N_2O \cdot HCl$): Cl, 15.14; Neut. Equiv., 234.5. Found: Cl, 15.06, 15.15; Neut. Equiv., 234.3, 234.8.

Reaction of 2-aminopyridine with benzoic anhydride. 2-Aminopyridine (2.82 g. = 0.03 mole) and benzoic anhydride (4.52 g. = 0.02 mole) dissolved in dry ether (50 ml.), on standing for 2 days at room temperature deposited hexagonal prisms melting at 145–148°. Evaporation of the ether gave a mixture of crystals and oil, the latter being readily dissolved by a little ether. The crystals of 2-aminopyridine benzoate (2.90 g. = 67% yield) after further purification melted 146–147° uncor.

Anal. Calc'd for $C_{12}H_{12}N_2O_2$ (*i.e.*, $C_5H_6N_2 \cdot C_6H_5COOH$): Neut. Equiv., 216. Found: Neut. Equiv., 214.8, 215.9.

Evaporation of the ether solution left a colorless oil which soon solidified. After repeated recrystallization from dilute ethanol, long, thin, white flakes of 2-(benzoylamino)-pyridinium benzoate, m.p. 93.5–94.5° uncor. were obtained.

Anal. Calc'd for $C_{19}H_{16}N_2O_3$ (*i.e.*, $C_{12}H_{10}N_2O \cdot C_6H_5COOH$): N, 8.75; Neut. Equiv., 320. Found: N, 8.81, 8.88; Neut. Equiv., 320, 321.

Upon shaking with dilute hydrochloric acid and ether, the salt gave 94% yield of benzoic acid. The aqueous layer eventually yielded 2-(benzoylamino)pyridine, m.p. 81–82°. These products failed to depress the melting points of authentic samples. Finally, a sample of the salt synthesized from 2-(benzoylamino)pyridine with benzoic acid, melted at 93–94° uncor. and did not depress the melting point of the material obtained from 2-aminopyridine and benzoic anhydride.

SUMMARY

1. Benzoylation of 2-aminopyridine by the Schotten-Baumann method gives in excellent yield 2-(dibenzoylamino)pyridine.

2. Reaction of 2-aminopyridine with benzoic anhydride in ether effects *mono*-benzoylation and both the 2-(benzoylamino)pyridine and the corresponding amount of 2-aminopyridine are obtained in the form of their benzoate salts.

3. Several anomalies in prior reports of 2-aminopyridine derivatives have been resolved.

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