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Note

Note on the Synthesis of 2-Ethyl-thioisonicotinoylamide*

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Several methods for the preparation of 2-ethyl-thioisonicotinoylamide are reported until now¹⁻⁵. In our experiments we have prepared the diethylacetal of 2-ethyl-isonicotinaldehyde by reaction of triethylorthoformate with the crude 2-ethylpyridine-4-magnesium bromide obtained by application of a Grignard type reaction on 2-ethyl-4-bromopyridine. Heating of an aqueous hydrochloric acid solution of the acetal yielded the free 2-ethyl-isonicotinaldehyde⁶. This was afterwards heated with sulphur and pyridine under conditions of the Willgerodt-Kindler reaction⁷ to yield the 2-ethyl-thioisonicotinoyl-amide.

To characterize the 2-ethyl-isonicotinaldehyde we have prepared its hydrazone. The last named compound was also obtained by heating *N*'-benzensulfonyl-2-ethyl-isonicotinoylhydrazide in glycerol⁸. The benzensulfonylhydrazide was prepared by usual method from the 2-ethyl-isonicotinoylhydrazide⁹.

EXPERIMENTAL

All melting points are uncorrected

2-Ethyl-isonicotinaldehyde diethylacetal.

Prepared according to the method given by Wibaut and Huls⁶ from 112.2 g. (1.056 moles) of ethylbromide, 33 g. (1.35 gramatoms) of magnesium turnings, 62 g. (0.335 mole) of 2-ethyl-4-bromopyridine, 180 g. (1.22 moles) of tri-ethylorthoformate and 215 g. (4 moles) of ammonium chloride. Yield: 61%, b. p. 125–128°/14 mm.

Anal. C₁₂H₁₉NO₂ (209.28)

calc'd.: C 68.86; H 9.15; N 6.69%

found: C 68.61; H 8.89; N 6.63%

2-Ethyl-isonicotinaldehyde.

Prepared from 15.3 g. (0.073 mole) of 2-ethyl-isonicotinaldehyde diethylacetal and 150 ml. (0.45 mole) of 10% hydrochloric acid. Yield: 83%, b. p. 92–95°/20 mm, colourless liquid with a characteristic slightly pungent odor.

Anal. C₈H₉NO (135.16)

calc'd.: C 71.09; H 6.71; N 10.36%

found: C 71.26; H 6.96; N 10.34%

* *Yug. Pat. Applic. 598/64*

2-Ethyl-isonicotinaldehyde hydrazone.

Prepared by usual method from 1.35 g. (0.01 mole) of 2-ethylisonicotinaldehyde and 5 ml. (0.083 mole) of 80% hydrazine hydrate. Yield: 86%, light yellow crystals from cyclohexane, m. p. 46–48°.

Anal. $C_8H_{11}N_3$ (149.19)
 calc'd.: C 64.40; H 7.43; N 28.17%
 found: C 64.11; H 7.41; N 28.14%

2-Ethyl-isonicotinaldehyde thiosemicarbazone.

Prepared by usual method from 2 g. (0.015 mole) of 2-ethyl-isonicotinaldehyde and 1.35 g. (0.015 mole) of thiosemicarbazide. Yield: 43.5%, m. p. 215–216°, light yellow crystals from 90% ethanol.

Anal. $C_9H_{12}N_4$ (208.22)
 calc'd.: C 51.91; H 5.81; N 26.91%
 found: C 51.77; H 5.59; N 26.69%

The same compound was obtained also by the method given by Fox⁸ from 3.05 g. (0.01 mole) of crude *N'*-benzene-sulfonyl-2-ethyl-isonicotinoylhydrazide, 2.4 g. (0.0226 mole) of sodium carbonate, 0.91 g. (0.01 mole) of thiosemicarbazide and 30 ml of glycerol. Yield: 50%, m. p. 213–214°.

N'-benzenesulfonyl-2-ethyl-isonicotinoylhydrazide hydrochloride.

Prepared according to the method given by Nieman et al⁹ from 1.65 g. (0.01 mole) of 2-ethyl-isonicotinoylhydrazide and 1.87 g. (0.01 mole) of benzenesulfonylchloride. Yield: 71.5%, m. p. 215–216° (from absolute ethanol).

Anal. $C_{14}H_{16}ClNO_2S$ (341.81)
 calc'd.: C 49.19; H 4.72; Cl 10.37; N 12.29%
 found: C 49.21; H 4.56; Cl 10.26; N 12.04%

2-Ethyl-thioisonicotinoylamide

In a steel pressure vessel a mixture of 0.75 g. (0.0055 mole) of 2-ethyl-isonicotinaldehyde, 0.16 g. (0.005 gramatom) of sulphur, 30 ml. of pyridine and 20 ml. (0.096 mole) of liquid ammonia was held at a temperature of 115–120° during 8 hours. The pyridine was then distilled off, the residue dissolved in 50 ml. benzene, the solution filtered after addition of activated carbon, evaporated to dryness under reduced pressure, and the residue crystallized from ethanol. The yield was 0.52 g. (56.5% of the theoretical amount) of 2-ethyl-thioisonicotinoylamide melting at 164–165° (lit.⁷ m. p. 166°).

The same compound was also obtained in 27.5% yield by introducing gaseous ammonia in a mixture of 0.75 g. (0.055 mole) of 2-ethyl-isonicotinaldehyde, 0.16 g. (0.005 gramatom) of sulphur and 30 ml. of pyridine for four hours at a temperature of 110–120° C and subsequent isolation in the above described manner; m. p. 164–165°.

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IZVOD

Sinteza amida 2-etil-tioizonikotinske kiseline

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Amid 2-etil-tioizonikotinske kiseline pripravljen je tako, da je 2-etil-brompiridin Grignardovom reakcijom preveden u 2-etilpiridin-4-magnezijev bromid i bez izolacije reakcijom s trietilnim esterom orto-mravlje kiseline preveden u dietilacetal 2-etilizonikotinaldehida, a ovaj zatim grijanjem u solno kiseloj otopini u slobodni aldehid. Aldehid je reakcijom po Willgerodtu i Kindleru zagrijavanjem u smjesi sa sumporom, piridinom i amonijakom preveden u tioamid. Za karakterizaciju aldehida priređen je njegov hidrazon i tiosemikarbazon. Posljednji je također dobiven i zagrijavanjem benzensulfonilhidrazida 2-etil-izonikotinske kiseline u glicerinu. Potrebni benzensulfonilhidrazid 2-etil-izonikotinske kiseline pripremljen je uobičajenim načinom iz hidrazida 2-etil-izonikotinske kiseline.

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