

acetone, giving a small amount of 8'-methoxy-1,3,3-trimethyl-4'-(1,3,3-trimethyl-2-indolylmethyl)-indoline-2-spiro-2'-benzopyran (IV), colorless crystals that melted to a pink liquid at 223-224°.

*Anal.* Calcd. for  $C_{22}H_{28}N_2O_2$ : C, 80.0; H, 7.6. Found: C, 80.0; H, 7.9.

From the mother and wash liquors there was obtained 1.3 g. of 8'-methoxy-1,3,3-trimethyl-2-spiro-2'-benzopyran (III), colorless crystals that gave a violet melt at 123-124°, and a purple solution in boiling diphenyl ether.

**Condensation with 5-Bromosalicylaldehyde (a).**—A solution of 6.7 g. of 5-bromosalicylaldehyde and 5.7 g. of 1,3,3-trimethyl-2-methyleneindoline in 90 ml. of alcohol was boiled for two hours and then cooled. The solid (0.35 g., VI) was removed, and the main product was precipitated with water. Recrystallization from alcohol gave 3.7 g. of 6'-bromo-1,3,3-trimethylindoline-2-spiro-2'-benzopyran (V), colorless crystals m.p. 86-87° to a colorless liquid. A solution of the compound in boiling xylene was colorless, in boiling diphenyl ether blue.

*Anal.* Calcd. for  $C_{19}H_{18}BrNO$ : C, 64.1; H, 5.1. Found: C, 64.4; H, 5.3.

(b).—A solution of 3.4 g. of 5-bromosalicylaldehyde and 5.7 g. of 1,3,3-trimethyl-2-methyleneindoline in 75 ml. of alcohol was boiled for two hours. The solid was removed, washed with acetone, and crystallized from benzene. There was obtained 7.1 g. of 6'-bromo-1,3,3-trimethyl-4'-(1,3,3-trimethyl-2-indolylmethyl)-indoline-2-spiro-2'-benzopyran (VI), colorless crystals, m.p. 199-200° to a pink liquid. A solution in boiling diphenyl ether was violet.

*Anal.* Calcd. for  $C_{21}H_{22}BrN_2O$ : C, 70.4; H, 6.3. Found: C, 70.6; H, 6.4.

**Condensation with 5-Nitrosalicylaldehyde.**—A solution of 1.8 g. of 5-nitrosalicylaldehyde and 1.7 g. of 1,3,3-trimethyl-2-methyleneindoline in 40 ml. of alcohol was kept at room temperature for eleven days. The green precipitate was then removed, dissolved in pyridine and treated with charcoal. Precipitation with water gave 1.9 g. of 1,3,3-trimethyl-6'-nitroindoline-2-spiro-2'-benzopyran (VII), pale orange crystals that melted at 179-180° to a blue liquid.

*Anal.* Calcd. for  $C_{19}H_{18}N_2O_3$ : C, 70.8; H, 5.6. Found: C, 70.8; H, 5.7.

**Condensation with 3,5-Dinitrosalicylaldehyde.**—A solution of 2.4 g. of 3,5-dinitrosalicylaldehyde and 1.7 g. of 1,3,3-trimethyl-2-methyleneindoline was treated as the preceding preparation. There was obtained a good yield of 6',8'-dinitro-1,3,3-trimethylindoline-2-spiro-2'-benzopyran (VIII), dark green crystals that charred at 270°. The compound evidently exists in a dipolar form, giving a violet solution in cold diphenyl ether that becomes blue when it is heated.

*Anal.* Calcd. for  $C_{19}H_{17}N_3O_5$ : C, 62.1; H, 4.6. Found: C, 62.3; H, 5.0.

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## A Synthesis of Isonicotinic Acid by Halogen-Metal Exchange and Its Application to the Preparation of Isonicotinic- $C^{14}$ Acid Hydrazide<sup>1</sup>

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The recent discovery of the tuberculostatic activity of isonicotinic acid hydrazide made it desirable to prepare the  $C^{14}$ -labeled drug for metabolic studies. Labeling isonicotinic acid in the ring, by any of the many known preparative routes, would require a long costly synthesis involving many steps with radioactive material. The halogen-metal interconversion reaction which has wide application<sup>2</sup> and which was used to prepare nicotinic-

(1) Work done under the auspices of the A.E.C.

(2) R. G. Jones and Henry Gilman, "Organic Reactions," Vol. VI, John Wiley and Sons, Inc., New York, N. Y., 1951, p. 330.

$C^{14}$  acid,<sup>3</sup> provided a synthesis of the desired compound in good yield with carboxyl labeling in the final step.

The very unstable intermediate, 4-bromopyridine, was first adequately described by Wibaut, *et al.*<sup>4</sup> Because of poor yields, these workers abandoned the preparation by halogenation of 4-hydroxypyridine in favor of the Sandmeyer reaction with 4-nitroaminopyridine. However, yields were reported to be small and no figures were given. Two runs, in this Laboratory, by the latter procedure gave less than 10% yield. The Craig<sup>5</sup> modification of the Sandmeyer procedure for  $\alpha$ -substituted pyridines does not appear to have been applied to 4-aminopyridine. By adapting this procedure and Wibaut's method of isolation, 4-bromopyridine was prepared in yields of 85-95%. The dry compound in ether solution, at concentrations of 0.3-0.4 millimole per ml., is satisfactorily stable for use, but storage in an ice-box is recommended. The hydrochloride was prepared and found to be quite stable, and 4-bromopyridine is readily regenerated quantitatively as needed.

### Experimental<sup>6</sup>

**4-Aminopyridine.**—The compound was prepared by two methods.<sup>7</sup> (a) The Hofmann reaction with isonicotinamide gave crude product (m.p. 155-159°) in 55-62% yield, isolated by continuous benzene extraction. (b) The method of Koenigs and Greiner<sup>8,4</sup> gave crude product (m.p. 155-158°) in yields of 70-78% from 4-pyridylpyridinium dichloride. A steel bomb, tested to 2000 p.s.i., was used in the ammonolysis. Recrystallization from water, alcohol, benzene or chloroform gave pure material melting at 159-160°.

**4-Bromopyridine.**—To 24 ml. of redistilled 48% hydrobromic acid, in a 100-ml. flask cooled in ice, was added 4.00 g. (0.0425 mole) of 4-aminopyridine. To this cold, stirred solution, 20.4 g. (0.128 mole) of bromine was added dropwise over a period of 10 minutes. The resulting slurry of perbromide was then diazotized at -10° by adding 7.57 g. (0.107 mole) of sodium nitrite in 11 ml. of water over a period of 30 minutes. After an additional 10-minute period of stirring, the bath was removed and the vigorously stirred reaction mixture was allowed to warm slowly to room temperature while a vigorous evolution of brown fumes ensued. The flask and contents were again chilled in the ice-bath and the stirred mixture was decolorized by adding saturated sodium sulfite solution. The mixture was then transferred to a 500-ml. flask with an equal volume of water and the resulting solution was heated under reflux for 7-10 minutes to expel sulfur dioxide. After making the cooled solution strongly basic, the product was submitted to steam distillation, without delay, and collected in a small separatory funnel. The colorless oil (4.5 ml., 6.539 g., 97.3%) was quickly separated and diluted with 100 ml. of absolute ether.<sup>9</sup> The solution was dried for at least 24 hours by stirring with powdered "Drierite" and then separated by gravity filtration through a large sintered glass funnel protected by "Drierite" guard tubes.

The solution was assayed for 4-bromopyridine by pipetting a 2-ml. aliquot into 20 ml. of dry ether saturated with mercuric chloride. The precipitate ( $C_5H_4NBr \cdot HgCl_2$ , m.p. 273° dec.) was washed with 2-3 ml. of ether and weighed,

(3) A. Murray, III, W. W. Foreman and W. Langham, *THIS JOURNAL*, **70**, 1037 (1948).

(4) J. P. Wibaut, J. Overhoff and H. Geldof, *Rec. trav. chim.*, **54**, 807 (1935).

(5) L. C. Craig, *THIS JOURNAL*, **56**, 232 (1934).

(6) All melting points are uncorrected.

(7) R. Camps, *Arch. Pharm.*, **240**, 345 (1902) [*Chem. Zentr.*, **73**, II, 647 (1902)]; D. G. Leis and B. C. Curran, *THIS JOURNAL*, **67**, 79 (1945).

(8) E. Koenigs and H. Greiner, *Ber.*, **64**, 1055 (1931).

(9) Unless the product is dispersed in solvent as soon as possible, it quickly decomposes to a yellow, ether-insoluble, water-soluble compound.

yield 95.3%. A solution stored in the refrigerator for one week was unchanged, while another was 17% decomposed after standing two days at room temperature.

The hydrochloride was prepared by saturating an ether solution of 4-bromopyridine with dry hydrogen chloride. The colorless, non-hygroscopic, crystalline compound melted with decomposition in a sealed capillary at 237–239°.

**Isonicotinic-C<sup>14</sup> Acid.**—The apparatus used was that described for the preparation of nicotinic-C<sup>14</sup> acid.<sup>3</sup> To a stirred solution of 5.12 millimoles of *n*-butyllithium in 25 ml. of ether cooled in a Dry Ice-acetone-bath was added, over a 5-minute period, 7.68 millimoles of 4-bromopyridine in 30 ml. of ether cooled to –50 to –40°. Two minutes later the reaction mixture was frozen in liquid nitrogen, evacuated, thawed in the Dry Ice-acetone-bath and carbonated with 2.56 millimoles of C<sup>14</sup>O<sub>2</sub> (0.5064 g. BaC<sup>14</sup>O<sub>3</sub>, 14.9 millicuries). The cold reaction mixture was hydrolyzed with 10 ml. of 6 *N* hydrochloric acid. The contents of the flask was made strongly basic with sodium hydroxide and extracted with ether for 24 hours, then made strongly acidic and re-extracted for four hours. The product was isolated by adjusting the aqueous phase to pH 3 and continuing the extraction four to five days. The yield of colorless product was 0.303 g., 96.0%.

Four trial preparations gave 83.5–96.5% yields of material melting with decomposition within the range 301–304° (authentic purified specimen m.p. 305° dec.). A mixed m.p. with the authentic specimen showed no depression. Another preparation gave 93.2% yield when carbonated with excess carbon dioxide.

**Isonicotinic-C<sup>14</sup> Acid Hydrazide.**—Isonicotinyl-C<sup>14</sup> chloride hydrochloride was made by treating the acid with 2 ml. of purified thionyl chloride, heating under reflux for 15 minutes and distillation of the excess reagent under reduced pressure. The residual solid mass was converted to the ester hydrochloride (solid) by reaction with 4 ml. of absolute ethanol, heating under reflux for one hour and distillation of the solvent under reduced pressure. The ester was isolated by treatment with excess sodium bicarbonate solution and extraction with ether (three hours). After evaporation of the solvent, the ester was heated under reflux for 30 hours with 0.23 g. of 85% hydrazine hydrate solution in 10 ml. of absolute ethanol. Treatment with "Norit" and evaporation to dryness gave 0.328 g. of crude product (93.4% yield from the acid). Purification by vacuum sublimation (130°, 0.01 mm.) and recrystallization from *n*-butyl alcohol yielded 0.260 g. of colorless needles, m.p. 166–168° (authentic purified specimen, m.p. 168–169.5°). The specific activity was 5.80 millicuries per millimole.

Four trial preparations gave crude material, m.p. 165–168°, in yields of 91.6–99.0% from pure isonicotinic acid. Another experiment gave a quantitative yield (m.p. 166–169°) from pure isonicotinic acid ethyl ester.

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## The Instability of Grignard Reagents from $\gamma$ -Bromopropyl Ethers

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In an attempt to prepare  $\gamma$ -ethoxypropyl 11-bromohendecyl ketone, the supposed di-( $\gamma$ -ethoxypropyl)-cadmium was treated with 11-bromohendecanoyl chloride. The reaction product isolated was found to be ethyl 11-bromohendecanoate. This result was unexpected in view of the fact that the Grignard reagent from  $\gamma$ -ethoxypropyl bromide has been employed numerous times with no apparent difficulty.

A brief investigation indicated that  $\gamma$ -ethoxypropylmagnesium bromide possesses a relatively

(1) Abstracted in part from a thesis submitted by M. S. Cohen to the Graduate College of the University of Missouri, 1952, in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

low order of thermal stability. When an ether solution of this Grignard reagent was distilled to a low volume, the residue in the flask underwent a vigorous decomposition to give cyclopropane and apparently magnesium bromide ethoxide. In another experiment, benzene was added to the ether solution of the Grignard reagent and decomposition took place gradually, with the evolution of cyclopropane, as the ether was removed by distillation and the temperature of the residue approached about 75°. Anhydrous cadmium chloride was added to the reaction mixture, but only a very small additional amount of cyclopropane was obtained.

A mixture of phenyl 11-bromohendecanoate, phenol and cyclopropane was isolated when a reaction mixture, which was thought to contain di-( $\gamma$ -phenoxypropyl)-cadmium was caused to react with 11-bromohendecanoyl chloride. The latter results are in agreement with the work of Paul<sup>2</sup> who has shown that  $\gamma$ -phenoxypropyl iodide is degraded by magnesium to a phenolate, 1,6-diphenoxyhexane and cyclopropane.

### Experimental<sup>3</sup>

**Reaction of 11-Bromohendecanoyl Chloride with the Supposed Di-( $\gamma$ -ethoxypropyl)-cadmium.**—A Grignard reagent was prepared from 10 g. (0.06 mole) of  $\gamma$ -ethoxypropyl bromide, 1.44 g. (0.06 gram atom) of magnesium turnings and 35 ml. of anhydrous ether. After the magnesium had disappeared, 6.4 g. (0.035 mole) of anhydrous cadmium chloride was added and the reaction mixture was heated to reflux for 45 minutes. The ether was removed by distillation and replaced with dry benzene. A solution of 15.3 g. (0.054 mole) of 11-bromohendecanoyl chloride in 25 ml. of dry benzene was added and the mixture was refluxed for 45 minutes. After cooling to room temperature, it was decomposed in the usual manner and the organic layer was washed, dried over anhydrous sodium sulfate and concentrated. The residual oil was distilled to give 6.3 g. (40% based on the acid chloride) of ethyl 11-bromohendecanoate, b.p. 144–145° (0.5 mm.), *n*<sub>D</sub><sup>20</sup> 1.4627. Bowman<sup>4</sup> has recorded a boiling point of 118–119° (0.15 mm.) for this ester. We have prepared the material, in relation to other work, and have obtained the following physical constants: b.p. 157–160° (3 mm.), *n*<sub>D</sub><sup>20</sup> 1.4610, *d*<sub>4</sub><sup>20</sup> 1.120.

The ester (6.3 g.) was saponified by refluxing it for 10 hours with a 10% aqueous alcohol solution of sodium hydroxide. There was obtained 3.7 g. (85% of 11-hydroxyhendecanoic acid which melted at 65–66° after two crystallizations from benzene, lit.<sup>5</sup> m.p. 65.5–66°.

**Decomposition Studies on  $\gamma$ -Ethoxypropylmagnesium Bromide.**<sup>6</sup>—The Grignard reagent was prepared from 25.3 g. (0.15 mole) of  $\gamma$ -ethoxypropyl bromide, 3.72 g. (0.155 gram atom) of magnesium turnings and 80 ml. of anhydrous ether in a flask which was equipped with a condenser carrying a trap for the removal of solvents. The top of the condenser was attached to a gas trap which was cooled by means of a Dry Ice-acetone-bath.

The reaction mixture was stirred and refluxed for one hour after the bromide had been added. Then the ether was distilled slowly until 70 ml. had been collected; at this point the residue decomposed rapidly and filled the flask with a white, porous solid. A total of 13 ml. of liquid was condensed in the cooling trap. This was allowed to vaporize, at about 0°, through a water cooled condenser and 8 ml. of a low-boiling distillate was collected in a Dry Ice-acetone cooled receiver.

A sample of the porous mass was ground, suspended in ether and treated with 3,5-dinitrobenzoyl chloride. After an initial slightly exothermic reaction, the mixture was refluxed for 30 minutes. There was obtained a white crystal-

(2) R. Paul, *Ann. chim.*, **18**, 311 (1932).

(3) All melting points are uncorrected. The semimicro analyses were performed by Mr. P. D. Strickler.

(4) R. E. Bowman, *J. Chem. Soc.*, 177 (1950).

(5) W. H. Lycan and R. Adams, *This Journal*, **51**, 625 (1929).

(6) This experiment was carried out by Mr. F. E. Martin.