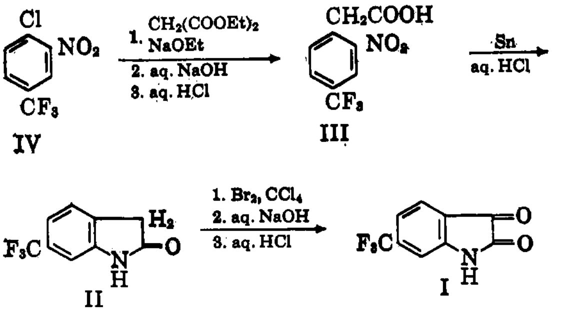
substituted α,α,α-trifluoro-*m*-toluidines, such as the Reissert, Stollé, and Martinet reactions,[3] failed in our laboratory to produce the desired isatin also.

The 6-trifluoromethylisatin was prepared finally from the corresponding oxindole II which was synthesized by the Baeyer method, *i.e.*, by acid reduction of the appropriately substituted (2-nitrophenyl)acetic acid III. This substituted acetic acid, in turn, was prepared by alkylation of ethyl malonate with 4-chloro-3-nitrobenzotrifluoride (IV), followed by hydrolysis and decarboxylation of the resulting malonate.



Although the position of the trifluoromethyl group is established by the route of synthesis, the 6-trifluoromethylisatin was, nevertheless, oxidized with hydrogen peroxide to the known 2-amino-α,α,α-trifluoro-4-toluic acid.

Experimental[6]

(2-Nitro-α,α,α-trifluoro-4-tolyl)acetic Acid (III).—A 5.4-g. sample (0.24 g.-atom) of sodium was dissolved in 200 cc. of absolute ethanol and 38.7 g. (0.24 mole) of ethyl malonate was added, followed by 51.3 g. (0.23 mole) of 4-chloro-3-nitrobenzotrifluoride (Aldrich Chemical Co.). The solution was refluxed for 2.5 hr. and the solvent was then removed under vacuum. Ethanol, 300 cc., and 300 g. of 10 wt. % aqueous potassium hydroxide solution were added to the residue and the solution was refluxed for 1.5 hr., then concentrated under vacuum to a volume of 240 cc. The concentrate was diluted with 350 cc. of water and made strongly acid with *ca.* 3 *N* hydrochloric acid, precipitating the product. The yield of crude acid, m.p. 137–142°, was about 60%. After recrystallization once from 12 cc./g. 1:2 isopropyl alcohol–water and twice from large volumes of water, 12.2 g. acid was obtained, m.p. 145–146.5°.

Anal. Calcd. for $C_9H_6F_3NO_4$: C, 43.39; H, 2.43; N, 5.62; F, 22.89. Found: C, 43.35; H, 2.27; N, 5.47; F, 23.14.

6-Trifluoromethyloxindole (II).—A 3.3-g. sample (0.013 mole) of (2-nitro-α,α,α-trifluoro-4-tolyl)acetic acid was suspended in 24 cc. of *ca.* 9 *N* hydrochloric acid and the mixture was heated to boiling. External heat was removed and 7.5 g. (0.063 g.-atom) of mossy tin was added at a rate that was rapid enough to keep the reaction mixture hot; 8 cc. of *ca.* 9 *N* hydrochloric acid was added when one-third of the tin was in the flask and another 8 cc. of hydrochloric acid was added when two-thirds of the tin had been added. After the addition of the tin was complete, the reaction mixture was refluxed for 45 min. and the oxindole was filtered off under suction while the mixture was still hot. A second crop of product was obtained by diluting the filtrate with 100 cc. of water. Both crops of product had the same melting range, 175–181°, and the combined yield of crude product was over 90%. A 1.2-g. yield of 6-trifluoromethyloxindole, m.p. 186–188°, was obtained after two recrystallizations from 17 cc./g. benzene.

Anal. Calcd. for $C_9H_6F_3NO$: C, 53.74; H, 3.01; N, 6.96; F, 28.34. Found: C, 53.56; H, 2.89; N, 6.97; F, 28.17.

6-Trifluoromethylisatin (I).—A solution of 2.5 g. (0.012 mole) of 6-trifluoromethyloxindole in 40 cc. of carbon tetrachloride was heated to reflux and treated with a solution of 4.1 g. (0.026 mole) of bromine in 27.5 cc. of carbon tetrachloride over 15 min. The reaction mixture was refluxed for 15 min. after the addition of bromine, then 5 cc. of ethanol was added dropwise. The carbon tetrachloride was removed under vacuum and the residue was refluxed for 30 min. with 40 cc. of ethanol and 40 g. of 5 wt. % aqueous sodium hydroxide solution; 40 cc. of this solution was distilled at atmospheric pressure and the remainder was diluted with 50 cc. of water. A little decolorizing carbon was added to the diluted solution and it was boiled briefly and filtered. The filtrate was acidified with hydrochloric acid, precipitating an oil which crystallized partially when allowed to stand for a few hours in an ice bath. The aqueous suspension of the solid material was decanted from the uncrystallized oil and the solid was then filtered off under suction. The yield of crude product was 1.0 g. (38%), m.p. 184–191°. Recrystallization from 60 cc. of 1:5 petroleum ether (b.p. 30–60°)-benzene yielded 0.4 g. of 6-trifluoromethylisatin, m.p. 192–194.5°.

Anal. Calcd. for $C_9H_4F_3NO_2$: C, 50.25; H, 1.87; N, 6.51; F, 26.50. Found: C, 50.12; H, 1.66; N, 6.52; F, 26.81.

Oxidation of 6-Trifluoromethylisatin.—A 0.32-g. sample (1.5 mmoles) of 6-trifluoromethylisatin was dissolved in 7 cc. of 2 wt. % aqueous sodium hydroxide solution, 4 cc. of 1.5 wt. % aqueous hydrogen peroxide solution (3.1 mmoles) was added, and the solution was heated to about 80°. The reaction mixture was allowed to cool and was then acidified with 5 cc. of *ca.* 6 *N* sulfuric acid, precipitating a solid. The suspension was heated to boiling, redissolving the solid, and filtered to remove some tarry material. The solid that precipitated on cooling was separated by filtration. Recrystallization from 35 cc. of water yielded 0.11 g. of 2-amino-α,α,α-trifluoro-4-toluic acid, m.p. 173–176°. A melting point of 172–174° is given in the literature for this compound.[7]

Anal. Calcd. for $C_8H_6F_3NO_2$: C, 46.84; H, 2.95; N, 6.83; F, 27.79. Found: C, 47.21; H, 2.53; N, 6.92; F, 27.88.

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[6] All melting points are uncorrected. Microanalyses were perfomed by the Galbraith Laboratories. Inc., Knoxville 21, Tenn.

(7) A. Mooradian and C. M. Suter, *J. Am. Chem. Soc.*, **71**, 3507 (1949).

Betaine Formation during Hydrogenation of Methyl Isonicotinate[1a]

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The need for quantities of various isonipecotate esters and their derivatives led us to investigate the catalytic hydrogenation of the readily available isonicotinate esters.

The hydrogenation of methyl isonicotinate (I) in absolute methanol with Raney nickel catalyst yields anomalous results. The reaction was carried out at 175–200° and 1000–1500 lb./in.^{2} hydrogen. When the filtered and concentrated reaction mixture was treated with acetone, a solid precipitate II was formed in very high yield. None of the expected product, methyl N-methylisonipecotate, was formed.

Known reactions of betaines are consistent with the structure of 1,1-dimethyl-4-carboxypiperidine betaine for II. Thus II yields the expected 1,1-dimethyl-4-carboxypiperidinium chloride (III) with hydrochloric acid and 1,1-dimethyl-4-carbomethoxypiperidinium iodide (IV) with methyl iodide. Dried II decomposes at 259–260°. By careful heating of II in a distilling flask, a high yield of a liquid is obtained.

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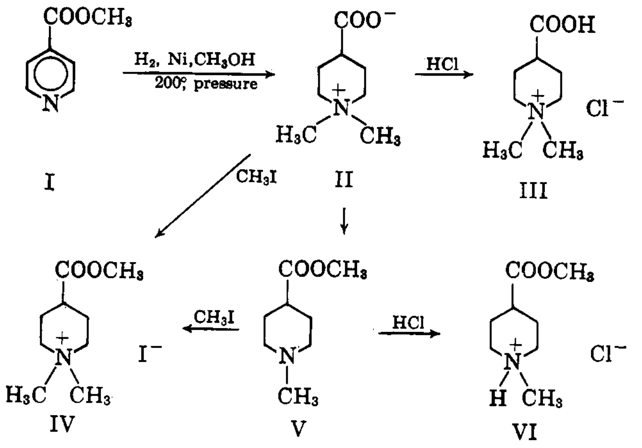
(1) (a) This work was supported by University of North Carolina Research Council Grant No. 324 ALU 1(292); (b) an Undergraduate Research Participant supported by National Science Foundation Grant No. 22866 and the North Carolina Pharmaceutical Research Foundation.

This liquid must be methyl N-methylisonipecotate (V) since V forms a methyl iodide identical with that from both an authentic sample of methyl N-methylisonipecotate and the solid betaine II. Likewise V yields a hydrochloride different from the hydrochloride of II.



While the attack of amines by alcohol solvents in hydrogenation reactions is a well established reaction,[2,3] the alkylation of nitrogen with an alkyl fragment from an ester is less expected. The ready alkylation of simple piperidines with alcohols ar 200° by Raney nickel has been reported.[3] The formation of alkyl N-alkylisonipecotates would be expected to be the predominant reaction under the conditions we have described as leading to a betaine. The formation of ethyl N-ethylnipecotate has been reported from the reduction of ethyl nicotinate with Raney nickel in ethanol.[2] No mention was made in the report of betaine formation.

Some generality of betaine formation from amino esters is suggested by the reduction of I to II in ethanol which gave a solid, very impure, but with the solubility characteristics of II. The presence of methanol is thus not essential to betaine formation, although methanol has been reported to be an inhibitor of some hydrogenation reactions.[4] Also, the reported hydrogenation of methyl isonicotinate in methanol with ruthenium proceeds nicely at 100—150° to yield methyl isonipecotate,[5] while our results indicate that if the temperature is allowed to rise to 200° some betaine formation is observed.

Several possible mechanisms are being investigated as well as the applications of this reaction.

Experimental[6]

1,1-Dimethyl-4-carboxypiperidine Betaine (II).—Methyl isonicotinate (137.1 g., 1.0 mole) was dissolved in 100 ml. of absolute methanol and treated with about 10 g. of W-2 Raney nickel and hydrogen at 1000–1500 lb./in.^{2} pressure in an Aminco shaking pressure apparatus. Hydrogen uptake began at 150°; the temperature was maintained at 175–200° until hydrogen absorption ceased (6 hr.). The cooled reaction mixture was filtered free of catalyst and evaporated in a rotating vacuum evaporator to a pasty mass. Treatment of this mass with acetone resulted in a copious precipitate which when filtered and dried in a vacuum desiccator weighed 137.8 g. (87.5%). The material is extremely hygroscopic. After drying over phosphorus pentoxide for 48 hr., the material decomposed at 259–260°.

Elemental analyses were completely irreproducible.

1,1-Dimethyl-4-carboxypiperidinium Chloride (III).—This compound was prepared by dissolving II in concentrated aqueous hydrochloric acid, evaporating first in a stream of air and then in a vacuum desiccator over potassium hydroxide and finally recrystallizing from ethanol–ether. The pure material melted at 244–245°.

Anal. Calcd. for $C_8H_{16}NO_2Cl$: C, 49.61; H, 8.33; N, 7.23. Found: C, 49.58; H, 8.12; N, 7.11.

Methyl N-Methylisonipecotate (V).—Crude II was heated in a distilling flask immersed in a silicone fluid bath at 270–280° whereupon the product slowly distilled. The distillate was dissolved in ether, dried with sodium sulfate, and redistilled to yield a clear, colorless oil boiling at 200–202°.

This material was also synthesized by the methylation of methyl isonipecotate with formaldehyde and formic acid according to the procedure used by Hanby and Rydon for the methylation of diethanolamine.[7] The product, after working up in the usual manner, boiled at 200–202° and displayed an infrared spectrum superimposable on that of the same compound prepared by the thermal rearrangement of II.

Anal. Calcd. for $C_8H_{15}NO_2$: C, 61.12; H, 9.62; N, 8.61. Found: C, 60.69; H, 9.61; N, 8.96.

Methyl Isonipecotate.—This ester was prepared according to the procedure of Freifelder and Stone.[5]

1,1-Dimethyl-4-carbomethoxypiperidinium Iodide (IV).—This compound was prepared according to identical procedures from II or V (V in turn prepared by two methods). The starting material was dissolved in anhydrous methanol and excess methyl iodide added. The solution was then evaporated to dryness in a vacuum and the solid recrystallized from ethanol–ether: from II, m.p. 145–148°; from V by way of authentic methyl isonipecotate, m.p. 149–150°; from V by way of rearrangement of II, m.p. 150–152°; lit.[8] m.p., 147–148°. The infrared spectra of all three samples described are superimposable. The compound prepared from V by way of rearrangement of II was analyzed.

Anal. Calcd. for $C_9H_{18}NO_2I$: C, 36.30; H, 6.04; N, 4.67. Found: C, 36.34; H, 5.92; N, 4.60.

1-Methyl-4-carbomethoxypiperidine Hydrochloride (VI).—Hydrogen chloride was slowly bubbled through a cold solution of V (prepared by rearrangement of II) in anhydrous ether. The precipitated salt was filtered and recrystallized from ethanol–ether to yield colorless crystals melting at 193–195°, lit.[9] m.p. 193°.

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(2) H. Adkins, L. F. Kuick, M. Farlow, and B. Wojcik, *J. Am. Chem. Soc.*, **56**, 2425 (1934).

(3) C. F. Winans, and H. Adkins, *ibid.*, **54**, 306 (1932).

(4) K. Folkers, and H. Adkins, *ibid.*, **54**, 1145 (1932).

(5) M. Freifelder, and G. R. Stone, *J. Org. Chem.*, **26**, 3805 (1961).

(6) Infrared spectra were obtained on a Perkin-Elmer Infracord. Melting points were uncorrected and were obtained in sealed capillaries in a Mel-Temp apparatus. Microanalyses were performed by Alfred Bernhardt, Max-Planck Institute für Kohlenforschung, Mulheim, Ruhr, Germany.

(7) W. E. Hanby, and H. N. Rydon, *J. Chem. Soc.*, 513 (1947).

(8) R. E. Lyle, E. F. Perlowski, H. J. Troscianiec, and G. G. Lyle, *J. Org. Chem.*, **20**, 1761 (1955).

(9) Beilstein, "Handbuch der Chemie," Vol. XXII (1), 1935, p. 486.

The Reaction of Calcium with Pyridine and Its Methyl Derivatives[1]

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We have found that calcium reacts with pyridine and its methyl derivatives to form deeply colored, highly reactive, nonvolatile, insoluble, thermally unstable products. Although these properties prevented purification and thoroughly adequate characterization, we

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(1) Taken from the dissertation submitted to the University of Iowa by A. R. U. in partial fulfillment of the requirements for a Ph.D. degree, 1963.

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