TABLE II

YIELDS AND PHYSICAL PROPERTIES OF PRODUCTS

				Carbon, %		Hydrogen, %	
Compound	Yield, %	B.p. (mm.), °C.	$n^{20}\mathrm{D}$	Calcd.	Found	Calcd.	Found
$C_6H_5COCF_3$[a]	50	151–152	1.4583				
m-$CH_3C_6H_4COCH_3$[b]	42	100–101 (15)	1.5296				
m-$CH_3C_6H_4COCF_3$	51	79 (24)	1.4576	57.45	57.75	3.72	3.89
p-$CH_3C_6H_4COCF_3$[c]	28	57 (5)	1.4661				
m-$CF_3C_6H_4COCH_3$[d]	66	85 (10)	1.4621				
p-$CF_3C_6H_4COCH_3$[e]	52	79–80 (8)	1.4604	57.45	57.17	3.72	3.78
m-$CH_3C_6H_4CHOHCH_3$[f]	79	104–105 (12)	1.5235				
p-$CH_3C_6H_4CHOHCH_3$[g]	84	108 (14)	1.5212				
$C_6H_5CHOHCF_3$[h,i]	93	87–88 (16)	1.4610	48.65	48.38	2.43	2.59
m-$CH_3C_6H_4CHOHCF_3$[j]	53	98 (14)	1.4641	56.84	56.81	4.74	4.81
p-$CH_3C_6H_4CHOHCF_3$[k]	84	102 (15)	1.4629	56.84	56.91	4.74	4.74
m-$CF_3C_6H_4CHOHCH_3$[l]	89	105–107 (19)	1.4585				
p-$CF_3C_6H_4CHOHCH_3$	80	106–107 (18)	1.4585	56.84	56.73	4.74	4.92
m-$CH_3C_6H_4C(CH_3)OHC_2H_5$	79	103–104 (8)	1.5189	80.48	80.80	9.76	9.87
p-$CH_3C_6H_4(CH_3)OHC_2H_5$[m]	82	109–110 (10)	1.5179				
$C_6H_5C(CF_3)OHC_2H_5$	70	91–92 (15)	1.4671	58.82	59.02	5.39	5.15
m-$CH_3C_6H_4C(CF_3)OHC_2H_5$	80	101 (13)	1.4710	60.55	60.80	5.96	6.20
p-$CH_3C_6H_4(CF_3)OHC_2H_5$	73	105–106 (15)	1.4714	60.55	60.55	5.96	6.11
m-$CF_3C_6H_4C(CH_3)OHC_2H_5$[n]	96	107 (16)	1.4629	60.55	60.29	5.96	5.95
p-$CF_3C_6H_4C(CH_3)OHC_2H_5$[o]	90	113–114 (18)	1.4632				

[a] Levine and Dishart[10] report b.p. 150–152°. [b] K. Y. Auwers, *Ann.*, **408**, 243 (1951), reports b.p. 109° (12 mm.), $n^{20}\mathrm{D}$ 1.5306. [c] J. H. Simmons, W. T. Black, R. F. Clark [*J. Am. Chem. Soc.*, **75**, 5621 (1953)] report b.p. 179.2°, $n^{25}\mathrm{D}$ 1.4664. [d] W. J. Humphlett, M. J. Weiss, and C. R. Hauser [*ibid.*, **70**, 4020 (1948)] report b.p. 198–200°. [e] W. T. Caldwell and G. C. Schweiker [*ibid.*, **75**, 5884 (1953)] report b.p. 81–84° (9 mm.). [f] K. v. Auwers and H. Kolligs [*Ber.*, **55**, 40 (1922)] report b.p. 108–109° (12 mm.), $n^{15}\mathrm{D}$ 1.5226. [g] A. Klages and R. Keil [*ibid.*, **36**, 1635 (1903)] report b.p. 120° (19 mm.). [h] E. T. McBee, O. R. Pierce, and J. F. Higgins [*J. Am. Chem. Soc.*, **74**, 1736 (1952)] report b.p. 64–65 (5 mm.), $n^{20}\mathrm{D}$ 1.4610. [i] Calcd. for 3,5-dinitrobenzoate, m.p. 119–120°: C, 48.65; H, 2.43; N, 7.57. Found: C, 48.38; H, 2.59; N, 7.78. [j] Calcd.: F, 30.00. Found: F, 29.72. [k] Calcd.: F, 30.00. Found. F, 29.89. [l] C. S. Marvel, C. G. Overberger, R. E. Allen, and J. F. Saunders [*J. Am. Chem. Soc.*, **68**, 736 (1946)] report b.p. 100–102° (17 mm.), $n^{20}\mathrm{D}$ 1.4585. [m] H. Rupe and J. Burgin [*Ber.*, **44**, 1219 (1911)] report b.p. 108.5–109° (10 mm.). [n] Calcd.: F, 26.15. Found: F, 26.40. [o] Calcd. for 3,5-dinitrobenzoate, m.p. 92–93°: C, 52.43; H, 3.64. Found: C, 52.44, H, 3.45.

trifluoromethylacetophenone were prepared by reaction of the appropriate acid chlorides with ethoxymagnesiomalonic ester according to Bowman.[11] Though known, with the one exception, most ketones were prepared by different procedures from those reported; their physical properties are included in Table II.

General Procedure for Reaction of Phenyl Ketone with Ethylmagnesium Bromide.—The Grignard reagent was prepared in the usual fashion from ethyl bromide (21.8 g., 0.2 mole) and sublimed magnesium turnings (6.8 g., 0.2 g.-atom) in 100 ml. of anhydrous ether. The solution was filtered under a nitrogen pressure into a dry reaction flask. The ketone (0.1 mole) was dissolved in 20 ml. of ether and added dropwise over a 1-hr. period at 0°. The solution was stirred for 6 hr. while warming to room temperature. Hydrolysis was effected with 100 ml. of saturated ammonium chloride. The organic layer was separated, dried over anhydrous sodium sulfate, and the ether distilled. The residue was subjected to v.p.c. analysis and vacuum distilled to give the products. The v.p.c. analysis was carried out on a Perkin-Elmer Model 154-B fractometer in conjunction with a Leeds and Northrup Speedomaz type G recorder. Helium was used as the carrier gas maintained at 18 lb./in.^{2} at a flow rate of 42 ml. per min. at a temperature of 179°, using a Carbowax 1500 column. Components were identified by comparison with the retention times of authentic samples. Areas under the peaks were measured with a polar planimeter.

General Procedure for Independent Preparation of the Secondary Alcohols.—The ketone (0.116 mole) was added dropwise to a solution of lithium aluminum hydride (1.52 g., 0.04 mole) in 100 ml. of anhydrous ether. The solution was stirred and the addition regulated to produce gentle reflux. Ten minutes after the addition was completed, water was added slowly and the reaction mixture poured onto 100 g. of ice in 400 ml. of 10% sulfuric acid. The organic layer was separated and the aqueous layer extracted with six 20-ml. portions of ether, whereupon the combined ether solution was dried over anhydrous potassium carbonate and distilled to give the products.

General Procedure for Independent Preparation of the Tertiary Alcohols.—A solution of the aryl Grignard was prepared from the aryl halide (0.2 mole) and sublimed magnesium turnings (0.2 g.-atom) in 150 ml. of anhydrous ether. The remaining procedure was identical with that described previously for the general Grignard reaction, using 2-butanone or 1,1,1-trifluoro-2-butanone (0.1 mole), depending on the alcohol desired. The products were distilled.

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(11) R. E. Bowman, *J. Chem. Soc.*, 322 (1950).

The Preparation of 6-Trifluoromethylisatin

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The 4-, 5-, and 7-trifluoromethylisatins have been prepared[1] by the cyclization in acid of α,α,α-trifluoro-2-oximinoacetotoluidides (Sandmeyer isatin synthesis[2,3]). The 6-trifluoromethylisatin (I), a valuable intermediate for the preparation of 7-trifluoromethylquinoline derivatives, has not been described to date. The Sandmeyer method yields none of the 6-isomer,[1,4,5] and other acid-catalyzed intramolecular cyclizations of N-

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(1) P. M. Maginnity and C. A. Gaulin, *J. Am. Chem. Soc.*, **73**, 3579 (1951).

(2) T. Sandmeyer, *Helv. Chim. Acta*, **2**, 234 (1919).

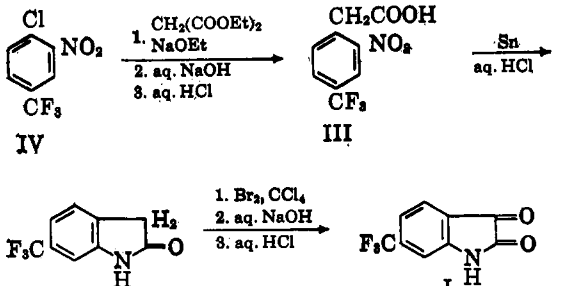
(3) Reviewed briefly by P. L. Julian, E. W. Meyer, and H. C. Printy, "Heterocyclic Compounds," Vol. 3, R. C. Elderfield, Ed., John Wiley and Sons, Inc., New York, N. Y., 1952, pp. 207–210.

(4) B. R. Baker, R. E. Schaub, J. P. Joseph, F. J. McEvoy, and J. H. Williams, *J. Org. Chem.*, **17**, 164 (1952).

(5) P. W. Sadler, *ibid.*, **21**, 169 (1956).

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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