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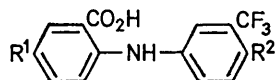
PERKIN TRANSACTIONS I Organic and Bio-organic Chemistry

Syntheses of Flufenamic Acid Metabolites I and II and Other *N*-Aryl-anthranilic Acids

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The syntheses of two metabolites of flufenamic acid, 5-hydroxy-*N*-($\alpha\alpha\alpha$ -trifluoro-*m*-tolyl)anthranilic acid and *N*-(4-hydroxy- $\alpha\alpha\alpha$ -trifluoro-*m*-tolyl)anthranilic acid, are described. Syntheses of a number of other *N*-aryl-anthranilic acids, mono-, di-, tri-, and tetra-substituted in the aryl ring lacking a carboxy-group, and with substituents in both aryl rings, are reported.

Two metabolites (I and II) [(1) and (2)] of the anti-inflammatory compound¹ *N*-($\alpha\alpha\alpha$ -trifluoro-*m*-tolyl)anthranilic acid (flufenamic acid) (3), have been isolated from the urine of animals and patients treated with the compound, by Dr. A. Glazko and his colleagues, Parke, Davis, Ann Arbor.² We now report the syntheses of these two acids.



- (1) R¹ = OH, R² = H
(2) R¹ = H, R² = OH
(3) R¹ = R² = H

Ethyl 2-chloro-5-hydroxybenzoate (prepared from 2-chloro-5-methoxytoluene by way of 2-chloro-5-methoxybenzoic acid and 2-chloro-5-hydroxybenzoic acid³) was converted into ethyl 5-benzyloxy-2-chlorobenzoate by the action of benzyl chloride and sodium ethoxide in ethanol solution. The ester was directly hydrolysed to give 2-chloro-5-benzyloxybenzoic acid,⁴ which was condensed, in the presence of cupric ion, with $\alpha\alpha\alpha$ -trifluoro-*m*-toluidine to give 5-(benzyloxy)-*N*-($\alpha\alpha\alpha$ -tri-

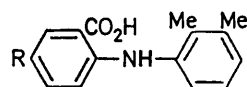
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‡ For details of Supplementary Publications, see *J. Chem. Soc. (A)*, 1970, Issue No. 20 (Notice to Authors No. 7).

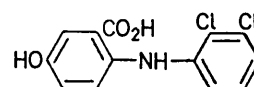
¹ C. V. Winder, B. Serrano, E. M. Jones, and M. L. McPhee, *Arthr. and Rheum.*, 1963, **6**, 36.

² F. W. Short, personal communication; cf. 'Fenamates in Medicine,' ed. P. Hume Kendall, Bailliere, Tindall, and Cassell, London, 1966, p. 30.

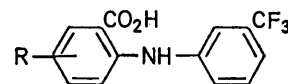
fluoro-*m*-tolyl)anthranilic acid. Catalytic hydrogenation of the latter compound yielded 5-hydroxy-*N*-($\alpha\alpha\alpha$ -trifluoro-*m*-tolyl)anthranilic acid (1). Details of the preparation and physical constants *etc.* of the related compounds (4)–(6) which were similarly prepared, and of the methoxy-acids (7; R = 5-OMe and 3-OMe) are given in Supplementary Publication No. SUP 20487 (61 pp., 2 microfiches).‡



- (4) R = PhCH₂O
(5) R = HO



(6)



(7)

2-Chloro- $\alpha\alpha\alpha$ -trifluoro-5-nitrotoluene⁵ was transformed into 2-benzyloxy- $\alpha\alpha\alpha$ -trifluoro-5-nitrotoluene by reaction with benzyl alcohol either in dimethylformamide⁶ at 160° or dimethyl sulphoxide⁶ at 100°, in the presence

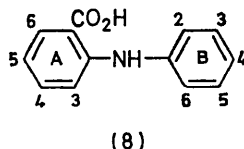
³ D. P. Spalding, E. C. Chapin, and H. S. Mosher, *J. Org. Chem.*, 1954, **19**, 357 and references therein.

⁴ C. D. Nenitzescu and D. Raileanu, *Chem. Ber.*, 1958, **91**, 1141.

⁵ I. G. Farbenind A.-G., Fr.P. 745,293 (*Chem. Abs.*, 1933, **27**, 4414).

⁶ G. C. Finger and C. W. Kruse, *J. Amer. Chem. Soc.*, 1956, **78**, 6034.

of anhydrous potassium fluoride.⁷ (We confirmed the finding of Fillar and Novar⁸ that the reaction of 2-chloro- $\alpha\alpha\alpha$ -trifluoro-5-nitrotoluene with sodium benzyloxide yields bis-4-nitro-2-trifluoromethylphenyl ether; for this reaction we used 1 equiv. of sodium benzyloxide in boiling benzene.) Hydrolysis of the nitro-compound



Ring B

- | | | |
|-------|---|--|
| (i) | 1. 2-SO ₂ NH-C ₆ H ₄ -CO ₂ H- <i>o</i> | 35. 2,4-Cl ₂ -3-NH ₂ |
| | 2. 2-H ₂ N-SO ₂ | 36. 2,4-Cl ₂ -3-N(COMe) ₂ |
| | 3. 4-H ₂ N-SO ₂ | 37. 2,4-Cl ₂ -3-NMe ₂ |
| | 4. 2-HO-S | 38. 3,6-Cl ₂ -2-NH ₂ |
| | 5. 2-MeHN | 39. 2,5-Cl ₂ -4-NH ₂ |
| | 6. 2-Me ₂ N | 40. 2,5-Cl ₂ -4-NHMe |
| | 7. 4-HO-(CH ₂) ₂ -N(Et) | 41. 3,5-Cl ₂ -4-Me |
| | | 42. 3,5-Cl ₂ -2-NO ₂ |
| | | 43. 3,5-Cl ₂ -2-NH ₂ |
| (ii) | 1. 2-NO ₂ -3-CF ₃ | 44. 2-Cl-6-Me-5-NO ₂ |
| | 2. 2-NO ₂ -5-CF ₃ | 45. 2-Cl-6-Me-5-NH ₂ |
| | 3. 2-NH ₂ -3-CF ₃ | 46. 2-Cl-6-Me-5-NMe ₂ |
| | 4. 2-Me-3-NMe ₂ | 47. 2-Cl-6-Me-3-NMe ₂ |
| | 5. 2-Me-3-CO-NMe ₂ | 48. 2-Cl-4-Me-3-MeO |
| | 6. 2-Me-3-CH ₂ -NMe ₂ | 49. 2-Cl-6-Me-3-CN |
| | 7. 2-Me-3-CH ₂ -OMe | 50. 2-Cl-6-Me-5-NEt ₂ |
| | 8. 2,6-(NO ₂) ₂ | 51. 3-Cl-6-Me-2-NO ₂ |
| | | 52. 3-Cl-6-Me-2-NH ₂ |
| | | 53. 3-Cl-6-Me-3-NH-CO-(CH ₂) ₂ -Me |
| (iii) | 1. 2,6-Me ₂ -3-Br | 54. 2-NO ₂ -5,6-CH ₂ CH-CH ₂ CH |
| | 2. 2,6-Me ₂ -3-CN | 55. 2-NH ₂ -5,6-CH ₂ CH-CH ₂ CH |
| | 3. 2,6-Me ₂ -3-CO ₂ H | 56. 2-Cl-5,6-CH ₂ CH-CH ₂ CH |
| | 4. 2,6-Me ₂ -3-CO ₂ Et | 57. 2-Cl-5,6-(CH ₂) ₂ |
| | 5. 2,6-Me ₂ -3-CO-NH ₂ | 58. 2-MeO-5,6-CH ₂ CH-CH ₂ CH |
| | 6. 2,6-Me ₂ -3-CO-NMe ₂ | 59. 2,5-(MeO) ₂ -4-Br |
| | 7. 2,6-Me ₂ -3-CH ₂ CH ₃ | 60. 2,3-Cl ₂ -6-NO ₂ |
| | 8. 2,6-Me ₂ -3-CH ₂ CH | 61. 2,3-Cl ₂ -6-NH ₂ |
| | 9. 2,6-Me ₂ -3-COPh | 62. 2,3-Cl ₂ -6-NHMe |
| | 10. 2,6-Me ₂ -3-CH(OH)Ph | |
| | 11. 2,6-Me ₂ -3-CH ₂ Ph | (iv) |
| | 12. 2,6-Me ₂ -3-CO-C ₆ H ₄ -Me- <i>p</i> | 1. 2,3,4,5-Cl ₄ |
| | 13. 2,6-Me ₂ -3-CH ₂ -C ₆ H ₄ -Me- <i>p</i> | 2. 2,3,5-Cl ₃ -4-Me |
| | 14. 2,6-Me ₂ -3-COPr | 3. 2,3-Cl ₂ -5-Me-4-NHAc |
| | 15. 2,6-Me ₂ -3-CO-CMe ₂ | 4. 2,3-Cl ₂ -5-Me-4-NH ₂ |
| | 16. 2,6-Me ₂ -3-CH(OH)-CMe ₂ | 5. 2,3-Cl ₂ -5-Me-NMe ₂ |
| | 17. 2,6-Me ₂ -3-NO ₂ | 6. 2,3-Cl ₂ -6-Me-4-NHAc |
| | 18. 2,6-Me ₂ -3-NH ₂ | 7. 2,3-Cl ₂ -6-Me-4-NH ₂ |
| | 19. 2,6-Me ₂ -3-NMe ₂ | 8. 2,3-Cl ₂ -6-Me-4-NMe ₂ |
| | 20. 2,6-Me ₂ -3-CH ₂ -NMe ₂ | 9. 2-Cl-3,6-Me ₂ -4-NHAc |
| | 21. 2,6-Me ₂ -3-N(COMe)Ph | 10. 2-Cl-3,6-Me ₂ -4-NH ₂ |
| | 22. 2,6-Me ₂ -3-NHPh | 11. 2-Cl-3,6-Me ₂ -4-NMe ₂ |
| | 23. 2,5-Me ₂ -3-Cl | 12. 2-Cl-3,6-Me ₂ -4-NO ₂ |
| | 24. 2,5-Me ₂ -6-Cl | 13. 3-Cl-2,5-Me ₂ -4-NHAc |
| | 25. 2,5-Me ₂ -6-NO ₂ | 14. 3-Cl-2,5-Me ₂ -4-NH ₂ |
| | 26. 2,5-Me ₂ -6-NH ₂ | 15. 3-Cl-2,5-Me ₂ -4-NMe ₂ |
| | 27. 2,4-Me ₂ -3-NO ₂ | 16. 4-Br-2-Cl-3,6-Me ₂ |
| | 28. 2,5-Cl ₂ -4-Br | 17. 3,4-Br ₂ -2,6-Me ₂ |
| | 29. 2,6-Cl ₂ -3-NH ₂ | 18. 3-Cl-4-OH-2,5-Me ₂ |
| | 30. 2,6-Cl ₂ -3-NMe ₂ | 19. 4-Br-2-Cl-5,6-CH ₂ CH-CH ₂ CH |
| | 31. 2,6-Cl ₂ -3-CO-NMe ₂ | 20. 2,3-Me ₂ -5,6-CH ₂ CH-CH ₂ CH |
| | 32. 2,6-Cl ₂ -3-CO-C ₆ H ₄ -Me- <i>p</i> | 21. 2,3,5,6-F ₄ |
| | 33. 2,3-Cl ₂ -4-OH | 22. 4-Br-2,6-Cl ₂ -3-NO ₂ |
| | 34. 2,3-Cl ₂ -5-Me | |

Ring A

(v)

Ring B

- | | |
|----------------------|---|
| 1. 5-NH ₂ | 3-CF ₃ |
| 2. 5-NO ₂ | 3-CF ₃ |
| 3. 5-NH ₂ | 3-CF ₃ |
| 4. 3-NO ₂ | 3-CF ₃ |
| 5. 5-F | 2,3-Me ₂ |
| 6. 5-NO ₂ | 2,3-Me ₂ |
| 7. 5-NO ₂ | 2,3-Cl ₂ |
| 8. 5-NO ₂ | 2-Me, 3-Cl |
| 9. 5-Br | 4-Br-2,5-(MeO) ₂ |
| 10. 5-Br | 2,6-Me ₂ -3-CO-CHBr ₂ |

with refluxing 70% sulphuric acid gave 5-nitrosalicylic acid, thus confirming the proposed orientation. 2-Benzyloxy- $\alpha\alpha\alpha$ -trifluoro-5-nitrotoluene was reduced to the 5-amino-compound either catalytically, or, better, with iron filings in acetic acid. Condensation of 5-amino-2-benzyloxy- $\alpha\alpha\alpha$ -trifluorotoluene with potassium *o*-bromobenzoate gave *N*-(4-benzyloxy- $\alpha\alpha\alpha$ -trifluoro-*m*-tolyl)anthranilic acid, which was catalytically debenzyl-

⁷ Cf. N. N. Vorozhtsov and G. G. Yakobson, *J. Chem. Chem. (U.S.S.R.)*, 1957, **27**, 1741.

⁸ R. Fillar and H. Novar, *J. Org. Chem.*, 1961, **26**, 2707.

ated to yield *N*-($\alpha\alpha\alpha$ -trifluoro-4-hydroxy-*m*-tolyl)anthranilic acid (2).

The discovery of the anti-inflammatory properties of *N*-($\alpha\alpha\alpha$ -trifluoro-*m*-tolyl)- and *N*-(2,3-xylyl)anthranilic acids⁹ prompted the preparation of a number of other substituted *N*-arylanthranilic acids (8) for pharmacological screening. The substituents are listed in the Table.

Most of the compounds were prepared by means of copper- or copper salt-catalysed condensation reactions between the appropriate anilines and the appropriate *o*-halogenobenzoic acids (as the potassium salts). In the case of category (v) the appropriately substituted known *o*-halogenobenzoic acids were employed [except for (v, 10)]. The remainder of the compounds were prepared by copper- or copper salt-catalysed condensation between potassium anthranilate and the appropriate aryl halides, or by reactions with other *N*-arylanthranilic acids, or by a rearrangement reaction. Details of the preparation and physical constants *etc.*, of the compounds listed in the Table are given in Supplementary Publication No. SUP 20487 (see before) as are similar details for compounds (9)—(22) which were also prepared during this work.

EXPERIMENTAL

Ethyl 2-Chloro-5-hydroxybenzoate.—2-Chloro-5-methoxytoluene (545 g) was refluxed in water (7.5 l) into which carbon dioxide was passed. Potassium permanganate (200 g) was added, followed by further amounts (5 × 100 g) at 0.5 h intervals. The mixture was refluxed until the colour of permanganate had disappeared. Unchanged 2-chloro-5-methoxytoluene (440 g) was removed during distillation of some (3 l) of the mixture. The manganese dioxide was filtered off and the filtrate acidified with concentrated hydrochloric acid to give 2-chloro-5-methoxybenzoic acid (74 g), m.p. 171—174° (lit.,⁴ 170—171°). The methoxy-acid (49.5 g) in 48% hydrobromic acid (150 ml) and acetic acid (150 ml) containing phenol (1.5 g) was refluxed for 3 h. The solution was evaporated to dryness. A sample of the residue crystallised from benzene-ethyl acetate had m.p. 180—182° (Found: C, 48.8; H, 2.7. Calc. for C₇H₅ClO₃: C, 48.7; H, 2.9%). The remainder of the residue was refluxed in benzene (400 ml) with absolute ethanol (200 ml) through a 12 cm Fenske column into a Dean-Stark head for 7.5 h (residual hydrogen bromide as esterification catalyst). The benzene solution was washed with saturated hydrogen carbonate solution and water, dried (Na₂SO₄), and evaporated, and the residue was distilled to give *ethyl 2-chloro-5-hydroxybenzoate* as a pale pink oil, b.p. 138—140° at 0.4 mmHg, *n*_D²⁵ 1.5474 (Found: C, 54.7; H, 4.4. C₉H₉ClO₃ requires C, 54.0; H, 4.5%).

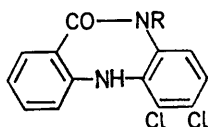
2-Chloro-5-benzyloxybenzoic Acid.⁹—The foregoing ester (41 g) was added to a solution of sodium (4.6 g) in ethanol (120 ml). Benzyl chloride (26 g) was then added and the mixture refluxed for 1 h. Then 10*N*-sodium hydroxide (30 ml) was added and the mixture was refluxed for 0.5 h, diluted with water (250 ml), and distilled until the b.p. reached 100° (the distillate at 100° was clear). The solution was cooled to 50°, acidified with concentrated hydrochloric

⁹ C. V. Winder, L. Scotti, R. A. Scherrer, E. M. Jones, and F. W. Short, *J. Pharmacol.*, 1962, **138**, 405.

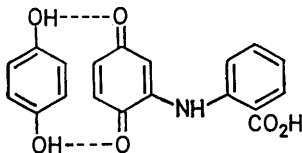
acid (40 ml), then cooled. The precipitate (51 g) was filtered off, washed with water, and dried. A sample crystallised from light petroleum (b.p. 60—80°)—benzene as *needles*, m.p. 124.5—125.5° (Found: C, 64.7; H, 3.8. $C_{14}H_{11}ClO_3$ requires C, 64.0; H, 4.2. Calc. for $C_{14}H_{11}ClO_3 \cdot 0.1C_6H_6$: C, 64.8; H, 3.55%).

5-(*Benzyloxy*)-*N*-($\alpha\alpha$ -trifluoro-*m*-tolyl)anthranilic Acid.—5-Benzyloxy-2-chlorobenzoic acid (55.9 g) in diethylene glycol dimethyl ether (420 ml) with anhydrous potassium carbonate (15.45 g), $\alpha\alpha$ -trifluoro-*m*-toluidine (36.06 g),

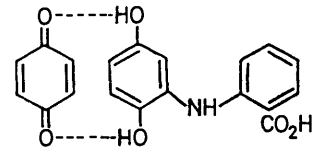
mmHg in 87 min; theory 1581 ml). Filtration, evaporation, and crystallisation from aqueous ethanol gave the product (15.93 g), m.p. 174—175°. This was purified by passage through sodium hydrogen carbonate solution and crystallisation of the acid obtained (by acidification of the latter) from 1 : 1 ethanol-water (200 ml) containing a little 2*N*-hydrochloric acid to give the 5-*hydroxy-acid* (12.4 g) as yellow needles, m.p. 176—178° (decomp.) (Found: C, 55.3; H, 3.1; N, 4.6. $C_{14}H_{10}F_3NO_3 \cdot 0.5H_2O$ requires C, 54.9; H, 3.6; N, 4.7. Found for sample dried at 100°



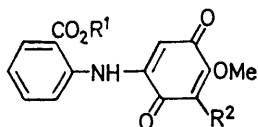
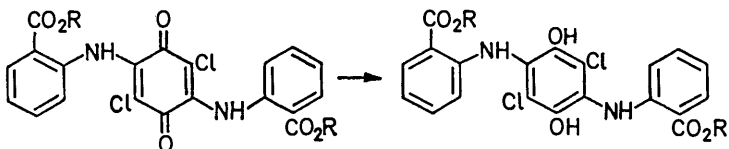
(9) R = H or Me



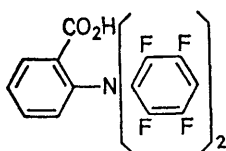
(10)



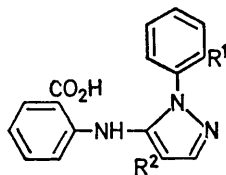
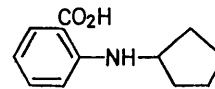
(11)

(12) R¹ = H, R² = OMe(13) R¹ = H or Me, R² = H

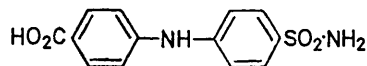
(14) R = H and Me



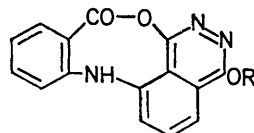
(15)

(16) R¹ = H, R² = CN(17) R¹ = Cl, R² = CN(18) R¹ = H, R² = CO-NH₂

(19)



(20)



(21) R = H (22) R = Ac

copper(II) bromide (1.68 g), and *N*-ethylmorpholine (25.76 g) were stirred and heated at 130—140° under nitrogen for 4.5 h. The mixture was poured into water (840 ml) and acidified with concentrated hydrochloric acid (41 ml). The supernatant liquor was decanted from the resulting gum, which was treated with methanol (100 ml) and left overnight to yield a solid (25.3 g), m.p. 164—169°. This was filtered off, washed with methanol, and dried. Crystallisation from aqueous methanol gave the *benzyloxy-acid* as yellow needles, m.p. 172—173° (Found: C, 65.5; H, 4.3; N, 3.7. $C_{21}H_{16}F_3NO_3$ requires C, 65.1; H, 4.1; N, 3.6%).

5-*Hydroxy-N*-($\alpha\alpha$ -trifluoro-*m*-tolyl)anthranilic Acid (1).—5-Benzyloxy-*N*-($\alpha\alpha$ -trifluoro-*m*-tolyl)anthranilic acid (25.28 g) in ethanol (500 ml) was hydrogenated over 10% palladised charcoal (2 g) (uptake 1675 ml at 23.5° and 764

and 1 mmHg: C, 56.55; H, 3.4. $C_{14}H_{10}F_3NO_3$ requires C, 56.65; H, 3.4%), ν_{max} (Nujol) 3295m, 3185m, 2710, 2602, 1699m, 1667s, 1614m, 1589s, and 1528s cm^{-1} , λ_{max} (EtOH-0.01*N*-HCl) 222, 289, and 370 nm (ϵ 6570, 2800 and 5640).

2-*Benzyloxy- $\alpha\alpha$ -trifluoro-5-nitrotoluene*.—Benzyl alcohol (5 ml) and 2-chloro- $\alpha\alpha$ -trifluoro-5-nitrotoluene (11.25 g) were mixed and treated with potassium fluoride (5.8 g; dried at 200° for 1.5 h), and dimethyl sulphoxide (100 ml) was added. The mixture was stirred at 100° for 6.5 h, cooled, poured into water (500 ml), and set aside overnight. The solid (4.33 g, 29%), m.p. 109—112° was filtered off, washed with water, and dried. A sample (1 g) crystallised from light petroleum (b.p. 60—80°) to give the *benzyloxytoluene* (0.88 g), m.p. 111—113°, as jagged laths (Found: C, 56.8; H, 3.45; F, 19.3; N, 4.7. $C_{14}H_9F_3NO_3$ requires C, 56.75; H, 3.0; F, 19.25; N, 4.7%), ν_{max} (Nujol) 1621,

1600 (Ar), and 1524 cm^{-1} (NO_2). The yield was 26% when 2-chloro- $\alpha\alpha\alpha$ -trifluoro-5-nitrotoluene (0.1 mol) and benzyl alcohol (0.3 mol) were heated at 160° for 3.75 h in dimethylformamide (27.5 ml). A sample (0.1 g) of the compound was refluxed in 70% sulphuric acid (10 ml) for 3 h; the mixture was cooled and filtered and the residue was recrystallised from methylated spirits to give 5-nitrosalicylic acid, m.p. and mixed m.p. 225–230°, showing a purple colour in ethanol when treated with iron(III) chloride.

5-Amino-2-benzyloxy- $\alpha\alpha\alpha$ -trifluorotoluene.— 2-Benzyloxy- $\alpha\alpha\alpha$ -trifluoro-5-nitrotoluene (7 g) in acetic acid (50 ml) and water (10 ml) was stirred at 90–95° and treated with iron filings (7 g) in portions during 1 hr. Water (10 ml) was added 0.75 h after the start of the reaction. The mixture was stirred for a further 0.25 h, treated with water (150 ml), and extracted with ether (5×100 ml). The extract was washed with saturated sodium hydrogen carbonate solution and saturated sodium chloride solution, dried (Na_2SO_4), and evaporated to leave an oil which yielded a solid hydrochloride (5.01 g) when treated with 2N-hydrochloric acid. This was recrystallised from 96% ethanol–2N-hydrochloric acid (5:1; 120 ml) to give 5-amino-2-benzyloxy- $\alpha\alpha\alpha$ -trifluorotoluene hydrochloride (3.66 g, 52%), m.p. 198–199° (decomp.) as tan plates (Found: C, 54.25; H, 3.9; N, 4.6. $\text{C}_{14}\text{H}_{12}\text{F}_3\text{NO}\cdot\text{HCl}$ requires C, 54.7; H, 4.3; N, 4.6%), ν_{max} (Nujol) 2602, 2015 (NH_3^+), 736, 698 (monosubstituted benzene), 833, and 814 cm^{-1} (1,2,4-trisubstituted benzene). Hydrogenation of the nitro-compound (0.59 g) in ethanol (40 ml) over 10% platinum-charcoal (50 mg) (uptake 158 ml at 19.5° and 760 mmHg in 46 min; theory 144 ml) and crystallisation of the product from ethanol–2N-hydrochloric acid gave the same hydrochloride (0.145 g), m.p. and mixed m.p. 198–199° (decomp.).

N-(4-Benzyloxy- $\alpha\alpha\alpha$ -trifluoro-*m*-tolyl)anthranilic Acid.— The foregoing hydrochloride (3.035 g), potassium *o*-bromobenzoate (3.585 g), potassium carbonate (0.69 g), *N*-ethylmorpholine (0.65 ml), and copper(II) bromide (0.3 g) in diethylene glycol dimethyl ether were stirred at 140–160° for 2 h [after 50 min further *N*-ethylmorpholine (0.6 ml) was added]. The mixture was poured into water (250 ml) and acidified with concentrated hydrochloric acid. The resulting gum solidified on treatment with a little ethanol. The product was filtered off, washed with water, and dried

to give a dark solid (3.72 g), m.p. 174–180° (decomp.). A sample (0.5 g) was dissolved in boiling sodium hydrogen carbonate solution (4.5%; 150 ml) (charcoal); filtration and acidification gave a solid which was twice crystallised from aqueous ethanol and then from light petroleum (b.p. 60–80°)–ethanol to give the 4-benzyloxy-compound (80 mg) as grey micro-plates, m.p. 190–192° (decomp.) (Found: C, 65.5; H, 4.3; N, 3.4. $\text{C}_{21}\text{H}_{16}\text{F}_3\text{NO}_3$ requires C, 65.1; H, 4.1; N, 3.6%). In a subsequent larger-scale preparation it was necessary to chromatograph the product (7.66 g) on silica (benzene eluant) to obtain 5.97 g of material and remove a persistent purple colour.

N-(4-Hydroxy- $\alpha\alpha\alpha$ -trifluoro-*m*-tolyl)anthranilic Acid (2).— The foregoing 4-benzyloxy-acid (3 g) in ethanol (100 ml) was hydrogenated over 10% palladium-charcoal (1.4 g) (uptake after 53 min 48 ml). Further catalyst (1 g) and acetic acid (10 ml), were added; total uptake 167 ml at 17° and 754 mmHg in 4 h (theory 186.2 ml). The catalyst and solvent were removed to yield material which was twice crystallised from aqueous ethanol and then from benzene to give the hydroxy-acid (2) (0.45 g), m.p. 172–173°, as pale yellow rhombs [Found (sample dried at 61° and 1 mmHg): C, 57.5; H, 3.3; F, 19.0; N, 4.7. $\text{C}_{14}\text{H}_{10}\text{F}_3\text{NO}_3$ requires C, 56.6; H, 3.4; F, 19.2; N, 4.7. $\text{C}_{14}\text{H}_{10}\text{F}_3\text{NO}_3\cdot 0.1\text{C}_6\text{H}_6$ requires C, 57.5; H, 3.5; F, 18.7; N, 4.5%), ν_{max} (Nujol) 3380, 3320 (OH and NH), 1663 (CO_2H), 1633, 1603, and 1571 cm^{-1} , λ_{max} (0.01N-HCl in EtOH) 212, 219, 236sh, 283, and 350 nm (ϵ 25,400, 24,300, 9390, 12,700, and 6980), λ_{max} (0.01N-NaOH in EtOH) 215, 261, 288, and 337 nm (ϵ 20,600, 7860, and 4770).

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