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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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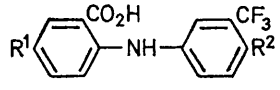
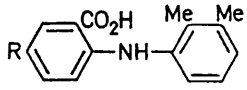
The syntheses of two metabolites of flufenamic acid, 5-hydroxy-*N*-(ααα-trifluoro-*m*-tolyl)anthranilic acid and *N*-(4-hydroxy-ααα-trifluoro-*m*-tolyl)anthranilic acid, are described. Syntheses of a number of other *N*-aryl-anthranilic acids, mono-, di-, tri-, and tetra-substituted in the aryl ring 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 compound [1] *N*-(ααα-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.

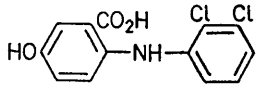


(1) R^1 = OH, R^2 = H
(2) R^1 = H, R^2 = OH
(3) R^1 = R^2 = H

Ethyl 2-chloro-5-hydroxybenzoate (prepared from 2-chloro-5-methoxytoluene by way of 2-chloro-5-methoxybenzoic acid and 2-chloro-5-hydroxybenzoic acid [3]) 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 ααα-trifluoro-*m*-toluidine to give 5-(benzyloxy)-*N*-(ααα-trifluoro-*m*-tolyl)anthranilic acid. Catalytic hydrogenation of the latter compound yielded 5-hydroxy-*N*-(ααα-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 = $PhCH_2O$
(5) R = HO



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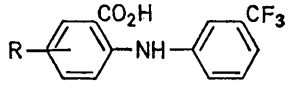

(7)

2-Chloro-ααα-trifluoro-5-nitrotoluene [5] was transformed into 2-benzyloxy-ααα-trifluoro-5-nitrotoluene by reaction with benzyl alcohol either in dimethylformamide [6] at 160° or dimethyl sulphoxide [6] at 100°, in the presence

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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.

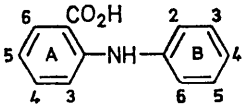
[3] D. P. Spalding, E. C. Chapin, and H. S. Mosher, *J. Org. Chem.*, 1954, **19**, 357 and references therein.

[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 Novar [8] that the reaction of 2-chloro-ααα-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



(8)

Ring B

(i) 1. 2-SO_3·NH·C_6H_4·CO_2H-*o*
2. 2-H_2N·SO_2
3. 4-H_2N·SO_2
4. 2-HO_2S
5. 2-MeHN
6. 2-Me_2N
7. 4-HO·$[CH_2]_2$·N(Et)

(ii) 1. 2-NO_2-3-CF_3
2. 2-NO_2-5-CF_3
3. 2-NH_2-3-CF_3
4. 2-Me-3-NMe_2
5. 2-Me-3-CO·NMe_2
6. 2-Me-3-CH_2·NMe_2
7. 2-Me-3-CH_2·OMe
8. 2,6-$(NO_2)_2$

(iii) 1. 2,6-Me_2-3-Br
2. 2,6-Me_2-3-CN
3. 2,6-Me_2-3-CO_2H
4. 2,6-Me_2-3-CO_2Et
5. 2,6-Me_2-3-$CO·NH_2$
6. 2,6-Me_2-3-CO·NMe_2
7. 2,6-Me_2-3-CH:CH_2
8. 2,6-Me_2-C:CH
9. 2,6-Me_2-3-COPh
10. 2,6-Me_2-3-CH(OH)Ph
11. 2,6-Me_2-3-CH_2Ph
12. 2,6-Me_2-3-CO·C_6H_4Me-*p*
13. 2,6-Me_2-3-CH_2·C_6H_4Me-*p*
14. 2,6-Me_2-3-COPr^n
15. 2,6-Me_2-3-CO·CMe$_3$
16. 2,6-Me_2-3-CH(OH)·CMe$_3$
17. 2,6-Me_2-3-NO_2
18. 2,6-Me_2-3-NH_2
19. 2,6-Me_2-3-NMe_2
20. 2,6-Me_2-3-CH_2·NMe_2
21. 2,6-Me_2-3-N(COMe)Ph
22. 2,6-Me_2-3-NHPh
23. 2,5-Me_2-3-Cl
24. 2,5-Me_2-6-Cl
25. 2,5-Me_2-6-NO_2
26. 2,5-Me_2-6-NH_2
27. 2,4-Me_2-3-NO_2
28. 2,5-Cl_2-4-Br
29. 2,6-Cl_2-3-NH_2
30. 2,6-Cl_2-3-NMe_2
31. 2,6-Cl_2-3-CO·NMe_2
32. 2,6-Cl_2-3-CO·C_6H_4Me-*p*
33. 2,3-Cl_2-4-OH
34. 2,3-Cl_2-5-Me
35. 2,4-Cl_2-3-NH_2
36. 2,4-Cl_2-3-N(COMe)$_2$
37. 2,4-Cl_2-3-NMe_2
38. 3,6-Cl_2-2-NH_2
39. 2,5-Cl_2-4-NH_2
40. 2,5-Cl_2-4-NHMe
41. 3,5-Cl_2-4-Me
42. 3,5-Cl_2-2-NO_2
43. 3,5-Cl_2-2-NH_2
44. 2-Cl-6-Me-5-NO_2
45. 2-Cl-6-Me-5-NH_2
46. 2-Cl-6-Me-5-NMe_2
47. 2-Cl-6-Me-3-NMe_2
48. 2-Cl-4-Me-3-MeO
49. 2-Cl-6-Me-3-CN
50. 2-Cl-6-Me-5-NEt_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·$[CH_2]_{16}$Me
54. 2-NO_2-5,6-CH:CH·CH:CH
55. 2-NH_2-5,6-CH:CH·CH:CH
56. 2-Cl-5,6-CH:CH·CH:CH
57. 2-Cl-5,6-$[CH_2]_4$
58. 2-MeO-5,6-CH:CH·CH:CH
59. 2,5-$(MeO)_2$-4-Br
60. 2,3-Cl_2-6-NO_2
61. 2,3-Cl_2-6-NH_2
62. 2,3-Cl_2-6-NHMe

(iv) 1. 2,3,4,5-Cl_4
2. 2,3,5-Cl_3-4-Me
3. 2,3-Cl_2-5-Me-4-NHAc
4. 2,3-Cl_2-5-Me-4-NH_2
5. 2,3-Cl_2-5-Me-NMe$_2$
6. 2,3-Cl_2-6-Me-4-NHAc
7. 2,3-Cl_2-6-Me-4-NH_2
8. 2,3-Cl_2-6-Me-4-NMe_2
9. 2-Cl-3,6-Me_2-4-NHAc
10. 2-Cl-3,6-Me_2-4-NH_2
11. 2-Cl-3,6-Me_2-4-NMe_2
12. 2-Cl-3,6-Me_2-4-NO_2
13. 3-Cl-2,5-Me_2-4-NHAc
14. 3-Cl-2,5-Me_2-4-NH_2
15. 3-Cl-2,5-Me_2-4-NMe_2
16. 4-Br-2-Cl-3,6-Me_2
17. 3,4-Br_2-2,6-Me_2
18. 3-Cl-4-OH-2,5-Me_2
19. 4-Br-2-Cl-5,6-CH:CH·CH:CH
20. 2,3-Me_2-5,6-CH:CH·CH:CH
21. 2,3,5,6-F_4
22. 4-Br-2,6-Cl_2-3-NO_2

	Ring A	Ring B
(v) 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	2,3-Me_2
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-ααα-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-ααα-trifluorotoluene with potassium *o*-bromobenzoate gave *N*-(4-benzyloxy-ααα-trifluoro-*m*-tolyl)anthranilic acid, which was catalytically debenzylated to yield *N*-(ααα-trifluoro-4-hydroxy-*m*-tolyl)anthranilic acid (2).

The discovery of the anti-inflammatory properties of *N*-(ααα-trifluoro-*m*-tolyl)- and *N*-(2,3-xylyl)anthranilic acids [9] 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

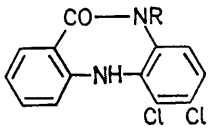
Ethyl 2-Chloro-5-hydroxybenzoate.—2-Chloro-5-methoxytoluene (545 g) was refluxed in water (7·5 l) into which carbon dioxide was passed. Potassium permanganate (200 g) was added, followed by further amounts (5 × 100 g) at 0·5 h intervals. The mixture was refluxed until the colour of permanganate had disappeared. 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 was crystallised from benzene–ethyl acetate had m.p. 180—182° (Found: C, 48·8; H, 2·7. Calc. for $C_7H_5ClO_3$: 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 (Na_2SO_4), 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_D^{22} 1·5474 (Found: C, 54·7; H, 4·4. $C_9H_9ClO_3$ 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 10N-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

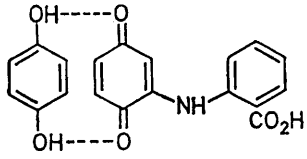
[7] *Cf.* N. N. Vorozhtsov and G. G. Yakobson, *J. Chem. Chem.* (*U.S.S.R.*), 1957, **27**, 1741.
[8] R. Fillar and H. Novar, *J. Org. Chem.*, 1961, **26**, 2707.
[9] C. V. Winder, L. Scotti, R. A. Scherrer, E. M. Jones, and F. W. Short, *J. Pharmacol.*, 1962, **138**, 405.

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 $C_{14}H_{11}ClO_3$,-$0{\cdot}1C_6H_6$: C, 64·8; H, 3·55%).

5-(*Benzyloxy*)-N-(*ααα-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), ααα-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 2N-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. $C_{14}H_{10}F_3NO_3{\cdot}0{\cdot}5H_2O$ requires C, 54·9; H, 3·6; N, 4·7. Found for sample dried at 100°



(9) R = H or Me



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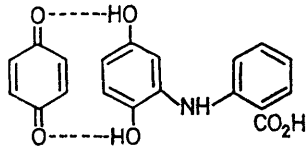

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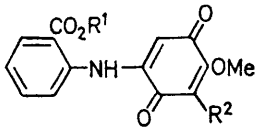
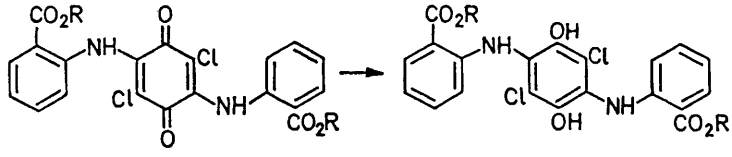
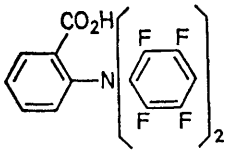


(12) R^1 = H, R^2 = OMe
(13) R^1 = H or Me, R^2 = H



(14) R = H and Me



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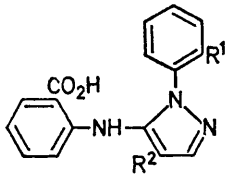
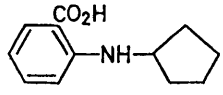


(16) R^1 = H, R^2 = CN
(17) R^1 = Cl, R^2 = CN
(18) R^1 = H, R^2 = $CO{\cdot}NH_2$



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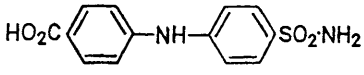

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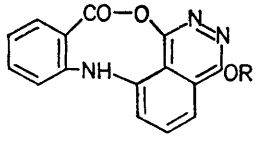

(21) R = H (22) R = Ac

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-(*ααα-trifluoro*-m-*tolyl*)*anthranilic Acid* (1).—5-Benzyloxy-*N*-(ααα-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%), $\nu_{max.}$ (Nujol) 3295m, 3185m, 2710, 2602, 1699m, 1667s, 1614m, 1589s, and 1528s cm^{-1}, $\lambda_{max.}$ (EtOH–0·01N-HCl) 222, 289, and 370 nm (ε 6570, 2800 and 5640).

2-*Benzyloxy-ααα-trifluoro-5-nitrotoluene*.—Benzyl alcohol (5 ml) and 2-chloro-ααα-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 *benzyl-oxytoluene* (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%), $\nu_{max.}$ (Nujol) 1621,

1600 (Ar), and 1524 cm^{-1} (NO_2). The yield was 26% when 2-chloro-ααα-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-ααα-trifluorotoluene.— 2-Benzyloxy-ααα-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-ααα-trifluorotoluene hydrochloride* (3·66 g, 52%), m.p. 198—199° (decomp.) as tan plates (Found: C, 54·25; H, 3·9; N, 4·6. $C_{14}H_{12}F_3NO,HCl$ requires C, 54·7; H, 4·3; N, 4·6%), $\nu_{max.}$ (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-ααα-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. $C_{21}H_{16}F_3NO_3$ 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-ααα-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. $C_{14}H_{10}F_3NO_3$ requires C, 56·6; H, 3·4; F, 19·2; N, 4·7. $C_{14}H_{10}F_3NO_3,0{\cdot}1C_6H_6$ requires C, 57·5; H, 3·5; F, 18·7; N, 4·5%], $\nu_{max.}$ (Nujol) 3380, 3320 (OH and NH), 1663 (CO_2H), 1633, 1603, and 1571 cm^{-1}, $\lambda_{max.}$ (0·01N-HCl in EtOH) 212, 219, 236sh, 283, and 350 nm (ε 25,400, 24,300, 9390, 12,700, and 6980), $\lambda_{max.}$ (0·01N-NaOH in EtOH) 215, 261, 288, and 337 nm (ε 20,600, 7860, and 4770).

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