64, 1021 (1969).
(12) I. D. Raacke, *Biochem. Biophys. Res. Commun.*, **43**, 168 (1971).
(13) K. C. Murdock and R. B. Angier, *J. Amer. Chem. Soc.*, **84**, 3758 (1962), and references cited therein.
(14) D. O. Spry and H. S. Aaron, *J. Org. Chem.*, **31**, 3838 (1966).

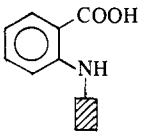
Acridan-4-carboxylic Acids and *N*-Aryl-2-amino-3-toluic Acids as Planar and Antiplanar Analogs of Antiinflammatory *N*-Arylanthranilic Acids

Tim R. Westby† and Charles F. Barfknecht*

Department of Medicinal Chemistry, College of Pharmacy, University of Iowa, Iowa City, Iowa 52240. *Received June 15, 1972*

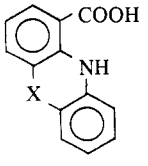
In an attempt to assess the importance of the relative conformation of the aryl rings of *N*-arylanthranilic acid and antiinflammatory agents, the title compounds were synthesized and tested for antiinflammatory activity. In the anti-uv erythema screen, antiplanar *N*-(2,3-xylyl)-2-amino-3-toluic acid had the same order of activity as planar 5,6-dimethylacridan-4-carboxylic acid while another antiplanar analog, *N*-(2,3,6-trimethylphenyl)anthranilic acid, was much more active than either. These results suggest that other factors are more important than relative conformation of the aryl rings in controlling antiinflammatory activity.

In 1964 Scherrer, Winder, and Short[1] proposed a hypothetical anti-uv-erythema and antibradykinin receptor designed to accommodate a number of classes of antiinflammatory agents including *N*-arylanthranilic acids. In order to fit this receptor, the two phenyl rings of *N*-arylanthranilic acids must assume an antiplanar conformation relative to each other as depicted in **1**.

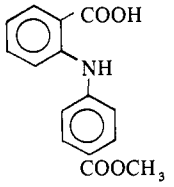


1

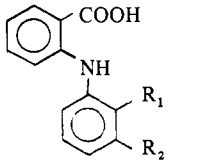
Several compounds which are closely related to *N*-arylanthranilic acids but which cannot exist in an antiplanar conformation have been shown to possess antiinflammatory activity. These include a phenothiazinecarboxylic acid **2**[2] and a phenoxazinecarboxylic acid **3**.[3] Also, many flexible *N*-arylanthranilic acids which are not restricted to an antiplanar conformation have antiinflammatory activity. Examples include *N*-(*p*-carbomethoxyphenyl)anthranilic acid (**4**),[4] mefenamic acid (**5a**),[5] and flufenamic acid (**5b**).[6]



2, X = S
3, X = O



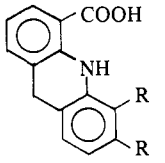
4



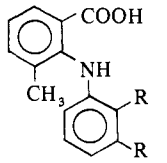
5a, $R_1 = R_2 = CH_3$
b, $R_1 = H$; $R_2 = CF_3$

In an attempt to further assess the importance of the relative conformation of the aryl rings of *N*-arylanthranilic acids for antiinflammatory activity, compounds **6–11** with aryl rings either coplanar or antiplanar were synthesized and tested for antiinflammatory activity.

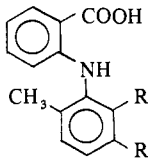
Chemistry. All compounds were prepared using a synthetic sequence which included the Chapman rearrangement.[7] The synthetic scheme to compounds **8**, **9**, and **11** is shown



6, R = CH_3
7, R = H



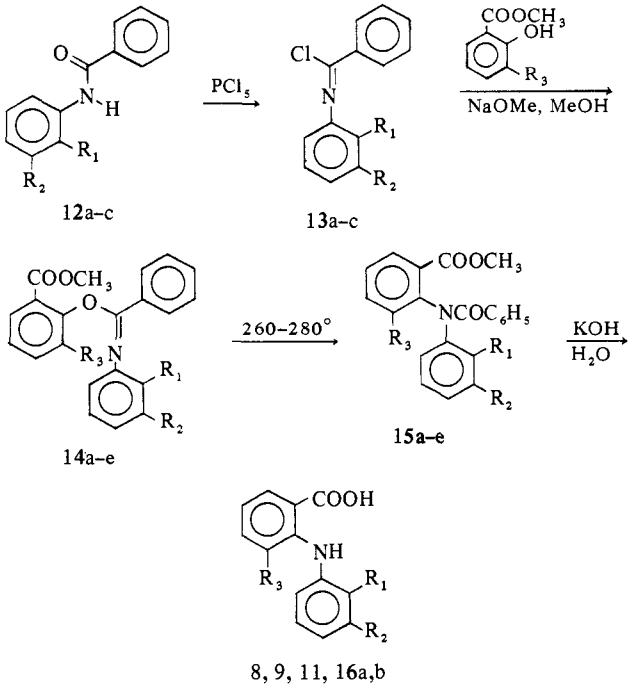
8, R = CH_3
9, R = H



10, R = CH_3
11, R = H

in Scheme I. Substituted benzanilides **12a–c** were prepared by the usual method.[8] *N*-Arylbenzimidoyl chlorides **13a–c** were prepared by treatment of the corresponding benzanilides with phosphorus pentachloride.[9] Aryl *N*-arylbenzimidates **14a–c** were prepared by condensation of the corresponding imino chloride with the appropriate phenol in a solution of sodium methoxide in methanol.[10] Chapman rearrangement[11] of these compounds to give substituted methyl *N*-benzoyl-*N*-arylanthranilates **15a–e** proceeded smoothly at 260–280°, despite the steric hindrance of the ortho substituents, as a result of steric acceleration due to

Scheme I



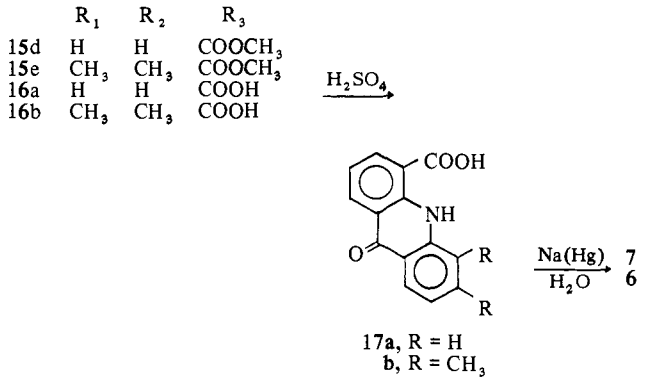
8, 9, 11, 16a,b

†Abstracted in part from the thesis submitted by T. R. W. in partial fulfillment of the requirements for the degree of Doctor of Philosophy, University of Iowa, 1971. Presented in part at Division of Medicinal Chemistry, 160th National Meeting of the American Chemical Society, Chicago, Ill., 1970, MEDI 048. NDEA Title IV Fellow, 1967–1970.

hindered rotation.[12] Hydrolysis of these compounds gave either desired final products **8**, **9**, and **11** or starting materials **16a-b** for the synthesis of acridans **6** and **7**. These hydrolysis reactions required quite severe conditions; refluxing aqueous alcoholic KOH cleaved only the esters. The *N*-benzoyl groups could be removed only by heating an aqueous KOH solution of the compounds in a stainless steel reaction bomb at 165° for 2-4 days.

Acridan-4-carboxylic acid (**7**) and 5,6-dimethylacridan-4-carboxylic acid (**6**) were prepared by the route shown in Scheme II. Cyclization of **16a** and **16b** with concentrated

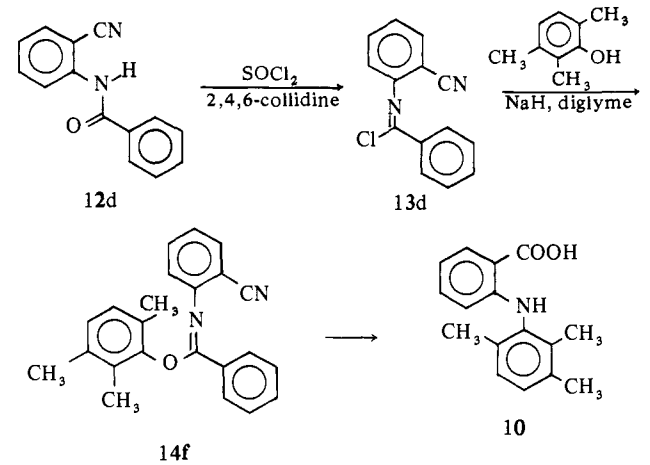
Scheme II



H_2SO_4 gave the corresponding acridones **17a** and **17b** in good yields.[13] These could also be obtained directly from **15d** and **15e**, respectively, also by treatment with concentrated H_2SO_4. Reduction of **17a** and **17b** to give **7** and **6** was accomplished with sodium amalgam in dilute aqueous sodium hydroxide.[14] Isolation and purification of the resulting acridans could be achieved only by working in an atmosphere of N_2 to avoid oxidation to the corresponding acridines. Without an N_2 atmosphere mixtures of the acridan and (presumably) the corresponding acridine were formed.

N-(2,3,6-Trimethylphenyl)anthranilic acid (**10**) was prepared as shown in Scheme III.‡ Compound **12d** was treated

Scheme III



with $SOCl_2$ in 2,4,6-collidine to give *N*-(*o*-cyanophenyl)-benzimidoyl chloride (**13d**).[15] Compound **14f** was prepared by treating a mixture of 2,3,6-trimethylphenol and NaH in diglyme with **13d**.[15] Chapman rearrangement of **14f** proceeded very slowly, even at 280-300°. The intermediate *N*-benzoyl-*N*-(2,3,6-trimethylphenyl)anthranilonitrile could not be isolated but instead the resulting reaction mixture was hydrolyzed with aqueous alcoholic KOH to give **10** in 31% overall yield.[15]

The conformation of the compounds in this study were determined from the ultraviolet and nuclear magnetic resonance spectra as shown in Table I. Two bands in the ultraviolet spectra are important; band a results from resonance interaction between the phenyl rings across the nitrogen as in diphenylamine; band b results from the anthranilic acid chromophore.[1] *N*-Phenylanthranilic acid, mefenamic acid (**5a**), and *N*-(*o*-tolyl)anthranilic acid (**11**) have absorption maxima similar to a combination of the two reference compounds. The uv spectra of **6** and **7** show a significant bathochromic shift of both bands relative to the reference compounds because coplanarity enhances the effect of the aryl rings. The anthranilic acid chromophore band b of compounds **8**, **9**, and **10** is not affected by the aryl ring in each case and band a is shifted to shorter wavelength; therefore, the rings of these compounds must be in an antiplanar conformation.

The nmr spectra of these compounds further substantiated their conformations (Table I). Yonomota, *et al.*,[16] have shown that chemical shifts of the amine protons of substituted anilines correlate with the pK_a values for the corresponding anilinium ion and that the chemical shifts are probably proportional to the π-electron density of the nitrogen atom. With reference to diphenylamine and anthranilic acid, both the carboxyl group and the second ring appear to decrease the electron density on the nitrogen atom as evidenced by the increase in chemical shift of the NH proton of **5a**, **11**, and *N*-phenylanthranilic acid. The decrease in electron density is even more pronounced in acridans **6** and **7**. However, the chemical shift of the NH protons of compounds **8**, **9**, and **10** is quite close to that of anthranilic acid, indicating that the aryl rings have little effect on the electron density of the nitrogen atoms and that the aryl rings of these compounds are indeed antiplanar.

The apparent pK_a of each compound was obtained from their relative neutralization curves; the pK_a' was not affected appreciably by relative conformation of the aryl rings.

Biological Activity. The antiinflammatory activity of the compounds was assessed by determining their ability to inhibit rat hind-paw carrageenin edema[17] and to delay the development of erythema induced by skin exposure to uv radiation in guinea pigs.[18] The results are shown in Table I. Compounds **7**, **9**, and **11** which are planar, antiplanar, and flexible, respectively, have similar activity, indicating that relative conformation of the aryl rings has no effect on antiinflammatory activity of the compounds in this series. However, compounds **6** and **8** which are coplanar and antiplanar, respectively, have similar activity while compound **10** which is also antiplanar is much more active. In addition, compound **8** is racemic. In the preparation of samples for biological evaluation, **6** and **7** may have been oxidized. The possibility that the activity observed may be due to oxidation products can not be excluded. These data suggest that factors other than conformation are more important in controlling antiinflammatory activity of these compounds and the importance of conformation cannot yet be ascribed.

Experimental Section

Melting points were determined in open-glass capillaries using a Thomas-Hoover Uni-Melt appratus and are corrected. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn., and by the Division of Medicinal Chemistry, University of

‡F. W. Short, Parke, Davis and Co., personal communication.

Table I

Compd	Uv_{max}, nm (EtOH) a	Uv_{max}, nm (EtOH) b	Nmr, ppm, NH (DMSO)	pK_a'	Rat paw edema, % inhibition at 50 mg/kg, $n = 5$	Uv erythema, ED_{50}, mg/kg, $n = 5$
Diphenylamine	284		8.10			
Anthranilic acid		333	8.55			
6	297	360	10.15	6.47	22	100
7	295	360	10.10	6.32	29	100
8	275	330	8.63	6.17	24	>100
9	275	330	8.66	6.20	25	>100
10	255	340	9.25	6.68		6
11	284	347	9.58	6.50	28[a]	>100
5a	282	349	9.50		50	10
N-Phenylanthranilic acid	287	349	9.70		54.3[b]	

[a]K. Sota, K. Noda, H. Maruyama, E. Fujihira, and M. Nakazawa, *Yakugaku Zasshi*, 89, 1392 (1969). [b]At 100 mg/kg; see footnote *a*.

Table II. Benzanilides

No.	R_1	R_2	Yield %	Mp, °C	Lit. mp
12a	H	H	62	161–162	162[a]
12b	CH_3	H	58	145–146	145–146[b]
12c	CH_3	CH_3	64	189–190	190[c]

[a]See ref 8. [b]C. D. Hodgman, Ed., "Handbook of Chemistry and Physics," 43rd ed, Chemical Rubber Publishing Co., Cleveland, Ohio, 1962, p 852. [c]M. Le Guyader and M. Le Demezet, *C. R. Acad. Sci.*, **259**, 4719 (1964).

Table III. *N*-Arylbenzimidoyl Chlorides

No.	R_1	R_2	Yield, %	Bp (mm), °C	Lit. bp
13a	H	H	96	105–108 (0.1)	115–120 (0.3)[a]
13b	CH_3	H	72	115 (0.1)	160–163 (6.0)[b]
13c	CH_3	CH_3	92	131 (0.13)	*c*

[a]See ref 9. [b]L. Levai, M. Ritvay, A. Vedres, L. Gyongyossy, and G. Balogh, Hungarian Patent 154,230 (Dec 22, 1967); *Chem. Abstr.*, **69**, 43635c (1968). [c]Satisfactory analyses for C, H, and N were obtained.

Table IV. Aryl *N*-Arylbenzimidates

No.	R_1	R_2	R_3	Yield, %	Mp, °C	Formula[a]
14a	H	H	CH_3	43	68–69[b]	$C_{22}H_{19}NO_3$
14b	CH_3	CH_3	CH_3	61	101–101.5	$C_{24}H_{23}NO_3$
14c	CH_3	H	H	60	84.5–85.5	$C_{22}H_{19}NO_3$
14d	H	H	$COOCH_3$	63	86.6–87	$C_{23}H_{19}NO_5$
14e	CH_3	CH_3	$COOCH_3$	67	92.5–94	$C_{25}H_{23}NO_5$

[a]Satisfactory analysis for C, H, and N were obtained. [b]Previously synthesized by M. M. Jamison and E. E. Turner, *J. Chem. Soc.*, 264 (1940), mp 93°.

Table V. *N*-Benzoyldiphenylamines

No.	R_1	R_2	R_3	Yield, %	Mp, °C	Formula[a]
15a	H	H	CH_3	79	105.5–107.5[b]	$C_{22}H_{19}NO_3$
15b	CH_3	CH_3	CH_3	90	151	$C_{24}H_{23}NO_3$
15c	CH_3	H	H	76	149–150	$C_{22}H_{19}NO_3$
15d	H	H	$COOCH_3$	87	121–122	$C_{23}H_{19}NO_5$
15e	CH_3	CH_3	$COOCH_3$	86	186	$C_{25}H_{23}NO_5$

[a]Satisfactory analysis for C, H, and N were obtained. [b]Previously synthesized by Jamison and Turner (see footnote *b*, Table IV), mp 106–107°.

lowa. Where analyses are indicated only by symbols of the elements, the analytical results for those elements were within ±0.4% of the theoretical value. Infrared spectra were recorded on Beckman IR-5A and IR-10 spectrophotometers. Nuclear magnetic resonance spectra were recorded on a Varian Associates T-60 spectrometer using tetramethylsilane as an internal standard. Ultraviolet spectra were recorded on a Beckman Model DK-2 spectrophotometer.

Benzanilides (**12a–c**). Experimental data for **12a–c** are given in Table II.

N-Arylbenzimidoyl Chlorides (**13a–c**). Experimental data for **13a–c** are given in Table III.

Aryl *N*-Arylbenzimidates (**14a–c**). Under N_2 a solution of 0.17 mol of the appropriate phenol in 250 ml of anhydrous MeOH was added to a solution of 0.2 mol of $NaOCH_3$ in 250 ml of anhydrous MeOH. Under N_2 a solution of 0.2 mol of the appropriate *N*-arylbenzimidoyl chloride (**13a–c**) in 150 ml of Et_2O was then added dropwise over 0.5 hr and the resulting mixture was stirred overnight. Most of the solvents were evaporated under reduced pressure; the residue was poured into water and extracted with ether. The ether was dried (Na_2SO_4), filtered, and removed under reduced pressure. The residue was crystallized from anhydrous EtOH. Experimental data for **14a–c** are given in Table IV.

2,3,6-Trimethylphenyl *N*-(2-Cyanophenyl)benzimidate (**14f**). To a warm (50°) suspension of 2.5 g (0.051 mol) of 50% sodium hydride in 25 ml of diglyme was added slowly 6.55 g (0.048 mol) of 2,3,6-trimethylphenol. When solution was complete, 11.5 g (0.0478 mol) of *N*-(*o*-cyanophenyl)benzimidoyl chloride[15] was added and the mixture was heated at 120° for 1 hr. The mixture was cooled and poured into a solution of 10 g of NaCl in 100 ml of H_2O. The product was collected and recrystallized from 60 ml of EtOH to give 13.2 g (80%) of tan **14f**, mp 114–116°. *Anal.* ($C_{23}H_{20}N_2O$) C, H, N.

N-Benzoyldiphenylamines (**15a–e**). A modification of the method of Schulenberg and Archer[11] was employed. The appropriate aryl *N*-arylbenzimidate (**14a–e**) (0.1 mol) was placed in a 125-ml erlenmeyer flask and heated neat in a Wood's metal bath. The temperature was maintained at 255–265° for 10 min. The melt was cooled slightly and poured into boiling EtOH, the solution was filtered and cooled, and the product was collected and dried (see Table V).

N-Phenyl-2-aminoisophthalic Acid (**16a**). To a solution of 16 g of KOH in 160 ml of H_2O was added 5 g (0.013 mol) of **15d**. The mixture was refluxed until a solution resulted and refluxing was continued for another 22 hr. The solution was filtered and acidified with concentrated HCl. The precipitate was collected while hot and suspended in water, the suspension was heated to boiling, and the precipitate was recollected. The product was dissolved in 250 ml of EtOH, the solution was filtered, and the EtOH evaporated under reduced pressure to give 2.3 g (76%) of yellow **16a**, mp 252–254°. *Anal.* ($C_{14}H_{11}NO_4$) C, H, N.

N-(2,3-Xylyl)-2-aminoisophthalic Acid (**16b**). A mixture of 20 g (0.045 mol) of **15e**, 20 g of KOH, 200 ml of H_2O, and 400 ml of EtOH was refluxed for 5 hr. The EtOH was evaporated under reduced pressure and the resulting aqueous solution was placed in a stainless steel reaction bomb and heated at 160° for 37 hr. The reaction mixture was diluted and filtered and the filtrate was acidified with concentrated HCl. The precipitate was collected, suspended in boiling H_2O, and recollected. Recrystallization from aqueous EtOH gave 8.7 g (64%) of crude product which required three additional recrystallizations to remove unhydrolyzed starting material, mp 241–242° dec (lit.[19] mp 233–234°).

Acridone-4-carboxylic Acid (**17a**). (A) A mixture of 10 g (0.04 mol) of **16a** and 20 ml of concentrated H_2SO_4 was heated in a boiling water bath for 4 hr. The resulting solution was added dropwise to 200 ml of boiling H_2O. The hot suspension was filtered and the product was resuspended in 140 ml of boiling H_2O, recollected, and dried overnight in a vacuum heater desiccator to give 7.3 g (75.5%), mp >300° (lit.[20] mp >300°).

(B) This compound was also prepared by refluxing a mixture of 5 g (0.013 mol) of **15d** and 40 ml of 70% H_2SO_4 for 30 min. The clear solution was diluted with water, the resulting suspension was heated to boiling and filtered, and the product was resuspended in

boiling water. The product was collected and dried to give 2.8 g (88% based on 15d) of **17a.**

5,6-Dimethylacridone-4-carboxylic Acid (17b). A mixture of 29 g (0.07 mol) of **15e**, 9.6 ml of H_2O, and 60 ml of concentrated H_2SO_4 was heated in a boiling water bath for 4 hr. The solution was poured gently into 500 ml of H_2O and the suspension was heated to boiling. The product was collected, resuspended in boiling H_2O, and recollected. Drying in a vacuum heater desiccator at 100° gave 17.7 g (96%), mp 342–344° dec. *Anal.* ($C_{16}H_{13}NO_3$) C, H, N.

Acridan-4-carboxylic Acid (7). Compound **17a**, 7.3 g (0.03 mol), was dissolved in a solution of 2 g of NaOH and 100 ml of H_2O. Over a period of 2 hr, 453 g (0.48 mol, 16 equiv of H_2) of 2.5% sodium amalgam [Na(Hg)] was added to this solution. During addition the mixture was stirred vigorously and heated to 80–85° in a hot water bath. The mixture was then heated and stirred for another hour.

The following isolation and purification was performed in a drybox with a nitrogen atmosphere. The solution was decanted from the mercury and filtered. The filtrate was acidified with concentrated HCl and the product collected. The product was dissolved in 400 ml of boiling EtOH, the solution was filtered, and water was added. The solution was cooled in the dark and bright yellow crystals of **7** were collected: 1.98 g (29%); mp 237–240° (lit.[21] mp 180–220°). *Anal.* ($C_{14}H_{11}NO_2$) C, H, N.

5,6-Dimethylacridan-4-carboxylic Acid (6). This compound was prepared from **17b** by the method described for **7**: yield, 35%; mp 193.5–195.5°. *Anal.* Calcd for ($C_{16}H_{15}NO_2$): C, 75.88; H, 5.97; N, 5.53. Found: C, 74.76; H, 5.95; N, 5.13.

***N*-(2,3-Xylyl)-2-amino-3-toluic Acid (8).** A mixture of 20 g (0.054 mol) of **15b**, 20 g of KOH, 200 ml of H_2O, and 400 ml of EtOH was refluxed for 2 hr. The EtOH was evaporated under reduced pressure and the resulting aqueous solution was placed in a stainless steel reaction bomb and heated in an oven at 160° for 61.5 hr. The reaction mixture was diluted and filtered and the filtrate acidified with concentrated HCl. The product was collected, suspended in boiling H_2O, and recollected. Recrystallization from aqueous EtOH gave 10 g (73%), mp 191.5–193.5°. *Anal.* ($C_{16}H_{17}NO_2$) C, H, N.

***N*-Phenyl-2-amino-3-toluic Acid (9).** A modification of the method of Schulenberg and Archer was employed.[11] To a solution of 30 g of KOH in 100 ml of MeOH and 200 ml of H_2O was added 12.6 g (0.04 mol) of **15a** and the mixture was refluxed 72 hr. The solution was filtered and acidified with concentrated HCl. The suspension was heated to boiling and the precipitate collected. The product was resuspended in boiling water and recollected. Recrystallization from EtOH gave 6.8 g (82%) of **9**, mp 190–191°. *Anal.* ($C_{14}H_{13}NO_2$) C, H, N.

***N*-(2,3,6-Trimethylphenyl)anthranilic Acid (10).** Compound **14f**, 7.2 g (0.002 mol), was heated at 280–300° for 5 hr in a Wood's metal bath to effect Chapman rearrangement. The melt was cooled and taken up in 72 ml of EtOH and 34.2 g of 50% aqueous NaOH was added. The mixture was refluxed for 4 hr. Most of the EtOH was evaporated under reduced pressure and the resulting mixture was diluted with H_2O and filtered. The filtrate was acidified with concentrated HCl and the precipitate collected. Recrystallization from diluted EtOH gave 1.7 g (31%), mp 249–251° (lit.‡ mp 251–251.5°). *Anal.* ($C_{16}H_{17}NO_2$) C, H, N.

***N*-(2-Tolyl)anthranilic Acid (11).** To a solution of 30 g of KOH in 200 ml of H_2O and 100 ml of MeOH was added 20 g (0.06 mol) of **15c** and the mixture was refluxed for 72 hr. The solution was filtered and acidified and the precipitate collected and recrystallized from EtOH. This material was dissolved in a solution of 17 g of KOH and 170 ml of H_2O and the solution was placed in a tightly sealed stainless steel reaction bomb and heated to 165° for 2 days. The reaction mixture was diluted, filtered, and acidified. The product was collected and recrystallized from EtOH: mp 192–193° (lit. mp 191–192°,[22] and 186.5°[23]); yield, 9.6 g (73%).

Determination of Apparent pK_a. The compound (0.5 mol) was dissolved with heating in 50 ml of a solution of 80:20 (w/w) ethylene glycol monomethyl ether–water. The cooled solution was titrated under N_2 with certified 0.1 *N* NaOH (Fisher Scientific Co.) using a Beckman automatic titrator with pH recorded. The pK_a' was taken from the neutralization curve as the pH at one-half neutralization.

Acknowledgments. The authors are grateful to Ortho Research Foundation for carrying out the rat paw edema assay, Parke, Davis and Company for carrying out the uv erythema assay, and Dr. F. W. Short for valuable suggestions.

References

(1) R. A. Scherrer, C. V. Winder, and F. W. Short, Abstracts, 9th National Medicinal Chemistry Symposium of the American Chemical Society, June 1964, p 11a.
(2) B. M. Sutton and J. H. Birnie, *J. Med. Chem.*, 9, 835 (1966).
(3) B. Blank and L. L. Baxter, *ibid.*, 11, 807 (1968).
(4) G. Picciola, R. Gaggi, and W. Caliari, *Farmaco, Ed. Sci.*, **23**, 502 (1968).
(5) C. V. Winder, J. Wax, L. Scotti, R. A. Scherrer, E. M. Jones, and F. W. Short, *J. Pharmacol. Exp. Ther.*, 138, 405 (1962).
(6) C. V. Winder, J. Wax, B. Serano, E. M. Jones, and M. L. McPhee, *Arthritis Rheum.*, **6**, 36 (1963).
(7) J. W. Schulenberg and S. Archer, *Org. React.*, 14, 1 (1965).
(8) A. I. Vogel, "A Textbook of Practical Organic Chemistry," 3rd ed, Wiley, New York, N. Y., 1956, p 582.
(9) J. W. Schulenberg and S. Archer, *Org. React.*, 14, 38 (1965).
(10) J. W. Schulenberg and S. Archer, *ibid.*, 14, 39 (1965).
(11) J. W. Schulenberg and S. Archer, *ibid.*, 14, 40 (1965).
(12) H. M. Relles, *J. Org. Chem.*, 33, 2245 (1968).
(13) A. Albert, "The Acridines," 2nd ed, St. Martin's Press, New York, N. Y., 1966, p 50.
(14) G. Stapleton and A. I. White, *J. Amer. Pharm. Ass., Sci. Ed.*, 43, 193 (1954).
(15) R. A. Scherrer and F. W. Short, U. S. Patent 3,313,848 (April 11, 1967).
(16) T. Yonemoto, W. F. Reynolds, H. M. Hutton, and T. Schaefer, *Can. J. Chem.*, 43, 2668 (1965).
(17) J. Hillebrecht, *Arzneim.-Forsch.*, 9, 625 (1959).
(18) C. V. Winder, *Arch. Int. Pharmacodyn. Ther.*, 116, 261 (1958).
(19) R. A. Scherrer, German Patent 1,188,609 (March 11, 1965); *Chem. Abstr.*, 63, 1741c (1965).
(20) N. S. Drozdov and A. F. Bekhli, *Zh. Obshch. Khim.*, 8, 1505 (1938).
(21) E. Ziegler, *Monatsh. Chem.*, 94, 698 (1963).
(22) S. P. Massie and P. K. Kadaba, *J. Org. Chem.*, 21, 347 (1956).
(23) L. Villemy, *Ann. Chim. (Paris)*, 5, 507 (1950).