this test; 1-[2-(dimethylamino)ethyl]-1-phenylindene hydrochloride (**2**) was the most active.[27] Relatively minor structural changes reduced the activity markedly. The corresponding indan (**23**) was only one-tenth as active as **2**. Moreover, 1-[2-(dimethylamino)-ethyl]-3-phenylindene (**1**) was even less active and 3-[2-(dimethylamino)ethyl]-2-phenylindene (**4**) was inactive. Extension of the side chain by one CH_2 (**10**) also lowered the activity considerably, a surprising result since the dimethylaminopropyl group is the side chain of both imipramine and amitriptyline. Changes in the amine portion of the molecule revealed an inverse relationship between the bulk of the amine group and the activity of the compounds. The demethyl derivative (**6**) and the N-oxide (**5**) both had activities on the same order as **2**, while the diethylaminoethyl derivative (**7**) was only weakly active and the morpholinoethyl analog (**9**) was inactive.

A comparison of some of the pharmacological activities of **2** and the clinically active compounds, imipramine and amitriptyline, is summarized in Table IV. 1-(2-Dimethylaminoethyl)-1-phenylindene hydrochloride (**2**) has a greater milligram potency in the reserpine test. Of special interest is the lack of central anticholinergic effects of **2** as shown in the antisinistro torsion[28] and antiparkinsonism[29] tests. Compound **2** does show considerable MAO inhibition *in vitro*, using as the criteria the change of the rate of kynuramine oxidation in liver homogenates, in the presence of the test compound. By the more indicative *in vivo* tests, using both tryptamine and 5-hydroxytryptophan potentiation as a measure of MAOI activity, **2** did not behave as an MAO inhibitor. Thus, the *in vitro* MAOI activity appears to be an artifact due to liver cell disruption, although some MAO inhibition *in vivo* is not completely ruled out. This combination of greater milligram potency and lack of anticholinergic effects of **2** may result in significant reduction of the undesirable atropine-like side effects encountered clinically with the standard agents.

Table V summarizes the results obtained in the antispasmodic and antiserotonin tests. The indans were the most potent compounds in this area. 3-(1-Methyl-3-pyrrolidinylmethyl)-1-phenylindan hydrochloride (**38**) was the most active of this series, having approximately twice the potency of the reference agent papaverine as a musculotropic agent with only 0.3–1.0% of the neurotropic effects of atropine sulfate. Its isomer, 1-(1-methyl-3-pyrrolidenylmethyl)-1-phenylindan hydrochloride (**39**), was equally active as a musculotropic agent; however, **39** had neurotropic effects which were ten times greater than its isomer (**38**).

Acknowledgments.—We wish to thank Drs. J. W. Kissel and A. Kandel and Mr. K. W. Dungan for the pharmacological evaluations. The assistance of Drs. D. E. Rivard and R. F. Majewski and Messrs. R. D. Dennis, J. P. Elkins, R. R. Covington, J. C. Simms, and L. Jones at various times during the course of this investigation is gratefully acknowledged. We also wish to thank Dr. A. A. Larsen for his many helpful suggestions.

(27) A. Kandel and F. M. Lish, Mead Johnson and Co., British Patent 1,041,989 (1966).

(28) M. C. DeJonge & A. B. H. Funcke, *Arch. Intern. Pharmacodyn.*, **137**, 375 (1962).

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Substituted Anilinopyridine Carboxylic Acids with Antiinflammatory Activity

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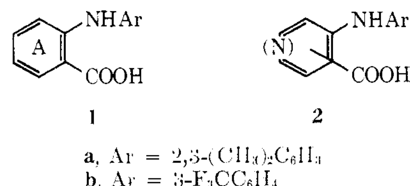
Received November 18, 1966

The synthesis of eleven substituted anilinopyridinecarboxylic acids, of which seven were novel, is described and their antiinflammatory activity is compared with that of mefenamic acid and flufenamic acid. Comparable activity was found with 2-(2,3-dimethylanilino)-, 2-(*m*-trifluoromethylanilino)-, and 4-(*m*-trifluoromethylanilino)-nicotinic acid. The novel 8,9-dimethylpyrido[2,3-*b*]quinol-5-one was also synthesized and found to be inactive.

The recent publication of a patent[1] claiming derivatives of 2-anilinonicotinic acid as analgesic–antiinflammatory agents prompts us to report our experience with these and related anilinopyridinecarboxylic acids in which the substituted anilino and carboxyl groups are in different positions around the heterocyclic nucleus.

This study was initiated to determine if the antiinflammatory activity of mefenamic acid[2a] (**1a**) and



a, Ar = 2,3-$(CH_3)_2C_6H_3$
b, Ar = 3-$F_3CC_6H_4$

flufenamic acid[2b] (**1b**) was affected appreciably when the phenyl ring A in these compounds was replaced by a pyridine nucleus as in **2**. For this reason the compounds which have been synthesized have been mostly confined to the 2,3-dimethylanilino and *m*-trifluoromethylanilino derivatives.

(1) Société Anonyme Laboratoires U.P.S.A., Belgian Patent 657,266 (April 16, 1965).

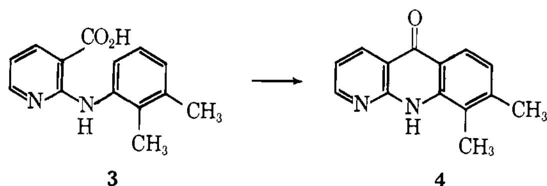
(2) (a) C. V. Winder, J. Wax, L. Scotti, R. A. Scherrer, E. M. Jones, and F. W. Short, *J. Pharmacol.*, **138**, 405 (1962); (b) C. V. Winder, J. Wax, B. Serrano, E. M. Jones, and M. L. McPhee, *Arthritis Rheumat.*, **6**, 36 (1963).

Chemistry.—2-(2,3-Dimethylanilino)nicotinic acid, 2- and 4-(*m*-trifluoromethylanilino)nicotinic acids, and 3-(*m*-trifluoromethylanilino)isonicotinic acid were prepared by heating 2,3-dimethylaniline or *m*-trifluoromethylaniline with the appropriate halogenopyridinecarboxylic acid. No catalyst was required with the 2- and 4-chloronicotinic acids but the deactivating effect of the ring nitrogen on the 3 position of the pyridine nucleus necessitated the use of more forcing Ullmann-type conditions when 3-iodoisonicotinic acid was used.

An alternative route was used to prepare 4-anilino-, 4-(2,3-dimethylanilino)-, and 4-(*m*-methoxyanilino)-nicotinic acids which involved the nucleophilic displacement of the nitro group of 4-nitronicotinic acid 1-oxide by the corresponding aniline.[3] The resulting anilinonicotinic acid 1-oxides were then reduced to the required compounds by catalytic hydrogenation over palladized charcoal. *m*-Trifluoromethylaniline did not react with 4-nitronicotinic acid 1-oxide under similar conditions.

In attempts to prepare 6-substituted anilinonicotinic acids *via* the corresponding amides, the substituted anilines were heated with 6-chloronicotinamide and the products were hydrolyzed. 6-(*m*-Trifluoromethylanilino)nicotinic acid was obtained in good yield from *m*-trifluoromethylaniline but the method was unsuccessful with 2,3-dimethylaniline.

In connection with this work, a new pyridoquinolone **4** was prepared in good yields by cyclization of 2-(2,3-dimethylanilino)nicotinic acid (**3**) in the presence of polyphosphoric acid. 2-(*m*-Trifluoromethylanilino)nicotinic acid gave a complex mixture of products under the same conditions.



Antiinflammatory Activity.—The compounds were tested for antiinflammatory activity by a modification of the rat paw edema test of Winter, Risley, and Nuss[4] who utilized carrageenin as the phlogistic agent.

In our experiments groups of four Sprague–Dawley rats (Animal Suppliers (London) Ltd.) weighing 140–170 g were dosed orally with the compounds at 0.5 and 3 hr prior to the injection of 0.1 ml of a 1% suspension of carrageenin[5] in 0.9% saline into the plantar surface of the right hind foot of each rat. The injected foot volumes were measured immediately following the carrageenin injection and 2.5 hr later using a "plethysmograph,"[6] and the difference was taken to be a reflection of the degree of inflammation produced. The mean increase in volume for each group was calculated and the results were expressed as a per cent inhibition of swelling compared to a control group of ten animals dosed with saline and tested concurrently.

Compounds active in the above test were then tested for activity against ultraviolet erythema in guinea pigs, using equipment and erythema assessment similar to that described by Haining.[7] Areas on the backs of groups of four (two male and two female) albino guinea pigs weighing 300–400 g were clipped and depilated with a proprietary depilatory cream.[8] The test compounds were given orally in suspension to each group and 0.5 hr later four sites on the depilated skin of each guinea pig were irradiated with the ultraviolet lamp for 60 sec. The degree of erythema produced was assessed 2.5 hr after irradiation using an arbitrary scoring system; the mean score for each animal was calculated. Results were expressed as a per cent reduction in erythema, compared to a control group, treated similarly but dosed with saline.

Results and Discussion

The antiinflammatory results are given in Table I and for comparative purposes we have tested mefenamic acid (**1a**) and flufenamic acid (**1b**) on our range of tests.

The only compounds showing antiinflammatory activity of the same order as **1a** and **1b** were the 2- and 4-substituted anilinonicotinic acids (**3**, **5**, and **8**). The other 4-substituted nicotinic acids (**6**, **7**, and **9**), the 6-substituted compound (**10**), and the related isonicotinic acid (**14**) showed no interesting activity and the pyridoquinolone (**4**) was similarly of low activity. The anilinonicotinic acid 1-oxides (**11–13**) showed only slight activity; the apparent activity of **11** on the carrageenin test was probably due to adrenal stimulation as it was later found to be inactive in adrenalectomized animals.

From these results it can be concluded that within the limited series of compounds we prepared, the phenyl ring A of mefenamic acid and flufenamic acids (**1**) can be replaced by a pyridine nucleus in certain instances without affecting activity.

Experimental Section[9]

Typical examples of all the reaction procedures involved are given below and further details are noted in Table I.

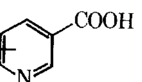
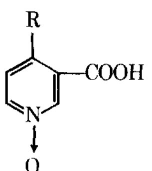
4-(2,3-Dimethylanilino)nicotinic Acid 1-Oxide. Method A.—4-Nitronicotinic acid 1-oxide[3] (3.0 g) and 2,3-dimethylaniline (15 ml) were stirred at 100° for 3 hr and the cooled mixture was equilibrated between ether (100 ml) and two 50-ml portions of 2 *N* NaOH. The aqueous solution was acidified with concentrated HCl and the precipitate was recrystallized from dimethylformamide–water to yield the substituted anilino acid as orange prisms (2.5 g, 60%), mp 272–274° dec.

4-(2,3-Dimethylanilino)nicotinic Acid. Method B.—The above anilinonicotinic acid 1-oxide (1.0 g) in methanol (200 ml) was hydrogenated at 4 atm and 50° in the presence of 10% Pd–C (0.3 g). The filtered solution was concentrated and the residue was recrystallized from methanol or aqueous ethanol to yield the expected acid (570 mg, 60%), mp 302–304° dec.

2-(*m*-Trifluoromethylanilino)nicotinic Acid.[1] **Method C.**—2-Chloronicotinic acid[10] (9.0 g) and *m*-trifluoromethylaniline (20 ml) were stirred at 160–180° for 1 hr, cooled, and equilibrated between benzene (100 ml) and two 100-ml portions of 2 *N* NaOH. Neutralization of the aqueous solution with concentrated HCl yielded a light yellow precipitate which was removed by filtration, washed with a small amount of water, and recrystallized from aqueous ethanol. The expected product was obtained as needles (10.8 g, 67%), mp 203–205°.

(3) W. Herz and D. R. K. Murty, *J. Org. Chem.*, **26**, 122 (1961).
(4) C. A. Winter, E. A. Risley, and G. W. Nuss, *Proc. Soc. Exptl. Biol. Med.*, **111**, 544 (1962).
(5) Gelozone S. T. I., Whiffen and Son Ltd., Loughborough, England.
(6) Volume differential meter manufactured by Ugo Basile, Milan, Italy. Mercury is used as the displacing fluid.
(7) C. G. Haining, *Brit. J. Pharmacol.*, **21**, 104 (1963).
(8) Veet O®, Dae Health Laboratories, London, W. 1.
(9) Melting points are uncorrected. Microanalyses were carried out by Dr. A. Bernhardt, Germany, and Drs. G. Weiler and F. B. Strauss, Oxford, England.
(10) E. C. Taylor, Jr., and A. J. Crovetti, *J. Org. Chem.*, **19**, 1633 (1954).

TABLE I

No.	R	Method	Reaction: Temp, °C	Reaction: Time, hr	Recrystn solvent[a]	Yield, %	Mp, °C	Formula	Calcd, %: C	Calcd, %: H	Calcd, %: N	Found, %: C	Found, %: H	Found, %: N	Antiinflam act.[b] vs. Carrageenin[c]	Antiinflam act.[b] vs. Uv erythema[d]
	I. Substituted Anilinonicotinic Acids 															
3	2-(3-$CF_3C_6H_4NH$)[e]	C	170	1	I–II	67	203–205	$C_{13}H_9F_3N_2O_2$	55.3	3.2	9.9	55.5	3.2	9.6	68.8	94.5
5	2-[2,3-$(CH_3)_2C_6H_3NH$][e]	C	100	4	I–II	67	242–243	$C_{14}H_{14}N_2O_2$	69.4	5.8	11.6	69.7	5.7	11.7	66.1	87.1
6	4-C_6H_5NH[f]	B	50	18[g]	III	54	267–269[h]	$C_{12}H_{10}N_2O_2$	67.3	4.7	13.1	67.0	4.9	12.9	21.2	. . .
7	4-[2,3-$(CH_3)_2C_6H_3NH$]	B	50	18[g]	III	60	302–304[h]	$C_{14}H_{14}N_2O_2$	69.4	5.8	11.6	69.4	5.8	11.6	5.8	. . .
8	4-(3-$CF_3C_6H_4NH$)	C	140	1.25	I–II	28	205–206	$C_{13}H_9F_3N_2O_2$	55.3	3.2	9.9	55.4	3.3	10.4	40.2	88.5
9	4-(3-$CH_3OC_6H_4NH$)	B	50	18[g]	III	60	281–282	$C_{13}H_{12}N_2O_3$	63.9	5.0	11.5	64.2	5.0	11.4	0	. . .
10	6-(3-$CF_3C_6H_4NH$)	E	175	4	I–II	40	243–246	$C_{13}H_9F_3N_2O_2$	55.3	3.2	9.9	55.8	3.4	9.8	1.1	. . .
	II. Substituted Anilinonicotinic Acid 1-Oxides 															
11	C_6H_5NH[f]	A	100	3	IV–II	58	244–245	$C_{12}H_{14}N_2O_3$	62.6	4.4	12.2	62.9	4.2	12.2	35.7	0
12	2,3-$(CH_3)_2C_6H_3NH$	A	100	3	IV–II	60	272–274[h]	$C_{14}H_{14}N_2O_3$	65.1	5.5	10.9	65.0	5.3	11.3	10.5	. . .
13	3-$CH_3OC_6H_4NH$	A	100	3	IV–II	44	261–262[h]	$C_{13}H_{12}N_2O_4$	60.0	4.7	10.8	60.1	4.2	10.7	14.2	
	III. Other Compounds															
14	3-(*m*-Trifluoromethylanilino)isonicotinic acid	D	[i]	24	I	11	280–282	$C_{13}H_9F_3N_2O_2$	55.3	3.2	9.9	55.7	3.5	9.5	29.7	0
4	8,9-Dimethylpyrido[2,3-*b*]quinol-5-one	F	160	1.25	I	81	243–244[h]	$C_{14}H_{12}N_2O$	75.0	5.4	12.5	74.9	5.1	12.4	13.9	. . .
Ia	Mefenamic acid														45.8	78.5 (50)
Ib	Flufenamic acid														69.9	78 (25)

[a] I, ethanol; II, water; III, methanol; IV, dimethylformamide. [b] Figures represent the per cent inhibition in groups of animals treated with the test compound compared to control. . . . = not tested. [c] Doses of 100 mg/kg were given orally at 0.5 hr and 3 hr prior to the carragenin. [d] A single dose of 100 mg/kg was given orally 0.5 hr before exposure to uv light. Figures in parentheses indicate the dose given when it was other than 100 mg/kg. [e] See ref 1. [f] See ref 3. [g] Overnight. [h] Melted with decomposition. [i] Reflux temperature.

3-(*m*-Trifluoromethylanilino)isonicotinic Acid. Method D.—A mixture of 3-iodoisonicotinic acid[11] (2.5 g), *m*-trifluoromethylaniline (4.0 g), K_2CO_3 (2.8 g), reduced copper powder (0.3 g), water (5 ml), and 1-pentanol (12 ml) was stirred under N_2 for 24 hr. The dark mixture was steam distilled, treated with charcoal, and acidified with concentrated HCl. The precipitate was removed by filtration and recrystallized from ethanol yielding the required acid (300 mg, 11%), mp 280–282°.

6-(*m*-Trifluoromethylanilino)nicotinic Acid. Method E.—6-Chloronicotinamide (6.0 g) and *m*-trifluoromethylaniline (15 ml) were stirred at 170–180° for 4 hr. The cooled reaction mixture was equilibrated between two 100-ml portions of benzene and two 50-ml portions of 2 *N* NaOH, and the combined organic solutions were washed with water, dried (Na_2SO_4), and evaporated under reduced pressure to yield a yellow solid (9.0 g). A portion of this solid (1.0 g), ethanol (25 ml), and 4 *N* NaOH (10 ml) were heated at 100° for 7 hr. Most of the solvent was removed by distillation, and water (25 ml) was added to the residue. The clear solution was neutralized with 4 *N* HCl and the precipitate was removed by filtration, washed with a small amount of water, and recrystallized from aqueous ethanol. The product was thus obtained as light yellow crystals (600 mg), mp 243–246°.

8,9-Dimethylpyrido[2,3-*b*]quinol-5-one. Method F.—2-(2,3-Dimethylanilino)nicotinic acid (1.0 g) and polyphosphoric acid (10 ml) were stirred at 160° for 75 min, poured onto crushed ice (30 g), and neutralized by the addition of 4 *N* NaOH. The solid which separated was removed by filtration, washed with a small amount of cold water, and recrystallized from ethanol yielding 4 as yellow needles (0.75 g, 81%), mp 243–244° dec.

(11) K. Palát, M. Čeladník, L. Nováček, and R. Urbančik, *Rozhledy Tuberk.*, **19**, 716 (1959).

Acknowledgment.—We thank Dr. S. S. Szinai for valuable discussion and Miss R. A. K. Finucane for technical assistance. The mefenamic and flufenamic acids used in the biological tests were kindly supplied by Dr. H. O. J. Collier, Parke, Davis and Company, Hounslow, Middlesex, England.

2,4,7-Triamino-6-*ortho*-substituted Arylpteridines. A New Series of Potent Antimalarial Agents

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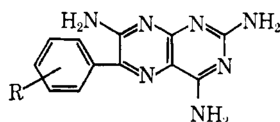
Received December 7, 1966

Activity against the experimental malarias caused by *Plasmodium berghei* in mice and *P. gallinaceum* in chicks has been demonstrated for several 2,4,7-triamino-6-*ortho*-substituted arylpteridines. The *o*-methyl and *o*-chloro derivatives were the most active compounds in the systems examined. A toxicity study in rats and dogs revealed that 2,4,7-triamino-6-*o*-tolylpteridine is sufficiently nontoxic to be administered in effective doses to humans.

From time to time reports of antimalarial activity in the pteridine series have appeared in the literature.[1-6] To the present, however, no compound of this type has achieved clinical significance in the treatment or prophylaxis of the disease. The present study originated in the observation that 2,4,7-triamino-6-*o*-tolylpteridine (I, R = *o*-CH_3)[7] was highly active against *Plasmodium berghei* infections in mice and that this activity was coupled with a relatively low toxicity in this species.



I

Results.—The activity of several of the most interesting 2,4,7-triamino-6-arylpteridines is compared with the standard antimalarial agents quinine sulfate and chloroquine diphosphate in Table I.

TABLE I

Compd	MTD, mg/kg[a]	Increase in mean survival time at MTD, days	Min. dose giving cure, mg/kg (cured/treated)	Increase in survival time at 160 mg/kg[b]
I, R = 2-CH_3	>1280	(Cure)[c]	320 (6/10)	15.6
I, R = 2-Cl	>1280	(Cure)	320 (3/10)	10.5
I, R = 2,6-Cl_2	>1280	(Cure)	320 (1/5)	10.6
I, R = H	160[d]	5.6	...	5.6
Quinine	640	5.4	...	2
Chloroquinine	160	10	...	10

[a] Maximum tolerated dose = dose at which no toxic deaths occur. [b] MTD of chloroquinine. [c] Cure defined as a survival of 30 days or more. [d] The MTD for this compound varied greatly in different tests as did the increase in MST (mean survival time).

From the table it can be seen that the activity of the compounds at 160 mg/kg falls in the following order taking quinine sulfate as 1: I, R = 2-CH_3 (7.7 Q) > I, R = 2-Cl (5.3 Q) = I, R = 2,6-$(Cl)_2$ (5.3 Q) > chloroquine diphosphate (5.0 Q) > I, R = H (2.8 Q). However the first three compounds differ from the remainder in that they are able to cure the infection. Similar results were obtained against *P. gallinaceum* in chicks. It should be noted that while the compounds fall in the expected order with respect to activity the quantitative value of the activity (Q) is probably not comparable with that obtained by other antimalarial tests against experimental infection,[8] where the intensity of parasitemia rather than death is taken as the criterion.

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