$n^{24}D$ 1.4800, $\lambda_{max}^{95\%EtOH}$ 260 mμ (ε 4300). A multiplet centered at 5.8 ppm was assigned to the four vinyl protons in the nmr spectrum of **16**. *Anal.* ($C_{10}H_{17}N$) C, H, N.

Its methiodide crystallized from Me_2CO–Et_2O as white needles, mp 179–180°. *Anal.* ($C_{11}H_{20}IN$) C, H, I, N.

Compound **16** was reduced as described for **12** to give 2-dimethylaminoethylcyclohexane. The methiodide of the reduced product was recrystallized from Me_2CO–Et_2O to furnish white needles, mp 223° (lit.[16] mp 224°).

1-Methyl-5-oxo-*cis*-octahydroindole (17).—A solution of 5-hydroxyindole (1 g) in 20 ml of MeOH was hydrogenated at 120–125° (initial pressure, 119.4 kg/cm²) with 3 g of Raney nickel for 1 hr. The cooled contents were filtered and evaporated to afford 1.0 g of a colorless syrup. CrO_3 (0.3 g, 0.0033 mole equiv) in 0.2 ml of H_2O and 2 ml of HOAc was added dropwise to a solution of 0.51 g (0.0033 mole) of the reduced indole in 10 ml of HOAc at 60–65°. The mixture was stirred at 60–65° until the solution was completely green. Most of the HOAc was removed, and the residue was made strongly basic with NaOH solution and extracted with three 20-ml portions of Et_2O. The Et_2O extracts were combined, dried ($MgSO_4$), and filtered. Removal of solvent at reduced pressure afforded a colorless liquid. Tlc of the liquid on neutral alumina using 1:1 EtOH–Skelly B showed spots for starting material and product **17**. The mixture was chromatographed on an alumina column made in Skelly B (Woelm, activity grade III, 40 g) using 5% EtOAc in Skelly B_1 and 20-ml fractions were collected. The ketone **17** (0.15 g, 30%) had an unresolved triplet at 3.05 ppm (band half-width 15 cps) assigned to the equatorial C-7a proton.

1-Methyl-5-oximino-*cis*-octahydroindole (18).—The ketone **17** (0.18 g, 0.0012 mole) was heated on a steam bath for 3 hr with a solution of 0.4 g of $NH_2OH \cdot HCl$ in 5 ml of H_2O. The solution was neutralized with Na_2CO_3 solution and heated on a steam bath for 30 min. Cooling of the solution did not precipitate the oxime. It was evaporated to dryness by codistillation with two 100-ml portions of absolute EtOH, and the dry residue was extracted with two 10-ml portions of boiling EtOAc. The extracts were concentrated to a small volume. The solution, on cooling, afforded 0.14 g (70%) of **18** as white crystals (EtOAc–Skelly B), mp 154.5–156.5°. *Anal.* ($C_9H_{16}N_2O$) C, H, N.

1-Methyl-5-*syn*-dimethylamino-*cis*-octahydroindole (15). A. From 18.—A solution of 0.50 g (0.003 mole) of **18** in 8 ml of absolute EtOH was heated to boiling; the heating was discontinued, and temperature was maintained by introducing pieces of Na (1 g) through the condenser. After the solution was refluxed for 30 min and cooled, it was diluted with an equal volume of H_2O, acidified with HCl, and evaporated. The residue was made strongly alkaline with NaOH solution and extracted with $CHCl_3$. The extraxts were dried and filtered. Solvent was removed under reduced pressure to give 0.17 g (37%) of a thick colorless liquid. To this was added 0.25 g of 37% CH_2O and 0.26 g of 88% HCOOH, and the mixture was heated on the steam bath for 2 hr. The solution was treated with 5 ml of dilute HCl and excess CH_2O and HCO_2H were removed by evaporation to dryness. The residue was made alkaline with NaOH solution and extracted with Et_2O. The solvent was evaporated to give 0.16 g of a liquid which was identical with 1-methyl-5-*syn*-dimethylamino-*cis*-octahydroindole (**15**) by infrared and tlc.

The amino ketone **17** (0.23 g, 0.0015 mole) was heated at 160–170° for 3 hr with 0.44 g (0.006 mole) of DMF and 0.41 g (0.008 mole) of 88% HCO_2H. The cooled solution was treated with 5 ml of 4 *N* HCl and evaporated to dryness. The residue was made alkaline with NaOH solution and extracted with Et_2O. The extract was dried ($MgSO_4$) and evaporated to afford 0.21 g of a yellowish liquid which was identical with **15** by infrared and tlc.

Catalytic Reduction of 1-Methyl-5-oximino-*cis*-octahydroindole (18).—A solution of 0.25 g of **18** in 10 ml of HOAc was hydrogenated overnight at 2.1 kg/cm² (room temperature) with 75 mg of PtO_2. After filtering, the solution was evaporated to remove most of the HOAc. The residue was made alkaline with NaOH solution and extracted with Et_2O to give (after drying and evaporation) 0.19 g of a thick liquid. The liquid was heated on the steam bath for 3 hr with 0.26 g of 37% H_2CO and 0.28 g of 88% HCOOH, treated with 5 ml of 4 *N* HCl, and evaporated to dryness. The residue was made strongly alkaline with NaOH solution, extracted with Et_2O, and dried ($MgSO_4$), and the solvent was removed to afford 0.18 g of a colorless liquid which was identical with **15** by ir and tlc.

Biological Testing.—The contractions of the isolated ileum were obtained by treatment with ganglionic stimulants, and the percentage reduction in the size of these contractions brought about by the antagonists was used as a measure of their effect. Each compound was examined three times on fresh ileum preparations.

The normal control contractions of the guinea pig ileum were obtained by the addition of 2-, 10 , and 20-μg doses of nicotine, acetylcholine, and histamine, respectively, in the bath in which the ileum was suspended. Then, the contractions were obtained with the same drugs after the previous addition (90 sec before) of the antagonist to the bath. The doses of the antagonists used were 100, 50, 25, 12.5, 6.25, 3.12, 1.56, and 0.78 μg.

Preparation and Antiinflammatory Properties of Some 5-(2-Anilinophenyl)tetrazoles[1]

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Received July 27, 1967

Tetrazole analogs of a series of known N-phenylanthranilic acid antiinflammatory agents were prepared. Some of these 5-(2-anilinophenyl)tetrazoles showed antiinflammatory activity comparable to the corresponding carboxylic acids when tested orally in rats.

The knowledge that 5-substituted tetrazoles and their carboxylic acid analogs have comparable acidic dissociation constants[2,3] has led a number of chemists to replace the carboxyl group in biologically active compounds with the 5-tetrazolyl group (–CN_4H). Hopes of maintaining or improving upon biological activity have been realized in some cases.

Tetrazole analogs of plant growth regulators such as 3-indolylacetic acid and 2,4-dichlorophenoxyacetic acid retained some activity.[4,5] Two out of three tetrazole analogs of glutamic acid acted as substrates for beef liver L-glutamic dehydrogenase,[6] whereas 5-(4-aminophenyl)tetrazole, an analog of *p*-aminobenzoic acid, was found to be inactive against *Staphylococcus aureus*

(1) Some of these compounds have been described by P. F. Juby, U. S. Patent 3,294,813 (1966).

(2) F. R. Benson, *Chem. Rev.*, **41**, 1 (1947).

(3) R. M. Herbst, "Essays in Biochemistry," John Wiley and Sons, Inc., New York, N. Y., 1956, p 141.

(4) C. van de Westeringh and H. Veldstra, *Rec. Trav. Chim.*, **77**, 1107 (1958).

(5) J. M. McManus and R. M. Herbst, *J. Org. Chem.*, **24**, 1464 (1959).

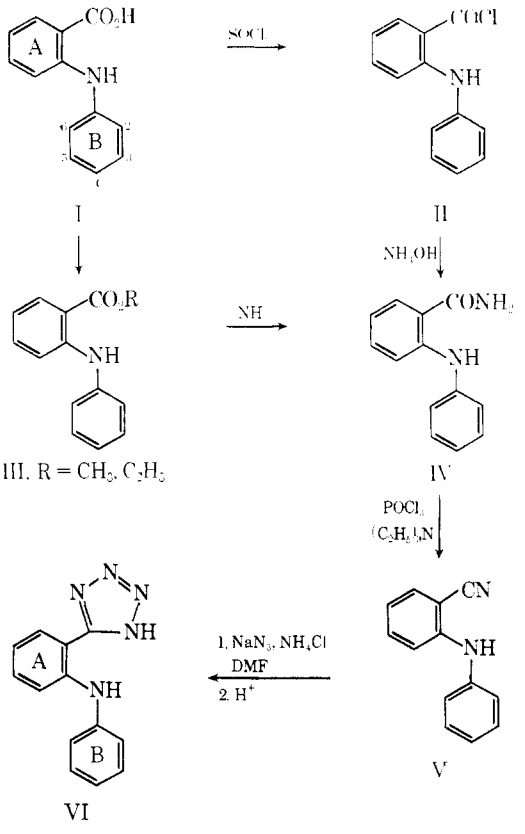
(6) J. K. Elwood, R. M. Herbst, and G. L. Kilgour, *J. Biol. Chem.*, **240**, 2073 (1965).

and *Escherichia coli*.[7] The tetrazole analog of the antituberculous *p*-aminosalicylic acid proved to be inactive when tested *in vitro*.[7] The tetrazole analog of nicotinic acid was effective in high concentrations as a growth factor for *Lactobacillus arabinosus*[7] and was found to be three to four times more potent than nicotinic acid in lowering serum cholesterol in man.[8]

As part of a program to provide nonsteroidal antiinflammatory agents without the characteristic side effects of presently available compounds, we have now prepared tetrazole analogs of a series of N-phenylanthranilic acids which have been reported to possess antiinflammatory activity in both pharmacological[9] and clinical[10] tests. This paper describes the preparation, some physical properties, and the preliminary pharmacology of these 5-(2-anilinophenyl)tetrazoles.

Chemistry.—All of the 5-(2-anilinophenyl)tetrazoles (Table I) were prepared from the corresponding N-phenylanthranilic acids by the procedures that are outlined for the unsubstituted compounds in Scheme I.

SCHEME I



Most of the compounds were prepared *via* the acid chloride route. In those cases in which the carboxylic acids (I) were unsubstituted in either or both of positions 2 and 6 of ring B, each acid was treated with 1 molar equiv of thionyl chloride in methylene chloride. This was to avoid any tendency of the resulting acid chlorides (II) to cyclize to the corresponding acridones when the reaction was run in neat thionyl chloride. In some cases a catalytic amount of dimethylformamide was required to initiate the reactions conducted in methylene chloride. The acid chlorides were not characterized, but were converted directly to the amides (IV) with aqueous ammonia. As an alternative route, two of the amides were prepared by treatment of the esters (III) of the corresponding acids (I) with ammonia in suitable solvents.

The amides were dehydrated to the nitriles (V) in excellent yields with phosphorus oxychloride and triethylamine. The nitriles were converted to the tetrazoles (VI) in high yields by the method of Finnegan, *et al.*,[11] using sodium azide and ammonium chloride in dimethylformamide.

Most of the starting N-phenylanthranilic acids were prepared by the reaction of sodium *o*-bromobenzoate with an aromatic amine in a modified Ullmann procedure.[12]

Since we suspected that the reaction between sodium *o*-bromobenzoate and the sterically hindered 2,6-dichloro-3-methylaniline would proceed in an unacceptable yield,[9a] N-(2,6-dichloro-3-methylphenyl)anthranilic acid[12] (XI) (Table I, **31**) was prepared by a route (Scheme II) first outlined by Scherrer and co-workers.[9a] The intermediate 2,6-dichloro-3-methylphenol[13] (VIII) was synthesized as shown in Scheme III. Treatment of 4-hydroxy-2-methylacetophenone[14] (XIII) with sodium hypochlorite brought about nuclear chlorination as well as the desired haloform reaction. The resulting 3,5-dichloro-4-hydroxy-2-methylbenzoic acid (XIV) was decarboxylated in excellent yield to give the phenol VIII. The Chapman rearrangement of the diphenoxyquinazoline IX derived from the reaction between the phenol VIII and 2,4-dichloroquinazoline[15] (VII) proceeded in good yield when carried out in mineral oil at about 350°. The resulting quinazolone X was hydrolyzed to give the required N-(2,6-dichloro-3-methylphenyl)anthranilic acid (XI). A by-product of this latter reaction was 2,6-dichloro-3-methylaniline[16] (XII).

After most of the above work had been completed an alternative synthesis (Scheme IV) for 5-[2-(3-trifluoromethylanilino)phenyl]tetrazole (XVII) (Table I, **4**) was devised. The coupling reaction between the sodium salt of either 5-(2-bromophenyl)tetrazole or 5-(2-chlorophenyl)tetrazole (XV) and the sodium salt of 3-trifluoromethylaniline (XVI) was conducted in hexamethylphosphoramide (HMPA).

(7) B. Brouwer-van Stratten, D. Solinger, C. van de Westeringh, and H. Veldstra, *Rec. Trav. Chim.*, **77**, 1129 (1958).

(8) (a) Reported by G. F. Holland at the Tenth National Medicinal Chemistry Symposium of the American Chemical Society, Bloomington, Ind., June 1966; (b) G. F. Holland and J. N. Pereira, *J. Med. Chem.*, **10**, 149 (1967).

(9) (a) CI-583; see R. A. Scherrer, C. V. Winder, and F. W. Short, Abstracts, Ninth National Medicinal Chemistry Symposium of the American Chemical Society, Minneapolis, Minn., June 1966, p 11a; (b) C. V. Winder, J. Wax, L. Scotti, R. A. Scherrer, E. M. Jones, and F. W. Short, *J. Pharmacol. Exptl. Therap.*, **138**, 405 (1962); (c) C. V. Winder, J. Wax, B. Serrano, E. M. Jones, and M. L. McPhee, *Arthritis Rheumat.*, **6**, 36 (1963); (d) C. V. Winder, J. Wax, and M. Welford, *J. Pharmacol. Exptl. Therap.*, **148**, 422 (1965); (e) F. Delbarre, N. P. Buu-Hoï, A. Kahan, P. Jacquignon, H. Brouilhet, M. Marty, and F. Périn, *Med. Exptl.*, **11**, 389 (1964).

(10) (a) L. J. Cass and W. S. Frederik, *J. Pharmacol. Exptl. Therap.*, **139**, 172 (1963); (b) P. Young, *Arthritis Rheumat.*, **6**, 307 (1963); (c) E. L. Coodley, *Western Med.*, **4**, 228 (1963); (d) D. E. Barnardo, H. L. F. Currey, R. M. Mason, W. R. Fox, and M. Weatherall, *Brit. Med. J.*, **2**, 342 (1966).

(11) W. G. Finnegan, R. A. Henry, and R. Lofquist, *J. Am. Chem. Soc.*, **80**, 3908 (1958).

(12) Parke, Davis and Co., British Patent 984,120 (1965).

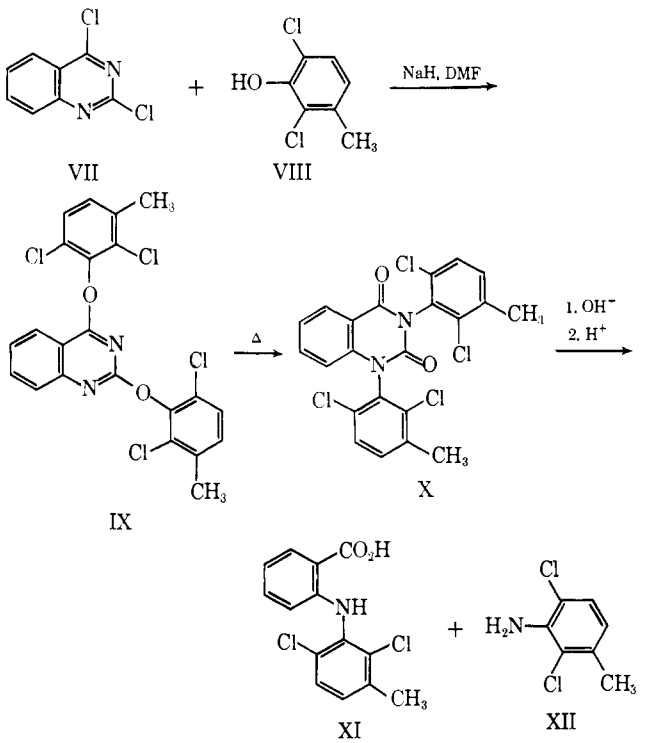
(13) R. C. Huston and P. S. Chen, *J. Am. Chem. Soc.*, **55**, 4211 (1933).

(14) A. H. Blatt, *Org. Reactions*, **1**, 354 (1942).

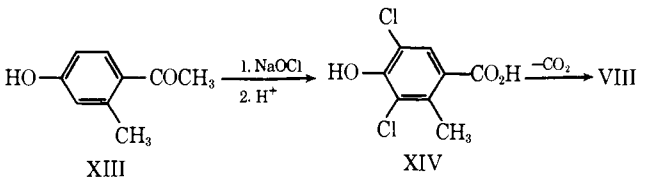
(15) N. A. Lange, W. E. Roush, and H. J. Asbeck, *J. Am. Chem. Soc.*, **52**, 3696 (1930).

(16) A similar use of a Chapman rearrangement to convert phenols to the corresponding anilines has also been reported by R. A. Scherrer, Abstracts, 145th National Meeting of the American Chemical Society, New York, N. Y., Sept 1963, p 33Q.

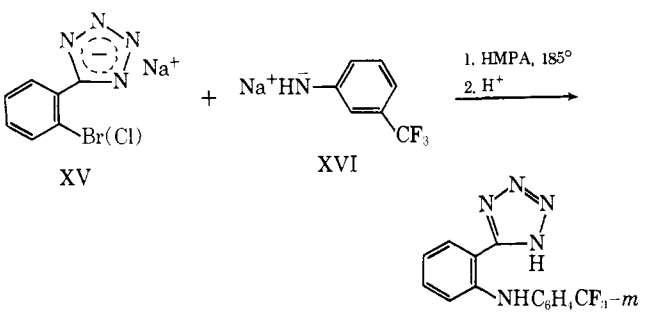
SCHEME II



SCHEME III

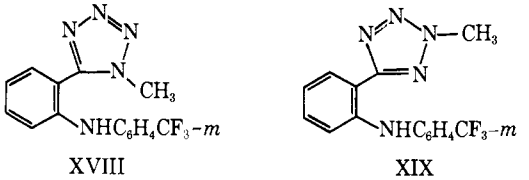


SCHEME IV



As might have been predicted,[3] the 5-(2-anilinophenyl)tetrazoles (Table I) would appear to be slightly stronger acids than the corresponding N-phenylanthranilic acids. 5-[2-(3-Trifluoromethylanilino)phenyl]tetrazole (**4**) and 5-[2-(2,6-dichloro-3-methylanilino)phenyl]tetrazole (**14**) have pK_a values of 5.31 and 5.66, respectively, compared with values of 6.28 and 6.88 for N-(3-trifluoromethylphenyl)anthranilic acid (**21**) and N-(2,6-dichloro-3-methylphenyl)anthranilic acid (**31**), respectively. All pK_a titrations were carried out in 2-methoxyethanol–water (2:1) solutions. The ultraviolet spectra of the tetrazole compounds are similar to those of the corresponding carboxylic acids.[9a]

Both of the possible N-methyltetrazole derivatives (XVIII and XIX) of 5-[2-(3-trifluoromethylanilino)-phenyl]tetrazole (XVII) were obtained after treatment of the latter compound with diazomethane in ether. Structural assignments were made from the nmr spectra.[17] One of the derivatives shows a chemical shift of 4.18 ppm for the N-methyl protons and was assigned structure XVIII. Structure XIX was assigned to the other isomer with a chemical shift of 4.39 ppm for the N-methyl protons.



Pharmacology.—All of the 5-(2-anilinophenyl)tetrazoles (**1–17**), as well as the corresponding N-phenylanthranilic acids (**18–34**), were evaluated orally for antiinflammatory activity in the carrageenin-induced rat foot edema test.[18] The results, expressed as the percentage inhibition of edema, are recorded in Table I. Any result of more than 30% inhibition is greater than three times the standard deviation of the result in control animals and is considered to indicate significant activity.

The two most active 5-(2-anilinophenyl)tetrazoles in the dose range of 100–150 mg/kg are **4** and **14**, which are the tetrazole analogs of the two most active N-phenylanthranilic acids, **21** (flufenamic acid) and **31**.[9a] There is also reasonable correlation in structure and antiinflammatory activity between most of the other tetrazole–acid pairs. Compound **4**, 5-[2-(3-trifluoromethylanilino)phenyl]tetrazole,[19] had a minimal effective dose (29% inhibition of edema) of 16 mg/kg, with an oral LD_{50} of 455 mg/kg in rats.

Both of the nonacidic N-methyltetrazole derivatives (XVIII and XIX in the Chemistry section) of **4** showed insignificant activity in the foot edema test. This suggests that both the 5-(2-anilinophenyl)tetrazoles and the N-phenylanthranilic acids owe their activity, in part, to their ability to provide an anionic center for a hypothetical cationic receptor site.[9a]

In summary, it may be stated that the 5-tetrazolyl group is an effective substitute for the carboxyl group for the retention of antiinflammatory activity in the series of N-phenylanthranilic acid agents studied.

Experimental Section[20]

N-Phenylanthranilic Acids.—N-Phenylanthranilic acid (**18**) (Aldrich Chemical Co., Inc.) was purified by recrystallization from MeCN. N-(3-Trifluoromethylphenyl)anthranilic acid[21] (**21**) and N-(2,3-dimethylphenyl)anthranilic acid[22] (**25**) were prepared by a method similar to that described for N-phenyl-

(17) J. H. Markgraf and W. T. Bachmann [*J. Org. Chem.*, **30**, 347 (1965)] reported that the signal from the N-methyl protons of 1,5-dimethyltetrazole appears upfield from the signal from the N-methyl protons of 2,5-dimethyltetrazole.

(18) C. A. Winter, E. A. Risley, and G. W. Nuss, *Proc. Soc. Exptl. Biol. Med.*, **111**, 544 (1962).

(19) A more detailed account of the pharmacology of 5-[2-(3-trifluoromethylanilino)phenyl]tetrazole (BL-R191) will be reported elsewhere.

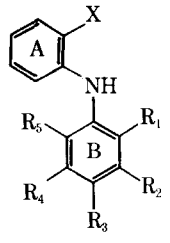
(20) Melting points were determined in a Mel-Temp apparatus and are uncorrected. Nmr spectra ($CDCl_3$) were obtained using a Varian Associates Model A-60 spectrometer. Chemical shifts (δ) were measured downfield from TMS.

(21) J. H. Wilkinson and I. L. Finar, *J. Chem. Soc.*, 32 (1948).

(22) R. A. Scherrer, French Patent 1,315,030 (1963); *Chem. Abstr.*, **59**, 1538 (1963).

TABLE I

5-(2-ANILINOPHENYL)TETRAZOLES AND INTERMEDIATES



No.	R_1	R_2	R_3	R_4	R_5	X	Mp, °C	Crystn solvent[a]	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Calcd, % Cl	Found, % C	Found, % H	Found, % N	Found, % Cl	Anti-inflam act., % inhib of edema[b]
									Tetrazoles									
1	H	H	H	H	H	CN_4H	210–211.5	A–B	$C_{13}H_{11}N_5$	65.81	4.67	29.53		65.64	4.91	29.64		19
2	Cl	H	H	H	H	CN_4H	203–203.5	A–B	$C_{13}H_{10}ClN_5$	57.46	3.71	25.78		57.53	3.87	25.77		13
3	H	Cl	H	H	H	CN_4H	207–208	A–B	$C_{13}H_{10}ClN_5$	57.46	3.71	25.78	13.05	57.74	3.78	25.95	13.42	0
4	H	CF_3	H	H	H	CN_4H	205–207	A–B	$C_{14}H_{10}F_3N_5$	55.07	3.30	22.94		55.30	3.25	22.92		50 (128)
5	H	H	Cl	H	H	CN_4H	238–239	A	$C_{13}H_{10}ClN_5$	57.46	3.71	25.78	13.05	57.65	3.76	25.88	13.38	39 (128)
6	H	H	F	H	H	CN_4H	231–231.5	A	$C_{13}H_{10}FN_5$	61.15	3.95	27.44		61.00	3.97	27.77		5
7	Cl	Cl	H	H	H	CN_4H	202–203	A–B	$C_{13}H_9Cl_2N_5$	51.00	2.96	22.88	23.16	51.21	3.12	22.87	23.47	25
8	CH_3	CH_3	H	H	H	CN_4H	203.5–205.5	A–B	$C_{15}H_{15}N_5$	67.90	5.70	26.40		68.01	5.72	26.43		29
9	$-(CH_2)_4-$		H	H	H	CN_4H	214–215.5	A	$C_{17}H_{17}N_5$	70.08	5.88	24.04		69.85	6.11	24.14		18
10	Cl	H	Cl	H	H	CN_4H	252.5–253.5	A	$C_{13}H_9Cl_2N_5$	51.00	2.96	22.88	23.16	51.30	3.14	22.89	23.36	0
11	Cl	H	H	CF_3	H	CN_4H	228–229	A–B	$C_{14}H_9ClF_3N_5$	49.49	2.67	20.62		49.55	2.91	20.79		35
12	Cl	H	H	H	Cl	CN_4H	187.5–189.5	C–B	$C_{13}H_9Cl_2N_5$	51.00	2.96	22.88	23.16	51.13	3.13	23.05	23.37	47
13	CH_3	H	H	H	CH_3	CN_4H	192–193	C–B	$C_{15}H_{15}N_5$	67.90	5.70	26.40		68.15	6.00	26.36		0
14	Cl	CH_3	H	H	Cl	CN_4H	207–208.5	C–B	$C_{14}H_{11}Cl_2N_5$	52.52	3.46	21.88	22.15	52.60	3.73	21.88	22.38	48 (128)
15	Cl	H	Cl	H	Cl	CN_4H	235–235.5	A–B	$C_{13}H_8Cl_3N_5$	45.85	2.37	20.57		46.10	2.51	20.54		0
16	H	Cl	CH_3	H	H	CN_4H	218.5–220	A–B	$C_{14}H_{12}ClN_5$	58.86	4.24	24.52	12.41	58.57	4.32	24.78	12.59	15
17	H	Cl	H	Cl	H	CN_4H	211.5–213	A–B	$C_{13}H_9Cl_2N_5$	51.00	2.96	22.88	23.16	50.87	3.24	22.84	23.29	36
									Carboxylic Acids									
18	H	H	H	H	H	CO_2H	185–187[c]	D	$C_{13}H_{11}NO_2$									8
19	Cl	H	H	H	H	CO_2H	196–198[c]	C	$C_{13}H_{10}ClNO_2$									25
20	H	Cl	H	H	H	CO_2H	170–171.5[c]	E	$C_{13}H_{10}ClNO_2$									8
21	H	CF_3	H	H	H	CO_2H	132–133[d]	F	$C_{14}H_{10}F_3NO_2$									39 (128)
22	H	H	Cl	H	H	CO_2H	176–178[e]	A–B	$C_{13}H_{10}ClNO_2$									0
23	H	H	F	H	H	CO_2H	199–200.5[e]	A	$C_{13}H_{10}FNO_2$									2
24	Cl	Cl	H	H	H	CO_2H	255–257[f]	A	$C_{13}H_9Cl_2NO_2$									29
25	CH_3	CH_3	H	H	H	CO_2H	229–230[g]	C	$C_{15}H_{15}NO_2$									35 (100)
26	$-(CH_2)_4-$		H	H	H	CO_2H	174–175.5[h]	E	$C_{17}H_{17}NO_2$									2
27	Cl	H	Cl	H	H	CO_2H	250–251 dec[c]	A	$C_{13}H_9Cl_2NO_2$									14
28	Cl	H	H	CF_3	H	CO_2H	185–186.5	C–B	$C_{14}H_9ClF_3NO_2$	53.26	2.87	4.44		53.55	2.99	4.26		18
29	Cl	H	H	H	Cl	CO_2H	218–220	C	$C_{13}H_9Cl_2NO_2$	55.34	3.22	4.97	25.14	55.55	3.32	4.83	25.42	29
30	CH_3	H	H	H	CH_3	CO_2H	207.5–209.5 dec[i]	C	$C_{15}H_{15}NO_2$									5
31	Cl	CH_3	H	H	Cl	CO_2H	256–256.5 dec[j]	G	$C_{14}H_{11}Cl_2NO_2$									52 (128)

No.	R_1	R_2	R_3	R_4	R_5	X	Mp, °C	Crystn solvent[a]	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Calcd, % Cl	Found, % C	Found, % H	Found, % N	Found, % Cl	Antiinflam act., % inhib of edema[b]
								Carboxylic Acids (*Continued*)										
32	Cl	H	Cl	H	Cl	CO_2H	246–249 dec	C	$C_{13}H_8Cl_3NO_2$	49.32	2.55	4.43		49.46	2.70	4.25		4
33	H	Cl	CH_3	H	H	CO_2H	189.5–192[k]	A–B	$C_{14}H_{12}ClNO$									21
34	H	Cl	H	Cl	H	CO_2H	251–252 dec[l]	A–E	$C_{13}H_9Cl_2NO_2$									10
								Amides										
35	H	H	H	H	H	$CONH_2$	127–128	A–B	$C_{13}H_{12}N_2O$	73.56	5.70	13.20		73.35	5.89	13.41		
36	Cl	H	H	H	H	$CONH_2$	123.5–124	C–B	$C_{13}H_{11}ClN_2O$	63.30	4.50	11.36		63.07	4.59	11.37		
37	H	Cl	H	H	H	$CONH_2$	140–141	E–F	$C_{13}H_{11}ClN_2O$	63.30	4.50	11.36	14.37	63.57	4.72	11.40	14.56	
38	H	CF_3	H	H	H	$CONH_2$	126.5–128.5	C–B	$C_{14}H_{11}F_3N_2O$	60.00	3.96	10.00		60.32	4.00	9.71		
39	H	H	Cl	H	H	$CONH_2$	156–157	E	$C_{13}H_{11}ClN_2O$	63.30	4.50	11.36	14.37	63.40	4.61	11.54	14.23	
40	H	H	F	H	H	$CONH_2$	120–121	A	$C_{13}H_{11}FN_2O$	67.83	4.81	12.12		67.51	4.89	12.40		
41	Cl	Cl	H	H	H	$CONH_2$	167–169	E	$C_{13}H_{10}Cl_2N_2O$	55.54	3.59	9.97	25.22	55.73	3.73	10.19	25.05	
42	CH_3	CH_3	H	H	H	$CONH_2$	149.5–151.5	C–B	$C_{15}H_{16}N_2O$	74.97	6.71	11.66		74.95	6.51	11.90		
43	$-(CH_2)_4-$		H	H	H	$CONH_2$	129–130	F	$C_{17}H_{18}N_2O$	76.66	6.81	10.52		76.67	6.77	10.57		
44	Cl	H	Cl	H	H	$CONH_2$	165–167	C	$C_{13}H_{10}Cl_2N_2O$	55.54	3.59	9.97		55.73	3.75	10.11		
45	Cl	H	H	CF_3	H	$CONH_2$	167–169	C–B	$C_{14}H_{10}ClF_3N_2O$	53.43	3.20	8.90		53.51	3.44	8.72		
46	Cl	H	H	H	Cl	$CONH_2$	140–142	E	$C_{13}H_{10}Cl_2N_2O$	55.54	3.59	9.97	25.22	55.55	3.61	9.95	25.09	
47	CH_3	H	H	H	CH_3	$CONH_2$	155.5–156.5	E–H	$C_{15}H_{16}N_2O$	74.97	6.71	11.66		75.19	6.92	11.51		
48	Cl	CH_3	H	H	Cl	$CONH_2$	178–179	A–B	$C_{14}H_{12}Cl_2N_2O$	56.96	4.10	9.49	24.02	56.98	4.17	9.28	23.99	
49	Cl	H	Cl	H	Cl	$CONH_2$	190–193	D	$C_{13}H_9Cl_3N_2O$	49.48	2.88	8.88		49.38	3.02	8.85		
50	H	Cl	CH_3	H	H	$CONH_2$	132–133	A–B	$C_{14}H_{13}ClN_2O$	64.51	5.03	10.75	13.60	64.47	4.94	10.85	13.73	
51	H	Cl	H	Cl	H	$CONH_2$	173–174.5	C	$C_{13}H_{10}Cl_2N_2O$	55.54	3.59	9.97	25.22	55.77	3.67	9.67	24.98	
								Nitriles										
52	H	H	H	H	H	CN	63–64.5	H	$C_{13}H_{10}N_2$	80.38	5.19	14.42		80.13	5.29	14.64		
53	Cl	H	H	H	H	CN	70.5–71.5	H	$C_{13}H_9ClN_2$	68.26	3.97	12.26		68.09	4.16	12.01		
54	H	Cl	H	H	H	CN	111–112.5	F	$C_{13}H_9ClN_2$	68.26	3.97	12.26	15.50	68.27	4.09	12.40	15.53	
55	H	CF_3	H	H	H	CN	81–82	H	$C_{14}H_9F_3N_2$	64.12	3.46	10.69		63.80	3.54	10.87		
56	H	H	Cl	H	H	CN	132.5–133.5	F	$C_{13}H_9ClN_2$	68.26	3.97	12.26	15.50	68.54	3.99	12.36	15.68	
57	H	H	F	H	H	CN	106–107	F	$C_{13}H_9FN_2$	73.57	4.28	13.20		73.85	4.55	12.94		
58	Cl	Cl	H	H	H	CN	126–127	F	$C_{13}H_8Cl_2N_2$	59.34	3.06	10.65	26.95	59.41	3.09	10.88	26.86	
59	CH_3	CH_3	H	H	H	CN	136–138	C	$C_{15}H_{14}N_2$	81.05	6.35	12.61		80.72	6.29	12.71		
60	$-(CH_2)_4-$		H	H	H	CN	91.5–92.5	C	$C_{17}H_{16}N_2$	82.22	6.50	11.28		82.29	6.57	11.34		
61	Cl	H	Cl	H	H	CN	132–134	C	$C_{13}H_8Cl_2N_2$	59.34	3.06	10.65	26.95	59.64	3.30	10.52	27.08	
62	Cl	H	H	CF_3	H	CN	102.5–104.5	H	$C_{14}H_8ClF_3N_2$	56.68	2.72	9.44		57.03	3.05	9.43		
63	Cl	H	H	H	Cl	CN	103–104	H	$C_{13}H_8Cl_2N_2$	59.34	3.06	10.65	26.95	59.64	3.18	10.61	26.81	
64	CH_3	H	H	H	CH_3	CN	109–112	H	$C_{15}H_{14}N_2$	81.05	6.35	12.60		80.93	6.65	12.73		
65	Cl	CH_3	H	H	Cl	CN	132–134	H	$C_{14}H_{10}Cl_2N_2$	60.67	3.64	10.11	25.59	60.69	3.82	10.25	25.21	
66	Cl	H	Cl	H	Cl	CN	121–122	C	$C_{13}H_7Cl_3N_2$	52.47	2.37	9.42		52.21	2.57	9.18		
67	H	Cl	CH_3	H	H	CN	128–129	F	$C_{14}H_{11}ClN_2$	69.31	4.57	11.54		69.48	4.86	11.69		
68	H	Cl	H	Cl	H	CN	169–171	C	$C_{13}H_7Cl_2N_2$	59.34	3.06	10.65		59.19	3.21	10.40		

[a] A = EtOH, B = H_2O, C = MeOH, D = MeCN, E = C_6H_6, F = cyclohexane, G = 95% EtOH, H = Skellysolve B (bp 60–80°). [b] All compounds were tested at a dose of 150 mg/kg of rat, unless otherwise indicated. The alternative doses are given in parentheses adjacent to the test results. [c] F. Ullmann, *Ann. Chem.*, **355**, 312 (1907). [d] See ref 21. [e] J. H. Wilkinson and I. L. Finar, *J. Chem. Soc.*, 759 (1947). [f] R. B. Moffett and B. D. Aspergren, *J. Am. Chem. Soc.*, **82**, 1600 (1960). [g] See ref 22. [h] Parke, Davis and Co., British Patent 930,477 (1963); *Chem. Abstr.*, **60**, 1670 (1964). [i] K. Fries, R. Böker, and F. Wallbaum, *Ann. Chem.*, **509**, 73 (1934). [j] See ref 12. [k] Farbenfabriken Bayer A.-G., British Patent 720,332 (1955); *Chem. Abstr.*, **50**, 7135 (1956). [l] L. A. Elson and C. S. Gibson, *J. Chem. Soc.*, 294 (1931).

anthranilic acid.[23] The acids **19**, **20**, **22–24**, **26–30**, and **32–34** were prepared by a modified Ullman procedure,[12] using $CuBr_2$, CaI_2, and diglyme.

3,5-Dichloro-4-hydroxy-2-methylbenzoic Acid (XIV). A solution of NaOCl was prepared by bubbling Cl_2 (252 g, 3.55 moles) into a solution of NaOH (341 g, 8.52 moles) in H_2O (470 ml) containing ice (1950 g). 4-Hydroxy-2-methylacetophenone[24] (83.0 g, 0.553 mole) was added to the stirred hypochlorite solution, the latter being cooled with an ice–water bath. Stirring was continued for 20 min, keeping the temperature of the reaction mixture at 10°. The exothermic reaction was then allowed to proceed, with the temperature of the reaction mixture being kept just below 40°. When the exothermic reaction was over, the solution was stirred for an additional 30 min at 40°. The solution was cooled to 25°, when a solution of $NaHSO_3$ (60.0 g) in H_2O (200 ml) was added. The resulting solution was acidified to pH 2 with concentrated HCl. The precipitated solid was collected and crystallized from aqueous EtOH to give XIV (100 g, 82%) as colorless needles, mp 197–210°.

A portion of the product was partitioned between aqueous $NaHCO_3$ and $CHCl_3$. The aqueous layer was separated and acidified with concentrated HCl. The precipitate was recrystallized from aqueous EtOH to give the product as long, colorless needles, mp 220–221.5°.

Anal. Calcd for $C_8H_6Cl_2O_3$: C, 43.47; H, 2.74; Cl, 32.08. Found: C, 43.75; H, 2.86; Cl, 32.16.

2,6-Dichloro-3-methylphenol[13] **(VIII).**—A suspension of XIV (191.6 g of the material with mp 197–210°) in *N*,*N*-dimethylaniline (422 g) was heated at 160° until the evolution of CO_2 had ceased. The reaction mixture was then heated at 190° for 0.5 hr. Concentrated HCl (450 ml) was carefully added, with stirring, to the cooled reaction mixture. The resulting solution was extracted (Et_2O, six 200-ml portions). The combined ether extracts were washed with 6 *N* HCl followed by water. After drying (Na_2SO_4), the ether was removed to leave a liquid which was distilled. VIII (148.6 g, 96.8%) was collected as the fraction with bp 103.5–105° (3.9 mm), lit.[13] bp 240.5–242.5°.

2,4-Bis(2,6-dichloro-3-methylphenoxy)quinazoline (IX).—A solution of VIII (97.8 g, 0.552 mole) in DMF (150 ml) was slowly added to a stirred suspension of NaH (22.6 g of a 58.6% NaH dispersion in mineral oil, 0.552 mole of NaH) in DMF (100 ml). When the evolution of H_2 had ceased, the resulting solution was heated to 100°. A solution of 2,4-dichloroquinazoline[15] (55.0 g, 0.276 mole) in DMF (275 ml) was then added and the mixture was heated at 144° for 18 hr. The DMF was removed under vacuum, and the residue was extracted (hot C_6H_6). The benzene extract (A) and the residue (B) were then worked up separately.

The extract A was concentrated until crystalline material separated. The pale yellow crystals (61.2 g), mp 196.5–200°, were collected by filtration. The filtrate was reduced to dryness and the black gummy residue was purified by chromatography in C_6H_6 over alumina (Merck, 450 g) to give a yellow crystalline product (22.9 g), mp 180–190°, ir spectrum identical with that of the product with mp 196.5–200°.

The residue B was partitioned between $CHCl_3$ and H_2O. The $CHCl_3$ layer was dried (Na_2SO_4) and reduced to dryness. The residue was recrystallized from Skellysolve B to give a colorless product (9.6 g), mp 198.4–201.5°, ir spectrum identical with that of the product with mp 196.5–200°. The total yield of once-crystallized IX was 93.7 g (70.7%). A portion of the product with mp 198.4–201.5° was recrystallized twice from Skellysolve B to give colorless crystals, mp 199–201°.

Anal. Calcd for $C_{22}H_{14}Cl_4N_2O_2$: C, 55.03; H, 2.94; Cl, 29.54; N, 5.84. Found: C, 55.32; H, 3.07; Cl, 29.67; N, 6.00.

1,3-Bis(2,6-dichloro-3-methylphenyl)-2,4-quinazolinedione (X).—A suspension of IX (10.0 g) in mineral oil (25 ml) was heated under N_2 by means of a bath at 345–350° for 2.2 hr.[9a] Skellysolve B (100 ml) was added to the cooled reaction mixture which was then filtered. The collected solid was powdered and extracted for 17 hr with Skellysolve B in a Soxhlet apparatus. The extract was reduced to dryness to leave an orange solid (4.0 g). Ir spectra of the extracted material and the residue (3.5 g) in the Soxhlet thimble were identical. The extracted solid was recrystallized twice (MeCN, Norit) to give pale yellow crystals, mp 272–274°.

Anal. Calcd for $C_{22}H_{14}Cl_4N_2O_2 \cdot 0.5C_2H_3N$: C, 55.17; H, 3.12; Cl, 28.33; N, 7.00. Found: C, 55.43; H, 3.03; Cl, 28.30; N, 6.98.

N-(2,6-Dichloro-3-methylphenyl)anthranilic Acid[12] **(31).** A suspension of X (50.0 g) in ethylene glycol (600 ml) and H_2O (100 ml) containing KOH (100 g) was heated under reflux, with stirring, until solution occurred (2.5 hr). Most of the water, containing some XII, was allowed to distil slowly from the refluxing mixture. The remaining aniline was then removed from the reaction mixture by steam distillation. The cooled reaction mixture was poured into cold H_2O (2 l.). The resulting solution was cooled (ice–water bath) and acidified to pH 2 with concentrated HCl. The precipitated solid was collected, washed (cold H_2O), and dried to give 28.5 g (92.6%) of the acid **31**, mp 245–248° dec. The aqueous distillates were combined and extracted ($CHCl_3$). The $CHCl_3$ solution was dried (Na_2SO_4) and evaporated to give 14.2 g (77.6%) of the liquid aniline XII, bp 135–136° (24 mm), lit.[24] mp 37–38°.

2-Anilinobenzamides. Method A.—Compounds **35–37**, **39–41**, **43–45**, **47**, **50**, and **51** were prepared by procedures similar to the one described for 2-(2-chloro-5-trifluoromethylanilino)-benzamide (**45**), as follows. A solution of *N*-(2-chloro-5-trifluoromethylphenyl)anthranilic acid (**28**) (24.2 g, 0.0767 mole) in CH_2Cl_2 (250 ml) containing $SOCl_2$ (9.6 g, 0.0806 mole) and DMF (0.5 ml) was heated under reflux for 3.25 hr. The cooled reaction mixture was poured, with good stirring, onto ice-cold, concentrated NH_4OH (400 ml). The mixture was stirred at 25° for 2 hr. The CH_2Cl_2 and aqueous layers were separated and the latter was extracted with fresh CH_2Cl_2. The combined CH_2Cl_2 solutions were dried (Na_2SO_4) and reduced to dryness to give **45** as tan crystals (22.0 g, 91%), mp 157–165°.

A catalytic amount of DMF was required to initiate acid chloride formation for some examples of this method.

Method B.—Compounds **46**, **48**, and **49** were prepared by procedures similar to the one described for 2-(2,4,6-trichloroanilino)benzamide (**49**), as follows. A suspension of *N*-(2,4,6-trichlorophenyl)anthranilic acid (17.0 g) in $SOCl_2$ (100 ml) was heated in an oil bath at 60° until the gaseous evolution ceased. The excess $SOCl_2$ was removed in a rotary evaporator, C_6H_6 (25 ml) was added, and the solution again was reduced to dryness. The tan, solid residue was added portionwise to cold, concentrated NH_4OH (225 ml) and the mixture was stirred for 16 hr at 25°. The colorless product was collected and dried to give 15.6 g (92.2%) of **49**, mp 186.5–189°.

Method C.—Compounds **38** and **42** were prepared by ammonolysis of ethyl *N*-(3-trifluoromethylphenyl)anthranilate[25] and methyl *N*-(2,3-dimethylphenyl)anthranilate,[26] respectively.

A solution of ethyl *N*-(3-trifluoromethylphenyl)anthranilate (225.0 g, 0.73 mole) and $NaOCH_3$ (40.0 g, 0.74 mole) in dry MeOH (1 l.) was saturated with NH_3. The reaction mixture was allowed to stand at room temperature for 156 hr. During this time the mixture was resaturated with NH_3 after 60, 84, 108, and 132 hr. The reaction mixture was reduced to dryness and the residue was poured onto ice-water. The precipitated product was extracted ($CHCl_3$). The $CHCl_3$ extract was washed (H_2O) and diluted with Skellysolve B. The solution was then reduced in volume in a rotary evaporator until crystallization commenced. The resulting mixture was cooled to yield 200 g (97.6%) of 2-(3-trifluoromethylanilino)benzamide (**38**), mp 125–127°.

A suspension of methyl *N*-(2,3-dimethylphenyl)anthranilate (84.0 g, 0.33 mole) and $NaOCH_3$ (17.8 g, 0.33 mole) in MeOH (1.2 l.) and C_6H_6 (400 ml) was saturated with NH_3. The suspension was allowed to stand at room temperature for 32 days, with resaturation with NH_3 after 1, 4, 7, and 12 days. The MeOH and C_6H_6 were removed, and a $CHCl_3$ solution of the residue was washed (H_2O), dried (Na_2SO_4), and reduced to dryness. The residue was washed with cold Skellysolve B to leave 34 g (42.8%) of 2-(2,3-dimethylanilino)benzamide (**42**), mp 148–151°.

2-Anilinobenzonitriles.—All of the nitriles in Table I were prepared by a method similar to that described for 2-(2,6-dichloro-3-methylanilino)benzonitrile (**65**), as follows.

Triethylamine (9.63 g, 0.0950 mole) was added to a cooled (ice–water bath) suspension of 2-(2,6-dichloro-3-methylanilino)-

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benzamide (**48**) (14.0 g, 0.0475 mole) in redistilled $POCl_3$ (100 ml), and the mixture was heated under reflux for 0.5 hr. The excess $POCl_3$ was removed under reduced pressure. A $CHCl_3$ solution of the residue was washed (aqueous K_2CO_3, H_2O). The solution was dried (Na_2SO_4) and the $CHCl_3$ was removed. The residue was exhaustively extracted with boiling Skellysolve B. The combined extracts were reduced in volume and cooled to yield 10.5 g (80.2%) of **65** as pale yellow needles, mp 129.5–132°.

5-(2-Anilinophenyl)tetrazoles.—All of the tetrazoles in Table I were prepared from the corresponding nitriles by the general procedure of Finnegan, *et al.*,[11] as illustrated for 5-[2-(2,6-dichloro-3-methylanilino)phenyl]tetrazole (**14**) as follows. A mixture of 2-(2,6-dichloro-3-methylanilino)benzonitrile (9.0 g, 0.0325 mole), NaN_3 (2.54 g, 0.039 mole), and NH_4Cl (2.09 g, 0.039 mole) in DMF (65 ml) was heated, with stirring, at an oil bath temperature of 127° for 17 hr. The DMF was removed under reduced pressure and the residue was suspended in cold H_2O (300 ml) which was acidified to pH 2 with concentrated HCl (beware of any liberated HN_3). The solid product was collected and recrystallized from aqueous MeOH (Norit) to give **14** (8.6 g, 82.7%) as yellow needles: mp 207–208.5° dec; uv maxima (95% EtOH, 0.01 *N* in HCl), 280 mμ (ε 7510), 329 mμ (ε 7360).

5-[2-(3-Trifluoromethylanilino)phenyl]tetrazole (**4**), mp 205–207°, had uv maxima (95% EtOH, 0.01 *N* in HCl), 287 mμ (ε 16,200), 336 mμ (ε 7500).

Alternative Preparation of 5-[2-(3-Trifluoromethylanilino)-phenyl]tetrazole (4).—A solution of 5-(2-bromophenyl)tetrazole[27] (5.0 g, 0.0222 mole) in dry hexamethylphosphoramide (20 ml) was added slowly to a cooled (ice–water), stirred suspension of NaH (1.80 g of a 59.4% NaH dispersion in mineral oil, 0.0446 mole of NaH) in hexamethylphosphoramide (20 ml). When the vigorous evolution of H_2 had ceased, 3-trifluoromethylaniline (3.58 g, 0.0222 mole) was added to the reaction mixture. The temperature of the mixture was slowly raised under N_2. At about 120° a further gaseous evolution occurred. When this reaction had subsided, the mixture was then heated at 185° for 1.5 hr. The cooled reaction mixture was diluted (cold H_2O, 400 ml). The resulting solution was acidified to pH 2 with concentrated HCl. The acidified mixture was extracted ($CHCl_3$, four 100-ml portions). The combined extracts were washed (cold H_2O, 100 ml). The $CHCl_3$ solution was then extracted with 10% aqueous NaOH (two 50-ml portions). The combined NaOH extracts were acidified to pH 2 with concentrated HCl. The resulting mixture was extracted ($CHCl_3$, four 50-ml portions). The combined $CHCl_3$ extracts were washed (H_2O, 50 ml), dried (Na_2SO_4), and filtered, and the filtrate was reduced to dryness. The brown oily residue (8.0 g) was purified by chromatography on silicic acid (300 g). The crude product was introduced onto the column in a mixture of Me_2CO (5 ml) and C_6H_6 (25 ml). The column was eluted with Me_2CO–C_6H_6 (1:20). After the first 400-ml fraction, the eluate was collected in 300-ml fractions. A buff, crystalline solid (1.9 g, 28% yield) was obtained after the removal of the solvent from fractions 2–4, inclusive. The solid had mp 198–202°, with mmp 202–205° with authentic 5-[2-(3-trifluoromethylanilino)phenyl]tetrazole (**4**). The solid was recrystallized from aqueous EtOH to give buff crystals, mp 205–207° (ir spectrum identical with authentic **4**).

A repeat of the above reaction using 5-(2-chlorophenyl)-tetrazole[27] in place of the 5-(2-bromophenyl)tetrazole gave **4** in 34.5% yield. A repeat using 5-(2-chlorophenyl)tetrazole (0.0222 mole), NaH (0.0666 mole), and 3-trifluoromethylaniline (0.0444 mole) gave **4** in 46% yield.

1-Methyl-5-[2-(3-trifluoromethylanilino)phenyl]tetrazole (XVIII) and 2-Methyl-5-[2-(3-trifluoromethylanilino)phenyl]-tetrazole (XIX).—A cooled (ice–water bath) suspension of 5-[2-(3-trifluoromethylanilino)phenyl]tetrazole (10.0 g) in Et_2O (100 ml) was treated with an ethereal solution of excess CH_2N_2. Excess CH_2N_2 and Et_2O were removed. Fractional recrystallization of the residue from MeOH gave two products. The first product (9.4 g) was recrystallized from MeOH to give colorless crystals of XIX, mp 119.5–121°, nmr peak ($CDCl_3$) at δ 4.39 (3 H singlet, $CH_3N<$).

Anal. Calcd for $C_{15}H_{12}F_3N_5$: C, 56.41; H, 3.79; N, 21.94. Found: C, 56.24; H, 3.87; N, 21.95.

The second product (0.9 g) was recrystallized from cyclohexane to give pale yellow crystals of XVIII, mp 116–117.5°, nmr peak ($CDCl_3$) at δ 4.18 (3 H singlet, $CH_3N<$).

Anal. Calcd for $C_{15}H_{12}F_3N_5$: C, 56.41; H, 3.79; N, 21.94. Found: C, 56.32; H, 3.98; N, 21.99.

Acknowledgment.—We are indebted to Dr. Max E. Bierwagen and his staff for all the pharmacological data. We also wish to thank Mr. J. Bomstein for the pK_a determinations, Mr. J. C. Heffernan and Mr. R. B. Babel for technical assistance, and the analytical and spectroscopic departments for their services.

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Steroids. CCCX.[1] Structure–Activity Relationship of Some Steroidal Hypnotic Agents

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Received June 28, 1967

A total of 62 steroids, some of them new, and belonging to different chemical classes were studied for hypnotic activity. A few members of the 5α- and 5β-pregnane and 19-norpregnane class were outstanding as hypnotic agents, markedly surpassing 21-hydroxy-5β-pregnane-3,20-dione and the commonly known short-acting barbiturates in potency. These compounds were particularly effective when given intravenously in nonaqueous solvents, *i.e.*, glycols or dimethyl sulfoxide. About half of the compounds were either inactive or gave rise to CNS stimulation. The water-soluble succinates of the potent pregnane derivatives were uniformly less effective and slower acting than the free alcohol and ketone forms. Pregn-4-enes, pregn-5-enes, and the few androstane- and estrane-type steroids studied exhibited negligible hypnotic activity.

Certain classes of hormonal and nonhormonal steroids are known to possess significant influence on the central nervous system of mammals. A large number of these compounds exhibit hypnotic effects,[3,4] while some produce CNS stimulation with convulsions.[4,5] The first observations of Selye[6] on the sedative and hypnotic actions of progesterone and some other pregnanes were followed by efforts concerned with the synthesis of therapeutically useful anesthetic steroids. Main emphasis was placed on the synthesis

(1) Part CCCIX: see P. Crabbé, A. Cruz, and J. Iriarte, submitted for publication.

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