**11-[4-(2-Hydroxyethyl)-1-piperazinyl]-2-trifluoromethoxydibenz[b,f][1,4]oxazepine (3).**—A mixture of 400 mg (0.87 mmol) of 11·HCl, 400 mg of $P_2O_5$, and 4 ml of $POCl_3$ was heated at reflux temperature for 18 hr. The product was isolated as described for **2**. The ethereal solution of **3** thus obtained was treated with ethereal $H_2SO_4$ to give a white solid having an indefinite melting point. This material was reprecipitated from acetone with $Et_2O$ to give 173 mg (33%) of the bis-bisulfate salt of **3**. *Anal.* ($C_{20}H_{20}F_3N_3O_3 \cdot 2H_2SO_4$): C, H, F, N, S.

**11-[4-(2-Chloroethyl)-1-piperazinyl]-2-trifluoromethoxydibenz[b,f][1,4]oxazepine (4).**—Repetition of the above experiment with 1.26 g of **11**·HCl, 1.26 g of $P_2O_5$, and 12.6 ml of freshly opened $POCl_3$ gave 1.02 g of an oil that was chromatographed on a synthetic magnesia–silica absorbent. The material (360 mg) eluted by 1% AcMe–$CH_2Cl_2$ crystallized from $Et_2O$–petroleum ether (bp 30–60°) to give 201 mg (17%) of white crystals, mp 103–105°. Further elution of the column with more polar solvents failed to give any appreciable material. *Anal.* ($C_{20}H_{19}ClF_3N_3O_2$): C, H, Cl, N.

***p*-Trifluoromethoxybenzanilide** was prepared by Schotten–Bauman acylation of *p*-trifluoromethoxyaniline with PhCOCl. The amide was recrystallized from AcMe–$C_6H_6$ to give crystals, mp 185–187°. *Anal.* ($C_{14}H_{10}F_3NO_2$): C, H, F, N.

***N*-Benzoyl-2-nitro-4'-trifluoromethoxydiphenylamine (13).**—A suspension of 10.38 g (0.037 mol) of *p*-trifluoromethoxybenzanilide and 7.7 g (0.037 mol) of $PCl_5$ in 185 ml of $C_6H_6$ was heated at reflux temperature for 1 hr. The solution was evaporated, and $C_6H_6$ addition and removal was repeated twice. The crude imino chloride was dissolved in 75 ml of $Et_2O$ and added dropwise to a MeOH solution of *o*-$NaOC_6H_4NO_2$ (prepared from 2.0 g (0.037 mol) of NaOMe, 5.15 g (0.037 mol) of *o*-nitrophenol, and 80 ml of MeOH). The mixture was stirred at room temperature for 3 hr and distributed between $Et_2O$ and $H_2O$. The dried extract was evaporated, and the residue was dissolved in hexane; the solution deposited 13.09 g of *o-nitrophenyl N-(p-trifluoromethoxyphenyl)benzimidate* (**12**) as white needles, mp 80–82°.

A solution of crude **12** in 130 ml of *o*-$Cl_2C_6H_4$ was heated at reflux temperature for 1.75 hr. The solvent was removed by steam distillation, and the residue was extracted with $CH_2Cl_2$. The dried extract was evaporated, and the residue was recrystallized from acetone–hexane to give 11.9 g (80%) of **13** as yellow needles, mp 122–123°. *Anal.* ($C_{20}H_{13}F_3N_2O_4$): C, H, F, N.

**2-Nitro-4'-trifluoromethoxydiphenylamine (14).**—A mixture of 7.60 g (18.9 mmol) of the *N*-benzoyl derivative **13**, 46 ml of ethanol, and 24 ml of 10% NaOH was heated at reflux temperature for 1 hr. The cooled solution was diluted ($H_2O$) to give 5.60 g (99%) of orange crystals, mp 68–70°. A similar preparation was recrystallized from MeOH–$H_2O$ to give crystals, mp 68–70°. *Anal.* ($C_{13}H_9F_3N_2O_3$): C, H, F, N.

**4-Methyl-2'-(*N*-methyl-*p*-trifluoromethoxyanilino)-1-piperazinecarboxanilide (18).**—A solution of 5.6 g (18.8 mmol) of **14** in 58 ml of MeAc was treated with 5.8 g of powdered KOH and 1.8 ml of $Me_2SO_4$. The mixture was swirled for 5 min, 4.0 ml of $Me_2SO_4$ was added, and the mixture was boiled 5 min. An additional 2.8 g of KOH and 2.8 g of $Me_2SO_4$ were added, and the mixture was swirled 5 min, boiled for 5 min, and distributed between $CH_2Cl_2$ and $H_2O$. The dried organic solution was evaporated, and the residue was azetropically evaporated with toluene to give 6.00 g of crude *N-methyl-2-nitro-4'-trifluoromethoxydiphenylamine* (**15**) as an oil.

A mixture of 5.80 g (18.6 mmol) of crude **15** and 8 g of wet Raney Ni was hydrogenated to give 5.2 g of *2-amino-N-methyl-4'-trifluoromethoxydiphenylamine* (**16**) as an amber oil.

Acylation of 5.0 g of **16** with phenyl chloroformate in pyridine as described above furnished 7.9 g of *phenyl 2-(N-methyl-p-trifluoromethoxyanilino)carbanilate* (**17**).

Treatment of **17** with 8 ml of 1-methylpiperazine in 120 ml of $C_6H_6$ as described in the preparation of **10** gave **18** as an oil. Treatment with 1 *N* HCl gave 7.30 g (87% from 14) of *4-methyl-2'-(N-methyl-p-trifluoromethoxyanilino)-1-piperazinecarboxanilide hydrochloride* as white crystals, mp 235–238°. A sample recrystallized from EtOH–$Et_2O$ had mp 238–240°. *Anal.* ($C_{20}H_{23}F_3N_4O_2 \cdot HCl$): C, H, F, N.

**5-Methyl-11-(4-methyl-1-piperazinyl)-2-trifluoromethoxy-5H-dibenz[b,e][1,4]diazepine (5).**—A mixture of 300 mg (0.68 mmol) of 4-methyl-2'-(*N*-methyl-*p*-trifluoromethoxyanilino)-1-piperazinecarboxanilide (**18**) and 285 mg (2.0 mmol) of $P_2O_5$ in 3 ml of $POCl_3$ was stirred at reflux temperature for 3.5 hr. The cooled mixture was cautiously diluted ($H_2O$) and filtered to give 25 mg (12%) of crude *5,10-dihydro-5-methyl-11H-dibenz[b,e][1,4]diazepin-11-one* (**19**); material from a similar preparation was recrystallized from dilute MeAc to give crystals, mp 230–232°. *Anal.* ($C_{15}H_{11}F_3N_2O_2$): C, H, F, N. The filtrate was rendered alkaline ($NH_4OH$) to give 180 mg (68%) of **5** as yellow crystals, mp 140–143°. Two recrystallizations from dilute MeAc gave mp 146–148°. *Anal.* ($C_{20}H_{24}F_3N_4O$): C, F, N; H: calcd, 5.42; found, 5.88.

---

## α,α,α-Trifluorotoluic Acid (5-Nitrofurfurylidene)hydrazides

DEAN E. WELCH,

*Research Division, Salsbury Laboratories, Charles City, Iowa 50616*

HARRY S. NAKAUE,

*Department of Agricultural Chemistry, Oregon State University, Corvallis, Oregon 97331*

AND ROBERT D. VATNE

*Animal Science Research and Development, Agricultural Department, The Dow Chemical Company, Midland, Michigan 48640*

*Received September 22, 1969*

Our interest in trifluoromethylbenzamides[1] and anilides[2] as antiprotozoal agents prompted us to prepare a series of nitrofurfurylidene derivatives of α,α,α-trifluorotoluic acids. The activities of some 5-trifluoromethyl furfurylidene derivatives have been reported and the utility of 3,5-dinitrosalicylic acid (5-nitrofurfurylidene)hydrazide (DNSNF) is also known.[3,4] The synthesis and screening of a series of compounds bearing both trifluoromethylbenzoyl and nitrofurfurylidene moieties seemed worthwhile to determine what effect replacement of a DNSNF nitro group with $CF_3$ would have on activity.

The compounds prepared for testing are listed in Table I. Primary emphasis was placed on structures similar to DNSNF or which might conceivably imitate its *in vivo* pathways. The synthesis steps were conventional and were accomplished *via* the acid chloride–5-nitrofurfural hydrazone route (**2**, **7**, **8**) or, for the other compounds, by treating the appropriate acid hydrazide with 5-nitro-2-furaldehyde.

Each compound was tested for efficacy against coccidiosis in chickens, histomoniasis (blackhead) in turkeys, helminthiasis in chickens and mice, and for inhibition of bacteria cultured *in vitro*. Growth promotion and feed efficiency effects were also determined in poultry and swine. The only significant activities found were for blackhead and growth-feed efficiency; these results are shown in Table I. The most effective compound tested (**6**) was structurally similar to DNSNF; however, the antiblackhead activity did not approach that of DNSNF.

This represents another example of replacement of $NO_2$ with $CF_3$ in a biologically active molecule without complete loss of activity.[1,3]

(1) D. E. Welch, R. R. Baron, and B. A. Burton, *J. Med. Chem.*, **12**, 299 (1969).

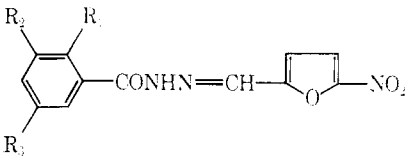
(2) D. E. Welch and R. R. Baron, *ibid.*, **12**, 957 (1969).

(3) R. E. Bambury, H. K. Yatkin, and K. K. Wyckoff, *J. Heterocycl. Chem.* **5**, 95 (1968).

(4) E. W. Berndt, H. Van Essen, B. G. Held, and R. D. Vatne, *J. Med. Chem.*, **12**, 371 (1969).

TABLE I

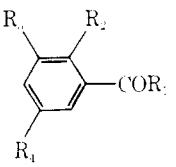
α,α,α-TRIFLUOROTOLUIC ACID 5-NITROFURFURYLIDENEHYDRAZIDES



| No. | $R_1$ | $R_2$ | $R_3$ | Mp °C[a] (recrystn solvent) | % yield | Formula[b] | Min. effect. dose[c] % in feed: Blackhead | Min. effect. dose[c] % in feed: Growth efficiency |
|---|---|---|---|---|---|---|---|---|
| 1 | H | $CF_3$ | H | 211–212[d] | 72 | $C_{13}H_8F_3N_3O_4$ | NE[c] | NE[c] |
| 2 | $CF_3$ | H | H | 207–209[e] | 99 | $C_{13}H_8F_3N_3O_4$ | NE | NE |
| 3 | H | $CF_3$ | $CF_3$ | 240.5–241.5[d] | 84 | $C_{14}H_7F_6N_3O_4$ | NE | NE |
| 4 | H | $CF_3$ | $NO_2$ | 241–242[d] | 74 | $C_{13}H_7F_3N_4O_6$[f] | NE | NE |
| 5 | Cl | H | $CF_3$ | 212–213[g] | 89 | $C_{13}H_7ClF_3N_3O_4$ | NE | NE |
| 6 | OH | $NO_2$ | $CF_3$ | 227 dec[h] | 78 | $C_{12}H_7F_3N_4O_7$ | 0.025 | 0.00125 |
| 7 | Cl | $NO_2$ | $CF_3$ | 192–193[e] | 30 | $C_{13}H_6ClF_3N_4O_6$ | NE | 0.005 |
| 8 | $OCH_3$ | $NO_2$ | $CF_3$ | 223–225[e] | 67 | $C_{14}H_9F_3N_4O_7$ | 0.05 | 0.005 |
| 9 | $NH_2$ | $NO_2$ | $CF_3$ | 256–257[g] | 81 | $C_{13}H_8F_3N_5O_6$[i] | 0.05 | 0.005 |

[a] Melting points reported here and in the Experimental Section are uncorrected and were taken in open capillaries using a Thomas-Hoover apparatus. [b] All compounds here and in the Experimental Section were analyzed for C, H, N using an F & M Model 185 analyzer; analytical results obtained were within ±0.4% of the theoretical values. Ir spectra were consistent with the structure and were determined in KBr disks with a Beckman IR4 spectrophotometer. [c] NE means not effective at highest dosage tested (0.05%). [d] EtOH. [e] MeCN–$H_2O$. [f] Also analyzed for F by Schwarzkopf Microanalytical Laboratories, Woodside, N. Y. Results obtained were within ±0.4% of the theoretical values. [g] MeCN. [h] AcOH. [i] N: calcd, 18.09; found, 17.47.

TABLE II



| $R_1$ | $R_2$ | $R_3$ | $R_4$ | Bp °C (mm) | Mp (°C) | % yield | Formula | Anal. |
|---|---|---|---|---|---|---|---|---|
| $OCH_3$ | Cl | H | $CF_3$ | 51–53 (0.17) | | 77 | $C_9H_6ClF_3O_2$ | C, H, F |
| $OCH_3$ | H | $CF_3$ | $CF_3$ | 37–40 (0.80) | | 77 | $C_{10}H_6F_6O_2$ | C, H, F |
| $NHNH_2$ | Cl | H | $CF_3$ | | 150–152 | 84 | $C_8H_6ClF_3N_2O$ | C, H, N |
| $NHNH_2$ | H | $CF_3$ | $CF_3$ | | 133–134 | 91 | $C_9H_6F_6N_2O$ | C, H, N, F |
| $NHNH_2$ | H | $CF_3$ | $NO_2$ | | 115–117 | 71 | $C_8H_6F_3N_3O_3$ | C, H, N, F |
| $NHNH_2$ | $NH_2$ | $NO_2$ | $CF_3$ | | 153–154 | 63 | $C_8H_7F_3N_4O_3$ | C, H, N |

## Experimental Section[5]

**General Synthesis Scheme for 2, 7, and 8.**—The chloride of the appropriate acid[1,6] (0.10 mol) was prepared by heating at reflux for about 4 hr in excess $SOCl_2$. $SOCl_2$ was removed under vacuum and the residue (neat or in $C_6H_6$) was slowly added to 0.10 mol of 5-nitro-2-furfural hydrazone in about 75 ml of pyridine cooled below 40°. After stirring at room temperature for 0.5 hr, the mixture was poured into ice–$H_2O$ and the solid recovered by filtration.

**General Synthesis Scheme for 1, 3–6, and 9.**—A solution of the appropriate acid hydrazide[7] (0.05 mol) and 5-nitro-2-furaldehyde (0.05 mol) in about 300 ml of EtOH was stirred and heated at reflux for 0.5 hr. The resulting thick, yellow suspension was cooled and filtered and the residue recrystallized.

**Hydrazides for 3–5 and 9.**—Fischer esterification of the appropriate acid[1,8] gave the methyl ester.[9] The ester was then heated at reflux for several hours in EtOH with excess hydrazine hydrate and then concentrated under vacuum to give the hydrazide which was recrystallized from $C_6H_6$. The results are given below. See Table II.

**Biological Methods.**—The efficacy of **1**–**9** against *Histomonas meleagridis* was determined in Broad Breasted Bronze or Broad Breasted White turkeys. Poults reared in wire-bottom cages were orally inoculated with approximately 1000 embryonated cecal worm (*Heterakis gallinarum*) ova per bird at approximately 6 weeks of age. Prior experimentation had confirmed the presence of *H. meleagridis* in these ova. All tests were 28 days in duration. Turkeys were infected on the first day of the test. Medicated feed was given the first 21 days and nonmedicated the final 7 days of each experiment. The criteria of efficacy were (1) the absence of typical blackhead cecal or liver lesions at postmortem examination and (2) the rate of mortality. The findings were compared with infected, unmedicated controls in each experiment.

Growth and feed efficiency studies were conducted on broiler-type chicks or turkey poults in battery brooders. Tests were of 4 weeks duration with medicated feed provided *ad libitum* throughout the 4-week period. Each bird was weighed initially and at the end of 4 weeks and the mean weight gain and feed conversion of each test group were compared to that of control groups fed nonmedicated feed. Swine growth and feed conversion studies were similarly conducted on young pigs. Data were evaluated for significance at $P \leq 0.05$ using analysis of variance and Duncan multiple range techniques. For a compound to be rated effective, the medicated groups had to show a statistically significant improvement over nonmedicated controls.

**Acknowledgments.**—The authors wish to thank Mr. W. Dunkel and Mr. H. Fratzke for assistance with some of the syntheses and Mrs. C. Barker and Mr. M. Carr for obtaining the analytical data. The statistical evaluations were obtained by Mr. J. Narveson.

(5) Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values.

(6) *o*-Trifluoromethylbenzoic acid and chloride are available from Pierce Chemical Co., Rockford, Ill.

(7) The hydrazides for **1** and **6** are described in ref 1.

(8) J. Lichtenberger and F. Weiss, *Bull. Soc. Chim. Fr.*, 487 (1962).

(9) The esters used in the preparation of **4** and **9** are described in ref 1.