reaction mixture and it was heated at 140° for 10 hr. After cooling, the reaction mixture was poured into H_2O and acidified with dilute HCl. The organic layer was separated and the aqueous layer was extracted with $CHCl_3$. The combined organic layer was washed with H_2O, dried ($MgSO_4$), and concentrated under reduced pressure. The oily residue crystallized on treatment with EtOH and was recrystallized from EtOH to give the corresponding 1-phenyl-2-styryl-4-*n*-butyl-3,5-dioxopyrazolidine derivative.

1-Phenyl-2-styryl-4-*n*-pentyl-3,5-dioxopyrazolidine (31). Method 1.—A solution of 5 g of phenylacetaldehyde phenylhydrazone and 17 g of diethyl *n*-pentylmalonate in 150 ml of xylene was added to a solution of NaOEt (3 g of Na) in 100 ml of EtOH. The mixture was stirred at 100° until the EtOH was removed from the mixture; stirring was continued at 140° for an additional 14 hr. The reaction mixture was poured into H_2O and acidified with dilute HCl. The organic layer was separated and the aqueous layer was extracted with EtOAc. The extract was combined with the organic layer, washed with H_2O, dried (Na_2SO_4), and evaporated under reduced pressure. The oily residue crystallized on treatment with EtOH. Recrystallization from EtOH–C_6H_6 gave 10 g of **31**.

Method 2.—A mixture of 6 g of phenylacetaldehyde and 5.5 g of phenylhydrazine in 150 ml of C_6H_6 was heated at 50–60° for 0.5 hr. The reaction mixture was decanted to remove H_2O and dried (Na_2SO_4). The solution of phenylacetaldehyde phenylhydrazone in C_6H_6 was added to a solution of NaOEt (2 g of Na) and 12 g of diethyl *n*-pentylmalonate in 100 ml of EtOH. After excess of the solvent was distilled off, 100 ml of xylene was added to the residual mixture and the mixture was heated at 140° for 10 hr. By subsequent treatment similar to that of method 1 1.5 g of **31** was obtained.

Pharmacological Tests.—The antiinflammatory activity of these compounds was tested in the carrageenin-induced foot edema in rats.[8] The results are shown in Table II.

Acknowledgment.—The authors wish to express their appreciation to Dr. H. Nakatani, Mr. C. Saito, and Mr. H. Awata for the pharmacological screening data and Mr. Iwai and coworkers for the analytical data.

(8) H. Yamamoto and M. Nakao, *J. Med. Chem.* **12**, 176–178 (1969).

2-Trifluoromethoxydibenz[*b*,*e*][1,4]diazepine and 2-Trifluoromethoxydibenz[*b*,*f*][1,4]-oxazepine Derivatives

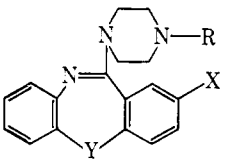
FRANCIS J. MCEVOY, E. N. GREENBLATT, A. C. OSTERBERG, AND GEORGE R. ALLEN, JR.

Process and Preparations Research Section and Experimental Therapeutics Research Section, Lederle Laboratories Division, American Cyanamid Company, Pearl River, New York 10965

Received October 13, 1969

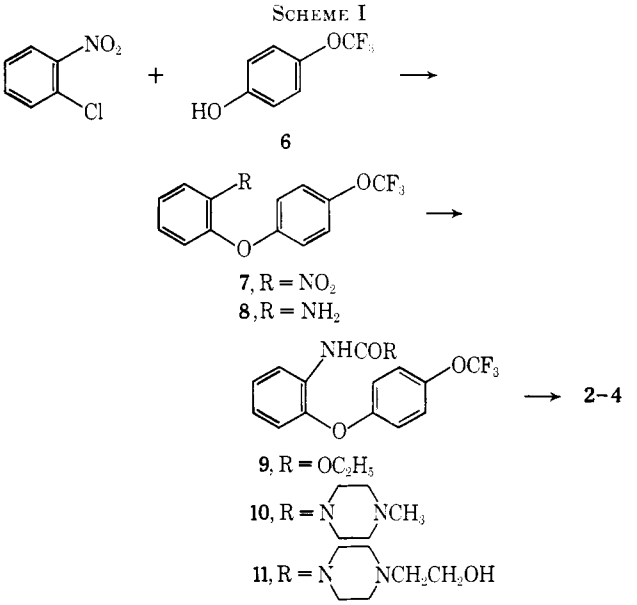
In view of the interest of these laboratories in the action on the central nervous system elicited by 2-chloro-11-(4-methyl-1-piperazinyl)dibenz[*b*,*f*][1,4]oxazepine (**1**)[1b,2] and the demonstrated ability of the trifluoromethoxy group to function as a pseudohalogen,[3] we have prepared the 2-trifluoromethoxy analogs, *e.g.*, **2–5**, of **1** and certain congeners in order to assess their effects on the CNS.

The preparation of the dibenz[*b*,*f*][1,4]oxazepines **2–4** from *p*-trifluoromethoxyphenol (**6**) proceeded as noted



1, R = CH_3; X = Cl; Y = O
2, R = CH_3; X = CF_3O; Y = O
3, R = CH_2CH_2OH; X = CF_3O; Y = O
4, R = CH_2CH_2Cl; X = CF_3O; Y = O
5, R = CH_3; X = CF_3O; Y = NCH_3

SCHEME I



6

7, R = NO_2
8, R = NH_2

9, R = OC_2H_5
10, R = N NCH$_3$
11, R = N NCH_2CH_2OH

in Scheme I. Ring closure of the piperazinecarboxanilide II ($POCl_3$, P_2O_5) gave the hydroxyethyl derivative **3** in one instance, but repetition with newly opened $POCl_3$ gave the cholorethyl derivative **4**.

With one exception the preparation of the related dibenz[*b*,*e*][1,4]diazepine **5** was accomplished by procedures previously found useful for the synthesis of members of this series.[4] Attempts to prepare the requisite diphenylamine **14** by Cu-catalyzed condensation of *p*-trifluoromethoxyaniline and 2-nitrochlorobenzene proved unsatisfactory. However, Chapman rearrangement[5] of imino ether **12** proved to be an excellent alternative. The conversion of **14** into the desired **4** is outlined in Scheme II.

Pharmacology.—Compounds **2–5** were tested for their ability to induce ataxia, to decrease locomotor activity, and to afford protection against electroshock-induced and strychnine-induced convulsions in mice. The activities of the more interesting trifluoromethoxy compounds are given in Table I. Comparable data for the corresponding chloro derivatives are included. These limited tests suggest that the replacement of 2-Cl by OCF_3 in the 11-(4-substituted 1-piperazinyl)dibenz[*b*,*f*][1,4]oxazepine series results in compounds having similar profiles of CNS effects.

Experimental Section

Melting points were determined in open capillary tubes on a Mel-Temp apparatus and are uncorrected. Where analyses are

(1) (a) C. M. Latimer and L. C. Malone, *Fed. Proc.*, **27**, 438 (1968); (b) C. F. Howell, *et al.*, 1st Northeast Regional Meeting of the American Chemical Society, Boston, Mass., Oct 13, 1968; (c) C. M. Latimer, *J. Pharmacol. Exp. Ther.*, **166**, 151 (1969).

(2) J. Schmutz, S. Künzler, S. Hunziker, and R. Gauch, *Helv. Chim. Acta*, **50**, 245 (1967).

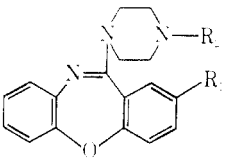
(3) F. J. McEvoy, *et al.*, *J. Med. Chem.*, **11**, 1248 (1968).

(4) F. Hunziker, E. Fischer, and J. Schmutz, *Helv. Chim. Acta*, **50**, 1588 (1967).

(5) J. W. Schulenburg and S. Archer, *Org. React.*, **14**, 1 (1965).

TABLE I

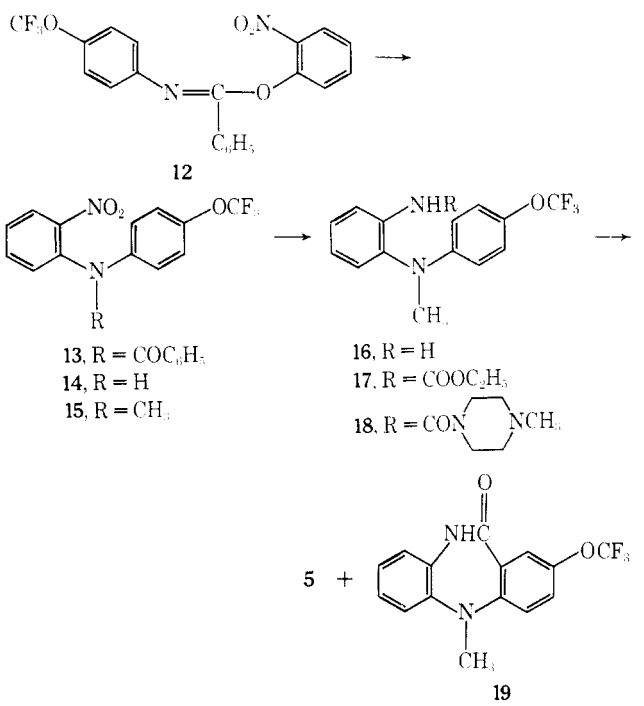
BIOLOGICAL ACTIVITIES OF REPRESENTATIVE 2-SUBSTITUTED 11-(4-SUBSTITUTED 1-PIPERAZINYL)DIBENZ[*b,f*][1,4]OXAZEPINES



Compound	R_1	R_2	Median effective dose, mg/kg ip: Ataxia[a]	Motor activity decrease[a]	Antielectroshock[b]	Antistrychninne[c]	Lethality
1[d]	Cl	Me	1.7	0.2	>50	>50	99
2[e]	OCF_3	Me	4.0	1.4	>50	>50	>14
20[d]	Cl	CH_2CH_2OH	15	2.2	>50	>50	>22
3[f]	OCF_3	CH_2CH_2OH	55	23			

[a] Determined as described by W. B. Wright, Jr., H. J. Brabander, R. A. Hardy, Jr., and A. C. Osterberg, *J. Med. Chem.*, **9**, 852 (1966). [b] Determined as described by E. A. Swinyard, W. C. Brown, and L. S. Goodman, *J. Pharmacol. Exp. Ther.*, **106**, 319 (1952). [c] Determined by a modification of the method of H. M. Hanson and C. A. Stone in "Animal and Clinical Pharmacological Techniques in Drug Evaluation," Vol. I, J. H. Nodine and P. E. Siegler, Ed., Yearbook Medical Publishers, Inc., Chicago, Ill., 1964, p 317. [d] Reference 1b. [e] As the dihydrochloride monohydrate. [f] As the bis bisulfate.

SCHEME II



indicated only by symbols of the elements, analytical results were within ±0.4% of the theoretical values. All evaporations were conducted under reduced pressure.

4-Methyl-2′-(*p*-trifluoromethoxyphenoxy)-1-piperazinecarboxanilide (10).—To a stirred, ice-cooled solution of 11.6 g (0.065 mol) of *p*-trifluoromethoxyphenol (**6**)[6] in 200 ml of dry Et_2O was added portionwise over a period of 15 min 3.06 g (0.065 mol) of NaH as an oil dispersion. When gas evolution subsided, the solution was heated at reflux for 10 min and evaporated. The white residue was dissolved in 100 ml of dry DMF and added to a solution of 10.3 g (0.065 mol) of *o*-$ClC_6H_4NO_2$ in 100 ml of DMF. The stirred solution was heated at reflux temperature for 90 min, cooled, and filtered. The filtrate was evaporated, and the residual oil was partitioned (Et_2O–H_2O). The organic solution was separated and washed successively with 10% NaOH and saline. The dried solution was treated with activated charcoal and evaporated to give 18.2 g (93%) of *2-nitro-4′-trifluoromethoxydiphenyl ether* (**7**) as a yellow oil.

A mixture of **7** and 16 g of wet Raney Ni in 200 ml of EtOHi was shaken under H_2 until the pressure became constant (21 min). It was filtered, and the filtrate was evaporated to furnish 16.0 g (97%) of *2-amino-4′-trifluoromethoxydiphenyl ether* (**8**) as a gum.

To an ice-chilled, stirred solution of **8** in 150 ml of pyridine was added dropwise 8.0 ml (0.059 mol) of phenyl chloroformate; stirring was continued 18 hr at ambient temperature. The mixture was diluted with 1 l. of H_2O and extracted with EtOAc. The organic extract was washed successively with 10% HCl, H_2O, 10% Na_2CO_3, and H_2O. The dried solution was evaporated to afford 24.8 g of crude *phenyl 2-(p-trifluoromethoxyphenoxy)-carbanilate* (**9**).

A solution of 23 ml of 1-methylpiperazine and 24.8 g of **9** in 150 ml of C_6H_6 was boiled in an open flask for 70 min and evaporated. The residual gum was heated in an open flask in a 110° oil bath for 90 min. H_2O was added and the mixture was evaporated. C_6H_6 was added and removed by evaporation. The residue was dissolved in a mixture of 250 ml of Et_2O and 250 ml of 1 *N* HCl. The acid solution was separated, cooled, and made alkaline with 10% NaOH. The alkaline solution was extracted (Et_2O), and the dried extract was evaporated. The residual solid was triturated with 100 ml of hexane to afford 18.0 g of solid, which was recrystallized (AcMe–H_2O) to yield 16.5 g (71%) of white crystals, mp 98–100°, in four crops. A sample recrystallized from Et_2O–petroleum ether (bp 30–60°) had mp 99–100°. *Anal.* ($C_{19}H_{20}F_3N_3O_3$): C, H, F, N.

Treatment of an Et_2O solution of 3.1 g of this substance with ethanolic HCl gave 3.34 g of hydrochloride, mp 214–216°. *Anal.* ($C_{19}H_{20}F_3N_3O_3 \cdot HCl$): C, H, F, N.

4-(2-Hydroxyethyl)-2′-(*p*-trifluoromethoxyphenoxy)-1-piperazinecarboxanilide (11).—A solution of 1.00 g (2.57 mmol) of crude **9** in C_6H_6 was treated with 665 mg (5.0 mmol, 0.44 ml) of 1-β-hydroxyethylpiperazine as described for **10**. Partial neutralization of the 1 *N* HCl extracts with NaOH gave 470 mg (40%) of a crude **11**·HCl as white crystals, mp 212–214°. The filtrate was rendered alkaline with 10% NaOH and extracted (Et_2O) to give 200 mg of **11**, which crystallized from Et_2O–petroleum ether (bp 30–60°) to give 76 mg (7%) of white crystals, mp 76–78°. *Anal.* ($C_{20}H_{22}F_3N_3O_4$): C, H, F, N.

11-(4-Methyl-1-piperazinyl)-2-trifluoromethoxydibenz[*b,f*][1,4]-oxazepine (2).—A mixture of 2.50 g (5.8 mmol) of **10**·HCl, 2.5 g (18 mmol) of P_2O_5, and 25 ml of $POCl_3$ was stirred at reflux temperature for 24 hr. The solution was evaporated and the residual glass was treated cautiously with 150 ml of H_2O. The solution then was treated with 25 ml of 6 *N* HCl, filtered, partially neutralized with 90 ml of 10% NaOH, and rendered alkaline with solid $NaHCO_3$. The mixture was extracted (Et_2O) and the dried extract was evaporated. The residue was dissolved in CH_2Cl_2 and chromatographed on a synthetic magnesia–silica gel adsorbent. The material eluted by 3–5% AcMe in CH_2Cl_2 was isolated by solvent removal to give 879 mg of **2** as an oil. This oil was dissolved in Et_2O and treated with ethanolic HCl to give 1.10 g (40%) of *11-(4-methyl-1-piperazinyl)-2-trifluoromethoxydibenz[b,f][1,4]oxazepine dihydrochloride monohydrate* as white crystals, mp 200–210°. The melting point was unaffected by crystallization from AcMe. *Anal.* ($C_{19}H_{18}F_3N_3O_2 \cdot 2HCl \cdot H_2O$): C, H, F, N, H_2O.

(6) W. A. Sheppard, *J. Org. Chem.*, **29**, 1 (1964).

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).