more recrystallizations [from EtOAc–$(i\text{-Pr})_2O$, then MeOH–H_2O] gave the analytical sample: λ_{max} 247, 289, 320 mμ (ε 37,400, 12,800, 4780); nmr absorption of τ 2.42 (singlet, assigned to proton in position 5), 3.02 (singlet, proton in position 8), 6.0 (singlet, 6 protons of 6,7-OCH_3), 6.58 (singlet, 3 protons of 3-CH_3), 6.75 (quartet, 4 CH_2 protons of $-N(CH_2CH_3)_2$), and 8.83 (triplet, 6 CH_3 protons of $-N(CH_2CH_3)_2$).

4,5-Dimethoxy-N-carboxyanthranilic Anhydride.—The procedure followed was analogous to that described by Wagner and Fegley[35] for the preparation of N-carboxyanthranilic anhydride, except that the product was recrystallized from DMF: yield 41%, mp 274–275°. *Anal.* ($C_{10}H_9NO_5$) C, H, N.

3-Dimethylamino-6,7-dimethoxy-4(3H)-quinazolinone (54).—To a suspension of 13.2 g of 4,5-dimethoxy-N-carboxyanthranilic anhydride in 450 ml of $CHCl_3$ was added 30 ml of Me_2NNH_2, and the mixture was refluxed to complete solution (approximately 1 hr). The solvent was evaporated, and the resulting oily residue was crystallized by trituration in ethanolic HCl. The crystals (11.4 g, mp 231–233°) were dissolved in H_2O, and the solution was made basic with K_2CO_3 solution. Extraction with $CHCl_3$ afforded 9.1 g of an oily residue which was dissolved in 40 ml of HCOOH. This solution was refluxed for 18 hr and concentrated to dryness. The residue was suspended in H_2O, and the solid material was filtered to give 7.7 g of **54**, λ_{max} 242, 286, 308, 319 mμ (ε 70,700, 6110, 5420, 4250).

3-(N-Homopiperidinyl)-6,7-dimethoxy-4(3H)-quinazolinone (57).—4,5-Dimethoxy-N-carboxyanthranilic anhydride (6.69 g, 0.03 mole) and 9.09 g (0.09 mole) of N-aminohomopiperidine were dissolved in 50 ml of DMF, and the solution was warmed to 70°. After 3 hr, the DMF was removed, 80 ml of H_2O was added, and the crystalline solids were filtered. Recrystallization from MeOH–H_2O furnished 4.7 g of crystalline hydrazide, mp 146–147°, which was dissolved in 30 ml of HCOOH. After boiling at reflux for 1 hr, the solution was concentrated to give a crystalline residue which was triturated with H_2O, filtered, and dried. Recrystallization from EtOH afforded 3.4 g of **57**.

Acknowledgment.—The authors wish to express their appreciation to Drs. B. M. Bloom and W. T. Moreland for their interest and advice during the course of this work.

(35) E. C. Wagner and M. F. Fegley, *Org. Syn.*, **27**, 45 (1947).

Notes

Some New 3-Amino-2H-1,2,4-benzothiadiazine 1,1-Dioxides

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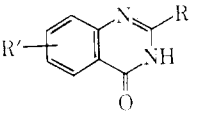
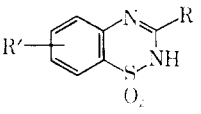
Several members of a series of amino-4(3H)-quinazolinones have been reported to cause antihypertensive effects when administered orally to conscious hypertensive dogs.[1] Particularly active were derivatives with methoxyl substitution in the 6 and 7 positions and dimethylamino, diethylamino, diallylamino, or N-methylpiperazino substitution in position 2 of the quinazoline ring system. These compounds (**1**) bear structural resemblances to certain 3-amino-2H-1,2,4-benzothiadiazine 1,1-dioxides (**2**),[2] which have been reported by others[3] to have hypotensive activity in anesthetized rats. However, in contrast to our observations with the 2-amino-4(3H)-quinazolinone (**1**) series, an unsubstituted amino group (R = NH_2) together with halogen substitution in the aromatic moiety or a secondary amino group (R = NHC_2H_5, NHC_6H_5) appeared to be optimal for activity in **2**. It has also been demonstrated previously that halogen substitution is advantageous for hypotensive activity in the related 3-alkyl-2H-1,2,4-benzothiadiazine 1,1-dioxides,[3,4] of which diazoxide (**2**, R = CH_3; R′ = 7-Cl) has attracted considerable interest, because it apparently lowers blood pressure by acting directly on the peripheral vasculature.[5]

In order to examine the effect of replacing the carbonyl function of the 2-amino-4(3H)-quinazolinones (**1**) with the isosteric sulfonyl moiety, or, alternatively, the effect of 6,7-dimethoxyl substitution in the 2H-1,2,-4-benzothiadiazines on antihypertensive activity, we have prepared the analogs **2** (R = dimethylamino, diethylamino, diallylamino, N-methylpiperazino; R′ = 6,7-OCH_3).



1



2

A suitable starting material was 4,5-dinitroveratrole (**3**)[6] (Scheme I). Reaction of **3** with aqueous sodium sulfite gave the sodium sulfonate **4**, which, without purification, was converted with thionyl chloride to the sulfonyl chloride **5**, in an over-all yield of 76%. Treatment of **5** with aqueous ammonia provided the sulfonamide (**6**) in 91% yield, which, upon reduction of the nitro group with stannous chloride, afforded **7** in 76% yield. The conversion of **7** to **8** was effected in the standard manner[7] by heating with urea. Attempts to chlorinate **8** in refluxing phosphorus oxychloride resulted only in the recovery of starting material.[8] Addition of N,N-dimethylaniline to the reaction mixture furnished the desired product, but

(1) H.-J. Hess, T. H. Cronin, and A. Scriabine, *J. Med. Chem.*, **11**, 130 (1968).

(2) It may be noted that the 3 position in the 2H-1,2,4-benzothiadiazine 1,1-dioxides corresponds to the 2 position in the 4(3H)-quinazolinones.

(3) E. Grana, L. Lilla, and L. Raffa, *Farmaco* (Pavia), *Ed. Sci.*, **17**, 974 (1962); **20**, 647 (1965).

(4) J. G. Topliss, M. H. Sherlock, H. Reiman, L. M. Konzelman, E. P. Shapiro, B. W. Pettersen, H. Schneider, and N. Sperber, *J. Med. Chem.*, **6**, 122 (1963); B. A. Bierbaum, J. J. Traverso, and C. W. Whitehead, *ibid.*, **6**, 272 (1963); J. G. Topliss, L. M. Konzelman, E. P. Shapiro, N. Sperber, and F. E. Roth, *ibid.*, **7**, 269 (1964); N. Pisanti and F. Cresci Mutti, *Farmaco* (Pavia), *Ed. Sci.*, **19**, 1003 (1964).

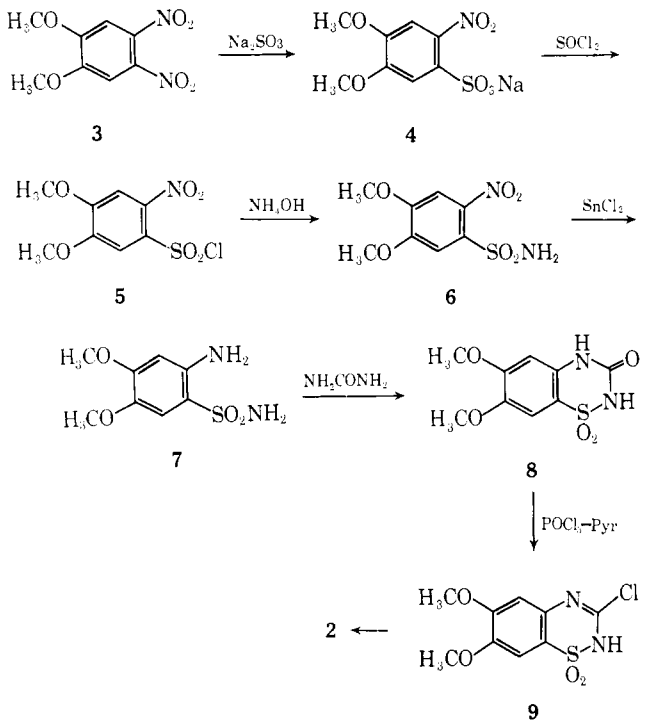
(5) A. A. Rubin, F. E. Roth, R. M. Taylor, and H. Rosenkilde, *J. Pharmacol. Exptl. Therap.*, **136**, 344 (1962); A. A. Rubin, L. Zitowitz, and L. Hausler, *ibid.*, **140**, 46 (1963); A. A. Rubin, *Angiology*, **14**, 74 (1963).

(6) J. Ehrlich and M. T. Bogert, *J. Org. Chem.*, **12**, 522 (1947).

(7) D. V. Parke and R. T. Williams, *J. Chem. Soc.*, 1760 (1950).

(8) Apparently, 3,4-dihydro-2H-3-oxo-1,2,4-benzothiadiazine 1,1-dioxides have not been halogenated previously.

SCHEME I
SYNTHESIS OF 3-AMINO-2H-1,2,4-BENZOTHIADIAZINE 1,1-DIOXIDES



highly colored side-products were formed, and the isolation of **9** was not always reproducible. Chlorination of **8** could be satisfactorily accomplished, however, in yields ranging from 45–50%, with phosphorus oxychloride in the presence of pyridine.[9] The introduction of the amino substituents to give **2** (R′ = 6,-7-OCH_3) was achieved in good yield by refluxing **9** with the appropriate amine in isoamyl alcohol, or by heating the reaction components in ethanolic solution in a pressure vessel at 140°.[10]

While the 2-amino-4(3H)-quinazolinones (**1**) had elicited marked antihypertensive responses in conscious, hypertensive dogs at oral doses of 10 mg/kg,[1] none of the isosteres (**2**) reported here exhibited significant antihypertensive activity at doses up to 30 mg/kg.[11] Furthermore, the isosteres did not exhibit significant hypotensive activity after intravenous administration to anesthetized, normotensive dogs[12] at doses of 10 mg/kg. In comparative studies, diazoxide (**2**, R = CH_3; R′ = 7-Cl) exhibited antihypertensive effects at oral doses of 10–20 mg/kg,[13] whereas its quinazolinone counterpart, 2-methyl-6-chloro-4(3H)-quinazolinone (**1**, R = CH_3; R′ = 6-Cl), was without effect at doses of 40 mg/kg.[14] These observations clearly demonstrate that structure–activity relationships in the 4(3H)-quinazolinone and 2H-1,2,4-benzothiadiazine 1,1-dioxide series, at least in dogs,[3,14] do not parallel each other.

(9) C. Hennart and E. Merlin, *Bull. Soc. Chim. France*, 741 (1959); M. Robba, M. C. Zaluski, and B. Roques, *Compt. Rend.*, **C263**, 813 (1966).

(10) L. Raffa, M. DiBella, M. Melegari, and G. Vampa, *Farmaco* (Pavia), *Ed. Sci.*, **17**, 331 (1962), prepared a series of 3-amino-2H-1,2,4-benzothiadiazine 1,1-dioxide derivatives from 3-methylmercapto precursors (*cf.* ref 3). For the preparation of other 3-amino-2H-1,2,4-benzothiadiazine 1,1-dioxides, see J. G. Topliss and L. M. Konzelman, *J. Org. Chem.*, **28**, 2313 (1963).

(11) The testing procedure was that of M. A. Prioli and M. M. Winbury, *J. Appl. Physiol.*, **15**, 323 (1960), described in ref 1, except that the compounds (**2**) were administered as sodium salts in aqueous solution; diazoxide and 2-methyl-6-chloro-4(3H)-quinazolinone were given in aqueous suspension by stomach tube.

(12) 2-Diethylamino-6,7-dimethoxy-4(3H)-quinazolinone hydrochloride elicited average blood pressure decreases of 67 mm of longer than 60-min duration, following intravenous administration of doses of 10 mg/kg to phenobarbital-anesthetized, normotensive dogs. At the same dose, 3-diethylamino-6,7-dimethoxy-2H-1,2,4-benzothiadiazine 1,1-dioxide (**2b**) lowered the blood pressure by 25 mm, but of only 1–2-min duration.

(13) *Cf.* A. A. Rubin, F. E. Roth, and M. M. Winbury, *Nature*, **192**, 176 (1961).

(14) See, however, the report by G. Pala and E. Marazzi-Uberti, *Arzneimittel-Forsch.*, **12**, 1204 (1962), that compound 2-methyl-6-chloro-4(3H)-quinazolinone has hypotensive properties in cats.

Experimental Section

Melting points (Thomas–Hoover capillary melting-point apparatus) are uncorrected. Ultraviolet absorption spectra were measured on a Cary recording spectrometer in EtOH. Nmr spectra were taken on a Varian A-60 spectrometer with tetramethylsilane as an internal standard.

3,4-Dimethoxy-6-nitrobenzenesulfonyl Chloride (5).—A slurry of 100 g (0.44 mole) of **3** in 1500 ml of 10% Na_2SO_3 was heated at reflux for 1 hr. Concentration of the solution *in vacuo* gave a heavy precipitate which was collected by filtration and washed with EtOH, then ether, to furnish **4** (140 g, containing Na_2SO_3). It was added to 600 ml of $POCl_3$ with cooling (exothermic reaction). The resulting mixture was refluxed for 1 hr (black solution) and then chilled and filtered from NaCl. The filtrate was concentrated *in vacuo* to a purple, solid residue. Trituration in 1 l. of ether and filtration of the solids yielded 82.8 g (76%) of **5**, mp 129–133°.

3,4-Dimethoxy-6-nitrobenzenesulfonamide (6).—To 300 ml of 28% NH_4OH was added with stirring, 81.0 g (0.29 mole) of **5** over a period of 15 min. An exothermic reaction occurred after stirring the solution for 15 min. When this had subsided, the solution was heated on the steam bath for 15 min and chilled. The precipitate was filtered, washed with water, and dried to give 68.9 g (91%) of **6**, mp 199–201°. It was recrystallized from ethanol.

Anal. Calcd for $C_8H_{10}N_2O_6S$: C, 36.63; H, 3.84; N, 10.68; S, 12.22. Found: C, 36.83; H, 3.92; N, 10.57; S, 12.19.

3,4-Dimethoxy-6-aminobenzenesulfonamide (7).—To a solution of 199.0 g (0.88 mole) of $SnCl_2 \cdot H_2O$ in 800 ml of concentrated HCl was added (stirring) 68.0 g (0.26 mole) of **6** over a period of 45 min. The temperature rose to 45°; the mixture was stirred for 3 hr and chilled. The precipitate was collected by filtration and washed with concentrated HCl. The filter cake was dissolved in 2 l. of H_2O, and the solution was filtered through Supercel to remove a small amount of insoluble material. Adjustment of the pH of the filtrate to 7.5 with $NaHCO_3$ solution gave a precipitate. This was collected, washed with H_2O, and dried, providing 43.8 g (76%) of **7**: mp 186–190°; λ_{max} 253, 312 mμ (ε 9270, 4340).

Anal. Calcd for $C_8H_{12}N_2O_4S$: C, 41.37; H, 5.20; N, 12.06; S, 13.80. Found: C, 41.38; H, 5.22; N, 11.81; S, 13.89.

3,4-Dihydro-2H-6,7-dimethoxy-3-oxo-1,2,4-benzothiadiazine 1,1-Dioxide (8).—An intimate mixture of **7** (48.9 g, 0.21 mole) and urea (13.9 g, 0.23 mole) was heated in an oil bath at 200° for 1 hr. An additional 6.9 g (0.116 mole) of urea was added portionwise over a 45-min period, and the reaction components were occasionally mixed with a spatula. The mixture was then cooled and triturated in 400 ml of hot H_2O. The insoluble material (13.9 g) was filtered, and the filtrate was treated with Darco G-60. Acidification with 125 ml of 1.0 *N* HCl and stirring the mixture at 5–10° for 1 hr gave 23.4 g (43%) of **8**, mp 260–263°. Recrystallization of a portion of this material from EtOH–$CHCl_3$ furnished the analytical sample: mp 271–273° dec, λ_{max} 255, 299 mμ (ε 9081, 2387); nmr (CF_3COOH), τ 0.28 (singlet, NH, proton in position 4), 2.50 (singlet, proton assigned to position 8), 3.10 (singlet, proton in position 5), and 5.95 (singlet, 6 protons of 6,7-OCH_3 groups). The proton in position 2 (NH) is believed to be covered by the solvent signal (*cf.* the nmr spectrum of compound **2a** for this resonance).

Anal. Calcd for $C_9H_{10}N_2O_5S$: C, 41.86; H, 3.87; N, 10.85; S, 12.41. Found: C, 41.32; H, 4.03; N, 10.64; S, 12.19.

3-Chloro-6,7-dimethoxy-2H-1,2,4-benzothiadiazine 1,1-Dioxide (9). A.—To 1.0 g (0.004 mole) of **8** in 8.0 ml of $POCl_3$ at 10° was added over a period of 30 min, 0.94 g (0.008 mole) of N,N-dimethylaniline. The slurry was warmed to room temperature, then refluxed for 18 hr. The solution that resulted was concentrated to a black oil. This was triturated in 100 ml of ice–H_2O, and the precipitate that formed was filtered, washed with H_2O,

and dried to yield 0.67 g of material melting at 232–237°. Two recrystallizations from EtOH provided **9** as white needles: mp 265–267°; λ_{max} 231, 285 mμ (ε 26160, 9940); nmr (CF_3COOH) at τ 2.45 (singlet, proton assigned to position 8), 3.07 (singlet, proton in position 5), 5.93 and 5.99 (two singlets, six protons of 6,7-OCH_3 groups). The proton in position 2 (NH) is believed to be covered by the solvent signal.

Anal. Calcd for $C_9H_9ClN_2O_4S$: C, 39.06; H, 3.28; Cl, 12.81; N, 10.12; S, 11.60. Found: C, 38.79; H, 3.47; Cl, 12.77; N, 10.10; S, 11.69.

B.—A suspension of 10.2 g (0.04 mole) of **8** in 100 ml of $POCl_3$ was cooled to 5°. Pyridine (6.2 g, 0.08 mole) was then added dropwise at such a rate that the temperature did not exceed 10°. The gummy mixture was heated to reflux, and after 18 hr the solution was cooled and concentrated *in vacuo* to a black oil. This was added to 400 ml of ice–H_2O. The resulting mixture was stirred for 1 hr, and the brown solids were collected by filtration. These were washed with ice–H_2O and dried to furnish 10.2 g of material melting at 142–154°. Crystallization from hot EtOH furnished 5.1 g (47%) of **9**, mp 252–256°, identical in infrared spectrum and mobility on thin layer chromatography with the material described under A.

3-Dimethylamino-6,7-dimethoxy-2H-1,2,4-benzothiadiazine 1,1-Dioxide (2a).—A mixture of 4.7 g (0.02 mole) of **9** and 2.3 g (0.05 mole) of Me_2NH in 75 ml of ethanol was heated in a stainless steel, pressure bomb at 140° for 5 hr. The solvent was then evaporated and the residue was triturated in H_2O. The solids were filtered (3.8 g, mp 309–311°) and recrystallized from $CHCl_3$–EtOH to give 2.7 g (58%) of **2a**: mp 318–320°; λ_{max} 225, 260 and 295 mμ (ε 40,110, 13,560, 4237); nmr (CF_3COOH), τ 0.67 (singlet, NH), 5.93 and 5.98 (two singlets, six protons of 6,7-OCH_3 groups), 6.60 (singlet, six protons of $N(CH_3)_2$ group).

Anal. Calcd for $C_{11}H_{15}N_3O_4S$: C, 46.30; H, 5.30; N, 14.73; S, 11.24. Found: C, 46.29; H, 5.42; N, 14.78; S, 11.46.

3-Diethylamino-6,7-dimethoxy-2H-1,2,4-benzothiadiazine 1,1-dioxide (2b) was obtained similarly in 76% yield: mp 193–195° (from ethanol–H_2O); nmr ($CDCl_3$), τ 1.0 (singlet, NH, exchanged with D_2O), 6.18 (singlet, six protons of 6,7-OCH_3 groups), 6.55 (quartet, four CH_2 protons of $N(CH_2CH_3)_2$, J = 7 cps), 8.83 (triplet, six CH_3 protons of $N(CH_2CH_3)_2$, J = 7 cps).

Anal. Calcd for $C_{13}H_{19}N_3O_4S$: C, 49.83; H, 6.11; N, 13.41; S, 10.23. Found: C, 49.59; H, 6.06; N, 13.14; S, 10.13.

3-(4-Methyl-1-piperazinyl)-6,7-dimethoxy-2H-1,2,4-benzothiadiazine 1,1-Dioxide (2c).—A mixture of 3.0 g (0.01 mole) of **9** and 2.2 g (0.02 mole) of N-methylpiperazine in 40 ml of *i*-AmOH was refluxed for 90 min. A solution was obtained at the beginning, followed by a precipitate toward the end of the reaction time. The mixture was chilled, and the solids were collected. Washing of the filtered material with isoamyl alcohol and ether gave 3.2 g (85%) of the desired product, mp 262–263°. The analytical sample (from EtOH–H_2O) melted at 264–266°.

Anal. Calcd for $C_{14}H_{20}N_4O_4S$: C, 49.40; H, 5.92; N, 16.46; S, 9.42. Found: C, 49.56; H, 5.75; N, 16.20; S, 9.49.

3-Diallylamino-6,7-dimethoxy-2H-1,2,4-benzothiadiazine 1,1-dioxide (2d) was prepared similarly in 92% yield, mp 154–156° (from EtOH).

Anal. Calcd for $C_{15}H_{19}N_3O_4S$: C, 53.39; H, 5.68; N, 12.46; S, 9.50. Found: C, 53.56; H, 5.58; N, 12.46; S, 9.61.

Acknowledgment.—The authors are grateful to Dr. Jay W. Constantine for kindly providing the pharmacological results.

Fluorinated Analogs of Leucine, Methionine, and Valine

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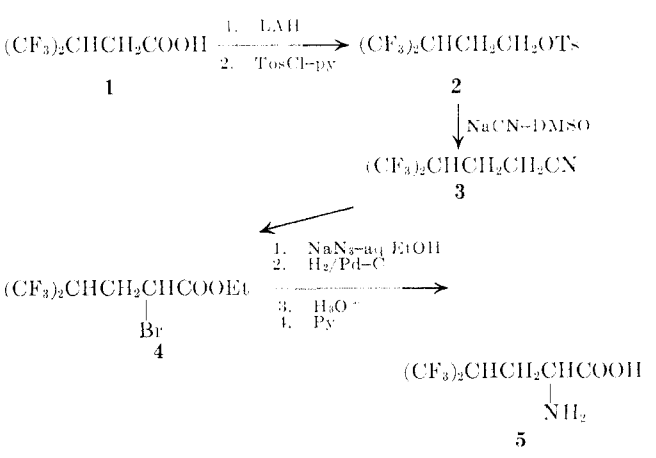
Many analogs of amino acids have been prepared and studied in a variety of biological systems,[1] but very few have been found that can effectively function like normal amino acids. Since a trifluoromethyl group appears to be approximately the same size as a methyl group, amino acids with CH_3 replaced by CF_3 groups should have approximately the same steric requirements. In addition, the trifluoromethyl group is chemically inert and nontoxic relative to the mono- or difluoromethyl groups as substituents; however, the strong electron-withdrawing effect of CF_3 will alter the acidity of the amino acid function (unless substituted in a remote position in the molecule) which could influence the function of the amino acid in the biological system. A study of fluorinated amino acids (with trifluoromethyl groups) has been reported,[2] but the biological studies were usually limited simply to observations of growth effects on microorganisms. We undertook to prepare selected fluorinated analogs of amino acids and to substitute them for naturally occurring ones in enzymatically active proteins of microorganisms. The fluorine would also be useful as a marker and a probe in elucidation of the structure of proteins and in studying mechanisms of enzyme action. *p*-Fluorophenylalanine has been reported to be incorporated into normal strains of *Escherichia coli* in place of phenylalanine but not into mutant strains with altered phenylalanine ribonucleic acid synthetase.[3] Recently 4-(trifluoromethyl)-2-aminopentanoic acid (trifluoroleucine) was claimed to replace leucine in certain leucine auxotrophs of *E. coli* without adversely influencing the growth of these microorganisms.[4]

Three of the fluorinated amino acid analogs (trifluorovaline, hexafluorovaline, and trifluoromethionine) are known and were prepared[2a,5,6] by literature procedures. Hexafluoroleucine was prepared by the procedure shown in Chart I.

CHART I



An interesting side reaction was observed during the displacement of the *p*-toluenesulfonate group of **2** by cyanide ion; in all instances equimolar amounts of

(1) W. Shive and C. G. Skinner in "Metabolic Inhibitors," Vol. I, R. M. Hochster and J. H. Quastel, Ed., Academic Press Inc., New York, N. Y., 1963, Chapter 1, pp 2–73.

(2) (a) D. F. Lonerini and B. M. Walborsky, *J. Med. Chem.*, **7**, 369 (1964); (b) H. M. Walborsky and M. Baum, *J. Org. Chem.*, **21**, 538 (1956); (c) H. M. Walborsky, M. Baum, and D. F. Lonerini, *J. Am. Chem. Soc.*, **77**, 3637 (1955); (d) H. M. Walborsky and M. Schwarz, *ibid.*, **75**, 3241 (1953).

(3) (a) R. Munier and G. N. Cohen, *Biochim. Biophys. Acta*, **21**, 347, 378 (1959); (b) W. L. Fangman and F. C. Neidhardt, *J. Biol. Chem.*, **239**, 1839, 1844 (1964).

(4) O. M. Rennert and B. S. Anker, *Biochemistry*, **2**, 471 (1963).

(5) J. L. Knunyants and Yu. A. Cherbakov, *Izv. Akad. Nauk. SSSR, Otd. Khim. Nauk*, 2162 (1960).

(6) R. L. Dannley and R. G. Taborsky, *J. Org. Chem.*, **22**, 1275 (1957).