the Clauberg test. Intact New Zealand rabbits weighing approximately 1 kg. were primed for 6 days with 5 γ of 17β-estradiol (s.c.)/day. On the following day, daily (oral) treatment was begun with test compound and continued for 5 days. On the day after the last treatment the rabbits were sacrificed and a uterine segment was taken for histological examination. The uteri were graded from 0–4 according to the standard scale of McPhail.[10] The compounds, 3β-(1-pyrrolidyl)-17α-acetoxypregn-5-en-20-one (**5**), 3β-(1-pyrrolidyl)-17α-ethynylandrost-5-en-17β-ol (**7**), and 3β-(1-pyrrolidyl)-17α-ethynyl-19-norandrost-5-en-17β-ol (**8**) (Table II) were inactive at 0.5-, 1.0-, and 5.0-mg. dose. However, 3β-(1-pyrrolidyl)-17α-acetoxy-6-methylpregn-5-en-20-one (**6**) showed a McPhail grading of 3.1 at the highest (5.0 mg.) dose level.

Experimental Section

General Method. Dienamines. 3-[1-Pyrrolidinyl]-6-methyl-17α-acetoxypregna-3,5-dien-20-one.—6α-Methyl-17α-acetoxyprogesterone (5.0 g.) was dissolved in 20 ml. of hot methanol and treated with 1.8 ml. of pyrrolidine. The mixture was heated on a steam bath for 5 min. and then allowed to cool. The crystals were filtered off and recrystallized from methanol to give 5.1 g. (89.5%) of product, m.p. 167–170°.

General Method. Borohydride Reduction. 3β-(1-Pyrrolidyl)-6-methyl-17α-acetoxypregn-5-en-20-one. — 3-[1-Pyrrolidinyl]-6-methyl-17α-acetoxypregna-3,5-dien-20-one (2.0 g.) was dissolved in methanol and treated with 1.5 g. of KBH_4. The mixture was stirred at room temperature for 12 hr., then poured into ice and water and extracted with ethyl acetate. The organic layer was washed with 10% HCl solution and the acid extracts were combined and neutralized with cold 10% KOH solution. The crystals thus precipitated were once again extracted with ethyl acetate. The ethyl acetate layer was washed with water, dried (Na_2SO_4), and evaporated to give a yellow oil. Recrystallization from ethyl acetate gave 1.2 g. (60%) of material: m.p. 183–186°; λ_{max}^{KBr} 5.75, 5.82, and 7.99 μ.

Acknowledgment.—I wish to thank Dr. I. Scheer for his encouragement and interest, Dr. R. P. Blye of our Division of Pharmacology for the biological data, and Mr. C. H. Harper and Mr. J. Grodsky for technical assistance.

(10) C. W. Emmens, "Hormone Assay," C. W. Emmens, Ed., Academic Press Inc., New York, N. Y., 1950.

New Compounds

Some 3,4,5-Trimethoxyphenyl Analogs of Anticonvulsants[1a]

VASANT S. PALKAR[1b] AND PIERRE F. SMITH

Department of Pharmaceutical Chemistry, University of Rhode Island, Kingston, Rhode Island

Received June 28, 1965

The possible influence of the 3,4,5-trimethoxyphenyl group on drugs having varying types of central nervous system activity has been evident in such diverse compounds as mescaline, reserpine, colchicine, and trimeglamide (3,4,5-trimethoxybenzoylglycine diethylamide). As part of a continuing study, 3,4,5-trimethoxyphenyl analogs of diphenylhydantoin, phensuximide (N-methyl-2-phenylsuccinimide), and related intermediates were prepared.

Experimental Section[2]

5-(3,4,5-Trimethoxyphenyl)-5-phenylhydantoin.—3,4,5-Trimethoxybenzophenone[3] (18.0 g., 0.067 mole), KCN (12.0 g., 0.18 mole), $(NH_4)_2CO_3$ (60.0 g., 0.62 mole), and 60% ethanol (500 ml.) were mixed together and stirred vigorously. The temperature of the reaction mixture was gradually increased from 23 to 63°. It was maintained at 54–56° for about 70 hr., 58–59° for about 50 hr., and finally 60–63° for another 50 hr. About one-third of the solvent was removed under vacuum and the reaction mixture was made acidic (10% HCl). The yellowish white solid thus precipitated was separated by filtration and treated with 5% aqueous NaOH. A part of the solid which remained insoluble (10.8 g.) was identified as the starting ketone. The greenish alkaline filtrate on acidification (10% HCl) in the cold gave a white solid; yield 8.9 g. (40%). Upon crystallization from ethanol (50%), white fluffy crystals, m.p. 102–104°, were obtained.

Anal. Calcd. for $C_{18}H_{18}N_2O_5$: C, 63.15; H, 5.26; N, 8.19. Found: C, 62.55; H, 5.27; N, 7.97.

4-Hydroxy-3,5-dimethoxyphenylsuccinic Acid (I).—To a solution of 3,4,5-trimethoxybenzaldehyde (19.6 g., 0.1 mole) and ethyl cyanoacetate (11.3 g., 0.1 mole) in 60% ethanol (50 ml.) was added a little piperidine[4] (1 ml.). The mixture was stirred mechanically. The addition of piperidine clarified the solution, and the temperature rose to about 35° from 20°. The clear solution became turbid (yellowish) in 10 min., and about 20 min. later, a yellowish solid separated. Water (20 ml.) and 60% ethanol (100 ml.) were now added to the mixture and then NaCN (4.9 g., 0.1 mole) was added within 20 min. The stirring was continued until the solution again clarified. The solution was acidified (10% HCl) and the oil that precipitated was stirred overnight until it solidified. The solid (27.5 g.) was hydrolyzed with concentrated HCl (50 ml.) by vigorous refluxing for over 6 hr. until the mixture clarified to a brown solution. The white solid, 15.0 g. (56%) crystallized on cooling, was recrystallized from boiling water after decolorization with Norit A. Fine fluffy crystals were obtained, m.p. 198–200°.

Anal. Calcd. for $C_{12}H_{14}O_7$: C, 53.33; H, 5.18; O, 41.48. Found: C, 53.17; H, 4.85; O, 41.35.

3,4,5-Trimethoxyphenylsuccinic Acid (II).—Compound I (15.0 g., 0.056 mole) was dissolved in 10% aqueous NaOH (100 ml.). Dimethyl sulfate (10 ml.) was added dropwise to the hot solution with stirring. The solution was refluxed for about 4 hr. In order to hydrolyze any ester formed at this stage, the solution was further refluxed for over 2 hr. with the addition of NaOH pellets (10 g.) and ethanol (80 ml.). The ethanol was removed by distillation and the sodium salt thus separated was dissolved in as little water as possible and acidified in the cold (10% HCl). The precipitate weighed 12.3 g. (78%), white fluffy crystals from boiling water, m.p. 185–187°.

Anal. Calcd. for $C_{13}H_{16}O_7$: C, 54.93; H, 5.63. Found: C, 55.04; H, 5.47.

N-Methyl-2-(3,4,5-trimethoxyphenyl)succinimide (III).—Compound II (10 g., 0.035 mole) was added to 40% aqueous

(1)(a) This work was supported by U. S. Public Health Service Research Grant MH 04132, National Institute of Mental Health. (b) Institute of Agriculture, Department of Biochemistry, University of Minnesota, St. Paul, Minn.

(2) Melting points were determined on a Fisher-Johns block and are uncorrected. Combustion analyses were carried out by Micro-Analysis Inc., Wilmington, Del. Infrared spectra were run on a Beckman Model IR 8 as KBr wafers.

(3) C. F. Koelsch and R. N. Flesch, *J. Org. Chem.*, **20**, 1275 (1955).

(4) A. Lapworth and J. A. McRae, *J. Chem. Soc.*, **127**, 1704 (1922).

methylamine[5] (20 ml.). The flask was heated until the temperature of the contents reached about 210°. The residue (viscous brown oil) was cooled, dissolved in hot 95% ethanol, decolorized with Norit A, and filtered. On cooling, 5.5 g. (56%) of white woolly crystals, m.p. 147–150°, was obtained. Two recrystallizations from the same solvent raised the melting point to 154–155° (short woolly needles).

Anal. Calcd. for $C_{14}H_{17}NO_5$: C, 60.21; H, 6.10; N, 5.01. Found: C, 60.32; H, 6.30; N, 5.21.

N-Methyl-2-(3,5-dimethoxy-4-hydroxyphenyl)succinimide (IV).—The reaction was carried out as for III. From I (10 g., 0.037 mole), IV (6.4 g., 66%) was obtained as yellowish white crystals, m.p. 183–186°. Two recrystallizations, using Norit A once for decolorization, raised the melting point to 186–187°, white crystals.

Anal. Calcd. for $C_{13}H_{15}NO_5$: C, 58.87; H, 5.66; N, 5.28. Found: C, 58.67; H, 5.76; N, 5.15.

(5) C. A. Miller and L. M. Long, *J. Am. Chem. Soc.*, **73**, 4893 (1951).

Synthesis of Some Hydroxylamine Derivatives of Pyrimidines and Purines[1]

PAULINE K. CHANG

Department of Pharmacology, Yale University School of Medicine, New Haven, Connecticut

Received July 27, 1965

Because of interest in orotic acid analogs in this laboratory,[2] 6-N-hydroxylaminouracil (I) and uracil-6-hydroxamic acid (II) have been synthesized. 6-N-Hydroxylaminopurine ribonucleoside (III) was regarded as an analog of adenosine, because 6-N-hydroxylaminopurine[3] is active as an analog of both adenine and hypoxanthine.[4]

2,4-Dimethoxy-6-chloropyrimidine[5,6] failed to react with hydroxylamine; however, the demethylated derivative, 6-chlorouracil,[7] reacted smoothly with hydroxylamine to give I. Compound II was prepared from methyl orotate,[8] whereas III was prepared from 6-chloropurine ribonucleoside[9] and hydroxylamine.

Experimental Section[10]

6-N-Hydroxylaminouracil (I).—A solution of KOH (11.2 g., 0.2 mole) in ethanol (40 ml.) was added to a solution of hydroxylamine hydrochloride (12 g., 0.17 mole) in boiling ethanol (200 ml.). The precipitated KCl was filtered. 6-Chlorouracil[7] (1 g., 0.007 mole) was added to the solution of hydroxylamine. The mixture was refluxed for 1 hr. and allowed to cool to room temperature with stirring (1 hr.). The product, which separated as a solid, was washed with water and ethanol to give analytically pure I (0.73 g., 74%), m.p. 280° dec., λ_{max}^{pH2} 264 mμ (ε 6250).

Anal. Calcd. for $C_4H_5N_3O_2$: C, 33.57; H, 3.52; N, 29.36. Found: C, 33.56; H, 3.77; N, 29.25.

Uracil-6-hydroxamic Acid (II).—A mixture of methyl orotate[8] (1.25 g., 0.0074 mole), $NH_2OH \cdot HCl$ (1.4 g., 0.02 mole), and water (10 ml.) was cooled to 0°. With stirring, NaOH (12.5 *N*, 3.6 ml.) was added to the mixture dropwise at 3°. The now clear solution was adjusted to pH 5 with concentrated HCl. Crude II, which separated out as a yellow solid, was recrystallized from water to yield the monohydrate (1.2 g., 86%), m.p. 250° dec., λ_{max}^{pH2} 274 mμ (ε 7420). It was recrystallized twice from water to give the analytical sample.

Anal. Calcd. for $C_5H_5N_3O_4 \cdot H_2O$ [sample dried at 60° (0.1 mm.)]: C, 31.75; H, 3.73; N, 22.22. Found: C, 31.72; H, 3.99; N, 22.29. Calcd. for $C_5H_5N_3O_4$ [sample dried at 120° (0.1 mm.)]: C, 35.10; H, 2.95; N, 24.56. Found: C, 35.22; H, 3.15; N, 24.37.

6-N-Hydroxylamino-9-β-D-ribofuranosylpurine (III).—To a solution of hydroxylamine hydrochloride (0.7 g., 0.01 mole) in boiling ethanol (10 ml.) was added a solution of KOH (0.56 g., 0.01 mole) in ethanol (3 ml.). The precipitated KCl was filtered. 6-Chloro-9-β-D-ribofuranosylpurine[9,11] (0.286 g., 0.002 mole), dissolved in ethanol (20 ml.), was added to the solution of NH_2OH. The mixture was refluxed for 1 hr. and then concentrated *in vacuo* at 40°. The residue (412 mg.) was recrystallized from hot ethanol to yield the pure product (200 mg., 70%), m.p. 195° dec., λ_{max}^{pH2} 262.5 mμ (ε 16,700). The analytical sample was recrystallized once more from ethanol.

Anal. Calcd. for $C_{10}H_{13}N_5O_5$: C, 42.40; H, 4.63; N, 24.72. Found: C, 42.42; H, 4.77; N, 24.94.

(11) Purchased from Cyclo Chemical Corp., Los Angeles, Calif.

(1) This work was supported by a grant (CA-02817) from the National Cancer Institute, U. S. Public Health Service.

(2) R. E. Handschumacher, *Cancer Res.*, **23**, 643 (1963).

(3) A. Giner-Sorolla and A. Bendich, *J. Am. Chem. Soc.*, **80**, 3932 (1958).

(4) A. C. Sartorelli, A. L. Bieber, P. K. Chang, and G. A. Fischer, *Biochem. Pharmacol.*, **13**, 507 (1964).

(5) H. J. Fisher and T. B. Johnson, *J. Am. Chem. Soc.*, **54**, 727 (1932).

(6) S. B. Greenbaum and W. L. Holmes, *ibid.*, **76**, 2899 (1954).

(7) J. P. Horwitz and A. J. Tomson, *J. Org. Chem.*, **26**, 3392 (1962).

(8) J. J. Fox, N. Yung, and I. Wempen, *Biochem. Biophys. Acta*, **23**, 295 (1957).

(9) B. R. Baker, K. Hewson, H. J. Thomas, and J. A. Johnson, Jr., *J. Org. Chem.*, **22**, 954 (1957).

(10) Melting points were determined in a capillary tube in a copper block and are corrected. Microanalyses were performed by Schwarzkopf Microanalytical Laboratories, Woodside, N. Y., and by Midwest Microlab, Inc., Indianapolis, Ind.

Quinoxaline Sulfonamides

S. H. DANDEGAONKER AND C. K. MESTA

Department of Chemistry, Karnatak University, Dharwar, India

Received June 16, 1965

The development of the field of chemotherapy has more recently led to a renewed interest in the quinoxalines in connection with their potential values as pharmaceuticals.[1-5] We have synthesized some halogenated quinoxaline sulfonamides in view of the reported effect of chlorine atoms on the activity of quinoxalines.[6]

Sulfonamides on condensation with 2,3-dichloroquinoxaline using the procedure of Wolf, *et al.*,[7] gave disulfonamide derivatives when 2 moles of sulfonamide was used, and a mixture of predominantly mono- and small amounts of disulfonamides when 1 mole of sulfonamide was employed. The reaction of sulfanilamide and 2,3-dichloroquinoxaline confirmed the findings of Wolf and co-workers[7] and Platt and Sharp[8] that the free amino group does not take part in condensation.

2,3-Dichloroquinoxaline on reaction with benzamide in different ratios gave only 2,3-dibenzamidoquinoxaline under similar conditions. Acetamide, on heating with dichloroquinoxaline at 130° or refluxing in ethanol, afforded a mixture of products, with or without chlorine. Interaction of sodamide with dichloroquinoxaline in boiling toluene either in a stoichiometric ratio or with an excess gave a mixture of unidentifiable products.

Experimental Section

2,3-Dihydroxyquinoxaline[9] (91%), white needles, m.p. 320°; 2,3-dichloroquinoxaline[10] (75%), colorless shining long needles,

(1) R. M. Acheson, *J. Chem. Soc.*, 4731 (1956).

(2) O. Gawron, and P. E. Spoerri, *J. Am. Chem. Soc.*, **67**, 514 (1945).

(3) R. H. Mizzoni and P. E. Spoerri, *ibid.*, **67**, 1652 (1945).

(4) K. Pfister, III, A. P. Sullivan, J. Weijlard, and M. Tishler, *ibid.*, **73**, 4955 (1951).

(5) J. Weijlard and M. Tishler, U. S. Patent 2,404,199 (July 16, 1946); *Chem. Abstr.*, **40**, 6100 (1946).

(6) A. F. Crowther, F. H. S. Curd, D. G. Davey, and G. S. Stacey, *J. Chem. Soc.*, 1260 (1949).

(7) F. J. Wolf, K. Pfister, III, R. H. Beutal, R. M. Wilson, C. A. Robinson, and J. R. Stevens, *J. Am. Chem. Soc.*, **71**, 6 (1949).

(8) B. C. Platt and T. M. Sharp, *J. Chem. Soc.*, 2129 (1948).

(9) M. A. Phillips, *ibid.*, 1143 (1931); 2393 (1928).

(10) O. Hinsberg and J. Pollak, *Ber.*, **29**, 784 (1896).