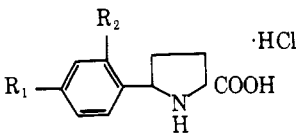
TABLE VII (*Continued*)

Compd.	R_1	R_2	S180 NTL,[b] mg./kg.	S180 T/C,[c] %	Ca775 or E.A. NTL,[b] mg./kg.		Ca775 or E.A. T/C,[c] %	L1210 NTL,[b] mg./kg.	L1210 T/C,[c] %
Vf	CH_3O	H	500	68	350	C	90	350	102
Vg	C_6H_5O	H	125	98	112	C	116	112	85
Vh	$NH_2 \cdot HCl$	H	250	50 61	112	C	68	225	87
Vi	F	F	125	99	88	C	108	88	103
Vj	Cl	Cl	125	78	100	C	59	100	103
									
Ref. 2	H	H	500	100	450	C	58	225	72
VIa	F	H	250	78	200	C	95	200	91
VIb	Cl	H	125	66	112	C	82	112	129
VIc	Br	H	500	99	350	E	82	350	73
VId	CH_3	H	250	75	100	C	100	100	104
VIe	C_6H_5	H	125	75	56	C	93	112	96
VIf	CH_3O	H	500	102	225	C	137	450	88
VIg	C_6H_5O	H	500	72	225	C	108	110	104
VIh	$NH_2 \cdot HCl$	H	375	80	320	C	55	320	106
VIi	F	F	500	62	200	C	70	400	89
VIj	Cl	Cl	100	89	80	C	63	80	104

[a] We are indebted to Dr. Howard W. Bond, Cancer Chemotherapy National Service Center, National Institutes of Health, Bethesda 14, Md., for making these data available to us. The details of the screening procedures can be found in *Cancer Chemotherapy Rept.*, **1**, 42 (1959). [b] NTL = maximum nontoxic level. [c] T/C = treated tumor/control tumor. [d] E = Ehrlich ascites, C = Carcinoma 755.

Anal. Calcd. for $C_{11}H_{12}ClNO_2$: C, 58.54; H, 5.32; N, 6.28. Found: C, 58.63; H, 5.80; N, 6.00.

Ethyl 2-Acetamido-4-(3-*p*-acetamidobenzoyl)-2-carbethoxybutyrate (IIh).—To a mixture of 76 g. (0.35 mole) of ethyl acetamidomalonate, 79 g. (0.35 mole) of Ih, and 150 ml. of anhydrous ethyl alcohol kept at 20° was added a solution of 9 g. (0.39 g.-atom) of sodium in 150 ml. of anhydrous ethyl alcohol, dropwise with agitation. Agitation was continued overnight at room temperature. Alcohol was removed by flash evaporation, and the residue was extracted with 500 ml. of methylene chloride and washed free of salts with two 100-ml. portions of water. Methylene chloride was flash evaporated, and the residue was crystallized from isopropyl alcohol and yielded 58 g. of product, m.p. 149–158°, 39.8% yield. An analytical sample was crystallized from isopropyl alcohol, m.p. 150–152°.

Acetamido[3-(*p*-acetamidophenyl)-3-oxopropyl]malonic Acid (IIIh).—IIh (20.5 g., 0.05 mole) was suspended in a solution prepared from NaOH (10 g., 0.25 mole) dissolved in a mixture of 90 ml. of water and 40 ml. of methyl alcohol. After standing overnight at 40°, the hydrolysate was acidified with concentrated HCl. The precipitate was filtered, washed free of chloride, and dried at 50° under vacuum. The yield of malonic acid was 13.5 g. (77.1%), m.p. 137–140° dec. Recrystallization from methyl alcohol did not change the melting point.

DL-2-Acetamido-4-(*p*-acetamidobenzoyl)butyric acid (IVh) was obtained by heating 12 g. (0.034 mole) of IIIh in 250 ml. of water for 2 hr. under reflux. Upon cooling, 5.5 g. (52.2%) of product was obtained, m.p. 155–166°. An analytical sample was prepared by crystallization from aqueous methyl alcohol, m.p. 165–168°.

2-(*p*-Aminophenyl)-1-pyrroline-5-carboxylic Acid Dihydrochloride (Vh).—IIh (22 g., 0.054 mole) was heated under reflux with 150 ml. of concentrated HCl overnight. The solution was evaporated to dryness under vacuum, and the residue was dissolved in water, decolorized with charcoal, and evaporated again. The product was then dissolved in methyl alcohol and allowed to stand in the freezer for several days when 12 g. (80%) of compound was obtained which melted at 240–242° dec. An analytical sample was obtained by crystallization from a mixture of methyl alcohol and ether, m.p. 252° dec.

5-(*p*-Aminophenyl)proline Dihydrochloride (VIh).—Compound Vh (14.7 g., 0.053 mole) was dissolved in 150 ml. of methyl alcohol and was hydrogenated in a Parr hydrogenator in the presence of 50 mg. of platinum oxide under 3–4 atm. When the theoretical uptake of hydrogen was observed, the catalyst was removed by filtration and the solvent was evaporated under a stream of air. The product (13 g., 88.8%) obtained melted at 131–137°. For analysis, a sample was recrystallized from a mixture of methyl alcohol and ether, m.p. 137°.

Microbiological Assay.—Aqueous medium (100 ml.) contained sucrose (10 g.); glucose (1.0 g.); yeast extract, Difco (1.0 g.); peptone, Difco (0.3 g.); beef extract, Difco (0.2 g.); and inorganic salts (0.3 g.). The salt mixture was composed of K_2HPO_4 (150 mg.), $(NH_4)_2SO_4$ (150 mg.), sodium citrate (149 mg.), $CaCl_2$ (25 mg.), $MgSO_4 \cdot 7H_2O$ (25 mg.), $FeNH_4SO_4$ (0.5 mg.), and $ZnSO_4 \cdot 7H_2O$ (0.5 mg.). Solutions of the test compounds were made in water and the pH was adjusted to 7 with NH_4OH. The levels of compound were set so that 1 ml. of solution when diluted to 10 ml. would yield final concentrations of 0.1, 0.5, and 1.0%, respectively. A solution (1 ml.) of test compound, made sterile by filtration through a Seitz filter, was added aseptically to 9 ml. of medium, also made sterile by filtration through a Seitz filter. Inoculation with *L. mesenteroides* P-60 was effected by addition of 2 loopfuls of an 18-hr. culture of the organism in Eugon broth (BBL). After incubation for 24 hr. at 37°, the culture tubes were examined for turbidity in a Klett–Summerson colorimeter using a No. 66 filter. The data recorded indicated 100% inhibition as compared to growth.

Reduction of Steroidal Enamines with Potassium Borohydride

ARVIN P. SHROFF

Ortho Research Foundation, Raritan, New Jersey

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de Winters, *et al.*, and others[1–4] have reported that the removal of the oxygen function at C-3 of Δ^4-3-keto steroids resulted in compounds with anabolic or progestational activity. Kincl and Dorfman[5] showed

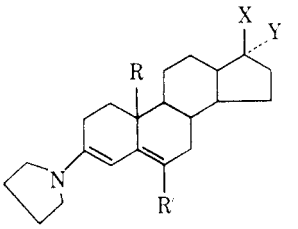
(1) M. S. de Winters, C. W. Siegmann, and S. A. Szpilfogel, *Chem. Ind.* (London), 905 (1959).

(2) N. E. Borglin, *Acta Endocrinol., Suppl.*, 58 (1960).

(3) O. Halpern, J. A. Edwards, and J. A. Zderic, *Chem. Ind.* (London), 1571 (1962).

(4) K. Irmscher, H. G. Kraft, and K. Bruckner, *J. Med. Chem.*, **7**, 345 (1964).

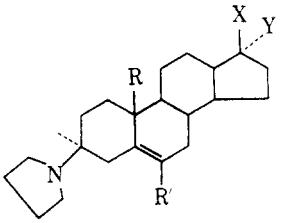
TABLE I
PYRROLIDYLDIENAMINES



Compd.	R	R'	X	Y	M.p., °C.[a]	λ_{max},[b] mμ	Formula	N, % Calcd.	N, % Found[c]
1	CH_3	H	$COCH_3$	$OCOCH_3$	247–249[d]	278	$C_{27}H_{39}NO_3$	...	..
2	CH_2	CH_3	$COCH_3$	$OCOCH_3$	167–170[e]	287	$C_{28}H_{41}NO_3$	3.19	3.42
3	CH_3	H	OH	C≡CH	158–159	278	$C_{25}H_{35}NO$	3.83	3.50
4	H	H	OH	C≡CH	124–125	279	$C_{24}H_{33}NO$	3.99	4.16

[a] Melting points taken on Fisher-Johns melting point apparatus and are uncorrected. [b] All ultraviolet data were obtained in alcohol solution on a Cary spectrophotometer Model 11. [c] All analyses were performed by Midwest Microlab, Inc., Indianapolis, Ind. [d] R. Joly and J. Warnant, *Bull. soc. chim. France*, 569 (1961). [e] Prepared by Mr. A. D. Mebane of our laboratory.

TABLE II
3β-(1-PYRROLIDYL) COMPOUNDS



Compd.	R	R'	X	Y	% yield	M.p., °C.	λ_{max},[a] mμ	Formula	Calcd., % C	Calcd., % H	Calcd., % N	Found, % C	Found, % H	Found, % N
5	CH_3	H	$COCH_3$	$OCOCH_3$	59	225–228	197	$C_{27}H_{41}NO_3$	75.83	9.66	3.28	75.88	9.84	3.52
6	CH_3	CH_3	$COCH_3$	$OCOCH_3$	60	183–186	197	$C_{28}H_{43}NO_3$	71.79	8.79	3.49	71.78	8.91	3.61
7	CH_3	H	OH	C≡CH	56	182–184	197	$C_{25}H_{37}NO$	81.69	10.15	3.81	81.83	10.34	3.48
8	H	H	OH	C≡CH	73	115–118	197	$C_{24}H_{35}NO$	81.53	9.98	3.96	81.37	9.94	3.70

[a] Ultraviolet data were obtained in cyclohexane.

that the C-3 oxygen function was not necessary for antiovulatory activity. We wish to report the synthesis and biological activity of a few steroids with a pyrrolidyl group at C-3.

The 3β-(1-pyrrolidyl) compounds shown in Table II were obtained by the reduction of the corresponding dienamines (Table I) with potassium borohydride. Reduction of enamines of α,β-unsaturated ketones has been reported in the literature.[6,7] Contrary to the findings of Marshall and Johnson,[7] we have found that the enamine reduction with KBH_4 did not require any addition of acetic acid. The only exception to this was 17α-acetoxyprogesterone where solubility seems to have been the factor. In all cases where reduction went smoothly it was observed that the dienamines dissolved in methanol on addition of KBH_4. The Δ^5 structures assigned to these compounds were based on the molecular rotation and the n.m.r. data (see Table III). The large negative values for the molecular rotations are in agreement[8] with the expected Δ^5 structures. The n.m.r. spectrum of 3β-(1-pyrrolidyl)-17α-acetoxy-6-methylpregn-5-en-20-one (**6**) (Table III) was devoid of vinyl hydrogens, thus confirming the structure assignment. The other C-6 proton resonances were assigned as indicated in Table III. These studies show that even at room temperature and without acid catalysis C-4 protonation is favored.

TABLE III
N.M.R.[a] AND OPTICAL ROTATION[b] DATA ON 3β-(1-PYRROLIDYL) COMPOUNDS

Compd.	$[\alpha]_D$, deg.	M_D, deg.	N.m.r. signals, p.p.m. C-18	C-19	C-6
5	−38.6	−165	0.62	0.98	5.30
6	−38.6	−170	0.64	0.99	..
7	−84.2	−309	0.84	1.00	5.30
8	−34.9	−123	0.88	..	5.34

[a] N.m.r. spectra were determined on a Varian A-60 spectrometer in deuteriochloroform using tetramethylsilane as an internal standard (0 p.p.m.). All p.p.m. values are the center of the signals. [b] Optical rotations were measured in chloroform.

The dienamines described in Table I were prepared in high yields by the general method of Heyl and Herr.[9] The reduction procedure for compounds **5**–**8** (Table II) was the same, except for 17α-acetoxyprogesterone where a few drops of formic acid was used to effect solution.

Biological Activity.—Progestational activity of 3β-(1-pyrrolidyl) compounds was quantitatively evaluated in

(5) F. A. Kinel and R. I. Dorfman, *Steroids*, **2**, 521 (1963).

(6) (a) J. Schmitt, J. J. Panouse, P. Comoy, P. Cornu, A. Mallot, and H. Pluchet, *Bull. soc. chim. France*, 798 (1962); (b) *ibid.*, 807 (1962); (c) *ibid.*, 816 (1962).

(7) J. A. Marshall and W. S. Johnson, *J. Org. Chem.*, **28**, 421 (1963).

(8) L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, N. Y., 1959, p. 177.

(9) F. W. Heyl and M. E. Herr, *J. Am. Chem. Soc.*, **75**, 1919 (1953).

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

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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).