Dipole Moments. 2-Bromofluorenone (m.p. 148°) was prepared according to Courtot[46] and 3-bromofluorenone (m.p. 165°) according to Miller and Bachman.[47] The latter procedure was modified as follows: the chloride of 2-(*p*-bromobenzoyl)-benzoic acid was prepared by refluxing 26.5 g. of the acid and 18.5 g. of phosphorus pentachloride in 100 ml. of benzene (until no more hydrogen chloride was evolved) and removing the solvent and the phosphorus oxychloride *in vacuo*. It was then dissolved in 100 ml. of dioxane and treated with dry gaseous ammonia until the exothermic reaction had subsided. The reaction product was poured into water and the solid 2-(*p*-bromobenzoyl)-benzamide (yield 90–95%) collected, washed with water and dried at 100°. It melted at 190°. When 24.5 g. of this amide was added at 10° to a solution, prepared from 15.4 g. of bromine and 14.5 g. of potassium hydroxide in 145 ml. of water, a clear yellow solution resulted. A solution of 20.5 g. of potassium hydroxide in 36 ml. of water was added, and the mass heated at 30°, whereupon 2-amino-4′-bromobenzophenone separated. The temperature then was raised to 80° and the product cooled again. Thus, 16.5 g. of the amine precipitated, and 5 g. of the starting material was recovered by addition of sodium bisulfite to the filtrate; the yield was, therefore, 93%. The amine was purified *via* the hydrochloride and converted further into 3-bromofluorenone, as previously described.[47]

The method used for the determination of the moments, and the meaning of the symbols have been described previously.[48,49] The solvent employed was benzene, the temperature 30°. The data are summarized in Tables I and II.

Acknowledgment.—The dipole measurements have been carried out by Dr. E. Fischer, Weizmann Institute of Science, Rehovoth, Israel, and Mrs. Hannah Weiler-Feilchenfeld of the Chemistry Department, Jerusalem. This study forms part of a thesis submitted by R. Barshai to the Technion, Israel Institute of Technology.

(46) Ch. Courtot, *Ann. chim.*, [10] **14**, 5 (1950).

(47) H. F. Miller and G. B. Bachman, THIS JOURNAL, **57**, 2443 (1935).

(48) E. Bergmann, A. Weizmann and E. Fischer, *ibid.*, **72**, 5009 (1950).

(49) E. Fischer, *J. Chem. Phys.*, **19**, 395 (1951).

JERUSALEM AND HAIFA, ISRAEL

[CONTRIBUTION FROM THE ORGANIC RESEARCH LABORATORIES OF THE U. S. VITAMIN AND PHARMACEUTICAL CORPORATION]

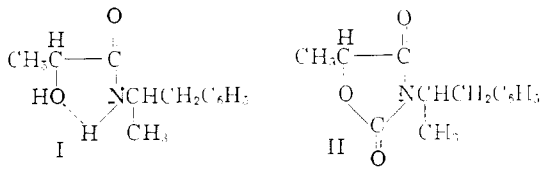
Analeptic Oxazolidinediones and Related Compounds

BY SEYMOUR L. SHAPIRO, IRA M. ROSE, FRANK C. TESTA AND LOUIS FREEDMAN

RECEIVED APRIL 13, 1959

The compound II, 5-methyl-3-(*d*-α-methylphenethyl)-oxazolidine-2,4-dione, has been synthesized and found to have high analeptic activity, comparable to that found with N-(*d*-α-methylphenethyl)-lactamide (I). Thio analogs of I depressed central nervous system activity.

The analeptic activity reported for N-(*d*-α-methylphenethyl)-lactamide (I),[1] indicated exploration of the related oxazolidinedione (II) in which an intact ring replaces the hydrogen-bonded ring proposed for I. Exploration of the scope of structural variation permissive with retention of

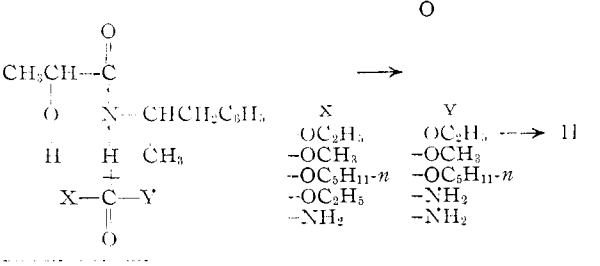


I II

analeptic activity in II also was indicated.[1] The preparation of the carbamate of I was suggested by the reported enhancement of pharmacological activity in hydroxy compounds through introduction of this substituent[2] and the presence of this substituent in effective muscle relaxants (*i.e.*, meprobromate). Additional variants considered were the thio analogs of I and II in view of recent recognition of the improved penetrability of thio analogs into the brain.[3]

For projected synthesis of the dione II, conventional syntheses[4] involving reaction of the acidic hydrogen at the 3-position of the oxazolidinedione ring with a required optically active halide did not appear promising. The halide, α-methylphenethyl chloride, would be difficult to obtain in optically active form and would impose too great a steric factor[5] for effective condensation. The method[6] used was reaction of the *d*,α-methylphenethylamine with ethyl lactate in diethyl carbonate under sodium alkoxide catalysis. The yields of the pure product proved to be low under these conditions, possibly through co-formation of appreciable quantities of the ethyl urethan of *d*-α-methylphenethylamine whose boiling point approximated that of II. Alternative synthesis employing dimethyl carbonate and di-*n*-amyl carbonate which would afford urethans boiling lower and higher than II did not improve the yield.

SCHEME I—VARIATION OF XCY



(1) S. L. Shapiro, I. M. Rose and L. Freedman, THIS JOURNAL, **80**, 6065 (1958).

(2) (a) R. E. McMahon, *ibid.*, **80**, 411 (1958); (b) J. Bauthier and H. Vandersmissen, *Arch. intern. pharmacodyn.*, **119**, 258 (1959); (c) R. Charlier, M. Prost, L. Dierickx, J. M. Ghuysen, M. Urbain and J. Singier, *ibid.*, **119**, 264 (1959).

(3) L. C. Mark, J. J. Burns, L. Brand, C. I. Campomanes, N. Trousof, E. M. Papper and B. B. Brodie, *J. Pharmacol. Exp. Therap.*, **123**, 70 (1958).

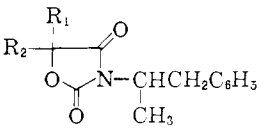
(4) J. W. Clark-Lewis, *Chem. Revs.*, **58**, 63 (1958).

(5) S. L. Jung, J. G. Miller and A. R. Day, THIS JOURNAL, **75**, 4664 (1953).

(6) S. L. Shapiro, I. M. Rose and L. Freedman, *ibid.*, **81**, 3083 (1959).

TABLE I

3-(α-METHYLPHENETHYL)-OXAZOLIDIONE-2,4-DIONES[a,b]



No.	R_1	Method	M.p.[c,d] or b.p., °C. (mm.)	Yield,[e] %	Formula	Analyses,[f] % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
1	H	A	107–127 (0.1)	27	$C_{12}H_{13}NO_3$					6.4	6.1
2	CH_3–	A	66–71	22	$C_{13}H_{15}NO_3$	66.9	67.2	6.5	6.3	6.0	6.0
3[ba]	CH_3–	C	96–104 (0.05)	82	$C_{13}H_{15}NO_3$					6.0	5.8
4[bb]	CH_3–	C	85–90 (0.03)	80	$C_{13}H_{15}NO_3$					6.0	6.0
5[aa]	CH_3–	A	108–109[da]	73	$C_{14}H_{17}NO_3$					5.7	5.7
6	C_7H_{16}–[g]	A	136–139 (0.005)	80	$C_{19}H_{27}NO_3$	71.9	72.3	8.6	8.8		
7	C_6H_5–	C	120–121	31	$C_{18}H_{17}NO_3$	73.2	73.7	5.8	6.0	4.7	4.7
8[ab]	C_6H_5–	C	180–220 (0.08)	56	$C_{24}H_{21}NO_3$	77.6	77.7	5.7	6.1	3.8	4.2

[a] R_2 is hydrogen unless otherwise specified; [aa] R_2 is methyl; [ab] R_2 is phenyl. [b] The structure is derived from *d*-α-methylphenethylamine unless otherwise specified; [ba] derived from "*dl*"-α-methylphenethylamine; [bb] derived from *l*-α-methylphenethylamine. [c] Melting points are not corrected and were established on a Fisher–Johns melting point block. [d] Recrystallization solvent is ethyl acetate–hexane unless otherwise noted; [da] hexane. [e] Yields are based on purified products. [f] Analyses are by Weiler and Strauss, Oxford, England. [g] C_7H_{16}– is $CH_3(CH_2)_3CH(C_2H_5)$–.

TABLE II

THIOAMIDES $R_3CN(H)-CH(CH_3)CH_2C_6H_5$ (=O)[a]

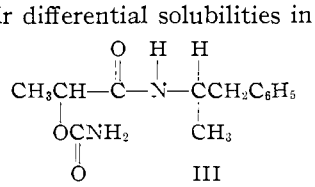
No.	R_3	M.p.[b,c] or b.p., °C. (mm.)	Yield,[d] %	Formula[e]	Analyses,[f] % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
1	$HSCH_2$–	140 (0.28)	25	$C_{11}H_{15}NOS$[g]	63.1	63.8	7.2	7.2	6.7	6.3
2	CH_3SCH_2–	59	55	$C_{12}H_{17}NOS$	64.5	64.5	7.7	7.4	6.3	6.5
3	$C_2H_5SCH_2$–	59–60	55	$C_{13}H_{19}NOS$	65.9	65.8	8.2	8.1	6.0	5.9
4	$C_6H_5SCH_2$–	85	60	$C_{17}H_{19}NOS$	71.6	71.3	6.7	6.7	4.9	5.0
5	4-$ClC_6H_4SCH_2$–	133–134	40	$C_{17}H_{18}ClNOS$	63.8	64.1	5.7	5.5	4.4	4.4
6	$C_6H_5CH_2SCH_2$–	66–67[ca]	41	$C_{18}H_{21}NOS$	72.2	71.6	7.1	7.1	4.7	4.6
6a	$C_6H_5CH_2SCH_2$–	88–90[ca]	10	$C_{18}H_{21}NOS$	72.2	72.2	7.1	6.8	4.7	4.3
7	4-$ClC_6H_4SCHCH_3$–	90–100[ca]	11	$C_{18}H_{20}ClNO_2$	64.8	64.6	6.0	6.0	4.2	3.9
8	$HSCHCH_3$–	76–77	70	$C_{12}H_{17}NOS$	64.5	64.8	7.7	7.7	6.3	6.4
9[a1]	$C_2H_5SCH_2$–	136–138 (0.1)	76	$C_{10}H_{12}ClNOS$					6.1	6.2
10[a2]	$C_2H_5SCH_2$–	53–54	45	$C_{11}H_{15}NOS$	63.1	62.8	7.2	6.7	6.7	6.9
11[a3]	$C_2H_5SCH_2$–	64–65	61	$C_{11}H_{14}ClNOS$	54.2	53.9	5.8	5.8	5.8	5.8
12[a4]	$C_2H_5SCH_2$–	134 (0.05)	82	$C_{12}H_{17}NOS$	64.5	64.5	7.7	8.1		

[a] Unless otherwise indicated, the amine used to form the amide was *d*-α-methylphenethylamine. In the following instances the compound is the amide derived from: [a1] *m*-chloroaniline, [a2] benzylamine, [a3] *p*-chlorobenzylamine, [a4] β-phenethylamine. [b] The melting points were determined on a Fisher–Johns melting point block and are uncorrected. [c] The recrystallizing solvent was ethyl acetate–hexane; [ca] or hexane. [d] Yields are reported as purified product. [e] The compounds were prepared by reaction of the amine with the requisite ester, compounds 5 and 7; or by reaction of the amine with the acid, compounds 1, 2, 3 and 8; or by reaction of the amine with the acid chloride, 4, 6, 6a and 9–12. [f] Analyses are by Weiler and Strauss, Oxford, England. [g] Characterized as the disulfide, m.p. 146–147° (methanol). Calcd. for $C_{22}H_{28}N_2O_2S$: C, 63.4; H, 6.8; N, 6.7. Found: C, 63.4; H, 7.0; N, 7.0; α_D(CHCl$_3$) −22.0°.

The difficulties involved in the isolation of II may be associated with the presence of diastereoisomeric forms.

The analeptic activity of II (see below) indicated inspection of congeners (Table I).

Treatment of the phenyl carbonate ester of I with ammonia yielded the carbamate III,[7] obtained as the mixture of diastereoisomeric forms separable through their differential solubilities in water.



III

Also explored was the hydrolysis[8] of selected diones (listed in Table I) to the carbamoylo acids. The 5,5-diphenyl analog of II (compound 8, Table I) gave virtually a quantitative yield of the N-(*d*-α-methylphenethyl)-benzilamide thus providing a synthesis for this previously unattainable compound.[1,9]

The thio analog of I depressed central nervous system response, and additional compounds in this series (Table II) were prepared.

The attempt to cyclize the thio analog of I to the corresponding thio analog of II has thus far failed following a variety of synthetic routes.

(7) Treatment of I with ethylurethan and aluminum isopropoxide following W. M. Kraft, THIS JOURNAL, **70**, 3569 (1948), yielded the dione II as shown in Scheme I above.

(8) S. L. Shapiro, I. M. Rose, E. Roskin and L. Freedman, *ibid.*, **81**, 386 (1959); see Scheme II of this reference.

(9) S. L. Shapiro, I. M. Rose, F. C. Testa, E. Roskin and L. Freedman *ibid.*, **81**, (in press (1959)), will consider hydrolyses of oxazolidinediones in some detail as to the effect of structure on the relative yields of (a) α-hydroxamide and (b) N-substituted carbamoylo-α-oxy acids.

Pharmacology.—High analeptic activity was noted with II, but with none of its congeners (Table I). The dione II (LD_{min} 300 mg./kg. s.c.), at 20 mg./kg. s.c. afforded a 605% increase in motor activity of rats. Compound 1 gave only an 88% increase (at 10 mg./kg. s.c.) while compound 5 decreased motor activity 19%. In contrast to the *l*- and *dl*-analogs (compounds 3 and 4, Table I), the dione II had no effect on blood pressure. The compound II also did not potentiate the convulsant threshhold of 50 mg./kg. of metrazole. The carbamate III (the form, m.p. 164–165°) had an LD_{min} of 750 mg./kg. s.c. and induced only a mild excitory effect.

For the compounds of Table II the most significant pharmacological effect was depression of motor activity,[10] with compound 5 also showing anti-inflammatory activity of 16 units/gram.[11]

Experimental[12]

Starting Materials.—The *d*-, *l*- and *dl*-α-methylphenethylamines were obtained as described previously.[1] The following compounds were prepared as described in the literature: methylmercaptoacetic acid,[13] b.p. 104° (10 mm.), $n^{20}D$ 1.4941; phenylmercaptoacetyl chloride,[14] b.p. 72–74° (0.12 mm.), $n^{20}D$ 1.5826; benzylmercaptoacetic acid,[15] m.p. 62.5–63° (hexane); benzylmercaptoacetyl chloride,[16] b.p. 90° (0.08 mm.), $n^{20}D$ 1.5718.

Ethyl (*p*-Chlorophenylmercapto)-acetate.—A solution of 34 g. (0.24 mole) of *p*-chlorothiophenol and 39.4 g. (0.24 mole) of ethyl bromoacetate in 75 ml. of acetone was treated with 32.6 g. (0.24 mole) of anhydrous potassium carbonate, stirred and heated under reflux for 4 hours. When cool, the inorganic salts were separated and the filtrate diluted with 100 ml. of water and extracted with three 100-ml. portions of ether. The ether extracts were dried (magnesium sulfate), the ether removed and the residue distilled. The product, 29 g. (53%), boiled at 116–120° (0.22 mm.).

Anal. Calcd. for $C_{10}H_{11}ClO_2S$: C, 52.1; H, 4.8. Found: C, 52.7; H, 4.7.

In a similar manner, ethyl α-(*p*-chlorophenylmercapto-propionate was prepared, b.p. 120–128° (0.4 mm.), in 54% yield. The product so obtained was not analytically pure but was used directly for further synthetic work.

Ethyl Mandelate.—Mandelic acid (304 g., 2.0 moles), ethanol (2.1 l.) and *p*-toluenesulfonic acid monohydrate (1.0 g.) were heated under reflux for 8 hours. The excess ethanol (1.9 l.) was removed and the residue on distillation gave 307 g. (85%) of ester, b.p. 88–95° (0.25 mm.), $n^{20}D$ 1.5134.[17]

3-(*d*-α-Methylphenethyl)-5-methyl-oxazolidine-2,4-dione (Compound 2, Table I. Method A).—A solution of N-(*d*-α-methylphenethyl)-lactamide (10.36 g., 0.05 mole) in 25 ml. of diethyl carbonate was treated with a solution prepared from 0.1 g. of sodium in 2 ml. of ethanol and the reaction mixture heated under reflux for 1 hour. After removal of the formed alcohol and excess diethyl carbonate, the product distilled at 103° at 0.05 mm. (bath 157°), there being obtained 9.9 g. (84%).

The oily material crystallized to a soft solid on standing, and was recrystallized from ethyl acetate–hexane mixture to yield crystals (2.2 g.), m.p. 66–71°.

Following a similar procedure, compounds 1, 5 and 6 (Table I) were prepared from the corresponding α-hydroxyamides.[1]

3-(*d*-α-Methylphenethyl)-5-methyl-oxazolidine-2,4-dione (Method C).—A solution of 13.5 g. (0.1 mole) of *d*-α-methylphenethylamine, 11.8 g. (0.1 mole) of ethyl lactate and 25 ml. of diethyl carbonate was maintained under reflux and a solution prepared from 0.1 g. of sodium in 2 ml. of ethanol added. When the internal temperature reached a minimum, the formed ethanol was removed. Addition of similar quantities of sodium ethoxide and removal of formed ethanol was repeated twice. In this manner there was obtained 22.6 ml. of ethanol (theory 23.3). When cool, the reaction mixture was filtered, the excess diethyl carbonate removed and the residue distilled, the product of 17.2 g. (74%) being collected at 108–116° (0.01 mm.). Solution in 100 ml. of hexane and chilling at 10° with addition of ethyl acetate to prevent oiling gave 4.3 g. (18%), m.p. 64–74°.

Following a similar procedure, compounds 3, 4, 7 and 8 of Table I were prepared. Compound 1 was prepared by this method in 36% yield. When the reaction conditions were reversed so that 0.1 mole of diethyl carbonate and 25 ml. of ethyl lactate were used, the product (compound 2) was obtained in 25% yield, m.p. 64–74°.

When di-(*n*-amyl) carbonate (25 ml.) was substituted for diethyl carbonate in the initial reaction, the product (m.p. 61–69°) was obtained in 25% yield.

When dimethyl carbonate was used as the solvent-reactant, the product (m.p. 63–71°) was obtained in 9% yield.

When sodium methoxide was substituted for sodium ethoxide, the product was obtained in 25% yield.

Reaction of N-(*d*-α-Methylphenethyl)-lactamide with Urea (Compound 2, Table I).—A mixture of 10.0 g. (0.050 mole) of N-(*d*-α-methylphenethyl)-lactamide and 3.0 g. (0.050 mole) of urea was placed in a bath at 190°. When the internal temperature reached 160° an evolution of ammonia occurred which became more vigorous at 172° (bath 196°) and subsided at 200° (bath 215°). After 1.5 hours, at the internal temperature 210° (bath 225°), the reaction was stopped. The residue was treated with 50 ml. of benzene, filtered, washed with dilute hydrochloric acid, water, filtered, and the benzene evaporated on the steam-bath. Distillation of the residue gave 1.12 g. (10%) of product, b.p. 110–120° (0.20 mm.), and 5.64 g. (56%) of unconverted reactant amide, b.p. 135–145° (0.20 mm.). The product crystallized when seeded and recrystallization (hexane–ethyl acetate) gave 0.15 g. of crystals, m.p. 64–74°.

Reaction of the N-(*d*-α-methylphenethyl)-lactamide with Ethylurethan and Aluminum Isopropoxide (Compound 2, Table I).—A solution of 17.8 g. (0.087 mole) of the N-(*d*-α-methylphenethyl)-lactamide and 7.67 g. (0.087 mole) of ethyl urethan in 60 ml. of xylene was heated under reflux, and three successive charges of 1.0 g. of aluminum isopropoxide added, each followed by removal of the ethanol by distillation. There was obtained a total of 5.8 ml. of alcohol fraction, corresponding to 50% reaction (allowing for 3.3. ml. from the catalyst). Ammonia was evolved constantly during the reaction. The xylene was evaporated and the residue treated with 75 ml. of benzene and 50 ml. of water, and acidified with dilute hydrochloric acid. The benzene was separated, washed with water, filtered, the benzene layer separated and, after removal of the solvent, the residue was distilled *in vacuo*. After a small amount of unreacted ethylurethan, 3.6 g. (18%) of compound 2 (Table I), b.p. 104–136° (0.2–0.5 mm.), and 10.2 g. (58%) of unconverted reactant amide, b.p. 140–154° (0.16 mm.), were obtained; each crystallized when seeded with the corresponding pure compounds.

Ethyl Carbamate of *d*-α-Methylphenethylamine.[18]—A solution of 13.5 g. (0.10 mole) of *d*-α-methylphenethylamine in 25 ml. of acetonitrile was maintained at 20° while 5.92 g. (0.11 mole) of ethyl chloroformate was added dropwise, with stirring, over 10 minutes. Stirring was continued for an additional 0.5 hour, the amine hydrochloride was

(10) The data for compounds of Table II follow as: compound no./% depression of motor activity/test dose mg./kg., s.c./LD_{min} mg./kg., s.c., respectively: 3/16/20/250; 5/30/20/350; 7/38/20/400; 8/22/100/250; 10/21/20/350; 12/25/20/350. The test procedure has been described in ref. 1.

(11) For method of testing see S. L. Shapiro, H. Soloway and L. Freedman, *J. Am. Pharm. Assoc.* (*Sci. Ed.*), **46**, 333 (1957).

(12) Descriptive data shown in the tables are not herein reproduced. The derivatives of *d*-α-methylphenethylamine throughout this paper have been designated as *d*- to reflect their origin from the dextrorotary form of the parent amine.

(13) E. Larsson, *Ber.*, **63B**, 1347 (1930), reports b.p. 130–131° (27 mm.), $n^{20}D$ 1.495.

(14) A. Mooradian, C. J. Cavallito, A. J. Bergman, E. J. Lawson and C. M. Suter, THIS JOURNAL, **71**, 3372 (1949), report b.p. 117–119° (6 mm.), $n^{25}D$ 1.5806.

(15) German Patent 814,596 (Sept. 24, 1951) [*C. A.*, **47**, 1741*d* (1953)], reports m.p. 61°.

(16) Reference 14 reports b.p. 130° (5.5 mm.), $n^{20}D$ 1.5682.

(17) This ester has been prepared in 77% yield by W. F. Barthel, J. Leon and S. A. Hall, *J. Org. Chem.*, **19**, 485 (1954). The procedure outlined above affords an improved yield and more simple operating conditions.

(18) R. L. Shriner and R. G. Child, THIS JOURNAL, **74**, 549 (1952), describe the lower alkyl carbamates of *dl*-α-methylphenethylamine.

separated and the acetonitrile removed under vacuum. The residue was treated with 75 ml. of benzene and 50 ml. of water and acidified with dilute hydrochloric acid. The benzene layer was separated, filtered, the benzene removed and the residue distilled, to give 9.0 g. (87%), b.p. 90–92° (0.05 mm.), $n^{20}D$ 1.5079. On standing, the product solidified and recrystallization (hexane) gave m.p. 46–47° (62%).

Anal. Calcd. for $C_{12}H_{17}NO_2$: C, 69.5; H, 8.3; N, 6.8. Found: C, 69.8; H, 8.4; N, 7.1.

N-(*d*-α-Methylphenethyl)-carbamoylolactic Acid (Alkaline Hydrolysis of Compound 2, Table I).—A suspension of 3-(*d*-α-methylphenethyl)-5-methyl-oxazolidine-2,4-dione (23.3 g., 0.10 mole) in 120 ml. of 2 *N* sodium hydroxide was stirred until dissolved. After 3 hours, extraction with chloroform and evaporation of the solvent gave 3.0 g. (15%) of N-(*d*-α-methylphenethyl)-lactamide. The aqueous layer was acidified and the carbamoylo acid extracted with chloroform. Evaporation of the solvent gave 19.5 g. (78%) of viscous sirup which could not be crystallized.

Anal. Calcd. for $C_{13}H_{17}NO_4$: C, 62.1; H, 6.8; N, 5.6. Found: C, 61.6; H, 7.0; N, 5.3.

The sodium salt was prepared by dissolving 2.6 g. (0.01 mole) of the acid in a solution of 0.84 g. (0.01 mole) of sodium bicarbonate in 15 ml. of water. The solution was washed with ether and evaporated *in vacuo* to give a gummy solid which was dissolved in 50 ml. of benzene, boiled to remove traces of water, filtered, and diluted with 200 ml. of hot hexane. The salt crystallized upon storage at 0° and there was obtained 1.7 g. (63%), m.p. 100–105°.

Anal. Calcd. for $C_{13}H_{16}NO_4Na$: N, 5.1. Found: N, 5.3.

The *d*-α-methylphenethylamine salt was prepared by treating a solution of 2.5 g. (0.01 mole) of the carbamoylo acid above in 10 ml. of ethanol with 1.4 g. (0.011 mole) of *d*-α-methylphenethylamine in 10 ml. of ethanol. The solution was warmed and diluted with 50 ml. of hot ethyl acetate. There was obtained 2.25 g. (58%) of product, m.p. 165–179°.

Anal. Calcd. for $C_{22}H_{30}N_2O_4$: C, 68.4; H, 7.8; N, 7.3. Found: C, 68.5; H, 7.9; N, 7.5.

Hydrolysis of compound 1 (Table I) in a similar manner gave a 22% yield of the crude N-(*d*-α-methylphenethyl)-glycolamide[1] and a 64% yield of N-(*d*-α-methylphenethyl)-carbamoyloglycolic acid, m.p. 108–112° (water).

Anal. Calcd. for $C_{12}H_{15}NO_4$: C, 60.8; H, 6.4; N, 5.9. Found: C, 61.4; H, 6.7; N, 5.8.

Similarly, hydrolysis of compound 7 (Table I) gave a 25% yield of crude N-(*d*-α-methylphenethyl)-mandelamide[1] and a 71% yield of N-(*d*-α-methylphenethylcarbamoylo)-mandelic acid, m.p. 104–106° (water). The analysis of this product indicated that it was hydrated.

Anal. Calcd. for $C_{18}H_{19}NO_4 \cdot H_2O$: N, 4.2. Found: N, 4.3.

Hydrolysis of compound 5 (Table I) in a similar manner after storage at 20° for two weeks afforded a 43% yield of N-(*d*-α-methylphenethylcarbamoylo)-α-hydroxyisobutyric acid, m.p. 125° (water). (The amide was not isolated in this reaction.)

Anal. Calcd. for $C_{14}H_{19}NO_4$: C, 63.4; H, 7.2; N, 5.3. Found: C, 63.6; H, 7.0; N, 5.6.

N-(*d*-α-Methylphenethyl)-benzilamide.—A suspension of 7.8 g. (0.021 mole) of 3-(*d*-α-methylphenethyl)-5,5-diphenyl-oxazolidine-2,4-dione and 14 ml. (0.040 equivalent) of 3 *N* sodium hydroxide was shaken for 48 hours at 20°. An oily suspension remained which was dissolved by addition of 30 ml. of ethanol. A solid formed which was separated (2.3 g.) and proved to be sodium carbonate monohydrate (theory, 2.5 g.). The ethanol was removed from the filtrate, the residue diluted with 60 ml. of water and the amide extracted with four 100-ml. portions of chloroform. The combined extracts were filtered and the chloroform removed to give 6.34 g. (87%) of the oily amide, which could not be crystallized.

Anal. Calcd. for $C_{23}H_{23}NO_2$: C, 80.0; H, 6.7; N, 4.1. Found: C, 79.8; H, 6.8; N, 3.9.

None of the corresponding carbamoylo acid was found.

Carbamate of N-(*d*-α-Methylphenethyl)-lactamide (Compound III, 2 Forms).—A solution of 10.36 g. (0.050 mole) of N-(*d*-α-methylphenethyl)-lactamide in 30 ml. of acetonitrile and 9 ml. of pyridine was cooled to −10°. Phenyl chloroformate (7.7 ml., 0.060 mole) was added dropwise over 10 minutes with continued stirring and cooling at −5°. The resulting solution was maintained at 20° for 2 hours. The acetonitrile was removed at 10–30 mm., the residue dissolved 100 ml. of ether and 50 ml. of dilute hydrochloric acid, the ether layer separated, washed with water and saturated sodium chloride solution, filtered and the ether evaporated on the steam-bath, yielding a thick sirup. This residue (crude phenyl carbonate ester of N-(*d*-α-methylphenethyl)-lactamide), was dissolved in 50 ml of ether and added over 5 minutes to 210 ml. of liquid amonia at −50°.

Complete solution was effected after 10 minutes and the solution was maintained for 15 hours under a Dry Ice condenser. Upon evaporation of the ammonia the residue obtained was triturated with 300 ml. of ether and separated (7.74 g.), m.p. 108–125°. Upon recrystallization (250 ml. of boiling water) the product separating from the slowly cooling solution (60°), was removed. It was washed thoroughly with warm (60°) water, and dried *in vacuo*, and gave 1.42 g. of the high melting form of the carbamate, m.p. 162–164°. The washes, on cooling, deposited an additional 0.17 g. of needles, m.p. 164–165° (total yield 13%), α_D ($CHCl_3$) − 24.5°.

Anal. Calcd. for $C_{13}H_{18}N_2O_3$: C, 62.4; H, 7.3; N, 11.2. Found: C, 62.0; H, 6.9; N, 11.2.

Extraction of the filtrates and wash solutions with five 50-ml. portions of chloroform yielded 2.4 g. of white solid which was recrystallized from a mixture of 25 ml. of hexane and 8 ml. of ethyl acetate. There was obtained 1.4 g. (11%) of the water-soluble form of the carbamate, m.p. 128–135°, $\alpha_D(CHCl_3)$ − 18.2°.

Anal. Calcd. for $C_{13}H_{18}N_2O_3$: C, 62.4; H, 7.3; N, 11.2. Found: C, 62.03; H, 7.0; N, 11.4.

The ultraviolet absorption spectra of the two forms of the carbamate were identical, λ_{max} 257 (ε1840) (methanol).

Methyl β-(*d*-α-Methylphenethylaminopropionate.—A solution of 10.0 g. (0.074 mole) of *d*-α-methylphenethylamine in 25 ml. of ethanol was cooled and maintained at −50° during the addition of 6.4 g. (0.074 mole) of methyl acrylate. After 24 hours storage at 20°, the mixture was distilled and the product, 15.5 g. (94%), was obtained, b.p. 98–103° (0.09 mm.).

Anal. Calcd. for $C_{13}H_{19}NO_2$: C, 70.6; H, 8.7. Found: C, 70.8; H, 9.0.

Heating an equimolar mixture (0.02 mole) of this ester with *d*-α-methylphenethylamine over 4 hours at a bath temperature of 190–200°, afforded the corresponding amide (30%), b.p. 190° (0.03 mm.).

Anal. Calcd. for $C_{21}H_{28}N_2O$: C, 77.7; H, 8.7; N, 8.6. Found: C, 78.0; H, 8.8; N, 8.6.

N-(*d*-α-Methylphenethyl)-thiolactamide (Compound 8, Table II).—A mixture of 21.24 g. (0.20 mole) of thiolactic acid, 28.02 g. (0.27 mole) of *d*-α-methylphenethylamine and 250 ml. of xylene was heated under reflux using a Dean–Stark trap. Over 15 hours the theoretical quantity of water was collected. The xylene was removed under diminished pressure and the residue, 34.5 g. (78%), crystallized. Titration with 0.1 *N* iodine solution showed 90% thioamide content. The disulfide (isolated from the iodine titration above) was recrystallized (benzene–hexane), m.p. 113–128°.

Anal. Calcd. for $C_{24}H_{32}N_2O_2S_2$: C, 64.8; H, 7.3; N, 6.3. Found: C, 64.7; H, 7.7; N, 6.2.

Ethyl Carbonate Ester of N-(*d*-α-Methylphenethyl)-thiolactamide.—A solution of 6.0 g. (0.025 mole) of compound 8 (Table II) in 25 ml. of acetonitrile and 4.0 ml. of pyridine was stirred and cooled to −10° during the addition of 5.0 ml. of ethyl chloroformate. After standing at 20° for 2 hours, the acetonitrile was removed and the residue treated with 75 ml. of benzene and 30 ml. of water and acidified with dilute hydrochloric acid. The benzene phase was separated. After removal of the benzene the residue was distilled to give 4.91 g. (72%) of product, b.p. 138–142° (0.08 mm.).

Anal. Calcd. for $C_{15}H_{21}NO_3S$: C, 61.0; H, 7.2; N, 4.7. Found: C, 61.1; H, 7.0; N, 4.7.

This compound was used for the attempted preparation of N-(*d*-α-methyl-β-phenethyl)-5-methyl-1,3-thiazolidine-2,4-dione as follows (method B): A mixture of 4.1 g. (0.014 mole) of the thiocarbonate ester above and 50 mg. of sodium methoxide was placed in a bath at 192°. A vigorous evolu-

tion of ethanol occurred over 10 minutes. The reaction was maintained at 190–200° for an additional 15 minutes. When cool, the reaction product was dissolved in 50 ml. of ether and after removal of the residue was distilled to give 2.3 g. (77%) of product, b.p. 104–110° (13 mm.), which partially crystallized. The crystals were separated by decantation and on recrystallization (hexane) melted at 67–85°. Analysis indicated that the thioamide (compound 8, Table II) had been formed.

N-(*d*-α-Methylphenethyl)-*p*-chlorophenylmercaptoacetamide (Compound 5, Table II).—A mixture of 11.5 g. (0.050 mole) of ethyl *p*-chlorophenylmercaptoacetate and 8.0 g. (excess) of *d*-α-methylphenethylamine was heated under reflux. Over 5 hours the internal reaction temperature fell from 182 to 133°. When cool the product crystallized. It was separated, washed with hexane, then water, and yielded 7.35 g., m.p. 126–130°.

The N-(*d*-α-Methylphenethyl)-benzylmercaptoacetamide (Compounds 6 and 6a, Table II).—The mixture of isomers obtained by reaction of 0.105 mole of *d*-α-methylphenethylamine with 0.05 mole of benzylmercaptoacetyl chloride weighed 13.8 g. (93%). It was dissolved in 1.1 l. of boiling hexane and allowed to cool. On standing, small hard crystals deposited. The solution decanted from these crystals and seeded afforded an additional crop which was collected. This step was repeated. The three portions of hard crystals were combined (2.0 g.), m.p. 80° after softening at 65°. Recrystallization from 100 ml. of boiling hexane gave 1.4 g. (10%), m.p. 88–90° (compound 6, Table II), $\alpha_D(CHCl_3)$ −5.0°.

On prolonged standing, the fluffy needles deposited from the hexane filtrate were separated (6.65 g.), m.p. 63–67°. This was dissolved in 1.1 l. of hexane at 45°, and on standing gave 2.7 g., m.p. 66–67°, $\alpha_D(CHCl_3)$ −40.0°.

The mother liquor, stored at 10°, gave an additional crop of 2.6 g. and 0.85 g., m.p. 66–67°; total 6.15 g. (41%) of compound 6a. The ultraviolet absorption spectra of compounds 6 and 6a were identical; λ_{max} (shoulder) 255–258, (ϵ540) (methanol). Since it is surprising that racemization could have occurred, the isolation of two forms of this compound requires additional clarification.

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[CONTRIBUTION FROM THE ORGANIC CHEMICAL RESEARCH SECTION, LEDERLE LABORATORIES DIVISION, AMERICAN CYANAMID CO.]

Pteridine Chemistry. IV. Structure of the Reaction Products Obtained from Acrylonitrile and 2-Amino-4-hydroxypteridines

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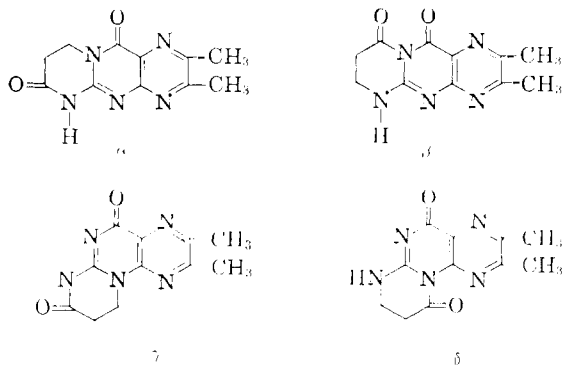
The structure of the product obtained by the reaction of 2-amino-4-hydroxy-6,7-dimethylpteridine (Ia) with excess acrylonitrile in a pyridine–water solution has been proved to be 2,3-dimethyl-8,9-dihydro-11H-pyrimido[2,1-b]pteridine-7(6H),11-dione (IIa), a representative of a previously unknown ring system. At *p*H 9.2 hydrolysis of the lactam linkage of IIa gave 2-amino-3-(2-carboxyethyl)-6,7-dimethyl-4-pteridone (IIIa) while in a sodium hydroxide solution a rearrangement occurred to produce 2-(2-carboxyethylamino)-4-hydroxy-6,7-dimethylpteridine (IVa). The application of this reaction to several other 2-amino-4-hydroxypteridines also was studied. The reaction of 2-methylmercapto-4-hydroxy-6,7-dimethylpteridine (VII) with acrylamide also gave IIa. This constituted the displacement of a methylmercapto group from the pteridine nucleus under unusually mild conditions.

While attempting to synthesize N^{10}-cyanoethylpteroylglutamic acid by direct cyanoethylation,[1] it was observed that under basic conditions the acrylonitrile attacked the pteridine portion of the molecule. Since the *p*-aminobenzoylglutamic acid moiety of pteroylglutamic acid was not involved, we resorted to the use of some simple 2-amino-4-hydroxypteridines in order to study the reaction and determine the structure of the products.

The 2-amino-4-hydroxy-6,7-dimethylpteridine (Ia) having been suspended in a water–pyridine solution,[2] was treated with a large excess of acrylonitrile and heated on a steam-bath until the reaction was complete as shown by paper chromatography. When the isolation procedure involved the use of slightly acidic conditions, the product had elemental analyses which indicated the addition of a C_3H_2O residue to Ia while the infrared absorption spectra exhibited no nitrile band. This could be explained by assuming a normal addition reaction between Ia and acrylonitrile involving any one of the three nitrogen atoms of the pyrimidine portion of the pteridine (Ia). A ring closure followed by hydrolysis of the resulting imino compound would then produce one of the four isomeric pyrimidopteridines (Chart I).

CHART I



Mild alkaline treatment of this pyrimidopteridine in 0.5 *N* sodium hydroxide solution at 90° for 30 minutes gave a new product (IVa) which was shown to be 2-carboxyethylamino-4-hydroxy-6,7-dimethylpteridine by elemental analysis and comparison of its ultraviolet absorption spectra with the spectra of a sample of 2-methylamino-4-hydroxy-

(1) A number of attempts to cyanoethylate pteroylglutamic acid under acidic conditions were entirely unsuccessful.

(2) Sodium hydroxide or Triton B also could be used as catalysts if the *p*H was maintained between 7 and 10.5. However, a pyridine-water solution was more satisfactory.