DL-5-Hydroxy-2-methyltryptophan.—A solution of 16.5 g. (0.0705 mole) of crude (m.p. 248–250°) DL-5-benzyloxy-2-methyltryptophan in 250 ml. of 0.5 *N* NaOH was hydrogenated [initial pressure 4.22 kg./cm.^{2} (60 lb./p.s.i.)] in the presence of 10 g. of 10% palladium on charcoal.[10] Hydrogenation stopped after 0.268 kg./cm.^{2} of hydrogen had been absorbed (theoretical uptake, 0.288 kg./cm.^{2}). The solution was filtered and evaporated *in vacuo*, and the residue was dissolved in water. The resulting solution was adjusted, to pH 5.86 with 6 *N* HCl, filtered to remove SiO_2, and evaporated to dryness. The residue was slurried twice with ice water (5-ml. portions) and recrystallized from 50% ethanol; yield 3.07 g. (15.8%), m.p. 292–293°.

Anal. Calcd. for $C_{12}H_{14}N_2O_3$: C, 61.53; H, 6.03; N, 11.96.

(10) This procedure was developed by J. Koo, S. Avakian, and G. J. Martin, *J. Org. Chem.*, **42**, 279 (1959), for the hydrogenolysis of 5-benzyloxytryptophan to 5-hydroxytrytophan.

The Synthesis of Disalicyl Alcohols

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Received January 2, 1965

Salicyl alcohol is used as an antipyretic and as a local anesthetic.[1] It is possible that the related compounds which we report might possess similar potential uses. Clemmensen and Heitman[2] have shown that 5,5′-methylenedisalicylic acid can be prepared by the condensation of formaldehyde and salicylic acid. In this investigation, the dimethyl ester of this acid has been reduced to its corresponding alcohol with $LiAlH_4$. It is shown that the efficiency of the reduction is related to the nature of the bridging group. A significant increase in yield was realized when a modification of the procedure was used to synthesize 5,5′-isopropylidenedisalicyl alcohol.

Experimental[3,4]

5,5′-Isopropylidenedisalicylic Acid.—A mixture of 32 g. (0.23 mole) of salicylic acid, 7.73 g. (0.133 mole) of acetone, and 180 g. of 60% sulfuric acid was heated under gentle reflux for 10–12 hr. with constant stirring. It was then allowed to cool and was filtered, and the residue was washed with cold water and air dried. Unchanged salicylic acid was removed by adding the powdered product to boiling water, with constant stirring, filtering while hot, and allowing the residue to dry in air. Purification was effected by dissolving the crude product in an excess of hot 95% ethanol, treating with Norit, filtering, and reprecipitating with cold water. The tan material was dried in a vacuum desiccator ($CaCl_2$); yield 11 g. (30.2%), m.p. 287–289°.

Anal. Calcd. for $C_{17}H_{16}O_6$: C, 64.60; H, 5.07. Found: C, 64.90; H, 5.35.

Dimethyl 5,5′-Isopropylidenedisalicylate.—This dimethyl ester was prepared by the Fischer–Speier[5] method. The product was isolated in the usual manner and recrystallized from absolute methanol. Fifty grams of acid gave 18 g. (33.3%) of pure ester, m.p. 98–99°.

5,5-Isopropylidenedisalicyl Alcohol.—A solution of 4.0 g. (0.1 mole) of $LiAlH_4$ in 225 ml. of absolute ether was made by stirring the slurry for 4 hr. The reaction mixture was protected from atmospheric moisture by attaching $CaCl_2$ tubes to all openings. Then a solution of 12.0 g. (0.035 mole) of dimethyl 5,5′-isopropylidenedisalicylate in 120 ml. of absolute ether was added through the dropping funnel at a rate which produced gentle reflux. After the addition, the reaction was gently heated at reflux temperature for 12 hr. and allowed to cool. The excess $LiAlH_4$ was decomposed by the cautious addition of water. The contents of the reaction flask were then added to a mixture of crushed ice and concentrated H_2SO_4, stirred for 10 min., and filtered. This residue was combined with the residue obtained by evaporating the dried ether layer of the filtrate. These solids were then repeatedly recrystallized from hot water until long white needles of the desired pure alcohol were obtained; yield 5.0 g. (25%), m.p. 146–147°.

Anal. Calcd. for $C_{17}H_{20}O_4$: C, 70.83; H, 6.94. Found: C, 70.85; H, 6.79.

5,5′-Methylenedisalicyl Alcohol.—This alcohol was prepared by the $LiAlH_4$ reduction of its dimethyl ester according to the procedure outlined above for the isopropylidene alcohol. The crude product was recrystallized from hot water to give glistening, pale gray plates; yield 2.0 g. (8%), m.p. 166–167°.

Anal. Calcd. for $C_{15}H_{16}O_4$: C, 69.23; H, 6.15. Found: C, 69.25; H, 6.20.

(1) C. O. Wilson and T. E. Jones, "The American Drug Index," J. B. Lippincott Co., Philadelphia, Pa., 1956, p. 419.

(2) E. Clemmensen and H. C. Heitman, *J. Am. Chem. Soc.*, **33**, 737 (1911).

(3) Microanalyses by Drs. Weiler and Strauss, Microanalytical Laboratory, Oxford, England.

(4) Melting points were determined in a standard capillary melting point bath with a calibrated thermometer.

(5) E. Fischer and A. Speier, *Ber.*, **28**, 3252 (1895).

Aromatic Fluorine Compounds. XIII. Substituted N-Phenylglycine Ethyl Esters and Hydrazides[1]

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Received December 21, 1964

Data on the herbicidal and medicinal properties of halogenated N-arylglycine esters and hydrazides are limited to a few compounds. In 1949 when the plant growth regulating properties of maleic hydrazide[2] were reported, N-(2,4-dichlorophenyl)-glycine[3] was found also to have herbicidal properties. The first biological data on fluorinated arylglycine derivatives appeared about a decade later. Tuberculostatic tests[4] were reported on N-(4-fluorophenyl)glycine, its ethyl ester, and its hydrazide. Tomato leaf curvature data[5] appeared in 1959 on N-(3-trifluoromethylphenyl)glycine and N-(3-trifluoromethyl-4-chlorophenyl)-glycine and their amides.

A large number of fluorine, other halogen, and methyl derivatives of N-phenylglycine was prepared as part of a program[6] on the synthesis of fluorinated herbicides and medicinals. Tables I and II summarize the physical data on 31 glycine ethyl esters and 28 glycine hydrazides, respectively.

Experimental[7]

N-Phenylglycine Ethyl Esters.—These compounds with substitution in the phenyl group were prepared by condensing the appropriately substituted primary anilines with ethyl chloroacetate.[4,8]

To a well-stirred mixture of 114 g. (0.75 mole) of sodium acetate trihydrate and 50–75 ml. of ethanol was added 0.5 mole of the appropriate aniline and 62 g. (0.5 mole) of ethyl chloroacetate. The reaction mixture was refluxed gently with stirring for 24–48

(1) This research was supported in part by contract with the U. S. Army Biological Laboratories, Fort Detrick, Frederick, Md., through the University of Illinois. The research was the responsibility of the Illinois State Geological Survey.

(2) D. L. Schoene and O. L. Hoffman, *Science*, **109**, 589 (1949).

(3) H. Veldstra and H. L. Booig, *Biochim. Biophys. Acta*, **3**, 278 (1949).

(4) N. B. Tien, Ng. Ph. Buu-Hoi, and Ng. D. Xuong, *J. Org. Chem.*, **23**, 186 (1958).

(5) A. Takeda, *Contrib. Boyce Thompson Inst.*, **20**, 191 (1959).

(6) (a) G. C. Finger, M. J. Gortatowski, R. H. Shiley, and R. H. White, *J. Am. Chem. Soc.*, **81**, 94 (1959); (b) G. C. Finger, D. R. Dickerson, D. E. Orlopp, and J. W. Ehrmantraut, *J. Med. Chem.*, **7**, 572 (1964); (c) G. G. Lu, G. C. Finger, and J. C. Krantz, Jr., *Toxicol. Appl. Pharmacol.*, **4**, 24 (1962).

(7) All melting points were taken in a capillary tube and are corrected (ASTM-specification thermometer).

(8) W. Baker, W. D. Ollis, and V. D. Poole, *J. Chem. Soc.*, 307 (1949).

TABLE I
N-PHENYLGLYCINE ETHYL ESTERS

R	B.p. (mm.) or m.p., °C.	Formula	Calcd., % C	Calcd., % H	Calcd., % N	Found, % C	Found, % H	Found, % N
2-F	120–121 (5)	$C_{10}H_{12}FNO_2$	60.90	6.09	7.09	60.70	6.02	7.27
3-F	78.5–79.5					60.83	6.20	7.27
4-F	73–74[a]					60.96	6.05	7.28
2-Cl	116 (1)[b]	$C_{10}H_{12}ClNO_2$	56.21	5.66	6.56	56.13	5.56	6.63
3-Cl	113–114[c,d]					56.00	5.68	6.53
4-Cl	92.5–93.5[c,d]					55.94	5.49	6.76
2-Br	37.5–38.5[e]	$C_{10}H_{12}BrNO_2$	46.53	4.69	5.42	46.67	4.66	5.49
3-Br	117–118[f]					46.70	4.76	5.64
4-Br	94–95[g]					46.53	4.72	5.31
3-I	115–116	$C_{10}H_{12}INO_2$	39.36	3.96	4.59	39.36	3.99	4.73
3-CF_3	84–85	$C_{11}H_{12}F_3NO_2$	53.44	4.89	5.67	53.56	4.83	5.76
4-CF_3	83.5–84.5					53.40	4.95	
2-Cl, 3-Cl	48–49	$C_{10}H_{11}Cl_2NO_2$	48.40	4.47	5.65	48.54	4.48	5.73
2-F, 4-F	92.5–93.5	$C_{10}H_{11}F_2NO_2$	55.81	5.15	6.51	56.02	5.33	6.49
3-F, 4-F	70–71					55.79	5.21	6.52
2-Br, 4-F	44–45.5	$C_{10}H_{11}BrFNO_2$	43.49	4.02	5.07	43.61	4.06	5.08
4-Br, 2-F	141 (2)					43.21	3.98	5.09
2-Cl, 4-F	84 (9)	$C_{10}H_{11}ClFNO_2$	51.85	4.79	6.04	51.97	4.70	6.88
3-Cl, 4-F	107.5–108					51.74	4.77	6.22
3-Cl, 2-F	101 (1.5)					51.89	4.79	6.27
4-Cl, 3-CH_3	94–95	$C_{11}H_{14}ClNO_2$	58.02	6.20	6.15	58.00	6.08	6.33
3-F, 4-CH_3	78–78.5	$C_{11}H_{14}FNO_2$	62.54	6.67	6.63	62.42	6.60	6.63
3-F, 2-CH_3	51.5–52.5[h]					62.74	6.63	6.83
4-Br, 3-CF_3	109.5–110.5	$C_{11}H_{11}BrF_3NO_2$	40.51	3.40	4.30	40.63	3.36	4.46
4-Cl, 3-CF_3	102.5–103	$C_{11}H_{11}ClF_3NO_2$	46.90	3.94	4.97	47.04	4.04	4.95
2-F, 5-CF_3	110 (2)	$C_{11}H_{11}F_4NO_2$	49.81	4.18	5.28	49.58	3.95	5.50
4-F, 3-CF_3	81–82					50.03	4.06	5.30
2-CH_3, 3-CH_3	64–65	$C_{12}H_{17}NO_2$	69.53	8.27	6.76	69.40	8.15	6.79
2-CH_3, 5-CH_3	51–52					69.26	8.19	6.86
2-CH_3, 6-CH_3	140 (7)					69.30	8.09	6.99
3-CH_3, 4-CH_3	49.5–50.5[i]					69.77	8.15	6.84

[a] Lit.[4] m.p. 72°. [b] $n^{25}D$ 1.5379; C. G. Schwalbe, W. Schultz, and H. Jockheim [*Chem. Ber.*, **41**, 3793 (1908)] reported b.p. 288–291°. [c] Lit.[8] m.p. 108°, 3-chloro; 88°, 4-chloro. [d] A. Bryson, N. R. Davies, and E. P. Serjeant [*J. Am. Chem. Soc.*, **85**, 1937 (1963)] report m.p. 110°, 3-chloro; 94°, 4-chloro. [e] W. Schoeller, W. Schrauth, and P. Goldacker, [*Chem. Ber.*, **44**, 1302 (1911)] report m.p. 82–83°. These investigators probably had an impure sample of the 4-bromo compound. [f] R. A. Eade and J. C. Earle [*J. Chem. Soc.*, 2307 (1948)] report m.p. 118.5–119°. [g] M. Dennstedt [*Chem. Ber.*, **13**, 238 (1880)] reports m.p. 95–96°. [h] B.p. 123° (3 mm.). [i] F. E. King, J. W. Clark-Lewis, and C. R. P. Morgan [*J. Chem. Soc.*, 3074 (1951)] report m.p. 49–50°.

hr. The anilines with an *ortho* substituent usually required the longer reaction time. When the reaction mixture was cooled and poured into 1500 ml. of cold water, the glycine ethyl ester separated as an oil or a solid; crude yield 25–50%. (Some *ortho*-substituted anilines failed to react and were not considered further.) The phenyl esters with an *ortho* substituent separated as liquids except N-(2,4-difluorophenyl)glycine ethyl ester which was a solid. The liquids were first flash vacuum distilled to remove gross impurities. Several fractional vacuum distillations through a 25-cm. column packed with stainless steel helices[9] gave the pure esters as colorless or pale yellow liquids. The solid products were first recrystallized several times from ethanol and, in some cases, subsequently sublimed *in vacuo* to give the pure esters as white needles or platelets.

The solid esters are insoluble in water and petroleum ether, soluble in ether and acetone, and slightly soluble in cold but soluble in hot ethanol, methanol, benzene, and carbon tetrachloride.

N-Phenylglycinehydrazides.—The glycine esters were converted to hydrazides by reaction with hydrazine.[4] To a solution of 0.5 mole of the N-phenylglycine ethyl ester in 1200 ml. ethanol was added 24 g. (0.75 mole) of technical hydrazine (95%). The mixture was refluxed gently for 22 hr. with stirring only during the first hour. Evaporation of the solvent in a rotary vacuum evaporator gave the crude hydrazides as tan crystalline solids or highly viscous oils which solidified gradually on standing; yield *ca.* 95%. The crude solids were then crushed and air dried in a hood for 2–4 hr. and decolorized with charcoal in hot ethanol solution. Recrystallization from the clear solution gave the pure hydrazides as white needles or platelets. Several hydrazides formed alcoholates during crystallization. Vacuum drying at 10–20° below the melting point removed the alcohol.

The hydrazides sublime very slowly under vacuum, and may gradually darken on long standing. They are partially soluble in cold and very soluble in hot ethanol or methanol, insoluble in petroleum ether, and insoluble in cold but partially soluble in hot benzene, carbon tetrachloride, and water. Some of the hydrazides could be recrystallized from acetone, whereas a number reacted rapidly with acetone to form the hydrazone derivative.

Acetone N-Phenylglycine Hydrazones.—The hydrazides with trifluoromethyl substitution in the phenyl group readily formed solid hydrazone derivatives upon heating in acetone. Recrystallization from acetone or vacuum sublimation gave the following pure compounds.

Acetone N-(3-trifluoromethylphenyl)glycine hydrazone, m.p. 133–134°.

Anal. Calcd. for $C_{12}H_{14}F_3N_3O$: C, 52.75; H, 5.16. Found: C, 53.05; H, 5.08.

Acetone N-(3-trifluoromethyl-4-bromophenyl)glycine hydrazone, m.p. 153–154°.

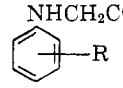
Anal. Calcd. for $C_{12}H_{13}BrF_3N_3O$: C, 40.90; H, 3.72. Found: C, 41.19; H, 3.61.

Acetone N-(3-trifluoromethyl-4-chlorophenyl)glycine hydrazone, m.p. 155–156°.

Anal. Calcd. for $C_{12}H_{13}ClF_3N_3O$: C, 46.84; H, 4.25. Found: C, 46.79; H, 4.38.

(9) Heli-Pak No. 3008, Podbielniak Co., Chicago 17, Ill.

TABLE II
N-PHENYLGLYCINE HYDRAZIDES



R	M.p., °C.	Formula	Calcd., % C	Calcd., % H	Calcd., % N	Found, % C	Found, % H	Found, % N
2-F	89.5–90.5	$C_8H_{10}FN_3O$	52.45	5.50	22.94	52.47	5.58	23.11
3-F	113.5–114					52.44	5.57	22.84
4-F	114.5–115[a]					52.36	5.43	22.83
2-Cl	92.5–93.5[b]	$C_8H_{10}ClN_3O$	48.13	5.05	21.05	48.25	4.94	21.06
3-Cl	87–88					48.24	5.01	20.88
4-Cl	146.5–147.5[a,c]					47.91	4.97	20.95
2-Br	106–107	$C_8H_{10}BrN_3O$	39.36	4.13	17.22	39.66	4.03	17.24
3-Br	84–85					39.64	4.14	16.94
4-Br	143.5–144.5[a]					39.41	4.22	17.16
3-I	124.5–125.5	$C_8H_{10}IN_3O$	33.01	3.46	14.43	33.28	3.49	14.44
3-CH_3	90–91	$C_9H_{13}N_3O$	60.32	7.31	23.44	60.39	7.07	23.50
4-CH_3	152.5–154[d]					60.53	7.14	...
2-Cl, 3-Cl	161–162[c]	$C_8H_9Cl_2N_3O$	41.05	3.87	17.95	41.59	3.83	17.97
2-F, 4-F	105–106	$C_8H_9F_2N_3O$	47.76	4.51	20.89	47.84	4.55	20.86
3-F, 4-F	95–96					47.84	4.58	20.78
2-Br, 4-F	129–130	$C_8H_9BrFN_3O$	36.66	3.46	16.03	36.75	3.53	15.94
4-Br, 2-F	116–117[b]					36.90	3.48	15.85
2-Cl, 4-F	127.5–128.5	$C_8H_9ClFN_3O$	44.15	4.17	19.31	44.39	4.32	19.20
3-Cl, 2-F	111–112[b]					44.57	4.27	19.37
3-Cl, 4-F	100–101					44.39	4.38	19.57
4-Cl, 3-CH_3	102–103	$C_9H_{12}ClN_3O$	50.59	5.66	19.66	50.88	5.62	19.48
3-F, 2-CH_3	120–121	$C_9H_{12}FN_3O$	54.80	6.09	21.32	54.70	6.27	21.48
3-F, 4-CH_3	150.5–151.5					54.97	6.07	21.29
2-F, 5-CF_3	150.5–151.5	$C_9H_9F_4N_3O$	43.04	3.61	16.73	43.28	3.59	17.07
2-CH_3, 3-CH_3	142.5–143.5	$C_{10}H_{15}N_3O$	62.15	7.82	21.76	62.29	7.63	21.62
2-CH_3, 5-CH_3	107.5–108.5					61.92	7.64	21.75
2-CH_3, 6-CH_3	99–101					62.13	7.62	21.50
3-CH_3, 4-CH_3	142–143					62.34	7.63	21.69

[a] Lit.[4] m.p. 115°, 4-fluoro; 140°, 4-chloro; 161°, 4-bromo. [b] Forms ethanol of crystallization. [c] S. Passeron and G. A. Brieux [*Bull. soc. chim. France*, 35 (1963)] reported m.p. 146°, 4-chloro; 150–152°, 2,3-dichloro. [d] T. Takahashi, J. Okada, and Y. Yamamoto [*Yakugaku Zasshi*, **77**, 645 (1957)] report m.p. 150°.

Book Reviews

Green Medicine. The Search for Plants that Heal. By MARGARET B. KREIG. Rand McNally and Co., Chicago, Ill. 1964. 462 pp. $5.95.

Magazine editors, mystery writers, lady ex-marines, past premedical students, fashion models, and even medical science writers do not often publish a book which should be read by medicinal and natural products chemists. Yet, Mrs. Kreig has been involved in all these activities before she became fascinated by medicinal plants. She acquired the background needed for this book by reading widely, from novels and semipopular accounts to the bona fide technical literature of botanical drugs. She joined expeditions into the South American rain forests and participated in searches for drug plants led by botanists, organic chemists, and physicians, and staffed by academic, governmental, and industrial scientists. In addition, she interviewed in person, by telephone, and by correspondence hundreds of the foremost scientists in the field all over the world, and by intuition and literary talent filled in the gaps to produce a continuous story.

The book, dedicated to the American Society of Pharmacognosy, is divided into three parts. The first one is called Medicine Scouts and Their Methods, and tells of the quest for strophantus species, field notes from Africa, encounters with Indians, witch doctors, primitive peoples, and truly moving and exciting adventures on botanical expeditions. The second part, Biographies of Botanicals, gives strikingly written, readable, and accurate histories of the discoveries and uses of quinine, digitalis glycosides, curare, chaulmoogra oil, sarsaparilla, and steroid raw materials from Mexican yams. This reviewer admits that the stories of contemporary phases of these searches, as gathered in personal interviews, sound at times different from accounts in text books in pharmacology which did not go to the trouble of tracing the stories back to their source. The accounts of the true roles of Russell E. Marker and of Albert Hofmann, to name just two of many, are told with restraint and care. If for no other reason, we owe Mrs. Kreig thanks for providing us with the results of her personal inquiries.

In the third part of the book, Frontiers of Research, opinions and uncertainties enter into the tales, as they must in unfinished phases of scientific work. Here the author feels less sure of herself. In her interpretations of the story of CNS active agents, originally from botanicals (reserpine, LSD, mescaline, etc.), she has tried so hard not to overstep scientifically established facts that these chapters are duller than those in the earlier sections. There are too many botanical and chemical names and too much medical reporting for the intelligent layman, and yet far too little for the therapeutically oriented scientist. But even in these chapters, much of real interest can be found, particularly for younger readers, and for those of us who want to read about the participation of many of our friends, of many members of the Medicinal Chemistry Division of the American Chemical Society, in these searches and researches, and to see their photographs in unusual settings. A surprisingly large and varied bibliography concludes this remarkable volume. In no case has the author permitted herself to be carried away with a feeling of an overwhelming importance of botanical agents, but she has placed them in nearly as true a perspective with regard to synthetic drugs as one can. Drugs from plants provide us with novel structures, and as a side issue with fascinating insights into