1,2-diol, 90 ml. of ether and 54 ml. of catalyst solution (about 2.7 g. of dicobalt octacarbonyl). The bomb was purged three times with carbon monoxide at 100 p. s. i., hydrogen introduced to a pressure of 1500 p. s. i. and carbon monoxide added to a total pressure of 3000 p. s. i. The bomb was heated with shaking for six hours at 180°. The pressure during the period of reaction reached a maximum of 4000 p. s. i., dropped to 3925 p. s. i. and then to 2250 p. s. i. when the bomb was cooled to room temperature. After removing the ether by distillation, the residue was distilled *in vacuo* to give, after a small forerun containing water, 5 g. of material boiling at 111–117° (30 mm.), $n^{25}D$ 1.4488. During the distillation, a large amount of residue of polymeric nature formed in the flask.

The 3,5-dinitrobenzoate was prepared and recrystallized from dilute ethanol, m. p. and mixed m. p. with the 3,5-dinitrobenzoate of 2-tetrahydrofurfuryl alcohol 83–84°.

Crotonaldehyde from 3-Butene-1,2-diol.—A mixture of 15 g. (0.17 mole) of 3-butene-1,2-diol and 15 g. of 10% hydrochloric acid in a 100-ml. flask fitted with a short Vigreux column was heated at 100°. The distillate which was a mixture of water and crotonaldehyde amounted to 10.5 g. A black, viscous residue (18.6 g.) remained in the flask. The crotonaldehyde layer was dried and redistilled to give material boiling at 103–105°, $n^{25}D$ 1.4420; reported b. p. 104–105°, $n^{17}D$ 1.4384.[7]

(7) "Handbook of Chemistry and Physics," 30th edition, Chemical Rubber Publishing Co., Cleveland, Ohio, 1947.

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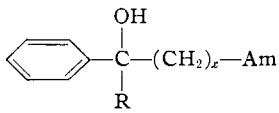
Antispasmodics. V.[1] Tertiary α- and γ-Amino Alcohols and Quaternary Salts of β-Amino Alcohols[1]

BY J. J. DENTON AND VIRGINIA A. LAWSON

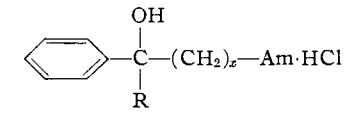
Our previous studies have shown the effect on the antispasmodic activity of variations in chemical structure of the R and Am groups of tertiary β-amino alcohols represented by the following formula (where x is 2 and where R and Am represent various hydrocarbon and disubstituted amino groups, respectively)



To determine further the effect of chemical structure on the antispasmodic activity of compounds of this type, we studied two additional modifications of structure: lower and higher homologs, compounds of the above formula where x is 1 and 3; and quaternary salts of the β-amino alcohols, where x is 2.

β-Amino alcohols, II,[2] V[2,3] and VII[1] in Table I, have been reported previously and were chosen for this study of homologs because they showed a low, medium and high order of antispasmodic activity, respectively. The α-amino alcohols, I and IV in Table I, were prepared essentially by the procedure of Henley,[4] who has described the latter compound. One of the γ-amino alcohols, compound VIII, has been reported by Marxer[5] and by Miescher and Marxer.[6] We have prepared the other two, compounds III and VI in Table I, by a similar procedure.

TABLE I



Number	R	x	Am	Activity
I	C_2H_5–	1	$(C_2H_5)_2N$–	–
II	C_2H_5–	2	$(C_2H_5)_2N$–	++
III	C_2H_5–	3	$(C_2H_5)_2N$–	+
IV	C_2H_5–	1	$C_5H_{10}N$–	+
V	C_2H_5–	2	$C_5H_{10}N$–	+++
VI	C_2H_5–	3	$C_5H_{10}N$–	++
VII	C_6H_5–	2	$C_5H_{10}N$–	++++
VIII	C_6H_5–	3	$C_5H_{10}N$–	++

In Table II, thirteen new quaternary salts of previously reported β-amino alcohols are listed. In general, the formation of these quaternary salts from the amino alcohols proceeds slowly if the latter are dissolved in an excess of the alkyl halide, and the resulting solution is allowed to stand. The use of solvents such as nitromethane gave more rapid quaternization in certain cases Attempts to increase the rate of quaternization by heating were unsuccessful.

Pharmacological Activity

The general significance of the antispasmodic rating has been given in paper I[7] of this series, and details of the testing method have been recently reported by Cunningham and co-workers.[8] The quantitative significance of the rating scheme used throughout this series of papers has not as yet been reported. The rating of + indicates that no less than 1 mg. of the compound in 100 ml. of the testing bath gives a 50% relaxation of the spasm of a rabbit ileum made spastic with 0.1 mg. of Furmethide per 100 ml. bath. A rating of ++ indicates that the same effect is produced with no less than 0.1 mg. of the compound. Ratings of +++ and ++++ likewise vary successively by factors of ten in concentration.

Table I shows that the lower homologs, the α-amino alcohols, are less active than the higher homologs, the γ-amino alcohols, which, in turn, are less active than the β-amino alcohols. It is concluded therefore, that, in this type of com-

(1) For paper IV in this series see THIS JOURNAL, **71**, 2054 (1949). Throughout this series of papers for generic names, we have preferred to use the term "alcohol" to mean the same as the term "carbinol." Thus, the amino alcohols retain the same prefix as the amino ketones from which they were usually derived.

(2) Denton, Neier and Lawson, *ibid.*, **71**, 2053 (1949).

(3) Denton, Lawson, Neier and Turner, *ibid.*, **71**, 2050 (1949).

(4) Henley and Turner, *J. Chem. Soc.*, 1182 (1931).

(5) Marxer, *Helv. Chim. Acta*, **24**, 209 (1941).

(6) Miescher and Marxer, United States Patent 2,411,664, November, 1946.

(7) Denton, Turner, Neier, Lawson and Schedl, THIS JOURNAL, **71**, 2048 (1949).

(8) Cunningham, *et al.*, *J. Pharmacol. Exptl. Therap.*, **96**, 151 (1949).

TABLE II

QUATERNARY SALTS OF

No.	R	Am	Alkyl halide	Formula	M. p.,[a] °C.	Yield,[b] %	Procedure	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Halogen,[i] % Calcd.	Halogen,[i] % Found	Activity
I	C_2H_5–	$C_5H_{10}N$–	C_2H_5Br	$C_{18}H_{30}BrNO$	213.0–214.4	65	A	60.67	60.8	8.49	8.59	3.94	3.84	22.43	22.7	++
II	C_3H_5–	$C_5H_{10}N$–	C_2H_5Br	$C_{19}H_{30}BrNO$	186.6–188.0 d.	59	A	61.95	61.4	8.21	8.06	3.80	4.06	21.70	21.9	+++
III	n-C_3H_7–	$C_5H_{10}N$–	C_2H_5Br	$C_{20}H_{32}BrNO$	169.8–172.3	37	A	61.61	61.4	8.71	8.69	3.78	3.94	21.58	21.6	+++
IV	n-C_4H_9–	$C_5H_{10}N$–	CH_3Cl	$C_{19}H_{32}ClNO\cdot H_2O$[c]	113–120[d]	36	B	66.35	66.6	9.97	10.3	4.07	4.10	10.31	10.3	+++
V	n-C_4H_9–	$C_5H_{10}N$–	CH_3I	$C_{19}H_{32}INO$	149.3–151.7 d.	41	A	54.67	54.8	7.73	8.17	3.36	3.39	30.41	30.8	++++
VI	n-C_4H_9–	$C_5H_{10}N$–	C_2H_5Br	$C_{20}H_{34}BrNO$	193.8–194.8	20	A	62.49	62.3	8.92	8.95	3.64	3.77	20.79	20.9	++++
VII	n-C_4H_9–	$C_5H_{10}N$–	$C_6H_5CH_2Cl$	$C_{26}H_{36}ClNO\cdot H_2O$[e]		59	A	71.48	71.5	9.12	9.24	3.34	3.68	8.44	8.53	+++
VIII	C_6H_{11}–	$C_5H_{10}N$–	C_2H_5Br	$C_{22}H_{34}BrNO$	210.0–214.0	29	A	63.4[f]	63.8	8.96	8.96	3.35	3.40	19.1	19.2	+++
IX	n-C_3H_7–	$O(C_2H_4)_2N$–	C_2H_5Br	$C_{19}H_{32}BrNO_2$	161.3–163.0	20	A	59.06	59.1	8.35	8.28	3.63	3.66	20.68	20.8	+++
X	C_2H_5–	$(C_2H_5)_2N$–	C_2H_5Br	$C_{17}H_{34}BrNO$	173.8–176.0	7	B	59.29	59.5	8.78	8.93	4.07	4.36	23.21	23.4	+++
XI	C_6H_{11}–	$(C_2H_5)_2N$–	C_2H_5Br	$C_{21}H_{38}BrNO$	181.3–183.0	30	A	63.30	63.4	9.11	9.26	3.52	3.63	20.01	20.0	+++
XII	C_2H_5–	$(CH_3)_2N$–	C_2H_5Br	$C_{16}H_{32}BrNO$	110.2–117.0	55	B	55.70[g]	56.1	8.35	7.92	4.33	4.34	24.71	25.0	++
XIII	C_2H_5–	$C_5H_{11}N_2$–[h]	CH_3Cl	$C_{17}H_{34}ClN_2O\cdot H_2O$[j]	241–242 d.	30	B	61.69	61.9	9.44	9.37	8.46	8.68	10.71	10.7	+++

[a] All melting points are corrected. [b] Yield of purified material based on starting amine. [c] Calcd. H_2O, 5.25; found (by Karl Fischer method), 5.1. [d] Compound sinters at about 75°. It is hygroscopic. [e] Calcd. H_2O, 4.3; found (by Karl Fischer method), 3.3. This compound sinters at about 97.5° and is completely melted only at about 175°. [f] Karl Fischer moisture determination showed presence of 1.7% H_2O. Calculations are based on this amount of water. [g] Calculations are based on a Karl Fischer moisture analysis showing presence of 2.2% H_2O. [h] 1-(4-Methylpiperazyl) radical. [i] Calcd. H_2O, 5.44; found (by Karl Fischer method), 5.9.

pound, the greatest antispasmodic activity results from a 1,3-relation of the hydroxyl and substituted amino groups.

In Table II, quaternary salts I, III, IV, VI, VII and XI have lower antispasmodic activity ratings than the hydrochlorides of the respective tertiary amines from which they were derived. Salts V, VIII and IX have the same rating as the corresponding amine hydrochloride. Higher antispasmodic ratings than the hydrochlorides, however, are shown by quaternary salts II, X, XII and XIII. Thus, there appears to be no consistent relationship between the activity of these quaternary salts and the corresponding hydrochlorides.

The alkyl halide used in forming the quaternary salt from 1-(1-piperidyl)-3-phenyl-3-heptanol has a marked effect on the antispasmodic activity. The methiodide (V) in Table II and the methochloride (IV) were as active or nearly as active, the ethobromide (VI) was less active, and the benzochloride was of a much lower order of activity than the corresponding amine hydrochloride.

Experimental

Compounds in Table I: 1-(1-Piperidyl)-2-phenyl-2-butanol Hydrochloride (IV).—This compound has been prepared by Henley[4]; the same procedure was used with the exception that butyl ether was substituted for ethyl ether; yield, 35%; m. p. 195.6–196.7° (lit. 170–173° with preliminary softening at 168°).

Anal. Calcd. for $C_{15}H_{23}NO\cdot HCl$: C, 66.79; H, 8.98; N, 5.19; Cl, 13.14. Found: C, 66.7; H, 8.69; N, 5.19; Cl, 13.3.

1-Diethylamino-2-phenyl-2-butanol (I).—The preparation was carried out by the method described for compound IV. Because of difficulty in obtaining crystalline salts, the product was distilled; b. p. 111.8–113.2° at 6 mm.; yield, 30%.

Anal. Calcd. for $C_{14}H_{23}NO$: N, 6.33. Found: N, 6.4.

The following two compounds were prepared by the method of Marxer.[5]

6-Diethylamino-3-phenyl-3-hexanol (III).—The base was purified by distillation, b. p. 141.5–143° at 4.5 mm. Neither the hydrochloride nor sulfate could be obtained as a solid. When, however, an alcoholic solution of the base was added to an alcoholic solution of citric acid, the dihydrogen citrate crystallized readily. Purified by recrystallization from an alcohol–ether mixture, it melted in approximately ten seconds when immersed in a bath at 174°; yield, 18%.

Anal. Calcd. for $C_{16}H_{27}NO\cdot C_6H_8O_7$: C, 59.84; H, 7.99; N, 3.17. Found: C, 59.9; H, 8.26; N, 3.46.

6-(1-Piperidyl)-3-phenyl-3-hexanol Hydrochloride (VIII).—Yield, 46.5%; m. p. 190.1–191.2° (sample immersed in bath at 185° and heated at 1°/min.).

Anal. Calcd. for $C_{17}H_{27}NO\cdot HCl$: C, 68.55; H, 9.49; N, 4.70; Cl, 11.91. Found: C, 68.3; H, 9.45; N, 4.77; Cl, 11.9.

Compounds in Table II: Procedure A.—To at least 3 moles of the alkyl halide in a single-necked flask was added one mole of the amine. The flask was stoppered and allowed to stand (3 weeks for compounds VI and VII, 6–10 months for the others). The solid formed was collected and recrystallized from an alcohol–ether mixture. Compound V was prepared similarly except that equimolar amounts of amine and methyl iodide were dissolved in ether and allowed to stand one day.

Procedure B.—To a solution of one mole of the amine in 700–1500 cc. of nitromethane in a single-necked flask was

added at least 5 moles of the alkyl halide (where methyl chloride was used, the reaction mixture was saturated with the gas). The flask was stoppered and allowed to stand (1.5 hr. for compound XIII, 2–3 days for X and XII, and 2 weeks for IV). The reaction mixture was diluted with ether. The solid which formed was collected on a filter. Compound IV was recrystallized from acetone–ether, compound X from acetone–alcohol, and compounds XII and XIII from alcohol–ether.

A solid which had formed before dilution with ether in the preparation of IV was removed by filtration and shown to be 1-(1-piperidyl)-3-phenyl-3-heptanol hydrochloride by halogen determination and mixed m. p. The filtrate, however, yielded the quaternary salt on dilution with ether.

Acknowledgments.—The authors are indebted to Dr. R. W. Cunningham, Dr. B. K. Harned and their assistants of the Pharmacology Department of the Lederle Laboratories Division for the determination of the antispasmodic activities of these compounds. The microanalytical services of Mr. O. E. Sundberg, Mrs. M. E. Nielson, and Miss I. H. Prokul are greatly appreciated.

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BOUND BROOK, NEW JERSEY

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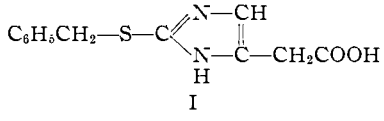
The Reaction of Ethyl α- and γ-Bromoacetoacetates with S-Alkylisothioureas

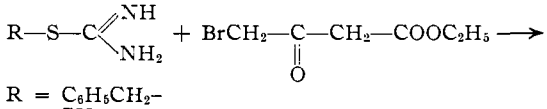
BY R. M. DODSON, ELWOOD R. PETERSON[1] AND JAY K. SEYLER

The preparation of substituted imidazoles by the reaction of α-haloketones with S-alkylisothioureas recently has been reported.[2] The reaction of ethyl γ-bromoacetoacetate with S-benzylisothiourea was studied with the hope of obtaining the substituted imidazolylacetic acid, I, which could then be converted to histamine. However,



I

it is well known that ethyl acetoacetate reacts with S-alkylisothioureas to yield substituted pyrimidines.[3] The reaction of S-benzylisothiourea with ethyl γ-bromoacetoacetate, under a variety of conditions, including those used in the previous preparation of imidazoles (sodium bicarbonate and dilute alcohol),[2] yielded 2-benzylthio-4-benzylthiomethyl-6-hydroxypyrimidine (II); no imidazole was obtained from the reaction.

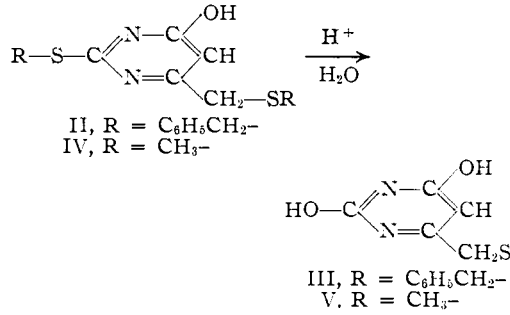


R = $C_6H_5CH_2$–
CH_3–

(1) From the M.S. Thesis of Elwood R. Peterson, September, 1949.

(2) R. M. Dodson, THIS JOURNAL, **70**, 2753 (1948); R. M. Dodson and F. Ross, *ibid.*, **72**, 1478 (1950).

(3) Wheeler and Merriam, *Am. Chem. J.*, **29**, 478 (1903).



II, R = $C_6H_5CH_2$–
IV, R = CH_3–

III, R = $C_6H_5CH_2$–
V, R = CH_3–

The structure of II was assigned on the basis of (1) analogy with known reactions, (2) analysis, (3) acid hydrolysis of II to 2,6-dihydroxy-4-benzylthiomethylpyrimidine (III),[4] and (4) desulfurization of II with Raney nickel[5] to the known 4-methyl-6-hydroxypyrimidine.

S-Methylisothiourea reacted with ethyl γ-bromoacetoacetate in an analogous manner to yield 2-methylthio-4-methylthiomethyl-6-hydroxypyrimidine (IV). This in turn was readily hydrolyzed to 2,6-dihydroxy-4-methylthiomethylpyrimidine (V).

Ethyl α-bromoacetoacetate and S-benzylisothiourea failed to give either 2-benzylthio-4-methyl-5-bromo-6-hydroxypyrimidine or 2,5-dibenzylthio-4-methyl-6-hydroxypyrimidine under the conditions used to prepare compound II. Rather, the ethyl α-bromoacetoacetate oxidized the benzyl mercaptan (from the decomposition of S-benzylisothiourea) to dibenzyl disulfide and was itself reduced, at least in part, to ethyl acetoacetate. The ethyl acetoacetate so formed then reacted with S-benzylisothiourea to form 2-benzylthio-4-methyl-6-hydroxypyrimidine. This oxidation of benzyl mercaptan with ethyl α-bromoacetoacetate was not unexpected. Finger and Hemmeter[6] have shown that equal molecular quantities of sodium phenylmercaptide and ethyl α-chloroacetoacetate react to form diphenyl disulfide and diethyl α,α′-diacetylsuccinate.

Experimental[7]

Ethyl γ-Bromoacetoacetate and Ethyl α-Bromoacetoacetate.—Ethyl γ-bromoacetoacetate was prepared by the bromination of ethyl acetoacetate in anhydrous ether.[8] Since Burger and Ullyot reported that attempts to distil the bromoester resulted in considerable decomposition, the crude material was used in the following experiments. Ethyl α-bromoacetoacetate was prepared either by the method of Smith[9] or by the method of Conrad.[9] It was not distilled but was used immediately after preparation.

2-Benzylthio-4-benzylthiomethyl-6-hydroxypyrimidine (II).—To a solution of 26.2 g. (0.125 mole) of ethyl γ-bromoacetoacetate and 50.6 g. (0.250 mole) of S-benzyl-

(4) The 2-alkylthioimidazoles are not hydrolyzed under these conditions. This is probably due to the great difference in electronegativity of imidazolyl and pyrimidyl groups.

(5) Mozingo, Wolf, Harris and Folkers, THIS JOURNAL, **65**, 1013 (1943); Howard, Lythgoe and Todd, *J. Chem. Soc.*, 556 (1945).

(6) Finger and Hemmeter, *J. prakt. Chem.*, [2] **79**, 449 (1909).

(7) Microanalyses by Messrs. R. Amidon, J. Buckley, W. Cummings, R. Kelly and H. Turner.

(8) Burger and Ullyot, *J. Org. Chem.*, **12**, 342 (1947).

(9) L. I. Smith, THIS JOURNAL, **44**, 216 (1922); M. Conrad, *Ber.*, **29**, 1042 (1896).