passed through the reaction mixture and then through 3% hydrochloric acid for 15 hours. The acid solution was evaporated to dryness *in vacuo* and the white, crystalline residue identified as a mixture of methylamine hydrochloride, m.p. 225°, and ammonium chloride, no m.p. to 300°, by recrystallization from methanol-ether and by vapor phase chromatography. For the latter a Perkin–Elmer model 154 Vapor Fractometer with a 1-m. triethanolamine impregnated Celite column was used at 79°. The mixture of amines was introduced in methanol solution after liberation from their hydrochlorides by addition of methanolic potassium hydroxide. Four sharp maxima were obtained corresponding to control peaks obtained for ammonia, methylamine, methanol and water. The area under the ammonia peak was smaller than that from methylamine.

Control Experiments.—(a) The above procedure was repeated with 1 g. (0.0032 mole) of 4-amino-6-chloro-N,N'-dimethyl-*m*-benzenedisulfonamide (Vb). Only a small amount of ammonium chloride was isolated in this case. No trace of methylamine could be detected by vapor phase chromatography.

(b) A suspension of 0.50 g. (0.0016 mole) of X was refluxed for 2 hours in 60 ml. of 10% hydrochloric acid, cooled and made strongly basic with saturated sodium hydroxide solution. A stream of nitrogen was passed through the solution and through a trap of 3% hydrochloric acid for 15 hours. Evaporation of the acid to dryness did not leave any residue.

SUMMIT, N. J.

[CONTRIBUTION FROM THE CHEMICAL RESEARCH LABORATORY, A. H. ROBINS CO., INC.]

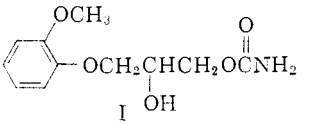
5-Aryloxymethyl-2-oxazolidinones

BY CARL D. LUNSFORD, RICHARD P. MAYS, JOHN A. RICHMAN, JR., AND ROBERT S. MURPHEY

RECEIVED JUNE 22, 1959

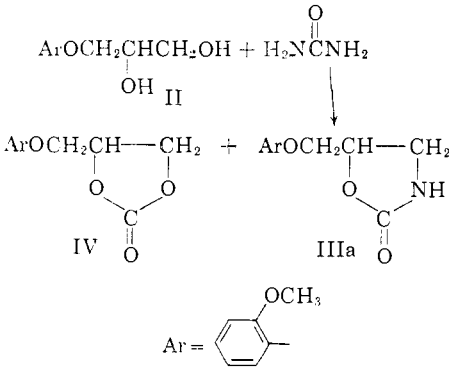
When (a) 3-(*o*-methoxyphenoxy)-1,2-propanediol (II) is fused at 180–200° with two molar equivalents of urea or when (b) 2-hydroxy-3-(*o*-methoxyphenoxy)-propyl carbamate (I) and one molar equivalent of urea are similarly fused, the major product is 5-(*o*-methoxyphenoxymethyl)-2-oxazolidinone (IIIa). A sequence of reactions by which the oxazolidinone ring is formed under these conditions has been investigated and these reactions are discussed. Following method (a) twenty-five 5-aryloxymethyl-2-oxazolidinones, in which the substitution in the aryl nucleus is alkyl, alkyloxy and/or halogen, have been prepared for pharmacological testing. A total of nineteen corresponding N-substituted-5-aryloxymethyl-2-oxazolidinones, prepared by condensation of 1-amino-3-aryloxy-2-propanols with ethyl carbonate or phosgene, are also reported.

In an effort to develop other processes of preparing the skeletal muscle relaxant 2-hydroxy-3-(*o*-methoxyphenoxy)-propyl carbamate (I)[1] the reaction between 3-(*o*-methoxyphenoxy)-1,2-propanediol (II) and urea was studied. Instead of yielding the desired carbamate, the fusion of these



I

materials at 180–200° gave 5-(*o*-methoxyphenoxymethyl)-2-oxazolidinone (IIIa) as the major isolable product as well as minor amounts of the cyclic carbonate of II (IV) which has been reported previously.[2]



While the present investigation was in progress, the same reaction was reported to have occurred between mephenesin and urea.[3] The reaction has been extended to other α-aryl ethers of glycerol and found to be a general one. The resulting 5-aryloxymethyl-2-oxazolidinones possess several interesting pharmacological activities. They are generally antagonists of strychnine convulsions in rats and have consequently been investigated for use as skeletal muscle relaxants and for related pharmacological indications.

These compounds have also been prepared by the fusion of 1-chloro-3-aryloxy-2-propanol or 3-aryloxy-1,2-epoxypropane with urea, and by the reaction of 3-aryloxy-1,2-epoxypropane with urethan or acidified sodium cyanate.[3]

A recent patent[4] reported the preparation of IIIa by the reaction of urethan and 3-(*o*-methoxyphenoxy)-1,2-propanediol (II), but the structure was reported with the *o*-methoxyphenoxymethyl group located at position 4 of the oxazolidinone ring. Repetition of this work has shown that the product is identical to IIIa prepared by the glycol–urea fusion.

In order to locate unequivocally the aryloxymethyl group of the compound IIIa at position 5 (rather than 4) of the oxazolidinone ring, it was subjected to basic hydrolysis which gave the expected 1-amino-3-(*o*-methoxyphenoxy)-2-propanol (V). Lithium aluminum hydride reduction of IIIa produced the corresponding N-methylamino alcohol VI. The identical amino alcohols were synthesized by condensation of 1-chloro-3-(*o*-methoxyphenoxy)-2-propanol (VII) with ammonia or methylamine, respectively. The corresponding oxazolidinones IIIa and IIIb were obtained again when V and VI were treated with phosgene or diethyl carbonate.

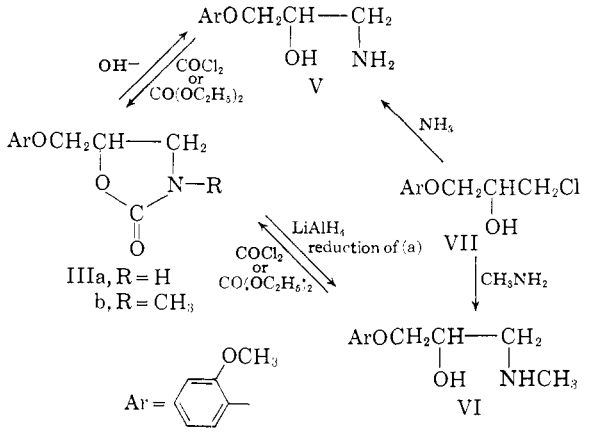
The mechanism by which the 5-aryloxymethyl-2-oxazolidinones are formed in the fusion of an α-

(1) R. S. Murphey, U. S. Patent 2,770,649 (1956); generic name, methocarbamol.

(2) M. M. Baizer, J. R. Clark and J. Swidinsky, THIS JOURNAL, **79**, 1595 (1957).

(3) Y. M. Beasley, V. Petrow, O. Stephenson and A. S. Thomas, *J. Pharm. and Pharmacol.*, **9**, 10 (1957).

(4) Belgian Patent 570,147 (1958).



aryl ether of glycerol and urea appears to follow the reaction sequence outlined:

$$2H_2NCONH_2 \rightleftharpoons 2HNCO + 2NH_3 \quad (1)$$

$$ArOCH_2CH(OH)CH_2OH + HNCO \rightleftharpoons \text{II}$$

$$\text{II} \rightleftharpoons ArOCH_2CH(OH)CH_2OCNH_2 \quad (2)$$

(I)

$$\text{I} \longrightarrow ArOCH_2CH(OH)CH_2NH_2 + CO_2 \quad (3)$$

(V)

$$V + HNCO \rightleftharpoons ArOCH_2CH(OH)CH_2NHCNH_2 \quad (4)$$

(VIII)

$$\text{VIII} \rightleftharpoons ArOCH_2CH(O)CH_2(NH)C{=}O + NH_3 \quad (5)$$

IIIa

Over-all reaction

$$\text{II} + 2H_2NCNH_2 \longrightarrow 2NH_3 + CO_2 + \text{IIIa} \quad (6)$$

Side reaction

$$\text{I} \longrightarrow NH_3 + ArOCH_2CH(O)CH_2(O)C{=}O \quad (7)$$

IV

When urea is heated at 180–200° the chief products are isocyanic acid and ammonia. Normally, the reaction between urea and primary alcohols under these conditions, which were those used in this study, results in the formation of urethans[5] (equations 1 and 2). It has been assumed then that this is the initial reaction between the 3-aryloxy-1,2-propanediol (II) and urea and that the originally desired carbamate I is formed as an intermediate. However, under the reaction conditions, the carbamate is unstable and can logically decompose in three ways which are: (a) by losing isocyanic acid according to the reverse of equation 2, which is usually the predominate reaction in the pyrolysis of carbamates; (b) by losing ammonia according to equation 7 with consequent formation of the cyclic carbonate IV, which is the major reaction at temperatures below 175°; or (c) by losing carbon dioxide to form the 1-amino-3-aryloxy-2-propanol (V) according to equation 3.

The amine V cannot be isolated under the conditions, but immediately reacts with more isocyanic acid from the decomposing urea forming the substituted urea VIII (equation 4) which then cyclizes by loss of ammonia and forms the oxazolidinone IIIa (equation 5).

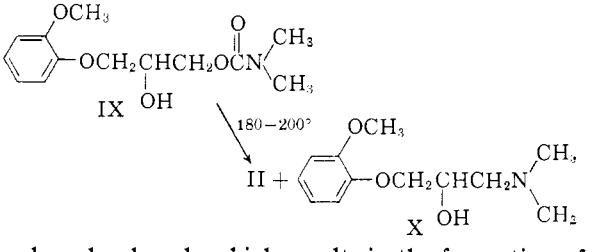
In order to support this reaction sequence, the feasibility of each reaction and the behavior of each proposed intermediate under the reaction conditions have been investigated.

It may be noted that the over-all reaction (equation 6) requires two molar equivalents of urea for each mole of glycol II, and it was found experimentally that maximum yield of the oxazolidinone IIIa was realized when this ratio was used. Although a larger ratio of urea to glycol had no effect on the yields, they were appreciably lowered when the amount of urea was decreased.

A rigorous proof has already been reported that I is the carbamate ester of the primary alcohol of the glycol II as opposed to the carbamate ester of the secondary alcohol.[2] Since it is assumed that the first molar equivalent of urea is consumed in the formation of this carbamate I, it was fused with a single molar equivalent of urea (equations 3. 4 and 5) and, as expected, the oxazolidinone IIIa was obtained. Although the crude yields using this process were generally of the same order as for the over-all glycol–urea process, the material was always of higher purity and consequently gave higher yields of purified compound.

An unsuccessful attempt was made to isolate the amino alcohol V by subjecting the carbamate I to the reaction conditions; however, the isolated products were 3-(*o*-methoxyphenoxy)-1,2-propanediol (II), together with a small amount of the oxazolidinone IIIa indicating that any Va formed reacted with isocyanic acid furnished by the reversal of equation 2.

To further investigate the formation of the amino alcohol by loss of carbon dioxide from the carbamate (equation 3), 2-hydroxy-3-(*o*-methoxyphenoxy)-propyl N,N-dimethylcarbamate (IX) was heated under the reaction conditions and this reaction yielded a minor amount of glycol II and as the major product, 1-dimethylamino-3-(*o*-methoxyphenoxy)-2-propanol (X). An analogy to this reaction is found in the pyrolysis of N-methoxy-



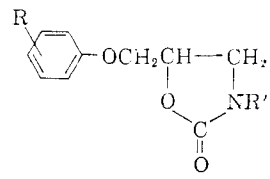
carbonylcarbazole which results in the formation of N-methylcarbazole and carbon dioxide.[6] Compound X was synthesized independently from

(5) T. L. Davis and S. C. Lane, "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1941, p. 140; W. M. Kraft, THIS JOURNAL, **70**, 3569 (1948).

(6) M. A. Fletcher, M. W. Lakin and S. G. P. Plant, *J. Chem. Soc.*, 3898 (1953).

TABLE I

5-ARYLOXYMETHYL-2-OXAZOLIDINONES



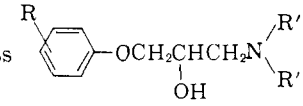
R	R'	M.p. or b.p. (mm.), °C.	Yield,[a] %	Elementary formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
H[3]	H	120.5–122[b]	49	$C_{10}H_{11}NO_3$	62.17	62.63	5.74	5.87	7.25	7.27
2-CH_3[3]	H	124.5–125.5[c]	94	$C_{11}H_{13}NO_3$	63.75	63.62	6.32	6.43	6.76	6.84
3-CH_3	H	102–103[b]	54	$C_{11}H_{13}NO_3$	63.75	63.60	6.32	6.54	6.76	6.65
		225–240 (0.35)								
4-CH_3	H	131–131.5[b]	58	$C_{11}H_{13}NO_3$	63.75	63.99	6.32	6.46	6.76	6.80
2-CH_3O	H	143–145[d]	67	$C_{11}H_{13}NO_4$	59.18	59.05	5.87	5.81	6.28	6.11
3-CH_3O	H	125–126.5[b]	48	$C_{11}H_{13}NO_4$	59.18	59.38	5.87	5.77	6.28	6.40
4-CH_3O	H	135–136[b]	50	$C_{11}H_{13}NO_4$	59.18	59.36	5.87	5.64	6.28	6.63
4-C_4H_9O	H	139.5–141.5[b]	45	$C_{14}H_{19}NO_4$	63.38	63.60	7.22	7.16	5.28	5.11
2-C_4H_9O	H	62–63[b]	71	$C_{14}H_{19}NO_4$	63.38	63.61	7.22	7.46	5.28	5.54
		235–255 (0.1)								
2-Cl[3]	H	147–148[b]	48	$C_{10}H_{10}ClNO_3$	52.76	52.85	4.43	4.27	6.15	6.26
3-Cl	H	96.5–97[b]	76	$C_{10}H_{10}ClNO_3$	52.76	52.95	4.43	4.52	6.15	6.15
4-Cl	H	143.5–146[b]	59	$C_{10}H_{10}ClNO_3$	52.76	52.96	4.43	4.60	6.15	6.14
4-Br	H	153–154[b]	47	$C_{10}H_{10}BrNO_3$	44.14	44.39	3.70	3.58	5.15	5.18
2-OH	H	84–86[b]	20	$C_{10}H_{11}NO_4$	57.41	57.67	5.30	5.22	6.70	6.76
3,4-$(CH_3)_2$	H	116–117[b]	37	$C_{12}H_{15}NO_3$	65.14	65.69	6.83	7.11	6.33	6.26
3,5-$(CH_3)_2$	H	121.5–123[b]	79	$C_{12}H_{15}NO_3$	65.14	65.89	6.83	6.92	6.33	6.03
		220–225 (1.5)								
2,6-$(CH_3)_2$	H	104–105[b]	74	$C_{12}H_{15}NO_3$	65.14	65.69	6.83	6.83	6.33	6.08
		230–235 (0.35)								
2,6-$(CH_3O)_2$	H	117.5–118.5[b]	52	$C_{12}H_{15}NO_5$	56.91	57.16	5.97	6.01	5.53	5.70
3,5-$(CH_3O)_2$	H	124–125[b]	75	$C_{12}H_{15}NO_5$	56.91	56.77	5.97	6.02	5.53	5.53
		245–257 (0.15)								
2,4-Cl_2	H	128–130[b]	42	$C_{10}H_9Cl_2NO_3$	45.82	46.08	3.47	3.52	5.36	5.32
5-Cl-2-CH_3	H	104–104.5[b]	57	$C_{11}H_{12}ClNO_3$	54.66	54.87	5.01	5.23	5.80	5.50
3-Cl-2-CH_3	H	124–125.5[b]	35	$C_{11}H_{12}ClNO_3$	54.66	54.89	5.01	5.19	5.80	5.94
4-Cl-3-CH_3	H	135–137[b]	36	$C_{11}H_{12}ClNO_3$	54.66	54.80	5.01	5.02	5.80	5.89
2,3,5-$(CH_3)_3$	H	125–126[b]	60	$C_{13}H_{17}NO_3$	66.36	66.34	7.28	7.23	5.95	5.75
3,4,5-$(CH_3O)_3$	H	129–132[b]	60	$C_{13}H_{17}NO_6$	55.12	55.13	6.05	6.06	4.95	4.90
		265–280 (0.15)								
H	C_2H_5	43–44[e]	77	$C_{12}H_{15}NO_3$	65.14	65.41	6.83	6.85	6.33	6.28
		182–185 (0.15)								
2-CH_3	C_2H_5	50–50.5[e]	59	$C_{13}H_{17}NO_3$	66.36	66.40	7.28	7.40	5.95	5.81
3-CH_3	C_2H_5	50–51[e]	40	$C_{13}H_{17}NO_3$	66.36	66.15	7.28	7.28	5.95	5.98
4-CH_3	C_2H_5	90–91[e]	52	$C_{13}H_{17}NO_3$	66.36	66.51	7.28	7.43	5.95	5.68
2-CH_3O	CH_3	77.5–78.5[e]	73	$C_{12}H_{15}NO_4$	60.75	60.90	6.37	6.15	5.90	5.59
		180–195 (0.08)								
2-CH_3O	*i*-C_3H_7	76–78[e]	28	$C_{14}H_{19}NO_4$	63.38	63.42	7.22	7.49	5.28	5.42
2-CH_3O	*n*-C_4H_9	186–188 (0.03)	76	$C_{15}H_{21}NO_4$	64.49	65.86	7.59	7.88	5.01	5.04
2-CH_3O	cy-C_6H_{11}	68–69[f]	84	$C_{17}H_{23}NO_4$	66.86	67.02	7.59	7.75	4.59	4.59
2-CH_3O	$PhCH_2$	59–59.5[f]	70	$C_{18}H_{19}NO_4$	68.99	69.08	6.11	6.15	4.47	4.59
4-CH_3O	C_2H_5	80–81[e]	96	$C_{13}H_{17}NO_4$	62.14	62.15	6.82	6.80	5.57	5.53
4-Cl	C_2H_5	116–117	99	$C_{12}H_{14}ClNO_3$	56.36	56.64	5.52	5.69	5.48	5.32
4-Br	C_2H_5	122.5	98	$C_{12}H_{14}BrNO_3$	48.02	48.19	4.70	4.89	4.67	4.44
2,4-$(CH_3)_2$	C_2H_5	37–38.5[e]	56	$C_{14}H_{19}NO_3$	67.44	67.51	7.68	7.74	5.62	5.56
3,5-$(CH_3)_2$	C_2H_5	71–72[e]	73	$C_{14}H_{19}NO_3$	67.44	68.92	7.68	7.84	5.62	5.63
		204–205 (0.08)								
2,4-Cl_2	C_2H_5	215–220 (0.12)	20	$C_{12}H_{13}Cl_2NO_3$	49.67	49.63	4.52	4.64	4.83	4.05
3-Cl-2-CH_3	C_2H_5	115–116[e]	85	$C_{13}H_{16}ClNO_3$	57.88	56.26	5.98	6.41	5.19	5.21
4-Cl-3-CH_3	C_2H_5	94–94.5[g]	82	$C_{13}H_{16}ClNO_3$	57.88	57.86	5.98	5.93	5.19	5.20
5-Cl-2-CH_3	C_2H_5	77[e]	45	$C_{13}H_{16}ClNO_3$	57.88	57.78	5.98	5.97	5.19	5.10
2,3,5-$(CH_3)_3$	C_2H_5	154–155[b]	14	$C_{15}H_{21}NO_3$	68.41	58.80	8.04	8.59	5.32	5.52

[a] The reported yields are generally the results of a single run. Recrystallized from [b] ethyl acetate, [c] methanol, [d] 95% ethanol, [e] isopropyl ether, [f] isoöctane–ethyl ether, [g] isoöctane.

1 - chloro - 3 - (*o* - methoxyphenoxy) - 2 - propanol (VII) and dimethylamine and proved to be identical to the amino alcohol obtained by pyrolysis of IX.

TABLE II

1-AMINO-3-ARYLOXY-2-PROPANOLS



R	—N(R′)(R′)	M.p., °C.	Yield,[a] %	Elementary formula	Nitrogen, % Calcd.	Nitrogen, % Found
2-CH_3	C_2H_5NH	85–87[d]	41	$C_{12}H_{19}NO_2$	6.69	6.80
3-CH_3	C_2H_5NH	70.5–71.5[c]	52	$C_{12}H_{19}NO_2$	6.69	6.56
4-CH_3	C_2H_5NH	75–76[d]	30	$C_{12}H_{19}NO_2$	6.69	6.70
2-CH_3O	NH_2	107–108.5[b]	28	$C_{10}H_{15}NO_3$	7.10	6.82
2-CH_3O	CH_3NH	77.5–78[c]	39	$C_{11}H_{17}NO_3$	6.63	6.73
2-CH_3O	i-C_6H_7NH	81–82[d]	72	$C_{13}H_{21}NO_3$	5.85	5.91
2-CH_3O	cy-$C_6H_{11}NH$	61.5–62[d]	35	$C_{16}H_{25}NO_3$	5.01	4.83
2-CH_3O	$(CH_3)_2N$	59–59.5[c]	59	$C_{12}H_{19}NO_3$	6.22	6.02
4-Cl	C_2H_5NH	93–93.5[c]	39	$C_{11}H_{16}ClNO_2$	6.10	6.18
4-Br	C_2H_5NH	98–99[c]	46	$C_{11}H_{16}BrNO_2$	5.11	4.98
3,5-$(CH_3)_2$	C_2H_5NH	95.5–96[c]	64	$C_{12}H_{21}NO_2$	6.27	6.06
2,4-Cl_2	C_2H_5NH	130–131[e]	95	$C_{11}H_{15}Cl_2NO_2$	5.30	5.10
3-Cl-2-CH_3	C_2H_5NH	98–98.5[c]	21	$C_{12}H_{18}ClNO_2$	5.75	5.68
4-Cl-3-CH_3	C_2H_5NH	95.5–96[c]	28	$C_{12}H_{18}ClNO_2$	5.75	5.31
5-Cl-2-CH_3	C_2H_5NH	114.5–115[c]	27	$C_{12}H_{18}ClNO_2$	5.75	5.92
2,3,5-$(CH_3)_3$	C_2H_5NH	121–122[d]	33	$C_{14}H_{23}NO_2$	5.90	5.95

[a] The yields are generally the result of a single run. Recrystallized from [b] methanol–isopropyl ether, [c] isopropyl ether, [d] isoöctane. [e] Calcd.: C, 63.98; H, 8.50. Found: C, 63.71; H, 8.28.

When heated alone at 180–200°, 1-amino-3-(*o*-methoxyphenoxy)-2-propanol (V) was stable; however, when a single molar equivalent of urea was added, the oxazolidinone IIIa was isolated in excellent yield. This reaction is depicted by equations 4 and 5.

Finally, to further support equation 5, 1-[2-hydroxy - 3 - (*o* - methoxyphenoxy) - propyl]-urea (VIII) (prepared from V and acidified potassium carbonate) was subjected to the reaction conditions and IIIa was again formed in good yield.

Ethylene glycol itself reacts with urea at 180–200° to form 2-imidazolidinone rather than an oxazolidinone.[7] The courses of these two reactions are quite compatible since ethylene glycol, having two primary hydroxyl groups, might be expected to form the dicarbamate as an intermediate and the reaction then proceed analogously to that outlined for the formation of the oxazolidinone.

Following the procedures indicated above, a series of 5-aryloxymethyl-2-oxazolidinones, in which the aryl substitution has been varied among alkyl, alkyloxy and halo substituents, have been prepared. These compounds are listed in Table I.

It was desirable to label one of the more pharmacologically interesting of these compounds, 5-(*o*-methoxyphenoxymethyl)-2-oxazolidinone, with C^{14} for use in tissue distribution studies. This was accomplished by condensing 1-amino-3-(*o*-methoxyphenoxy)-2-propanol (V) with phosgene-C^{14}.

It was of interest to examine the changes in pharmacological activity resulting when the nitrogen of the oxazolidinone ring was substituted with an alkyl group. The ethyl radical was arbitrarily chosen except in the case of the N-substituted-5-(*o*-methoxyphenoxymethyl)-2-oxazolidinones (III) where the substituent was more extensively varied.

The N-substituted-5-aryloxymethyl-2-oxazolidinones which have been prepared are also included in Table I. These compounds were all prepared from the corresponding amino alcohol by condensation with ethyl carbonate[8] under basic catalysis or with phosgene While most of the amino alcohols have been previously reported, the properties of those which are new are given in Table II.

Many of the oxazolidinones reported here have shown pharmacological activity as skeletal muscle relaxants, psychotherapeutic agents, etc. A report of these findings will appear elsewhere.

Experimental[9]

All of the phenols used in this study were either obtained commercially or prepared by known methods except 3,4,5-trimethoxyphenol[10] which was prepared by diazotization of 3,4,5-trimethoxyaniline which, in turn, was prepared from 3,4,5-trimethoxybenzamide by the Hofmann hypobromite method. The 3-aryloxy-1,2-propanediols (II) were prepared by the condensation of the sodium salt of the phenol with α-glyceryl-monochlorohydrin according to known methods.[11]

In the preparation of the oxazolidinones by fusion of the 3-aryloxy-1,2-propanediols (II) with urea it was found to be advantageous to bring the urea–glycol mixture rapidly to the reaction temperature of 180–200° to minimize the formation of the cyclic carbonate ester IV. In runs smaller than 0.25 molar, this was conveniently done by placing the flask containing the mixture in a preheated metal-bath. In larger runs the glycol was heated to the reaction temperature and molten urea was added with stirring. Reaction times of 3–5 hours were required. The 5-aryloxymethyl-2-oxazolidinones (III) which have been prepared by this method are listed in Table I. The following (method A) is a typical example:

5-(*o*-Methoxyphenoxymethyl)-2-oxazolidinone (IIIa). (Method A).—A mixture of 39.6 g. (0.2 mole) of 3-(*o*-methoxyphenoxy)-1,2-propanediol (II) and 24 g. (0.4 mole) of urea was heated in a flask equipped with a thermometer and

(7) H. R. Dittmar, U. S. Patent 2,416,046 (1947); *J. Org. Chem.*, **15**, 471 (1950).

(8) A. H. Homeyer, U. S. Patent 2,399,118 (1942).

(9) All melting points are corrected. Carbon and hydrogen analysis by Schwarzkopf Microanalytical Laboratory, 56-19 37th Ave., Woodside 77, N. Y. Nitrogen analysis by Mrs. Ruby Higgins of the A. H. Robins Co., Inc., Control Laboratory.

(10) S. Hattori, *Acta Phytochim.*, **5**, 219 (1931); and P. L. Pauson and B. C. Smith, *J. Org. Chem.*, **18**, 1403 (1953).

(11) For some typical procedures, see R. I. Meltzer and J. Doczi, THIS JOURNAL, **72**, 4986 (1950); and H. L. Yale, E. J. Pribyl, W. Baker, F. H. Bergeim and W. A. Lott, *ibid.*, **72**, 3710 (1950).

air condenser. The mixture was heated rapidly to the range of 180–200° by immersing the flask in a Wood's metal-bath which had previously been heated to 190°. Heating in this temperature range was continued for 5 hours and then the reaction mixture was poured into 200 ml. of water and extracted with chloroform. The chloroform extract was dried over sodium sulfate, filtered and concentrated. The residue was fractionated at reduced pressure and gave a small amount of low boiling material and 30 g. (67%) of IIIa, b.p. 220–225° (0.1 mm.). After crystallization from 95% ethanol, the compound melted 143–145°.

Alternatively, the residue from the chloroform extract was crystallized from 95% ethanol, acetone or ethyl acetate without distillation. When this method of isolation was used, the yields were of the order of 40%.

The lower boiling fraction proved to be 3-(*o*-methoxyphenoxy)-1,2-propanediol cyclic carbonate (IV)[2] which, after crystallization from 95% ethanol, melted 60.5–61°. A mixture of this material and a sample prepared from phosgene and 3-(*o*-methoxyphenoxy)-1,2-propanediol as described below melted 62–63°. When the reaction was run at 150–175° no oxazolidinone could be isolated and the cyclic carbonate was the major product.

The Fusion of 2-Hydroxy-3-(*o*-methoxyphenoxy)-propyl Carbamate (I) and Urea. (Method B).—A mixture of 24.1 g. (0.10 mole) of I and 6.0 g. (0.10 mole) of urea was heated rapidly to the temperature of 180–200° and maintained there for 5 hours. The reaction melt was crystallized from 50% ethanol; yield 18.3 g. (82%), m.p. 131.5–137°. Crystallization from water and 95% ethanol gave 9.0 g. (40%), m.p. 141–143°. This melting point was not depressed when the material was mixed with an authentic sample prepared according to method A. The infrared spectra of the two samples were identical.

The Fusion of 1-Amino-3-(*o*-methoxyphenoxy)-2-propanol (V) and Urea. (Method C).—Under the conditions of reaction and isolation outlined in method B, 4.93 g. (0.025 mole) of V and 1.50 g. (0.025 mole) of urea gave 3.8 g. (68%) of pure IIIa. Identification was again by methods of mixture melting point and infrared spectra.

Pyrolysis of 1-[2-Hydroxy-3-(*o*-methoxyphenoxy)-propyl]-urea (VIII). (Method D).—The pyrolysis of 1.2 g. (0.005 mole) of VIII at 185–200° for 4.5 hours followed by crystallization of the reaction melt from 95% ethanol gave 0.8 g. (72%) of IIIa, m.p. 141–144.5°. When the material was mixed with an authentic sample of oxazolidinone prepared according to method A, this melting point was not depressed.

Pyrolysis of 2-Hydroxy-3-(*o*-methoxyphenoxy)-propyl N, N-Dimethylcarbamate (IX).—Compound IX (31.9 g., 0.118 mole) was heated rapidly to the reaction temperature of 190–200° and maintained there for 5 hours. The mixture was partitioned between 50 ml. of benzene and 50 ml. of water. The benzene layer (extract A) was washed with ten 25-ml. portions of water and then extracted with 6 *N* hydrochloric acid. The acid extract was basified with dilute sodium hydroxide and extracted with benzene (extract B). The original benzene extract (A) was concentrated and the residue was distilled and 8.05 g. was collected at 165–170° (0.07 mm.). This was crystallized from carbon tetrachloride and melted 78–78.5°. When mixed with an authentic sample of 3-(*o*-methoxyphenoxy)-1,2-propanediol (II) of melting point 78–79° the melting point was not depressed. The infrared spectra of this compound and of the known glycol were identical. The benzene extract (B) from the basic layer was washed with water and concentrated and the residue was distilled and 7.9 g. was collected at 120–125° (0.08 mm.). The material solidified and after recrystallization from isopropyl ether melted 58–59°; when mixed with an authentic sample of 1-dimethylamino-3-(*o*-methoxyphenoxy)-2-propanol (X), prepared from 1-chloro-3-(*o*-methoxyphenoxy)-2-propanol (VII) and dimethylamine, the melting point was not depressed. The infrared spectra of the two compounds were identical.

Anal. Calcd. for $C_{12}H_{19}NO_3$: C, 63.98; H, 8.50; N, 6.22. Found: C, 63.71; H, 8.28; N, 6.02.

Pyrolysis of 2-Hydroxy-3-(*o*-methoxyphenoxy)-propyl Carbamate (I).—When 12.0 g. (0.05 mole) of I was subjected to the conditions of reaction and isolation outlined for the pyrolysis of 2-hydroxy-3-(*o*-methoxyphenoxy)-propyl N,N-dimethylcarbamate (IX), 4.3 g. of 3-(*o*-methoxyphenoxy)-1,2-propanediol (II) was isolated which, after recrystallization from benzene, melted 70.5–77° and when mixed with an authentic sample of melting point 78–79° the mixture melted 73.5–78°. Also obtained was 1.1 g. of 5-(*o*-methoxyphenoxymethyl)-2-oxazolidinone (IIIa), m.p. 140–142.5°. The product was identified by the method of mixture melting point with an authentic sample prepared according to method A. The infrared spectra of the two samples were identical.

Hydrolysis of 5-(*o*-Methoxyphenoxymethyl)-2-oxazolidinone (IIIa).—A mixture of 101.0 g. (0.45 mole) of IIIa and 45.2 g. (1.13 moles) of sodium hydroxide (in 300 ml. of water) and 600 ml. of 95% ethanol was refluxed for 24 hours, filtered and concentrated *in vacuo* to approximately 200 ml. The residue which solidified was dissolved in methyl alcohol and the solution was acidified with ethereal hydrogen chloride. The hydrochloride salt of 1-amino-3-(*o*-methoxyphenoxy)-2-propanol (V) was precipitated by displacing some of the methanol with boiling butanone and cooling the resulting solution, yield 87.2 g. (83%), m.p. 172–173.5° (lit.[12] 173–175°).

Anal. Calcd. for $C_{10}H_{15}NO_3 \cdot HCl$: Cl^-, 15.17. Found: Cl^-, 14.98.

The base was precipitated from an aqueous solution of the salt with aqueous sodium carbonate and recrystallized from a methanol–isopropyl ether mixture; m.p. 107–108.5°. This compound proved to be identical by methods of mixture melting point and infrared spectra to a sample prepared from 1-chloro-3-(*o*-methoxyphenoxy)-2-propanol and ammonia.[12]

Anal. Calcd. for $C_{10}H_{15}NO_3$: C, 60.89; H, 7.67. Found: C, 61.08; H, 7.52.

Lithium Aluminum Hydride Reduction of 5-(*o*-Methoxyphenoxymethyl)-2-oxazolidinone (IIIa).—A suspension of 37.9 g. (1.0 mole) of lithium aluminum hydride in 200 ml. of dry ether and 800 ml. of dry tetrahydrofuran was stirred and refluxed under anhydrous conditions for 1.5 hours. There was added to this mixture, 112 g. (0.5 mole) of IIIa portionwise so that gentle refluxing was maintained. After complete addition, the mixture was stirred and refluxed for 2-hours and cooled; the excess hydride was decomposed with water. About 1 liter of chloroform was then added and the mixture was filtered. The filtrate was concentrated until most of the chloroform was removed and diluted with 800 ml. of dry ether. On standing, the product precipitated as white needles; yield 56 g. (53%), m.p. 77.5–78°. The melting point was not elevated by recrystallization from isopropyl ether and proved to be identical to that of a sample of 3-(*o*-methoxyphenoxy)-1-methylamino-2-propanol (VI) prepared from 1-chloro-3-(*o*-methoxyphenoxy)-2-propanol (VII) and monomethylamine according to the method outlined below. An admixture of the two exhibited no melting point depression and the infrared spectra were identical.

The hydrochloride salt was prepared by treating a solution of the base in butanone with ethereal hydrogen chloride. The resulting precipitate was recrystallized from a butanone–methanol mixture; m.p. 115–116°.

Anal. Calcd. for $C_{11}H_{17}NO_3 \cdot HCl$: C, 53.33; H, 7.33; Cl^-, 14.31. Found: C, 53.08; H, 7.13; Cl^-, 14.46.

Although many of the 1-amino-3-aryloxy-2-propanols used in this study have not previously been described in the literature, they were all prepared by a known method; namely, the condensation of 1-chloro-3-aryloxy-2-propanol or 3-aryloxy-1,2-epoxypropane with amines.[13] Those compounds which have not been described in the literature previously are listed in Table II. The following is a typical example:

3-(*o*-Methoxyphenoxy)-1-methylamino-2-propanol (VI).—A solution of 56 g. (0.39 mole) of 1-chloro-3-(*o*-methoxyphenoxy)-2-propanol and 34 g. (1.1 moles) of methylamine in 500 ml. of absolute ethanol was heated in a sealed bottle on the steam-bath for 22 hours. The excess amine and alcohol were removed by distillation and the product was distilled at 164° (0.6 mm.) and crystallized from isopropyl ether; yield 23 g. (29%), m.p. 78–79°.

3-(*o*-Methoxyphenoxy)-1,2-propanediol Cyclic Carbonate (IV).[2]—A mixture of 54.5 g. (0.275 mole) of 3-(*o*-methoxyphenoxy)-1,2-propanediol (II) and 27.2 g. (0.275 mole) of phosgene in *ca.* 500 ml. of dry benzene was stirred at 5–10° for 2 hours. Pyridine (43.6 g., 0.55 mole) was then added

(12) V. Petrow and O. Stephenson, *J. Pharm. and Pharmacol.*, **5**, 359 (1953).

(13) Y. M. Beasley, V. Petrow and O. Stephenson, *ibid.*, **10**, 47 (1958).

dropwise at 5–10° with stirring and the stirring was then continued for 15 hours. Approximately 200 ml. of water was then added and the benzene layer was separated, dried over sodium sulfate and concentrated. The residue was distilled at reduced pressure and the fraction boiling at 172–178° (0.04 mm.) was collected. This was crystallized from 95% ethanol; yield 33.5 g. (54%), m.p. 66.5–67.5° (lit.[2] 68.4–69.0°).

Anal. Calcd. for $C_{11}H_{12}O_5$: C, 58.92; H, 5.39. Found: C, 59.06; H, 5.54.

3-(*o*-Methoxyphenoxy)-2-hydroxypropyl N,N-Dimethylcarbamate (IX).—A solution of 98 g. (1.0 mole) of phosgene in 200 ml. of cold benzene was added dropwise with stirring at 30° to a suspension of 198 g. (1.0 mole) of 3-(*o*-methoxyphenoxy)-1,2-propanediol (II) and stirring was continued for 3 hours after which all of the propanediol had dissolved. The solution was then cooled to 10° and 79 g. (1.0 mole) of pyridine was added portionwise so that the temperature did not rise above 30° and the mixture was held at this temperature with stirring for an additional 30 minutes. The benzene solution was then washed with two 500-cc. portions of ice-water and added to a cold, saturated aqueous solution of dimethylamine with stirring and cooling. These reaction conditions were continued for 6 hours; the benzene layer was separated and concentrated; and the residual oil was fractionated; yield 222 g. (82.5%), b.p. 172–178° (0.1 mm.).

Anal. Calcd. for $C_{13}H_{19}NO_5$: N, 5.21. Found: N, 5.10.

1-[2-Hydroxy-3-(*o*-methoxyphenoxy)-propyl]-urea (VIII).—A solution of 10.3 g. (0.127 mole) of potassium cyanate in 25 ml. of water was added to a solution of 25 g. (0.127 mole) of 1-amino-3-(*o*-methoxyphenoxy)-2-propanol (V) and 12 ml. of concentrated hydrochloric acid in 100 ml. of water. The resulting solution was warmed to 50° during a 10-minute period and then cooled in an ice-bath for 1 hour, which caused precipitation of the product; yield 28 g. (92%), m.p. 124–126°. After several crystallizations from absolute ethanol the m.p. was 129.5–130.5°.

Anal. Calcd. for $C_{11}H_{16}N_2O_4$: N, 11.66. Found: N, 11.64.

The N-substituted oxazolidinones were prepared by the condensation of the amino alcohol with diethyl carbonate or phosgene. The following are typical examples of these procedures:

5-(*p*-Bromophenoxymethyl)-3-ethyl-2-oxazolidinone.—To a solution of 45.0 g. (0.16 mole) of 3-(*p*-bromophenoxy)-1-ethylamino-2-propanol and 19.4 g. (0.16 mole) of diethyl carbonate in 200 ml. of isoöctane was added 0.1 g. of sodium metal; and the mixture was stirred and heated at 95–100° for 30 minutes while the ethanol–isoöctane azeotrope was allowed to distil out. The reaction was practically complete in 15 minutes and the insoluble oxazolidinone precipitated from solution; yield 48.4 g. (98.2%), m.p. 122.5°. Recrystallization from isoöctane did not elevate the melting point.

5-(*o*-Methoxyphenoxymethyl)-2-oxazolidinone-2-C^{14}.—A solution of 0.99 g. (10 mmoles) of phosgene containing 3 mc. of phosgene-C^{14} in 9 ml. of chloroform was added to a cooled solution of 1.97 g. (10 mmoles) of 1-amino-3-(*o*-methoxyphenoxy)-2-propanol (V) at 5° with stirring over a 30-minute period. The mixture was then allowed to stir at 30° for 1 hour, cooled to 5° and 1.58 g. (20 mmoles) of pyridine in 10 ml. of chloroform was added dropwise over a 15-minute period. The mixture was then stirred for 3 hours at 30°, extracted with two 20-ml. portions of cold water, dried over sodium sulfate, concentrated to *ca.* 15 ml. and diluted with *ca.* 30 ml. of petroleum ether (b.p. 30–60°) which caused crystallization of the product, yield 0.435 g., 1.25 mc. of C^{14} (41.6%), m.p. 141.5–142°.

RICHMOND 20, VA.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF CALIFORNIA, BERKELEY]

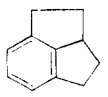
2,2a,3,3a,4,5-Hexahydro-1H-cyclopent[jkl]-*as*-indacene

BY HENRY RAPOPORT AND GERALD SMOLINSKY[1]

RECEIVED MAY 7, 1959

The synthesis of 2,2a,3,3a,4,5-hexahydro-1H-cyclopent[jkl]-*as*-indacene (II) has been achieved by pyrolysis of the lead salt of the appropriate dibasic acid VII and Wolff reduction of the resulting ketone VIII. This tetracyclic hydrocarbon containing three five-membered rings contiguously fused and each fused to the benzene ring shows a marked decrease in the usual aromatic resonance stabilization because of bending in the benzene ring as a result of strain. In its chemical reactivity, it resembles an olefin, being easily hydrogenated, reacting with oxygen of the air ,and rapidly consuming three hundred mole per cent. of perbenzoic acid. The effect of bending a benzene ring on ultraviolet absorption—a distinct bathochromic shift—is clearly demonstrated by comparison of compounds (ketone and hydrocarbon) of this tetracyclic (6,5,5,5) system with the corresponding and identically substituted but unstrained compounds of the hexahydro-*as*-indacene (XXII) system.

Introduction.—The possibility of influencing the resonance stabilization of benzene by forcing a departure from the planarity of the aromatic nucleus has been the subject of much investigation.[2] We have sought to achieve this effect through strain introduced by means of fused five-membered rings. Although statements in the literature predicted otherwise,[3] synthesis of the first member of this series, 2,2a,3,4-tetrahydro-1H-cyclopent[cd]-indene (I), showed that the fused cyclopentane rings had very little effect on the stability of the benzene nucleus other than to markedly increase the ease of catalytic hydrogenation.[2a] A rough calculation[4] using the equations of Howlett[5] and assuming normal bond lengths bore out this result. However, similar calculations made for 2,2a,3,-3a,4,5 - hexahydro - 1H - cyclopent[jkl] - *as* - indacene (II) indicated that this molecule would possess considerable strain. Spurred by this prediction and encouraged by the ease with which the tricyclic (6,5,5) system I had been prepared, the synthesis of the tetracyclic (6,5,5,5) system II was undertaken.[6]



I

Synthesis of 2,2a,3,3a,4,5-Hexahydro-1H-cyclopent[jkl]-*as*-indacene (II).—The synthetic sequence used in preparing the tetracyclic (6,5,5,5) system essentially parallels that used in the pre-

(1) National Science Foundaton Predoctoral Fellow, 1956–1958.

(2) For example, see the following and references therein: (a) H. Rapoport and J. Z. Pasky, THIS JOURNAL, **78**, 3788 (1956); (b) D. J. Cram, N. L. Allinger and H. Steinberg, *ibid.*, **76**, 6132 (1954).

(3) The first eight references cited in ref. 2a.

(4) J. Z. Pasky, Ph.D. Dissertation, University of California, Berkeley, 1956.

(5) K. E. Howlett, *J. Chem. Soc.*, 1249 (1955).

(6) A preliminary report of this work has appeared in THIS JOURNAL, **79**, 5831 (1957).