[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF ILLINOIS]

BETA-ARYLAMINO ETHANOLS

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The amino alcohols and their derivatives, particularly those having 2 or 3 carbon atoms between the oxygen and nitrogen atoms ($>NCH_2CH_2O-$ and $>NCH_2CH_2CH_2O—$) are of special interest because these linkages occur in many of the most important natural alkaloids, such as cocaine, atropine, morphine, quinine, adrenaline, choline, etc. The preparation of various synthetic alkaloids which already have been made, has involved the use of amino alcohols. A more thorough knowledge of these amino alcohols is necessary as future work in the alkaloids is carried on.

The tertiary amino ethanols corresponding to the formula, $R_2NCH_2CH_2OH$, have been extensively studied. They may be prepared most readily by the action of secondary amines upon ethylene oxide or ethylene chlorohydrin. Since, however, the substituted ethylene oxides or ethylene chlorohydrins are in general difficult substances to prepare, this method is not particularly satisfactory for the synthesis of complex tertiary amino ethanols. A more recent method which is suitable for certain of the complex homologs, has been studied by Karrer;[1] the esters of substituted α-amino acids are reduced readily by means of sodium and alcohol to the corresponding amino alcohols.

The preparation of secondary amino ethanols, $RNHCH_2CH_2OH$, by analogous methods is not entirely satisfactory. A mixture is always formed when a primary amine and ethylene oxide or ethylene chlorohydrin are allowed to react, and even under the best conditions the yield of the pure secondary amino alcohol is not very large, especially when aliphatic amines are used. A search for a satisfactory method for the preparation of these compounds has been made and details have been developed whereby these substances may be produced in excellent yields. The following equations represent the procedure adopted.

$$RNH_2 + ClCO_2CH_2CH_2Cl \longrightarrow RNHCO_2CH_2CH_2Cl + HCl \quad (1)$$

$$RNHCO_2CH_2CH_2Cl + KOH \longrightarrow RNCO_2CH_2CH_2 + KCl + H_2O \quad (2)$$

$$RNCO_2CH_2CH_2 + 2KOH \longrightarrow RNHCH_2CH_2OH + K_2CO_3 \quad (3)$$

The first step consists in the condensation of β-chloro-ethyl chloroformate (readily made from phosgene and ethylene chlorohydrin) with a primary amine in benzene. β-Chloro-ethyl carbamates are thus produced in amounts which are nearly quantitative. These substances are, in general, stable, easily purified, low-melting solids, readily distilled under diminished pressure without decomposition.

[1] Karrer, *Helvetica Chim. Acta*, **4**, 74 (1921); **5**, 469 (1922). See also *Compt. rend.*, **145**, 126 (1907); *Bull. soc. chim.*, [4] **3**, 366 (1908); [4] **13**, 971 (1913).

The carbamates, when refluxed with 1 molecule of aqueous or alcoholic potassium or sodium hydroxide, are converted to oxazolidones according to Equation 2. These substances are stable, well-crystallized solids.

When the oxazolidones are refluxed with 4 mol. or more of aqueous or alcoholic potassium or sodium hydroxide, an excellent yield of amino ethanol is produced according to Equation 3. In preparing the amino alcohols, however, it is more convenient to convert the crude chloro-ethyl carbamates directly into the amino alcohols by treating them with excess of alkali and thus avoid the isolation of the oxazolidones. The amino alcohols, thus formed, are high-boiling, viscous oils, colorless when absolutely pure, but generally straw-colored as formed in the laboratory. They turn dark upon long standing and gradually decompose, probably due to intermolecular condensation.

The formation of chloro-ethyl carbamates and their conversion into oxazolidones by alkali, was first noticed by Nemirowsky.[2] These reactions were studied more extensively by Otto[3] and by Johnson and Langley.[4] Otto[3] first reported the conversion of the oxazolidones to amino alcohols. Particular attention has been given to the most satisfactory details for carrying out the conversion of the substituted carbamates to amino alcohols and those that have been developed are reported in this communication.

On account of the ease of preparation of the oxazolidones and the similarity of their structure to that of certain aniline derivatives which have been shown to have important antipyretic and analgesic properties,[5] a comparison of the pharmacological action of phenacetin ($C_2H_5OC_6H_4NHCOCH_3$) and 3-*p*-ethoxyphenyl-2-oxazolidone ($C_2H_5OC_6H_4NCO_2CH_2CH_2$) was undertaken. This work was kindly carried out by the Abbott Laboratories of Chicago with materials furnished by the University of Illinois Laboratories.

The animals used were rabbits and dogs and the drugs were given by mouth. Non-febrile rabbits were first used. The toxicity of phenacetin and the oxazolidone was found to be approximately the same, about 3 g. per kg. of weight. Both caused symptoms which may be referred to the central nervous system. In fatal doses the phenacetin caused depression and paralysis, whereas the oxazolidone caused convulsions or stimulation. In doses which were toxic but non-lethal, phenacetin apparently was somewhat

[2] Nemirowsky, *J. prakt. Chem.*, [2] **31**, 173 (1885).

[3] Otto, *ibid.*, [2] **44**, 15 (1890).

[4] Johnson and Langley, *Am. Chem. J.*, **44**, 352 (1910).

[5] Of the various analgesics and antipyretics derived from *p*-aminophenol, undoubtedly phenacetin is the best known. Nevertheless, it is reported that other and still better ones have been developed, particularly urethane derivatives of which the most important is "Thermodin," the acetyl derivative of ethyl *p*-ethoxy carbanilate, $C_2H_5OC_6H_4N(CO_2C_2H_5)COCH_3$; see *Therap. Monatsh.*, **1893**, 582. The similarity between this substance and the oxazolidone is close.

more powerful as a depressant of body temperature and as a sedative to the central nervous system.

Other experiments were carried out upon rabbits rendered febrile by the intravenous injection of sterile horse serum. It was then found that in doses of 1 g. per kg., the oxazolidone was somewhat more effective than phenacetin in the same dosage. The oxazolidone caused the temperature of the animals to drop to lower points in every instance.

When administered by mouth to dogs in dosages up to 0.5 g. per kg., no essential difference was noticed between phenacetin and oxazolidone.

Experimental Part

β-Chloro-ethyl Carbanilates

A solution of 1 mol. of β-chloro-ethyl chloroformate in benzene was added slowly to a benzene solution of 2 mol. of primary aromatic amine while the mixture was stirred. The hydrochloride of the amine separated as a solid and was filtered. The amount of benzene employed was immaterial providing it was in sufficient quantity to prevent the formation of a very thick paste which would hinder stirring. The filtrate from the salt was washed with dil. hydrochloric acid, then with water, and the benzene was finally distilled. The residue was either distilled under diminished pressure, or crystallized directly, if a solid. The yields were in every case very good.

The general method just described was followed for the preparation of the various β-chloro-ethyl aryl carbamates before it was found that when using trimethylene chlorohydrin in place of ethylene chlorohydrin the reaction with amines could be carried out to greater advantage in aqueous suspension[6] than in benzene solution. It is possible also for the ethylene derivatives to be produced in aqueous suspension.

TABLE I

β-CHLORO-ETHYL CARBANILATES

Compound	Formula	Form, from Bz	M. p. °C.	B. p. °C.	Analysis Wt. G.	Obt. or req.	Calc. %	Found %
o-methyl-	$C_{10}H_{12}O_2NCl$	wh. needles	45	209–10 37 mm.	0.4994	30.3 cc. of N_2; 29°, 743.4 mm.	N, 6.5	5.6
p-methyl-	$C_{10}H_{12}O_2NCl$	wh. crystals	61		0.3108	AgCl, 0.2051	Cl, 16.6	16.3
o-chloro-	$C_9H_9O_2NCl_2$	wh. needles	56.5–57		0.6106	10.09 cc. of 0.2418 *N* HCl	N, 5.98	5.6
p-chloro-	$C_9H_9O_2NCl_2$	wh. needles	62–63		0.2332	AgCl, 0.2900	Cl, 30.3	30.8
p-ethoxy-	$C_{11}H_{14}O_3NCl$	wh. needles	94		0.2689	AgCl, 0.1594	Cl, 14.5	14.6

Oxazolidones

One mol. of β-chloro-ethyl aryl carbamate was heated under a reflux condenser with 1.5 mol. of sodium hydroxide dissolved in water. The solution could be varied in strength from 5 to 15% without affecting the results. After 2 hours, an insoluble layer remained which was separated and washed with water. Any small amount of oil (arylamino ethanol) which was produced at the same time could be filtered by suction. The oxazolidone was then purified by crystallization from the proper solvent or, in certain cases, by distillation under diminished pressure. The yields varied from 55 to 70%.

It is probable that still better yields would have been obtained if an alcoholic solution of the alkali had been used in preference to an aqueous solution. In the case of

[6] THIS JOURNAL, **45**, 790 (1923).

TABLE II
OXAZOLIDONES

Compound	Formula	Form	M. p. °C.	B. p. °C.	$d_{20°}^{25°}$	$n_{D}^{20°}$	Wt. G.	Analysis Obt. or req.	Calc. % N	Found % N
3-*o*-Tolyl-2-	$C_{10}H_{11}O_2N$	straw-col. oil	..	180–185 3 mm.	1.2024	1.5503	0.3339	31.8 cc. of N_2: 33°, 739 mm.	7.9	8.1
3-*p*-Tolyl-2-	$C_{10}H_{11}O_2N$	wh. need. fr. alc.	91	.....	....	....	....	....	...	...
3-*o*-Chlorophenyl-2-	$C_9H_8O_2NCl$	straw-col. oil	..	185–188 3 mm.	1.2300	1.5640	0.7051	13.17 cc. of 0.2418 *N* HCl	6.6	6.3
3-*p*-Chlorophenyl-2-	$C_9H_8O_2NCl$	wh. need. fr. alc.	118.5–119	.....	....	....	0.4513	8.74 cc. of 0.2418 *N* HCl	6.6	6.6
3-*p*-Ethoxy-phenyl-2-	$C_{11}H_{13}O_3N$	wh. cryst. from alc. and ether	96	.....	....	...	.....	....	...	...

TABLE III
ANILINO-ETHANOLS

Compound	Formula	Form	M. p. °C.	B. p. °C.	Press Mm. Hg	$d_{20°}^{25°}$	$n_{D}^{20°}$	Wt. G.	Analysis Obt. or req.	Calc. % N	Found % N
2-	$C_8H_{11}ON$	straw-col. oil	.....	280–285 or 167–170	755 19	1.1129	1.5749	....	....	...	...
2-*o*-Methyl-	$C_9H_{13}ON$	straw-col. oil	.....	145–150	3	1.0962	1.5675	0.3339	29.3 cc. of N_2; 33°, 739 mm.	9.3	9.3
2-*p*-Methyl-	$C_9H_{13}ON$	straw-col. oil and wh. plates fr. ether and lig.	42–43	153–155	4	....	....	0.4475	40.6 cc. of N_2; 28°, 747.6 mm.	9.3	9.1
2-*o*-Chloro-	$C_8H_{10}ONCl$	straw-col. oil	.....	148–152	3	1.2576	1.5185	0.4348	9.71 cc. of 0.2418 *N* HCl	8.16	7.6
2-*p*-Chloro-	$C_8H_{10}ONCl$	wh. needles fr. ether and lig.	77–77.5	.....	...	....	....	0.2241	17.2 cc. of N_2; 29°, 743.4 mm.	8.2	8.3
2-*p*-Ethoxy-	$C_{10}H_{15}O_2N$	wh. cryst. fr. alc.	68.5–69	.....	...	....	....	0.2922	23.0 cc. of N_2; 30°, 745 mm.	7.7	7.9

the trimethylene compounds,[6] it was found that when alcoholic in place of aqueous alkali was used the reaction took place more quantitatively and rapidly and only 1 mol. of alkali was necessary.

As the amount of alkali was increased from 1 to 4 mol., the yield of amino alcohol gradually increased and of oxazolidone gradually decreased.

β-Arylamino Ethanols

The β-chloro-ethyl aryl carbamates were refluxed for 2 to 4 hours with 5 mol. of sodium hydroxide made up to a 20% solution. The products were separated or extracted with ether and purified by distillation under diminished pressure. The yields of product amounted to 70 to 75%.

A somewhat more satisfactory procedure is to use 4 mol. of sodium or potassium hydroxide dissolved in alcohol equal to 5 times the weight of carbamate used. The mixture was heated on a water-bath for 2 hours, filtered from inorganic salts, and evaporated.

Pharmacological Action of 2-*p*-Ethoxyphenyl-2-oxazolidone.—The drugs phenacetin and 2-*p*-ethoxyphenyl-2-oxazolidone were administered by mouth to both rabbits and dogs. This was most conveniently done in the case of rabbits by weighing out the desired amount and mixing it with an appropriate volume of 0.2% potato starch paste. This mixture can be readily injected through any stomach tube. Careful observations were made of the animals before and after administration. In no case was there a change in the urine or in the hemoglobin.

When 1.0, 1.5, 2.0, 2.5 g. of drug per kg. of weight were administered to non-febrile rabbits, there appeared in the case of the oxazolidone a temporary increase in the respiratory rate, then a decrease which was more marked as the dosage increased. There was also a decrease in the pulse rate which was more marked when the larger doses were used. The temperature changes in the animals were only slight until the dosage reached 2.5 g. per kg., when a fall of 1.1° in 1.5 hours was observed and the temperature remained below normal for 3.5 hours.

When similar doses of phenacetin were used upon non-febrile rabbits, practically the same effect was noticed upon the respiration and pulse rate as with oxazolidone, but the temperature lowering was greater with the corresponding dose. In the case of 2.5 g. per kilo, the temperature lowering amounted to 2.4° and remained below normal for longer than 12 hours.

From the above experiments it was readily observed that the phenacetin was more toxic as shown by the fact that the animals treated with oxazolidone remained perfectly quiet while those treated with phenacetin lost the control of their legs and were abnormally affected in other ways.

None of the doses just mentioned proved fatal. With doses of 3.0 g. per kg., 1 out of 3 rabbits treated with oxazolidone died, and 1 out of 2 treated with phenacetin. Very marked decreases in respiration and pulse rates were noted with both drugs and the temperature change was great. With the oxazolidone, body temperature fell 4° in 5 hours, after which death occurred. With those animals which recovered, there was a gradual increase in temperature after the minimum had been reached. With phenacetin, the temperature drop amounted to 4.6° and in the animal that lived the temperature remained below normal over a much longer period of time.

In the case of the animal that died from the administration of oxazolidone, violent convulsions were noticed after 3 hours, which became spasmodic, then continuous just before death. Trismus was marked. An autopsy showed the bladder and stomach distended and the heart dilated and filled with asphyxial blood.

With the animal that died from phenacetin, no convulsions occurred, but paralysis

took place until the animal became limp and coma ensued. Corneal reflux disappeared and the pupils were dilated before death, a condition obviously due to gradual asphyxia. The left ventricle was contracted, the blood was dark and of asphyxial hue. Marked depression was evident which did not appear with the oxazolidone.

Since the slight drop in temperature with small doses of oxazolidone or phenacetin might have been due to temperature depression with consequent inhibition of muscular tone, a study of the effect of the drugs on the temperature of rabbits artificially rendered febrile was undertaken. For the experimental fever, sterile horse serum was injected intravenously in the ear vein, (7.5 cc. per kg.). The dosage of drugs used was 1 g. per kg. From a comparison of several animals, the following conclusions were drawn: (1) both oxazolidone and phenacetin produced sharp drops in the fever temperature; (2) they both brought the temperature back to normal; (3) instead of holding the temperature at normal, both drugs eventually forced the temperature below the normal for 2 to 3 hours; (4) ultimately, there was not the rise above the normal which appeared in the untreated animals and fever controls at the end of the experiments. The results showed practically the same effect with both drugs except that the oxazolidone forced the temperature somewhat lower.

Summary

1. Details for a satisfactory method of formation of arylamino ethanols have been developed. The procedure consists in the condensation of an aryl amine with chloro-ethyl chloroformate, then decomposition of the resulting ester with excess of potassium or sodium hydroxide.

2. Oxazolidones can be isolated as intermediate products in the second step.

3. The 3-*p*-ethoxyphenyl-2-oxazolidone was compared with phenacetin as regards its antipyretic and analgesic properties. It was found that the new product had properties very similar to those of phenacetin.

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TETRAHYDRO-1,3,2-OXAZONES AND SUBSTITUTED GAMMA-AMINO PROPANOLS

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In the preceding paper[2] it has been pointed out that the amino ethanol and amino propanol groupings occur very frequently in many of the most important alkaloids. Although the amino ethanols have been studied and used frequently in synthetic work, the γ-amino propanols have seldom been used and are less well-known. This has been due to the fact that until recently, the raw materials necessary for making these substances according to the methods applicable to the formation of amino ethanols

[1] This paper is an abstract of Part I of the material contained in a thesis by J. S. Pierce presented in partial fulfilment of the requirements for the degree of Doctor of Philosophy in Chemistry at the University of Illinois.

[2] Adams and Segur, THIS JOURNAL, **45**, 785 (1923).