Aminophenylpropanols.—To a solution of 0.6 mole of Grignard reagent in ether was added 150 ml. of dry benzene. Then keeping the inner temperature at 0° or below there was added 0.25 mole of Mannich base or 0.2 mole of the corresponding hydrochloride. Heat was then applied and the ether removed until the inner temperature reached 65°. The mixture was hydrolyzed by pouring into a cold solution of ammonium chloride. The benzene layer was separated, washed with water and dried over potassium carbonate. After removing the solvent, the lower-boiling materials were removed under reduced pressure and the residue was recrystallized from methanol. Those amino-alcohols which were slow to crystallize were purified by distilling under reduced pressure. The products are described in Table III.

Substituted 3-Phenylpropylpiperidines.—A mixture of 0.7 mole of a substituted 1-phenyl-3-(1-piperidyl)-1-propanol, 0.9 mole of red phosphorus and 1.15 moles of 47% hydriodic acid in 550 ml. of glacial acetic acid was refluxed for three hours. The hot solution was filtered through a sintered glass funnel and the filtrate diluted with 1500 ml. of water and cooled. The hydriodide was filtered and washed with cold water, then resuspended in water and made strongly alkaline with sodium hydroxide. The liberated base was extracted with ether and dried over potassium carbonate. The ether was removed and the product distilled under reduced pressure. The products were converted to their hydrochlorides, and when racemates were present they were separated as their hydrochlorides by fractional crystallization. The products are described in Table II.

N-(3-Cyclohexyl-3-phenylpropyl)-piperidine.—N-(3,3-Diphenylpropyl)-piperidine[4] was hydrogenated by the method of Zenitz, *et al.*,[16] until three moles of hydrogen had been added and the hydrogenation had ceased. The product was purified by distilling under reduced pressure and then converting to its hydrochloride. See compound no. 7 of Table II.

Acknowledgments.—The authors are indebted to Dr. C. M. Suter for his guidance of the problem, to Mrs. M. Wilson for technical assistance and to Mr. M. E. Auerbach and his staff for the analytical data.

Summary

1. A number of N-(3-phenylpropyl)-amines have been described.

2. The Mannich reaction has been utilized to prepare new aryl α-alkyl-β-aminoalkyl ketones.

3. These aminoketones have been used in the preparation of a number of 3-amino-1-phenyl-1-propanols.

(16) Zenitz, Macks and Moore, THIS JOURNAL, **69**, 1117 (1947).

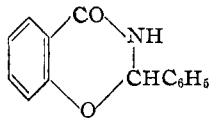
RENSSELAER, NEW YORK RECEIVED MAY 10, 1949

[CONTRIBUTION FROM THE DEPARTMENT OF ORGANIC CHEMISTRY, THE ABBOTT RESEARCH LABORATORIES]

The Condensation of Salicylamide with Aldehydes and Ketones

BY BRUCE W. HORROM AND HAROLD E. ZAUGG

The reaction of salicylamide with benzaldehyde to give 2-phenyl-2,3-dihydro-1,3,4-benzoxaz-4-one



I

was discovered independently by Titherley[1] and by Keane and Nicholls.[2] The latter workers also reported the same reaction with anisaldehyde. Since then the only extension of this reaction to other aldehydes has been with *m*-nitrobenzaldehyde,[3] chloral,[4] acetaldehyde,[5] isobutyraldehyde[6] and isovaleraldehyde.[6] In addition, the reactions of 5-chloro- and 5-bromosalicylamides with benzaldehyde have been described,[7] as well as the condensations of 3,5-dichlorosalicylamide[8] and 5-acetamidosalicylamide[9] with chloral. All of the reactions with chloral, in contrast with other carbonyl compounds, required dehydration by concentrated sulfuric acid of the first-formed acyclic chloral–salicylamide derivatives in order to bring about ring closure to the dihydrobenzoxazones. The only published case of the participation of a ketone in this reaction seems to be that of acetone.[10] A closely related reaction has been noted recently[11] in which treatment of salicylamide with vinyl acetate gave the same 2-methyldihydrobenzoxazone as the one obtained by Hicks[5] in the reaction with acetaldehyde.

The present work was undertaken when the observation was made[12] that the 2-phenyldihydrobenzoxazone I, in spite of its insolubility, showed analgesic activity in dogs of the same order as that of salicylamide.[13] In addition to the resynthesis of all of the above unsubstituted salicylamide derivatives, a number of new reaction products of salicylamide with aldehydes (Table I), ketones (Table II), and cyclic ketones (Table III) is reported. Although several derivatives were equal to it, none of them showed anal-

(1) Titherley, *J. Chem. Soc.*, **91**, 1425 (1907).

(2) Keane and Nicholls, *ibid.*, **91**, 266 (1907).

(3) Glaser and Frisch, *Arch. Pharm.*, **266**, 103 (1928).

(4) Kaufmann, *ibid.*, **265**, 226 (1927).

(5) Hicks, *J. Chem. Soc.*, **97**, 1032 (1910).

(6) Moucka and Rögl, *Ber.*, **59**, 756 (1926).

(7) Titherley and Hughes, *J. Chem. Soc.*, **97**, 1368 (1910); **99**, 23 (1911).

(8) Hirwe and Rana, *J. Univ. Bombay*, **8**, 243 (1939); *C. A.*, **34**, 2819 (1940).

(9) Rana, *J. Indian Chem. Soc.*, **19**, 299 (1942); *C. A.*, **37**, 2361 (1943).

(10) Fischer, Dangschat and Stettiner, *Ber.*, **65**, 1032 (1932).

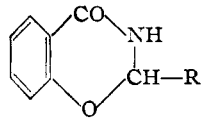
(11) Mowry, Yanko and Ringwald, THIS JOURNAL, **69**, 2358 (1947).

(12) The authors are indebted to Dr. R. K. Richards and Mr. K. E. Kueter of the Abbott Pharmacological Research Department for the analgesic tests.

(13) Kaufmann[4] had prepared the chloral derivatives of salicylamide for testing as an analgesic, apparently with negative results. Early in the present work the preparation of this compound was repeated. It proved to be completely inactive.

TABLE I

DIHYDROBENZOXAZONES PREPARED FROM ALDEHYDES:

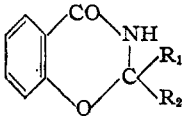


	Method	Yield,[a] %	M. p.,[b] °C.	Recryst. solvent	Formula	Analyses, % Calcd. C	Calcd. H	Found C	Found H
Methyl[5]	B	33[c]	144–146	MeOH	$C_9H_9NO_2$				
n-Hexyl	A[d]	14	82–83	Hexane	$C_{14}H_{19}NO_2$	72.07	8.21	72.36	8.16
i-Propyl[6]	B	47	104–106	Hexane	$C_{11}H_{13}NO_2$				
i-Butyl[6]	B[e]	50	98–99	Hexane	$C_{12}H_{15}NO_2$				
$-CCl_3$		61[f]	174–175	EtOH (95%)	$C_9H_6Cl_3NO_2$[g]				
Cyclohexyl	B	56	123–125	EtOAc	$C_{14}H_{17}NO_2$[h]				
2-Methyl-1-dimethylamino-2-propyl	A	58	96–97	Hexane	$C_{14}H_{20}N_2O_2$	67.71	8.11	67.90	7.92
1-Dimethylaminomethylcyclohexyl	A	45	139–140	Heptane	$C_{17}H_{24}N_2O_2$	70.79	8.38	70.96	8.25
Phenyl[1,2]	C[i]	57	168–169	EtOH (95%)	$C_{14}H_{11}NO_2$				
m-Tolyl	A	37	129–130	*i*-PrOH	$C_{15}H_{13}NO_2$	75.29	5.48	75.31	5.41
o-Chlorophenyl	A	80	156–157	EtOH (abs.)	$C_{14}H_{10}ClNO_2$	64.74	3.88	64.97	3.98
p-Chlorophenyl	A	78	205–206	EtOH (abs.)	$C_{14}H_{10}ClNO_2$	64.74	3.88	64.97	4.13
2,4-Dichlorophenyl	A	92	195–197	MeOH	$C_{14}H_9Cl_2NO_2$	57.16	3.08	57.25	3.14
3,4-Dichlorophenyl	A	73	211–212	*n*-$C_5H_{11}OH$	$C_{14}H_9Cl_2NO_2$	57.16	3.08	57.36	3.03
o-Nitrophenyl	A	69	187–188	EtOAc	$C_{14}H_{10}N_2O_4$	62.21	3.73	62.31	3.74
m-Nitrophenyl[3]	A	87	218–219	CH_3NO_2	$C_{14}H_{10}N_2O_4$	62.21	3.73	62.36	3.91
p-Nitrophenyl	A	87	222–223	CH_3NO_2	$C_{14}H_{10}N_2O_4$	62.21	3.73	62.45	3.72
o-Methoxyphenyl	A	39	176–177	EtOAc	$C_{15}H_{13}NO_3$	70.57	5.13	70.51	5.34
p-Methoxyphenyl[2]	A	51	166–167	EtOH (95%)	$C_{15}H_{13}NO_3$				
Piperonyl	A	32	199–200	*n*-C_4H_9OH	$C_{15}H_{11}NO_4$	66.90	4.11	66.94	4.33
3-Nitro-4-methoxyphenyl	A	40	197–198	EtOAc	$C_{15}H_{12}N_2O_5$	59.99	4.03	60.06	4.01
p-Cyanophenyl	A	73	226–227	*i*-PrOH	$C_{15}H_{10}N_2O_2$	71.98	4.01	72.06	3.86
o-Carboxyphenyl	A	35	172–174	CH_3OH	$C_{15}H_{11}NO_4$	66.91	4.11	66.88	4.19
p-Dimethylaminophenyl	A[j]	37	180–181	Dioxane	$C_{16}H_{16}N_2O_2$	71.61	6.01	71.80	5.98
p-Dimethylaminophenyl	A	44	178–179	EtOAc	$C_{18}H_{20}N_2O_2$	72.94	6.80	72.92	6.54
m-Aminophenyl	[k]	66	172–173	EtOH (95%)	$C_{14}H_{12}N_2O_2$	69.98	5.03	69.77	5.12
o-Aminophenyl	[k]	44	162–163	EtOAc	$C_{14}H_{12}N_2O_2$	69.98	5.03	69.84	4.97

[a] Based on salicylamide except where otherwise indicated. [b] Uncorrected. [c] Based on aldehyde. [d] Method B failed. [e] Method C, 25% yield. [f] Over-all yield of two steps according to procedure of Kaufmann.[4] [g] *Anal.* Calcd.: N, 5.25. Found: N, 5.28. [h] *Anal.* Calcd.: N, 6.06. Found: N, 6.23. [i] Method A, 82% yield; Method B, 46% yield. [j] Refluxed twelve hours. [k] From corresponding nitro compound by reduction. See Experimental.

TABLE II

DIHYDROBENZOXAZONES PREPARED FROM KETONES:



R_1	R_2	Yield,[a] %	M. p.,[b] °C.	Recryst. solvent	Formula	Analyses, % Calcd. C	Calcd. H	Found C	Found H
CH_3[10]	CH_3	47	135–137	EtOAc–Hexane	$C_{10}H_{11}NO_2$				
C_2H_5	C_2H_5	18	101–102	Hexane	$C_{12}H_{15}NO_2$	70.21	7.36	70.63	7.61
Δ-3-Cyclohexenyl	CH_3	28	158–159	EtOH (95%)	$C_{15}H_{17}NO_2$	74.04	7.04	74.33	6.92
$C_6H_5OCH_2-$	CH_3	35	107–108	EtOH (70%)	$C_{16}H_{15}NO_3$	71.35	5.61	71.57	5.55
$-CH_2COOC_2H_5$	CH_3	32	103–104	EtOH (30%)	$C_{13}H_{15}NO_4$	62.63	6.06	62.48	6.01
$C_6H_5CH_2-$	CH_3	36	121–122	EtOH (80%)	$C_{16}H_{15}NO_2$	75.86	5.96	75.82	5.93
C_6H_5	CH_3	20[c]	226–227	MeOH	$C_{15}H_{13}NO_2$	75.29	5.48	75.50	5.51

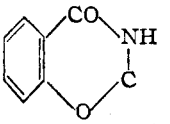
[a] Based on salicylamide. Method A used in all cases except dimethyl compound in which Method B was used. [b] Uncorrected. [c] Methods B and C gave no product.

gesic activity greater than that of the benzaldehyde derivative I. The *p*-dimethylaminophenyl derivative was one of these; and it also showed hypnotic activity in mice, but only at one-third to one-half of the toxic dose.

Three modifications for the preparation of these compounds were employed. Method A proved to be of greatest use and in several cases succeeded after the other methods failed. It consisted in a variation of the procedure of Titherley and

TABLE III

DIHYDROBENZOXAZONES PREPARED FROM CYCLIC KETONES:



Ketone used	Yield,[a] %	M. p.,[b] °C.	Recryst. solvent	Formula	Analyses, % Calcd. C	Calcd. H	Found C	Found H
Cyclopentanone	47	135–137	EtOAc	$C_{12}H_{13}NO_2$[c]				
Cyclohexanone	82	188–190	*i*-PrOH	$C_{13}H_{15}NO_2$[d]	71.86	6.96	72.19	6.73
4-Methylcyclohexanone	93	150–165[e]	EtOH (95%)	$C_{14}H_{17}NO_2$	72.69	7.41	72.79	7.45
4-Cyclohexylcyclohexanone	85	170–175[e]	EtOH (abs.)	$C_{19}H_{25}NO_2$	76.21	8.41	76.14	8.31
4-Phenylcyclohexanone	94	197–207[e]	CH_3NO_2	$C_{19}H_{19}NO_2$	77.78	6.53	77.72	6.49
7-Methoxy-2-tetralone	56	185–186	EtOH (95%)	$C_{18}H_{17}NO_3$	73.19	5.80	73.39	5.95
N-Methyl-4-piperidone	87	192–193[f]	EtOAc	$C_{13}H_{16}N_2O_2$	67.21	6.94	67.17	6.94

[a] Based on salicylamide. Method B used with cyclopentanone and cyclohexanone. Method A used with all others. [b] Uncorrected. [c] *Anal.* Calcd.: N, 6.89. Found: N, 6.99. [d] *Anal.* Calcd.: N, 6.45. Found: N, 6.57. [e] Range of m. p. probably due to mixture of two geometric isomers. [f] Hydrochloride, m. p. 293–296° (dec.) (from concentrated H_2O solution). *Anal.* Calcd. for $C_{13}H_{17}ClN_2O_2$: C, 58.09; H, 6.35; N, 10.43. Found: C, 58.28; H, 6.27; N, 10.80.

Hicks[14] whereby the ether solvent used by them was replaced by chloroform, and water formed in the reaction was removed azeotropically. Method B utilized excess carbonyl compound as solvent and was the method most commonly used by previous workers.[1,2,5,6,7,10] Method C was essentially that of Glaser and Frisch[3] in which ethanol was used as the solvent.

From inspection of the Tables, it can be seen that with the aldehyde reactions yields were quite variable, even when the preferred Method A was used. However, in most cases conditions leading to maximum yields were not studied. The reactions with ketones (Table II) were uniformly poor in yield, but cyclic ketones (Table III) gave yields comparable with those of the best aldehyde reactions. The products obtained from the cyclic ketones contain a type of spirocyclic system which apparently has not been reported previously. Those derived from 4-substituted cyclohexanones seemed to consist of a mixture of the two possible geometric isomers. Separation of these mixtures was not attempted. A number of carbonyl compounds failed to give any isolable product even when Method A was employed. These are listed in the Experimental section.

A new method for the preparation of one of the intermediates, phthalaldehydic acid, is reported, involving chromic acid oxidation of methyl *o*-toluate. No advantage of this method over those previously reported[15] is claimed.

Acknowledgment.—The authors are indebted to Mr. Morris Freifelder for carrying out the hydrogenations. Grateful acknowledgment is due to Mr. E. F. Shelberg, Head of the Abbott Microanalytical Laboratory, and to Mr. Robert Berg, Mr. Dan McCallum and Mr. Rodger Barron for the microanalyses.

Experimental

Intermediates.—Salicylamide was prepared according to the method of Anschütz.[16] The *o*-nitrobenzaldehyde,[17] 3-nitro-4-methoxybenzaldehyde,[18] *p*-cyanobenzaldehyde[19] and N-methyl-4-piperidone[20] were prepared by published methods. 4-Phenyl and 4-cyclohexylcyclohexanone were prepared from the corresponding carbinols by chromic acid oxidation according to the procedure given by Bedos[21] for the corresponding 2-cyclohexylcyclohexanone. Generous samples of hexahydrobenzaldehyde, Δ-3-cyclohexenyl methyl ketone, β-dimethylaminopivaldehyde, and 1-dimethylaminomethylhexahydrobenzaldehyde were supplied by the Rohm and Haas Company. All other intermediates for which a procedure is not given were obtained from well-known commercial sources.

7-Methoxy-2-tetralone.—2,7-Dihydroxynaphthalene was methylated with alkaline dimethyl sulfate in 73% yield to 2,7-dimethoxynaphthalene. Sodium in alcohol reduction of this compound, in the manner prescribed[22] for the preparation of similar β-tetralones, gave a 55% yield of 7-methoxy-2-tetralone, b. p. 123–125° (0.4 mm.), $n^{24}D$ 1.5589. The product is semi-solid at room temperature (23°).

Anal. Calcd. for $C_{11}H_{12}O_2$: C, 74.97; H, 6.87. Found: C, 74.83; H, 6.80.

7-Methoxy-2-tetralone oxime, prepared in the usual manner from the corresponding ketone, recrystallized from benzene, m. p. 126–127.5° with decomposition.

Anal. Calcd. for $C_{11}H_{13}NO_2$: N, 7.33. Found: N, 7.06.

Phthalaldehydic Acid.—Oxidation of the methyl ester of *o*-toluic acid[23] by chromium trioxide, in exactly the same way as is prescribed[19] for the oxidation of *p*-nitrotoluene to *p*-nitrobenzaldiacetate, gave a 47% yield of *o*-carbomethoxybenzaldiacetate, b. p. 139–143° (0.5 mm.), m. p. 55–56°.

Anal. Calcd. for $C_{13}H_{14}O_6$: C, 58.64; H, 5.29. Found: C, 58.56; H, 5.49.

A mixture of 26.6 g. (0.1 mole) of this benzaldiacetate and 133 cc. of 10% sodium hydroxide was refluxed for thirty minutes, then heated with a little charcoal, filtered and acidified with concentrated hydrochloric acid. Cooling in ice gave 8.9 g., m. p. 67–70°. Recrystallization from water gave 7.0 g. (47% yield) of phthalaldehydic acid, m. p. 98–99.5°, checking with the melting point usually reported[15] for this compound.

Anal. Calcd. for $C_8H_6O_3$: C, 63.98; H, 4.03. Found: C, 64.07; H, 3.61.

(14) Titherley and Hicks, *J. Chem. Soc.*, **95**, 908 (1909).
(15) *Org. Syn.*, **23**, 74 (1943).
(16) Anschütz, *Ber.*, **52**, 1886 (1919).
(17) *Org. Syn.*, **24**, 75 (1944).
(18) Johnson and Kohmann, THIS JOURNAL, **37**, 162 (1915).
(19) "Organic Syntheses," Coll. Vol. II, p. 441.
(20) Craig and Tarbell, THIS JOURNAL, **71**, 465 (1949).
(21) Bedos, *Bull. soc. chim.*, **39**, 473 (1926).
(22) Cornforth, Cornforth and Robinson, *J. Chem. Soc.*, 689 (1942).
(23) *Org. Syn.*, **27**, 84 (1947).

By acid hydrolysis of *o*-carbomethoxybenzaldiacetate, the pseudo methyl ester of phthalaldehydic acid was obtained. A mixture of 24 g. of *o*-carbomethoxybenzaldiacetate, 70 cc. of water, 70 cc. of methanol and 8 cc. of concentrated sulfuric acid was refluxed for one hour. The mixture was neutralized with sodium bicarbonate and filtered. The filtrate was concentrated on the steam-bath, cooled and extracted with ether. Drying and distillation, first of the ether and then of the residue *in vacuo*, gave 4 g., b. p. 100–104° (0.6 mm.), $n^{28}D$ 1.5326. This product solidified and after several recrystallizations from dilute methanol melted at 43.5–44°. Published[24] melting point for the pseudo methyl ester of phthalaldehydic acid is 44°.

Anal. Calcd. for $C_9H_8O_3$: C, 65.85; H, 4.91. Found: C, 65.84; H, 4.77.

Condensations of Carbonyl Compounds with Salicylamide. Method A. Chloroform Reflux. Condensation with Piperonal.—A mixture of 14.4 g. (0.141 mole) of salicylamide, 21.6 g. (0.144 mole) of piperonal, 2 cc. of concentrated sulfuric acid and 150 cc. of chloroform was refluxed with stirring in a flask fitted with a modified Soxhlet extractor containing anhydrous calcium chloride in the thimble. In this way water formed during the reaction was eliminated. After refluxing for five or six hours, the chloroform was removed by distillation and the residual red oil was stirred vigorously with 100 cc. of cold 2 *N* sodium hydroxide. The solid which formed was filtered, washed, dried and recrystallized from 150 cc. of *n*-amyl alcohol. There was obtained 12.3 g. (32% yield) of 2-piperonyl-2,3-dihydro-1,3,4-benzoxaz-4-one, m. p. 195–197°. Another recrystallization from *n*-butanol raised the melting point to 199–200°. See Table I for analyses.

When carbonyl compounds containing a basic group were used in this condensation, sufficient sulfuric acid to neutralize the basic group was added over and above the catalytic amount of acid. In working up the products containing aliphatic amino groups purification was usually facilitated by their solubility (as sulfate) in water. Products containing aromatic amino groups required relatively strong aqueous acid for effective solubilization.

Carbonyl compounds from which no solid product could be obtained by this method include thiophene-aldehyde, furfural, 2,3-dimethoxybenzaldehyde, salicylaldehyde, citral, γ-acetopropanol, di-isobutyl ketone, benzophenone, *p*-aminoacetophenone, pyruvic acid, anisalacetone, *n*-butyl glyoxylate, benzoylformic acid, *p*-hydroxybenzaldehyde, and 1-diethylamino-4-pentanone. Formaldehyde gave a polymer.

Method B. No Solvent. Excess Carbonyl Compound. Condensation with Cyclohexanone.—To a solution of 2 g. of dry hydrogen chloride in 200 cc. of freshly distilled cyclohexanone was added 20 g. of salicylamide. The amide went into solution rapidly and on standing colorless prisms were deposited. After twenty-two hours at room temperature, the product was filtered, washed with a small amount of cyclohexanone and a large amount of pentane. There was obtained 26.0 g. (82% yield) of 2,2-pentamethyleno-2,3-dihydro-1,3,4-benzoxaz-4-one, m. p. 188–190°. Recrystallization from 400 cc. of benzene gave 22.5 g. of shiny white needles of the same melting point. For analysis a sample was recrystallized from isopropyl alcohol, m. p. 188.5–190.5°.

In most cases where this method was used the product did not crystallize from the reaction mixture. It was then necessary to remove the excess carbonyl compound *in vacuo* and treat the residue with cold alkali as in method A. Also, in nearly every other case an elevated temperature (40° to 70°) was used during the reaction. At 40° the reaction time was usually extended to a period of at least twenty hours. At 60–70° the time was shortened to thirty minutes to two hours depending on the amount of decomposition apparent in the mixture. The amount of dry hydrogen chloride catalyst used in most cases was quite arbitrary as was the amount of excess carbonyl compound.

Method C. Ethanol Solvent. Condensation with Benzaldehyde.—A mixture of 38.7 g. (0.28 mole) of salicylamide, 30.5 g. (0.287 mole) of benzaldehyde and 50 cc. of dry ethanol was heated to 50° and a stream of dry hydrogen chloride was passed in until a homogeneous solution formed (one or two minutes). The temperature rose some twenty degrees during this process and stirring was continued at 60–65° for thirty minutes. On cooling, product separated and was filtered off. Washing with 50% ethanol followed by trituration with 2 *N* sodium hydroxide gave 36 g. (57% yield) of crude product, m. p. 155–158°. Recrystallization from 95% ethanol gave 23.5 g., m. p. 168–169°. This method was little used since its convenience depended on the insolubility of the product in ethanol.

2-(*m*-Aminophenyl)-2,3-dihydro-1,3,4-benzoxaz-4-one.—A suspension of 12 g. of the corresponding nitro compound (prepared from salicylamide and *m*-nitrobenzaldehyde) in 250 cc. of methyl cellosolve was hydrogenated in the presence of 3 g. of Raney nickel at room temperature and forty pounds hydrogen pressure. After fifteen hours the hydrogen uptake was complete. The filtered reaction mixture was poured into 1200 cc. of water and the precipitate was filtered and washed. There was obtained 7 g. (66% yield), m. p. 156–160°. Recrystallization from 95% ethanol gave 3.8 g., m. p. 169–171°. For analysis, a sample was recrystallized several more times and was obtained in the form of fine light yellow needles, m. p. 172–173°.

The corresponding *o*-aminophenyl derivative was obtained from the *o*-nitrophenyl compound in exactly the same way. Reduction in this case was complete in five hours. Further details for both of these compounds are given in Table I.

Attempts to prepare the corresponding *p*-aminophenyl derivative by reduction of the *p*-nitrophenyl compound were unsuccessful, as was attempted reduction of the *p*-cyanophenyl derivative to the *p*-aminomethylphenyl homolog.

Summary

The preparation is reported of a number of 2-mono- and disubstituted 2,3-dihydro-1,3,4-benzoxaz-4-ones by the reaction of salicylamide with aldehydes, ketones and cyclic ketones containing both functional and non-functional substituents. These compounds were prepared for testing as analgesics, but none exceeded in activity the benzaldehyde derivative which provided the original lead.

A new synthesis of one of the intermediates, phthalaldehydic acid, is described.

NORTH CHICAGO, ILLINOIS RECEIVED JULY 8, 1949

(24) Beilstein's "Handbuch der org. Chem.," **18**, p. 17.