although in some cases the color of the catalyst suspension changed.

The effect of piperylene (80–85% *trans*) on 20 ml. of active catalyst per 30 ml. of butadiene is shown in Table VII for a 2-pentoxide/allylsodium and an isopropoxide/allylsodium catalyst. The polymerization time was 30 minutes and the alkoxide to allylsodium ratio was 1 to 1.

Table VIII records similar results for several dienes.

TABLE VII

INFLUENCE OF PIPERYLENE ON THE POLYMERIZATION OF BUTADIENE BY ALFIN CATALYSTS

Catalyst	Piperylene, ml.	Contact[a] time, min.	Conversion, %	Gel %	Intrin. visc.
P_2P	0		52	65	6.6
	1	2	48	47	7.6
	5	2	41	0	6.3
	10	2	36	0	6.9
	10	5	69	0	6.9
	20	5	60	0	6.7
PP	1.3	90	91	11	14.0
	5	60	36	0	13.5

[a] Contact time of piperylene with catalyst before addition of butadiene.

TABLE VIII

EFFECT OF DIENES ON POLYMERIZATION

Catalyst[a]	Dienes[b]	Moles of diene	React. time, min.	Poly. time, min.	Conversion, %	Intrin. viscosity	Gel, %
PP No. 1	0	0	0	90	100	16.9	96
PP No. 1	Pip.	0.02	30	90	96	14.2	18
PP No. 1	Iso.	0.12	30	90	100	11.5	13
PP No. 2	0	0	0	60	100	15.4	44
PP No. 2	Pip.	0.02	0	60	100	20.4	28
PP No. 2	Pip.	.01	30	60	100	11.5	0
PP No. 2	Pip.	.02	30	60	100	8.5	0
PP No. 2	Iso.	.12	0	60	100	11.4	4.9
PP No. 2	Mep.	.05	30	60	100	17	20
Benz.	0	0	0	60	63	3.9	38
Benz.	Pip.	.02	30	60	63	7.5	0

[a] PP no. 1 and PP no. 2 are different catalysts, one of which caused the formation of much gel. Benz. catalyst means sodium isopropoxide benzylsodium. [b] Pip. refers to piperylene (80–85% *trans*), iso to isoprene, and Mep. to methyl-1,3-pentadiene, a mixture of 85% 2-methyl and 15% 4-methyl.

Summary

Ethylene and straight and branched chain 1-alkenes are metalated on the methylene or methyl group next to a double bond, if present, otherwise on a vinyl carbon. If only one hydrogen is on the adjacent carbon, rearrangement or other changes occur. Allyl isomerism of metalated straight chain olefins occurs and three carbonated products form, but branched chain olefins usually form only one. Isobutene forms two. Carbonated and Wurtz products are possible.

Diallyl and piperylene are metalated. Carbonation yields at least four acids from diallyl and one from piperylene.

The metalated olefins and piperylene make poor Alfin catalysts, but metalated diallyl is fair. Olefins do not affect a good Alfin catalyst but dienes may possibly do so by reacting with the catalyst.

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[CONTRIBUTION FROM THE RESEARCH DEPARTMENT OF THE CALCO CHEMICAL DIVISION, AMERICAN CYANAMID COMPANY]

Antispasmodics. VI.[1] Additional Substituted Beta Amino Ketones

BY J. J. DENTON, H. P. SCHEDL, W. B. NEIER AND MARY BROOKFIELD

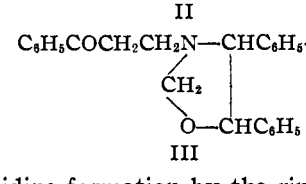
In paper I[2] of this series we attempted to correlate the structures of various β-aminoethyl aromatic ketones with their antispasmodic activities. Because of the activity of some of these ketones, we became interested in extending our series, studying principally (a) more complex amino groups, and (b) more complex aromatic nuclei.

The majority of the ketones reported in this paper were prepared by the Mannich reaction, which, in most of the cases, was carried out by the method of Winstein.[3] By this method acetophenone, paraformaldehyde, and *dl*-iso-1,2-diphenyl-2-aminoethanol hydrochloride in the molar ratio of 1:1.5:1 interacted to give a good yield of β-[*dl*-iso-(1,2-diphenyl-2-hydroxyethylamino)] - propiophenone hydrochloride (II). Under the same conditions, the same starting materials in the molar ratio of 1:3:2 gave β-[3-(4,5-diphenyloxazolidyl)]-propiophenone hydrochloride (III).

Compound III, less soluble than II, crystallized directly from the reaction mixture. Neutralization of an aqueous solution of III gave a base with one less carbon atom and identical with the base from II. That the carbon atom was lost as formaldehyde was shown by the formation of a suitable derivative.

$$C_6H_5COCH_2CH_2NHCH(C_6H_5)CHOH(C_6H_5)\cdot HCl$$

II



III

Oxazolidine formation by the ring closure of a 2-amino alcohol with an aldehyde has recently been reported by Heinzelman.[4] Their products,

(1) For paper V of this series see THIS JOURNAL, **72**, 3279 (1950).

(2) Denton, Turner, Neier, Lawson and Schedl, *ibid.*, **71**, 2048 (1949).

(3) Winstein, Jacobs, Seymour and Linden, *J. Org. Chem.*, **11**, 215 (1946).

(4) Heinzelman, Kolloff and Hunter, THIS JOURNAL, **70**, 1386 (1948).

TABLE I

Number	Hydrochlorides, -propiophenone	Activity	Number	Hydrochlorides, -propionaphthone	Activity
I	β-[1-(4-Carbethoxypiperazyl)]-	−	XIII	β-Dimethylamino-4-chloro-1-[3]	−
II	β-[*dl*-Iso-(1,2-diphenyl-2-hydroxyethylamino)]-	−	XIV	β-[2-(1,2,3,4-Tetrahydroisoquinolyl)]-4-chloro-1-	−
III	β-[3-(4,5-Diphenyloxazolidyl)]-[a]		XV	β-(4-Morpholinyl)-4-methyl-1-	−
IV	β-[1-(3-Benzoyl-4-hydroxy-4-phenylpiperidyl)]-[b]	+	XVI	β-(1-Piperidyl)-4-methyl-1-	+
V	Nitrilotri-β-[5]	+		Fluorene	
VI	β-(4-Morpholinyl)-2,4,6-trimethyl-	−	XVII	2-(β-Dimethylaminopropionyl)-[6]	−
VII	β-(4-Morpholinyl)-4-isopropyl-	−	XVIII	2-[β-(4-Morpholinyl)-propionyl]-[6]	−
VIII	β-(1-Piperidyl)-4-hydroxy-	−	XIX	2-[β-(1-Piperidyl)-propionyl]-[6]	+
IX	β-(1-Piperidyl)-3,4-dihydroxy-	−		Miscellaneous	
X	β-(1-Piperidyl)-2,5-dimethyl-	+	XX	1-(1-Piperidyl)-4,4-dimethyl-3-pentanone[7]	−
XI	β-(1-Piperidyl)-2,4,6-trimethyl-	+	XXI	Di-4-[β-(1-piperidyl)-propionyl]-phenyl ether	−
XII	β-(1-Piperidyl)-4-isopropyl-	++	XXII	3-[β-(1-Piperidyl)-propionyl]-thianaphthene	−
			XXIII	2-[β-(1-Piperidyl)-propionyl]-dibenzofuran	−

Number	Formula	M. p.,[b] °C.	Yield,[c] %	Procedure	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Chlorine, % Calcd.	Chlorine, % Found
I	$C_{16}H_{22}N_2O_3 \cdot HCl$	171.6–171.8	20.5	C	58.80	58.9	7.09	7.08	8.57	8.40	10.85	10.81
II	$C_{23}H_{23}NO_2 \cdot HCl$	190.4–191.3	61.3	C	72.33	72.5	6.33	6.34	3.67	3.73	9.28	9.32
IIA[d]	$C_{23}H_{23}NO_2$	125.5–126.0			79.97	79.3	6.71	6.70	4.06	4.07		
III	$C_{24}H_{23}NO_2 \cdot HCl$	145.1–146.1	15.7	C[e]	73.18	73.0	6.14	6.24	3.56	3.57	9.00	9.08
IV	$C_{27}H_{27}NO_3 \cdot HCl$	196.0–196.5			71.16[f]	71.0	6.19	6.30	3.07	3.14	7.78	7.80
IVA[d]	$C_{27}H_{27}NO_3$	148.0–148.5	61.7		78.42	78.5	6.58	6.85	3.39	3.45		
VI	$C_{16}H_{23}NO_2 \cdot HCl$	182.8–183.3[g]	31.9	B	64.52	64.7	8.12	8.06	4.70	4.70	11.91	11.9
VII	$C_{16}H_{23}NO_2 \cdot HCl$	196.5–197.3[h]	63.0	A	64.52	64.3	8.12	8.10	4.70	4.61	11.91	12.0
VIII	$C_{14}H_{19}NO_2 \cdot HCl$	219.5–220.0	10.0		62.29	62.0	7.47	7.67	5.19	5.07	13.14	12.8
IX	$C_{14}H_{19}NO_3 \cdot HCl \cdot H_2O$[i]	196.5–198.0	31.2		55.4	55.5	7.3	7.26	4.61	4.49	11.7	12.0
X	$C_{16}H_{23}NO \cdot HCl$[j]	175.0–175.8	0.8	B	68.19	68.0	8.58	8.54	4.97	4.84	12.58	12.7
XI	$C_{17}H_{25}NO \cdot HCl$	170.1–170.3[k]	26.7	B	67.24[l]	67.9	8.63	9.15	4.61	4.75	11.68	11.8
XII	$C_{17}H_{25}NO \cdot HCl$	180.1–181.5[m]	23.2	A	69.01	69.1	8.86	8.88	4.74	4.65	11.99	12.0
XIV	$C_{22}H_{20}ClNO \cdot HCl$	228.0–229.5	14.0	C	68.40	68.6	5.48	5.67	3.63	3.74	18.36	18.2
XV	$C_{16}H_{21}NO_2 \cdot HCl$	210.0–212.0 d.	15.3	C	67.60	67.8	6.94	7.05	4.38	4.16	11.09	11.1
XVI	$C_{19}H_{23}NO \cdot HCl$	214.0–215.0 d.	7.9	C	71.78	71.4	7.61	7.40	4.41	4.20	11.15	11.2
XVII	$C_{18}H_{19}NO \cdot HCl$	187.0–188.6[n] d.	71.9	C	67.97[o]	67.3	6.34	6.76	4.40	4.43	11.15	11.2
XVIII	$C_{20}H_{21}NO_2 \cdot HCl$	224.5–225.5[p] d.		C	69.85	69.8	6.45	6.32	4.07	3.92	10.31	10.4
XVIIIA[d]	$C_{20}H_{21}NO_2$	115.5–116.0	71.0[q]		78.14	78.3	6.89	6.94	4.56	4.42		
XIX	$C_{21}H_{23}NO \cdot HCl$	215.0–216.0 d.	74.6	C	73.77	73.7	7.08	7.25	4.10	4.16	10.37	10.5
XX	$C_{12}H_{23}NO \cdot HCl$	209.0–210.0 d.	64.4	C	61.64	61.8	10.35	10.6	5.99	6.11	15.17	15.2
XXI	$C_{28}H_{36}N_2O_3 \cdot 2HCl$	212.7–213.0 d.	31.1	C	64.48	64.4	7.34	7.55	5.37	5.33	13.60	13.6
XXII	$C_{16}H_{19}NOS \cdot HCl$[r]	228.5–228.8 d.	45.8	C	62.01[s]	61.8	6.51	6.69	4.52	4.40	11.44	11.5
XXIII	$C_{20}H_{21}NO_2 \cdot HCl$	226.5–228.3[t] d.	62.2	C	69.86	70.1	6.45	6.48	4.07	4.04	10.3	10.3

[a] Antispasmodic activity not determined because compound decomposes under test conditions. [b] All melting points are corrected. [c] Yields refer to pure hydrochlorides and are based on starting ketones. [d] Refers to free amine corresponding to preceding hydrochloride. [e] The molar ratio of ketone:paraformaldehyde:amine was 2:3:1. [f] Calculations are based on a Karl Fischer moisture analysis of 1.25% water. [g] Sample immersed in bath at 179° and heated at 1° (min.). [h] Sample immersed in bath at 195°. [i] Calcd. % H_2O, 5.94. Found (by Karl Fischer method), 3.40. [j] Obtained from the distilled base, b. p. 116–119° (4 mm.). [k] Sample immersed in bath at 165° and heated at 1° (min.). [l] Calculations are based on a Karl Fischer moisture analysis showing the presence of 2.60% water. [m] Sample immersed in bath at 175° and heated at 1° (min.). [n] Sample immersed in bath at 185°. [o] Calculations are based on a Karl Fischer moisture analysis showing the presence of 5.11% water. [p] Sample immersed in bath at 195°. [q] The crude hydrochloride obtained directly from the reaction was dissolved in water, and the aqueous solution treated with ammonia to liberate the base. [r] Calcd. S, 10.35; found, 10.2. [s] Sample immersed in bath at 200°.

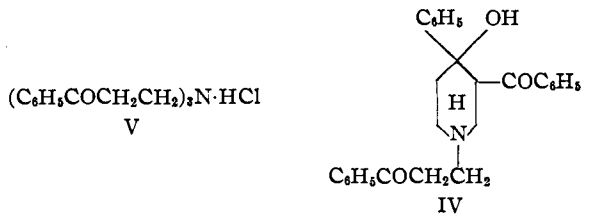
substituted 2-phenyl-4H-indeno[2,1-d]oxazolidines, were more stable than the base corresponding to III. Simpler oxazolidines prepared by Knorr[8] also show this greater stability as the free base. The salts of the latter appear to be less stable than III.

(5) Mannich and Abdullah, THIS JOURNAL, **68**, 113 (1935).
(6) Roy and MacGregor, *ibid.*, **69**, 587 (1947).
(7) Mannich and Hof, *Arch. Pharm.*, **265**, 589 (1927).
(8) Knorr and Matthes, *Ber.*, **34**, 3484 (1901).

Compound V (Table I) was prepared in low yield from ammonium chloride, acetophenone and formalin by Mannich[5]; this compound was shown to cyclize readily to compound IV (Table I).

We have obtained IV directly in good yield by the trialkylation of ammonia in an amine exchange reaction with β-(1-piperidyl)-propiophenone.

A similar but less complex amine exchange reaction of a β-amino ketone has recently been re-



ported by Snyder,[9] in which β-dimethylaminopropiophenone was converted to β-(4-morpholinyl)-propiophenone in boiling morpholine.

Table I gives the substituted β-amino ketones prepared in this study. A numerical superscript in the name column of this table refers to a previous preparation of this compound in the literature; while a capital letter in the procedure column refers to our own preparation in the experimental part. The detailed preparations of compounds III, IV, VIII and IX are given in the experimental part. In the case of compound XX, where both reference and procedure are given, a difference in physical properties between the compound which we have prepared and that disclosed in the literature is indicated. In the other cases, complete analytical data are given for the first time.

Pharmacological Activity.—The antispasmodic activity ratings in Table I have the same significance as previously reported.[1] Seven of the twenty-three ketones listed show antispasmodic activity. Compounds VIII–XII show that simple substituents in the aromatic ring of β-(1-piperidyl)-propiophenones do not enhance the activity over that of the parent.[2] From this and the lack or low order of activity of the other compounds listed, it is concluded that in substituted β-amino ketones of this type, the increase in complexity of both the amino group and the aromatic nucleus decreases the antispasmodic activity.

Experimental

Procedures A, B and C are identical with those described in paper I of this series.[2]

β-[3-(4,5-Diphenyloxazolidyl)]-propiophenone Hydrochloride (III).—Acetophenone (24 g., 0.2 mole), paraformaldehyde (9 g., 0.3 mole), and *dl*-iso-1,2-diphenyl-2-aminoethanol hydrochloride (25 g., 0.1 mole)[7] reacted according to the method of Winstein[8] for a thirty-minute period. The precipitate which formed in the cooled reaction mixture, when recrystallized from ethanol, gave the product whose physical and analytical data are recorded in Table I. The reaction mother liquor, on dilution with ether, gave a copious precipitate. This solid when collected and recrystallized from ethanol gave 13.1 g. (34.4% yield) of pure β-[*dl*-iso-(1,2-diphenyl-2-hydroxyethylamino)]-propiophenone hydrochloride (II).

β-[*dl*-Iso-(1,2-diphenyl-2-hydroxyethylamino)]-propiophenone (IIA).—A cold aqueous-methanolic solution of β-[3-(4,5-diphenyloxazolidyl)]-propiophenone hydrochloride (III) was made basic with aqueous ammonia and diluted with water. The resulting precipitate, when collected and recrystallized from ethanol, had the same melting point as an authentic sample of the base (IIA) from β-[*dl*-iso-(1,2-diphenyl-2-hydroxyethylamino)]-propiophenone hydrochloride (II). A mixture of the samples gave no melting point depression.

(9) Snyder and Brewster, THIS JOURNAL, 70, 4230 (1948).

Identification of Formaldehyde.—An aqueous solution of pure β-[3-(4,5-diphenyloxazolidyl)]-propiophenone hydrochloride (III) was slowly distilled into a neutral aqueous-alcoholic solution of dimethyldihydroresorcinol. The precipitate which formed in the distillate when collected and dried gave no melting-point depression when mixed with an authentic sample of the formaldehyde dimedon derivative.

β-[1-(3-Benzoyl-4-hydroxy-4-phenylpiperidyl)]-propiophenone Hydrochloride (IV).—A solution of 25 g. (0.1 mole) of β-(1-piperidyl)-propiophenone hydrochloride in one liter of water at 93° was made alkaline with concd. aqueous ammonia. The suspension thus obtained was allowed to cool to room temperature with occasional stirring. The solid was collected and recrystallized from ethanol. The hydrochloride was prepared from the purified base in the usual way.

Physical and analytical data on the base and its hydrochloride are recorded in Table I. No depression in melting point was observed when IV was mixed with an authentic sample of β-[1-(3-benzoyl-4-hydroxy-4-phenylpiperidyl)]-propiophenone hydrochloride prepared according to the method of Mannich.[6] Mixtures of the corresponding bases also showed no melting point depression.

β-(1-Piperidyl)-4-hydroxypropiophenone Hydrochloride (VIII).—A stirred mixture of 14.0 g. (0.05 mole) of β-(1-piperidyl)-4-methoxypropiophenone hydrochloride, 75 cc. of glacial acetic acid, and 80 cc. of 48% aqueous hydrobromic acid were heated under reflux for 6.5 hr. After distillation of the solvent under reduced pressure, an aqueous solution of the residue was adjusted to *p*H 8 with dilute sodium hydroxide. After extraction with ether, the aqueous layer was acidified to *p*H 3 with concd. hydrochloric acid. The solid which precipitated on cooling in an ice-bath, was collected and recrystallized from ethanol. The solid was then slurried in an aqueous sodium bicarbonate solution and extracted with ether. The dried ethereal solution was acidified with anhydrous hydrogen chloride, giving the product whose analytical and physical data are recorded in the table.

β-(1-Piperidyl)-3,4-dihydroxypropiophenone Hydrochloride (IX).—To a refluxing solution of 17.2 g. (0.11 mole) of 3,4-dihydroxypropiophenone and 13.5 g. (0.11 mole) of piperidine hydrochloride in 75 cc. of ethanol was added, over a two-hour period, 3.3 g. (0.11 mole) of paraformaldehyde. After a 30-minute reflux period, the reaction mixture was cooled and treated with 3 drops of concd. hydrochloric acid. The product was collected and recrystallized from ethanol. Physical and analytical data are recorded in the table.

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Summary

Of twenty-three substituted β-aminoethyl aromatic ketones prepared and tested for antispasmodic activity, seven showed a low order of activity. In ketones of this type it is concluded that in general a decrease in activity results from (a) increasing the complexity of the amino group and (b) the introduction of more complex aromatic radicals than the phenyl group.

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