TABLE II

METHYL β-AMINOPROPIONATES[a]

$R^1CH_2CHR^2COOMe$

No.	Reaction time, days	% yield	Bp, °C (mm)	Formula	HCl mp, °C
11[b]	5	74	109–110 (15)[d]	$C_{10}H_{19}NO_2$	183–184
12	5	78	107–108 (18)[e]	$C_{10}H_{19}NO_2$	157–158
13	7	60	138–140 (2)	$C_{14}H_{26}N_2O_4$	203–204.5
14	7	90	66–68 (2)	$C_{11}H_{21}NO_2$	145–146
15	7	80	88–90 (2)	$C_{13}H_{25}NO_2$	164–165
16	7	85	143–145 (2)	$C_{16}H_{23}NO_2$	180–181
17	7	91	120–122 (19)[f]	$C_9H_{17}NO_3$	165–166
18	7	95	76–78 (2)	$C_{11}H_{21}NO_3$	148–149
19	1.25	80	76–78 (2)[g]	$C_{11}H_{21}NO_2$	133–134
20	2	62	100–104 (1)[h]	$C_{11}H_{15}NO_2$	158–159[h]

[a] Substituents R^1 and R^2 in esters **11–20** are identical with those listed for hydroxamic acids **1–10**, respectively, in Table I. [b] Et ester. [c] All compounds were analyzed for C, H. Analytical results obtained were within ±0.3% of theoretical values. [d] J. F. Arens, D. H. Koerts, and P. Plieger, *Rec. Trav. Chim.*, **75**, 1454 (1956), gave bp 106–108° (11 mm). [e] P. Bieber, *Compt. Rend.*, **231**, 291 (1950), gave bp 102–103° (18 mm). [f] A. Vystrcil and S. Hudecek, *Chem. Listy*, **44**, 262 (1950), gave bp 112° (13 mm). [g] D. I. Barron, G. H. Hall, I. L. Natoff, H. F. Ridley, R. G. W. Spickett, and D. K. Vallance, *J. Med. Chem.*, **8**, 836 (1965), gave bp 60° (0.05 mm). [h] P. L. Southwick and R. T. Crouch, *J. Am. Chem. Soc.*, **75**, 3413 (1953), gave bp 145–147° (7 mm) and mp 164–165°, respectively.

Table III. These results show that the duration of action of the hydroxamates is more prolonged than that of the esters.

TABLE III

EFFECT OF β-AMINOPROPIONOHYDROXAMIC ACIDS AND METHYL β-AMINOPROPIONATES ON ARTERIAL BLOOD PRESSURE OF THE ANESTHETIZED CAT[a]

Compd	Dose, mg/kg	Blood pressure fall, mm[b]	Duration,[c] min
1	25	45	5
2	25	60	10
3	25	35	10
4	25	70	10
5	5	40	5
5	10	40	30
5	25	40	120
5	50	55	>120
6	5	70	>80
6	10	65	>120
6	25	90	≫120
7	25	45	5
8	25	25	30
9	25	40	5
10	25	45	>60
11	25	50	5
12	25	(25)[d]	5
13	25	50	15
14	25	30	5
15	25	45	5
16	25	55	10
17	25	45	5
18	25	40	3
19	25	25	10
20	25	25	3

[a] Aqueous solutions were administered intravenously. Averages of at least two results are given. [b] Blood pressure (carotid artery). [c] Time required for blood pressure to return to normal. [d] Rise in blood pressure.

Experimental Section[4]

Esters.—The appropriate acrylate (0.25 mole) and amine (0.25 mole) were dissolved in anhydrous MeOH (50 ml) and heated under reflux for 30 hr to 7 days, as indicated in Table II. The solvent was removed, and the residue was dissolved in Et_2O (100 ml) and extracted with 5% HCl (three 25-ml portions). The aqueous extract was treated with excess 10% NH_3 and re-extracted with Et_2O (three 50-ml portions). The combined Et_2O extract was washed with H_2O and dried (Na_2SO_4), and the Et_2O was removed. The oil which resulted was fractionally distilled and the appropriate fraction was collected (Table II). Each ester was characterized by analysis and by nmr and ir spectra. A C=C stretching band near 1630 cm^{-1} (due to the acrylate starting material) was absent from each spectrum.

Ester hydrochlorides were obtained by adding ethereal HCl to an Et_2O solution of the ester. The hydrochlorides were characterized by their ir spectra. All showed strong $^+$N–H stretching bands in the 2350–2710-cm^{-1} region.[5] Melting points are listed in Table II.

Hydroxamic Acids.—A constantly stirred solution of $NH_2OH \cdot HCl$ (0.02 mole) in MeOH (40 ml) was cooled to 0° and to it was added dropwise, over 0.5 hr, a solution of the ester III (0.02 mole) in dry MeOH (20 ml). Stirring was continued at room temperature for a further 10 hr and then the MeOH was removed *in vacuo*. The resulting semisolid was redissolved in the minimum of dry MeOH and the solution was cooled to 0°. Dry Me_2CO was added until the solution remained cloudy. The products separated on standing, and in all instances the yield of product was in excess of 75% of theory. The hydroxamate hydrochlorides were crystallized from dry MeOH and each was characterized by elemental analysis (Table II) and by ir spectrum. All showed strong carbonyl stretching bands within the range 1650–1680 cm^{-1}.

Acknowledgment.—The authors wish to thank Dr. J. W. Hubbard and Dr. D. C. Secord for their helpful suggestions and Mr. E. Mah for technical assistance.

(4) Melting points were determined with a Fisher-Johns apparatus. Melting points and boiling points are uncorrected; ir spectra were taken on a Beckman IR10 spectrophotometer and nmr spectra were recorded on a Varian A-60D spectrophotometer. All the hydroxamic acids prepared in this study gave a violet color with ethanolic $FeCl_3$.

(5) W. E. Thompson, R. J. Warren, I. B. Eisdorfer, and J. E. Zarembo *J. Pharm. Sci.*, **54**, 1819 (1965).

Hypoglycemic Esters of 2-Chloroethanol

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In the course of a program unrelated to hypoglycemic agents some chloroalkyl esters of α-keto acids were prepared as intermediates. They were, surprisingly, found to possess hypoglycemic activity in glucose-primed intact fasted rats. Accordingly a study

TABLE I

$$RCOOCHCHCl \quad (R^2 = R^3)$$

No.	R	R^2	R^3	Bp (mm) or mp, °C	Yield,[a] %	$n^{25}D$	Formula	Analyses	Rel act.[b]
1	CH_3CO	H	H	105 (15)	56	1.4440	$C_5H_7ClO_3$	C, H, Cl	1.2
2	CH_3CO	CH_3	H	85 (5)	76	1.4395	$C_6H_9ClO_3$	C, H, Cl	0
3	$CH_3C(OC_2H_5)_2$	H	H	109 (7)	61	1.4360	$C_9H_{17}ClO_4$	C, H, Cl	1.0
4	C_6H_5CO	H	H	115 (0.08)	93	1.5353	$C_{10}H_9ClO_3$	C, H, Cl	1.0
5	C_6H_5CO	CH_2Cl	H	142 (0.03)	58	1.5447	$C_{11}H_{10}Cl_2O_3$	C, H, Cl	0
6	C_6H_5CO	CH_3	H	121 (0.2)	73	1.5243	$C_{11}H_{11}ClO_3$	C, H, Cl	0
7	C_6H_5CO	$(CH_2)_4$		55[c]	63		$C_{14}H_{15}ClO_3$	C, H, Cl	0
8	C_6H_5CO	H	Cl	104–106 (0.03)	79	1.5408	$C_{10}H_8Cl_2O_3$	C, H, Cl	0
9	C_6H_5CO	H	CH_3	82–85 (0.01)	31	1.5254	$C_{11}H_{11}ClO_3$	C, H, Cl	0
10	C_6H_5CO	H	$CH_3(CH_2)_2$	113–115 (0.03)	66	1.5165	$C_{13}H_{15}ClO_3$	C, H, Cl	0.6
11	C_6H_5CO	H	$CH_3(CH_2)_3$	131–134 (0.03)	64	1.5125	$C_{14}H_{17}ClO_3$	C, H, Cl	0
12	p-$CH_3OC_6H_4CO$	H	H	141–143 (0.02)	73	1.5597	$C_{11}H_{11}ClO_4$	C, H, Cl	0
13	p-ClC_6H_4CO	H	H	111 (0.03)	80	1.5521	$C_{10}H_8Cl_2O_3$	C, H, Cl	0
14	o-$O_2NC_6H_4CH_2CO$	H	H	140–144 (0.03)	73	1.5535	$C_{11}H_{10}ClNO_5$	C, H, N	0
15	m-$O_2NC_6H_4CO$	H	H	162–164 (0.02)	88	1.5588	$C_{10}H_8ClNO_5$	C, H, N	0
16	$C_6H_5CH_2$	H	H	74 (0.01)	85	1.5169	$C_{12}H_{13}ClO_2$	C, H, N	0.7
17	$C_{10}H_7CO$	H	H	151 (0.02)	68	1.6144	$C_{14}H_{11}ClO_3$	C, H, Cl	0
18	C_4H_3SCO	H	H	111 (0.01)	82	1.5707	$C_8H_7ClO_3S$	C, H, S	0
19	p-$CH_3C_6H_4CO$	H	H	116 (0.08)	63	1.5374	$C_{11}H_{11}ClO_3$	C, H, Cl	0

[a] Per cent refers only to the esterification step. [b] Activity in the rat: tolbutamide = 1. [c] Solidified in the receiver after distillation.

TABLE II

$$RCOCOOCH_2CH_2X$$

No.	R	X	Bp, °C (mm)	Yield,[a] %	$n^{25}D$	Formula	Analyses	Rel act.[b]
20	CH_3	CH_2Cl	129–131 (29)	58	1.4459	$C_6H_9ClO_3$	C, H, Cl	0
21	CH_3	OCH_3	84 (8)	24	1.4226	$C_6H_{10}O_4$	C, H	0
22	C_6H_5	Br	141–142 (0.01)	65	1.5532	$C_{10}H_9BrO_3$	C, H, Br	0.5
23	C_6H_5	F	115 (0.08)	78	1.5128	$C_{10}H_9FO_3$	C, H, F	0.4
24	C_6H_5	OAc	131–133 (0.04)	46	1.5092	$C_{12}H_{12}O_5$	C, H	0
25	C_6H_5	CH_2Cl	125–127 (0.02)	77	1.5286	$C_{11}H_{11}ClO_4$	C, H, Cl	0

[a] Per cent refers only to the esterification step. [b] Activity in the rat: tolbutamide = 1.

was made of the structure–activity relationships in compounds of this general class.

The synthetic routes used to prepare these compounds are described in the Experimental Section. Their physical properties are summarized in Tables I and II.

Biological Testing and Results.—Male rats of the Charles River CD strain weighing 90–100 g were employed. The compounds of Tables I and II were tested following overnight fast. The rats were injected subcutaneously with 100 mg of glucose in 0.5 ml of 0.85% saline. This was followed immediately by oral administration of 100 mg/kg of the test compound in water. Blood glucose concentrations were determined at intervals up to 5 hr after medication by the method of Reinecke.[1] The ratio of the maximum depression due to the compound to the maximum depression due to tolbutamide is recorded in Tables I and II.

The highest activity in Tables I and II lies with the esters **1**, **3**, and **4**. The carboxylic acids from which these esters are derived were inactive. However, for 2-chloroethanol at a dose of 40 mg/kg the maximum depression was 0.7 times that due to tolbutamide. Toxicity prevented the use of higher doses.

The following structural changes appear to eliminate activity: replacement of phenyl by a heterocycle and substitution in the phenyl ring. In the alcohol moiety of the ester, substituents in the 1 position abolish activity. Activity may be preserved when Br or F is substituted for Cl. Alkyl substituents added in the 2 position decrease activity or eliminate it entirely.

(1) R. M. Reinecke, *J. Biol. Chem.*, **143**, 351 (1942).

Experimental Section[2]

The esters in Tables I and II, except for **9** and **15** described below, were made by reaction of an alcohol with a carboxylic acid. The typical procedure is illustrated by preparation of **4**. The alcohols used were commercial samples with the exception of 2-chloropentanol[3] and 2-chlorohexanol.[3] The carboxylic acids were known materials synthesized by literature procedures, or commercial samples carefully purified before use. 2-Naphthylglyoxylic acid,[4] *p*-methoxyphenylglyoxylic acid,[5] and 2-thiopheneglyoxylic acid[6] were made from the corresponding known aryl methyl ketones by alkaline MnO_4^- oxidation, using the procedure of Cymerman-Craig, *et al.*[4] Both *p*-tolylglyoxylic acid[7] and *p*-chlorophenylglyoxylic acid (see below) resulted from Friedel-Crafts acylation.

Procedure for Esterification. 2-Chloroethyl Phenylglyoxylate (4).—A solution of 75 g (0.5 mole) of phenylglyoxylic acid, 50 ml (0.75 mole) of 2-chloroethanol, and 3 g of *p*-toluenesulfonic acid monohydrate in 350 ml of 1,2-dichloroethane was heated on the steam bath under a water separator. After 5 hr the volume of the aqueous phase was 9.5 ml and did not increase further. After 8 hr the mixture was cooled and poured into H_2O. The organic phase was washed (H_2O) until the washings were neutral, dried

(2) Melting points were taken in a modified Hershberg apparatus and are uncorrected. Each analytical sample gave an ir spectrum compatible with the assigned structure, showed a single spot by tlc, and gave combustion values within 0.4% of the theoretical.

(3) S. J. Cristol and K. R. Eilar, *J. Am. Chem. Soc.*, **72**, 4353 (1950).

(4) J. Cymerman-Craig, J. W. Loder, and B. Moore, *Aust. J. Chem.*, **9**, 222 (1956).

(5) C. Erba, Italian Patent 475,964 (1952); *Chem. Abstr.*, **49**, 12539c (1955).

(6) F. F. Blicke and M. U. Tsao, *J. Am. Chem. Soc.*, **66**, 1645 (1944).

(7) M. Julia and M. Baillarge, *Bull. Soc. Chim. France*, 850 (1959).

(Na_2SO_4), and charcoaled to give 107 g of yellow oil. Distillation through a 7.5-cm Vigreux column gave 98.8 g (93%) of crude ester. A center cut served as analytical sample.

p-Chlorophenylglyoxylic Acid.—A mixture of 37 ml (0.35 mole) of PhCl, 48.4 g (0.35 mole) of ethoxalyl chloride, and 200 ml of $Cl_2CHCHCl_2$ was cooled to 0°. With stirring 47 g (0.35 mole) of $AlCl_3$ was added at 0° during 30 min. The mixture was stirred 30 min more at 0° and warmed gradually over 30 min up to 45° where a brisk evolution of HCl began. Heating was interrupted until the HCl evolution stopped. The mixture was stirred on the steam bath for 3 hr, cooled, and poured onto a mixture of 200 g of ice and 200 ml of 12 *N* HCl. Steam distillation removed the solvent; the brown tar remaining was taken into Et_2O and the aqueous phase was extracted with Et_2O. The combined Et_2O extracts were washed with H_2O followed by dilute HCl, charcoaled, and dried (Na_2SO_4) to give 57 g of brown gum. The gum was taken up in hot PhH and hexane was added to the cloud point. On cooling there was obtained 21.7 g (33%) of crude tan solid, mp 89–91°, lit.[8] mp 90°.

2-Chloroethyl Pyruvate Diethyl Ketal (3).—A mixture of 15.0 g (0.1 mole) of 2-chloroethyl pyruvate, 26 ml (0.15 mole) of ethyl orthoformate, 1.5 g of *p*-toluenesulfonic acid monohydrate, and 24 ml of absolute EtOH was allowed to stand 48 hr and then refluxed 8 hr. Using a minimum amount of heat, low-boiling components were removed at the aspirator and the residue was poured into ice water containing 40 ml of 5% $NaHCO_3$. After extraction into 1,2-dichloroethane, the organic phase was washed with H_2O until the washings were neutral, dried, charcoaled, and stripped to give a residue of yellow oil. Careful removal of forerun in a 5-cm Vigreux column gave the crude product, 13.7 g (61%), bp 106–113° (6 mm). On redistillation a center cut furnished the analytical sample.

2-Chloropropyl Phenylglyoxylate (9).—To a stirred solution of 25.5 g (0.17 mole) of phenylglyoxylic acid in 100 ml of DMF was added 23.5 ml (0.17 mole) of Et_3N followed by 17.5 ml (0.17 mole) of 1-bromo-2-chloropropane. With the protection of a drying tube the mixture was stirred on the steam bath 5 hr and cooled. The precipitate was filtered and washed with 25 ml of hexane. The DMF solution was poured into ice water, the oil was taken into $CHCl_3$, and the aqueous phase was extracted with $CHCl_3$. The hexane extract was concentrated and taken into $CHCl_3$. The combined $CHCl_3$ extracts were washed with 2% $NaHCO_3$ and H_2O, dried (Na_2SO_4), charcoaled, and concentrated to an oil which was fractionated in a 7.5-cm Vigreux column to yield 12.1 g (31%). A center cut served as analytical sample.

2-Chloroethyl *m*-Nitrophenylglyoxylate (15).—*m*-Nitrobenzaldehyde was converted into the cyanohydrin using the procedure of Buck.[9] Without characterization the cyanohydrin was hydrolyzed by heating in concentrated HCl on the steam bath 18 hr to give *m*-nitromandelic acid,[10] mp 114–116°, in 20% yield. This acid was esterified with 2-chloroethanol in 88% yield to give 2-chloroethyl *m*-nitromandelate (**26**), mp 86–87°. *Anal.* ($C_{10}H_{10}ClNO_5$) C, H, Cl. N-Bromosuccinimide (4.25 g, 0.0238 mole) was stirred in 100 ml of refluxing CCl_4. To this was added a solution of 6.2 g (0.0238 mole) of 2-chloroethyl *m*-nitromandelate in 75 ml of CCl_4. After 12 hr of heating under reflux the mixture was cooled and the solid was filtered off and discarded. A drop of allyl alcohol was added to decolorize. The solution was dried ($NaSO_4$) and charcoaled. After the solvent was removed by careful distillation on the steam bath the oily residue distilled to give 83% yield of **15**, bp 162–164° (0.02 mm).

Acknowledgment.—The authors are indebted for spectroscopic data to Dr. R. Kullnig and staff and for elementary analytical data to Mr. K. Fleischer and staff.

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Quaternary Oxazolylpyridinium Salts. Oral Hypoglycemic Agents

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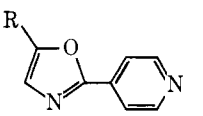
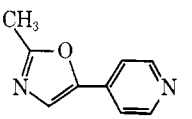
A number of quaternary azolylpyridinium salts, including members of the pyrazolyl-,[1] isoxazolyl-,[2–4] and 1,2,4-oxadiazolylpyridinium[5] salt families, have been found to display hypoglycemic activity in laboratory animals. As part of a comprehensive development of this lead, we have investigated the replacement of the azolyl ring with other five-membered heterocycles. We describe herein the synthesis of some novel 4-(oxazolyl)pyridinium salts.

The 4-(oxazolyl)pyridinium salts **6–12** (Table I) were obtained by quaternization of the appropriate oxazolylpyridine bases **1**, **2**, and **3**. The base **1** was prepared as described by Dadkah and Prijns.[6] The



1, R = H
2, R = CH_3



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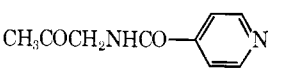

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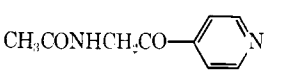

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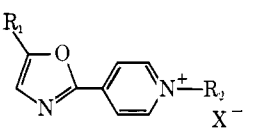

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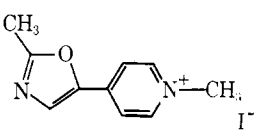

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bases **2** and **3** were obtained by dehydration of the amido ketones **4** and **5**,[7] respectively, using a procedure developed by Ott, *et al.*,[8] for the preparation of aryloxazoles. In the nmr spectrum of the base **1** the pyridyl protons appear as two doublets at δ 7.73 and 8.75. Upon quaternization to **6**, these signals shift to new values of δ 8.42 and 9.02. These changes, a downfield displacement of both doublets, as well as a smaller separation between chemical shifts, are diagnostic

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