benzene, II a mixture of *n*-propylbenzene and propenylbenzene, III phenylacetone and IV 1-phenyl-2-propanol. Phenylacetone was also identified by conversion into its dinitrophenylhydrazone and 1-phenyl-2-propanol by conversion into its 3,5-dinitrobenzoate. Minor amounts of other compounds were also present but no attempts to identify them were made.

The acidic solution from the ether extraction was made alkaline and continuously extracted with ether for 12 hr. The ether solution was washed with a small volume of water, dried with anhydrous potassium carbonate and distilled. PIH, 1.1 g., b.p. 70–75° (0.02 mm.) was recovered, identified by conversion into the hydrochloride.

Polymerization of Methyl Methacrylate.—Methyl methacrylate (8.0 g., 0.08 mole), PIH (0.25 g., 0.0013 mole) and cupric chloride (0.2 mg., 1.2×10^{-6} mole) were dissolved in a mixture of water (40 g.) and ethanol (55 g.). The solution was shaken overnight after which time a solid polymer had precipitated, which was collected, washed with water and dried. It weighed 8.0 g. (100% yield). A control solution, which had the same composition except that PIH was omitted, had not polymerized after standing for 3 weeks.

Pyrrolidines. VII. 3-Hydroxy-1-Pyrrolidinecarboxylic Acid Esters

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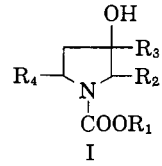
N-Alkoxycarbonylamino acid esters were condensed with ethyl esters of α,β-unsaturated carboxylic acids in the presence of sodium hydride and dry benzene to form alkyl ethyl 4-oxo-1,3-pyrrolidinedicarboxylates, which were hydrolyzed and decarboxylated to the corresponding 3-oxo-1-pyrrolidinecarboxylic acid esters. The carbonyl groups at the 3-position of these esters were reacted selectively with appropriate Grignard reagents to yield various 3-substituted 3-hydroxy-1-pyrrolidinecarboxylic acid esters, which were submitted for screening as hypnotic agents.

For a drug producing central activity an adequate lipid-water solubility ratio is important in order to enable it to reach the site of its action.[1,2] With this hypothesis in mind we prepared a series of compounds of structure (I) for screening as hypnotic agents,

(1) T. Sollmann, "A Manual of Pharmacology and Its Application to Therapeutics and Toxicology," W. B. Saunders Company, Philadelphia, Pa., 1957, p. 846.

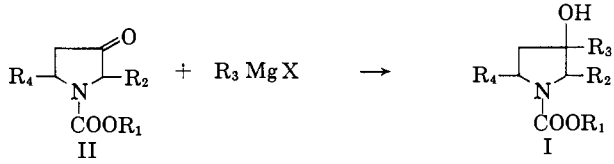
(2) R. B. Barlow, "Introduction to Chemical Pharmacology," John Wiley & Sons, Inc., New York, N.Y., 1955, p. 29.



I

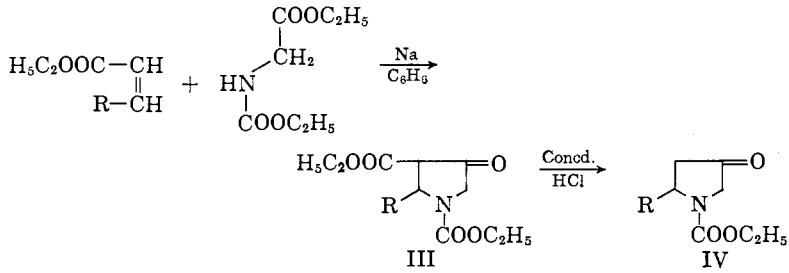
wherein R_1 represents a lower alkyl radical and R_2, R_3 and R_4 represent hydrogen, alkyl or aryl radicals. The structure was chosen as a part of our broad study in the chemistry of pyrrolidine derivatives.[3] Also certain carbamates are known to possess central activity.[4]

These compounds were synthesized by treating alkyl 3-oxo-1-pyrrolidinecarboxylate esters (II) with an appropriate Grignard reagent. The reagent attacked the ketonic carbonyl group at the 3-position of the nucleus selectively to yield the corresponding 3-substituted 3-hydroxy-1-pyrrolidinecarboxylates (I).



II I

Two different methods are available in the literature for the preparation of the intermediate alkyl 3-oxo-1-pyrrolidinecarboxylates (II). The method of Kuhn and Osswald[5] involves the reaction of N-ethoxycarbonylglycine ethyl ester with an ester of an α,β-unsaturated carboxylic acid in the presence of metallic sodium and an inert solvent such as benzene to form a diethyl 4-oxo-1,3-pyrrolidinedicarboxylate (III), which is partially hydrolyzed and decarboxylated to IV,



III IV

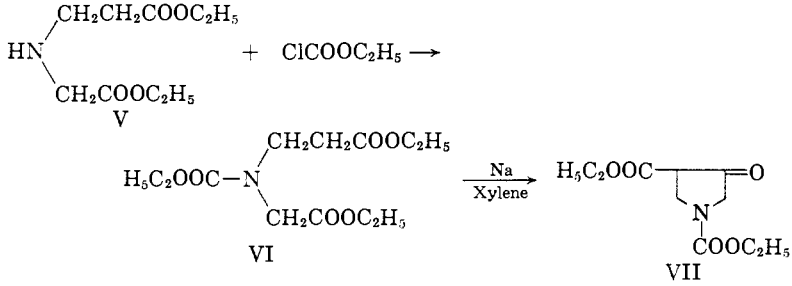
(3) Previous paper in this series, Pyrrolidines. VI H. C. Scarborough, B. C. Lawes, J. L. Minielli, and J. L. Compton, *J. Org. Chem.*, **27**, 957 (1962).

(4) A. Burger, "Medicinal Chemistry," Interscience Publishers, New York, N. Y., 1960, pp. 372, 379, 414.

(5) R. Kuhn and G. Osswald, *Chem. Ber.*, **89**, 1423 (1956).

wherein R represents a hydrogen, methyl, phenyl or ethoxycarbonyl group.

The Miyamoto process[6] comprises the reaction of ethyl chloroformate with ethyl N-ethoxycarbonylmethyl-β-aminopropionate (V). The resulting compound (VI) is ring-closed to form diethyl 4-oxo-1,3-pyrrolidinedicarboxylate (VII) under the usual Dieckmann conditions.



We have used both processes for the preparation of diethyl 4-oxo-1,3-pyrrolidinedicarboxylate. The physical constants of the products from the two different methods are essentially the same.

The Kuhn and Osswald method was extended for the synthesis of twelve alkyl ethyl 4-oxo-1,3-pyrrolidinedicarboxylates. Their physical properties are listed in Table I. In contrast to the concentrated hydrochloric acid used by Kuhn and Osswald we found that very dilute (0.4%) hydrochloric acid was all that was necessary to catalyze the hydrolysis and decarboxylation of these cyclic β-keto esters. The physical properties of the alkyl 3-oxo-1pyrrolidinecarboxylates are given in Table II.

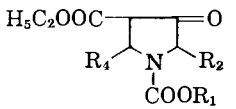
These alkyl 3-oxo-1-pyrrolidinecarboxylates are stable oils or low melting solids. Their reaction with Grignard reagents goes smoothly and usually gives 3-substituted 3-hydroxy-1-pyrrolidinecarboxylates in fair to good yields. Forty-seven pyrrolidinols have been synthesized with different substituents at the 2-, 3- and 5-positions of the pyrrolidine ring as shown in Table III.

Pharmacology.—Compounds listed in Table III were screened for hypnotic activity in fasted albino mice. Loss of the righting reflex following oral administration was used as the criterion for hypnosis. The most potent of the compounds were No. 5, 46, 1, 37, 6, 4, 3, and 8 in the order of descending potency. The median hypnotic doses for these eight agents ranged from 150 to 760 mg./kg. in comparison to 453 mg./kg. for chloral hydrate as the standard. Their ratios of

(6) Masuo Miyamoto, *Yakuzaku Zasshi*, **77**, 568 (1957); *Chem. Abstr.*, **51**, 16422e (1957).

TABLE I

ALKYL ETHYL 4-OXO-1,3-PYRROLIDINEDICARBOXYLATES

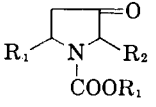


R_1	R_2	R_4	Procedure	Yield,[a] %	M.p. °C.	B.p. °C.	Mm.	$n^{25}D$	Formula	Nitrogen, % Calcd.	Found
CH_3	H	H	A	53		113–115	0.15	1.4783	$C_9H_{13}NO_5$	6.51	6.64
C_2H_5	H	H	A	78	61–63[b,c]				$C_{10}H_{15}NO_5$	Known compound	
C_2H_5	H	CH_3	A	79		125–131	0.8[d]	1.4667	$C_{11}H_{17}NO_5$	Known compound	
C_2H_5	H	C_2H_5	A	53		105–110	0.15	1.4671	$C_{12}H_{19}NO_5$	5.44	5.26
C_2H_5	H	C_6H_5	B	33	108–110[e,f]				$C_{16}H_{19}NO_5$	Known compound	
C_2H_5	H	4-ClC_6H_4	B	18	120–123[g]				$C_{16}H_{18}ClNO_5$	4.12	4.05
C_2H_5	H	4-$CH_3OC_6H_4$	B	21	92–94[f]				$C_{17}H_{21}NO_6$	4.18	4.18
C_2H_5	CH_3	H	A	68		106–125	0.2	1.4652	$C_{11}H_{17}NO_5$	5.76	5.64
C_2H_5	CH_3	CH_3	A	64		86–87	0.2	1.4672	$C_{12}H_{19}NO_5$	5.44	5.45
C_2H_5	C_2H_5	H	A	67		100–105	0.2	1.4683	$C_{12}H_{19}NO_5$	5.44	5.69
C_2H_5	C_2H_5	CH_3	A	50		101–105	0.3	1.4694	$C_{13}H_{21}NO_5$	5.16	5.25
i-C_4H_9	H	H	A	65		135–143	0.3	1.4676	$C_{12}H_{19}NO_5$	5.46	5.37

[a] Based on purified products. [b] Recrystallized from Skelly F. [c] Reported[5]: b.p. 110–115° (0.02 mm.), m.p. 59–62°. [d] Reported[5]: 105–106° (0.02 mm.). [e] Reported[5]: 108–109°. [f] Recrystallized from aqueous ethanol. [g] Recrystallized from ethanol.

TABLE II

ALKYL 3-OXO-1-PYRROLIDINECARBOXYLATES



R_1	R_2	R_4	Yield,[a] %	M.p., °C.	B.p. °C.	Mm.	$n^{25}D$	Formula	Nitrogen, % Calcd.	Found
CH_3	H	H	62	62–64[b]				$C_6H_9NO_3$	9.79	9.87
C_2H_5	H	H	83		151–152	31[c]	1.4668	$C_7H_{11}NO_3$	Known compound	
C_2H_5	H	CH_3	80		138–145	20[d]	1.4597	$C_8H_{13}NO_3$	Known compound	
C_2H_5	H	C_2H_5	85		155–160	33	1.4598	$C_9H_{15}NO_3$	7.56	7.35
C_2H_5	H	C_6H_5	95		118–119	0.2[e]	1.5288	$C_{13}H_{15}NO_3$	Known compound	
C_2H_5	H	4-ClC_6H_4	83	63–65[f]				$C_{13}H_{14}ClNO_3$	5.24	5.18
C_2H_5	H	4-$CH_3OC_6H_4$	79		144–146	0.2		$C_{14}H_{17}NO_4$	5.32	5.18
C_2H_5	CH_3	H	75		126–130	14	1.4598	$C_8H_{13}NO_3$	8.18	8.30
C_2H_5	CH_3	CH	90		130–132	22	1.4546	$C_9H_{15}NO_3$	7.56	7.25
C_2H_5	C_2H_5	H	82		121–122	8	1.4603	$C_9H_{15}NO_3$	7.56	7.48
C_2H_5	C_2H_5	CH_3	85		140–141	20	1.4557	$C_{10}H_{17}NO_3$	7.03	7.04
i-C_4H_9	H	H	80	25–35	154–158	15	1.4620	$C_9H_{15}NO_3$	7.56	7.31

[a] Based on purified products. [b] Recrystallized from isopropyl ether. [c] Reported[5]: 122–132° (12 mm.). [d] Reported[5]: 127–128° (15 mm.). [e] Reported[5] 115–120° (0.02 mm.). [f] Recrystallized from isopropyl ether-Skelly B.

median lethal dose to median hypnotic dose ranged from 1.6 to 2.7. with the exception of No. 5 and 46, whose ratios equalled 6.7 and 7.9, respectively. The corresponding ratio for chloral hydrate was 1.9. The central depression produced by some of these agents was accompanied by muscular twitching and excitement.

Experimental[7]

Diethyl 4-Oxo-1,3-pyrrolidinedicarboxylate.—This compound was prepared in 65% yield according to the procedure of Miyamoto,[6] b.p. 116–120° (0.5 mm.), m.p. 62–64°[8] [reported[6] b.p. 138° (1.3 mm.), m.p. 60–62°].

N-Alkoxycarbonylamino Acid Esters. General Procedure.—A solution of 1 mole of the amino acid ester hydrochloride in 140 ml. of water was cooled in an ice bath and neutralized with 100 ml. of 40% sodium hydroxide. While the temperature was kept below 10°, alkyl chloroformate (1 mole) was added dropwise with stirring in 2 hr. After the mixture was stirred for an additional 30 min., a second 100-ml. portion of 40% sodium hydroxide was added, followed by a thorough extraction with ether. The combined ethereal extracts were dried over anhydrous magnesium sulfate. The ether was removed by distillation. The residue was either distilled under reduced pressure or recrystallized from a suitable solvent.

$ROOCNH—X—COOC_2H_5$

R	X	Yield, %	B.p., (°C.)[a]	mm.[a]	$n^{25}D$	Composition	Nitrogen, % Calcd.	Found
Me	CH_2	65	137–139	17	1.4370	$C_6H_{11}NO_4$	8.68	8.68
Et	CH_2	85	151–153	30[b]	1.4357			
Et	$CH(CH_3)$	82	125–127	15[c]	1.4332			
Et	$CH(C_2H_5)$	80	144–146	22	1.4369	$C_9H_{17}NO_4$	6.89	6.94
i-Bu	CH_2	60	150–154	17	1.4367	$C_9H_{17}NO_4$	6.89	6.61

[a] Colorless oils. [b] Reported[9] b.p. 135° (16 mm.), 126° (12 mm.). [c] Reported[10] m.p. 25°.

α,β-Unsaturated Esters. Ethyl 4-Methoxycinnamate.—The procedure of Bowden and Adkins[11] was modified slightly by substituting sodium hydride-oil suspension for sodium powder. The product was obtained in an 86% yield, b.p. 100–102° (0.08 mm.), m.p. 45–50° from ethanol (reported[11] b.p. 132° (1 mm.), m.p. 48–50°).

Ethyl 4-Chlorocinnamate.—A mixture of 4-chlorobenzaldehyde (100 g., 0.7 mole), malonic acid (150 g., 1.5 moles), piperidine (5 ml.) and pyridine (300 ml.) was heated on a steam bath for 3 hr. After having been refluxed for 30 min., the reaction mixture was cooled and poured into 4 l. of ice–water mixture contain-

(7) All melting points and boiling points are uncorrected. Microanalyses by Schwarzkopf Microanalytical Laboratories, Woodside, New York.

(8) A mixture melting point determination with a sample prepared according to the method of Kuhn and Osswald[5] showed no depression.

(9) E. Fischer and E. Ott, *Ber.*, **36**, 2106 (1903).

(10) E. Fischer and W. Axhausen, *Ann.*, **340**, 128 (1905).

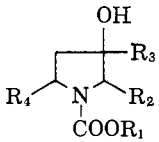
(11) E. Bowden and H. Adkins, *J. Am. Chem. Soc.*, **62**, 2422 (1940).

TABLE III

3-SUBSTITUTED 3-HYDROXY-1-PYRROLIDINECARBOXYLATES

No.	R_1	R_2	R_3	R_4	Proc.	Yield, %[a]	M.p. or B.p. °C.	Mm.
1	CH_3	H	C_6H_5	H	A	58	94–95	
							150–155	0.15
2	C_2H_5	H	C_2H_5	H	A	55	116–118	0.08
3	C_2H_5	H	CH≡C	H	C	50	124–129	0.1
4	C_2H_5	H	CH≡CCH$_2$	H	D	44	110–116	0.7
5	C_2H_5	H	C_6H_5	H	A	76	87–89	
6	C_2H_5	H	4-ClC_6H_4	H	A	62	95–97	
7	C_2H_5	H	4-$CH_3OC_6H_4$	H	A	47	77–79	
8	C_2H_5	H	4-$CH_3C_6H_4$	H	A	38	74–76	
9	C_2H_5	H	2-C_4H_3S[c]	H	A	69	79–81	
10	C_2H_5	H	4-$C_6H_5CH_2OC_6H_4$	H	B	30	126–127	
11	C_2H_5	H	3-ClC_6H_4	H	A	75	112–113	
12	C_2H_5	H	3-$C_6H_5CH_2OC_6H_4$	H	B	43	94–96	
13	C_2H_5	H	4-$ClC_6H_4CH_2$	H	A	70	118–120	
14	C_7	H	4-FC_6H_4	H	A	92	79–82	
15	C_2H_5	H	4-BrC_6H_4	H	A	65	111–113	
							150–160	0.1
16	C_2H_5	H	4-$C_2H_5OC_6H_4$	H	A	46	100–101	
17	C_2H_5	H	C_6H_{11}[e]	H	E	70	130–135	0.1
18	C_2H_5	H	3-ClC_6H_4	CH_3	A	46	113–115	
19	C_2H_5	H	4-FC_6H_4	CH_3	A	55	128–130	
20	C_2H_5	H	C_6H_5	CH_3	A	31	126–127	
21	C_2H_5	H	4-ClC_6H_4	CH_3	A	41	78–90	
22	C_2H_5	H	4-ClC_6H_4	C_2H_5	A	55	117–119	
23	C_2H_5	H	C_6H_5	C_6H_5	A	60	151–153	
24	C_2H_5	H	4-ClC_6H_4	C_6H_5	A	58	127–129	
25	C_2H_5	H	C_6H_5	4-Cl-C_6H_4	A	29	103–105	
26	C_2H_5	H	C_6H_5	4-$CH_3OC_6H_4$	A	66	121–123	
27	C_2H_5	CH_3	C_6H_5	H	A	58	95–97	
28	C_2H_5	CH_3	2-$CH_3C_6H_4$	H	A	41	152–155	0.5
29	C_2H_5	CH_3	4-$CH_3OC_6H_4$	H	A	56	103–105	
30	C_2H_5	CH_3	3-ClC_6H_4	H	A	61	93–95	
31	C_2H_5	CH_3	$C_6H_5CH_2$	H	A	58	145–147	0.15
32	C_2H_5	CH_3	4-ClC_6H_4	H	A	72	93–96	
33	C_2H_5	CH_3	4-$C_6H_5CH_2OC_6H_4$	H	B	69	152–155	
34	C_2H_5	CH_3	3-$C_6H_5CH_2OC_6H_4$	H	B	75	112–115	
35	C_2H_5	CH_3	3,4-$Cl_2C_6H_3$	H	A	81	122–124	
36	C_2H_5	CH_3	4-$C_2H_5OC_6H_4$	H	A	35	91–92	
37	C_2H_5	CH_3	CH≡CCH$_2$	H	D	60	105–115	0.07
38	C_2H_5	CH_3	C_6H_5	CH_3	A	52	130–135	0.2
39	C_2H_5	CH_3	4-ClC_6H_4[h]	CH_3	A	22	120–121	
40	C_2H_5	CH_3	4-ClC_6H_4[h]	CH_3	A	24	145–170	0.15
41	C_2H_5	C_2H_5	C_6H_5	H	A	68	104–106	
42	C_2H_5	C_2H_5	4-$C_6H_5CH_2OC_6H_4$	H	B	47	115–117	
43	C_2H_5	C_2H_5	4-ClC_6H_4	H	A	63	87–89	
44	C_2H_5	C_2H_5	C_6H_5[i]	CH_3	A	39	111–116	
45	C_2H_5	C_2H_5	C_6H_5[i]	CH_3	A	17	80–82	
46	i-C_4H_9	H	C_6H_5	H	A	48	170–172	0.4
47	i-C_4H_9	H	4-ClC_6H_4	H	A	60	195–200	0.2

[a] Based on purified products. [b] Cl: Calcd. 13.15. Found: 12.93. [c] 2-Thienyl. [d] S: Calcd.



Recryst. solvent	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
Acetone							
	$C_{12}H_{15}NO_3$	65.14	65.08	6.83	6.69	6.33	6.37
	$C_9H_{17}NO_3$	57.73	57.42	9.15	9.43	7.48	7.70
	$C_9H_{15}NO_3$	59.00	58.56	7.15	7.20	7.65	7.71
	$C_{10}H_{15}NO_3$	60.89	60.98	7.67	7.55	7.10	7.12
(*i*-Pr)$_2$O	$C_{13}H_{17}NO_3$	66.36	66.38	7.29	7.26	5.95	6.06
(*i*-Pr)$_2$O	$C_{13}H_{16}ClNO_3$[b]	57.87	58.02	5.98	5.81		
(*i*-Pr)$_2$O	$C_{14}H_{19}NO_4$	63.38	63.31	7.22	7.25	5.28	5.59
(*i*-Pr)$_2$O	$C_{14}H_{19}NO_3$	67.45	67.62	7.69	7.63	5.62	5.57
Acetone	$C_{11}H_{15}NO_3S$[d]	54.75	54.81	6.29	6.29		
EtOH-(*i*-Pr)$_2$O	$C_{20}H_{23}NO_4$	70.36	70.67	6.79	6.84	4.10	3.99
(*i*-Pr)$_2$O	$C_{13}H_{16}ClNO_3$	57.87	57.99	5.98	6.08	5.19	5.08
i-PrOH	$C_{20}H_{23}NO_4$	70.36	70.35	6.79	6.68	4.10	3.80
EtOH-(*i*-Pr)$_2$O	$C_{14}H_{18}ClNO_3$	59.26	59.00	6.39	6.14	4.94	4.99
(*i*-Pr)$_2$O	$C_{13}H_{16}FNO_3$	61.64	61.79	6.37	6.33	5.53	5.75
(*i*-Pr)$_2$O	$C_{13}H_{16}BrNO_3$	49.69	49.62	5.14	5.20	4.46	4.33
Skelly B	$C_{15}H_{21}NO_4$	64.50	64.33	7.58	7.51	5.00	4.99
	$C_{13}H_{23}NO_3$	64.70	64.74	9.61	9.52	5.80	5.87
(*i*-Pr)$_2$O	$C_{14}H_{18}ClNO_3$	59.26	59.32	6.39	6.33	4.94	4.77
(*i*-Pr)$_2$O	$C_{14}H_{18}FNO_3$	62.90	63.16	6.79	6.92	5.24	5.34
EtOH	$C_{14}H_{19}NO_3$	67.44	67.23	7.68	7.74	5.62	5.68
(*i*-Pr)$_2$O	$C_{14}H_{18}ClNO_3 \cdot H_2O$	55.72	56.02	6.68	6.72	4.64	4.83
i-PrOH(*i*-Pr)$_2$O	$C_{15}H_{20}ClNO_3$	60.49	60.56	6.77	6.71	4.70	4.70
i-PrOH	$C_{19}H_{21}NO_3$	73.29	73.06	6.80	6.82	4.50	4.59
i-PrOH(*i*-Pr)$_2$O	$C_{19}H_{20}ClNO_3$	66.00	66.07	5.83	5.74	4.05	3.96
(*i*-Pr)$_2$O	$C_{19}H_{20}ClNO_3$	66.00	65.93	5.83	5.93	4.05	4.02
i-PrOH(*i*-Pr)$_2$O	$C_{20}H_{23}NO_4$	70.36	70.51	6.79	6.77	4.10	4.13
(*i*-Pr)$_2$O	$C_{14}H_{19}NO_3$	67.45	67.75	7.68	7.86	5.62	5.44
	$C_{15}H_{21}NO_3$	68.41	68.73	8.04	8.93	5.32	5.14
i-PrOH(*i*-Pr)$_2$O	$C_{15}H_{21}NO_4$	64.49	64.35	7.58	7.65	5.02	4.96
(*i*-Pr)$_2$O	$C_{14}H_{18}ClNO_3$	59.26	59.52	6.39	6.05	4.94	4.67
	$C_{15}H_{21}NO_3$	68.41	68.55	8.04	8.08	5.32	5.52
(*i*-Pr)$_2$O	$C_{14}H_{18}ClNO_3$[g]					4.94	4.97
i-PrOH	$C_{21}H_{25}NO_4$	70.96	71.15	7.09	7.08	3.94	3.92
aq. EtOH	$C_{21}H_{25}NO_4$	70.96	71.20	7.09	7.17	3.94	3.93
(*i*-Pr)$_2$O	$C_{14}H_{17}Cl_2NO_3$	52.84	52.89	5.39	5.57	4.40	4.39
Skelly B	$C_{16}H_{23}NO_4$	65.51	65.63	7.91	7.74	4.78	4.83
	$C_{11}H_{17}NO_3$	62.53	62.46	8.11	7.94	6.63	6.47
	$C_{15}H_{21}NO_3$	68.41	68.65	8.04	8.10	5.32	5.37
(*i*-Pr)$_2$O	$C_{15}H_{20}ClNO_3$	60.50	60.61	6.77	6.88	4.70	4.72
	$C_{15}H_{20}ClNO_3$	60.50	60.79	6.77	6.94	4.70	4.60
(*i*-Pr)$_2$O	$C_{15}H_{21}NO_3$	68.41	68.57	8.04	8.13	5.32	5.14
i-PrOH-(*i*-Pr)$_2$O	$C_{22}H_{27}NO_4$	71.52	71.27	7.37	7.15	3.79	3.81
(*i*-Pr)$_2$O	$C_{15}H_{20}ClNO_3$	60.50	60.38	6.77	6.78	4.70	4.69
(*i*-Pr)$_2$O	$C_{16}H_{23}NO_3$	69.28	69.30	8.36	8.19	5.05	5.00
Hexane	$C_{16}H_{23}NO_3$	69.28	69.13	8.36	8.41	5.05	5.08
	$C_{16}H_{21}NO_3$	68.41	68.40	8.04	8.13	5.32	5.49
	$C_{15}H_{20}ClNO_3$	60.50	60.36	6.77	6.60	4.70	4.91

13.29. Found: 13.17. [e] Cyclohexyl. [f] H_2O: Calcd. 6.35. Found: 6.43. [g] Cl:Calcd. 12.50 Found: 12.55. [h,i] Diastereoisomers.

ing 380 ml. of concd. hydrochloric acid. The 4-chlorocinnamic acid was collected on a filter and washed with water. After recrystallization from 95% ethanol, the acid melted at 249–250° (reported[12], 247°), yield 123.6 g. (97%). A mixture of the acid and 700 ml. of 10% anhydrous ethanolic hydrogen chloride was stirred and refluxed for 20 hr. The residue obtained after removal of ethanol was dissolved in ether. The ethereal solution was washed with 10% sodium hydroxide, dried over anhydrous magnesium sulfate, filtered and concentrated. The residue was distilled under reduced pressure; yield, 128.3 g. (90%), of ethyl 4-chlorocinnamate, b.p. 178–179° (22 mm.) (reported[13] 166° (12 mm.)), $n^{25}D$ 1.5756.

2-Pentenoic Acid.—Propionaldehyde (200 g., 3.4 moles) was added dropwise to a stirred mixture of 312.3 g. (3 moles) of malonic acid, 10 ml. of piperidine and 500 ml. of pyridine. After having been stirred for 24 hr. at room temperature, the mixture was poured into 1 l. of ice containing 650 ml. of concd. hydrochloric acid and extracted with 2 l. of ether. The ethereal solution was dried over anhydrous magnesium sulfate, filtered and the ether was removed by distillation. The residue was distilled under reduced pressure to give 255.6 g. (85%) of 2-pentenoic acid, b.p. 105–107° (20 mm.), [reported[14] 71° (2 mm.), 99° (10 mm.), 108° (17 mm.)], $n^{25}D$ 1.4482.

Ethyl 2-Pentenoate.—A mixture of 1 mole of 2-pentenoic acid, 50 ml. of ethanol, 300 ml. of ethylene dichloride and 3 ml. of concd. sulfuric acid was stirred and refluxed for 15 hr.[15] The cooled mixture was washed successively with water, sodium bicarbonate solution and again with water. The ethylene dichloride solution was dried over anhydrous magnesium sulfate, filtered and concentrated. The residue was fractionated to give a 75% yield of a colorless oil, b.p. 156–158°; [reported[14] 157.6–158° (745 mm.), 48° (11 mm.)] $n^{25}D$ 1.4294.

Alkyl Ethyl 4-Oxo-1,3-pyrrolidinedicarboxylates. A.—N-Alkoxycarbonylamino acid ethyl ester (1 mole) was added dropwise to a stirred suspension of sodium hydride (1 mole) in 1 l. of anhydrous benzene at such a rate as to maintain gentle refluxing. After the addition was completed, the reaction mixture was refluxed for 30 min. A solution of 1 mole of α,β-unsaturated ester in 200 ml. of dry benzene was added dropwise to the hot reaction mixture. After having been refluxed for 3 hr., the mixture was cooled and 335 ml. of 3 *N* hydrochloric acid was added. The benzene layer was separated. The aqueous layer was extracted with chloroform. The combined organic solutions were dried over anhydrous magnesium sulfate and filtered. The residue obtained after concentration of the filtrate was fractionated under reduced pressure.

B.—The sodio derivative of N-alkoxycarbonylamino acid ester (1 mole) was prepared in 2 l. of anhydrous benzene as in Procedure A. A solution of 1 mole of the α,β-unsaturated ester in 500 ml. of anhydrous benzene was added dropwise to the hot reaction mixture. The reaction was completed by refluxing for 4 hr. Ethanol (20 ml.) was added after 2 hr. of refluxing. The reaction mixture was cooled and poured into 3 l. of ice–water. The benzene layer was separated and extracted with 2 l. of water. After being washed with 2 l. of ether, the combined aqueous solutions were acidified with dil. sulfuric acid. The acidic solution was extracted with 4 l. of ether. The ethereal solution was dried over anhydrous

(12) K. C. Pandya and R. B. Pandya, *Proc. Indian Acad. Sci.*, **14A**, 112 (1941); *Chem. Abstr.*, **36**, 1599 (1942).

(13) K. Kindler, *Ann.*, **452**, 99 (1926).

(14) K. v. Auwers, T. Meissner, O. Seydel, and H. Wissebach, *Ann.*, **432**, 46 (1923).

(15) R. O. Clinton and S. C. Laskowski, *J. Am. Chem. Soc.*, **70**, 3135 (1948).

magnesium sulfate, filtered and concentrated. The solid residue was recrystallized from isopropyl alcohol.

Alkyl 3-Oxo-1-pyrrolidinecarboxylates.—A mixture of alkyl ethyl 4-oxo-1,3-pyrrolidinedicarboxylate (1 mole) and 900 ml. of water containing 9 ml. of concd. hydrochloric acid was refluxed for 15 hr. The resulting solution was saturated with sodium chloride and extracted with 750 ml. of chloroform in several portions. The combined extracts were dried over anhydrous magnesium sulfate, filtered and concentrated. The residue was distilled under reduced pressure.

Grignard Reagents.—Grignard reagents were prepared from appropriate halides in the usual manner. Except 3-benzyloxy-1-bromobenzene, all the other halides were known.

3-Benzyloxy-1-bromobenzene.—A mixture of benzyl chloride (36.5 g., 0.29 mole), 3-bromophenol (50.0 g., 0.29 mole), potassium carbonate (40.0 g., 0.29 mole) and acetone (25 ml.) was stirred and refluxed for 5 hr. The mixture was cooled to room temperature, treated with 500 ml. of water and extracted with ether. After being washed successively with 100 ml. of 10% sodium hydroxide and water, the ethereal solution was dried over anhydrous magnesium sulfate. The residue obtained after removal of ether was recrystallized from methanol to give 53.5 g. (78%) of 3-benzyloxy-1-bromobenzene, m.p. 59–63°.

Anal. Calcd. for $C_{13}H_{11}BrO$: C, 59.33; H, 4.21. Found: C, 59.46; H, 4.13.

3-Substituted 3-Hydroxy-1-pyrrolidinecarboxylic Acid Esters. A.—A solution of 0.1 mole of an alkyl 3-oxo-1-pyrrolidinecarboxylate in 50 ml. of anhydrous ether was added dropwise to 100 ml. of an ethereal solution of 0.15 mole of a Grignard reagent. After the addition was completed, the reaction mixture was refluxed for 2–4 hr. The mixture was cooled to room temperature and poured into 400 g. of ice containing 20 g. of ammonium chloride. The ether layer was separated. The aqueous layer was extracted with ether. The combined ethereal solutions were dried over anhydrous magnesium sulfate. The ether was removed by distillation. The residue was either fractionated under reduced pressure or recrystallized from a suitable solvent.

B.—The reaction was carried out similarly to Procedure A, but tetrahydrofuran was used as the solvent in place of ether.

C. Ethyl 3-Ethynyl-3-hydroxy-1-pyrrolidinecarboxylate.—A solution of ethynylmagnesium chloride in tetrahydrofuran was prepared in the following manner. Acetylene gas was bubbled into 150 ml. of tetrahydrofuran at room temperature for 1 hr. The saturated acetylene solution was treated dropwise at room temperature and over a period of 1.5 hr. with a butylmagnesium chloride solution prepared from *n*-butyl chloride (18.5 g., 0.2 mole), magnesium (4.8 g., 0.2 g. atom) and 100 ml. of tetrahydrofuran. During the addition and 15 min. thereafter, the introduction of acetylene was continued. A solution of ethyl 3-oxo-1-pyrrolidinecarboxylate (23.6 g., 0.15 mole) in 50 ml. of tetrahydrofuran was added with stirring over a period of 30 min. to the ethynylmagnesium chloride solution. The reaction mixture was stirred at room temperature for 20 min. and on a steam bath for an additional 30 min. The Grignard complex was decomposed by adding 50 ml. of a saturated ammonium chloride solution. The clear tetrahydrofuran layer was decanted from a viscous mass which was extracted with two 100-ml. portions of ether. The ethereal extracts and the tetrahydrofuran solution were combined. The residue obtained after removal of the solvents was fractionated under reduced pressure to yield 13.7 g. (50%) of product.

D. Ethyl 3-Hydroxy-2-methyl-3-(2-propynyl)-1-pyrrolidinecarboxylate.—A

solution of 2-propynyl bromide (29.7 g., 0.25 mole) in 50 ml. of anhydrous ether was added dropwise to a stirred mixture of 6.1 g. (0.25 atom) of magnesium, 0.06 g. of mercuric chloride and 100 ml. of anhydrous ether. As soon as the reaction initiated, the mixture was maintained at -5 to $-10°$ throughout the addition. After being stirred for an additional hr. at $-5°$, the mixture was treated dropwise over a period of 1 hr. with a solution of ethyl 2-methyl-3-oxo-1-pyrrolidinecarboxylate (34.3 g., 0.2 mole) in 60 ml. of dry benzene, the temperature kept at 0°. To facilitate the stirring a liberal amount (about 50 ml.) of anhydrous ether was added. Stirring was continued for 15 hr. at room temperature. The Grignard complex was decomposed by pouring the mixture into 500 g. of ice containing 25 g. of ammonium chloride. The aqueous layer was separated and extracted with three 200-ml. portions of ether. The organic solution and the ethereal extracts were combined and dried over anhydrous magnesium sulfate. The residue obtained after removal of the solvents was fractionated under reduced pressure to give 21.5 g. (50%) of ethyl 3-hydroxy-2-methyl-3-(2-propynyl)-1-pyrrolidinecarboxylate as a light colored oil. Similarly prepared was ethyl 3-hydroxy-3-(2-propynyl)-1-pyrrolidinecarboxylate in a 32% yield.

E. Ethyl 3-Cyclohexyl-3-hydroxy-1-pyrrolidinecarboxylate.—A solution of 6 g. (0.025 mole) of ethyl 3-hydroxy-3-phenyl-1-pyrrolidinecarboxylate in 100 ml. of ethanol and 2 g. of 5% rhodium-on-alumina were hydrogenated at 3.5 kg./cm.^{2} pressure and at room temperature until the calculated amount of hydrogen had been absorbed. The mixture was filtered, the residue obtained after concentration of the filtrate was distilled under reduced pressure.

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Pyrrolidines. VIII. 3-Acyloxy-3-Aryl-1-Ethyl- and -1-Methylpyrrolidines[1]

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The method of Kuhn and Osswald[5] for the synthesis of ethyl 3-oxo-1-pyrrolidinecarboxylates has been extended for the preparation of 1-acyl-3-pyrrolidones. Reaction of 1-acetyl-3-pyrrolidones and ethyl 3-oxopyrrolidinecarboxylates with arylmagnesium halides yielded respectively 3-aryl-1-acetyl-3-pyrrolidinols and ethyl 3-aryl-3-hydroxy-1-pyrrolidinecarboxylates, which were reduced

(1) Since the completion of this manuscript, another report covering certain 3-acyloxy-3-phenylpyrrolidines has been published [J. F. Cavalla, J. Davoll, M. J. Dean, C. S. Franklin-D. M. Temple, J. Wax, and C. V. Winder, *J. Med. Pharm. Chem.*, **4**, 1 (1961)]. As the synthetic approaches in our work were somewhat different from the published paper, we wish to report our studies in the present paper.