activity will be the progressive increase in van der Waals forces and "distribution effect." As the homologous series is ascended, therefore, the activity should first fall because of factor (1) but there will come a point where factor (2) becomes more significant than factor (1) and at that point activity will begin to increase. This is exactly the pattern of results which was obtained.

# The Synthesis and Antitussive Properties of Some Cyclopentane Derivatives

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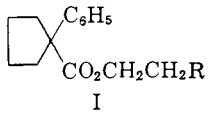
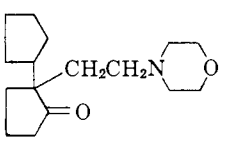
*Received August 13, 1962*

A number of derivatives of 1-hydroxycyclopentane-1-carboxylic acid has been synthesized; these include compounds in which one or both of the functional groups of the hydroxy acid carry basic substituents. The resulting compounds are mono- or diesters or ester-amides. A few compounds derived from 1-aminocyclopentane-1-carboxylic acid also were synthesized. The compounds were tested for antitussive properties in the cat; activity equal to one half of that of codeine is exhibited by several compounds. The relationship between chemical structure and antitussive potency is discussed briefly.

A variety of chemical structures exhibit antitussive activity. Several of the non-narcotic type of antitussive compounds contain a cyclopentane ring, for example, the (2-diethylaminoethoxy)ethyl ester (carbetapentane, Ia) and 2-diethylaminoethyl ester (caramiphen as the ethanedisulfonate salt, Ib) of 1-phenylcyclopentane-1-carboxylic acid. Of the analogs of carbetapentane in which the size of the alicyclic ring only was varied between cyclopropane and cyclohexane, that with the cyclopentane ring was the most active compound.[1] A compound (II) containing two cyclopentane rings has been evaluated.[2] The presence of the cyclopentane ring in these compounds suggested the synthesis of a series of derivatives of 1-hydroxycyclopentane-1-carboxylic acid for examination of their antitussive properties.




I

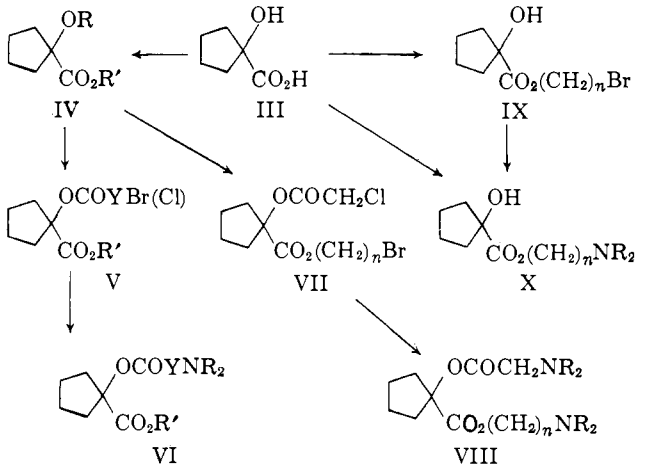



II

a. R = $OCH_2CH_2N(C_5H_5)_2$
b. R = $N(C_2H_5)_2$

Although the starting material, 1-hydroxycyclopentane-1-carboxylic acid, is readily available,[3] relatively little work has been published on its derivatives. The diethylaminoethyl esters of 1-hydroxycyclopentane-1-carboxylic acid and three of its O-acyl derivatives have been prepared[4] and tested for local anesthetic activity. Other simple derivatives of the hydroxy acid have been described[5] but no systematic study has been made of the effect on pharmacological properties of varying the substituent groups.

The present investigation has been concerned with the synthesis of (a) substituted aminoacyl derivatives of the parent hydroxyacid esters, (b) substituted aminoalkyl esters of 1-hydroxycyclopentane-1-carboxylic acid and (c) a series of compounds in which the features of both of these types are combined by preparing substituted aminoacyl derivatives of substituted aminoalkyl 1-hydroxycyclopentane-1-carboxylates. In addition the mono- or bisquaternary derivatives of several of these compounds have been prepared. The work is summarized in the accompanying scheme. A few derivatives of 1-aminocyclopentane-1-carboxylic acid have been prepared and tested in order to compare their properties with those of the corresponding compounds derived from the hydroxy acid.




The starting material for this investigation, 1-hydroxycyclopentane-1-carboxylic acid (III), was prepared by the cyanohydrin synthesis from cyclopentanone by a modification of Tchoubar's method.[3] The esters (IV, R = H, R' = alkyl, aralkyl; IX, $n$ = 2 or 3) were prepared by azeotropic esterification of the acid (III) in benzene with the appropriate alcohol using a little sulfuric acid as catalyst.[6] Yields were about 80–90% (Table I). The hydroxyesters (IV, R = H) were esterified with the appropriate halogeno acid halide in chloroform using pyridine as the acid-binding agent. The haloesters (V, Y = $CH_2$, $CHCH_3$, $CH_2CH_2$. Table I) were treated with various secondary amines

(1) S. Levis, S. Preat, and F. Moyersoons, *Arch. intern. pharmacodynamie*, **103**, 200 (1955).

(2) D. W. Archibald, L. B. Slipp, and S. J. Shane, *Can. Med. Assoc. J.*, **80**, 734 (1959).

(3) B. Tchoubar and C. Collin, *Bull. soc. chim. France*, 680 (1947); B. Tchoubar, *ibid.*, 160 (1949).

(4) R. Giuliano and M. L. Stein, *Il Farmaco* (Pavia), *Ed. sci.*, **11**, 3 (1956).

(5) R. Giuliano and G. Leonardi, *Farm. sci. e tec.* (Pavia), **7**, 29 (1952).

(6) J. Leon, W. F. Barthel, and S. A. Hall, *J. Org. Chem.*, **19**, 490 (1954).

TABLE I

ALKYL 1-HYDROXYCYCLOPENTANE-1-CARBOXYLATES AND THEIR CHLOROACYL DERIVATIVES (IV)

| No. | R' | R | B.p. °C. | B.p. mm. | Yield, % | Formula | Calcd., % C | Calcd., % H | Calcd., % Halogen | Found, % C | Found, % H | Found, % Halogen |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | $C_2H_5$[a] | H | 92–93 | 15 | 79 | $C_8H_{14}O_3$ | | | | | | |
| 2 | $(CH_2)_2C_6H_5$ | H | 131–132 | 1 | 90 | $C_{14}H_{18}O_3$ | 71.7 | 7.8 | | 71.5 | 7.9 | |
| 3 | $(CH_2)_4CH_3$ | H | 123–126 | 13 | 84 | $C_{11}H_{20}O_3$ | 66.0 | 10.1 | | 65.6 | 10.2 | |
| 4 | $(CH_2)_2Br$ | H | 144–148 | 15 | 78 | $C_8H_{13}BrO_3$ | | | 33.7 | | | 33.9 |
| 5 | $(CH_2)_3Br$ | H | 155–165 | 15 | 78 | $C_9H_{15}BrO_3$ | 43.0 | 6.0 | 31.8 | 42.5 | 6.0 | 31.7 |
| 6 | $C_2H_5$ | $COCH_2Cl$ | 93–99 | 0.5 | 66 | $C_{10}H_{15}ClO_4$ | | | 15.1 | | | 15.3 |
| 7 | $(CH_2)_2C_6H_5$ | $COCH_2Cl$ | 170–182 | 1–1.5 | 79 | $C_{16}H_{19}ClO_4$ | | | 11.4 | | | 10.8 |
| 8 | $(CH_2)_4CH_3$ | $COCH_2Cl$ | 113–118 | 0.4 | 68 | $C_{13}H_{21}ClO_4$ | | | 12.8 | | | 13.4 |
| 9 | $(CH_2)_2C_6H_5$ | $COCHClCH_3$ | 142–146 | 0.35 | 79 | $C_{17}H_{21}ClO_4$ | | | 10.9 | | | 10.9 |
| 10 | $(CH_2)_4CH_3$ | $COCHClCH_3$ | 100–115 | 0.25 | 60 | $C_{14}H_{23}ClO_4$ | 57.8 | 8.0 | 12.2 | 57.6 | 8.1 | 12.0 |

[a] Giuliano and Leonardi[5] give b.p. 99° (20 mm.).

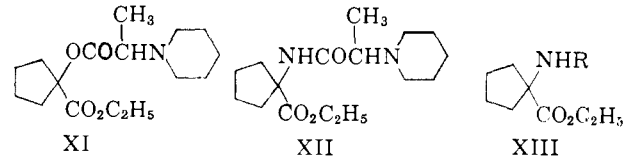
to give the aminoesters (VI) which were isolated as their hydrochlorides (Table II).

The 2-bromoethyl and 3-bromopropyl esters (IX, $n$ = 2 and 3) of the acid (III) were treated with various secondary amines to give the basic esters (X, $n$ = 2 and 3), listed in Table III. Direct isolation of the products as their hydrochlorides avoided the need for purification of the free bases by distillation. In an extension of the work of Giuliano and coworkers,[4,5] similar compounds have been prepared in which the hydroxyl group is acetylated or benzoylated. The starting materials, prepared from the acid (III) and the appropriate acid chloride, were 1-acetoxy- and 1-benzoyloxycyclopentane-1-carboxylic acids. Conversion into the corresponding acid chlorides was followed by treatment with the appropriate substituted amino alcohol or N,N-dialkylaminoalkylamine to give the desired esters or amides,[4,5] which usually were isolated as the citrates (Table IV).

An extension of the above work led to compounds having the same substituted aminoalkyl chain on both functional groups of the hydroxy acid (III). For this purpose 2-bromoethyl 1-chloroacetoxycyclopentane-1-carboxylate (VII, $n$ = 2) and 3-bromopropyl 1-chloroacetoxycyclopentane-1-carboxylate (VII, $n$ = 3) were treated with an excess of various amines and the resulting aminoalkyl 1-aminoacyloxycyclopentane-1-carboxylates (VIII) were isolated as the dihydrochlorides (Table V). Some of the tertiary aminoesters were converted into the corresponding methiodides.

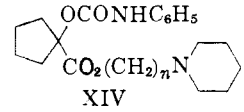
The interesting pharmacological properties of ethyl 1-(2-piperidinopropionoxy)cyclopentane-1-carboxylate (XI, Table II-27) indicated the desirability of preparing the corresponding propionamide (XII). 1-Aminocyclopentane-1-carboxylic acid was prepared from cyclopentanone by the Bucherer hydantoin synthesis.[7] Ethyl 1-aminocyclopentane-1-carboxylate[8] (XIII, R = H) was treated with 2-chloropropionyl chloride, and this amide (XIII, R = $COCHClCH_3$) was condensed with piperidine to give the desired ethyl 1-(2-piperidinopropionamido)cyclopentane-1-carboxylate (XII, Table VI-96) as its hydrochloride. The corresponding 2-morpholino- and 2-diethylaminopropionamido esters also were prepared (Table VI).

For the purposes of further comparison, the quaternary methiodide of ethyl 1-(2-piperidinopropionamido)-cyclopentane-1-carboxylate has been prepared. Table



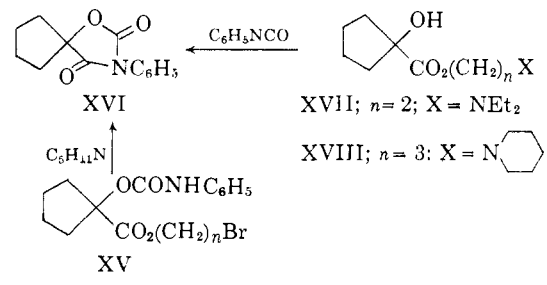

VI also includes the N-*p*-nitrobenzoyl derivative of ethyl 1-aminocyclopentane-1-carboxylate, and the N-*p*-aminobenzoyl derivative prepared from it by catalytic reduction.

Attempts were made to synthesize substituted aminoalkyl esters of 1-phenylcarbamoyloxycyclopentane-1-carboxylic acid. The 2-bromoethyl and 3-bromopropyl esters (IX) of the hydroxy acid were treated with phenyl isocyanate to give the corresponding N-phenylcarbamates of the general formula (XV). On at-




tempting to condense these products with piperidine to prepare the piperidinoalkyl 1-phenylcarbamoyloxycyclopentane-1-carboxylates (XIV, $n$ = 2 and 3) however, the same compound was isolated in each case and was shown to be 3-phenyl-1-oxa-3-aza-spiro[4.4]nonane-2,4-dione (XVI). This type of ring closure is normally brought about by heating the phenylcarbamates of $\alpha$-hydroxy esters alone or in the presence of sodium.[9]

An alternative route to the desired compounds was sought. The 2-diethylaminoethyl[4] and 3-piperidinopropyl esters (XVII and XVIII) of the acid (III) were treated with phenyl isocyanate and in each case the same spiro compound (XVI) was isolated as before, thus confirming the structure.




(7) R. N. MacDonald, U. S. Patent 2,560,584, *Chem. Abstr.*, **46**, 3573 (1952); H. R. Henze and R. J. Speer, *J. Am. Chem. Soc.*, **64**, 522 (1942).

(8) T. A. Connors and W. C. J. Ross, *J. Chem. Soc.*, 2119 (1960).

(9) J. W. Clark-Lewis, *Chem. Revs.*, **58**, 63 (1958).

TABLE II

AMINOACYL DERIVATIVES OF ALKYL 1-HYDROXYCYCLOPENTANE-1-CARBOXYLATES (IV)

| No. | R' | R | M.p., °C. | Formula | Calcd., % C | Calcd., % H | Calcd., % Cl | Found, % C | Found, % H | Found, % Cl |
|---|---|---|---|---|---|---|---|---|---|---|
| 11 | $C_2H_5$ | Piperidinoacetyl | 92–93.5 | $C_{15}H_{25}NO_4 \cdot HCl$[a] | | | 11.1 | | | 10.6 |
| 12 | | | 122–123 | $C_{15}H_{25}NO_4 \cdot CH_3I$[b] | | | | | | |
| 13 | $C_2H_5$ | Morpholinoacetyl | 164–165 | $C_{14}H_{23}NO_5 \cdot HCl$ | 52.3 | 7.5 | 11.0 | 52.3 | 7.5 | 11.0 |
| 14 | | | 143–144 | $C_{14}N_{23}NO_5 \cdot CH_3I$[c] | | | | | | |
| 15 | $C_2H_5$ | N-1,2,5,6-Tetrahydropyridylacetyl | 118–119 | $C_{15}H_{23}NO_4 \cdot HCl$ | 56.7 | 7.6 | 11.2 | 56.5 | 7.6 | 11.2 |
| 16 | $C_2H_5$ | 4-Methylpiperazinoacetyl | 186–188 | $C_{15}H_{26}N_2O_4 \cdot 2HCl \cdot 2H_2O$ | 44.2 | 7.9 | 17.4 | 44.5 | 7.6 | 16.9 |
| 17 | $C_2H_5$ | 4-(2-Hydroxyethyl)-piperazinoacetyl | 195–198 | $C_{16}H_{28}N_2O_5 \cdot 2HCl$ | 47.9 | 7.5 | 17.7 | 47.9 | 7.6 | 17.4 |
| 18 | $C_2H_5$ | 2-Methylpiperidinoacetyl | 115.5–116.5 | $C_{16}H_{27}NO_4 \cdot C_6H_8O_7$[d] | 54.0 | 7.2 | | 53.7 | 7.2 | |
| 19 | $CH_2CH_2C_6H_5$ | Piperidinoacetyl | 152–154 | $C_{21}H_{29}NO_4 \cdot HCl$ | 63.7 | 7.6 | 9.0 | 63.5 | 7.7 | 8.9 |
| 20 | | | 124.5–125.5 | $C_{21}H_{29}NO_4 \cdot CH_3I$[e] | | | | | | |
| 21 | $CH_2CH_2C_6H_5$ | Morpholinoacetyl | 152–154 | $C_{20}H_{27}NO_5 \cdot HCl$ | 60.4 | 7.1 | 8.9 | 60.6 | 7.2 | 9.1 |
| 22 | $CH_2CH_2C_6H_5$ | N-1,2,5,6-Tetrahydropyridylacetyl | 132–134 | $C_{21}H_{27}NO_4 \cdot HCl$ | 64.0 | 7.2 | 9.0 | 64.1 | 7.3 | 9.1 |
| 23 | $CH_2CH_2C_6H_5$ | 4-Methylpiperazinoacetyl | 205–207 | $C_{21}H_{30}N_2O_4 \cdot 2HCl$ | 56.4 | 7.2 | 15.9 | 56.3 | 7.4 | 15.9 |
| 24 | $CH_2CH_2C_6H_5$ | 4-(2-Hydroxyethyl)-piperazinoacetyl | 189–191 | $C_{22}H_{32}N_2O_5 \cdot 2HCl$ | 55.3 | 7.2 | 14.9 | 54.8 | 7.2 | 14.9 |
| 25 | $(CH_2)_4CH_3$ | 4-(2-Hydroxyethyl)-piperazinoacetyl | 192–193 | $C_{19}H_{34}N_2O_5 \cdot 2HCl$ | 51.5 | 8.2 | 16.0 | 50.9 | 7.9 | 16.1 |
| 26 | $(CH_2)_4CH_3$ | Morpholinoacetyl | 152–153 | $C_{17}H_{29}NO_5 \cdot HCl$ | 56.1 | 8.3 | 9.7 | 55.8 | 8.2 | 10.0 |
| 27 | $C_2H_5$ | 2-Piperidinopropionyl | 161–164 | $C_{16}H_{27}NO_4 \cdot HCl$ | 57.6 | 8.5 | 10.6 | 57.1 | 8.4 | 10.5 |
| 28 | | | 151–153 | $C_{16}H_{27}NO_4 \cdot CH_3I$[f] | | | | | | |
| 29 | $C_2H_5$ | 2-Piperidinopropionyl | 113–114 | $C_{16}H_{27}NO_4 \cdot C_4H_4O_4$[g] | 58.1 | 7.6 | | 57.9 | 7.5 | |
| 30 | $C_2H_5$ | 2-Morpholinopropionyl | 157–158 | $C_{15}H_{25}NO_5 \cdot HCl$ | 53.7 | 7.8 | 10.6 | 53.7 | 7.9 | 10.4 |
| 31 | $C_2H_5$ | 2-(N-1,2,5,6-Tetrahydropyridyl)propionyl | 140.5–141.5 | $C_{16}H_{25}NO_4 \cdot HCl$ | 57.9 | 7.9 | 10.7 | 57.8 | 8.0 | 10.8 |
| 32 | $C_2H_5$ | 2-(4-Methylpiperidino)-propionyl | 156–157 | $C_{17}H_{29}NO_4 \cdot HCl$ | 58.7 | 8.7 | 10.2 | 58.4 | 8.6 | 10.4 |
| 33 | $C_2H_5$ | 2-(4-Methylpiperazino)-propionyl | 192-195 | $C_{16}H_{28}N_2O_4 \cdot 2HCl$ | 49.9 | 7.9 | 18.4 | 49.9 | 8.0 | 18.3 |
| 34 | $C_2H_5$ | 2-Hexamethyleneimino-propionyl | 103-105 | $C_{17}H_{29}NO_4 \cdot HCl$[h] | | | 10.2 | | | 10.3 |
| 35 | $C_2H_5$ | 2-(4-(2-Hydroxyethyl)-piperazino)propionyl | 202–203 | $C_{17}H_{30}N_2O_5 \cdot 2HCl$ | 49.2 | 7.8 | 17.1 | 49.0 | 7.8 | 17.3 |
| 36 | $CH_2CH_2C_6H_5$ | 2-Piperidinopropionyl | 125–127 | $C_{22}H_{31}NO_4 \cdot HCl$ | 64.4 | 7.9 | 8.7 | 64.6 | 8.0 | 8.5 |
| 37 | | | 145.5–146.5 | $C_{22}H_{31}NO_4 \cdot CH_3I$[i] | | | | | | |
| 38 | $CH_2CH_2C_6H_5$ | 2-Morpholinopropionyl | 137–138 | $C_{21}H_{29}NO_5 \cdot HCl$ | 61.2 | 7.3 | 8.6 | 61.0 | 7.2 | 8.7 |
| 39 | $CH_2CH_2C_6H_5$ | 2-Pyrrolidinopropionyl | 126.5–128.5 | $C_{21}H_{29}NO_4 \cdot HCl$ | 63.7 | 7.6 | 9.0 | 63.5 | 7.5 | 9.1 |
| 40 | $CH_2CH_2C_6H_5$ | 2-(4-Methylpiperazino)-propionyl | 171–173 | $C_{22}H_{32}N_2O_4 \cdot 2HCl$[j] | | | 15.4 | | | 14.9 |
| 41 | $CH_2CH_2C_6H_5$ | 2-(4-(2-Hydroxyethyl)-piperazino)propionyl | 191–192 | $C_{23}H_{34}N_2O_5 \cdot 2HCl$ | 56.2 | 7.4 | 14.4 | 55.9 | 7.5 | 14.4 |
| 42 | $CH_2CH_2C_6H_5$ | 2-(3-Methylpiperidino)-propionyl | 108–110 | $C_{23}H_{33}NO_4 \cdot HCl$ | 65.1 | 8.1 | 8.4 | 64.6 | 8.2 | 8.4 |
| 43 | $CH_2CH_2C_6H_5$ | 2-(2,6-Dimethylmorpholino)-propionyl | 135.5–137 | $C_{23}H_{33}NO_5 \cdot HCl$ | 62.8 | 7.8 | 8.1 | 62.1 | 7.6 | 8.4 |
| 44 | $(CH_2)_4CH_3$ | 2-Piperidinopropionyl | 118–120 | $C_{19}H_{33}NO_4 \cdot HCl$ | 60.7 | 9.1 | 9.4 | 60.9 | 9.4 | 9.6 |
| 45 | | | 118.5–120 | $C_{19}H_{33}NO_4 \cdot CH_3I$[k] | | | | | | |
| 46 | $(CH_2)_4CH_3$ | 2-Morpholinopropionyl | 145.5–146.5 | $C_{18}H_{31}NO_5 \cdot HCl$ | 57.2 | 8.6 | 9.4 | 57.2 | 8.7 | 9.5 |
| 47 | $(CH_2)_4CH_3$ | 2-(4-Methylpiperazino)-propionyl | 179–182 | $C_{19}H_{34}N_2O_4 \cdot 2HCl$ | 53.4 | 8.5 | 16.6 | 52.9 | 8.5 | 16.5 |
| 48 | $(CH_2)_4CH_3$ | 2-(4-(2-Hydroxyethyl)-piperazino)propionyl | 178–180 | $C_{20}H_{36}N_2O_5 \cdot 2HCl$ | 52.5 | 8.4 | 15.5 | 51.9 | 8.8 | 15.4 |
| 49 | $C_2H_5$ | 3-Piperidinopropionyl | 182–183 | $C_{16}H_{27}NO_4 \cdot HCl$ | 57.6 | 8.5 | 10.6 | 57.8 | 8.6 | 10.7 |
| 50 | $C_2H_5$ | 3-Morpholinopropionyl | 195–196 | $C_{15}H_{25}NO_5 \cdot HCl$ | 53.7 | 7.8 | 10.6 | 53.6 | 7.9 | 10.8 |
| 51 | | | 131–132 | $C_{15}H_{25}NO_5 \cdot CH_3I$[l] | | | | | | |
| 52 | $C_2H_5$ | 3-(N-1,2,5,6-Tetrahydropyridyl)propionyl | 138–139 | $C_{16}H_{25}NO_4 \cdot HCl$ | 57.9 | 7.9 | 10.7 | 58.0 | 8.0 | 11.2 |
| 53 | $C_2H_5$ | 3-(4-Methylpiperazino)-propionyl | 216–217 | $C_{16}H_{28}N_2O_4 \cdot 2HCl \cdot H_2O$ | 47.6 | 8.0 | 17.6 | 47.5 | 7.7 | 17.6 |
| 54 | $C_2H_5$ | 3-(4-(2-Hydroxyethyl)-piperazino)propionyl | 213–214 | $C_{17}H_{30}N_2O_5 \cdot 2HCl$ | 49.2 | 7.8 | 17.1 | 48.9 | 7.8 | 17.1 |
| 55 | $CH_2CH_2C_6H_5$ | 3-Piperidinopropionyl | 135–136 | $C_{22}H_{31}NO_4 \cdot HCl$ | 64.4 | 7.9 | 8.7 | 63.9 | 8.0 | 8.8 |
| 56 | $CH_2CH_2C_6H_5$ | 3-Morpholinopropionyl | 155–156 | $C_{21}H_{29}NO_5 \cdot HCl$ | 61.2 | 7.3 | 8.6 | 61.1 | 7.4 | 8.6 |
| 57 | $C_2H_5$ | 2-Piperidinobutyryl | 117–118.5 | $C_{17}H_{29}NO_4 \cdot HCl$ | 58.7 | 8.7 | 10.2 | 58.7 | 8.7 | 10.2 |
| 58 | $C_2H_5$ | 2-Piperidinobutyryl | 136-137 | $C_{17}H_{29}NO_4 \cdot CH_3I$[m] | 47.7 | 7.1 | | 47.8 | 6.8 | |

TABLE II (*continued*)

| No. | R' | R | M.p., °C. | Formula | Calcd., % C | H | Cl | Found, % C | H | Cl |
|---|---|---|---|---|---|---|---|---|---|---|
| 59 | $C_2H_5$ | 2-Morpholinobutyryl | 124.5–125.5 | $C_{16}H_{27}NO_5 \cdot HCl$ | 54.9 | 8.1 | 10.1 | 55.4 | 8.2 | 10.1 |
| 60 | $C_2H_5$ | 2-(N-1,2,5,6-Tetrahydropyridyl)butyryl | 90–93 | $C_{17}H_{27}NO_4 \cdot HCl$ | 59.0 | 8.2 | 10.3 | 58.9 | 8.2 | 10.3 |
| 61 | $C_2H_5$ | 2-(4-Methylpiperazino)-butyryl | 221–222 | $C_{17}H_{30}N_2O_4 \cdot 2HCl$ | 51.1 | 8.1 | 17.8 | 51.0 | 7.8 | 17.7 |
| 62 | $C_2H_5$ | 2-(4-(2-Hydroxyethyl)-piperazino)butyryl | 188–190 | $C_{18}H_{32}N_2O_5 \cdot 2HCl$ | 50.4 | 8.0 | 16.5 | 50.0 | 7.9 | 16.4 |

[a] *Anal.* Calcd.: N, 4.4. Found: N, 4.1. [b] *Anal.* Calcd.: I, 29.8. Found: I, 29.8. [c] *Anal.* Calcd.: I, 29.8. Found: I, 29.9. [d] Citrate. *Anal.* Calcd.: N, 2.9. Found: N, 3.0. [e] *Anal.* Calcd.: I, 25.3. Found: I, 25.4. [f] *Anal.* Calcd.: I, 28.9. Found: I, 28.5. [g] Maleate. [h] *Anal.* Calcd.: N, 4.0. Found: N, 4.2. [i] *Anal.* Calcd.: I, 24.6. Found: I, 25.0. [j] *Anal.* Calcd.: N, 6.1. Found: N, 5.9. [k] *Anal.* Calcd.: I, 26.4. Found: I, 26.5. [l] *Anal.* Calcd.: I, 28.8. Found: I, 29.2. [m] *Anal.* Calcd.: I, 28.0. Found: I, 28.0.

TABLE III. AMINOALKYL 1-HYDROXYCYCLOPENTANE-1-CARBOXYLATES (X)

| No. | *n* | $NR_2$ | M.p., °C. | Formula | Calcd., % C | H | Cl | Found, % C | H | Cl |
|---|---|---|---|---|---|---|---|---|---|---|
| 63 | 2 | Morpholino | 222–224 | $C_{12}H_{21}NO_4 \cdot HCl$ | 51.5 | 7.9 | 12.7 | 51.6 | 8.0 | 12.7 |
| 64 | 2 | Piperidino | 226–228 | $C_{13}H_{23}NO_3 \cdot HCl$ | 56.2 | 8.7 | 12.8 | 56.2 | 8.8 | 12.8 |
| 65 | 3 | Piperidino | 185–187 | $C_{14}H_{25}NO_3 \cdot HCl$ | 57.6 | 9.0 | 12.2 | 57.7 | 8.9 | 12.3 |
| 66 | | | 103–105 | $C_{14}H_{25}NO_3 \cdot CH_3I$[a] | 45.4 | 7.1 | | 45.7 | 7.2 | |
| 67 | 3 | Morpholino | 172–173 | $C_{13}H_{23}NO_4 \cdot HCl$ | 53.1 | 8.2 | 12.1 | 52.5 | 8.0 | 12.3 |
| 68 | 3 | N-1,2,5,6-Tetrahydropyridyl | 158–160 | $C_{14}H_{23}NO_3 \cdot HCl$ | 58.0 | 8.3 | 12.2 | 58.1 | 8.6 | 12.4 |
| 69 | | | 129–131 | $C_{14}H_{23}NO_3 \cdot CH_3I$[b] | 45.6 | 6.6 | | 45.8 | 7.0 | |
| 70 | 3 | Pyrrolidino | 151–154 | $C_{13}H_{23}NO_3 \cdot HCl$ | 56.2 | 8.7 | 12.8 | 56.6 | 8.8 | 13.0 |
| 71 | | | 94–96 | $C_{13}H_{23}NO_3 \cdot CH_3I$[c] | 43.9 | 6.8 | | 43.7 | 7.0 | |
| 72 | 3 | Hexamethyleneimino | 183–185 | $C_{15}H_{27}NO_3 \cdot HCl$ | 58.9 | 9.2 | 11.6 | 59.1 | 9.1 | 12.0 |
| 73 | | | 90–91 | $C_{15}H_{27}NO_3 \cdot CH_3I$[d] | 46.7 | 7.4 | | 46.9 | 7.4 | |

[a] *Anal.* Calcd.: I, 32.0. Found: I, 31.9. [b] *Anal.* Calcd.: I, 32.1. Found: I, 32.6. [c] *Anal.* Calcd.: I, 33.1. Found: I, 33.2. [d] *Anal.* Calcd.: I, 30.8. Found: I, 30.2.

TABLE IV

1-ACETOXY- AND 1-BENZOYLOXYCYCLOPENTANE-1-CARBOXYLIC ACID DERIVATIVES: $C_5H_8$(OCOR)(COR')

| No. | R | R' | M.p., °C. | Formula | Calcd., % C | H | N | Found, % C | H | N |
|---|---|---|---|---|---|---|---|---|---|---|
| 74 | $C_6H_5$ | OH | 130–132 | $C_{13}H_{14}O_4$ | 66.7 | 6.0 | | 66.7 | 6.1 | |
| 75 | $CH_3$ | 2-Morpholinoethoxy | 153–154 | $C_{14}H_{23}NO_5 \cdot HCl$[a] | 52.3 | 7.5 | | 52.2 | 7.5 | |
| 76 | $CH_3$ | $NH(CH_2)_3N(C_2H_5)_2$ | 84–85 | $C_{15}H_{28}N_2O_3 \cdot C_6H_8O_7$[b] | 52.9 | 7.6 | 5.9 | 52.6 | 7.6 | 5.8 |
| 77 | $CH_3$ | $OCH_2CH_2N(C_2H_5)_2$ | 85–86[c] | $C_{14}H_{25}NO_4 \cdot C_6H_8O_7$[b] | 51.8 | 7.2 | 3.0 | 52.0 | 7.2 | 3.0 |
| 78 | $CH_3$ | $OCH_2CH_2N(CH_3)_2$ | 99–100 | $C_{12}H_{21}NO_4 \cdot C_6H_8O_7$[b] | 49.7 | 6.7 | 3.2 | 49.6 | 6.7 | 3.4 |
| 79 | $C_6H_5$ | $NH(CH_2)_3N(C_2H_5)_2$ | 83–85 | $C_{20}H_{30}N_2O_3 \cdot C_6H_8O_7 \cdot H_2O$[d] | 56.1 | 7.2 | 5.0 | 56.0 | 7.2 | 5.0 |
| 80 | $C_6H_5$ | $OCH_2CH_2N(C_2H_5)_2$ | 100–102.5 | $C_{19}H_{27}NO_4 \cdot C_6H_8O_7 \cdot H_2O$[d] | 55.2 | 6.9 | 2.6 | 54.7 | 6.9 | 3.0 |
| 81 | $C_6H_5$ | $(OCH_2CH_2)_2N(C_2H_5)_2$ | 74.5–75 | $C_{21}H_{31}NO_5 \cdot C_6H_8O_7 \cdot H_2O$[d] | 55.2 | 7.0 | 2.4 | 54.7 | 6.9 | 2.7 |

[a] *Anal.* Calcd.: Cl, 11.0. Found: Cl, 11.0. [b] Citrate. [c] Giuliano and Leonardi[5] give free base b.p. 147° (10 mm.). [d] Citrate monohydrate.

TABLE V. AMINOALKYL 1-AMINOACYLOXYCYCLOPENTANE-1-CARBOXYLATES (VIII)

| No. | *n* | $NR_2$ | M.p., °C. | Formula | Calcd., % C | H | Cl | Found, % C | H | Cl |
|---|---|---|---|---|---|---|---|---|---|---|
| 82 | 2 | Piperidino | 188–190 | $C_{20}H_{34}N_2O_4 \cdot 2HCl \cdot H_2O$ | 52.5 | 8.4 | 15.5 | 52.5 | 8.2 | 15.5 |
| 83 | | | 181–183 | $C_{20}H_{34}N_2O_4 \cdot 2CH_3I$[a] | 40.6 | 6.2 | | 40.1 | 6.0 | |
| 84 | 2 | N-1,2,5,6-Tetrahydropyridyl | 133.5–135 | $C_{20}H_{30}N_2O_4 \cdot 2HCl \cdot 2H_2O$ | 51.0 | 7.7 | 15.0 | 51.0 | 7.4 | 15.4 |
| 85 | | | 180–182 | $C_{20}H_{30}N_2O_4 \cdot 2CH_3I$[b] | 40.9 | 5.6 | | 40.8 | 5.8 | |
| 86 | 3 | Piperidino | 230–232 | $C_{21}H_{36}N_2O_4 \cdot 2HCl \cdot H_2O$ | 53.5 | 8.6 | 15.0 | 53.7 | 8.8 | 15.0 |
| 87 | | | 189–190 | $C_{21}H_{36}N_2O_4 \cdot 2CH_3I$[c] | 41.6 | 6.4 | | 41.9 | 6.2 | |
| 88 | 3 | N-1,2,5,6-Tetrahydropyridyl | 221–222 | $C_{21}H_{32}N_2O_4 \cdot 2HCl \cdot H_2O$ | 54.0 | 7.8 | 15.2 | 54.4 | 7.5 | 15.4 |
| 89 | | | 204–205 | $C_{21}H_{32}N_2O_4 \cdot 2CH_3I$[d] | 41.8 | 5.8 | | 41.9 | 5.9 | |
| 90 | 3 | Morpholino | 230–231 | $C_{19}H_{32}N_2O_6 \cdot 2HCl$ | 49.9 | 7.5 | 15.5 | 49.6 | 8.0 | 15.4 |
| 91 | 3 | Pyrrolidino | 192–194 | $C_{19}H_{32}N_2O_4 \cdot 2HCl \cdot 2H_2O$ | 49.5 | 8.3 | 15.4 | 49.1 | 7.9 | 15.7 |
| 92 | | | 110–116 | $C_{19}H_{32}N_2O_4 \cdot 2CH_3I$[e] | | | | | | |
| 93 | 3 | Hexamethyleneimino | 206–209 | $C_{23}H_{40}N_2O_4 \cdot 2HCl$ | 57.4 | 8.8 | 14.7 | 57.4 | 8.8 | 14.7 |
| 94 | | | 196–197 | $C_{23}H_{40}N_2O_4 \cdot 2CH_3I$[f] | 43.1 | 6.7 | | 43.3 | 6.9 | |

[a] *Anal.* Calcd.: I, 39.0. Found: I, 38.6. [b] *Anal.* Calcd.: I, 39.3. Found: I, 38.8. [c] *Anal.* Calcd.: I, 38.2. Found: I, 38.1. [d] *Anal.* Calcd.: I, 38.4. Found: I, 38.1. [e] *Anal.* Calcd.: I, 39.9; N, 4.1. Found: I, 39.0; N, 4.3. [f] *Anal.* Calcd.: N, 4.0. Found: N, 3.9.

TABLE VI

DERIVATIVES OF ETHYL 1-AMINOCYCLOPENTANE-1-CARBOXYLATE (XIII)

| No. | R | M.p., °C. | Formula | Calcd., % | | | Found, % | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Cl | | N | Cl | | N |
| 95 | $COCH(CH_3)Cl$ | B.p. 162–165° (14 mm.) M.p. 62–64 | $C_{11}H_{18}ClNO_3$ | 14.3 | | 5.7 | 14.3 | | 5.6 |
| 96 | 2-Piperidinopropionyl | 156–158 | $C_{16}H_{28}N_2O_3 \cdot HCl$ | 10.7 | | 8.4 | 10.7 | | 8.4 |
| 97 | | 188–190 | $C_{16}H_{28}N_2O_3 \cdot CH_3I$[a] | | | 6.4 | | | 6.3 |
| 98 | 2-Morpholinopropionyl | 138-142 | $C_{15}H_{26}N_2O_4 \cdot HCl$ | 10.6 | | 8.4 | 10.6 | | 8.3 |
| 99 | $COCH(CH_3)N(C_2H_5)_2$ | 175–176 | $C_{15}H_{28}N_2O_3 \cdot HCl$ | 11.1 | | 8.7 | 11.5 | | 8.8 |
| | | | | C | H | N | C | H | N |
| 100 | $p$-$COC_6H_4NO_2$ | 126–127 | $C_{15}H_{18}N_2O_5$ | 58.8 | 5.9 | 9.2 | 58.6 | 5.8 | 9.2 |
| 101 | $p$-$COC_6H_4NH_2$ | 190–192 dec. | $C_{15}H_{20}N_2O_3 \cdot HCl$[b] | 57.6 | 6.8 | 9.0 | 57.0 | 6.8 | 8.9 |

[a] *Anal.* Calcd.: I, 29.0. Found: I, 28.5. [b] *Anal.* Calcd.: Cl, 11.3. Found: Cl, 11.4.

## Pharmacological Results

**Antitussive Testing.**—Cats of either sex were lightly anesthetized with 6% pentobarbitone sodium, 45 mg./kg. intraperitoneally. The trachea was then cannulated with a short polythene tube; the carotid artery was connected to a mercury manometer for recording the blood pressure. Injections were made intravenously in the femoral vein. Coughs were recorded on a smoked paper kymograph by a lightly sprung lever attached by a cotton thread to the skin just below the sternum. Three methods of cough production were used—electrical, mechanical and chemical. The electrical method was that described by Domenjoz[10] in which the superior laryngeal nerve was stimulated by means of a constant-current square-wave stimulator. The mechanical method consisted of tickling the tracheal mucosa by means of a thin polythene tube passed in and out of the trachea two or three times. In our experience, however, a modification of the method of Stefko and Denzel,[11] using ammonia as the tussigen, gave the most consistent responses and was most frequently used. In this test, ammonia vapor from a flask containing 7% ammonia was led into the respiratory system by means of a three-way tap connecting the flask to the tracheal cannula. The cat was allowed to inhale ammonia vapor for one inspiration; the cough usually commenced immediately afterward. The cough stimuli were applied every 3 min. until three or four control cough responses of similar intensity and duration were obtained. The test drug then was administered intravenously and cough stimuli were repeated at similar intervals until the cough response returned to normal. Each animal could normally be used to compare the efficacy of several drugs. Codeine was used as the standard antitussive preparation in these comparisons.

Table VII lists those compounds which were found to have antitussive activity. None of the compounds was as active as codeine, but several, designated as ++ in Table VII, had an activity approximately one half that of codeine. Those compounds not listed in Table VII were tested and found to be inactive at an intravenous dose of 4 mg./kg. (chemical method) or 10 mg./kg. (mechanical and electrical methods).

Ethyl 1-(2-piperidinopropionoxy)cyclopentane-1-carboxylate hydrochloride (27) was one of the most active and least toxic compounds, $LD_{50}$ in mice 300 mg./kg. after intravenous injection, and 3000 mg./kg. after oral administration. Its activity also was established, using the chemical method, after intraduodenal administration of 10 mg./kg.

## Structure–Activity Relationships

From a comparison of the antitussive properties of the more active members of the present series of compounds (Table VII) with their chemical structures (Tables II, III, IV, V, and VI) certain patterns of activity emerge.

(10) R. Domenjoz, *Arch. exp. Path. Pharmakol.*, **215**, 19 (1952).

(11) P. L. Stefko and J. Denzel, *J. Pharmacol. Exptl. Therap.*, **119**, 185 (1957).

TABLE VII

ANTITUSSIVE TESTS

M = Mechanical; E = Electrical; C = Chemical

| Compound | Test method | Activity | Compound | Test method | Activity |
|---|---|---|---|---|---|
| Codeine | M, E, C | +++ | 41 | C | + |
| Pholcodine | M. E | +++ | 44 | C | ++ |
| Dihydrocodeine | M, E | +++ | 45 | C | + |
| 4 | C | + | 46 | C | ++ |
| 8 | C | + | 47 | C | + |
| 10 | C | + | 49 | C | + |
| 11 | M, E | + | 52 | C | + |
| 13 | M, E | + | 53 | C | + |
| 17 | M, E | + | 55 | C | + |
| 19 | C | ++ | 56 | C | + |
| 20 | C | ++ | 57 | C | + |
| 25 | C | + | 58 | C | + |
| 27 | C | ++ | 59 | C | + |
| 28 | C | ++ | 65 | C | + |
| 29 | C | ++ | 72 | C | + |
| 31 | C | + | 80 | M, E | + |
| 32 | C | + | 81 | C | + |
| 34 | C | + | 83 | C | ++ |
| 36 | C | ++ | 87 | C | ++ |
| 37 | C | + | 93 | C | + |
| 38 | C | + | 96 | C | + |
| 39 | C | ++ | 99 | C | + |
| 40 | C | + | 101 | C | + |

TABLE VIII

ACTIVITY CODE

| Activity | Mechanical (M) Dose(mg./kg. i.v.) for Suppression | | Electrical (E) Dose(mg./kg. i.v.) for Suppression | | Chemical (C) Dose(mg./kg. i.v.) for Suppression | |
|---|---|---|---|---|---|---|
| | Complete | Partial | Complete | Partial | Complete | Partial |
| +++ | 4 | | 2 | | 2 | |
| ++ | | 4 | | 4 | 4 | |
| + | | 10 | | 10 | | 4 |

When the amine function only is varied, the greatest antitussive activity is exhibited by piperidino compounds; one pyrrolidino and one morpholino derivative (39 and 46, Table II), however, have activities comparable with that of the piperidino compounds. The simplest compound to have pronounced activity is the piperidinoacetate (19); in the homologous 2-aminopropionate series, not only is this activity maintained in the corresponding compound (36), but other compounds in this series show comparable activity (27, 39, 44, and 46). Less activity is shown by the isomeric 3-aminopropionates and the homologous

2-aminobutyrates (Table II). The general activity of the 2-piperidinopropionate ester group (27, 36 and 44) is retained to some extent by the corresponding propionamide (96, Table VI). It appears that antitussive activity in the 2-aminopropionates is independent of the nature of the alkyl or aralkyl ester group (R′ in VI). Quaternization of the active compounds usually leads to a retention of activity as in the case of 19 and 27 and their corresponding methiodides (20 and 28). Moreover, pronounced activity is introduced into the comparatively inactive diamines (82 and 86) by conversion into their bismethiodides (83 and 87, respectively).

Within the limits of the present investigation, maximum activity in this series therefore is associated with a 2-piperidinopropionyl group, and is independent of the nature of the alcohol used to esterify the carboxyl group of 1-hydroxycyclopentane-1-carboxylic acid. Compounds which possess a free hydroxyl group (Table III), those with two tertiary amino groups (Table V) and those in which only the carboxyl carries a tertiary amino group (Tables III and IV) show little or no activity.

## Experimental

Where a number of compounds was synthesized by a similar method, a typical preparation is given.

**1-Hydroxycyclopentane-1-carboxylic Acid (III).**[3,5]—Hydrochloric acid (740 ml., d 1.18) was added dropwise to a stirred mixture of cyclopentanone (292 g.), water (500 ml.), ether (300 ml.) and sodium cyanide (430 g.) maintaining the temperature below 15° by immersion in an ice-bath. After completion of the addition, the mixture was stirred for 1 hr. at room temperature and the cyanohydrin was extracted with ether. The solvent was removed from the dried ether solution and the cyanohydrin was hydrolyzed by heating with hydrochloric acid (450 ml., d 1.18) on the steam bath under reflux with stirring for 4 hr. The mixture was cooled and the solid was filtered off. The product was extracted thoroughly with ether to separate it from the inorganic salts, filtered, dried and the solvent removed. The hydroxy acid (255.5 g.), m.p. 103.5–104.5°, was sufficiently pure for further synthetic work. An additional quantity of the acid (63.7 g.) was obtained by ether extraction of the solution remaining after hydrolysis.

**Phenethyl 1-Hydroxycyclopentane-1-carboxylate (IV,** R = H, (R′ = $C_6H_5CH_2CH_2$, Table I).—1-Hydroxycyclopentane-1-carboxylic acid (26 g., 0.2 mole), 2-phenylethanol (24.4 g., 0.2 mole), sulfuric acid (4 ml., 20% by volume) and benzene (150 ml.) were heated together under reflux in a Dean and Stark apparatus. When all the water had been distilled off, the benzene solution was cooled, washed with water, dilute sodium carbonate solution, and again with water and dried. After removal of the benzene the ester was distilled; yield 42.2 g. (90%).

**Phenethyl 1-(2-Chloropropionoxy)cyclopentane-1-carboxylate.**—Phenethyl 1-hydroxycyclopentane-1-carboxylate (28 g., 0.12 mole), chloroform (50 ml.) and 2-chloropropionyl chloride (23 g., 0.18 mole) were mixed carefully. With cooling, pyridine (9.5 g., 0.12 mole) was added slowly and the mixture was heated on the steam bath for 2 hr. under reflux. It was poured into water, and the chloroform layer was separated. The aqueous portion was extracted twice with ether. The combined chloroform and ether solutions were washed successively with water, dilute sodium carbonate solution and again with water. After drying and removing the solvents, the desired product (30.7 g.) was distilled.

In addition to the products of this class listed in Table I, some others also were prepared as intermediates for the succeeding aminoacyl derivatives of alkyl 1-hydroxycyclopentane-1-carboxylates (Table II) and the aminoalkyl 1-aminoacetoxycyclopentane-1-carboxylates (Table V). The boiling point and percentage yield of these additional compounds are given:

| | B.p., °C. | Mm. | Yield, % |
|---|---|---|---|
| 2-Bromoethyl 1-chloroacetoxycyclopentane-1-carboxylate | 142–154 | 0.7 | 60 |
| 3-Bromopropyl 1-chloroacetoxycyclopentane-1-carboxylate | 140–160 | 0.3 | 50 |
| Ethyl 1-(2-chloropropionoxy)cyclopentane-1-carboxylate | 138–142 | 14 | 77 |
| Ethyl 1-(3-bromopropionoxy)cyclopentane-1-carboxylate | 110–115 | 0.9 | 30 |
| Ethyl 1-(2-bromobutyroxy)cyclopentane-1-carboxylate | 150–158 | 10–12 | 60 |
| Phenethyl 1-(3-chloropropionoxy)cyclopentane-1-carboxylate | 158–165 | 0.5 | 35 |

Satisfactory analytical data were not obtained for these six liquids and therefore they have been omitted from Table I. Their precursors, as well as the amines derived from them (Table II) gave satisfactory analyses.

**Ethyl 1-(2-Piperidinopropionoxy)cyclopentane-1-carboxylate Hydrochloride (XI).**—Ethyl 1-(2-chloropropionoxy)-cyclopentane-1-carboxylate (48.2 g., 0.194 mole) and piperidine (33.0 g., 0.388 mole) were heated together under reflux in benzene (520 ml.) for 16 hr. After cooling, ether was added and the piperidine hydrochloride (20.1 g.), m.p. 247–248°, was filtered off. The filtrate was washed with water[12] (3 × 100 ml.) and extracted with dilute hydrochloric acid. The acid extracts were washed once with ether and then basified with dilute sodium carbonate solution. The liberated free base was extracted with ether and to the dried extracts was added ethereal hydrogen chloride (125 ml., 2 *N*). The mixture was diluted with ether and the hydrochloride (55.2 g., 85%), was filtered off and crystallized from an ethanol–ether mixture to give 51.4 g. (79%) of pure material.

The *methiodide* (1.8 g.) was obtained from the hydrochloride (2 g.) *via* its free base with methyl iodide in ether.

**3-Piperidinopropyl 1-Hydroxycyclopentane-1-carboxylate Hydrochloride** (X, *n* = 3, $NR_2$ = $NC_5H_{10}$).—3-Bromopropyl 1-hydroxycyclopentane-1-carboxylate (2.51 g., 0.01 mole), piperidine (1.7 g., 0.02 mole) and toluene (30 ml.) were allowed to react as described above for ethyl 1-(2-piperidinopropionoxy)-cyclopentane-1-carboxylate hydrochloride, to give the product (1.7 g.).

The methiodide was prepared by allowing the free base obtained from the purified hydrochloride to react with methyl iodide in ethereal solution.

**1-Acetoxycyclopentane-1-carboxylic acid**[4] was prepared from III by treatment with acetyl chloride. Heating the product with thionyl chloride gave the acid chloride.[4]

**1-Benzoyloxycyclopentane-1-carboxylic Acid and Acid Chloride.**—1-Hydroxycyclopentane-1-carboxylic acid (20 g., 0.154 mole) was dissolved in chloroform (30 ml.) and pyridine (40 ml.) was added. Benzoyl chloride (21.7 g., 0.154 mole) was added slowly with shaking and cooling. The mixture was heated on the steam bath under reflux for 30 min., cooled, and poured into water. The aqueous layer was washed with chloroform and the combined chloroform solution was washed with dilute hydrochloric acid. The product was extracted from the chloroform into dilute sodium carbonate solution, the alkaline extract acidified with dilute hydrochloric acid, and the precipitated acid (30.4 g., 85%) was filtered off, washed, dried and crystallized from aqueous ethanol.

1-Benzoyloxycyclopentane-1-carboxylic acid (30.4 g.) was heated with thionyl chloride (50 ml.) under reflux on the steam bath for 1 hr. Excess of thionyl chloride was removed and the acid chloride (31.2 g., 95%), b.p. 133–136° (0.2 mm.), was distilled.

**2-Diethylaminoethyl 1-Benzoyloxycyclopentane-1-carboxylate.**—1-Benzoyloxycyclopentane-1-carboxylic acid chloride (2.53 g., 0.01 mole) was added to a solution of 2-diethylaminoethanol (1.2 g., 0.01 mole) in chloroform (15 ml.). The mixture was heated under reflux for 30 min., cooled, and ether was added. Excess of dilute sodium carbonate solution was added and the chloroform–ether solution was washed with water (3 × 10 ml.) and dried. After removing the solvents, the residue was dissolved in a little ethanol and an ethanolic solution of citric acid monohydrate (2.1 g.) was added. Upon the introduction of ether, a solid (2.15 g.) was obtained and crystallized from an ethanol–

(12) It was necessary to reduce this wash in the case of the piperazine derivatives because of their high water-solubility.

ether solution to give the desired amino ester (1.73 g.) as its citrate monohydrate.

**3-Piperidinopropyl 1-Piperidinoacetoxycyclopentane-1-carboxylate Dihydrochloride Monohydrate** (VIII, $n$ = 3, $NR_2$ = $NC_5H_{10}$).—3-Bromopropyl 1-chloroacetoxycyclopentane-1-carboxylate (3.28 g., 0.01 mole), piperidine (6.8 g., 0.08 mole) and benzene (40 ml.) were made to react as described above for ethyl 1-(2-piperidinopropionoxy)cyclopentane-1-carboxylate hydrochloride, and yielded the dihydrochloride (2.51 g.). Conversion of a portion of this material into the free base and treatment of an ethereal solution of this with an excess of methyl iodide gave the bismethiodide, crystallized from an ethanol-ether solution.

**Ethyl 1-(2-Chloropropionamido)cyclopentane-1-carboxylate**—Ethyl 1-aminocyclopentane-1-carboxylate hydrochloride[7] (9.7 g., 0.05 mole) was dissolved in water and the solution was basified with excess dilute sodium carbonate solution. The base was extracted with ether and dried. After removal of the solvent by distillation, chloroform (20 ml.) was added, then 2-chloropropionyl chloride (10 g.) with cooling and shaking. Pyridine (3.95 g., 0.05 mole) in chloroform (10 ml.) was added slowly with cooling. The mixture was heated on the steam bath under reflux for 2 hr., cooled, poured into water, and the chloroform layer was separated. The aqueous layer was extracted with ether and the combined chloroform and ether solution was washed successively with water, dilute sodium carbonate solution and again water. After drying, the solvent was removed and the residue was distilled to give the product (9.7 g.) which was crystallized from petroleum ether (b.p. 60–80°).

**Ethyl 1-(2-Piperidinopropionamido)cyclopentane-1-carboxylate Hydrochloride** (XII).—Ethyl 1-(2-chloropropionamido)-cyclopentane-1-carboxylate (2.48 g., 0.01 mole), piperidine (1.7 g., 0.02 mole) and benzene (25 ml.) were treated as described in the preparation of ethyl 1-(2-piperidinopropionoxy)cyclopentane-1-carboxylate hydrochloride. The product (1.87 g.) crystallized from ethyl acetate–light petroleum ether. Treatment of a portion of the product with sodium carbonate solution and addition of methyl iodide to the isolated free base gave the methiodide.

**Ethyl 1-(*p*-Nitrobenzamido)cyclopentane-1-carboxylate.**—Ethyl 1-aminocyclopentane-1-carboxylate hydrochloride[7] (12.0 g.) was mixed with *p*-nitrobenzoyl chloride (14.4 g.) and pyridine (48 ml.) with cooling. The mixture was heated on the steam bath for 1 hr., cooled and poured into water. The product was extracted into ether and the combined ether extracts were washed with dilute hydrochloric acid, water, dilute sodium carbonate solution, water, and dried. After removal of the solvent, the residual solid was crystallized twice from aqueous ethanol and again from ethyl acetate-light petroleum ether (b.p. 60–80°) to give the ester-amide (13.3 g.)

**Ethyl 1-(*p*-Aminobenzamido)cyclopentane-1-carboxylate Hydrochloride.**—Ethyl 1-(*p*-nitrobenzamido)cyclopentane-1-carboxylate (6.12 g., 0.02 mole) was dissolved in ethanol (150 ml.) containing ethereal hydrogen chloride (20 ml., 1.7 *N*), and 5% palladium on charcoal catalyst (0.5 g.) was added. The mixture was shaken at atmospheric pressure in hydrogen. When the uptake of hydrogen ceased, the catalyst was filtered off and most of the solvent was removed *in vacuo* at 70°. Ether was added to the residue and the solid (5.25 g.) was filtered off and crystallized twice from an ethanol–ether mixture to give the product (4.90 g.).

**2-Bromoethyl 1-Phenylcarbamoyloxycyclopentane-1-carboxylate** (XV, $n$ = 2).—2-Bromoethyl 1-hydroxycyclopentane-1-carboxylate (2.37 g., 0.01 mole) and phenyl isocyanate (1.19 g., 0.01 mole) were mixed and heated on the steam bath for 1 hr. On cooling, a solid (2.55 g.) was obtained; it was filtered off and washed with a little petroleum ether. It yielded the phenylcarbamate (1.82 g.), m.p. 89–90.5° (from petroleum ether, b.p. (60–80°).

*Anal.* Calcd. for $C_{15}H_{18}BrNO_4$: C, 51.0; H, 5.2; N, 4.1; Br, 22.8. Found: C, 50.6; H, 5.1; N, 3.9; Br, 22.4.

In a similar manner starting with 3-bromopropyl 1-hydroxycyclopentane-1-carboxylate, 3-bromopropyl 1-phenylcarbamoyloxycyclopentane-1-carboxylate (XV, $n$ = 3) was prepared, m.p. 93–94° (from petroleum ether, b.p. 60–80°).

*Anal.* Calcd. for $C_{16}H_{20}BrNO_4$: C, 52.2; H, 5.6; Br, 21.6. Found: C, 51.9; H, 5.5; Br, 21.6.

**3-Phenyl-1-oxa-3-aza-spiro[4.4]nonane-2,4-dione** (XVI).—(a) 2-Bromoethyl 1-phenylcarbamoyloxycyclopentane-1-carboxylate (2.7 g., 0.0075 mole), piperidine (1.28 g., 0.015 mole) and benzene (30 ml.) were heated under reflux for 16 hr. After cooling and adding ether, piperidine hydrobromide (1.17 g.) was filtered off and identified. The remainder of the piperidine was extracted from the filtrate with water and hydrochloric acid (2 *N*). The organic solution was washed again with water and dried. Evaporation to dryness gave a crystalline solid (1.60 g.), m.p 120–125°, which was recrystallized from ethanol to give the spiro compound (1.33 g.), m.p. 128–130°, as colorless needles.

*Anal.* Calcd. for $C_{13}H_{13}NO_3$: C, 67.5; H, 5.8; N, 6.1. Found: C, 67.5; H, 5.7; N, 6.1.

(b) Treatment of 3-bromopropyl 1-phenylcarbamoyloxycyclopentane-1-carboxylate with piperidine in a manner similar to (a) also gave the spiro compound; m.p. and mixture m.p. with that previously obtained, 128–130°.

(c) 2-Diethylaminoethyl 1-hydroxycyclopentane-1-carboxylate[4] (XVII) (2.30 g., 0.01 mole) and phenyl isocyanate (1.20 g., 0.01 mole) were mixed and heated on the steam bath for 1 hr. After cooling, a little petroleum ether, b.p. 60–80°, was added and the solid (1.10 g.) which was obtained was crystallized from petroleum ether as long colorless needles (0.70 g.), m.p. 127.5–129°, not depressed on admixture with a sample prepared as in (a).

(d) 3-Piperidinopropyl 1-hydroxycyclopentane-1-carboxylate hydrochloride (Table III) (2.92 g., 0.01 mole) was converted into its base (XVIII) by treatment with dilute sodium carbonate solution. The free base was extracted into ether and dried. After removal of all the solvent by distillation, the residue was treated with phenyl isocyanate as in (c). The product was again shown to be identical with the spiro compound described under (a) above.

**Acknowledgments.**—The authors thank the Directors of Benger Laboratories Limited for permission to publish these results, and are indebted to Mr. J. McQuillan for assistance with the experimental work and to the Analytical Department of Benger Laboratories Limited for the analyses.