United States Patent [19]

Aristoff

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[54] **INTERPHENYLENE CARBACYCLIN DERIVATIVES**

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[21] Appl. No.: **690,803**

[22] Filed: **Jan. 11, 1985**

[51] **Int. Cl.**[4] **C07C 177/00**

[52] **U.S. Cl.** **560/51;** 544/155; 544/380; 546/203; 546/204; 546/283; 546/284; 546/285; 548/540; 549/66; 549/78; 549/79; 549/305; 549/465; 549/496; 549/499; 549/501; 549/502; 549/65; 560/45; 560/56; 562/444; 562/466; 562/499; 562/453; 564/80; 564/88; 564/89; 564/90; 564/92; 564/93; 564/95; 564/97; 564/98; 564/99; 564/152; 564/158; 564/171; 564/174; 564/374; 564/384; 564/427; 564/453; 564/454; 568/633; 568/808; 568/817

[58] **Field of Search** 560/51, 45, 56; 562/444, 466, 499, 453; 542/429; 544/155, 380; 564/80, 88, 89, 90, 92, 93, 95, 97, 98, 99, 171, 174, 152, 158, 374, 384, 427, 453

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4,306,075	12/1981	Aristoff	560/56
4,306,076	12/1981	Nelson	560/56
4,349,689	9/1982	Aristoff	560/117

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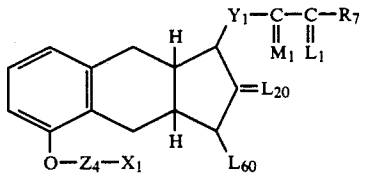
[57] **ABSTRACT**

A compound of the formula



and intermediates useful in preparing same.

11 Claims, No Drawings

INTERPHENYLENE CARBACYCLIN DERIVATIVES

FIELD OF THE INVENTION

The present invention relates to novel pharmaceutically useful compounds which are carbacyclin analogs having a tricyclic nucleus.

PRIOR ART

Related interphenylene carbacyclins are described and claimed in U.S. Pat. No. 4,306,075, U.S. Pat. No 4,306,076, and EP No. 87237 (Derwent No. 754477). Compounds having a 5-membered oxa ring are described in European Pat. No. 24-943 (Derwent No. 19801D).

Carbacyclin and closely related compounds are known in the art. See Japanese Kokai Nos. 63,059 and 63,060, also abstracted respectively as Derwent Farmdoc CPI Numbers 48154B/26 and 48155B/26. See also British published specifications No. 2,012,265 and German Offenlungsschrift No. 2,900,352, abstracted as Derwent Farmdoc CPI Number 54825B/30. See also British published applications Nos. 2,017,699 and 2,013,661 and U.S. Pat. No. 4,238,414.

The synthesis of carbacyclin and related compounds is also reported in the chemical literature, as follows: Morton, D. R., et al, J. Org. Chem., 44:2880–2887 (1979); Shibasaki, M., et al, Tetrahedron Lett., 433–436 (1979); Kojima, K., et al, Tetrahedron Lett., 3743–3746 (1978); Nicolaou, K. C., et al, J. Chem. Soc., Chemical Communications, 1067–1068 (1978); Sugie, A., et al, Tetrahedron Lett., 2607–2610 (1979); Shibasaki, M., Chem. Lett., 1299–1300 (1979), and Hayashi, M., Chem. Lett., 1437–40 (1979); Aristoff, P. A., J. Org. Chem. 46, 1954–1957 (1981); Yamazaki, M., et al, Chem. Lett., 1245–1248 (1981); and Barco, A., et al, J. Org. Chem. 45, 4776–4778 (1980); and Skuballa, W., et al, Angew. Chem. 93, 1080–1081 (1981). The utility and synthesis of compounds closely related to those claimed herein is described in Aristoff, P. A., and Harrison, A. W., Tetrahedron Lett. 23, 2067–2070 (1982) and in Advances in Prostaglandin, Thromboxane, and Leukotriene Research, Vol. 11, 267 (1983).

7-Oxo and 7-hydroxy-CBA_2 compounds are apparently disclosed in U.S. Pat. No. 4,192,891. 19-Hydroxy-CBA_2 compounds are disclosed in U.S. Pat. No. 4,225,508. CBA_2 aromatic esters are disclosed in U.S. Pat. No. 4,180,657. 11-Deoxy-Δ^{10}- or Δ^{11}-CBA_2 compounds are described in Japanese Kokai No. 77/24,865, published Feb. 24, 1979.

SUMMARY OF THE INVENTION

The present invention provides compounds of Formula I wherein:

X_1 is

(1) $-COOR_1$, wherein R_1 is
- (a) hydrogen;
- (b) (C_1–C_{12}) alkyl;
- (c) (C_3–C_{10}) cycloalkyl;
- (d) (C_7–C_{12}) aralkyl;
- (e) phenyl, optionally substituted with one, 2 or 3 chloro or (C_1–C_3) alkyl;
- (f) phenyl substituted in the para position by
  - (i) $-NHCOR_{25}$,
  - (ii) $-COR_{26}$,
  - (iii) $-OCR_{54}$,

    O

    ‖

  or
  - (iv) $-CH{=}N{-}NHCONH_2$ wherein R_{25} is methyl, phenyl, acetamidophenyl, benzamidophenyl, or $-NH_2$; R_{26} is methyl, phenyl, $-NH_2$, or methoxy; R_{54} is phenyl or acetamidophenyl; inclusive; or
- (g) a pharmocologically acceptable cation;

(2) $-CH_2OH$;

(3) $-COL_4$, wherein L_4 is
- (a) amino of the formula $-NR_{51}R_{52}$ wherein R_{51} and R_{52} are
  - (i) hydrogen,
  - (ii) (C_1–C_{12}) alkyl,
  - (iii) (C_3–C_{10}) cycloalkyl,
  - (iv) (C_7–C_{12}) aralkyl,
  - (v) phenyl, optionally substituted with one 2 or 3 chloro, (C_1–C_3) alkyl, hydroxy, carboxy, (C_2–C_5) alkoxycarbonyl, or nitro,
  - (vi) (C_2–C_5) cyanoalkyl,
  - (vii) (C_2–C_5) carboxyalkyl,
  - (viii) (C_2–C_5) carbamoylalkyl,
  - (ix) (C_3–C_6) acetylalkyl,
  - (x) (C_7–C_{11}) benzoalkyl, optionally substituted by one, 2 or 3 chloro, (C_1–C_3) alkyl, hydroxy, (C_1–C_3) alkoxy, carboxy, (C_2–C_5) alkoxy carbonyl, or nitro,
  - (xi) pyridyl, optionally substituted by one, 2 or 3 chloro, (C_1–C_3) alkyl, or (C_1–C_3) alkoxy,
  - (xii) (C_6–C_9) pyridylalkyl optionally substituted by one, 2 or 3 chloro, (C_1–C_3) alkyl, hydroxy, or (C_1–C_3) alkoxy,
  - (xiii) (C_1–C_4) hydroxyalkyl,
  - (xiv) (C_1–C_4) dihydroxyalkyl,
  - (xv) (C_1–C_4) trihydroxyalkyl, with the proviso that not more than one of R_{51} and R_{52} is other than hydrogen or alkyl;
- (b) cycloamino selected from the group consisting of pyrrolidino, piperidino, morpholino, piperazino, hexamethylenimino, pyrrolino, or 3,4-didehydropiperidinyl optionally substituted by one or 2 (C_1–C_{12}) alkyl of one to 12 carbon atoms, inclusive;
- (c) carbonylamino of the formula $-NR_{53}COR_{51}$ wherein R_{53} is hydrogen or (C_1–C_4) alkyl and R_{51} is other than hydrogen, but otherwise defined as above;
- (d) sulfonylamino of the formula $-NR_{53}SO_2R_{51}$, wherein R_{51} and R_{53} are defined in (c);

(4) $-CH_2NL_2L_3$ wherein L_2 and L_3 are hydrogen or (C_1–C_4) alkyl, being the same or different, or the pharmacologically acceptable acid addition salts thereof when X_1 is $-CH_2NL_2L_3$;

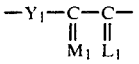
(5) $-CN$;

wherein Z_4 is $-CH_2-$, $-CH_2CH_2-$, $-CF_2-$ or $-CH_2CF_2$;

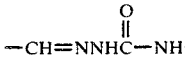
wherein L_{20} is α—OH,β—H; α—H,β—OH; H,H; α—CH_3,β—H; α—CH_2OH,β—H; =O; or $=CH_2$; wherein L_{60} is hydrogen or L_{20} and L_{60} taken together form a double bond between positions 10 and 11;

wherein Y_1 is $-CH_2CH_2-$, $-SCH_2-$, $-C{\equiv}C-$, trans—CH=CH—, or cis—CH=CH—;

wherein



taken together is



wherein M_1 is α—H:β—H; =O; α—OH:β—R_5; or α—R_5:β—OH; wherein R_5 is hydrogen or methyl;

wherein L_1 is

(1) α—R_3:β—R_4, α—R_4:β—R_3, or mixtures thereof wherein R_3 and R_4 are hydrogen, methyl, or fluoro, being the same or different, with the proviso that one of R_3 and R_4 is fluoro only when the other is hydrogen or fluoro;

(2) or when M_1 is α—H:β—H, L_1 is α—OH:β—R_3, α—R_3:β—OH; or a mixture of α—OH:β—R_3 and α—R_3:β—OH wherein R_3 is hydrogen, methyl, vinyl, or ethynyl;

wherein R_7 is

(1) —$C_mH_{2m}CH_3$, wherein m is an integer from one to 8, inclusive;

(2) phenoxy optionally substituted by one, 2 or 3 chloro, fluoro, trifluoromethyl, (C_1–C_3) alkyl, or (C_1–C_3) alkoxy, with the proviso that not more than two substituents are other than alkyl with the proviso that R_7 is phenoxy or substituted phenoxy, only when R_3 and R_4 are hydrogen or methyl, being the same or different;

(3) phenyl, benzyl, phenylethyl, or phenylpropyl optionally substituted on the aromatic ring by one, 2 or 3 chloro, fluoro, trifluoromethyl, (C_1–C_3) alkyl, or (C_1–C_3) alkoxy, with the proviso that not more than two substituents are other than alkyl;

(4) cis—CH=CH—CH_2CH_3;

(5) —$(CH_2)_2$—CH(OH)—CH_3;

(6) —$(CH_2)_3$—CH=$C(CH_3)_2$;

(7) —C_pH_{2p}CH=CH_2 wherein p is an integer from 2 to 6, inclusive;

wherein

taken together is

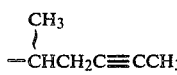
(1) (C_4–C_7) cycloalkyl optionally substituted by one to 3 (C_1–C_5) alkyl, or (C_1–C_5)alkenyl;

(2) 2-(2-furyl) ethyl;

(3) 2-(3-thienyl) ethoxy;

(4) 3-thienyloxymethyl; or

(5)



and the individual optical enantiomers thereof with the proviso that each compound is other than one formed when the substituents X_1, Z_4, L_{20}, Y_1, M_1, L_1, and R_7 have the following meanings:

X_1 is as defined above;

Z_4 is —CH_2—, —CF_2—, or —CH_2CF_2—;

L_{20} is α—OH,β—H; α—H,β—OH; H,H; α—CH_2OH,β—H;

Y_1 is —CH_2CH_2—, —C≡C—, trans—CH=CH—, or cis—CH=CH—;

M_1 is α—OH:β—R_5, or α—R_5:β—OH wherein R_5 is hydrogen or methyl;

L_1 is α—R_3:β—R_4, α—R_4:β—R_3, or a mixture thereof wherein R_3 and R_4 are hydrogen, methyl, or fluoro, being the same or different, with the proviso that one of R_3 and R_4 is fluoro only when the other is hydrogen or fluoro; and

R_7 is as defined above except R_7 is other than —$(CH_2)_2$—CH=CH_2 and R_7 is other than —$C(L_1)R_7$ taken together is as defined above except —$C(L_1)R_7$ is other than (C_4–C_7)cycloalkyl optionally substituted with (C_1–C_5)alkenyl.

The present invention also provides a new procedure for preparing compounds of Formula I(a) wherein X_1 is

(1) —$COOR_1$, wherein R_1 is

(a) hydrogen;

(b) (C_1–C_{12}) alkyl;

(c) (C_3–C_{10}) cycloalkyl;

(d) (C_7–C_{12}) aralkyl;

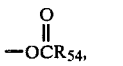
(e) phenyl, optionally substituted with one, 2 or 3 chloro or (C_1–C_3) alkyl;

(f) phenyl substituted in the para position by

(i) —$NHCOR_{25}$,

(ii) —COR_{26},

(iii)



or

(iv) —CH=N—$NHCONH_2$ wherein R_{25} is methyl, phenyl, acetamidophenyl, benzamidophenyl, or —NH_2; R_{26} is methyl, phenyl, —NH_2, or methoxy; R_{54} is phenyl or acetamidophenyl; inclusive; or

(g) a pharmacologically acceptable cation;

(2) —CH_2OH;

(3) —COL_4, wherein L_4 is

(a) amino of the formula —$NR_{51}R_{52}$ wherein R_{51} and R_{52}

(i) hydrogen,

(ii) (C_1–C_{12}) alkyl,

(iii) (C_3–C_{10}) cycloalkyl,

(iv) (C_7–C_{12}) aralkyl,

(v) phenyl, optionally substituted with one 2 or 3 chloro, (C_1–C_3) alkyl, hydroxy, carboxy, (C_2–C_5) alkoxycarbonyl, or nitro,

(vi) (C_2–C_5) cyanoalkyl,

(vii) (C_2–C_5) carboxyalkyl,

(viii) (C_2–C_5) carbamoylalkyl,

(ix) (C_3–C_6) acetylalkyl,

(x) (C_7–C_{11}) benzoalkyl, optionally substituted by one, 2 or 3 chloro, (C_1–C_3) alkyl, hydroxy, (C_1–C_3) alkoxy, carboxy, (C_2–C_5) alkoxy carbonyl, or nitro,

(xi) pyridyl, optionally substituted by one, 2 or 3 chloro, (C_1–C_3) alkyl, or (C_1–C_3) alkoxy,

(xii) (C_6–C_9) pyridylalkyl optionally substituted by one, 2 or 3 chloro, (C_1–C_3) alkyl, hydroxy, or (C_1–C_3) alkoxy,

(xiii) (C_1–C_4) hydroxyalkyl,

(xiv) (C_1–C_4) dihydroxyalkyl,

(xv) (C_1–C_4) trihydroxyalkyl,

with the proviso that not more than one of R_{51} and R_{52} is other than hydrogen or alkyl;

(b) cycloamino selected from the group consisting of pyrrolidino, piperidino, morpholino, piperazino, hexamethylenimino, pyrrolino, or 3,4-didehydropiperidinyl optionally substituted by one or 2 (C_1–C_{12}) alkyl of one to 12 carbon atoms, inclusive;

(c) carbonylamino of the formula $—NR_{53}COR_{51}$ wherein R_{53} is hydrogen or (C_1–C_4) alkyl and R_{51} is other than hydrogen, but otherwise defined as above;

(d) sulfonylamino of the formula $—NR_{53}SO_2R_{51}$, wherein R_{51} and R_{53} are defined in (c);

(4) $—CH_2NL_2L_3$ wherein L_2 and L_3 are hydrogen or (C_1–C_4) alkyl, being the same or different, or the pharmacologically acceptable acid addition salts thereof when X_1 is $—CH_2NL_2L_3$;

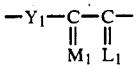
(5) —CN;

wherein Z_4 is $—CH_2—$, $—CH_2CH_2—$, $—CF_2—$ or $—CH_2CF_2$;

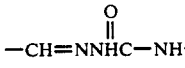
wherein L_{20} is α—OH,β—H; α—H,β—OH; H,H; α—CH_3,β—H; α—CH_2OH,β—H; =O; or $=CH_2$; wherein L_{60} is hydrogen or L_{20} and L_{60} taken together form a double bond between positions 10 and 11;

wherein Y_1 is $—CH_2CH_2—$, $—SCH_2—$, —C≡C—, trans—CH=CH—, or cis—CH=CH—;

wherein



taken together is



wherein M_1 is α—H:β—H; =O; α—OH:β—R_5; or α—R_5:β—OH; wherein R_5 is hydrogen or methyl;

wherein L_1 is

(1) α—R_3:β—R_4, α—R_4:β—R_3, or mixtures thereof wherein R_3 and R_4 are hydrogen, methyl, or fluoro, being the same or different, with the proviso that one of R_3 and R_4 is fluoro only when the other is hydrogen or fluoro;

(2) or when M_1 is α—H:β—H, L_1 is α—OH:β—R_3, α'R_3:β—OH; or a mixture of α—OH:β—R_3 and α—R_3:β—OH wherein R_3 is hydrogen, methyl, vinyl, or ethynyl;

wherein R_7 is

(1) $—C_mH_{2m}CH_3$, wherein m is an integer from one to 8, inclusive;

(2) phenoxy optionally substituted by one, 2 or 3 chloro, fluoro, trifluoromethyl, (C_1–C_3) alkyl, or (C_1–C_3)alkoxy, with the proviso that not more than two substituents are other than alkyl with the proviso that R_7 is phenoxy or substituted phenoxy, only when R_3 and R_4 are hydrogen or methyl, being the same or different;

(3) phenyl, benzyl, phenylethyl, or phenylpropyl optionally substituted on the aromatic ring by one, 2 or 3 chloro, fluoro, trifluoromethyl, (C_1–C_3) alkyl, or (C_1–C_3) alkoxy, with the proviso that not more than two substituents are other than alkyl;

(4) cis—CH=CH—CH_2CH_3;

(5) $—(CH_2)_2—CH(OH)—CH_3$;

(6) $—(CH_2)_3—CH=C(CH_3)_2$;

(7) $C_pH_{2p}CH=CH_2$ where p is an integer from 2 to 6, inclusive;

wherein

taken together is

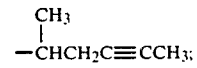
(1) (C_4–C_7) cycloalkyl optionally substituted by one to 3 (C_1–C_5) alkyl, or (C_1–C_5)alkyl;

(2) 2-(2-furyl) ethyl;

(3) 2-(3-thienyl) ethoxy;

(4) 3-thienyloxymethyl; or

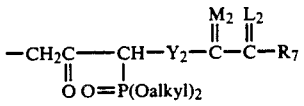
(5)



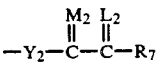
and the individual optical enantiomers thereof.

In the event it is not readily apparent the difference between the compounds of Formula I and those of Formula I(a) lies in the fact that certain compounds of Formula I are excluded by the proviso beginning on page 4, line 35. The compounds excluded by the proviso in Formula I are described and claimed in U.S. Pat. No. 4,306,075 and copending U.S. application Ser. No. 351,069 filed Feb. 22, 1982. The novel process described herein is applicable to the prior claimed compounds and the novel compounds described and claimed herein

Also, the present invention provides novel intermediates of Formulas I(b), I(c), I(d) and II as set forth in the Formula Chart. In Formulas I(b) and I(c) the group Q is cis-$CH_2CH=CH_2$, $—CH_2COOH$, or



wherein alkyl has from 1 to 4 carbon atoms; L is the same as L_1 in Formula I only any hydrous group is protected with an Rx group as defined below; Y_2 is $—SCH_2—$ or $—CH_2CH_2—$, M_2 is α-H,β-ORx, α-ORx,β-H or H,H wherein Rx is a protecting group as defined below, and R_7 has the meaning defined in Formula I(a). In Formula I(d) Q_2 is



as defined above or CO_2 alkyl wherein alkyl has from 1 to 4 carbon atoms. The intermediates of Formulas I(a), I(b), I(c), I(d) and II are useful in the preparation of the compounds of Formuls I and I(a).

The compounds of Formula I and I(a) have useful pharmacological properties as defined below.

DETAILED DESCRIPTION OF INVENTION

In the compounds of the present invention, and as used herein, (‴) denotes the α-configuration, ( ) denotes the β-configuration, (~) denotes α- and/or β-configuration or the E and/or Z isomer.

With regard to the divalent groups described above, i.e., L_{20}, M_1 and L_1 said divalent groups are defined in terms of an α-substituent and a β-substituent which means that the α-substituent of the divalent group is in the alpha configuration with respect to the plane of the C-8 to C_{12} cyclopentane ring and the β-substituent is in the beta configuration with respect to said cyclopentane ring.

The carbon atom content of various hydrocarbon containing groups is indicated by a prefix designating the minimum and maximum number of carbon atoms in the moiety. For example, in defining the moiety L_4 in the $-COL_4$ substituent group the definition (C_1-C_{12})alkyl means that L_4 can be an alkyl group having from one to 12 carbon atoms. Additionally, any moiety so defined includes straight chain or branched chain groups. Thus (C_1-C_{12})alkyl as set forth above includes straight or branched chain alkyl groups having from 1 to 12 carbon atoms and as additional illustration, when L_4 represents, for example, (C_2-C_5)carboxyalkyl, the alkyl moiety thereof contains from 1 to 4 carbon atoms and is a straight chain or a branched chain alkyl group. Similarly a C_3-C_5 alkenyl group as may be present on the cycloalkyl group represented by $-C(L_1)R_7$ contains from 3 to 5 carbon atoms and one double bond in the chain.

In Formula I when the hydrogen at position 9 is beta the compounds are named as 9-deoxy-2′,9α-methano-3-oxa-4,5,6-trinor-3,7-(1′,3′-interphenylene)PGF_1 compounds, and when it is alpha the compounds are named as 9-deoxy-2′,9β-methano-3-oxa-4,5,6-trinor-3,7-(1′,3′-interphenylene)PGF_1 compounds.

When Z_4 is $-CF_2-$ the compounds of Formula I are also characterized as 2,2-difluoro and when Z_4 is $-CH_2CF_2-$ the compounds are characterized as 2α-homo-2,2-difluoro.

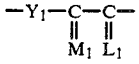
When R_5 is methyl, the carbacyclin analogs are all named as "15-methyl-" compounds. Further, except for compounds wherein Y_1 is cis-CH=CH—, *compounds wherein the* M_1 moiety contains an hydroxyl in the beta configuration are additionally named as "15-epi-" compounds.

For the compounds wherein Y_1 is cis-CH=CH—, then compounds wherein the M_1 moiety contains an hydroxyl in the alpha configuration are named as "15-epi-CBA" compounds. For a description of this convention of nomenclature for identifying C-15 epimers, see U.S. Pat. No. 4,016,184, issued Apr. 5, 1977, particularly columns 24–27 thereof.

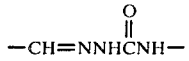
The compounds of the present invention which contain $-(CH_2)_2-$, cis-CH=CH—, trans —CH=CH— or —C≡C— as the Y_1 moiety, are accordingly referred to as "13,14-dihydro", "cis-13", "trans-13", or —13,14-didehydro" compounds, respectively. Compounds wherein Y_1 is $-SCH_2-$ are named as "13-thio" compounds.

Compounds wherein M_1 is H,H are named as "15-deoxy" compounds. Compounds wherein M_1 is =O are named as "15-oxo" compounds.

Compounds wherein

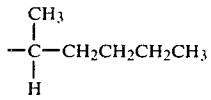


taken together is



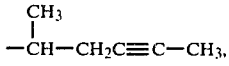
are are named as 13,14,15,16,17,18,19,20-octanor-12-[N-R_7-carbamoyl)hydrazono-methyl].

When R_7 is



the compounds so described are named as 17(S),20-dimethyl compounds.

When $-C(L_1)-R_7$ is



the compounds are named as "16-(R,S)methyl-18,19-tetradehydro" compounds.

When $-C(L_1)R_7$ is $-CH_2CH=CH_2$ the compounds so described are named as "19,20-didehydro".

When at least one of R_3 and R_4 is not hydrogen then there are described the "16-methyl" (one and only one of R_3 and R_4 is methyl), "16,16-dimethyl" (R_3 and R_4 are both methyl), "16-fluoro" (one and only one of R_3 and R_4 is fluoro), "16,16-difluoro" (R_3 and R_4 are both fluoro) compounds. For those compounds wherein R_3 and R_4 are different, the carbacyclin analogs so represented contain as asymmetric carbon atom at C-14. Accordingly, two epimeric configurations are possible: "(16S)" and "(16R)". Further, there is described by this invention the C-16 epimeric mixture: "(16RS)".

When X_1 is $-CH_2OH$, the compounds so described are named as "2-decarboxy-2-hydroxymethyl" compounds.

When X_1 is $-CH_2NL_2L_3$, the compounds so described are named as "2-decarboxy-2-aminomethyl" or "2-(substituted amino)methyl" compounds.

When X_1 is $-COL_4$, the novel compounds herein are named as amides. Further, when X_1 is $-COOR_1$ and R_1 is other than hydrogen the novel compounds herein are named as esters and salts.

When X_1 is CN the novel compounds herein are named as 2-decarboxy-2-cyano compounds.

Examples of phenyl esters substituted in the para position (i.e., X_1 is $-COOR_1$, R_1 is p-substituted phenyl) include p-acetamidophenyl ester, p-benzamidophenyl ester, p-(p-acetamidobenzamido)phenyl ester, p-(p-benzamidobenzamido)phenyl ester, p-amidocarbonylaminophenyl ester, p-acetylphenyl ester, p-benzoylphenyl ester, p-aminocarbonylphenyl ester, p-methoxycarbonylphenyl ester, p-benzoyloxyphenyl ester, p(p-acetamidobenzoyloxy)phenyl ester, and p-hydroxybenzaldehyde semicarbazone ester.

Examples of novel amides herein (i.e., X_1 is $-COL_4$) include the following:

(1) Amides within the scope of alkylamino groups of the formula NR_9R_{10} are methylamide, ethylamide, n-propylamide, isopropylamide, n-butylamide, n-pentylamide, tert-butylamide, neopentylamide, n-hexylamide, n-heptylamide, n-octylamide, n-nonylamide, n-decylamide, n-undecylamide, and n-dodecylamide, and isomeric forms thereof. Further examples are dimethyla-

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