($C_{20}H_{26}N_2$) C, H, N. The maleate salt, mp 127–130°, was recrystd from *i*-PrOH–Et_2O. *Anal.* ($C_{20}H_{26}N_2 \cdot C_4H_4O_4$) C, H, N.

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Synthesis of Fatty Acids with Smooth Muscle Stimulant Activity. 3. Acetylenic Analogs of 12-Hydroxyheptadeca-*trans*-8,*trans*-10-dienoic Acid[1]

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12-Hydroxyheptadeca-*trans*-8,*trans*-10-dienoic acid and analogs in which one or both double bonds are replaced by triple bonds have been prepared by methods which give products essentially free from cis isomers. These acids have been tested for smooth muscle stimulant activity and found to be approximately as active as ricinelaidic acid.

The prostaglandins are alicyclic hydroxy fatty acids with a very wide range of pharmacological actions (for a recent summary see ref 2) including luteolytic activity, of potential use in the control of conception, and uterine muscle stimulant activity, usable for therapeutic abortion. They may also have related physiological functions, particularly in the normal induction of labor. Simpler analogs with these activities, or with antagonistic actions, would therefore be of great interest.

$$C_6H_{13}CH(OH)CH_2CH{=}CH(CH_2)_7CO_2H$$
1

The simple fatty acids which have stimulant effects on smooth muscle fall into three classes. Unsaturated acids may become peroxidized and then act like other, nonacidic, peroxides.[3] Particular polyunsaturated acids may be metabolized to prostaglandins.[4] Some hydroxy unsaturated acids, for example, ricinoleic acid (**1**, cis isomer), which cannot act as prostaglandin precursors, have however an independent stimulant action[5] and can be distinguished from peroxides by correct choice of muscle preparation. The positions of functional groups in these acids were considered and compared with those in prostaglandins. It was consequently proposed in paper 1 of this series[6] that smooth muscle stimulant activity may occur in fatty acids possessing a hydroxyl group at position 12 and unsaturation or structural rigidity between positions 8 and 11. Of the monounsaturated acids then examined, 12-hydroxyheptadec-*trans*-10-enoic acid was found to be the most active. Synthesis of diunsaturated analogs was therefore undertaken.

Introduction of a triple bond at position 8 gives 12-hydroxyheptadec-*trans*-10-en-8-ynoic acid (**5**, X = CO_2H). The hydroxy-*trans*-enyne system occurs in helenynolic acid[7] (9-hydroxyoctadec-*trans*-10-en-12-ynoic acid) but in reverse order. It can be obtained,[8,9] among other products, by

$$C_5H_{11}\overset{trans}{CH{=}CHCHO} \longrightarrow C_5H_{11}\overset{trans}{CH{=}CHCH(OH)C{\equiv}CH} \longrightarrow$$
2 **3**

$$C_5H_{11}CH(OR)\overset{trans}{CH{=}CHC{\equiv}CH} \longrightarrow C_5H_{11}CH(OH)\overset{trans}{CH{=}CHC{\equiv}C(CH_2)_6X}$$
4 **5**

base-catalyzed cleavage of a methylene-interrupted epoxyacetylenic acid.

In our approach oct-*trans*-2-enal[10] (**2**) was converted to dec-*trans*-4-en-1-yn-3-ol (**3**) which was rearranged[11] to dec-3-en-1-yn-5-ol (cis:trans ratio 1:3). Pure trans alcohol (**4**, R = H) was elaborated *via* the nitrile (**5**, X = CN) to the desired acid (**5**, X = CO_2H). The corresponding cis nitrile gave on hydrolysis and esterification also some methyl 8-(5′-pentylfur-2′-yl)octanoate, homologous with the furanoid acid obtained[12] from a seed oil. Preparation of this acid and of acids with cis double bonds will be reported elsewhere.

The isomeric 12-hydroxyheptadec-*trans*-8-en-10-ynoic acid (**11**, X = CO_2H) incorporates a hydroxy-yne-*trans*-ene sequence found naturally only in reverse order, in ximenynolic acid[13] (9-hydroxyoctadec-*trans*-12-en-10-ynoic acid) which has been synthesized[14] *via* acylation of a silver acetylide.

$$Cl(CH_2)_6CHO \qquad Cl(CH_2)_6CH(OH)CH_2C{\equiv}CH$$
6 **7**

$$PhOCH_2C{\equiv}CH \longrightarrow PhOCH_2C{\equiv}C(CH_2)_7Cl \longrightarrow$$
8 **9**

$$HC{\equiv}C\overset{trans}{CH{=}CH(CH_2)_6Cl} \longrightarrow C_5H_{11}CH(OH)C{\equiv}C\overset{trans}{CH{=}CH(CH_2)_6X}$$
10 **11**

Synthesis was initially attempted *via* the chloroynol (**7**) but elimination of the hydroxyl group, either as such or as

the tosylate or mesylate, was accompanied by loss of chloride. The 1,4 elimination of 2-alkynyl ethers[15] was therefore exploited. 3-Phenoxyprop-1-yne (**8**) was converted to the chloroalkynyl ether (**9**) which with $NaNH_2$ gave a 1:1 mixture of the cis:trans isomers of 10-chlorodec-3-en-1-yne containing only traces of terminal olefinic material. Pure trans isomer (**10**) was elaborated *via* the hydroxyenyne chloride (**11**, X = Cl) to the acid (**11**, X = CO_2H).

The diacetylenic analog 12-hydroxyheptadeca-8,10-diynoic acid (**14**, R = H) was synthesized by Cadiot-Chodkie-

$$\underset{\mathbf{12}}{C_5H_{11}CH(OH)C{\equiv}CBr} + \underset{\mathbf{13}}{HC{\equiv}C(CH_2)_6CO_2H} \longrightarrow$$

$$\underset{\mathbf{14}}{C_5H_{11}CH(OH)C{\equiv}CC{\equiv}C(CH_2)_6CO_2R}$$

wicz coupling.[16,17] It was purified and characterized as its methyl ester. This hydroxydiyne system occurs in reverse order in 8-hydroxyoctadeca-9,11-diynoic acid, isolated from Onguekoa gore.[18,19]

Incorporation of further trans unsaturation in 12-hydroxyheptadec-*trans*-10-enoic acid affords 12-hydroxyheptadeca-*trans*-8,*trans*-10-dienoic acid (**18**, X = CO_2H) which has been isolated[20,21] as a by-product of prostaglandin biosynthesis.

$$\underset{\mathbf{15}}{CH_3O\overset{cis}{CH{=}CHC{\equiv}CCH(OH)(CH_2)_6Cl}} \longrightarrow$$

$$\underset{\mathbf{16}}{CH_3O\overset{cis}{CH{=}CH}\overset{trans}{CH{=}CH}CH(OH)(CH_2)_6X} \longrightarrow$$

$$\underset{\mathbf{17}}{O\overset{trans}{CH{=}CH}\overset{trans}{CH{=}CH}(CH_2)_6X} \longrightarrow$$

$$\underset{\mathbf{18}}{C_5H_{11}CH(OH)\overset{trans}{CH{=}CH}\overset{trans}{CH{=}CH}(CH_2)_6X}$$

The trans,trans dienol system occurs in reverse order in dimorphecolic acid.[22] The total synthesis by the route shown has been outlined and the difficulties discussed in a preliminary publication.[23]

The pharmacological preparation used for testing the smooth muscle stimulant activity of fatty acids must be carefully selected.[5] The guinea pig ileum has been shown to be insensitive to pure hydroxy unsaturated fatty acids but responsive to peroxides from these and other unsaturated fatty acids. In contrast the hamster colon[3] and rat colon[24] are sensitive to hydroxy unsaturated acids but insensitive to peroxides.

Because of the extremely ready peroxidation of ricinoleic acid and its general instability on storage, the equiactive, ricinelaidic acid (**1**, trans isomer) was prepared[25] and used as the biological standard. This was found† to stimulate the rat colon at 5-20 μg/ml with a shallow dose-response relationship. The four diunsaturated acids were all equiactive over the same concentration range but with a steep dose-response relationship making them about half as active as ricinelaidic acid at 5 μg/ml and rather more active at 20 μg/ml.

The trans,trans acid was also tested on the guinea pig uterus and found‡ to have about 0.001 of the activity of prostaglandin F2α. It showed no activity as an inhibitor of prostaglandin in the same test. The trans,trans acid was also examined in an antifertility test in the hamster and found‡ inactive at five times the effective dose of PGF2α.

It appears that the position and nature of the unsaturation in 12-hydroxyheptadecanoic acids does not materially affect the smooth muscle stimulant activity, even when, as in the *trans*-8,*trans*-10-dienoic acid, the arrangement of the functional groups is similar to the corresponding arrangement of the groups in prostaglandins.

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Experimental Section

All mp (determined on a Kofler hot-stage microscope) and bp are uncorrected. The structures of all compounds are supported by their ir and nmr spectra, and where appropriate, by uv spectra. Ir spectra were measured on a Perkin-Elmer Model 257 spectrophotometer as liquid films, or in the case of solids, as KBr discs; nmr spectra on a Perkin-Elmer R-10 60-MHz spectrometer in CCl_4 (Me_4Si), unless otherwise stated; uv on Unicam SP 500 and SP 800 spectrophotometers in 95% EtOH; glc on a Perkin-Elmer F11 flame-ionization instrument with N_2 as carrier gas. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values.

trans-4-Decen-1-yn-3-ol (3). To a soln of ethynylmagnesium bromide[26] (from EtBr, 0.65 mole) in dry THF (380 ml), cooled in ice, was added oct-*trans*-2-enal[10] (57.0 g, 0.45 mole) in dry THF (65 ml) over 1 hr. The mixture was stirred at room temp for 18 hr, decompd with satd NH_4Cl soln (150 ml), and extd (Et_2O). The exts were combined, washed (brine), dried (Na_2SO_4), concd, and distd to give 38.77 g (56%) of 3, bp 74–78° (0.8 mm). *Anal.* ($C_{10}H_{16}O$) C, H.

trans-3-Decen-1-yn-5-ol (4, R = H). 3 (36.0 g) was shaken under N_2 with 25% w/v H_2SO_4 (288 ml) for 24 hr and then extd (Et_2O). The exts were combined, washed (sat $NaHCO_3$ soln, brine), dried ($MgSO_4$), concd, and distd to give 24.8 g (69.5%) of 3-decen-1-yn-5-ol, bp 56–60° (0.06 mm). *Anal.* ($C_{10}H_{16}O$) C, H. Glc (5% Carbowax 20M TPA on Chromosorb G AW-DMCS, 125°) showed cis:trans 1:3. Spinning-band distn gave 15.0 g of 4 (R = H) (containing 4% cis), bp 78–79° (0.5 mm). *Anal.* ($C_{10}H_{16}O$) C, H.

5-Trimethylsiloxydec-*trans*-3-en-1-yne (4, R = $Si(CH_3)_3$). To a stirred soln of chlorotrimethylsilane (32.60 g, 0.30 mole) in dry C_6H_6 (25 ml) was added 4 (R = H) (15.24 g, 0.10 mole) in dry pyridine (23.73 g, 0.30 mole) over 40 min. The mixture was kept at reflux for 2 hr and at room temp overnight, and then concd *in vacuo* and filtered, and the residue washed with petroleum ether (bp 40–60°). The filtrate and washings were combined, dried ($MgSO_4$), concd, and distd to give 22.44 g (85.5%) of 4 (R = $Si(CH_3)_3$), bp 46–49° (0.02 mm). Glc (2.5% SE-30 on Chromosorb G AW-DMCS) showed isomer ratio trans:cis 96:4. Spinning-band distn gave 16.01 g (containing 0.83% cis) of 4 (R = $Si(CH_3)_3$), bp 70–74° (1.8 mm). *Anal.* ($C_{13}H_{24}OSi$) C, H.

16-Chlorohexadec-*trans*-7-en-9-yn-6-ol (5, X = Cl). To a suspension of $LiNH_2$ (from Li, 0.06 g-atom) in liq NH_3 (750 ml) 4 (R = $Si(CH_3)_3$) (6.73 g, 0.03 mole) was added over 25 min followed by anhyd Et_2O (20 ml). After stirring for 3 hr, 1-chloro-6-iodohexane (7.40 g, 0.03 mole) was added over 10 min, then anhyd Et_2O (20 ml) was added, and the mixture was stirred for 18 hr. The reaction was decompd with NH_4Cl (4.97 g), anhyd Et_2O (100 ml) added, and the NH_3 evaporated on a water bath. H_2O (50 ml) was added to the residue, the Et_2O soln removed, and the aqueous phase further extd (Et_2O). The exts (Et_2O) were combined, washed alternately with dil HCl and satd $NaHCO_3$ soln and finally with H_2O and brine, dried ($MgSO_4$), concd, and distd to give 5.20 g (64%) of impure 5 (X = Cl), bp 124–134° (0.005 mm). Chromatography on silica impregnated with 5% $AgNO_3$ and elution with 10% Et_2O in *n*-hexane gave an oil which, when distd, yielded 4.49 g (55%) of 5 (X = Cl), bp 134–139° (0.005 mm). *Anal.* ($C_{16}H_{27}ClO$) C, H, Cl.

12-Hydroxyheptadec-*trans*-10-en-8-ynoic acid (5, X = CO_2H). The chloride 5 (X = Cl) (2.01 g, 0.0075 mole) was converted by methods previously described[6] to the crude acid, as a yellow oil (1.60 g). Low temp (−15°) recrystn (petroleum ether, bp 40–60°) gave 1.40 g (68%) of 5 (X = CO_2H), mp 5–6°. *Anal.* ($C_{17}H_{28}O_3$) C, H.

7-Chloroheptanonitrile. To a suspension of NaCN (14.5 g, 0.29 mole) in DMF (285 ml) was added 1,6-dichlorohexane (89.94 g, 0.58 mole) and the mixture stirred for 22 hr at 65–70°, cooled, diluted with H_2O (860 ml), and extd (Et_2O). The exts were combined, washed (H_2O, brine), dried ($MgSO_4$), concd, and distd to give 26.09 g of 7-chloroheptanonitrile, bp 77–85° (0.6 mm). *Anal.* ($C_7H_{12}ClN$) C, H, Cl, N.

7-Chloroheptanal (6). 7-Chloroheptanonitrile (32.27 g, 0.22

mole) was reduced with $LiAl(OEt)_3H$[27] to give 18.24 g (55%) of **6**, bp 56–62° (0.6 mm), 2,4-dinitrophenylhydrazone, mp 93.5–94.5°. *Anal.* ($C_{13}H_{17}ClN_4O_4$) C, H, Cl, N

10-Chlorodec-1-yn-4-ol (7). The aluminum derivative of 3-bromoprop-1-yne (23.8 g, 0.2 mole) was treated with 7-chloroheptanal (9.35 g, 0.063 mole) under conditions similar to those described[28] to give 11.2 g (94%) of **7**, bp 88–93° (0.15 mm). *Anal.* ($C_{10}H_{17}ClO$) C, H, Cl.

10-Chloro-1-phenoxydec-2-yne (9). The sodio derivative of 3-phenoxyprop-1-yne (36.02 g, 0.27 mole) reacted with 1-chloro-7-iodoheptane (67.0 g, 0.26 mole) under conditions similar to those described[15] to give 57.55 g (84.5%) of **9**, bp 130–134° (0.009 mm). *Anal.* ($C_{16}H_{21}ClO$) C, H, Cl.

10-Chlorodec-*trans*-3-en-1-yne (10). The chloride **9** (57.0 g, 0.22 mole) was treated with $NaNH_2$ (0.5 mole) as described.[15] After acidification with NH_4Cl (35 g) and evaporation of the NH_3, isolation in the normal way gave 14.05 g (38%) of 10-chlorodec-3-en-1-yne, bp 61–66° (0.65 mm). *Anal.* ($C_{10}H_{15}Cl$) C, H, Cl. Glc (5% Carbowax 20M TPA on Chromosorb G AW-DMCS, 96°) showed cis:trans 1:1. Spinning-band distn gave 6.28 g of **10** (containing 0.9% cis), bp 63.5–65° (0.9 mm). *Anal.* ($C_{10}H_{15}Cl$) C, H. Cl.

16-Chlorohexadec-*trans*-9-en-7-yn-6-ol (11, X = Cl). The bromomagnesium derivative of **10** (2.99 g, 0.0175 mole) reacted with 1-hexanal (2.46 g, 0.025 mole) under conditions similar to those described[29] to give 4.27 g (90%) of **11** (X = Cl), bp 137–144° (0.005 mm). *Anal.* ($C_{16}H_{27}ClO$) C, H, Cl.

12-Hydroxyheptadec-*trans*-8-en-10-ynoic Acid (11, X = CO_2H). The chloride **11** (X = Cl) (2.0 g, 0.0074 mole) was converted to the acid in a way similar to that described for **5** (X = CO_2H). Recrystn (petroleum ether, bp 40–60°) gave 1.25 g (60%) of **11** (X = CO_2H), mp 32.5–33.5°. *Anal.* ($C_{17}H_{28}O_3$) C, H.

1-Bromooct-1-yn-3-ol (12). 1-Octyn-3-ol[6] (6.31 g, 0.05 mole) was treated with NaOBr by the method described[16] to give 8.85 g (85%) of **12**, bp 57–60° (0.01 mm). *Anal.* ($C_8H_{13}BrO$) C, H, Br.

Methyl 12-Hydroxyheptadeca-8,10-diynoate (14, R = CH_3). 8-Nonynoic acid[30] (3.08 g, 0.02 mole) was coupled with **12** (4.1 g, 0.02 mole) by the method described[16] to give 5.70 g of a yellow oil which was treated with ethereal CH_2N_2. Concn and distn gave 2.87 g (50%) of **14** (R = CH_3), bp 169–172° (0.008 mm). *Anal.* ($C_{18}H_{28}O_3$) C, H. Treatment of **14** (R = CH_3) with aqueous ethanolic KOH under reflux for 30 min gave **14** (R = H). *Anal.* ($C_{17}H_{26}O_3$) C, H.

11-Chloro-1-methoxyundeca-*cis*-1,*trans*-3-dien-5-ol (16, X = Cl). To a soln of ethylmagnesium bromide (from EtBr, 0.15 mole) in dry THF (90 ml), 3-methoxybut-*cis*-3-en-1-yne (11.04 g, 0.135 mole) in dry THF (40 ml) was added over 37 min such that the temp was maintained at 40–45°. After stirring at room temp for 1 hr and then cooling in ice, **6** (18.0 g, 0.12 mole) in dry THF (40 ml) was added over 40 min and stirred at room temp for 2.25 hr. With ice cooling abs EtOH (6.20 g, 0.135 mole) was added, the product stirred at room temp for 20 min and again cooled in ice, and $LiAlH_4$ (5.10 g, 0.135 mole) added over 22 min. The mixture was stirred in ice for 18 min and then at room temp for 2 hr. EtOAc (7 ml) and H_2O (82 ml) were successively added and the solid filtered off and washed (Et_2O). The washings and filtrate were combined, the aqueous phase was removed, and the organic soln was washed (H_2O, brine), dried ($MgSO_4$), and concd to give 30.57 g of crude **16** (X = Cl).

Acidification with tartaric acid after decomposition of the aluminum complexes gave **11-chloroundeca-*trans*-2,*trans*-4-dienal** (17, X = Cl), bp 101–106° (0.01 mm). *Anal.* ($C_{11}H_{17}ClO$) H; C: calcd, 65.82; found, 66.28; Cl: calcd, 17.67; found, 18.77; 2,4-dinitrophenylhydrazone, mp 115–116° [*Anal.* ($C_{17}H_{21}ClN_4O_4$) C, H, Cl, N]; semicarbazone, mp 175–176.5° [*Anal.* ($C_{12}H_{20}ClN_3O$) C, H, Cl, N].

11-Formylundeca-*trans*-8,*trans*-10-dienoic Acid (17, X = CO_2H). Crude **16** (X = Cl) (32.0 g, 0.14 mole) was stirred under N_2 with a suspension of NaCN (13.78 g, 0.28 mole) in DMF (275 ml) at 58–65° for 24 hr. The product was diluted with H_2O (825 ml) and extd (Et_2O). The exts were combined, washed (H_2O, brine), dried ($MgSO_4$), and concd to give 27.52 g of crude **16** (X = CN). This was kept at reflux for 64 hr with a soln of KOH (13.88 g, 0.25 mole) in abs EtOH (110 ml) and H_2O (30 ml), and the product poured into H_2O (300 ml) and washed (Et_2O). The aqueous phase was acidified with dil HCl (150 ml), allowed to stand for 10 min, and extd ($CHCl_3$). The exts were combined, washed (H_2O, brine), dried ($MgSO_4$), and concd to give 33.05 g of crude **17** (X = CO_2H), which was chromatographed on silica gel. Elution with 10% Et_2O in $CHCl_3$ gave a solid which recrystd (Et_2O) to give 11.95 g of **17** (X = CO_2H) as cream crystals, mp 98–98.5°. *Anal.* ($C_{12}H_{18}O_3$) C, H.

12-Hydroxyheptadeca-*trans*-8,*trans*-10-dienoic Acid (18, X = CO_2H). To a rapidly stirred soln of pentylmagnesium bromide (from *n*-$C_5H_{11}Br$, 0.006 mole) in dry THF (15 ml), cooled in ice, was added **17** (X = CO_2H) (0.420 g, 0.002 mole) in dry THF (20 ml) over 15 min. After stirring in ice for 1 hr, satd NH_4Cl (17 ml) and H_2O (40 ml) were successively added. The aqueous phase was acidified with dil HCl (4 ml) and extd (Et_2O). The exts were combined, washed (H_2O, brine), dried ($MgSO_4$), and concd to give a solid which recrystd (petroleum ether, bp 40–60°) to give 0.338 g (60%) of **18** (X = CO_2H), mp 62.5–63°. *Anal.* ($C_{17}H_{30}O_3$) C, H.

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