

(C₂₀H₂₆N₂) C, H, N. The maleate salt, mp 127–130°, was recrystd from *i*-PrOH-Et₂O. *Anal.* (C₂₀H₂₆N₂·C₄H₄O₄) C, H, N.

Acknowledgment. The authors are indebted to the members of the Biological Division of the Schering Corp. for the biological results herein reported and for permission to use some of their data. We are especially indebted to Dr. Irving I. Tabachnick, the late Dr. Franklin Roth, and Mr. Salvatore Tozzi and their staffs for the antianaphylactic and antihistamine data.

References

- (1) F. J. Villani, C. A. Ellis, and T. A. Mann, *J. Pharm. Sci.*, **60**, 1586 (1971) (paper 5).
- (2) F. J. Villani, C. A. Ellis, C. Teichman, and C. Bijos, *J. Med. Chem.*, **5**, 373 (1962).

- (3) F. J. Villani, C. A. Ellis, R. F. Tavares, and C. Bijos, *ibid.*, **7**, 457 (1964).
- (4) F. J. Villani, P. J. L. Daniels, C. A. Ellis, T. A. Mann, and K. C. Wang, *J. Heterocycl. Chem.*, **8**, 73 (1971).
- (5) J. A. Gautier, M. Mioque, C. Fauran, and M. Duchon d'Engenieres, *Bull. Soc. Chim. Fr.*, 3162 (1965).
- (6) (a) F. J. Villani, C. A. Ellis, R. F. Tavares, M. Steinberg, and S. Tolksdorf, *J. Med. Chem.*, **13**, 359 (1970); (b) F. J. Villani and C. A. Ellis, *ibid.*, **13**, 1245 (1970).
- (7) A. Sabbah, *La Vie Medicale*, **41**, 5401 (1969).
- (8) P. Amblard, *Lyon Mediterranee Med.*, **50**, 57 (1969).
- (9) G. Dumon, M-T. Brouillet-Gabriel and J. F. Dumon, *Marseille Med.*, **106**, 989 (1969).
- (10) B. Sigal and M. Herblot, *Gaz. Med. Fr.*, **77**, 364 (1970).
- (11) P. Chavanis, *Cah. Med. Lyon*, **46**, 1492 (1970).
- (12) M. L. Texier, *Bordeaux Med.*, 941 (1971).
- (13) E. Engelhardt, H. Zell, W. Saari, M. Christy, and C. Colton, *J. Med. Chem.*, **8**, 829 (1965).

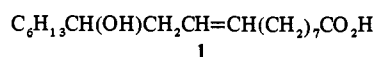
Synthesis of Fatty Acids with Smooth Muscle Stimulant Activity. 3. Acetylenic Analogs of 12-Hydroxyheptadeca-*trans*-8,*trans*-10-dienoic Acid¹

E. Crundwell* and A. L. Cripps

School of Pharmacy, Portsmouth Polytechnic, Hampshire, England. Received November 30, 1971

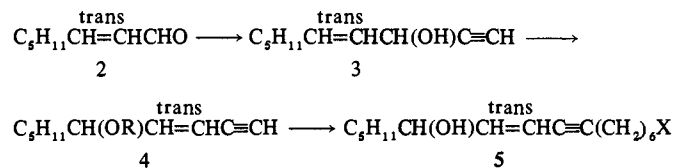
12-Hydroxyheptadeca-*trans*-8,*trans*-10-dienoic acid and analogs in which one or both double bonds are replaced by triple bonds have been prepared by methods which give products essentially free from *cis* isomers. These acids have been tested for smooth muscle stimulant activity and found to be approximately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



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, non-acidic, 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 action⁵ 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 series⁶ 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 mono-unsaturated acids then examined, 12-hydroxyheptadeca-*trans*-10-enoic acid was found to be the most active. Synthesis of diunsaturated analogs was therefore undertaken.

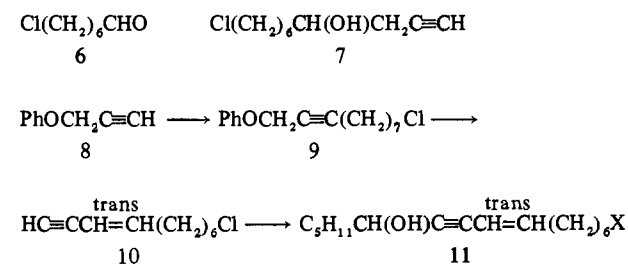
Introduction of a triple bond at position 8 gives 12-hydroxyheptadeca-*trans*-10-en-8-ynoic acid (5, X = CO₂H). The hydroxy-*trans*-enyne system occurs in helenynolic acid⁷ (9-hydroxyoctadeca-*trans*-10-en-12-ynoic acid) but in reverse order. It can be obtained,^{8,9} among other products, by



base-catalyzed cleavage of a methylene-interrupted epoxy-acetylenic acid.

In our approach oct-*trans*-2-enal¹⁰ (2) was converted to dec-*trans*-4-en-1-yn-3-ol (3) which was rearranged¹¹ 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 = CO₂H). The corresponding *cis* nitrile gave on hydrolysis and esterification also some methyl 8-(5'-pentylfur-2'-yl)octanoate, homologous with the furanoid acid obtained¹² from a seed oil. Preparation of this acid and of acids with *cis* double bonds will be reported elsewhere.

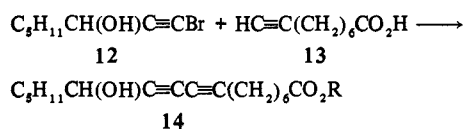
The isomeric 12-hydroxyheptadeca-*trans*-8-en-10-ynoic acid (11, X = CO₂H) incorporates a hydroxy-yne-*trans*-ene sequence found naturally only in reverse order, in ximenynolic acid¹³ (9-hydroxyoctadeca-*trans*-12-en-10-ynoic acid) which has been synthesized¹⁴ *via* acylation of a silver acetylide.



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

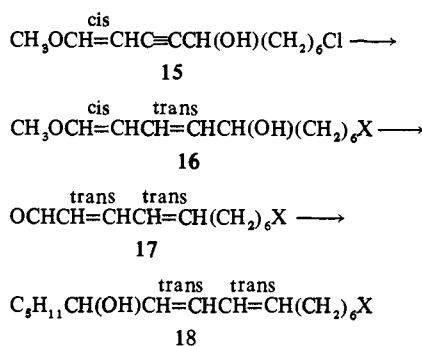
the tosylate or mesylate, was accompanied by loss of chloride. The 1,4 elimination of 2-alkynyl ethers¹⁵ was therefore exploited. 3-Phenoxyprop-1-yne (8) was converted to the chloroalkynyl ether (9) which with NaNH₂ gave a 1:1 mixture of the *cis*:*trans* isomers of 10-chlorodec-3-en-1-yne containing only traces of terminal olefinic material. Pure *trans* isomer (10) was elaborated *via* the hydroxyenyne chloride (11, X = Cl) to the acid (11, X = CO₂H).

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



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-diy-noic acid, isolated from *Onguekoa* gore.^{18,19}

Incorporation of further *trans* unsaturation in 12-hydroxy-heptadec-*trans*-10-enoic acid affords 12-hydroxyheptadeca-*trans*-8,*trans*-10-dienoic acid (18, X = CO₂H) which has been isolated^{20,21} as a by-product of prostaglandin biosynthesis.



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 colon³ and rat colon²⁴ 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 prepared²⁵ 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 F_{2α}. 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 PGF_{2α}.

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.

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 CCl₄ (Me₄Si), 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 N₂ 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 bromide²⁶ (from EtBr, 0.65 mole) in dry THF (380 ml), cooled in ice, was added oct-*trans*-2-enal¹⁰ (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 NH₄Cl soln (150 ml), and extd (Et₂O). The exts were combined, washed (brine), dried (Na₂SO₄), concd, and distd to give 38.77 g (56%) of 3, bp 74–78° (0.8 mm). *Anal.* (C₁₀H₁₆O) C, H.

trans-3-Decen-1-yn-5-ol (4, R = H). 3 (36.0 g) was shaken under N₂ with 25% w/v H₂SO₄ (288 ml) for 24 hr and then extd (Et₂O). The exts were combined, washed (sat NaHCO₃ soln, brine), dried (MgSO₄), concd, and distd to give 24.8 g (69.5%) of 3-decen-1-yn-5-ol, bp 56–60° (0.06 mm). *Anal.* (C₁₀H₁₆O) 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.* (C₁₀H₁₆O) C, H.

5-Trimethylsilyloxydec-*trans*-3-en-1-yne (4, R = Si(CH₃)₃). To a stirred soln of chlorotrimethylsilane (32.60 g, 0.30 mole) in dry C₆H₆ (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 (MgSO₄), concd, and distd to give 22.44 g (85.5%) of 4 (R = Si(CH₃)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(CH₃)₃), bp 70–74° (1.8 mm). *Anal.* (C₁₃H₂₄OSi) C, H.

16-Chlorohexadec-*trans*-7-en-9-yn-6-ol (5, X = Cl). To a suspension of LiNH₂ (from Li, 0.06 g-atom) in liq NH₃ (750 ml) 4 (R = Si(CH₃)₃) (6.73 g, 0.03 mole) was added over 25 min followed by anhyd Et₂O (20 ml). After stirring for 3 hr, 1-chloro-6-iodohexane (7.40 g, 0.03 mole) was added over 10 min, then anhyd Et₂O (20 ml) was added, and the mixture was stirred for 18 hr. The reaction was decompd with NH₄Cl (4.97 g), anhyd Et₂O (100 ml) added, and the NH₃ evaporated on a water bath. H₂O (50 ml) was added to the residue, the Et₂O soln removed, and the aqueous phase further extd (Et₂O). The exts (Et₂O) were combined, washed alternately with dil HCl and satd NaHCO₃ soln and finally with H₂O and brine, dried (MgSO₄), 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% AgNO₃ and elution with 10% Et₂O 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.* (C₁₆H₂₇ClO) C, H, Cl.

12-Hydroxyheptadec-*trans*-10-en-8-ynoic acid (5, X = CO₂H). The chloride 5 (X = Cl) (2.01 g, 0.0075 mole) was converted by methods previously described⁶ 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 = CO₂H), mp 5–6°. *Anal.* (C₁₇H₂₉O₂) 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 H₂O (860 ml), and extd (Et₂O). The exts were combined, washed (H₂O, brine), dried (MgSO₄), concd, and distd to give 26.09 g of 7-chloroheptanonitrile, bp 77–85° (0.6 mm). *Anal.* (C₇H₁₂ClN) C, H, Cl, N.

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

[†]We thank Dr. B. Jones for assistance in the experiments.

[‡]We are grateful to Dr. J. Hutton of I.C.I. Ltd. for these results.

mole) was reduced with $\text{LiAl}(\text{OEt})_3\text{H}^{27}$ to give 18.24 g (55%) of 6, bp 56–62° (0.6 mm), 2,4-dinitrophenylhydrazone, mp 93.5–94.5°. *Anal.* ($\text{C}_{13}\text{H}_{17}\text{ClN}_4\text{O}_4$) 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 described²⁸ to give 11.2 g (94%) of 7, bp 88–93° (0.15 mm). *Anal.* ($\text{C}_{10}\text{H}_{17}\text{ClO}$) 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 described¹⁵ to give 57.55 g (84.5%) of 9, bp 130–134° (0.009 mm). *Anal.* ($\text{C}_{18}\text{H}_{21}\text{ClO}$) 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.* ($\text{C}_{10}\text{H}_{15}\text{Cl}$) 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.* ($\text{C}_{10}\text{H}_{15}\text{Cl}$) 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 described²⁹ to give 4.27 g (90%) of 11 (X = Cl), bp 137–144° (0.005 mm). *Anal.* ($\text{C}_{16}\text{H}_{27}\text{ClO}$) 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.* ($\text{C}_{17}\text{H}_{29}\text{O}_3$) C, H.

1-Bromo-1-yn-3-ol (12). 1-Octyn-3-ol⁶ (6.31 g, 0.05 mole) was treated with NaOBr by the method described¹⁶ to give 8.85 g (85%) of 12, bp 57–60° (0.01 mm). *Anal.* ($\text{C}_8\text{H}_{13}\text{BrO}$) C, H, Br.

Methyl 12-Hydroxyheptadeca-8,10-dienoate (14, R = CH_3). 8-Nonynoic acid³⁰ (3.08 g, 0.02 mole) was coupled with 12 (4.1 g, 0.02 mole) by the method described¹⁶ to give 5.70 g of a yellow oil which was treated with ethereal CH_2N_2 . Conc and distn gave 2.87 g (50%) of 14 (R = CH_3), bp 169–172° (0.008 mm). *Anal.* ($\text{C}_{19}\text{H}_{28}\text{O}_3$) C, H. Treatment of 14 (R = CH_3) with aqueous ethanolic KOH under reflux for 30 min gave 14 (R = H). *Anal.* ($\text{C}_{17}\text{H}_{26}\text{O}_3$) 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.* ($\text{C}_{11}\text{H}_{17}\text{ClO}$) H; C: calcd, 65.82; found, 66.28; Cl: calcd, 17.67; found, 18.77; 2,4-dinitrophenylhydrazone, mp 115–116° [*Anal.* ($\text{C}_{17}\text{H}_{21}\text{ClN}_4\text{O}_4$) C, H, Cl, N]; semicarbazone, mp 175–176.5° [*Anal.* ($\text{C}_{12}\text{H}_{20}\text{ClN}_3\text{O}$) 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.* ($\text{C}_{12}\text{H}_{18}\text{O}_3$) C, H.

12-Hydroxyheptadeca-trans-8,trans-10-dienoic Acid (18, X = CO_2H). To a rapidly stirred soln of pentylmagnesium bromide (from $n\text{-C}_5\text{H}_{11}\text{Br}$, 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.* ($\text{C}_{17}\text{H}_{29}\text{O}_3$) C, H.

References

- (1) E. Crundwell and P. Farmer, *J. Med. Chem.*, 12, 547 (1969) (paper 2).
- (2) P. W. Ramwell and J. E. Shaw, *Ann. N. Y. Acad. Sci.*, 180, 10 (1971).
- (3) T. Dakhil and W. Vogt, *Arch. Exp. Pathol. Pharmacol.*, 243, 174 (1962).
- (4) F. C. Jager, *Experientia*, 26, 731 (1970).
- (5) N. Ambache, *Mem. Soc. Endocrinol.*, 14, 19 (1965).
- (6) E. Crundwell, M. A. Pinnegar, and W. Templeton, *J. Med. Chem.*, 8, 41 (1965).
- (7) R. G. Powell, C. R. Smith, C. A. Glass, and I. A. Wolff, *J. Org. Chem.*, 30, 610 (1965).
- (8) H. B. S. Conacher and F. D. Gunstone, *Chem. Commun.*, 281 (1968).
- (9) H. B. S. Conacher and F. D. Gunstone, *Lipids*, 5, 137 (1970).
- (10) L. Crombie, *J. Chem. Soc.*, 1007 (1955).
- (11) E. R. H. Jones and J. T. McCombie, *ibid.*, 261 (1943).
- (12) L. J. Morris, M. O. Marshall, and W. Kelly, *Tetrahedron Lett.*, 4249 (1966).
- (13) S. P. Lighthelm, *Chem. Ind. (London)*, 249 (1954).
- (14) L. Crombie and B. P. Griffin, *J. Chem. Soc.*, 4435 (1958).
- (15) P. H. Montijn, H. M. Schmidt, J. H. van Boom, H. J. T. Bos, L. Brandsma, and J. F. Arens, *Recl. Trav. Chim. Pays-Bas*, 84, 271 (1965).
- (16) R. Riemenschneider, G. Kasang, and C. Böhme, *Monatsh. Chem.*, 96, 1766 (1965).
- (17) W. Chodkiewicz, J. S. Alhuwalia, P. Cadiot, and A. Willemart, *C. R. Acad. Sci., Ser. C*, 245, 322 (1957).
- (18) F. D. Gunstone and A. J. Sealy, *J. Chem. Soc.*, 5772 (1963).
- (19) L. J. Morris, *ibid.*, 5779 (1963).
- (20) M. Hamberg and B. Samuelsson, *J. Biol. Chem.*, 242, 5344 (1967).
- (21) D. H. Nugteren, R. K. Beerthuis, and D. A. van Dorp, *Recl. Trav. Chim. Pays-Bas*, 85, 405 (1966).
- (22) C. R. Smith, T. L. Wilson, E. H. Melvin, and I. A. Wolff, *J. Amer. Chem. Soc.*, 82, 1417 (1960).
- (23) E. Crundwell and A. L. Cripps, *Chem. Ind. (London)*, 767 (1971).
- (24) T. Dakhil and W. Vogt, *J. Physiol.*, 160, 21P (1962).
- (25) J. P. Kass and S. B. Radlove, *J. Amer. Chem. Soc.*, 64, 2253 (1942).
- (26) E. R. H. Jones, L. Skatteböl, and M. C. Whiting, *J. Chem. Soc.*, 4765 (1956).
- (27) H. C. Brown and C. P. Garg, *J. Amer. Chem. Soc.*, 86, 1085 (1964).
- (28) M. Gaudemar, *Ann. Chim. (Paris)*, 1, 202 (1956).
- (29) A. S. Bailey, V. G. Kendall, P. B. Lumb, J. C. Smith, and C. H. Walker, *J. Chem. Soc.*, 3027 (1957).
- (30) L. Crombie, *ibid.*, 3055 (1962).