961. *Synthesis of Potential Antibacterial Agents. Part II.* A Pyrimidine Analogue of Chaulmoogric Acid.*

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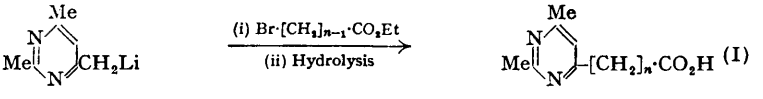
A general synthesis for ω-(2 : 6-dimethyl-4-pyrimidyl)alkane-1-carboxylic acids has been devised. Two such acids have been prepared and their tuberculostatic activities (*in vitro*) recorded. Attempts to prepare ω-(2-pyrimidyl)- and ω-(5-pyrimidyl)-alkane-1-carboxylic acids failed.

Chaulmoogra oil, and esters and salts of its predominating constituent fatty acids, chaulmoogric and hydnocarpic acid, have been used in the treatment of leprosy, a disease caused by an acid-fast bacterium, *Mycobacterium leprae*. Since *Mycobacterium tuberculosis* is also an acid-fast organism, interest has developed in the possibility of using these acids (or related synthetic compounds) as tuberculostatic agents (for a review see Burger, "Medicinal Chemistry," Intersci. Publ., New York, 1951, Vol. II). In view of the chemotherapeutic potentialities of pyrimidine compounds we have prepared 12-(2 : 6-dimethyl-4-pyrimidyl)dodecane-1-carboxylic acid (I; $n = 12$)—an analogue in which the *cyclo*pentenyl radical of chaulmoogric acid has been replaced by the 2 : 6-dimethyl-4-pyrimidyl radical.



(I)

In preliminary work, we failed to condense 11-carbethoxyundecanamidine with acetylacetone and to prepare ethyl 11-acetyl-12-ketotridecane-1-carboxylate (required as a possible precursor of a 5-pyrimidyl derivative) from sodioacetylacetone and ethyl 10-bromodecane-1-carboxylate. Having established (*J.*, 1951, 328; 1952, 3065) that 2 : 4 : 6-trimethylpyrimidine will undergo a chain-lengthening process in the 4-position by reaction of its lithium derivative with an alkyl halide, we tried to modify this procedure for our purpose. First, 2 : 6-dimethyl-4-pyrimidylmethyl-lithium was caused to react with 9-carbomethoxynonanoyl chloride and the product hydrolysed (cf. Graef, Fredericksen, and Burger, *J. Org. Chem.*, 1946, **11**, 257), but the keto-acid was

* Part I, *J.*, 1950, 2842.

produced only in poor yield and proved difficult to purify. In the second attempt, the ester obtained from the lithium derivative and ethyl 10-bromodecane-1-carboxylate yielded, on hydrolysis, the required acid containing eleven methylene groups in the side chain.

For preparation of the true 2 : 6-dimethyl-4-pyrimidyl analogue of chaulmoogric acid we required an 11-bromoundecane-1-carboxylic ester. The methyl ester had been prepared by Hunsdiecker and Hunsdiecker (*Ber.*, 1942, **75**, 291) and (impure) by Bhattacharya, Saletore, and Simonsen (*J.*, 1928, 2680). We obtained the required halogeno-ester from 10-bromodecane-1-carboxylic acid by the Arndt–Eistert method. The product was somewhat impure, probably owing to contamination with the 11-ethoxy-ester produced by reaction of the bromo-compound with the silver oxide and ethanol during the homologation process. This, however, was irrelevant for our purpose, so the impure ethyl 11-bromoundecane-1-carboxylate was caused to react with 2 : 6-dimethyl-4-pyrimidylmethyllithium, yielding an ester which, on hydrolysis, gave the 2 : 6-dimethyl-4-pyrimidyl analogue of chaulmoogric acid.

In view of the general availabillty of ω-halogeno-esters (Hunsdiecker and Hunsdiecker, *loc. cit.*) this synthesis may be regarded as general for acids of this type. Unfortunately, it apparently cannot be extended to acids containing other pyrimidyl radicals (Heyes and Roberts, *J.*, 1951, 328).

ω-(2 : 6-Dimethyl-4-pyrimidyl)undecane-1-carboxylic acid (I; $n = 11$) possessed a tuberculostatic activity of only 1, and the corresponding derivative of dodecane-1-carboxylic acid (I; $n = 12$) of 5 (10).* We are much indebted to Messrs. Boots Pure Drug Co. for determining these activities.

Experimental

Ethyl 10-Cyanodecane-1-carboxylate.—A solution of 14·6 g. (1·0 mol.) of ethyl 10-bromodecane-1-carboxylate (Ashton, Robinson, and Smith, *J.*, 1936, 284) and potassium cyanide (13 g., 4·0 mols.) in ethanol (100 c.c.) and water (20 c.c.) was boiled under reflux for 3 hours, cooled, and shaken with water (500 c.c.). The insoluble portion was collected in ether, and the ethereal extract was washed with water, dried (Na_2SO_4), and filtered. Removal of the ether and distillation *in vacuo* of the residue yielded *ethyl 10-cyanodecane-1-carboxylate* (5 g.), b. p. 196—198°/11 mm. (Found: N, 5·8. $C_{14}H_{25}O_2N$ requires N, 5·9%).

11-Carbethoxyundecanamidinium Chloride.—Dry hydrogen chloride was passed into ethyl 10-cyanodecane-1-carboxylate (5 g., 1 mol.) and dry ethanol (1 g., 1·04 mols.), cooled in ice, until 0·82 g. had been absorbed. After the mixture had been left at room temperature for 14 hours, ether (5 c.c.) was added and the precipitated ethyl imidate hydrochloride was filtered off. To a solution of this in dry ethanol (15 c.c.) was added dry ethanolic ammonia (50 c.c. of 9%), and the whole was shaken thoroughly. After 1 hour at room temperature, the solution was concentrated. The precipitated ammonium chloride was filtered off and the filtrate taken to dryness. The wax-like residue was purified by dissolution in 2-ethoxyethanol and precipitation by dry ether. Crystallisation from benzene yielded the *chloride* (2·0 g.) as wax-like plates, m. p. 79° (Found: C, 57·7; H, 9·6; N, 9·7. $C_{14}H_{29}O_2N_2Cl$ requires C, 57·4; H, 10·0; N, 9·6%).

10-Carbamyldecane-1-carboxylic Acid.—The amidinium chloride (1 g., 1·1 mols.), in ethanol (10 c.c.), was added to acetylacetone (0·3 g., 1·0 mol.) and sodium ethoxide (0·8 g., 4 mols.) in dry ethanol (15 c.c.), kept for 6 days at room temperature, diluted with water (20 c.c.), and heated under reflux for 1 hour. The resulting solution, after dilution with water, was strongly acidified and filtered. Ether-extraction of the filtrate (after it had been brought to pH 6·5) yielded no product. The precipitate (*ca.* 0·7 g.), crystallised from aqueous ethanol, yielded *10-carbamyldecane-1-carboxylic acid* as prisms, m. p. 143° (Found: C, 62·4; H, 9·7. $C_{12}H_{23}O_3N$ requires C, 62·8; H, 10·1%).

9-Carbomethoxynonanoyl Chloride—Methyl hydrogen sebacate (20 g.) and thionyl chloride (60 g.) were heated together under reflux for 4 hours and the product, b. p. 166—168°/14 mm., was isolated in the usual way. Morgan and Walton (*J.*, 1936, 902) record b. p. 177°/23 mm.

10-(2 : 6-Dimethyl-4-pyrimidyl)-9-ketodecane-1-carboxylic Acid.—2 : 4 : 6-Trimethylpyrimidine (*J.*, 1952, 3066) (10·4 g., 1 mol.) in dry ether (50 c.c.) was added with stirring and cooling to phenyl-lithium (7·14 g., 0·97 mol.) in dry ether (150 c.c.) under nitrogen. After the mixture had been heated under reflux and stirred for 15 minutes, 9-carbomethoxynonanoyl

* For explanation of these figures and details of bacteriological test see Part I, *loc. cit.*

chloride (18 g., 0·90 mol.) in dry ether (50 c.c.) was added. The mixture was heated under reflux with continuous stirring for 3 hours and was then set aside overnight under nitrogen. The mixture was shaken with water, and the ethereal layer extracted with 2N-hydrochloric acid. The acid extracts were made alkaline and extracted with ether. The ethereal extracts were dried ($MgSO_4$) and filtered and the solvent was removed. The residue was heated under reflux for 2½ hours with 10% ethanolic potassium hydroxide (50 c.c.) and then diluted with water, extracted with ether, made distinctly acid with a 2N-hydrochloric acid, and again extracted with ether. (Both lots of these ethereal extracts were discarded.) The pH of the aqueous layer was brought to 6·5 and the emulsion so formed was extracted with ether. This ethereal extract was dried ($MgSO_4$), filtered, and evaporated. The residue was extracted with hot light petroleum (b. p. 100—120°). When this extract was cooled crystals were deposited (0·05 g.), which were heated with charcoal in methanol and filtered. Evaporation of the solvent from the filtrate and crystallisation of the residue from light petroleum (b. p. 100—120°) yielded tan-coloured needles, to a solution of which in benzene there was added light petroleum (b. p. 60—80°) until a turbidity appeared. The first-formed yellow precipitate was filtered off. Addition of more light petroleum precipitated 10-(2 : 6-*dimethyl*-4-*pyrimidyl*)-9-*ketodecane*-1-*carboxylic acid* (8·5 mg.) as prisms, m. p. 96—97° (Found : C, 66·7; H, 9·1. $C_{17}H_{26}O_3N_2$ requires C, 66·6; H, 8·6%), insoluble in water but readily soluble in hydrochloric acid or sodium hydroxide solution.

11-(2 : 6-*Dimethyl*-4-*pyrimidyl*)*undecane*-1-*carboxylic Acid* (I; $n = 11$).—2 : 6-Dimethyl-4-pyrimidylmethyl-lithium (from 2 : 4 : 6-trimethylpyrimidine, 10·0 g., and phenyl-lithium, 6·7 g.) was treated with ethyl 10-bromodecane-1-carboxylate (22·6 g., 0·94 mol.). The product was isolated and hydrolysed as before. The diluted alkaline solution of the product was washed with ether, then made distinctly acid, and again washed with ether. The ethereal washings were discarded. When the pH of the washed aqueous layer was adjusted to 6·5 a tarry precipitate was obtained which was filtered off, dried, and extracted with hot light petroleum (b. p. 100—120°). The light petroleum solution was cooled and the deposited crystalline material (1·8 g.) was collected. A solution of this crude material in N-hydrochloric acid was warmed with charcoal and filtered. Adjustment of the pH to 6·5 led to the separation of a solid which on recrystallisation from light petroleum (b. p. 100—120°) yielded 11-(2 : 6-*dimethyl*-4-*pyrimidyl*)*undecane*-1-*carboxylic acid*, prisms, m. p. 94° [Found : C, 70·3; H, 9·9; N, 8·9%; equiv. (by titration of an ethanolic solution with aqueous potassium hydroxide), 306·1. $C_{18}H_{30}O_2N_2$ requires C, 70·6; H, 9·9; N, 9·1%; equiv., 306·4].

Ethyl 11-*Bromoundecane*-1-*carboxylate*.—10-Bromodecane-1-carboxylic acid (22 g.) (Ashton and Smith, *J.*, 1934, 438) was heated under reflux with thionyl chloride (19 c.c.) for 1 hour and the excess of the reagent removed in a vacuum. Distillation gave a fraction (14·7 g.), b. p. 186°/16 mm., which was added in dry ether (50 c.c.) during 15 minutes at 0—5° to ethereal diazomethane (from methylnitrosourea, 30 g.). The mixture was kept at room temperature for 1 hour and then evaporated *in vacuo* at 25°. The solid residue was heated in dry ethanol (100 c.c.) to 55—60°. Dry silver oxide (6·8 g.) in dry ethanol (30 c.c.) was added, in portions. The mixture was then raised to the b. p. and filtered. Distillation then gave impure ethyl 11-bromoundecane-1-carboxylate (7 g.), b. p. 139—142°/0·4 mm. (Found : C, 56·0; H, 9·7; Br, 24·5. $C_{14}H_{27}O_2Br$ requires C, 54·7; H, 8·9; Br, 26·0%. Calc. for a mixture with 8% of ethyl 11-ethoxyundecane-1-carboxylate : C, 56·0; H, 9·1; Br, 23·9%).

12-(2 : 6-*Dimethyl*-4-*pyrimidyl*)*dodecane*-1-*carboxylic Acid* (I; $n = 12$).—The lithium derivative, prepared from 2 : 4 : 6-trimethylpyrimidine (2·8 g., 1·0 mol.), was caused to react with the foregoing ester (7·0 g., *ca.* 0·9 mol.). The product was isolated and hydrolysed and the 12-(2 : 6-*dimethyl*-4-*pyrimidyl*)*dodecane*-1-*carboxylic acid* purified as described for the lower homologue. Recrystallisation of the purified material (0·1 g.) from light petroleum (b. p. 100—120°) yielded platelets, m. p. 96·5° (Found : C, 71·2; H, 10·0; N, 8·0. $C_{19}H_{32}O_2N_2$ requires C, 71·2; H, 10·1; N, 8·7%).

Note.—In the case of the ω-dimethylpyrimidylketoalkanecarboxylic acid and the two ω-dimethylpyrimidylalkanecarboxylic acids it was not possible to obtain satisfactory analytical figures for nitrogen. In general, results by the Dumas method were high and those by the Kjeldahl method low. The two values quoted above were obtained by the Kjeldahl method. The literature contains instances in which unsatisfactory nitrogen values (with concomitant, excellent values for carbon and hydrogen) are recorded for derivatives of methylpyrimidines (see, *e.g.*, Grewe, *Z. physiol. Chem.*, 1936, **242**, 94).

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