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131. The Synthesis and Some Reactions of N-Alkyl-4-Quinolone-3-Carboxylic Acids

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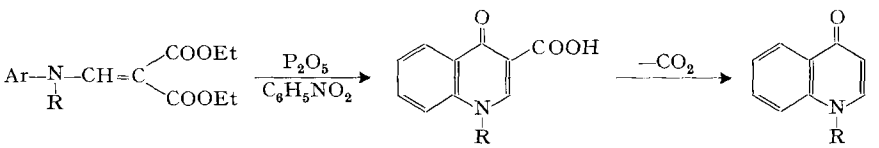
(6. III. 72)

Summary. A modification of the *Gould-Jacobs* reaction, particularly useful for the preparation of N-alkyl-4-quinolone-3-carboxylic acids, is described. Decarboxylation of these acids leads to N-alkyl-4-quinolones or, in the case of N-ethyl-benzo[h]-4-quinolone-3-carboxylic acid, to 4-ethoxy-benzo[h]quinoline. Evidence for the structure of the products is presented and the synthesis of relevant compounds is described.

During the last few years there has been considerable interest in substituted N-alkyl-4-quinolone-3-carboxylic acids because some congeners of this type of acid, notably oxolinic acid and nalidixic acid, exhibit significant antibacterial activity [1]. In connection with other problems we developed a very convenient modification of the *Gould-Jacobs* reaction for the preparation of such acids, and the recent paper by *Nakagome et al.* [2], which deals with similar procedures, prompts us to report our results on the cyclization of diethyl arylalkylaminomethylene-malonates (**1**), as well as some reactions of the resulting acids.



1 **2** **3**

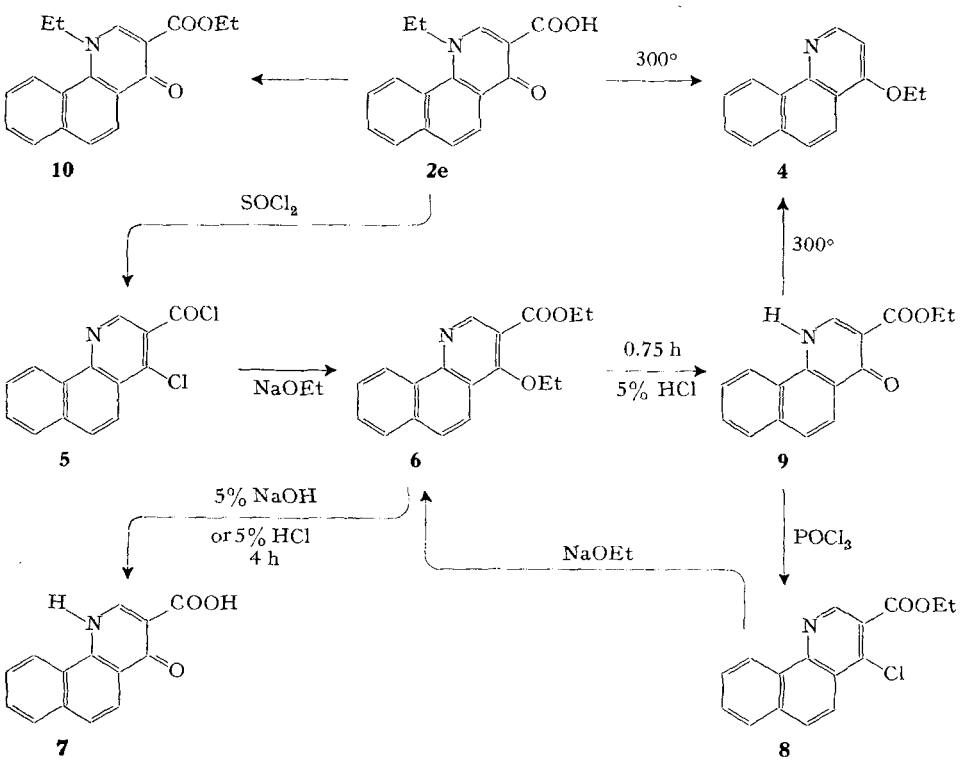
	Ar	R	Substituent on benzene ring
a	C_6H_5	CH_3	–
b	C_6H_5	C_2H_5	–
c	C_6H_5	n-C_4H_9	–
d	o-$CH_3C_6H_5$	CH_3	8-CH_3
e	1-$C_{10}H_7$	C_2H_5	7,8-benzo
f	2-$C_{10}H_7$	C_2H_5	5,6-benzo

Taylor & *Bartulin* prepared a few examples of dialkyl arylalkylaminomethylene-malonates by reaction of secondary amines with ethoxymethylene-malonates [3]. In our experience slightly higher reaction temperatures than those used with primary amines seemed to favor formation of the amino-esters. Cyclization in boiling diphenyl ether failed, as observed also by the Japanese authors [2]. We found, however, that in presence of phosphorous pentoxide, ring closure to quinolone derivatives took place readily, and, if the reaction was carried out in nitrobenzene, excellent yields of 1-alkyl-4-quinolone-3-carboxylic acids (**2**) were obtained.

Heating the acids **2a**, **b**, **c**, **f** to 300° or above gave the corresponding N-alkyl-4-quinolones (**3**). In contrast, acid **2e** yielded 4-ethoxy-benzo[h]quinoline (**4**) under similar conditions, and acid **2d** gave a mixture of 1,8-dimethyl-4-quinolone and 4-methoxy-8-methylquinoline (**13a**). An authentic sample of the last compound was also prepared by reaction of 4-chloro-8-methylquinoline (**12a**) with sodium methoxide.

The formation of O-alkylated products casts some doubt on the structures of the acids **2d** and **2e**, and by implication on those of the other acids as well. For instance, decarboxylation of 4-alkoxyquinoline-3-carboxylic acids would be expected to yield as primary products 4-alkoxyquinolines which in many cases rearrange to N-alkyl-quinolones under reaction conditions [4]. However, 4-ethoxy-benzo[h]quinoline (**4**) is known to resist the thermal rearrangement to the N-ethyl-benzo[h]quinolone [4], and in the present study we were able to show that 4-methoxy-8-methylquinoline

Scheme I

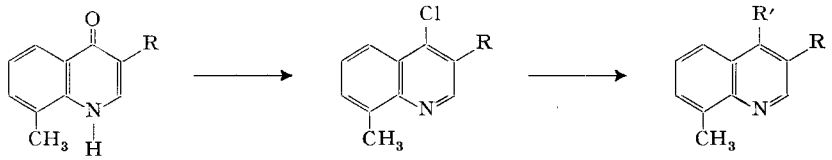


(**13a**) also fails to rearrange under conditions which bring about rapid rearrangement of 4-methoxyquinoline. Because of these observations we wished to ascertain that the cyclization products were indeed the N-alkylated compounds **2**.

Since 4-ethoxy-benzo[h]quinolone-3-carboxylic acid is not accessible for comparison with its N-alkylated isomer, we attempted to prepare the ethyl ester of acid **2e** for comparison with ethyl 4-ethoxy-benzo[h]quinoline-3-carboxylate. N-ethyl-4-quinolone-3-carboxylic acid has been esterified by successive treatment with thionyl chloride and ethanol [5], and the product was found to be different from ethyl 4-ethoxy-quinoline-3-carboxylate [4]. However, a similar approach failed when applied to acid **2e**, which on reaction with thionyl chloride gave 4-chloro-benzo[h]quinoline-3-carboxylic acid chloride (**5**). Reaction of this compound with sodium ethoxide readily gave ethyl 4-ethoxy-benzo[h]quinoline-3-carboxylate (**6**). The formation of compound **5** is reminiscent of the reaction of certain N-alkylpyridonecarboxylic acids with thionyl chloride [6] and seems to be consistent with a quinolone structure of the starting material.

The desired ethyl benzo[h]-4-quinolone-3-carboxylate (**10**) could be prepared by direct esterification of acid **2e** in concentrated sulfuric acid and was found to be different from its O-alkylated isomer **6**.

Scheme II



11

a) R = H
b) R = $COOC_2H_5$
c) R = COOH

12

a) R = H
b) R = $COOC_2H_5$

13

a) R = H, R′ = CH_3O
b) R = $COOCH_3$
R′ = CH_3O

Further support for the N-alkylquinolone structure of acids **2d** and **2e** was implied by the observation that they remained unaltered when refluxed with either dilute sodium hydroxide or dilute hydrochloric acid. In contrast, esters of O-alkylated isomeric acids suffer ether cleavage under such conditions. Thus, methyl 4-methoxy-8-methylquinoline-3-carboxylate was hydrolyzed to acid **11c** by dilute acid or base. Similarly, ethyl 4-ethoxy-benzo[h]quinoline-4-carboxylate yielded benzo[h]-4-quinolone-3-carboxylic acid (**7**) when treated with dilute base or by reflux with dilute hydrochloric acid for several hours. Interestingly, brief heating with 5% hydrochloric acid causes only ether cleavage, and ethyl benzo[h]-4-quinolone-3-carboxylate (**9**) is obtained in good yield. Most of these transformations are summarized in schemes I and II.

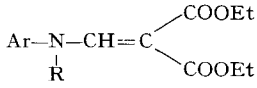
The biological evaluation of the compounds reported in this paper is still outstanding.

Experimental Part

Melting points were determined on a *Mel-Temp* apparatus and are uncorrected. Boiling points are also uncorrected. The analyses were performed by Mr. *J. F. Alicino*, Metuchen, New Jersey, and by Mr. *R. N. Boos* and associates of *Merck, Sharp and Dohme* Research Laboratories, Rahway, New Jersey. IR. spectra were taken on a *Beckman* IR.-8 spectrometer.

Starting Materials. Diethyl ethoxymethylenemalonate and most secondary amines were commercial preparations. N-Ethyl-β-naphthylamine was obtained in 71% yield by refluxing a solution of β-naphthylamine in absolute alcohol in presence of a large amount of *Raney* nickel for 10 h, b.p. 148–150°/2.5 Torr (lit. 167°/10–12 Torr [7]).

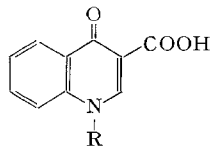
Preparation of Diethyl Alkylarylaminomethylene-malonates. Equimolecular amounts of secondary amine and diethyl ethoxymethylene-malonate were warmed to 120–140° for approximately 20 min; ethanol distilled and the last traces were removed at reduced pressure. The residue was cooled and, if solid, recrystallized from petroleum ether (b.p. 30–60°); if liquid, distilled *in vacuo*. Additional experimental information and analytical data are summarized in Table I.

Table I. *Diethyl Aminomethylene-malonates* 

Ar	R	M.p. or b.p. °C	Solvent[a]	% Yield	Formula	Calc. C	Calc. H	Calc. N	Found C	Found H	Found N
C_6H_5	CH_3	54–56	A	81	$C_{15}H_{19}NO_4$	64.97	6.91	5.05	65.18	6.89	5.59
C_6H_5	C_2H_5	49–51	A	54	$C_{16}H_{21}NO_4$	65.96	7.27	4.81	66.02	7.31	4.76
C_6H_5	n-C_4H_9	192/ 1.0 Torr		75	$C_{18}H_{25}NO_4$	67.69	7.89	4.39	67.95	7.84	4.28
o-$CH_3C_6H_4$	CH_3	58–61	B, C	80	$C_{16}H_{21}NO_4$	65.96	7.27	4.81	66.12	7.27	4.69
1-$C_{10}H_7$	C_2H_5	224/ 1.5 Torr		79	$C_{20}H_{21}NO_4$	70.36	6.79	4.10	70.41	6.55	4.07
2-$C_{10}H_7$	C_2H_5	229/ 1.0 Torr		76	$C_{20}H_{23}NO_4$			4.10			3.99

[a] A, petroleum ether, b.p. 30–60°; B, petroleum ether, b.p. 60–70°; C, heptane.

Preparation of N-Alkyl-4-quinolone-3-carboxylic Acids (2). – *Method A.* A mixture of appropriate aminomethylene-malonate (crude) and an equal amount of phosphorous pentoxide was warmed to about 130°. An exothermic reaction ensued (temperature rose to about 190°,

Table II. *Substituted 4-Quinolone-3-carboxylic Acids* 

Substitution on benzene ring of quinolone	R	M.p. °C	Method	% Yield	Formula	Calc. C	Calc. H	Calc. N	Found C	Found H	Found N
none	CH_3	296–298[a]	A	63	$C_{11}H_9NO_3$			7.10			6.89
			B	88							
none	C_2H_5	251–254	A	60	$C_{12}H_{11}NO_3$	66.35	5.10	6.45	66.51	5.22	6.31
			B	96							
none	n-C_4H_9	167–169	B	78	$C_{14}H_{15}NO_3$	68.56	6.16	5.71	68.86	6.23	5.55
8-CH_3	CH_3	257–259	A	63	$C_{12}H_{11}NO_3$	66.35	5.10	6.45	65.78	5.01	6.38
			B	85							
5,6-Benzo	C_2H_5	252–254	B	94	$C_{16}H_{13}NO_3$	71.90	4.90	5.24	71.74	4.88	5.13
7,8-Benzo	C_2H_5	241–242	A	41	$C_{16}H_{13}NO_3$	71.90	4.90	5.24	71.79	4.95	5.19
			B	76							

[a] Recrystallized from methoxyethanol (lit.: m.p. 295–296° [5]).

considerable effervescence and foaming). Water was added to the cooled mixture and the product was collected after brief warming.

Method B. Equal amounts of appropriate aminomethylene-malonate and phosphorus pentoxide were suspended in nitrobenzene (2 ml per g of ester) and the mixture was warmed to about 120–140°. An exothermic reaction took place with the temperature rising to about 160–190°. After slight cooling a small amount of water was added, the nitrobenzene driven off by indirect steam distillation and the product collected.

The crude acids were purified by recrystallization from ethanol. More experimental information and analytical data are summarized in Table II.

Decarboxylations. – *1-Methyl-4-quinolone* (**3a**). A 1 g sample of 1-methyl-4-quinolone-3-carboxylic acid was heated to 320° (bath temp.). Carbon dioxide was evolved and the residue was taken up with alcohol, the solution charcoaled, and the solvent evaporated. The crude product (0.6 g, 77%) was sublimed repeatedly and recrystallized from ethyl acetate: m.p. 149–152° (lit.: 152–153° [5]). The IR. spectrum of this compound was indistinguishable from that of a specimen prepared by rearrangement of 4-methoxyquinoline.

$C_{10}H_9NO$ (159.2) Calc. N 8.80 Found 8.62%

1-Ethyl-4-quinolone (**3b**) was prepared similarly; yield 71%, m.p. 100–102° (lit.: 100–101° [4]). Identified by comparison of the IR. spectrum with that of an authentic specimen.

1-Butyl-4-quinolone (**3c**). Heating 10 g of acid **2c** over a free flame and distilling rapidly at 25 Torr gave 5.9 g (64%) of an oil, which was taken up with a mixture of ether and chloroform, washed with dilute NaOH and NaCl solution, and the solvent removed after drying with sodium sulfate. The remaining oil was distilled, b.p. 221°/0.4 Torr.

$C_{13}H_{15}NO$ (201.3) Calc. N 6.96 Found N 6.68%

N-Ethyl-benzo[f]-4-quinolone (**3f**). Decarboxylation at 300–305° (bath temp.) of 0.3 g acid **2f** gave 0.13 g of sublimed material. Recrystallization from aqueous alcohol and from toluene (charcoal) gave the pure sample, m.p. 186–188° (lit. 185–187° [4]), which was identified by comparison of its IR. spectrum with that of an authentic sample.

1,8-Dimethyl-4-quinolone (**3d**). A mixture of 2.2 g of acid **2d**, 25 ml of dibutyl phthalate and a small amount of copper bronze was heated to 280° for about 20 min. The reaction mixture was cooled, diluted with 125 ml of chloroform, filtered and extracted with 5% hydrochloric acid. The acidic extract was made alkaline with 10% sodium hydroxide and the quinolone was taken up with chloroform. The crude product (0.7 g, 41%) obtained after evaporation of the chloroform was recrystallized from toluene and sublimed at 250°/0.1 Torr, m.p. 150–151°. Analysis and IR. spectrum indicated presence of water.

$C_{11}H_{11}N \cdot 0.5\,H_2O$	Calc.	C 72.50	H 6.64	N 7.69	H_2O 4.95%
(182.2)	Found	,, 72.57	,, 6.49	,, 7.41	LOD 4.95%
		,, 72.49	,, 6.62	,, 7.49%	

Decarboxylation of dry acid **2d** (3.0 g) at 310–330° (bath) led to a mixture which could be partially separated by distillation. Material (0.3 g) distilling at 0.5 Torr and bath temperature of 220° solidified and was recrystallized from petroleum ether (b.p. 30–60°); identified as *4-methoxy-8-methylquinoline* by m.p., mixed m.p., and IR. spectrum. A second fraction, distilling at 0.7 Torr and at a bath temperature of 245–265°, crystallized readily. Repeated sublimation *in vacuo* gave a product m.p. 145–147°, identified as *1,8-dimethyl-4-quinolone* by mixed m.p., and by IR. spectrum.

4-Methoxy-8-methylquinoline. Crude 4-chloro-8-methylquinoline [8] (3.5 g) in 20 ml dimethylformamide was added to a solution of 0.5 g sodium in 10 ml methanol. After refluxing for 24 h, the volatile parts were removed and water was added to the residue. The crystallized product (3.3 g, 97%) was collected and dried. The pale yellow analytical sample melted at 91° (from petroleum ether b.p. 60–70°).

$C_{11}H_{11}NO$ (173.2) Calc. C 76.28 H 6.40 N 8.09% Found C 76.14 H 6.56 N 7.96%

4-Ethoxy-benzo[h]quinoline (**4**). Crude N-ethyl-benzo[h]-4-quinolone-3-carboxylic acid (**2e**, 0.55 g) was decarboxylated at 300° bath temperature and the residue was sublimed to give 0.21 g (46%) crude product. Repeated recrystallization from aqueous alcohol gave a sample of m.p.

119–121° (lit. 119–120°, 116–117° [4] [9]) which was identified by mixed m.p. and by IR. spectrum. The same compound was obtained on appropriate work-up after heating a sample of ethyl benzo-[h]-4-quinolone-3-carboxylate (**9**) to 300°.

Other reactions of 4-quinolone-3-carboxylic acids. – *Ethyl N-ethyl-4-quinolone-3-carboxylate.* A mixture of 3.0 g of acid **2b** and 30 ml of thionyl chloride was refluxed for 5 h. Excess thionyl chloride was removed. The crystalline residue was washed with petroleum ether, but not further purified. A 1 g sample of this material was dissolved in 10 ml of warm absolute alcohol. The excess alcohol was distilled and the residue was made alkaline with 1 M sodium carbonate. Extraction with ethyl acetate furnished 0.3 g of the desired ester, m.p. 102.5–105° (lit.: 110–111°, 104–105° [2]).

$C_{14}H_{15}NO_3$ (245.3) Calc. C 68.56 H 6.16 N 5.71% Found C 68.67 H 6.32 N 5.88%

4-Chloro-benzo[h]quinoline-3-carboxylic acid chloride (**5**). A mixture of 5.0 g crude acid **2e** and 20 ml of thionyl chloride was refluxed for 3 h. Benzene was added after cooling and the crystalline product (4.2 g, 81%) was collected. Recrystallization from toluene gave the analytical sample, pale yellow crystals of m.p. 164–166°.

$C_{14}H_7Cl_2NO$	Calc.	C 60.90	H 2.56	N 5.07	Cl 25.68%
(276.14)	Found	,, 61.02	,, 2.54	,, 5.14	,, 25.86%

A 1 g sample of this compound was mixed with a solution of 0.3 g of sodium in 10 ml of absolute alcohol. Ether (40 ml) was added and the solid which formed was removed. The ethereal solution was washed with water, dried, and the solvent was evaporated leaving *ethyl 4-ethoxy-benzo[h]quinoline-3-carboxylate* (**6**), m.p. 59–60°, identified by mixed m.p. and IR. spectrum.

Ethyl 4-chloro-benzo[h]quinoline-3-carboxylate (**8**). A mixture of 20.0 g of ethyl benzo[h]-4-quinolone-3-carboxylate (**9**) [5] and 60 ml of phosphorus oxychloride was refluxed for 6 h. The volatile material was removed at reduced pressure and the remainder was treated with ice and water. The product was collected after neutralization with 2.5 M sodium hydroxide and recrystallized from alcohol (recovery 19 g, 89%), m.p. 120–121° after further recrystallization from the same solvent.

$C_{16}H_{12}ClNO_2$ (285.7) Calc. C 67.26 H 4.23 N 4.90% Found C 67.10 H 4.10 N 4.70%

Ethyl 4-ethoxy-benzo[h]quinoline-3-carboxylate (**6**). A solution of 11.4 g of the chloroester **8** in a mixture of dimethylformamide and absolute alcohol (40 ml of each) was added to a solution of 1.0 g of sodium in 25 ml of ethanol. The prompt reaction was completed by refluxing for 0.75 h. The mixture was concentrated to about one third of its original volume and poured onto ice and water. The crystalline product (8.8 g 74%) was collected and air-dried, m.p. 60–61.5° after repeated recrystallization from ethanol.

$C_{18}H_{17}NO_3$ (295.3) Calc. C 73.20 H 5.80 N 4.74% Found C 73.44 H 5.74 N 4.61%

Ethyl N-ethyl-benzo[h]-4-quinolone-3-carboxylate (**10**)[1]. Absolute ethanol (18 ml) was added to a cooled and stirred suspension of 3 g of acid **2e** in 9 ml of concentrated sulfuric acid. The mixture was gradually heated (0.5 h) to boiling. The clear solution was cooled and poured into 150 ml of 2 M sodium carbonate and ice. The product was extracted into ethyl acetate, the extract washed with sodium carbonate and water and dried with sodium sulfate. After treatment with charcoal this solution was concentrated to about one half of its original volume and the product (0.91 g, 28%) was precipitated with low-boiling petroleum ether. The hygroscopic ester melted at 140.5–141.5° after several recrystallizations from ethyl acetate.

$C_{18}H_{17}NO_3$ (295.3) Calc. C 73.20 H 5.80 N 4.74% Found C 73.04 H 5.81 N 5.03%

Synthesis of methyl 4-methoxy-8-methylquinoline-3-carboxylate (13b) (Scheme II). – *Ethyl 4-chloro-8-methylquinoline-3-carboxylate* (**12b**). This compound was prepared essentially according to the method of *Surry* [10] by refluxing 10.0 g of ester **11b** [11], 5 ml of phosphorous oxychloride and 70 ml of methylene dichloride for 1 h. After cooling overnight the mixture was

[1]) This compound (m.p. 136–137°) has been reported by *Nakagome et al.* [2]. However, the published analytical data (calculated and found values) do not agree with those required for this ester.

poured onto ice and made weakly alkaline with 3M ammonia. The organic layer was separated, washed with 1% sodium hydroxide and water and dried with sodium sulfate. The solvent was distilled and the residue (10.4 g, 94%) solidified. The analytical sample was obtained by repeated recrystallization from aqueous alcohol (cooling to $-10°$ necessary), m.p. 40–41°.

$C_{13}H_{12}ClNO_2$ (249.7) Calc. C 62.53 H 4.85 N 5.61% Found C 62.65 H 4.96 N 5.52%

Methyl 4-methoxy-8-methylquinoline-3-carboxylate (**13b**). A solution of 6.5 g of crude ethyl 4-chloro-8-methylquinoline-3-carboxylate in 15 ml of dimethylformamide was added to sodium methoxide prepared by dissolving 0.7 g of sodium in 15 ml of methanol, followed by evaporation of most of the methyl alcohol. The exothermic reaction was completed by brief reflux, the solvent was removed at reduced pressure, water and ether were added to the residue and the ether layer was separated and combined with two additional ether extracts. Upon evaporation of the ether 4.0 g (67%) of solid was obtained. Recrystallization from cyclohexane gave the analytical sample, m.p. 74°.

$C_{13}H_{13}NO_3$ (231.3) Calc. C 67.52 H 5.67 N 6.06% Found C 67.50 H 5.63 N 5.90%

This compound (m.p. 73–74°) was also obtained by reaction of diazomethane with 8-methyl-4-quinolone-3-carboxylic acid.

Comparison of behavior of 4-methoxyquinoline and 4-methoxy-8-methylquinoline on heating. – Samples of 4-methoxyquinoline and 4-methoxy-8-methylquinoline were placed in separate test tubes and immersed simultaneously into a metal bath preheated to 250°. Heating was continued and temperature slowly increased to 280° over a period of 25 minutes. 4-Methoxy-8-methylquinoline refluxed under these conditions while 4-methoxyquinoline rearranged to N-methyl-4-quinolone. Both samples darkened and crystallized after cooling and were identified by m.p. and IR. spectrum.

Hydrolyses of esters. – Reflux of esters **6**, **13b**[2]) with 5% sodium hydroxide or 5% hydrochloric acid gave the results listed in Table III. Similar treatment of acids **2b**, **d**, **e**, did not cause any change. All products were identified by m.p. and IR. determinations.

Table III. *Hydrolyses of Esters*

Ester	Reagent	Reflux time	Product	% Yield[a])
6	NaOH	4.5	**7**	100
6	HCl	4	**7**	100
6	HCl	0.75	**9**	90
13b	NaOH	2	**11c**	90
13b	HCl	2	**11c**	90

[a]) Rounded off.

The authors wish to thank Mrs. *Stuart Thompson* (*Jane A. Beach*, Wells College 1970) for her valuable contributions in the early stages of this investigation.

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132. Terpene Compounds as Drugs, XVI. Characterization of the Anabolic 19-Nortestosterone 17β-*trans*, *trans*- and -*cis*, *trans*-Homofarnesate

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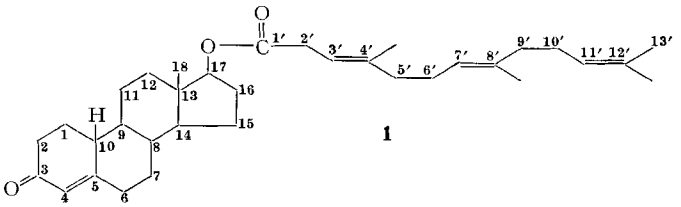
(30. 3. 72)

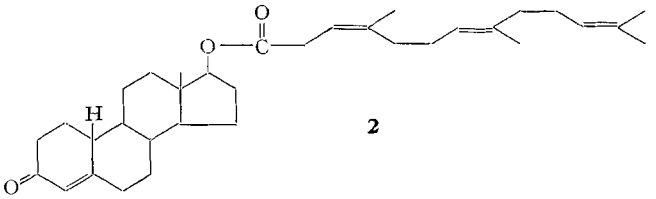
Summary. 19-Nortestosterone 17β-*trans*,*trans*- and -*cis*,*trans*-homofarnesate **1** and **2** have been prepared and characterized. Their structure and configuration were identified by mode of formation, elemental analyses, IR. and particularly by NMR. spectra.

Recently we have reported on the anabolic potency of 19-nortestosterone 17β-homofarnesate [1], as a stereoisomeric mixture consisting of 19-nortestosterone 17β-3′,4′-*trans*,7′,8′-*trans*- (**1**) and -3′,4′-*cis*,7′,8′-*trans*-homofarnesates (**2**). This paper deals with the preparation and characterization of the two stereoisomers.



1

19-Nortestosterone 17β-3′,4′-*trans*,7′,8′-*trans*-homofarnesate



2

19-Nortestosterone 17β-3′,4′-*cis*,7′,8′-*trans*-homofarnesate

19-Nortestosterone homofarnesates were obtained according to one of the methods previously described: the appropriate farnesyl bromide gave with sodium cyanide