cannot accommodate rigid para substituents with a linear length exceeding 5.0 Å.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are corrected. IR spectra were recorded in KBr disks on a Perkin-Elmer grating infrared spectrophotometer Model 257. NMR spectra were taken on a Jeol C-60HL spectrometer for 10% solutions in either $CDCl_3$ or CCl_4 containing Me_4Si as an internal standard. Mass spectra were taken with a Hitachi Perkin-Elmer RMU-6 instrument, the samples being introduced directly into the ion source through a vacuum lock, electron energy 70 eV, electron current 20 μA, source temperature 150–350 °C, secondary electron multiplier as the detector. TLC's were performed on either neutral aluminum oxide precoated plates (Al F, 0.25 mm, Riedel-De Haen AG, Germany) or silica gel precoated plates (Si F, Riedel-De Haen, AG, Germany), both containing fluorescent indicator. Spots were detected by UV light at 254 nm and by exposure to I_2 vapor. Preparative gas chromatography of cis and trans isomers of isoeugenol was carried out on a Varian 90P GC instrument with thermal conductivity detector (column, Apiezon L 20% on Chromosorb W, AW, DMCS, 80–100 mesh). Helium was used as a carrier, column temperature 180 °C, detector and injector temperature 230 °C.

Reaction products were routinely analyzed by IR, NMR, and mass spectrometry and by TLC. All compounds showed the expected spectral characteristics. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.3% of the theoretical results.

Pharmacology. β_1-Blocking activity was determined on isolated rat atria.[10] β_2-Blocking activity was determined on isolated rat stomach fundus.[10] The rationale for using this organ rather than tracheal or vascular muscle is the relative simplicity of the test and its clear distinction from β_1 responses.

Chemistry. 2-(4′-Hydroxybenzyl)-2-methyl-1,3-dioxolane (16). Ketalization of 3-(4′-hydroxyphenyl)propan-2-one was accomplished in two ways.

(**a**) 3-(4′-Hydroxyphenyl)propan-2-one (2.40 g, 16 mmol) was dissolved in 120 mL of benzene, and ethylene glycol (36 mL, 640 mmol) and *p*-TosOH–H_2O (710 mg) were added. Following azeotropic distillation of the reaction mixture (72 h), the benzene layer was separated, washed with water, dried ($MgSO_4$), and evaporated. The ketalic product (1.65 g, 53% yield), obtained as a colorless viscous oil, lacked the carbonyl absorption at 1700 cm^{-1}. The product was used without further purification in the reaction with epichlorohydrin.

(**b**) 3-(4′-Hydroxyphenyl)propan-2-one (2.50 g, 17 mmol) was dissolved in a chloroform–ethylene glycol mixture (20:40 mL, respectively), and 4 Å molecular sieves and 1 mL of concentrated H_2SO_4 were added. The reaction mixture was stirred at room temperature for 7 days. The mixture was then extracted with ether, washed with $NaHCO_3$ solution and water, dried ($MgSO_4$), and evaporated. The resulting ketalic product was obtained in 77% yield (2.5 g).

1-Aryloxy-2,3-epoxypropanes. The epoxypropanes were prepared according to published procedures.[7] The compounds were purified by column chromatography on neutral alumina grade II. The eluting solvents were mixtures of petroleum ether (bp 40–60 °C) and chloroform. Solid products were recrystallized: 1-(7′-oxy-2′,3′-dihydro-3′-oxo-1′,4′-benzisoxazinyl)-2,3-epoxypropane, mp 164–166 °C, C, H, N, M^+; 1-[4′-(*N*-carboxamidomethyl)phenoxy]-2,3-epoxypropane, mp 108–109 °C (toluene), C, H, N, M^+.

The final aryloxypropanolamines were prepared by the addition of isopropylamine to 1-(aryloxy)-2,3-epoxypropanes by the general method described before.[7]

Acknowledgment. The able technical assistance of Miss C. Weiss is gratefully acknowledged.

References and Notes

(1) Presented in part at the Vth International Symposium on Medicinal Chemistry, Paris, July 1976.
(2) (a) This work forms part of a Ph.D. Thesis submitted by M. Erez to Tel-Aviv University Medical School; (b) The Institute for Clinical Physiology and Bio-Medical Engineering, Beilinson Medical Center, Petah-Tikva, Israel.
(3) Department of Pharmacology and Experimental Therapeutics, Hebrew University Medical Center, Ein Kerem, Jerusalem, Israel.
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Antiallergic Activity of Tetracyclic Derivatives of Quinoline-2-carboxylic Acids. 1

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Substitution of 1,4-dihydro-4-oxoquinoline-2-carboxylic acid by acetyl, benzoyl, and phenylsulfonyl substituents was found to enhance activity in the rat passive cutaneous anaphylaxis assay. A further increase in activity, to equipotency with DSCG, was achieved by incorporation of the 8-benzoyl moiety into a tetracyclic structure to give 1,4-dihydro-4,11(1*H*,11*H*)-dioxoindeno[1,2-*b*]quinoline-2-carboxylic acid (**20**). In contrast, the reverse isomer **19** was found to have little activity.

Reports[1-3] describing the antiallergic activity of quinoline-2-carboxylic acids (**1**) lead us to report on a parallel series of investigations within our laboratories. Following the introduction of disodium cromoglycate (DSCG, **2**),[4]

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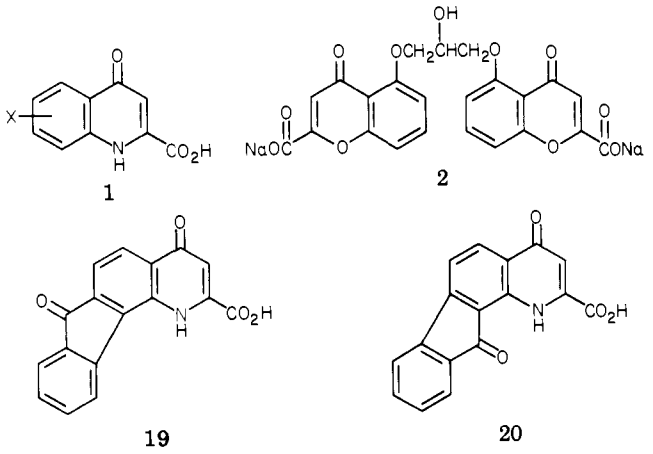


1 2

19 20

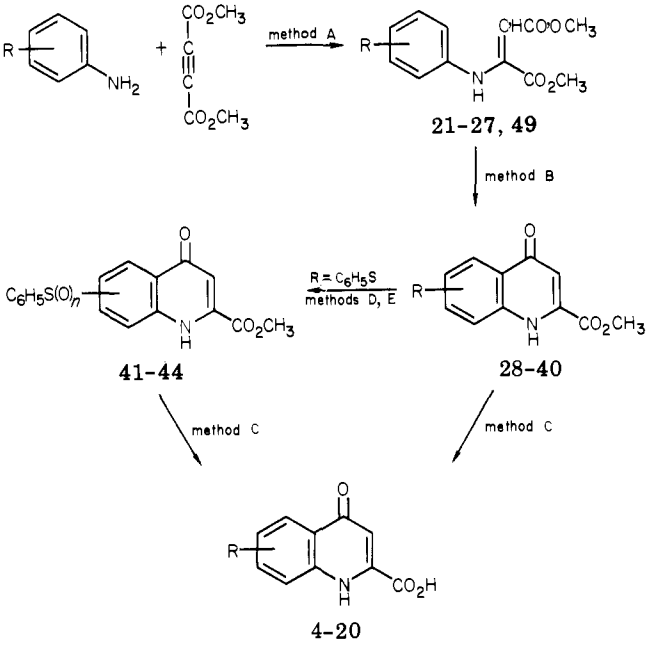
workers in our English laboratory independently established that quinoline-2-carboxylic acid derivatives have similar activity in laboratory models[5] but were unable to pursue their initial findings. In this note we report our continuation of our co-workers' studies in which we find that the activity of quinoline-2-carboxylic acid is enhanced by acetyl, benzoyl, and phenylsulfonyl substituents. Furthermore, incorporation of the benzoyl moiety into a tetracyclic structure has a pronounced effect on activity leading in one case to an indenoquinoline **20** equipotent to DSCG (**2**) while its reverse isomer **19** was not active.

Chemistry. The acetyl-, benzoyl-, and phenylthioquinoline-2-carboxylic acids **4**–**14** as well as the indenoquinolines **19** and **20** listed in Table I were synthesized from appropriately substituted anilines and dimethyl acetylenedicarboxylate (DMAD) by the procedure previously described by others[2,3,6] and illustrated in Scheme I. The phenylsulfinyl and phenylsulfonyl derivatives **15**–**18** were obtained from the respective phenylthioquinoline esters **36**–**38** (Table III) by oxidation with hydrogen peroxide in acetic acid. With meta-substituted anilines it is possible that mixtures of 5- and 7-substituted quinolines could be obtained. However, only single isomers were isolated and they were all assigned as the 7-substituted quinolines from their ^{1}H NMR spectra which showed the splitting patterns expected for 1,2,4-trisubstituted benzenes.

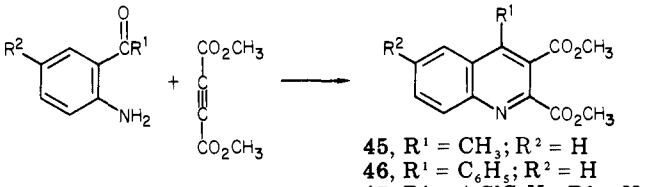
Anilines with an *o*-carbonyl moiety can react either as shown in Scheme I or can condense with the carbonyl moiety as illustrated in Scheme II.[7] For example, Taylor and Heindel reported[8] that the butenedioate **21** from *o*-aminoacetophenone and DMAD reacts in high-boiling solvents as illustrated in Scheme I to give methyl 8-acetyl-1,4-dihydro-4-oxoquinoline-2-carboxylate (**30**) but that under basic conditions it can react as shown in Scheme II to give dimethyl 4-methylquinoline-2,3-dicarboxylate (**45**). These same authors found[8] that 2-aminobenzophenone and DMAD reacted in refluxing benzene to give the 4-phenylquinoline derivative **46** as the only isolated product.

In contrast, we found that by using methanol as a solvent 2-aminobenzophenone and 2-amino-4-methylbenzophenone gave the butenedioates **23** and **24**, respectively, and these intermediates could be cyclized to the desired 8-benzoylquinolines in refluxing phenyl ether. In attempting to extend these conditions to other substituted 2-aminobenzophenones we found that 2-amino-4′-chlorobenzophenone gave only the 2,3-dicarboxylate derivative **47**, while 2-amino-5-chlorobenzophenone gave a mixture of the dicarboxylate derivative **48** and the butenedioate **49** (R = 2-benzoyl-4-chloro). In this latter case the butenedioate could be separated and cyclized to the 8-benzoylquinoline **35**. These data show that the products from the reaction of *o*-aminobenzophenones and DMAD are influenced by both solvent and substituent and suggest a need for further study.

Scheme I



Scheme II



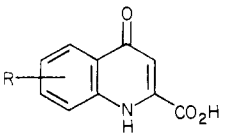
45, $R^1 = CH_3$; $R^2 = H$
46, $R^1 = C_6H_5$; $R^2 = H$
47, $R^1 = 4\text{-}ClC_6H_4$; $R^2 = H$
48, $R^1 = C_6H_5$; $R^2 = Cl$

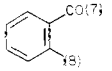
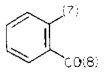
Biological Methods and Results. The quinoline-2-carboxylic acids and esters were tested for their ability to inhibit the passive cutaneous anaphylaxis (PCA) reaction in Sprague–Dawley rats by a method substantially the same as that described by others.[2,3,9] Briefly, antibody for passive sensitization was obtained from rats sensitized to egg albumin using *Bordetella pertussis* as an adjuvant. The antibody was injected intradermally into the mid-dorsal region of the rat and sensitivity was allowed to develop for 24 h. Compounds were then administered intraperitoneally 5 min or orally 15 min prior to intravenous administration of egg albumin and Evans blue dye. The size and the intensity of the characteristic blue weal were compared to non-drug-treated animals and the percent inhibition was determined. Compounds were initially tested via intraperitoneal injection at doses of 50 or 25 mg/kg. Active compounds were then further tested at 10, 5, 2.5, and 1.25 mg/kg. Groups of six animals were used for all dose levels and control groups.

The lowest intraperitoneal dose giving >50% inhibition with a $p \leq 0.05$ (Student's t test) is recorded in Table I as the minimum effective dose (MED) and is the result of a single series of experiments except where noted. None of the active compounds was found to have activity when given orally. With the exception of **30** which had an MED = 25 mg/kg, none of the esters showed activity at the screening doses.

No consistent structure–activity relationships are apparent to us from examining the data in Table I. What

Table I. Quinoline-2-carboxylic Acids[a]



compd	R	formula[b]	mp, °C	yield, %	crystn solvent	MED, mg/kg[c]
3	H	$C_{10}H_7NO_3$[d]	278 dec			50[e]
4	6-CH_3CO	$C_{12}H_9NO_4$[f]	266-268[f]	75	DMF	25[e]
5	7-CH_3CO	$C_{12}H_9NO_4$	286-287 dec	45	DMF	10
6	8-CH_3CO	$C_{12}H_9NO_4$	>250	46	DMF	25
7	6-C_6H_5CO	$C_{17}H_{10}NNaO_4$[g]	>300	59	H_2O	10[g]
8	7-C_6H_5CO	$C_{17}H_{11}NO_4$	263 dec	20	methoxyethanol	25
9	8-C_6H_5CO	$C_{17}H_{11}NO_4$	265-268	66	Me_2SO	25
10	8-*p*-$CH_3C_6H_4CO$	$C_{18}H_{13}NO_4$	245 dec	91	H_2O	25
11	6-Cl-8-C_6H_5CO	$C_{17}H_{10}ClNO_4$	262-264 dec	32	EtOH	50
12	6-C_6H_5S	$C_{16}H_{11}NO_3S \cdot H_2O$[h,i]	255-260 dec	75	MeOH-H_2O[j]	>50
13	7-C_6H_5S	$C_{16}H_{11}NO_3S$	258-260	100	MeOH-H_2O[j]	>25
14	8-C_6H_5S	$C_{16}H_{11}NO_3S$	230-232	70	H_2O[j]	25
15	6-C_6H_5SO	$C_{16}H_{11}NO_4S \cdot 0.5H_2O$[h]	255-258	25	MeOH-H_2O[j]	25
16	6-$C_6H_5SO_2$	$C_{16}H_{11}NO_5S \cdot H_2O$[h]	>185 dec	85	MeOH-H_2O[j]	>25
17	7-$C_6H_5SO_2$	$C_{16}H_{11}NO_5S \cdot 0.5H_2O$[h]	260 dec	87	MeOH-H_2O[j]	>25
18	8-$C_6H_5SO_2$	$C_{16}H_{11}NO_5S$	264-269 dec	96	EtOH-H_2O	10
19		$C_{17}H_9NO_4 \cdot 0.25H_2O$[h]	>270	84	H_2O-acetone	>25
20		$C_{17}H_9NO_4$	280-282	73	DMF	2.8 (2.2-3.3)[k]
2	DSCG					2.6 (1.9-3.3)[k]

[a] Prepared by method C; see the Experimental Section. [b] Unless otherwise indicated, C, H, and N analyses were within ±0.4% of the theoretical values. [c] MED = minimum effective dose, mg/kg. See text for discussion. [d] Obtained from Aldrich Chemical Co. [e] Determined from three experiments. [f] Lit.[12] mp 280 °C. N: calcd, 6.1; found, 6.6. [g] Characterized and tested as the sodium salt. [h] Karl Fisher water determinations were within ±0.3% of the calculated values. [i] C and H analyses only. [j] Not recrystallized, washed with the indicated solvent. [k] ID_{50} value with 95% confidence limits; 20, 156 animals; 2, 264 animals.

is notable, however, is the effect that incorporating the benzoyl moiety into a tetracyclic system has on activity. While the 7- and 8-benzoyl derivatives **8** and **9** are equipotent, incorporation of the 7-benzoyl moiety into the tetracyclic indenoquinoline derivative **19** resulted in a loss of activity, while the identical process with the 8-benzoyl derivative gave **20**, a compound equipotent to DSCG (**2**) in the passive cutaneous anaphylaxis assay. The equivalence of **20** and DSCG was further supported by the results[10] of testing these compounds against antigen-induced bronchospasms in dogs and monkeys.

A second observation on the data in Table I is that, in general, the activity of the phenylthio derivatives is more sensitive to the position of substitution than in the case of the carbonyl derivatives; i.e., the 8-substituted derivatives **14** and **18** were active while, with the exception of **15**, the other positional isomers showed little activity at the screening dose.

These results stimulated further work on tetracyclic derivatives of quinoline-2-carboxylic acids, initially with benzothienoquinolines and later with other systems. The results from these studies will be described in future publications.

Experimental Section

Melting points were determined in capillary tubes on a Mel-Temp block or a Uni-melt oil bath and are uncorrected. The IR spectra were measured as Nujol mulls on a Perkin-Elmer infrared spectrometer. The ^1H NMR spectra were measured in $CDCl_3$, Me_2SO-d_6, or CF_3CO_2D solution on a Varian A-60 or a Varian T-60 spectrometer. The IR and ^1H NMR spectra were consistent with the assigned structure in all cases. The results of elemental analysis were within ±0.4% of the theoretical values except where noted.

The aminoacetophenones, aminobenzophenones, and aminofluorenones utilized as starting materials were commercially available while the phenylmercaptoanilines were available from other work in this laboratory.[11]

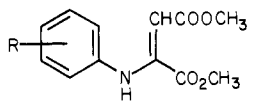
The general procedures outlined in Scheme I and listed in Tables I–III are illustrated by the following examples.

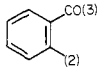
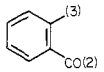
Method A. Dimethyl *o*-Benzoylanilinobutenedioate (23). To a stirred solution of 19.7 g (100 mmol) of 2-aminobenzophenone in 100 mL of methanol was added 14.2 g (100 mmol) of dimethyl acetylenedicarboxylate dissolved in 100 mL of methanol. The solution was heated under reflux for 18 h. The methanol was removed under reduced pressure and the resulting yellow oil was dissolved in 250 mL of benzene. The benzene solution was then washed successively with 5% HCl (2 × 250 mL), 5% NaOH (2 × 250 mL), and water (1 × 100 mL). After drying ($MgSO_4$), the benzene was removed under reduced pressure to give a yellow oil which was crystallized under hexane. Recrystallization from ethanol gave 21.3 g (62 mmol, 62%), mp 103–106 °C. Anal. ($C_{19}H_{17}NO_5$) C, H, N.

Method B. Methyl 8-Benzoyl-1,4-dihydro-4-oxoquinoline-2-carboxylate (33). To 100 g of diphenyl ether was added 16 g (47 mmol) of **23**, and the resulting solution was rapidly heated to reflux, reflux was continued for 5 min, then the heat was removed, and the reaction mixture was allowed to cool to room temperature. The reaction mixture was diluted with 4 vol of *n*-hexane and the resulting precipitate was collected on a filter and dried to give 3.4 g (16 mmol, 35%) of **33**. Three recrystallizations from ethanol gave the analytical sample, mp 193–195 °C. Anal. ($C_{18}H_{13}NO_4$) C, H, N.

Method C. 8-Benzoyl-1,4-dihydro-4-oxoquinoline-2-carboxylic Acid (9). A mixture of 3.0 g (9.8 mmol) of **33**, 30 mL of 1 N NaOH, and 30 mL of ethanol was refluxed until solution was complete. Reflux was continued for an additional 15 min. The solution was allowed to cool and then adjusted to pH ~2 with 1 N HCl. The resulting precipitate was collected on a filter and recrystallized twice from dimethyl sulfoxide to give 1.9 g (6.5 mmol, 66%) of **9**, mp 270–275 °C. Anal. ($C_{17}H_{11}NO_4$) C, H, N.

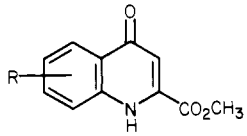
Table II. Intermediate Butenedioates[a]

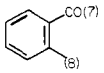
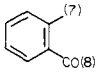


compd	R	formula[b]	mp, °C	yield, %	crystn solvent
21	2-CH_3CO	$C_{14}H_{15}NO_5$	92-94[c]	49	MeOH[d]
22	4-C_6H_5CO	$C_{19}H_{17}NO_5$	96-97	76	*n*-hexane
23	2-C_6H_5CO	$C_{19}H_{17}NO_5$	123-124	63	EtOH
24	2-(4-$CH_3C_6H_5CO$)	$C_{20}H_{19}NO_5$[e]	142-145	63	MeOH
25	2-C_6H_5S	$C_{18}H_{17}NO_4S$	59-61	50	hexane
26		$C_{19}H_{15}NO_5$	195-197	82	MeOH[d]
27		$C_{19}H_{15}NO_5$	165-167	89	methoxyethanol

[a] Prepared by method A, see the Experimental Section. Butenedioates not listed here were used directly in method B without characterization. [b] See footnote *b*, Table I. [c] Lit.[8] mp 95.5-96.7 °C. [d] See footnote *j*, Table I. [e] C and H analyses only.

Table III. Methyl Quinoline-2-carboxylates[a]



compd	R	formula[b]	mp, °C	method	yield, %	crystn solvent
28	6-CH_3CO	$C_{13}H_{11}NO_4$	289-290	B	41	methoxyethanol
29	7-CH_3CO	$C_{13}H_{11}NO_4$	285-288	B	13	HOAc
30	8-CH_3CO	$C_{13}H_{11}NO_4$	168-171[c]	B	23	MeOH
31	6-C_6H_5CO	$C_{18}H_{13}NO_4$	252-255	B	35	methoxyethanol
32	7-C_6H_5CO	$C_{18}H_{13}NO_4$	269-270 dec	B	20	DMF
33	8-C_6H_5CO	$C_{18}H_{13}NO_4$	193-195	B	35	EtOH
34	8-(4-$CH_3C_6H_5CO$)	$C_{19}H_{15}NO_4$[d]	185-187	B	50	Et_2O[e]
35	6-Cl-8-C_6H_5CO	$C_{18}H_{12}ClNO_4$	181-182	B	2	EtOH
36	6-C_6H_5S	$C_{17}H_{13}NO_3S$[d]	227-230	B	32	MeOH-DMF
37	7-C_6H_5S	$C_{17}H_{13}NO_3S$	218-220	B	29	MeOH-acetone
38	8-C_6H_5S	$C_{17}H_{13}NO_3S$	111-113	B	14	CCl_4
39		$C_{18}H_{11}NO_4$	251-254	B	54	MEK
40		$C_{18}H_{11}NO_4$	288-291	B	61	DMF
41	6-C_6H_5SO	$C_{17}H_{13}NO_4S$	255-256	D	61	H_2O[e]
42	6-$C_6H_5SO_2$	$C_{17}H_{13}NO_5S$	285-290	E	85	HOAc[e]
43	7-$C_6H_5SO_2$	$C_{17}H_{13}NO_5S$	268-270	E	73	HOAc[e]
44	8-$C_6H_5SO_2$	$C_{17}H_{13}NO_5S$	202-204	E	70	MeOH-H_2O[e]

[a] Except for 30 which had an MED = 25 mg/kg, none of the esters had activity at the screening dose. [b] See footnote *b*, Table I. [c] Lit.[8] mp 176-177 °C. [d] C and H analyses only. [e] See footnote *j*, Table I.

Dimethyl 6-Chloro-4-phenylquinoline-2,3-dicarboxylate (47). To a stirred solution of 46.4 g (200 mmol) of 2-amino-5-chlorobenzophenone and 200 mL of methanol was added dropwise 28.4 g (200 mmol) of dimethyl acetylenedicarboxylate in 200 mL of methanol. The solution was then refluxed 18 h and allowed to cool, and the precipitated yellow solid (21 g) was collected on a filter. Evaporation of the filtrate gave 37 g of crude dimethyl 2-benzoyl-4-chloroanilinobutenedioate (**49**) which was used directly in method B. The precipitated yellow solid was recrystallized from methanol to give 15.5 g (44 mmol, 22%) of **47** as white needles, mp 150–160 °C. Two additional recrystallizations from methanol gave the analytical sample, mp 160–163 °C. Anal. ($C_{19}H_{14}ClNO_4$) C, H, N.

Method D. Methyl 1,4-Dihydro-4-oxo-6-phenylsulfinylquinoline-2-carboxylate (41). To 2.8 g (9 mmol) of **36** in 100 mL of refluxing acetic acid was added 1 g (9 mmol) of 30% hydrogen peroxide over 15 min. After refluxing 18 h the solution was filtered to remove insoluble by-products and diluted with water. The resulting precipitate was collected on a filter, washed with methanol–water, and dried to give 1.8 g (5.5 mmol, 61%) of tan solid, mp 255–262 °C. Anal. ($C_{17}H_{13}NO_4S$) C, H, N.

Method E. Methyl 1,4-Dihydro-4-oxo-6-phenylsulfonylquinoline-2-carboxylate (42). To 3.5 g (11 mmol) of **36** in 150 mL of refluxing acetic acid was added excess 30% H_2O_2. After the addition was complete heating was continued until solution was complete and then for an additional 10 min. The hot solution was filtered and on cooling a precipitate formed which was collected, washed with acetic acid, and dried to afford 3.3 g (9.3 mmol, 85%) of **42**, mp 285–290 °C. Anal. ($C_{17}H_{13}NO_5S$) C, H, N.

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Synthesis and Prostaglandin-like Activity of 2-(*trans*-3-Hydroxy-1-octenyl)-3-indoleheptanoic Acid

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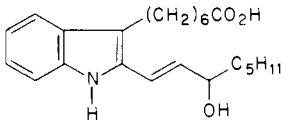
The synthesis of 2-(*trans*-3-hydroxy-1-octenyl)-3-indoleheptanoic acid (1) is described. The title compound appeared to show a weak prostaglandin-like activity in two different systems. It contracted rat stomach fundus strips and guinea-pig ileum preparations only at concentrations about 10^3- and 10^2-fold higher, respectively, than PGE_1. Moreover, it stimulated adenylate cyclase from rat liver plasma membrane, but the relative potency was 4–5 × 10^2-fold lower than the natural compound. The title compound showed also a certain degree of PGE_1 antagonism.

In recent years many synthetic analogues of prostaglandins, including derivatives of some heterocyclic systems, have been investigated.[1] We became particularly interested in an indole analogue which has the two common prostaglandin side chains attached to the C_2 and C_3 position (**1**). We chose this heterocycle since indole is a biological nucleus and 3-substituted indolealkanoic acids have shown interesting pharmacological actions.[2] Furthermore, analogue **1** has the indole ring system found in



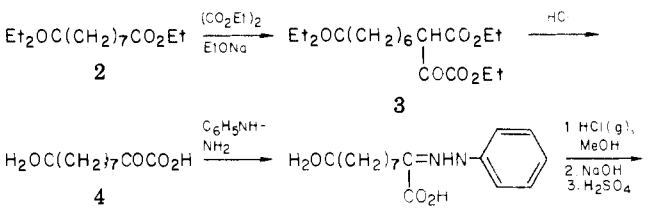
1

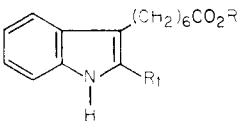
some nonsteroidal antiinflammatory drugs (e.g., indomethacin, which has been reported to inhibit the binding of PGE_1 to thymocytes[3] and to cell membrane fraction from bovine corpora lutea[4]) and so it might behave similarly with other prostaglandin receptors.

Conceptually one might consider the indole ring as being stereochemically equivalent to a 9,10-benzo analogue of the cyclopentane moiety in PGE_1, with the indole NH group mimicking the 11α-hydroxy. In addition, because the indole analogue **1** is devoid of the chiral centers which are present in the cyclopentane moiety of prostaglandins, it would allow easy preparation of substituted derivatives to follow any interesting biological activities found.

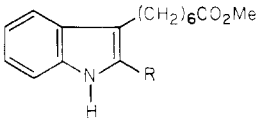
Chemistry. Condensation of diethyl azelate (**2**) with diethyl oxalate in the presence of sodium ethoxide in anhydrous diethyl ether afforded a 70% yield of the triester **3**, which, without purification, was hydrolyzed in 72% yield by means of diluted hydrochloric acid to the α-ketodicarboxylic acid **4**.

Scheme I





6, R = Me; R_1 = CO_2Me
7, R = H; R_1 = CO_2H



8, R = CO_2H
9, R = COCl
10, R = CH_2OH
11, R = CHO
12, R = $CH{=}CHC(=O)C_5H_{11}$
13, R = $CH{=}CHCH(OH)C_5H_{11}$

Fisher's indolization promoted by methanolic hydrochloric acid of the phenylhydrazone **5** obtained by action of phenylhydrazine on **4** (acetic acid–water, 3:2) produced the diester **6**, which, upon alkaline hydrolysis with aqueous–methanolic sodium hydroxide, gave a quantitative yield of the dicarboxylic acid **7** (see Scheme I). The latter was transformed into the half-ester **8** by treatment for 3

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