[CONTRIBUTION FROM THE DEPARTMENT OF ORGANIC CHEMISTRY, RADIUM INSTITUTE, UNIVERSITY OF PARIS]

THE PFITZINGER REACTION IN THE SYNTHESIS OF QUINOLINE DERIVATIVES

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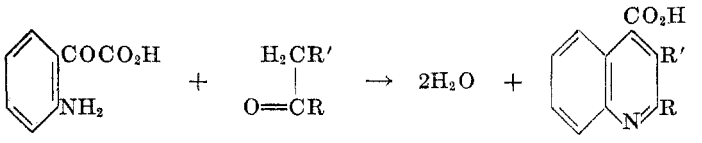
In the framework of a broad investigation into the experimental production, by pure chemical substances, of precancerous conditions and tumors of the liver, the group of quinoline compounds has come especially to our attention. Quinoline itself is a substance of pronounced general toxicity toward both animals (1) and plants (2), and in some of its homologs, such as quinaldine and lepidine, these toxic properties are enhanced. In small doses, 2,6-dimethylquinoline has a growth-accelerating effect on certain plant tissues (3). More directly pertaining to cancer problems are the observation by Shear (4) that quinaldine accentuates the carcinogenic action of 3,4-benzpyrene, and numerous works on the production of sarcomas (5) with 2-(*p*-aminostyryl)-6-(*p*-acetaminobenzoylamino)quinoline methoacetate ("Styryl 430"). 2-Phenylcinchoninic acid ("Atophan") in high dosage and in susceptible subjects, readily produces a degeneration of the liver tissue similar to the action of azo-dyes in early stages of carcinogenesis.

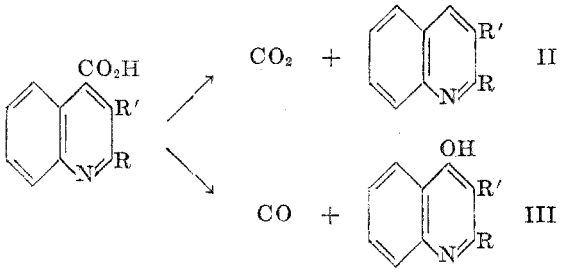
These considerations led us to synthesize a large number of diversely substituted cinchoninic acids and quinolines, for biological testing as potential liver poisons. Attention is also being paid to the possibility that compounds wholly inactive with respect to epithelioma or sarcoma production, may enhance the occurence of lung tumors (6).

The method used throughout for synthesizing these quinoline derivatives was the Pfitzinger reaction, involving condensation in alkaline medium of an isatin with a ketone of the general formula $RCOCH_2R'$ (7):



I

Decarboxylation of the 2-substituted cinchoninic acids (I) thus obtained, which was readily effected by heating them above their melting points, and vacuum-distillation of the residues, yielded in most cases the corresponding 2-substituted quinolines (II). In a few instances, observed mostly in the 2-alkylcinchoninic acids, decarboxylation was accompanied by a decarbonylation (8) which gave the corresponding 4-hydroxyquinolines (III):



Whereas the Pfitzinger reaction is very convenient for syntheses in the quinoline group, in view of the ease of its technique and the ready availability of intermediates, its high sensitivity toward steric hindrance presents a serious disadvantage. This phenomenon is known to produce abnormal courses of reaction, and greatly reduces or even nullifies the yield of the expected cinchoninic acids. Thus, except for methyl ethyl ketone, ketones of the type CH_3COCH_2R in the aliphatic series react preferentially through their methyl group (9), to give 2-alkylcinchoninic acids, whereas in most other reactions, such as formation of indoles, or halogenation, the methylene group is the more active (10). In the aromatic series, ketones of the type $ArCO(CH_2)_nCH_3$ give a Pfitzinger reaction with isatin, under normal conditions of time and temperature, only when n is less than 3 (11). Homologs of n-butyrophenone, such as caprophenone, are able to react to a sizable extent, only when the aryl radicals are very simple and the duration of reactions greatly prolonged (12).

These recorded observations on the effect of steric hindrance in Pfitzinger reactions have been confirmed and extended in the course of the present study.

The ketones used in the Pfitzinger reactions involved in this work fall into three categories: (a) aliphatic ketones; (b) alicyclic ketones; (c) aromatic and heterocyclic ketones. The isatins brought to condensation with these ketones were isatin itself, 5- and 7-methylisatin, 5-chloro- and 5-bromo-isatin, and β-naphthisatin.

1. *Pfitzinger reactions with aliphatic ketones.* The aliphatic ketones used can be divided into two classes: (a) the *methyl ketones* of the general formula $RCOCH_3$, whose reaction is expected for steric reasons to involve the $—COCH_3$ part of the molecule, and the *dialkyl ketones* of formula RCH_2COR', in which R′ is a secondary alkyl group, whose reaction necessarily involves the $—COCH_2—$ part of the molecule. The various new alkylcinchoninic and 2,3-dialkylcinchoninic acids thus obtained are listed in Table I, and the corresponding quinolines and their picrates in Table II. Further proof of the selective reactivity of the methyl group in ketones $RCOCH_3$ was the identification of the acids from the Pfitzinger reaction between β-naphthisatin and octan-2-one and undecan-2-one respectively, with the 2-n-hexyl- and 2-n-nonyl-5,6-benzocinchoninic acids prepared by the Doebner condensation, with pyruvic acid and β-naphthylamine, of n-heptanal and n-decanal respectively (13).

(b) The unsymmetrical *dialkyl ketones* of general formula RCH_2COCH_2R',

TABLE I

2-ALKYL- AND 2,3-DIALKYLCINCHONINIC ACIDS

SUBSTITUENT	M.P., °C.	ANALYSES				FORMULA	STARTING KETONE
		Calc'd		Found			
		C	H	C	H		
2-*n*-Undecyl	129–130	76.0	8.8	76.2	8.9	$C_{21}H_{29}NO_2$	*n*-Undecyl methyl ketone
8-Methyl-2-*n*-undecyl	83–84	77.4	9.0	77.1	9.1	$C_{22}H_{31}NO_2$	*n*-Undecyl methyl ketone
2-*n*-Amyl	135	74.0	6.9	74.0	6.8	$C_{15}H_{17}NO_2$	*n*-Amyl methyl ketone
6-Methyl-2-*n*-amyl	174	76.2	7.4	76.0	7.6	$C_{16}H_{19}NO_2$	*n*-Amyl methyl ketone
6-Bromo-2-*n*-amyl	180	55.9	4.9	55.6	4.8	$C_{15}H_{16}BrNO_2$	*n*-Amyl methyl ketone
6-Methyl-2-*n*-hexyl	135	75.2	7.7	75.0	7.7	$C_{17}H_{21}NO_2$	*n*-Hexyl methyl ketone
6-Chloro-2-*n*-hexyl	143	65.9	6.1	65.6	6.2	$C_{16}H_{18}ClNO_2$	*n*-Hexyl methyl ketone
3-Methyl-2-*n*-hexyl	197	75.2	7.7	75.1	7.7	$C_{17}H_{21}NO_2$	*n*-Hexyl methyl ketone
3-Ethyl-2-isobutyl	239	74.7	7.3	74.8	7.4	$C_{16}H_{19}NO_2$	Isobutyl ethyl ketone
3-*n*-Propyl-2-isobutyl[a]	205	75.2	7.7	75.0	7.9	$C_{17}H_{21}NO_2$	Isobutyl *n*-propyl ketone
6-Bromo-3-methyl-2-*n*-pentadecyl	189	65.5	7.9	65.4	7.9	$C_{26}H_{38}BrNO_2$	*n*-Pentadecyl ethyl ketone
2-Cyclopropyl	206	73.2	5.1	73.0	5.2	$C_{13}H_{11}NO_2$	Cyclopropyl methyl ketone
8-Methyl-2-cyclopropyl	212 (dec. > 200)	74.0	5.7	73.9	5.9	$C_{14}H_{13}NO_2$	Cyclopropyl methyl ketone
6-Chloro-2-cyclopropyl	230 (dec. > 220)	62.9	4.0	62.9	4.2	$C_{13}H_{10}ClNO_2$	Cyclopropyl methyl ketone
6-Bromo-2-cyclopropyl	268–270 (dec. > 252)	53.4	3.4	53.1	3.6	$C_{13}H_{10}BrNO_2$	Cyclopropyl methyl ketone
6-Methyl-2,3-pentamethylene	308 (dec. > 270)	75.2	6.6	75.1	6.4	$C_{16}H_{17}NO_2$	Cycloheptanone
6-Bromo-2,3-pentamethylene	309	56.2	4.3	56.2	4.5	$C_{15}H_{14}BrNO_2$	Cycloheptanone
6-Chloro-2,3-pentamethylene	251	65.4	5.0	65.6	5.1	$C_{15}H_{14}ClNO_2$	Cycloheptanone

[a] The substance melted first at 176°, then resolidified, and melted again at 205°.

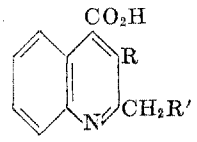
TABLE II

2-ALKYL- AND 2,3-DIALKYLQUINOLINES

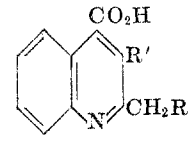
SUBSTITUENT	B.P., °C./MM.	ANALYSES		M.P., °C. OF PICRATE	FORMULA
		Calc'd	Found		
2-*n*-Undecyl	233/14	4.9	4.9	83–84	$C_{20}H_{29}N$
2-*n*-Undecyl-4-hydroxy	270–280/14	4.6	4.5		$C_{20}H_{29}NO$
8-Methyl-2-*n*-undecyl	235–238/14	4.7	4.9	76	$C_{21}H_{31}N$
2-*n*-Amyl-4-hydroxy[a]	m.p. 128	6.5	6.3		$C_{14}H_{17}NO$
6-Bromo-2-*n*-amyl	207–208/14	5.0	4.8	192	$C_{14}H_{16}BrN$
6-Methyl-2-*n*-amyl	300–302	6.5	6.4	188–189	$C_{15}H_{19}N$
2-Cyclopropyl	145–148/17	8.2	8.0	175	$C_{12}H_{11}N$
6-Bromo-3-methyl-2-*n*-pentadecyl	m.p. 54–55	3.2	3.0	114	$C_{25}H_{38}BrN$
3-Methyl-2-*n*-pentadecyl	m.p. 55	3.9	3.6	105–106	$C_{25}H_{39}N$
3-Ethyl-2-isobutyl	298–300	6.5	6.3	160–161	$C_{15}H_{19}N$
6-Chloro-2,3-pentamethylene	m.p. 109	5.7	5.5	191–192	$C_{15}H_{14}ClN$
6-Bromo-2,3-pentamethylene	m.p. 128	4.9	5.0	200–201	$C_{15}H_{14}BrN$
6-Methyl-2,3-pentamethylene	m.p. 105	6.3	6.2	189–190	$C_{16}H_{17}N$

[a] Obtained as by-product in the preparation of the foregoing base; formed silky, colorless needles, m.p. 123°, from ethanol.

whose Pfitzinger reactions could *a priori* involve the methylene group on either side of the keto group, to yield either the cinchoninic acid (IV), or the cinchoninic acid (V), or both. Even in such complicated cases, the various alternatives seem often to be limited by steric hindrance. Thus, condensation of *n*-propyl isobutyl ketone with isatin gave only one reaction product, which, in the absence of rigid



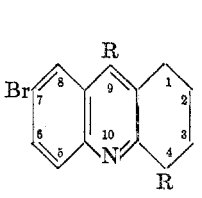
IV



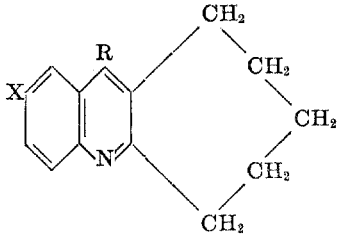
V

structure-proof, might tentatively be assigned the constitution of 2-isobutyl-3-ethylcinchoninic acid (IV; R = C_2H_5, R′ = iso-C_3H_7), the methylene group of the isobutyl radical being assumed to be the more sterically hindered. For a similar reason, the reaction-product from isatin and *n*-butyl isobutyl ketone might be tentatively be termed 2-isobutyl-3-*n*-propylcinchoninic acid (IV; R = *n*-C_3H_7, R′ = iso-C_3H_7). For dialkyl ketones such as *n*-decan-4-one, in whose molecules the two alkyl groups are less differentiated, it is more difficult to assign a formula to the cinchoninic acids actually isolated, although Pfitzinger reactions might possibly be thought to involve the smallest alkyl group to a greater extent, giving, for instance, with isatin, 3-ethyl-2-*n*-hexylcinchoninic acid (IV; R = C_2H_5, R′ = *n*-C_5H_{11}) as the main product. Unfortunately, this point too has not yet been settled, in view of the difficulty of preparing unsymmetrical 2,3-dialkylquinolines in a pure state for comparison.

2. *Pfitzinger reactions with alicyclic ketones.* Borsche (14) showed that cyclanones are highly responsive to Pfitzinger reactions, and Buu-Hoï (15) extended these observations to molecules as large as the musk-smelling cyclanones with fifteen and more carbon atoms in the ring. In the present work, 2-methyl- and 2-ethyl-cyclohexanone were found to condense readily with 5-bromoisatin, despite the presence of the *ortho* alkyl substituent. 7-Bromo-4-methyl- and 7-bromo-4-ethyl-1,2,3,4-tetrahydroacridine-9-carboxylic acid (VI; R = CO_2H) were thus prepared in good yield, and decarboxylated to the corresponding quinolines



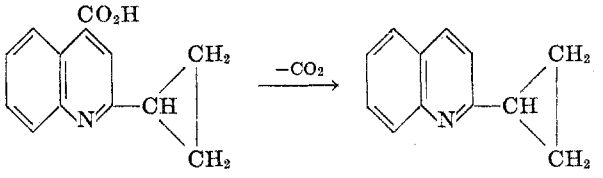
VI



VII

(VI; R = H). Similar reactions performed with cycloheptanone afforded a series of 6-substituted 2,3-pentamethylenecinchoninic acids (VII; R = CO_2H and 6-substituted 2,3-pentamethylenequinolines (VII; R = H).

An interesting ketone which also underwent Pfitzinger reactions smoothly was methyl cyclopropyl ketone; with isatin, 2-cyclopropylcinchoninic acid (VIII) was obtained, and yielded on decarboxylation the rather unstable 2-cyclopropylquinoline (IX). Both substances, and those obtained in a similar way from



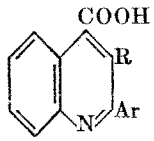
VIII IX

substituted isatins, belong to a class of compounds hitherto unknown.

3. *Pfitzinger reactions with aromatic ketones.* In this work, a number of diversely ring-substituted acetophenones, propiophenones, *n*-butyrophenones, and deoxybenzoins were submitted to Pfitzinger condensations. Once more it was observed that, under normal conditions of reaction (ethanol medium and 24 hours' heating), no sizable amounts of cinchoninic acids were obtained with the ketones $ArCO(CH_2)_nCH_3$ when n was more than two. A similar steric hindrance was noticed with *n*-butyrophenones bearing a methyl or alkoxy group in the *ortho* position; thus, 2,4-dimethyl- (X), 2,5-dimethyl- (XI), 2,4,5-trimethyl- (XII), and 2,4-dimethoxy-*n*-butyrophenone (XIII) failed to give with isatin any sub-

TABLE III

2-ARYLCINCHONINIC ACIDS (XVI)



RADICAL Ar	R	M.P., °C.	ANALYSES				FORMULA	STARTING KETONE
			Calc'd		Found			
			C	H	C	H		
4-Biphenylyl	CH_3	303–304	81.4	5.0	81.3	5.3	$C_{23}H_{17}NO_2$	4-Propionylbiphenyl
4-Biphenylyl	C_2H_5	>310	81.6	5.4	81.4	5.5	$C_{24}H_{19}NO_2$	4-*n*-Butyroylbiphenyl
6-Tetralyl	CH_3	254–255	79.5	6.0	79.2	6.2	$C_{21}H_{19}NO_2$	6-Propionyltetralin
6-Tetralyl	C_2H_5	dec. > 300	79.8	6.3	79.9	6.4	$C_{22}H_{21}NO_2$	6-*n*-Butyroyltetralin
4-Tolyl	CH_3	>305	78.0	5.4	77.7	5.4	$C_{18}H_{15}NO_2$	4-Methylpropiophenone
4-Tolyl	C_2H_5	>310	78.4	5.8	78.1	6.0	$C_{19}H_{17}NO_2$	4-Methyl-*n*-butyrophenone
3,4-Dimethylphenyl	H	209–210	78.0	5.4	77.8	5.3	$C_{18}H_{15}NO_2$	3,4-Dimethylacetophenone
2,5-Dimethylphenyl	H	200–201	78.0	5.4	77.9	5.6	$C_{18}H_{15}NO_2$	2,5-Dimethylacetophenone
2,5-Dimethylphenyl	CH_3	301	78.4	5.8	78.3	6.0	$C_{19}H_{17}NO_2$	2,5-Dimethylpropiophenone
2,4-Dimethylphenyl	CH_3	>305	78.4	5.8	78.3	5.9	$C_{19}H_{17}NO_2$	2,4-Dimethylpropiophenone
4-Ethylphenyl	H	190	78.0	5.4	77.8	5.7	$C_{18}H_{15}NO_2$	4-Ethylacetophenone
4-Ethylphenyl	CH_3	dec. > 290–292	78.4	5.8	78.4	6.0	$C_{19}H_{17}NO_2$	4-Ethylpropiophenone
4-Ethylphenyl	C_2H_5	296	78.7	6.2	78.6	6.3	$C_{20}H_{19}NO_2$	4-Ethyl-*n*-butyrophenone
4-Isopropylphenyl	H	195	78.4	5.8	78.2	6.1	$C_{19}H_{17}NO_2$	4-Isopropylacetophenone
4-Isopropylphenyl	CH_3	297	78.7	6.2	78.5	6.5	$C_{20}H_{19}NO_2$	4-Isopropylpropiophenone
4-Isopropylphenyl	C_2H_5	267	79.0	6.6	78.7	6.8	$C_{21}H_{21}NO_2$	4-Isopropyl-*n*-butyrophenone
4-*tert*-Butylphenyl	CH_3	298	79.2	6.3	79.0	6.5	$C_{21}H_{20}NO_2$	4-*tert*-Butylpropiophenone
2,4,5-Trimethylphenyl	CH_3	313	78.7	6.2	78.5	6.4	$C_{20}H_{19}NO_2$	2,4,5-Trimethylpropiophenone
4-Methyl-1-naphthyl	CH_3	>305	81.2	4.6	81.0	4.9	$C_{22}H_{15}NO_2$	4-Methyl-1-propionaphthone
3-Pyrenyl	CH_3	>310	83.7	4.4	83.4	4.3	$C_{27}H_{17}NO_2$	3-Propionylpyrene
3-Pyrenyl	C_2H_5	>310	83.8	4.7	83.5	4.8	$C_{28}H_{19}NO_2$	3-*n*-Butyroylpyrene
4-Chlorophenyl	H	241–242	67.7	3.5	67.5	3.8	$C_{16}H_{10}ClNO_2$	4-Chloroacetophenone

4-Chlorophenyl	CH_3	310–311	68.6	4.0	68.3	4.2	$C_{17}H_{12}ClNO_2$	4-Chloropropiophenone
4-Chlorophenyl	C_2H_5	310	69.3	4.5	69.2	4.4	$C_{18}H_{14}ClNO_2$	4-Chloro-*n*-butyrophenone
4-Bromophenyl	H	250	58.5	3.0	58.2	3.2	$C_{16}H_{10}BrNO_2$	4-Bromoacetophenone
3,4-Dichlorophenyl	H	258	60.4	2.8	60.3	3.0	$C_{16}H_9Cl_2NO_2$	3,4-Dichloroacetophenone
4-Bromophenyl	CH_3	>320	59.6	3.5	59.5	3.3	$C_{17}H_{12}BrNO_2$	4-Bromopropiophenone
4-Bromophenyl	C_2H_5	329–330	60.7	3.9	60.4	3.8	$C_{18}H_{14}BrNO_2$	4-Bromo-*n*-butyrophenone
4-Ethoxyphenyl	H	222	73.7	5.1	73.8	5.3	$C_{18}H_{15}NO_3$	4-Acetylphenetole
4-Ethoxyphenyl	CH_3	302	74.3	5.5	74.0	5.8	$C_{19}H_{17}NO_3$	4-Propionylphenetole
4-Ethoxyphenyl	C_2H_5	305	74.8	5.9	74.6	6.0	$C_{20}H_{19}NO_3$	4-*n*-Butyroylphenetole
4-Ethoxyphenyl	C_6H_5	295	77.6	6.4	77.4	6.2	$C_{24}H_{24}NO_3$	4-Phenacetylphenetole
4-Methylmercaptophenyl	CH_3	305	69.9	4.9	69.6	4.8	$C_{18}H_{15}NO_2S$	4-*Propionylthioanisole*
4-Methylmercaptophenyl	CH_2CO_2H	325	67.6	4.2	67.3	4.4	$C_{19}H_{15}NO_4S$	β-(4-Methylmercaptobenzoyl)-propionic acid
4-Ethylmercaptophenyl	H	195	69.9	4.9	70.0	4.6	$C_{18}H_{15}NO_2S$	4-Acetylthiophenetole
4-Ethylmercaptophenyl	CH_3	278	70.6	5.3	70.5	5.4	$C_{19}H_{17}NO_2S$	4-Propionylthiophenetole
4-Ethylmercaptophenyl	C_2H_5	269	71.2	5.6	71.0	5.5	$C_{20}H_{19}NO_2S$	4-*n*-Butyroylthiophenetole
4-Phenoxyphenyl	H	203	77.1	4.6	77.0	4.9	$C_{22}H_{16}NO_3$	4-Phenoxyacetophenone
4-Phenoxyphenyl	CH_3	303	77.5	5.0	77.3	5.1	$C_{23}H_{18}NO_3$	4-Phenoxypropiophenone
4-Phenoxyphenyl	C_2H_5	282	77.8	5.4	77.5	5.4	$C_{24}H_{20}NO_3$	4-Phenoxy-*n*-butyrophenone
4-Phenoxyphenyl	C_6H_5	283	77.4	4.3	77.1	4.5	$C_{22}H_{15}NO_3$	4-Phenacetylphenoxybenzene
4-Phenylmercaptophenyl	H	215	73.9	4.2	73.8	4.1	$C_{22}H_{15}NO_2S$	4-Phenylmercaptoacetophenone
4-Phenylmercaptophenyl	CH_3	275	74.3	4.5	74.0	4.8	$C_{23}H_{17}NO_2S$	4-Phenylmercaptopropiophenone
4-Phenylmercaptophenyl	C_6H_5	289	77.5	4.3	77.3	4.1	$C_{28}H_{19}NO_2S$	4-Phenacetyldiphenyl sulfide
4′-Methoxy-4-biphenylyl	H	237	77.7	4.7	77.4	5.0	$C_{23}H_{17}NO_3$	4′-Methoxy-4-acetylbiphenyl
4′-Methoxy-4-biphenylyl	CH_3	295	78.0	5.1	77.9	5.0	$C_{24}H_{19}NO_3$	4′-Methoxy-4-propionylbiphenyl

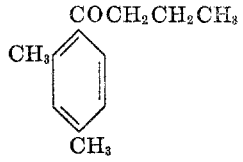
TABLE IV

2-ARYL-6-BROMOCINCHONINIC ACIDS

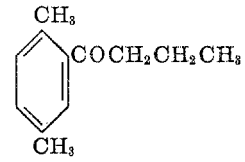
RADICAL Ar	R	M.P., °C.	ANALYSES				FORMULA	STARTING KETONE
			Calc'd		Found			
			C	H	C	H		
4-Biphenylyl	H	306	65.3	3.5	65.2	3.8	$C_{22}H_{14}BrNO_2$	4-Acetylbiphenyl
4-Biphenylyl	CH_3	316–317	66.0	3.8	65.8	4.0	$C_{23}H_{16}BrNO_2$	4-Propionylbiphenyl
4-Biphenylyl	C_2H_5	292	66.7	4.2	66.3	4.1	$C_{24}H_{18}BrNO_2$	4-*n*-Butyroylbiphenyl
2-Tetralyl	C_2H_5	310	64.4	4.9	64.6	4.8	$C_{22}H_{20}BrNO_2$	2-*n*-Butyroyltetralin
6-Tetralyl	H	235	62.8	4.2	62.7	4.4	$C_{20}H_{16}BrNO_2$	6-Acetyltetralin
6-Tetralyl	CH_3	316	63.6	4.5	63.3	4.6	$C_{21}H_{18}BrNO_2$	6-Propionyltetralin
Phenyl	CH_3	328	59.6	3.5	59.2	3.3	$C_{17}H_{12}BrNO_2$	Propiophenone
3,4-Dimethylphenyl	H	227	60.7	3.9	60.5	4.0	$C_{18}H_{14}BrNO_2$	3,4-Dimethylacetophenone
2,4-Dimethylphenyl	H	235	60.7	3.9	60.5	4.1	$C_{18}H_{14}BrNO_2$	2,4-Dimethylacetophenone
2,4-Dimethylphenyl	CH_3	>321	61.6	4.3	61.3	4.2	$C_{19}H_{16}BrNO_2$	2,4-Dimethylpropiophenone
2,5-Dimethylphenyl	H	239	60.7	3.9	60.4	3.8	$C_{18}H_{14}BrNO_2$	2,5-Dimethylacetophenone
2,5-Dimethylphenyl	CH_3	345	61.6	4.3	61.3	4.5	$C_{19}H_{16}BrNO_2$	2,5-Dimethylpropiophenone
4-Ethylphenyl	CH_3	301	61.6	4.3	61.5	4.5	$C_{19}H_{16}BrNO_2$	4-Ethylpropiophenone
4-Isopropylphenyl	H	218	61.6	4.3	61.3	4.3	$C_{19}H_{16}BrNO_2$	4-Isopropylacetophenone
4-Isopropylphenyl	CH_3	298–299	62.5	4.7	62.3	4.6	$C_{20}H_{18}BrNO_2$	4-Isopropylpropiophenone
4-Isopropylphenyl	C_2H_5	275–276	63.3	5.0	63.2	5.1	$C_{21}H_{20}BrNO_2$	4-Isopropyl-*n*-butyrophenone
4-*tert*-Butylphenyl	CH_3	>311	63.3	5.0	63.0	5.2	$C_{21}H_{20}BrNO_2$	4-*tert*-Butylpropiophenone
4-Methyl-1-naphthyl	CH_3	>307	65.0	3.9	65.1	3.6	$C_{22}H_{16}BrNO_2$	4-Methyl-1-propionaphthone
5-Acenaphthyl	CH_3	>310	66.0	3.8	65.7	3.8	$C_{23}H_{16}BrNO_2$	5-Propionylacenaphthene
3-Pyrenyl	H	>310	69.0	3.1	69.2	3.3	$C_{26}H_{14}BrNO_2$	3-Acetylpyrene
3-Pyrenyl	CH_3	>310	69.5	3.4	69.6	3.3	$C_{27}H_{16}BrNO_2$	3-Propionylpyrene
3-Pyrenyl	C_2H_5	>310	70.0	3.8	70.2	3.8	$C_{28}H_{18}BrNO_2$	3-*n*-Butyroylpyrene
4-Chlorophenyl	H	271	53.0	2.5	52.9	2.8	$C_{16}H_9BrClNO_2$	4-Chloroacetophenone
4-Chlorophenyl	CH_3	307	54.2	2.9	54.0	3.0	$C_{17}H_{11}BrClNO_2$	4-Chloropropiophenone
4-Chlorophenyl	C_2H_5	>310	55.3	3.3	55.2	3.6	$C_{18}H_{13}BrClNO_2$	4-Chloro-*n*-butyrophenone
4-Chlorophenyl	C_6H_5	>328	60.2	3.0	60.0	3.1	$C_{22}H_{13}BrClNO_2$	4-Phenacetylchlorobenzene
4-Bromophenyl	H	259	47.2	2.2	47.1	2.2	$C_{16}H_9Br_2NO_2$	4-Bromoacetophenone

4-Bromophenyl	CH_3	325	48.5	2.6	48.2	2.8	$C_{17}H_{11}Br_2NO_2$	4-Bromopropiophenone
4-Bromophenyl	CH_2CO_2H	307	46.5	2.4	46.2	2.6	$C_{18}H_{11}Br_2NO_4$	β-(4-Bromobenzoyl)propionic acid
4-Bromophenyl	C_2H_5	>310	49.6	3.0	49.5	3.3	$C_{18}H_{13}Br_2NO_2$	4-Bromo-*n*-butyrophenone
4-Bromophenyl	C_6H_5	>310	54.7	2.7	54.8	2.8	$C_{22}H_{13}Br_2NO_2$	4-Phenacetylbromobenzene
4-Iodophenyl	H	277–278	42.2	1.9	42.0	2.2	$C_{16}H_9BrINO_2$	4-Iodoacetophenone
3,4-Dichlorophenyl	H	252	48.4	2.0	48.2	2.3	$C_{16}H_8BrCl_2NO_2$	3,4-Dichloroacetophenone
2,4-Dimethoxyphenyl	C_6H_5	297–298	62.1	3.9	62.0	4.0	$C_{24}H_{18}BrNO_4$	4-Phenacetyl-1,3-dimethoxybenzene
3,4-Dimethoxyphenyl	C_2H_5	240	57.7	4.3	57.7	4.2	$C_{20}H_{18}BrNO_4$	4-*n*-Butyroylveratrole

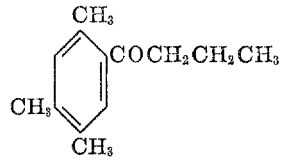
stantial amount of the expected cinchoninic acids, even when the duration of reaction was extended to 36 hours.



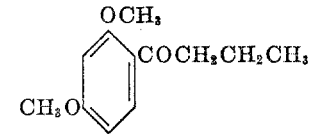
X



XI



XII



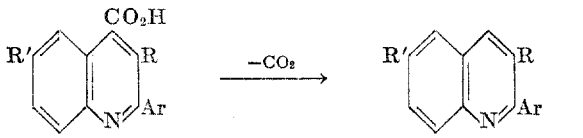
XIII

Similar observations were made with the ketones $ArCOCH_2R$ in whose molecules Ar is a polycyclic radical, such as the 4-xenyl, 1,2,3,4-tetrahydro-2-naphthyl, 4-methyl-1-naphthyl, 5-acenaphthyl, 3-pyrenyl, and 4-fluoranthyl radicals.

It should be noted that β-aroylpropionic acids (XIV) were found highly reactive, and readily yielded 3-carboxymethyl-2-arylcinchoninic acids of the general formula (XV).

XIV XV

The numerous new arylcinchoninic acids obtained in the course of this study are listed in Table III (2-arylcinchoninic acids of formula XVI, bearing no substitution at the position 6) and Table IV (6-bromo-2-arylcinchoninic acids of formula XVII). The corresponding quinolines are listed along with their picrates in Table V (2-arylquinolines of formula XVIII), and Table VI (6-bromo-2-arylquinolines of formula XIX). Similar 6-chloro- and 6-methyl-2-arylcinchoninic acids are described in the experimental part, and in Table VII are recorded several cinchoninic acids derived from thiophene.



XVI; R′ = H
XVII; R′ = Br

XVIII; R′ = H
XIX; R′ = Br

TABLE V

2-ARYLQUINOLINES

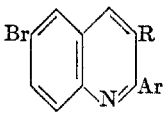
RADICAL AR	R	M.P., °C.	ANALYSES N		M.P., °C., of PICRATE	FORMULA
			Calc'd	Found		
4-Biphenylyl	CH_3	121	4.7	4.5	230	$C_{22}H_{17}N$
4-Biphenylyl	C_2H_5	100	4.5	4.4	211	$C_{23}H_{19}N$
6-Tetralyl	CH_3	70	5.1	4.8	—	$C_{20}H_{19}N$
6-Tetralyl	C_2H_5	b.p. 275–280°/16 mm.	4.9	5.0	196–197	$C_{21}H_{21}N$
3,4-Dimethylphenyl	H	90–91	6.0	5.9	—	$C_{17}H_{15}N$
2,5-Dimethylphenyl	H	60	6.0	6.1	179	$C_{17}H_{15}N$
4-Isopropylphenyl	H	50	5.7	5.5	190	$C_{18}H_{17}N$
4-Isopropylphenyl	CH_3	61	5.4	5.2	193	$C_{19}H_{19}N$
4-*tert*-Butylphenyl	CH_3	66 b.p. 250–260°/15 mm.	5.1	5.0	—	$C_{20}H_{21}N$
4-Tolyl	CH_3	59	6.0	6.1	220	$C_{17}H_{15}N$
2,4,5-Trimethylphenyl	CH_3	b.p. 230°/13 mm.	5.4	5.2	212–213	$C_{19}H_{19}N$
4-Methyl-1-naphthyl	CH_3	liquid b.p. (270–272°/13 mm.)	4.9	4.9	224	$C_{21}H_{17}N$
4-Chlorophenyl	H	112	5.8	5.5	192–193	$C_{15}H_{10}ClN$
4-Chlorophenyl	CH_3	92	5.5	5.3	—	$C_{16}H_{12}ClN$
4-Chlorophenyl	C_2H_5	42	5.2	5.0	181	$C_{17}H_{14}ClN$
4-Bromophenyl	H	123–124	4.9	4.6	181–182	$C_{15}H_{10}BrN$
3,4-Dichlorophenyl	H	112	5.1	5.0	204	$C_{15}H_9Cl_2N$
4-Bromophenyl	CH_3	108	4.7	4.5	195–196	$C_{16}H_{12}BrN$
4-Bromophenyl	C_2H_5	62	4.5	4.2	192	$C_{17}H_{14}BrN$
4-Ethoxyphenyl	H	127	5.6	5.5	218	$C_{17}H_{15}NO$
4-Ethoxyphenyl	CH_3	92	5.3	5.0	177	$C_{18}H_{17}NO$
4-Ethoxyphenyl	C_2H_5	liquid	5.1	5.1	190	$C_{19}H_{19}NO$
4-Ethoxyphenyl	C_6H_5	100	4.3	4.2	192	$C_{23}H_{19}NO$
4-Methylmercaptophenyl	CH_3	86	5.3	5.0	180	$C_{17}H_{15}NS$
4-Ethylmercaptophenyl	CH_3	70	5.0	4.8	186	$C_{18}H_{17}NS$
4-Ethylmercaptophenyl	C_2H_5	liquid	4.8	4.5	184	$C_{19}H_{19}NS$
4-Phenoxyphenyl	H	121	4.7	4.5	—	$C_{21}H_{15}NO$
4-Phenoxyphenyl	CH_3	91	4.5	4.4	—	$C_{22}H_{17}NO$
4-Phenoxyphenyl	C_2H_5	75	4.3	4.1	188	$C_{23}H_{19}NO$
4-Phenoxyphenyl[a]	C_6H_5	109	3.7	3.4	201	$C_{27}H_{19}NO$
4-Phenylmercaptophenyl	H	119	4.4	4.1	—	$C_{21}H_{15}NS$
4-Phenylmercaptophenyl	CH_3	76	4.3	4.2	175	$C_{22}H_{17}NS$
4-Phenylmercaptophenyl	C_6H_5	62	3.6	3.3	192	$C_{27}H_{19}NS$
4′-Methoxy-4-biphenylyl	H	219	4.5	4.6	202	$C_{22}H_{17}NO$
4′-Methoxy-4-biphenylyl	CH_3	149	4.3	4.1	180	$C_{23}H_{19}NO$
4-Ethylphenyl	H	50	6.0	5.9	196–197	$C_{17}H_{15}N$
4-Ethylphenyl	CH_3	liquid (220–225°/15 mm.)	5.7	5.7	191–192	$C_{18}H_{17}N$
4-Ethylphenyl	C_2H_5	liquid (228–230°/15 mm.)	5.4	5.2	182–183	$C_{19}H_{19}N$

[a] The bromhydrate had m.p. 215°.

The alkyl aryl ketones used in this work were mostly known substances, and were mostly prepared by Friedel-Crafts reactions; the new ones are reported in the experimental section. Aliphatic ketones were prepared by Grignard reactions of appropriate alkylmagnesium bromides on aliphatic nitriles.

TABLE VI

2-ARYL-6-BROMOQUINOLINES (XIX)



RADICAL Ar	R	M.P., °C.	ANALYSES N		M.P., °C., of PICRATE	FORMULA
			Calc'd	Found		
4-Biphenylyl	H	222	3.9	4.0	224–225	$C_{21}H_{14}BrN$
4-Biphenylyl	CH_3	196	3.7	3.5	—	$C_{22}H_{16}BrN$
4-Biphenylyl	C_2H_5	172	3.6	3.5	215	$C_{23}H_{18}BrN$
6-Tetralyl	C_2H_5	97	3.8	3.6	217–218	$C_{21}H_{20}BrN$
6-Tetralyl	H	133	4.1	4.0	212	$C_{19}H_{16}BrN$
6-Tetralyl	CH_3	123	4.0	4.1	216	$C_{20}H_{18}BrN$
2-Phenyl	CH_3	129	4.7	4.5	—	$C_{16}H_{12}BrN$
3,4-Dimethylphenyl	H	135	4.5	4.3	206–207	$C_{17}H_{14}BrN$
2,4-Dimethylphenyl	H	98	4.5	4.3	194	$C_{17}H_{14}BrN$
2,4-Dimethylphenyl	CH_3	122	4.3	4.4	209	$C_{18}H_{16}BrN$
2,5-Dimethylphenyl	H	124	4.5	4.4	205	$C_{17}H_{14}BrN$
2,5-Dimethylphenyl	CH_3	109	4.3	4.1	192	$C_{18}H_{16}BrN$
4-Isopropylphenyl	CH_3	130	4.1	4.0	185	$C_{19}H_{18}BrN$
4-Isopropylphenyl	C_2H_5	93	4.0	3.8	204	$C_{20}H_{20}BrN$
4-*tert*-Butylphenyl	CH_3	132	4.0	3.9	154	$C_{20}H_{20}BrN$
4-Isopropylphenyl	H	143	4.3	4.3	194	$C_{18}H_{16}BrN$
4-Methyl-1-naphthyl	CH_3	181	3.9	3.6	228	$C_{21}H_{16}BrN$
3-Pyrenyl	H	205	3.4	3.5	240–242	$C_{25}H_{14}BrN$
4-Chlorophenyl	H	177	4.4	4.2	—	$C_{15}H_9BrClN$
4-Chlorophenyl	CH_3	160	4.2	4.0	206–207	$C_{16}H_{11}BrClN$
4-Chlorophenyl	C_2H_5	147	4.0	4.0	196	$C_{17}H_{13}BrClN$
4-Chlorophenyl	C_6H_5	161	3.5	3.6	194	$C_{21}H_{13}BrClN$
4-Bromophenyl	H	188	3.9	3.6	207	$C_{15}H_{19}Br_2N$
4-Bromophenyl	CH_3	189–190	3.7	3.5	163	$C_{16}H_{11}Br_2N$
4-Bromophenyl	C_2H_5	110	3.6	3.6	—	$C_{17}H_{13}Br_2N$
4-Bromophenyl	C_6H_5	171–172	3.2	3.0	192–193	$C_{21}H_{13}Br_2N$
3,4-Dichlorophenyl	H	169	3.9	4.1	192	$C_{15}H_8BrCl_2N$
2,4-Dimethoxyphenyl	C_6H_5	89	3.5	3.4	202–203	$C_{23}H_{18}BrNO_2$
4-Ethylphenyl	CH_3	115	4.2	4.0	—	$C_{18}H_{16}BrN$
4-Iodophenyl	H	185	3.4	3.2	197–198	$C_{15}H_9BrIN$

Theory of steric hindrance in Pfitzinger reactions. Any such theory must account primarily for the sharp decrease in reactivity observed in passing from the ketones of the *n*-butyrophenone series to those of the *n*-valerophenone group and those with longer chains. A satisfactory explanation can be found in extending to ketones a structural theory proposed by Smith and McReynolds (16) to account

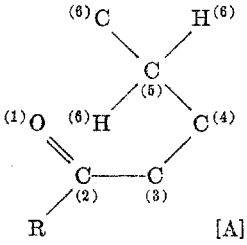
TABLE VII

6-BROMOCINCHONINIC ACIDS DERIVED FROM THIOPHENE

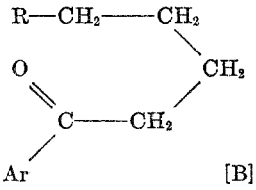
RADICAL Ar	R	M.P., °C.	ANALYSES				FORMULA	STARTING KETONE
			Calc'd		Found			
			C	H	C	H		
2,5-Dimethyl-3-thienyl	H	234–235	53.0	3.3	52.8	3.6	$C_{16}H_{12}BrNO_2S$	2,5-Dimethyl-3-acetylthiophene
2-Thienyl[a]	H	271–272	50.3	2.3	50.0	2.5	$C_{14}H_8BrNO_2S$	2-Acetylthiophene
2-Thienyl[b]	CH_3	290–291	51.7	2.9	51.4	3.2	$C_{15}H_{10}BrNO_2S$	2-Acetylthiophene
5-Chloro-2-thienyl	H	270–271	45.6	1.9	45.3	2.2	$C_{14}H_7BrClNO_2S$	5-Chloro-2-acetylthiophene
5-Chloro-2-thienyl	CH_3	278–279	41.1	2.4	47.0	2.5	$C_{15}H_9BrClNO_2S$	5-Chloro-2-propionylthiophene
5-Chloro-2-thienyl	C_2H_5	281–282	48.4	2.8	48.2	3.1	$C_{16}H_{11}BrClNO_2S$	5-Chloro-2-*n*-butyroylthiophene
5-Bromo-2-thienyl	H	247–248	40.6	1.6	40.3	2.0	$C_{14}H_7Br_2NO_2S$	5-Bromo-2-acetylthiophene
5-Bromo-2-thienyl[c]	CH_3	284–285	42.2	2.1	42.0	2.2	$C_{15}H_9Br_2NO_2S$	5-Bromo-2-propionylthiophene
5-Bromo-2-thienyl	C_2H_5	260–261	43.5	2.5	43.2	2.8	$C_{16}H_{11}Br_2NO_2S$	5-Bromo-2-*n*-butyroylthiophene
5-Bromo-2-thienyl[d]	C_6H_5	274–275	49.1	2.2	48.8	2.4	$C_{20}H_{11}Br_2NO_2S$	5-Bromo-2-phenacetylthiophene

[a] *6-Bromo-2-(2-thienyl)quinoline* crystallized from methanol as slender, yellowish needles, m.p. 124° (Found: N, 4.6. Calc'd for $C_{13}H_8BrNS$: N, 4.8.). [b] *6-Bromo-3-methyl-2-(2-thienyl)quinoline* had m.p. 90° (Found: N, 4.5. Calc'd for $C_{14}H_{10}BrNS$: N, 4.6.). [c] *6-Bromo-3-methyl-2-(5-bromo-2-thienyl)quinoline* crystallized from ethanol as yellow needles, m.p. 147–148° (Found: N, 3.5. Calc'd for $C_{14}H_9Br_2NS$: N, 3.6.). *6-Bromo-2-(5-bromo-2-thienyl)quinoline* had m.p. 175–176° (Found: N, 3.6. Calc'd for $C_{13}H_7Br_2NS$: N, 3.9). [d] All the Pfitzinger reactions with thiophene ketones were run for four hours only; otherwise, extensive decomposition takes place.

for the rate decrease of esterification of *n*-butyric acid as compared with that of propionic acid, and recently extended by Newman (17). In this theory, *n*-butyric acid and similar compounds are to be represented by coiled structures [A], and, according to Newman's rule of six, "in reactions involving addition to an unsaturated function, the greater the number of atoms in the six position, the greater will be the steric effect". Ketones such as *n*-valerophenone and higher homologs could be represented by coiled structures of type [B], and their observed behavior in Pfitzinger reactions can be readily accounted for on that basis.



[A]



[B]

Biological tests. The various cinchoninic acids and quinoline bases described in this work have been tested for potential carcinogenic activity by Dr. Zajdela of this Institute; no substance has been found active, although some produced degenerative changes in the liver.

EXPERIMENTAL

Pfitzinger reactions of n-propyl hexyl ketone. (a) *With isatin.* A solution of 6 g. of the ketone, 5.9 g. of isatin, and 6.9 g. of potassium hydroxide in 25 ml. of ethanol was refluxed for 24 hours. After distillation of most of the solvent, water was added, the neutral impurities were removed by ether extraction, and the aqueous layer was acidified with acetic acid. Yield, 6 g. of a mixture of cinchoninic acids, from which the higher-melting component (possibly *3-ethyl-2-n-hexylcinchoninic acid,* colorless needles, m.p. 108–109°) could be isolated by repeated crystallization from methanol.

Anal. Calc'd for $C_{18}H_{23}NO_2$: C, 75.8; H, 8.1.
Found: C, 75.5; H, 8.2.

(b) *With 5-bromoisatin.* A solution of 3.5 g. of the ketone, 5 g. of 5-bromoisatin, and 4 g. of potassium hydroxide in 25 ml. of ethanol was treated as above. Yield, 5.5 g. of a mixture of bromocinchoninic acids, from which the higher-melting isomer, possibly *6-bromo-3-ethyl-2-n-hexylcinchoninic acid,* could be isolated by fractional crystallization from methanol (colorless needles, m.p. 162–163°).

Anal. Calc'd for $C_{18}H_{22}BrNO_2$: C, 59.3; H, 6.0.
Found: C, 59.2; H, 6.2.

7-Bromo-4-methyl-1,2,3,4-tetrahydroacridine-9-carboxylic acid was similarly prepared in 80% yield from 2 g. of 5-bromoisatin, 2 g. of 2-methylcyclohexanone, and 2 g. of potassium hydroxide. It crystallized from ethanol as yellowish needles, m.p. 272–273° (decomp. above 260°).

Anal. Calc'd for $C_{15}H_{14}BrNO_2$:. C, 56.3; H, 4.4.
Found: C, 56.0; H, 4.2.

The *picrate* of its decarboxylation product (7-bromo-4-methyl-1,2,3,4-tetrahydroacridine) crystallized from ethanol as yellow prisms, m.p. 196–197°.

Anal. Calc'd for $C_{20}H_{17}BrN_8O_7$: N, 8.6. Found: N, 8.7.

7-Chloro-4-methyl-1,2,3,4-tetrahydroacridine-9-carboxylic acid crystallized from methanol as silky, colorless needles, m.p. 224–225°.

Anal. Calc'd for $C_{15}H_{14}ClNO_2$: C, 65.3; H, 5.1.
Found: C, 65.1; H, 5.2.

7-Bromo-4-ethyl-1,2,3,4-tetrahydroacridine-9-carboxylic acid was similarly prepared from 2-ethylcyclohexanone. It crystallized from methanol as yellowish needles, m.p. 298–299°.

Anal. Calc'd for $C_{16}H_{16}BrNO_2$: C, 57.5; H, 4.8.
Found: C, 57.2; H, 5.0.

7-Bromo-4-ethyl-1,2,3,4-tetrahydroacridine, obtained from the above acid, crystallized from petroleum ether as slender, pale yellow prisms, m.p. 92°.

Anal. Calc'd for $C_{15}H_{16}BrN$: N, 4.8. Found: N, 4.8.

Pfitzinger condensation of β-naphthisatin with octan-2-one. A solution of 2 g. of β-naphthisatin, 2 g. of octan-2-one, and 1.7 g. of potassium hydroxide in 10 ml. of ethanol was refluxed for 24 hours; after dilution with water, ether extraction, and acidification with acetic acid, 2.4 g. of *2-n-hexyl-5,6-benzocinchoninic acid* was obtained, crystallizing from ethanol as pale yellow needles, m.p. 245–246° (decomp. above 230°), identical with the product obtained from β-naphthylamine, pyruvic acid, and *n*-heptanal. Thermal decarboxylation afforded *2-n-hexyl-5,6-benzoquinoline*, an oily base whose picrate crystallized from ethanol as silky yellow needles, m.p. 147°.

2-n-Nonyl-5,6-benzocinchoninic acid, similarly prepared from undecan-2-one, had m.p. 245–247° (decomp. above 230°), and was identical with a sample prepared from *n*-decanal, β-naphthylamine, and pyruvic acid.

6-Chloro-2-phenylcinchoninic acid was prepared in 90% yield from 5-chloroisatin, acetophenone, and potassium hydroxide in the usual way; colorless prisms (from water), m.p. 282°.

Anal. Calc'd for $C_{16}H_{10}ClNO_2$: C, 67.7; H, 3.5.
Found: C, 67.6; H, 3.8.

6-Chloro-2-phenylquinoline crystallized from methanol as silky colorless needles, m.p. 110–111° (*picrate* m.p. 189–190°).

Anal. Calc'd for $C_{15}H_{10}ClN$: N, 5.8. Found: N, 5.5.

6-Chloro-2-(p-tolyl)cinchoninic acid crystallized from aqueous methanol as colorless needles, m.p. 270–271°.

Anal. Calc'd for $C_{17}H_{12}ClNO_2$: C, 68.6; H, 4.0.
Found: C, 68.4; H, 4.2.

6-Methyl-2-(p-chlorophenyl)cinchoninic acid crystallized from aqueous methanol as silky colorless prisms, m.p. 219–220°.

Anal. Calc'd for $C_{17}H_{12}ClNO_2$: C, 68.6; H, 4.0.
Found: C, 68.3; H, 4.2.

6-Methyl-2-(p-chlorophenyl)quinoline crystallized from methanol as silky colorless needles, m.p. 164° (*picrate* m.p. 185–186°).

Anal. Calc'd for $C_{16}H_{12}ClN$: N, 5.5. Found: N, 5.2.

3,6-Dimethyl-2-(p-chlorophenyl)cinchoninic acid crystallized from methanol as colorless needles, which did not melt below 320°.

Anal. Calc'd for $C_{18}H_{14}ClNO_2$: C, 69.3; H, 4.5.
Found: C, 69.1; H, 4.4.

Friedel-Crafts acylations of diphenyl sulfide. (a) *4-Phenacetyldiphenyl sulfide* was prepared in 75% yield in the usual way with phenacetyl chloride and aluminum chloride in carbon disulfide; it crystallized from methanol as shiny colorless leaflets, m.p. 105–106°.

Anal. Calc'd for $C_{20}H_{16}OS$: C, 78.9; H, 5.3.
Found: C, 78.6; H, 5.2.

(b) *4-Isobutyryldiphenyl sulfide* was a mobile, colorless oil, b.p. 224–226°/12 mm., n_D^{23} 1.6234.

Anal. Calc'd for $C_{16}H_{16}OS$: C, 75.0; H, 6.3.
Found: C, 74.9; H, 6.3.

(c) *4-Caproyldiphenyl sulfide* formed a pale yellow oil of unpleasant odor, b.p. 204–205°/0.9 mm., $n_D^{23.5}$ 1.6062, solidifying as colorless leaflets, m.p. 29–30°.

Anal. Calc'd for $C_{18}H_{20}OS$: C, 76.1; H, 7.0.
Found: C, 76.0; H, 7.2.

(d) *4-n-Octanoyldiphenyl sulfide* was likewise a viscous, pale yellow oil, b.p. 219–220°/2 mm., n_D^{23} 1.5934, which on prolonged standing set to a colorless crystalline mass, m.p. 31–32°.

Anal. Calc'd for $C_{20}H_{24}OS$: C, 76.9; H, 7.7.
Found: C, 76.7; H, 7.7.

(e) *4-Benzoyldiphenyl sulfide* crystallized from ethanol in slender colorless prisms, m.p. 70°.

Anal. Calc'd for $C_{19}H_{14}OS$: C, 78.6; H, 4.8.
Found: C, 78.4; H, 4.7.

(f) *4-(p-Methoxybenzoyl)diphenyl sulfide* crystallized from ethanol in silky colorless needles, m.p. 81°.

Anal. Calc'd for $C_{20}H_{16}O_2S$: C, 75.0; H, 5.0.
Found: C, 74.9; H, 5.3.

Friedel-Crafts acylations of thiophenetole. The reactions were performed according to the von Auwers and Arndt procedure (18); *4-propionylthiophenetole* had b.p. 178–180°/15 mm., and crystallized from methanol in large colorless prisms, m.p. 45°.

Anal. Calc'd for $C_{11}H_{14}OS$: C, 68.0; H, 7.2.
Found: C, 68.1; H, 7.0.

4-n-Butyrylthiophenetole had b.p. 189–190°/15 mm., and formed from methanol large colorless plates, m.p. 43°.

Anal. Calc'd for $C_{12}H_{16}OS$: C, 69.2; H, 7.7.
Found: C, 69.0; H, 8.0.

SUMMARY

1. The Pfitzinger reaction has been extensively investigated both as a method of preparation of quinoline derivatives, and with regard to the influence of steric hindrance.

2. A wide series of new cinchoninic acids and the corresponding quinoline bases, destined for biological testing, is recorded.

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