[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF COLUMBIA UNIVERSITY]

THE SYNTHESIS OF SUBSTITUTED 5,6-BENZOCINCHONINIC ACIDS BY THE DOEBNER AND BY THE PFITZINGER REACTIONS*

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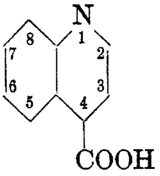
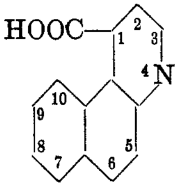
In view of the rather widespread use to which cinchoninic acid (I) derivatives have been put, to increase the excretion of uric acid in the urine in gout and rheumatic fevers, as well as in the treatment of other diseases because of their claimed analgesic, antipyretic, and antiseptic properties, it seemed desirable to study the benzocinchoninic acid group more fully, in the hope that there might be discovered therein some derivatives which retain the beneficial properties of the simple cinchoninic acids and are free from their objectionable ones.



I



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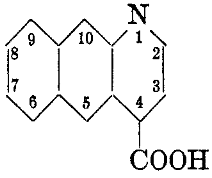

III

For the synthesis of such acids, we had recourse to both the Doebner and the Pfitzinger reactions.

In the familiar Doebner reaction, when a primary aromatic amine, an aldehyde, and a pyruvic acid, interact in a suitable neutral menstruum, the products formed vary not only with the nature of the initial materials, but also with the solvent, its temperature, and the duration of the reaction. Conspicuous among these products are the cinchoninic acids. The mechanism of the reaction has been the topic of many papers and is still under discussion. It is not our purpose to review the subject here.

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* Based upon the dissertation submitted by Mr. Robinson, May, 1933, for the Ph.D. degree under the Faculty of Pure Science, Columbia University, New York, N. Y., to which dissertation the reader is referred for further experimental details and literature citations.—M. T. B.

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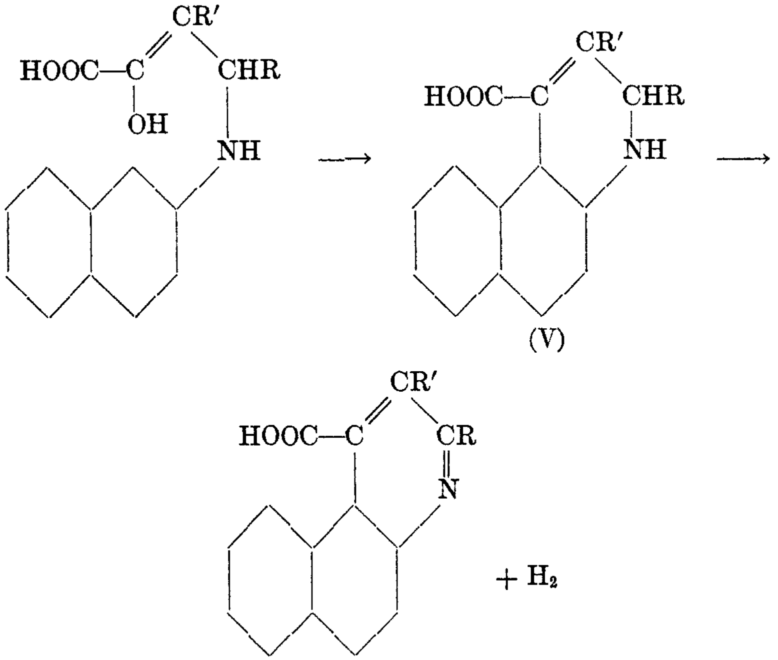
In the experiments described beyond, the amine used was 2-naphthylamine; the aldehydes were formaldehyde, acetaldehyde, benzaldehyde, *p*-anisaldehyde, and piperonal; the acids, pyruvic and benzoylpyruvic; and the solvent, boiling ethyl alcohol. The results are in favor of the assumption that, under the conditions employed by us, the principal course of the reaction was probably as follows:

$$\mathrm{C_{10}H_7NH_2 + O\underset{\rightarrow}{C}HR \rightarrow \underset{(IV)}{C_{10}H_7N{=}CHR} + R'\underset{\rightarrow}{CH_2}COCOOH}$$

$$\mathrm{C_{10}H_7NHCHRCHR'COCOOH} \rightleftarrows$$



(V)

(VI)

$$\mathrm{C_{10}H_7N{=}CHR + H_2 \rightarrow C_{10}C_7NHCH_2R}$$

The oxidation of the supposititious intermediate dihydrocinchoninic (V) to the cinchoninic acid (VI) appears to be at the expense of the anil (IV) which is compensatingly reduced to the dihydroanil. Hence, increasing the proportion of anil present increased the yield of the cinchoninic acid. This is in entire agreement with the conclusions of Ciusa and Musajo.[1]

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[1] Ciusa and Musajo, *Gazz. chim. ital.*, **59**, 796 (1929).

It is obvious that, in the application of this reaction to 2-naphthylamine, the cyclization may result in either the 5,6- (II), or the 6,7-benzocinchoninic acids (III).

Previous investigators in this field have shown, mostly by the removal of the carbon dioxide from these benzocinchoninic acids and oxidation of the resultant benzoquinolines, that the acids are evidently of type (II). Our own experiments corroborate this conclusion, for by the simple Pfitzinger reaction, using 2-amino-1-naphthaleneglyoxylic acid (from β-naphthisatin) and substituted acetophenones, we have prepared 3-R-5,6-benzocinchoninic acids identical with those obtained by the Doebner method from pyruvic acid, 2-naphthylamine and the appropriate aldehyde, since both series of products, on decarboxylation, yielded the same 3-R-5,6-benzoquinolines.

Our studies were concerned chiefly with the products of the interaction of benzoylpyruvic acid, 2-naphthylamine and the aldehydes mentioned. The only previous work we found in this field was that of Borsche,[2] who condensed benzoylpyruvic acid and 2-naphthylamine with formaldehyde and with benzaldehyde. His benzocinchoninic acids, however, were neither purified nor analyzed, but were converted directly into the corresponding 2-benzoyl-3-R-5,6-benzoquinolines by heating above their melting points. Further, none of the by-products were isolated.

The 2-benzoyl-3-R-5,6-benzocinchoninic acids prepared by us were purified without difficulty, and were characterized by their properties and analyses, by their conversion into the corresponding 2-benzoyl-3-R-5,6-benzoquinolines when heated alone, and into the 3-R-5,6-benzoquinolines when distilled with caustic soda; by the analysis of the resultant 2-benzoyl-3-R-5,6-benzoquinolines, their picrates and oximes, as well as of the 3-R-5,6-benzoquinolines and their picrates.

The formation of 3-R-5,6-benzoquinolines from the 2-benzoyl-3-R-5,6-benzocinchoninic acids is evidence that the benzoyl group in the latter is attached as a side-chain to the benzocinchoninic acid nucleus, and benzoic acid was separated as the by-product.

Dihydroanils were isolated and identified as by-products in these Doebner reactions, but no tetrahydrobenzocinchoninic acids were encountered.

By the action of thionyl chloride, the benzoyl benzocinchoninic acids were changed to the acid chlorides, and from the latter the esters were prepared.

Attempts to prepare these benzoylbenzocinchoninic acids by the Pfitzinger reaction, from β-naphthisatin and dibenzoylmethane, were defeated by the hydrolysis of the latter during the reaction.

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[2] Borsche, *Ber.*, **42**, 4072 (1909).

EXPERIMENTAL

Unless otherwise stated, all the melting points determined by us are corrected and were read while raising the temperature of the bath at the rate of approximately 3° per minute, and the melting points found for previously known compounds agree with those recorded in the literature.

β-Naphthisatin (1,2-β-Naphthazoledione).—*Sym*-Di-2-naphthylthiourea[3,4] was converted into α-(2-naphthylimino)-α-(2-naphthylamino)-acetonitrile according to the process covered by the Dreyfus patent.[5]

Following a modification of this patent, which omitted the isolation of the intermediate anil, a 60% yield of the β-naphthisatin was obtained as follows:

To 200 g. of concentrated sulfuric acid at room temperature, there was added gradually and with vigorous mechanical stirring, 15 g. of the above acetonitrile. After three hours, the solution was dark red. It was left for 12 hours at room temperature, then warmed for an hour at 40°, cooled and poured into ice water. The dark red-brown precipitate crystallized from alcohol in glistening dark red needles, m.p. 249°, in agreement with the literature.[6]

TABLE I

3-R-5,6-BENZOCINCHONINIC ACIDS

R	APPEARANCE	DEC. PT. (°C.)	REF.
H	Tan needles	302 (uncorr.)	
CH_3	Colorless needles	310 (uncorr.)	7
C_6H_5	Colorless needles	296 (uncorr.)	8, 9
p-Anisyl	Pale yellow needles	283	7, 10
Piperonyl	Pale yellow needles	292	7, 10

3-R-5,6-Benzocinchoninic acids, by the Doebner reaction.—This condensation was carried out in practically the same way as described beyond for the synthesis of the analogous 2-benzoyl-3-R-5,6-benzocinchoninic acids, except that pyruvic was substituted for the benzoylpyruvic acid.

The 3-phenyl derivative was the only one which could be purified by crystallization from diluted glacial acetic acid. The others were purified by solution in warm dilute alkali, decolorizing, and precipitating the filtered solution with dilute acetic acid.

5,6-Benzocinchoninic acid was obtained in a yield of 35%.

Anal. Calc'd for $C_{14}H_9NO_2$: C, 75.31; H, 4.07.
Found: C, 75.09; H, 4.09.

All of these acids melted with decomposition. With the exception of 5,6-benzocinchoninic acid itself, they have been described by previous investigators, with whose results our own agreed.

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[3] COSINER, *Ber.*, **14**, 61 (1881).

[4] HUGERSHOFF, *ibid.*, **32**, 2246 (1899).

[5] C. & A. DREYFUS, *Ger. Pat.* 152,019; *Friedländer*, **7**, 276 (1904).

[6] WAHL AND LOBECK, *Ann. chim. phys.* [10], **12**, 166 (1929).

[7] DOEBNER, *Ber.*, **27**, 2020 (1894).

[8] DOEBNER AND KUNTZE, *Ann.*, **249**, 129 (1888).

[9] SIMON AND MAUGUIN, *Compt. rend.*, **143**, 466 (1906).

[10] CIUSA AND ZERBINI, *Gazz. chim. ital.*, **50**, II, 317 (1920).

From the mother-liquors of these benzocinchoninic acids, the dihydroanils were isolated, but no search was made for tetrahydrobenzocinchoninic acids.

3-R-5,6-Benzocinchoninic acids by the Pfitzinger reaction.—By condensing the isatic acid from β-naphthisatin with acetophenone, or with *p*-methoxyacetophenone,[11] the 3-phenyl and 3-*p*-anisyl-5,6-benzocinchoninic acids were prepared as follows:

A mixture of 0.01 mole of β-naphthisatin (1,2-β-naphthazoledione) with 9 cc. of a 30% sodium hydroxide solution was boiled for five minutes. The isatin dissolved to a dark green solution, which changed to a yellow as the sodium salt of the corresponding isatic acid (2-amino-1-naphthaleneglyoxylic acid) was formed. To this solution there was added 0.01 mole of the appropriate acetophenone in 20 cc. of alcohol, and the mixture was refluxed for eight hours. The alcohol was then distilled off, the residue diluted with water and the solution acidified with acetic acid. After four hours' standing, the pale yellow precipitated benzocinchoninic acid was removed, dissolved in warm dilute caustic alkali, the solution decolorized and reprecipitated by dilute acetic acid. The 3-phenyl derivative was further purified by crystallization accomplished by adding two volumes of hot water to its solution in glacial acetic acid.

TABLE II

3-R-5,6-BENZOQUINOLINES

R	APPEARANCE	M.P. (°C.)	SOLVENT	REF.
H	Colorless plates	93.5	H_2O	12
CH_3	Colorless needles	82	Alc. + H_2O	7, 13, 14
C_6H_5	Colorless plates	188	Ether + alc.	8, 9
p-Anisyl	Colorless plates	190–1[a]	EtAc + alc.	7
Piperonyl	Colorless needles	178[b]	Alcohol	7

[a, b] Doebner gave a melting point of 184° for (*a*), but recorded no analysis for either (*a*) or (*b*). Our analytical results were as follows:

	Calc'd	*Found*
$C_{20}H_{15}NO$ (*a*)	C, 84.17; H, 5.30	C, 84.35; H, 5.47
$C_{20}H_{13}NO_2$ (*b*)	C, 80.24; H, 4.38	C, 80.42; H, 4.35

Melting point determinations carried out on mixtures of these products with those prepared by the Doebner Reaction showed no depression. In addition to this, the two sets of acids, when heated above their melting points until the evolution of carbon dioxide ceased, yielded the same benzoquinolines, as shown by mixed melting point determinations and by their other properties.

Table I thus summarizes the results we obtained by the two methods.

The 3-R-5,6-benzoquinolines formed by decarboxylation of the acids listed in Table I are given in Table II, including the solvent used in their recrystallization. The yields were generally about 80%.

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[11] NOLLER AND ADAMS, *J. Am. Chem. Soc.*, **46**, 1889 (1924).

[12] LELLMANN AND SCHMIDT, *Ber.*, **20**, 3154 (1887).

[13] DOEBNER AND V. MILLER, *ibid.*, **17**, 1698 (1884).

[14] SEITZ, *ibid.*, **22**, 254 (1889).

The same benzoquinolines were obtained by debenzoylation of the 2-benzoyl-3-R-5,6-benzoquinolines, or by simultaneous decarboxylation and debenzoylation of the 2-benzoyl-3-R-5,6-benzocinchoninic acids, both of which groups are described beyond.

A mixture of 0.01 mole of the benzoylbenzoquinoline, or benzoylbenzocinchoninic acid, with 12 g. of finely pulverized sodium hydroxide, in a small distilling flask, was treated with 1 cc. of water and then heated gradually. The 3-R-5,6-benzoquinolines formed distilled over gradually, and were purified by crystallization from the solvents noted in Table II; yield, 80–85%. These products melted at the same points as the corresponding compounds prepared by decarboxylation of the 3-R-5,6-benzocinchoninic acids, and mixtures of corresponding compounds from the two sets showed no alteration in the melting point. But when these benzoquinolines were mixed with the analogous 2-benzoyl derivatives, there resulted an immediate and decided drop in the melting point.

These debenzoylation reactions failed with the 3-piperonyl derivatives of both the 2-benzoyl-5,6-benzocinchoninic acid and of the 2-benzoyl-5,6-benzoquinoline, presumably because of hydrolysis of the acetal portion of the piperonyl radical, followed by decomposition.

TABLE III

PICRATES OF 3-R-5,6-BENZOQUINOLINES

R	M.P. (°C.)	REF.
H	251–252[a]	15
CH_3	228–230 (dec.)[b]	14
C_6H_5	250	8
p-Anisyl	224	

[a] Darkens.

[b] Seitz[14] gives 220–221°.

In all of these debenzoylations, there remained in the distilling flask a black mass, from which benzoic acid was isolated and identified by its m.p. (121.5°), by the m.p. of a mixture with an authentic sample of benzoic acid, and by conversion into its anilide.

As additional proof of their identity, the quinolines obtained by these debenzoylation reactions were converted into their picrates, which crystallized from alcohol in yellow needles. Picrates were prepared also from the 3-R-5,6-benzoquinolines resulting from the decarboxylation of the benzocinchoninic acids. The two series were shown to be identical by separate and mixed melting points of corresponding compounds.

Table III shows these melting points, which agree with the literature, except as there indicated.

3-p-Anisyl-5,6-benzoquinoline picrate was not found in the literature. It was therefore analyzed.

Anal. Calc'd for $C_{26}H_{18}N_4O_8$: N, 10.90. Found, 10.99.

Benzoylpyruvic-2-naphthylamide.—A solution of 3 g. of benzoylpyruvic acid[16] in

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[15] SKRAUP AND COBENZL, *Monatsh.*, **4**, 436 (1883).

[16] BRÖMME AND CLAISEN, *Ber.*, **21**, 1131 (1888).

a small quantity of hot alcohol was mixed with a warm alcoholic solution of 2.3 g. of 2-naphthylamine. As the solution cooled, the amide separated in yellow prisms, which, after being recrystallized twice from alcohol, darkened at about 125° and decomposed at 144–146°; yield, 90%. The product was insoluble in dilute alkali.

Anal. Calc'd for $C_{20}H_{15}NO_3$: C, 75.68; H, 4.77.
Found: C, 75.55; H, 4.88.

2-Benzoyl-3-R-5, 6-benzocinchoninic acids.—In the case of the aromatic aldehydes, the anil was prepared first with 2-naphthylamine; but with formalin (40%) and acetaldehyde, the aldehyde and naphthylamine were added separately to the benzoylpyruvic acid.

TABLE IV

2-BENZOYL-3-R-5,6-BENZOCINCHONINIC ACIDS

NO.	R	APPEARANCE	YIELD (%)	DEC. (°C.)	H_2SO_4 SOLN.
1	H	Pale yellow	40	247	Green
2	CH_3	Colorless	22	271	Pale yellow
3	C_6H_5	Colorless	62	249	Pale yellow
4	*p*-Anisyl	Pale yellow	51	237	Orange yellow
5	Piperonyl	Pale yellow	56	259	Dark brown-green

ANALYSES

NO.	FORMULA	CALC'D	FOUND
1	$C_{21}H_{13}NO_3$	C, 77.03; H, 4.00	C, 76.67; H, 4.04[a]
2	$C_{22}H_{15}NO_3$	C, 77.39; H, 4.44	C, 77.50; H, 4.55
3	$C_{27}H_{17}NO_3$	C, 80.37; H, 4.21	C, 80.17; H, 4.26[a]
4	$C_{28}H_{19}NO_4$	C, 77.57; H, 4.42	C, 77.29; H, 4.25
5	$C_{28}H_{17}NO_5$	C, 75.14; H, 3.83	C, 75.28; H, 4.01

[a] These two compounds were prepared by Borsche[2] but, as already mentioned, were neither purified, analyzed nor identified, except by their conversion into the corresponding benzoylbenzoquinolines.

When a suspension of 0.1 mole of benzoylpyruvic acid and 0.2 mole of the anil in 250 cc. of 95% ethyl alcohol was refluxed for four hours, the benzocinchoninic acid separated as a crystalline insoluble precipitate, which was filtered out of the hot mixture, washed thoroughly with alcohol and with ether, and dried. From the combined filtrates and washings, after standing for 48 hours at room temperature, the dihydroanils crystallized; except in those reactions where formalin or acetaldehyde was used, when only a tarry oil separated. In the case of formaldehyde, this may have been due to the fact that N-methylene-2-naphthylamine polymerizes rapidly when heated.[17]

The benzoylbenzocinchoninic acids were dissolved in warm dilute alkali, decolorized, and precipitated by the addition of dilute acetic acid. From boiling glacial acetic acid, they crystallized in short needles, when two to three volumes of

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[17] Möhlau and Haase, *Ber.*, **35**, 4167 (1902).

hot water was added. Dried at 100°, they melted with decomposition, and this decomposition-point was not altered by three to four recrystallizations. They were soluble in dilute caustic alkali and formed mineral salts readily. In concentrated sulfuric acid, they dissolved to colored solutions, from which they were reprecipitated unchanged when water was added. The yields were calculated to the amount of benzoylpyruvic acid employed.

2-Naphthylamine dihydroanils.—As noted above, the mother-liquors and washings from the benzoylbenzocinchoninic acids, on standing, separated crystalline dihydroanils when the aldehydes employed in the reaction were aromatic. As *N*-benzyl-2-naphthylamine is very freely soluble in alcohol, it was frequently necessary to make the dark filtrate alkaline and extract this base with ether.

When the dihydroanils crystallized, additional quantities of the benzocinchoninic acids often were deposited with them. They were freed from these acids by washing with dilute ammonium hydroxide solution. The bases were obtained in yields of 45–50%, and were purified by recrystallization from hot diluted alcohol.

The mother-liquors from the dihydroanils were examined repeatedly for tetrahydrobenzoylbenzocinchoninic acids, but none were found.

TABLE V

2-NAPHTHYLAMINE DIHYDROANILS

R	APPEARANCE	M.P. (°C.)	REF.	HYDROCHLORIDE	
				M.p. (°C.)	Ref.
C_6H_5	Colorless prisms	68	18, 19	219	20
p-Anisyl	Colorless plates	104.5[a]	19	195[c]	21
Piperonyl	Colorless plates[b]	119	10	192	

[a] Ciusa and Zerbini[10] gave the m.p. as 98°.

[b] Ciusa and Zerbini described this compound as existing in red scales.

[c] Steinhart[21] recorded this salt as forming yellow crystals.

The dihydroanils obtained by us are shown in Table V. They agreed in their properties with the literature, except where noted, and were identical with the dihydroanils obtained as by-products when the condensation was carried out with pyruvic acid and the corresponding anil.

Because the melting point of the dihydroanil, in the case of the *p*-anisyl and piperonyl derivatives, was so close to that of the corresponding anil, it seemed desirable to provide additional proof that these by-products were actually the dihydroanils.

Alcoholic suspensions of the carefully purified anils, therefore, were reduced to the dihydroanils with sodium amalgam, following the general method of Steinhart,[21] and the products were crystallized from hot diluted alcohol; yields, 90%. In the case of the reduction product of benzal-2-naphthylamine, it was necessary to add

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[18] KOHLER, *Ann.*, **241**, 358 (1887).

[19] ZECHMEISTER AND TRUKA, *Ber.*, **63B**, 2883 (1930).

[20] CIUSA AND CREMONINI, *Gazz. chim. ital.*, **58**, 153 (1928).

[21] STEINHART, *Ann.*, **241**, 332 (1887).

water to the reaction mixture, in order to isolate it. When these dihydroanils were mixed with the corresponding ones obtained as by-products in the Doebner reaction, no change in melting point occurred; but when the dihydroanils of either origin were mixed with the corresponding anils, there was an immediate and marked lowering of the melting point.

As a further proof of identity, the hydrochlorides of both sets of dihydroanils were prepared by the addition of the calculated amount of concentrated hydrochloric acid to a hot alcohol solution of the base. Recrystallized from alcohol, they formed colorless plates; yield, 95%. The melting points of the corresponding hydrochlorides in the two series were the same, and remained unchanged when the two were mixed. These melting points are recorded in Table V above.

TABLE VI

2-BENZOYL-3-R-5,6-BENZOQUINOLINES

R	M.P. (°C.)	SOLVENT	REF.
H	108–109	Alc.	2
CH_3	132–133	Dil. alc.	
C_6H_5	189[a]	Alc.	2
p-Anisyl	186	EtAc	
Piperonyl	210.5–211	Dil. alc.	
OXIMES			
CH_3	242		
Piperonyl	262 (dec.)		
PICRATES			
CH_3	216–217		
C_6H_5	243–244		
p-Anisyl	199.5–200		

[a] Borsche[2] reported a m.p. of 185° for this compound.

N-*Piperonyl-2-naphthylamine hydrochloride* was not located in the literature. It was therefore analyzed.

Anal. Calc'd for $C_{18}H_{16}ClNO_2$: C, 68.91; H, 5.14.
Found: C, 69.01; H, 5.08.

The basic by-products isolated by Ciusa and Zerbini[10] in the Doebner reaction, were reported by them as dihydroanils, but without the conclusive evidence of their identity which the above experimental facts supply.

2-Benzoyl-3-R-5, 6-benzoquinolines.—Heating the benzoylbenzocinchoninic acids for four or five minutes above their melting points, sufficed to decarboxylate them completely, as evidenced by the cessation of the carbon dioxide evolution, with production of the corresponding benzoylbenzoquinolines. The crude products were purified by adding water carefully to their decolorized hot alcohol solutions. As these solutions cooled, the quinolines separated in colorless needles; yield, 80%. The *oximes* crystallized from alcohol in colorless plates or needles, the *picrates* in yellow needles. The melting points, recrystallization solvents, etc., are recorded in Table VI, and the analytical results in Table VII.

TABLE VII

ANALYSES OF 2-BENZOYL-3-R-5,6-BENZOQUINOLINES, THEIR OXIMES, AND PICRATES

R	FORMULA	CALCULATED			FOUND		
		C	H	N	C	H	N
CH_3	$C_{21}H_{15}ON$	84.81	5.09		85.02	5.02	
p-Anisyl	$C_{27}H_{19}O_2N$	83.25	4.92		83.08	5.10	
Piperonyl	$C_{27}H_{17}O_3N$	80.37	4.22		80.15	4.26	
OXIMES							
CH_3	$C_{21}H_{16}ON_2$	80.73	5.17	8.98	80.93	5.22	9.07
Piperonyl	$C_{27}H_{18}O_3N_2$	77.48	4.34	6.70	77.65	4.60	6.81
PICRATES							
CH_3	$C_{27}H_{18}O_8N_4$			10.65			10.69
C_6H_5	$C_{32}H_{20}O_8N_4$			9.53			9.47
p-Anisyl	$C_{33}H_{22}O_9N_4$			9.06			8.97

TABLE VIII

2-BENZOYL-3-R-5,6-BENZOCINCHONINYL CHLORIDES

R	APPEARANCE	M.P. (°C.)	FORMULA	Cl, CALC'D	Cl, FOUND
H	Yellow prismatic needles	197–199	$C_{21}H_{12}O_2NCl$	10.26	10.08
C_6H_5	Pale yellow needles	205–206	$C_{27}H_{16}O_2NCl$	8.41	8.47
p-Anisyl	Pale yellow needles	181–183	$C_{28}H_{18}O_3NCl$	7.85	7.91
Piperonyl	Orange yellow needles	188–189	$C_{28}H_{16}O_4NCl$	7.62	7.59

TABLE IX

ETHYL 2-BENZOYL-3-R-5,6-BENZOCINCHONINATES

R	APPEARANCE	M.P. (°C.)
H	Short colorless needles	146.5–147
C_6H_5	Pale yellow plates	144[a]
p-Anisyl	Yellow needles	160–161[b]
Piperonyl	Lemon yellow prisms	158–159

ANALYSES

R	FORMULA	C, CALC'D	C, FOUND	H, CALC'D	H, FOUND
H	$C_{23}H_{17}NO_3$	77.71	77.65	4.82	4.79
C_6H_5	$C_{29}H_{21}NO_3$	80.71	80.68	4.91	4.86
p-Anisyl	$C_{30}H_{23}NO_4$	78.06	78.00	5.02	5.05
Piperonyl	$C_{30}H_{21}NO_5$	75.76	76.00	4.45	4.64

[a] Shrinks at 137–140°.

[b] The methyl ester formed yellow needles, m.p. 175–176°.

As reported in an earlier section of this communication, these benzoyl derivatives can be debenzoylated by caustic alkali, with production of the 3-R-5,6-benzoquinolines.

2-Benzoyl-3-R-5,6-benzocinchoninyl chlorides were prepared from the corresponding acids by the action of thionyl chloride, the crude products being purified by recrystallization from dry benzene; yield, 85%. They dissolved readily in warm dilute sodium hydroxide, with formation of the sodium salts of the acids.

The 2-benzoyl-3-methyl-5,6-benzocinchoninic acid behaved abnormally with thionyl chloride, giving a pale brown solid, which contained nitrogen and sulfur, but no chlorine, decomposed at 199–201°, and did not react with ethyl alcohol.

These melting points were read with the bath temperature rising 5° per minute.

Ethyl 2-Benzoyl-3-R-5,6-benzocinchoninates.—The above acid chlorides were refluxed for 15–20 minutes with absolute ethanol and, as the solutions cooled, the esters crystallized. After treatment with warm dilute sodium hydroxide, to remove any contaminating benzocinchoninic acid, they were recrystallized from 95% ethyl alcohol; yield, 90%. They were insoluble in water, but dissolved in alcohol, ether, or benzene.

SUMMARY

1. From pyruvic and benzoylpyruvic acids, 2-naphthylamine, and various aldehydes, 3-R and 2-benzoyl-3-R-5,6-benzocinchoninic acids have been synthesized.

2. The by-products in these reactions have been shown to be the corresponding dihydroanils of 2-naphthylamine.

3. By utilization of the Pfitzinger reaction, 3-R-5,6-benzocinchoninic acids have been synthesized from acetophenones and β-naphthisatin.

4. By decarboxylation of the 3-R-5,6-benzocinchoninic acids, 3-R-5,6-benzoquinolines have been obtained and their picrates prepared.

5. By decarboxylation of the 2-benzoyl-3-R-5,6-benzocinchoninic acids, the 2-benzoyl-3-R-5,6-benzoquinolines have been obtained and identified also through their oximes and picrates.

6. When the 2-benzoyl-3-R-5,6-benzocinchoninic acids, or the 2-benzoyl-3-R-5,6-benzoquinolines, are heated with caustic alkali, the 3-R-5,6-benzoquinolines result.

7. It is hoped to have some of the new benzocinchoninic acid derivatives examined pharmacologically.