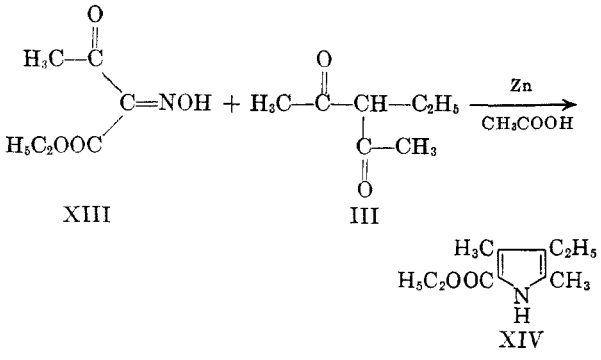

XIII III XIV

EXPERIMENTAL[15]

2-Acetyl-4-ethyl-3,5-dimethylpyrrole (IV). The reductive condensation of 50 mmol. of 3-oximino-2,4-pentanedione[16,17] with 50 mmol. of 3-ethyl-2,4-pentanedione[18,19] was carried out in the presence of zinc dust, sodium acetate, and aqueous acetic acid using the procedure[6] described for the preparation of 2-carbethoxy-3,5-dimethylpyrrole from diethyl oximinomalonate and 2,4-pentanedione. Yield of crude product, 1.3 g. or 16%. A product melting at 112–114.5° was obtained after a single recrystallization from methanol. Additional recrystallization from aqueous methanol and from isoöctane afforded an analytically pure sample of m.p. 114.5–115.5°; lit.,[10,11] m.p. 114–115°, 111–112°.

Anal. Calcd. for $C_{10}H_{15}NO$: C, 72.69; H, 9.15. Found: C, 72.36; H, 9.09.

2-Benzoyl-4-ethyl-3,5-dimethylpyrrole (V). The procedure was essentially that employed for the preparation of IV with a few minor modifications. In this instance 25 mmol. each of 3-ethyl-2,4-pentanedione[18,19] and of 2-oximino-1,3-diphenyl-1,3-propanedione[20] were employed. Zinc dust was removed from the brown viscous, semisolid product by filtration of its solution in hot benzene-methanol. Evaporation of the filtrate to a sirupy, semicrystalline residue and trituration of this residue with a little ether produced a viscous slurry of the crystalline product, which was collected on the filter. Yield of crude product, 0.6 g. or 11%; m.p. 132–139°. Recrystallization from aqueous methanol gave a purer product of m.p. 140.5–141.5°; lit.,[11] m.p. 143°.

Anal. Calcd. for $C_{15}H_{17}NO$: C, 79.26; H, 7.54. Found: C, 79.13; H, 7.63.

Isolation and identification of ethyl 5-ethyl-4-methyl-2-pyrrolecarboxylate (XI) *from the reductive condensation of diethyl oximinomalonate* (VI) *with 2-methyl-3-oxovaleraldehyde* (VIII). To 30 ml. of glacial acetic acid previously heated to 85° was added with stirring 1) 7.9 g. of anhydrous sodium acetate, 2) a solution of 7.7 g. (57 mmol.) of the sodium salt of 2-methyl-3-oxovaleraldehyde in 10 ml. of water and 5 ml. of acetic acid, and 3) a solution of 9.5 g. (50 mmol.) of diethyl oximinomalonate in 7 ml. of acetic acid. Addition of 11 g. of zinc dust was then begun at such a rate that the temperature rose to and remained in the range 100–106°. When all of the zinc dust had been introduced with vigorous stirring, the reaction mixture was heated 15 min. longer, then poured into 150 ml. of ice water. An oil containing some solid separated upon refrigeration. This was extracted with ether, and the residue remaining after evaporation of the ether was distilled under reduced pressure in order to separate the pyrrole from less volatile materials. A broad fraction of b.p. 80–155° at 16–20 mm. was collected, treated with aqueous sodium hydroxide, then extracted with ether. Recrystallization from ethanol of the oily crystalline solid obtained upon evaporation of this ether extract gave 170 mg. or 2% yield of pyrrole XI, m.p. 72–77°; lit.,[3] m.p. 79°.

Since the isomeric ethyl 3-ethyl-4-methyl-2-pyrrolecarboxylate (X)[11,14] is reported to melt at 75° or 76°, the identification of our pyrrolecarboxylic ester product of m.p. 72–77° was achieved through conversion to diethyl 3,3′-methylenebis(5-ethyl-4-methyl-2-pyrrolecarboxylate) (XII). Crude XII was obtained in 65% yield by heating our product with formaldehyde in aqueous ethanol in the presence of a small amount of concd. hydrochloric acid. Recrystallization from ethanol afforded a pure product of m.p. 193–196°; lit.,[4] m.p. 190°. The isomeric diethyl 5,5′-methylenebis(3-ethyl-4-methyl-2-pyrrolecarboxylate)[21] is reported to melt at 148°.

Anal. Calcd. for $C_{21}H_{30}N_2O_4$: C, 67.35; H, 8.07. Found: C, 67.28; H, 8.30.

Ethyl 4-ethyl-3,5-dimethyl-2-pyrrolecarboxylate (XIV). The preparative procedure was the same as that employed in the preparation of IV except that the zinc dust rather than the oximino compound was added gradually to the other reactants. Condensation of 30 mmol. each of ethyl α-oximinoacetoacetate and of 3-ethyl-2,4-pentanedione in this manner gave 2.75 g. or 47% yield of product of m.p. 89–90°; lit.,[6] m.p. 90–91°.

Anal. Calcd. for $C_{11}H_{17}NO_2$: C, 67.66; H, 8.78. Found: C, 67.46; H, 8.94.

CHEMICAL LABORATORIES
THE JOHNS HOPKINS UNIVERSITY
BALTIMORE 18, MD.

(15) All melting points were determined on the Fisher-Johns melting point apparatus.

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(17) The authors wish to thank Mr. Peter M. Eller for the preparation of this intermediate.

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(19) The authors wish to thank Mr. Wilford L. Mendelson for the preparation of this intermediate.

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Substituted Aminobenzoquinolines

A. K. CHATTERJEE

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This communication deals with the preparation of a number of substituted 1-amino-3-methylbenzo[*f*]quinolines and 4-amino-2-methylbenzo[*h*]quinolines for trials against *E. histolytica*.

The compounds were prepared by the action of 1-chloro-3-methylbenzo[*f*]quinoline or 4-chloro-2-methylbenzo[*h*]quinoline on the appropriate amine in boiling ethanol (Method I). Benzylamine, 2-phenylethylamine, 4-phenoxybutylamine, and 3-diethylaminopropylamine did not react under these conditions; in these cases, the reaction was carried out by heating the reactants in phenol (Method II) and the products isolated as the salicylate.

The condensation of 1-naphthylamine and ethyl acetoacetate in the presence of iodine and subsequent cyclization of the resulting anil in hot liquid paraffin yielded 4-hydroxy-2-methylbenzo[*h*]quinoline which on treatment with phosphorus oxychloride gave the intermediate 4-chloro-2-methylbenzo[*h*]quinoline; a similar procedure with 2-naphthylamine yielded 1-chloro-3-methylbenzo[*f*]quinoline.[1]

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TABLE I

SUBSTITUTED 1-AMINO-3-METHYLBENZO[*f*]QUINOLINES AND 4-AMINO-2-METHYLBENZO[*h*]QUINOLINES

Ser. No.	Base	M.P.[a]	Formula	Carbon, %		Hydrogen, %		Nitrogen, %		Water, %	
				Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found
1	1-*p*-Chloroanilino-3-methylbenzo[*f*]quinoline	208	$C_{20}H_{15}N_2Cl$	75.35	75.47	4.71	5.09	8.79	8.71	—	—
2	1-*m*-Chloroanilino-3-methylbenzo[*f*]quinoline	220	$C_{20}H_{15}N_2Cl$	75.35	75.22	4.71	4.94	8.79	8.82	—	—
3	1-*p*-Bromoanilino-3-methylbenzo[*f*]quinoline	208	$C_{20}H_{15}N_2Br$	66.12	65.99	4.13	4.31	7.71	7.75	—	—
4	1-*m*-Bromoanilino-3-methylbenzo[*f*]quinoline	223	$C_{20}H_{15}N_2Br$	66.12	66.32	4.13	4.19	7.71	7.65	—	—
5	1-Anilino-3-methylbenzo[*f*]quinoline	221	$C_{20}H_{16}N_2$	84.51	84.38	5.63	5.74	9.86	9.90	—	—
6	1-*p*-Iodoanilino-3-methylbenzo[*f*]quinoline	207	$C_{20}H_{15}N_2I \cdot {}^1/_4H_2O$	57.90	57.69	3.74	4.04	6.76	6.76	1.09	1.23
7	1-*m*-Iodoanilino-3-methylbenzo[*f*]quinoline	218	$C_{20}H_{15}N_2I \cdot {}^1/_4H_2O$	57.90	58.12	3.74	3.96	6.76	6.80	1.09	1.19
8	1-*p*-Anisidino-3-methylbenzo[*f*]quinoline	218	$C_{21}H_{18}N_2O \cdot {}^1/_4H_2O$	79.12	79.31	5.81	6.05	8.79	8.83	1.41	1.45
9	1-*p*-Toluidino-3-methylbenzo[*f*]quinoline	196	$C_{21}H_{18}N_2 \cdot {}^1/_4H_2O$	83.31	83.15	6.12	6.22	9.26	9.30	1.49	1.48
10	1-*m*-Toluidino-3-methylbenzo[*f*]quinoline	234	$C_{21}H_{18}N_2 \cdot {}^1/_2H_2O$	82.08	82.23	6.19	6.19	9.12	9.10	2.93	3.12
11	1-*p*-Carboxyanilino-3-methylbenzo[*f*]quinoline	266	$C_{21}H_{16}N_2O_2 \cdot 1{}^1/_4H_2O$	71.90	72.12	5.28	5.47	7.99	7.82	6.42	6.46
12	1-Benzylamino-3-methylbenzo[*f*]quinoline salicylate	248	$C_{21}H_{18}N_2, C_7H_6O_3 \cdot {}^1/_2H_2O$[b]	75.41	75.43	5.62	5.71	6.29	6.33	2.02	2.12
13	1-(2-Phenylethyl)amino-3-methylbenzo[*f*]quinoline salicylate	227	$C_{22}H_{20}N_2, C_7H_6O_3 \cdot H_2O$	74.36	74.27	5.98	5.79	5.98	6.09	3.85	3.88
14	1-(4-Phenoxybutyl)amino-3-methylbenzo[*f*]quinoline salicylate	178	$C_{24}H_{24}N_2O, C_7H_6O_3 \cdot {}^1/_2H_2O$	73.96	73.74	6.16	6.63	5.57	5.59	1.79	1.84
15	1-(3-Diethylaminopropyl)amino-3-methylbenzo[*f*]-quinoline salicylate	230	$C_{21}H_{27}N_3, 3C_7H_6O_3 \cdot {}^1/_2H_2O$	67.74	67.67	6.18	6.14	5.65	5.68	1.21	1.25
16	4-*p*-Chloroanilino-2-methylbenzo[*h*]quinoline	161	$C_{20}H_{15}N_2Cl \cdot {}^1/_3H_2O$	73.96	73.94	4.83	4.89	8.63	8.58	1.85	1.95
17	4-*m*-Chloroanilino-2-methylbenzo[*h*]quinoline	92	$C_{20}H_{15}N_2Cl \cdot 1{}^1/_2H_2O$	69.47	69.54	5.21	5.35	8.10	8.10	7.81	7.85
18	4-*p*-Bromoanilino-2-methylbenzo[*h*]quinoline	181	$C_{20}H_{15}N_2Br \cdot {}^2/_3H_2O$	64.00	64.06	4.35	4.05	7.47	7.48	3.20	3.10
19	4-*m*-Bromoanilino-2-methylbenzo[*h*]quinoline	133	$C_{20}H_{15}N_2Br \cdot H_2O$	62.99	62.85	4.46	4.75	7.35	7.38	4.72	4.85
20	4-Anilino-2-methylbenzo[*h*]quinoline	140	$C_{20}H_{16}N_2 \cdot {}^1/_2H_2O$	81.91	81.61	5.80	5.83	9.56	9.50	3.08	3.12
21	4-*p*-Iodoanilino-2-methylbenzo[*h*]quinoline	174	$C_{20}H_{15}N_2I \cdot H_2O$	56.07	56.26	3.97	3.97	6.54	6.58	4.21	4.23
22	4-*m*-Iodoanilino-2-methylbenzo[*h*]quinoline	156	$C_{20}H_{15}N_2I \cdot {}^1/_2H_2O$	57.28	57.12	3.82	4.01	6.68	6.75	2.15	2.30
23	4-*p*-Anisidino-2-methylbenzo[*h*]quinoline	168	$C_{21}H_{18}N_2O \cdot {}^1/_2H_2O$	78.02	77.92	5.88	6.15	8.67	8.55	2.79	2.68
24	4-*p*-Toluidino-2-methylbenzo[*h*]quinoline	176	$C_{21}H_{18}N_2 \cdot {}^1/_3H_2O$	82.90	82.84	6.14	6.40	9.21	9.00	1.97	2.10
25	4-*m*-Toluidino-2-methylbenzo[*h*]quinoline picrate	216	$C_{21}H_{18}N_2 \cdot C_6H_3N_3O_7$[c]	61.48	61.66	3.98	4.24	13.28	13.25	—	—
26	4-(2-Phenylethyl)amino-2-methylbenzo[*h*]quinoline salicylate	232	$C_{22}H_{20}N_2 \cdot C_7H_6O_3$	77.33	77.44	5.78	5.98	6.22	6.12	—	—

[a] Melting points are uncorrected. [b] $C_7H_6O_3$ = salicylic acid. [c] $C_6H_3N_3O_7$ = picric acid; the base was an oil and was converted into the picrate and crystallized from ethanol.

EXPERIMENTAL

Method I. 1-Chloro-3-methylbenzo[*f*]quinoline (0.005 mole) and an equivalent amount of the appropriate amine were dissolved in 90% ethanol and boiled under reflux for 5 to 10 hr. The hydrochloride of the base crystallized during this period and was filtered and washed with ethanol. It was dissolved in hot dilute acetic acid, and the solution neutralized with ammonia to precipitate the base. It was filtered, washed with water, and crystallized from 90% ethanol.

The 4-amino-2-methylbenzo[*h*]quinoline derivatives were prepared in the same way as above, by boiling under reflux for 40 hr.

Method II. A mixture of 0.005 mole of 1-chloro-3-methylbenzo[*f*]quinoline or 4-chloro-2-methylbenzo[*h*]quinoline and a slight excess of thea ppropriate amine was heated in phenol in an oil bath at 130–140° for 30 hr. The reaction mixture was poured into an excess of a solution of sodium hydroxide. The base was obtained as a sticky precipitate which solidified in a day. It was dried in the desiccator, dissolved in ether, and after filtration, the ether solution was treated with a solution of salicylic acid in ether. The salicylate of the base which precipitated was filtered, washed with ether, and crystallized from 90% ethanol.

DEPARTMENT OF PREVENTIVE MEDICINE
ARMED FORCES MEDICAL COLLEGE
POONA, INDIA

Reactions of Pyrones Catalyzed by Trifluoroacetic Acid

L. L. WOODS[1] AND HAROLD L. WILLIAMS

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Previous experiments[2,3] with pyrones have shown that trifluoroacetic acid catalyzes the reaction of acyl halides with pyrones to form either mono or diacylated products. These reactions have indicated that the activated complex of a 2- or 4-pyrone with trifluoroacetic acid is a carbanion.

It was therefore decided to try the reaction of pyrones with nitriles and with substituted acrylic acids such as cinnamic acid and crotonic acid.

In every instance in which condensation between a pyrone and a nitrile was attempted, experimental evidence indicated that a reaction had taken place.

The resulting imides are characterized in the I_{A-F} series given in Table I. Compound I_F is a ketone formed from the easily hydrolyzed imide. As Compound I_E represents the simplest molecule, it was selected as representative of the group for hydrolysis to the ketone and thus to the malononitrile derivative (IV). Malononitrile has been demonstrated[3,4] to indicate the presence of the pyrone carbonyl as well as the ketonic carbonyl.

Table II describes the three instances in which the authors were able to isolate the condensation product from the reaction of pyrones with substituted acrylic acids. The *p*-bromophenacyl bromide derivative (V) of II_A was prepared to characterize the acid because it was representative of the group and had the simplest molecule.

The compounds of the III_{A-C} series in Table III represent the nearest approach of a continuing search over a period of several years for a method by which pyrones may be carboxylated. However, every attempt to hydrolyze the carbethoxy compounds was a failure.

In the face of such limited data and so few cases one can only speculate that the position of the carboxyl or carboxyls on the pyrone ring of the carbethoxy compound is such that in the presence of boiling mineral acids the substances rapidly decarboxylate.

EXPERIMENTAL[5]

Compounds I_{A-F} *series.* A mixture of 0.1 mole of the pyrone and 0.1 mole of the nitrile in 20 ml. of trifluoroacetic acid was refluxed for at least 90 min. The cooled solution was diluted with 200 ml. of water and chilled in the freezing compartment of the refrigerator. The precipitate was dried in air and recrystallized twice from absolute ethanol to give the analytical sample.

Compounds of II_{A-C} *series.* One tenth mole of cinnamic or crotonic acid was mixed with 0.1 mole of the pyrone in 15 ml. trifluoroacetic acid and the mixture refluxed for a minimum of 15 hr. At the termination of the reflux period, 100 ml. of water was added to the mixture. The material was cooled somewhat and then filtered. The residue was dried in air and the analytical samples were obtained by recrystallizing the crude compounds twice from boiling heptane.

Compounds of III_{A-C} *series.* To a mixture consisting of 0.1 mole of the pyrone and 30 ml. of trifluoroacetic acid, thoroughly shaken, was added, all at once, either 0.1 mole or 0.2 mole of ethyl chloroformate. The solution was heated under reflux in an all-glass refluxing assembly in the hood for 2 hr. or for a sufficiently longer time that hydrogen chloride vapors were no longer evolved.

At the termination of the reaction period the mixture was poured into 200 ml. distilled water, chilled, and filtered. The air dried precipitate was recrystallized twice from heptane. Compounds of this series are listed in Table III.

Preparation of compound IV. A 5.0-g. sample of compound of I_E was refluxed in a mixture of 90 ml. distilled water and 10 ml. concd. hydrochloric acid for several hours. The solution was filtered while hot and the residue remaining on the paper was dried, then refluxed with 2.5 g. of malononitrile in 15 ml. of acetic anhydride for 1 hr. The solution was poured into water and the light brown precipitate when recrystallized several times from absolute ethanol melted at 122°.

Anal. Calcd. for $C_{21}H_{13}N_5O_3$: N, 18.26. Found: N, 18.27.

p-Bromophenacyl derivative of II_A (V). Two and seven tenths grams (0.01 mole) of II_A was mixed with 0.8 g. of sodium bicarbonate in 8 ml. of water. After the effervescence had subsided, 40 ml. of ethanol and 0.01 mole of *p*-bromophenacyl bromide (2.7 g.) was added. The mixture was

(1) The person to whom correspondence regarding the contribution should be addressed.

(2) L. L. Woods and P. A. Dix, *J. Org. Chem.*, **24**, 1126 (1959).

(3) L. L. Woods, *J. Org. Chem.*, **24**, 1804 (1959).

(4) L. L. Woods, *J. Am. Chem. Soc.*, **80**, 1440 (1958).

(5) All analyses were performed by Dr. Carl Tiedcke and all melting points were determined on a Fisher-Johns melting point assembly.