

red do not obscure the end-point, which can be found to 0.05 cc. of 0.1 *N* alkali in volumes of less than 50 cc. The equivalents of alkali used are equal to the equivalents of ammonia present.

### Summary

The alkaline hydrolysis of quaternary ammonium substituted acetonitrile to the betaine cannot be expressed as a simple second order reaction between positive and negative ions. In excess hydroxide ion the rate is proportional to the 1.3 power of the ammonium ion and to the 1.6 to 1.8 power of the hydroxide ion. When in equal concentrations the sum of the necessary exponents is about 2.4. These facts are unchanged by changes in salt concentration, temperature and in the homolog used, and should furnish a useful system for the study of electrolyte solutions.

The effect upon nitrile hydrolysis of the presence of the ammonium group has been studied, together with the effect of alkyl substitutions.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF THE UNIVERSITY OF THE  
PUNJAB]

## STUDIES IN CHEMOTHERAPY: ATTEMPTS TO FIND ANTIMALARIALS. II. PYRRYL INDOLES

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The most prolific method for the synthesis of indoles has been the well-known Fischer reaction<sup>1</sup> but the exact mechanism of this excellent reaction is still uncertain. However, the application of this method to the aliphatic and aromatic ketones has resulted in the synthesis of a large class of indoles mostly substituted in the  $\alpha$ -position. This explanatory piece of research was undertaken with a view to ascertain whether pyrroyl methyl ketones would respond to the Fischer reaction and yield  $\alpha$ -pyrroyl indoles (III) and also to decide if possible between the rival theories of the reaction. These  $\alpha$ -pyrroyl indoles are likely antimalarials because of their analogy to harmine; moreover, the pyrrole nucleus might endow a certain amount of local anesthetic property to the compounds because of the partial resemblance to the tropine structure.<sup>2</sup>

The only heterocyclic ketone which hitherto has been found to give the Fischer reaction is 2-thionyl methyl ketone.<sup>3</sup> Tetrahydroquinolone,<sup>4</sup> also has been converted into an indole.

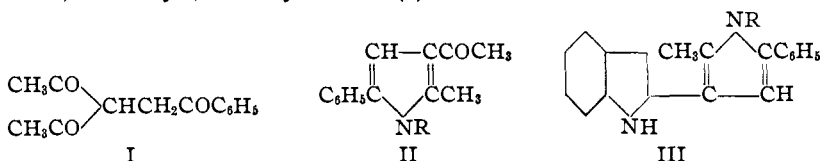
<sup>1</sup> Fischer, *Ber.*, **16**, 2245 (1883).

<sup>2</sup> Blicke and Blake, *THIS JOURNAL*, **53**, 1015 (1931).

<sup>3</sup> Brunck, *Ann.*, **272**, 201-208 (1893).

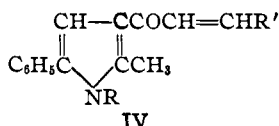
<sup>4</sup> Clemo and Perkin, *J. Chem. Soc.*, **125**, 1612 (1924).

The pyrrol methyl ketones used in this investigation were prepared from  $\alpha,\alpha$ -diacetyl- $\beta$ -benzoylthane (I)<sup>5</sup>



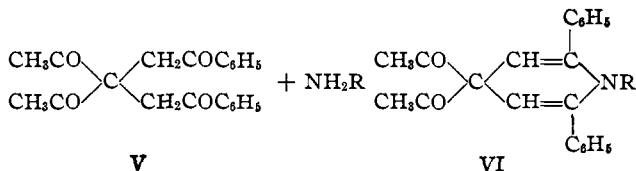
5-Phenyl-3-aceto-2-methylpyrrole (II, R = H) although it furnished a phenylhydrazone in the usual manner was not converted into an indole. Aniline, *o*-, *m*-, and *p*-toluidine, *o*-, *m*-, and *p*-nitraniline, phenetidine, anisidine and naphthylamines and a variety of other amines were condensed with the substance (I) to give the *N*-arylated pyrrol methyl ketones analogous to (II). Of these, the phenylhydrazones of the substances (II, R = C<sub>6</sub>H<sub>5</sub>, *m*-C<sub>6</sub>H<sub>4</sub>CH<sub>3</sub>, *p*-C<sub>6</sub>H<sub>4</sub>CH<sub>3</sub>, *p*-C<sub>6</sub>H<sub>4</sub>OCH<sub>3</sub>) were only converted to the corresponding indoles, III, when heated with zinc chloride. Reddelien's mechanism of the Fischer indole transformation<sup>6</sup> does not furnish an explanation of the non-formation of an indole from the phenylhydrazone of the substance (II, R = H).

The pyrrol methyl ketones now described condense with aldehydes to give condensation products of the type (IV)



With salicylaldehyde, the corresponding chalcones are formed but these are not converted into a pyrrolium chloride with hydrogen chloride which simply forms an addition compound at the exocyclic double bond. These hydrochlorides are curiously fairly stable to boiling water, being reconverted into the unsaturated ketone only on prolonged heating of an aqueous alcoholic solution.

During the preparation of  $\alpha,\alpha$ -diaceto- $\beta$ -benzoylthane by the method of March,<sup>5</sup> we isolated varying amounts of a solid of m. p. 125°. This substance is now identified as the interesting tetraketone (V), formed

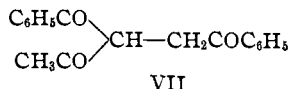


no doubt by diacylation of acetylacetone. If this is the correct view of the constitution of the substance, then it should be possible to prepare it from

<sup>5</sup> March, *Compt. rend.*, **133**, 46 (1901).

<sup>6</sup> Reddelien, *Ann.*, **388**, 179 (1912).

acetylacetone by taking appropriate amounts of sodium and bromoacetophenone. This has been done and the substance (V) has been prepared in good yield. This substance (V) can only react with an amine to give a dihydropyridine (VI). With aniline, the substance VI ( $R = C_6H_5$ ) has been prepared which after oxidation with sodium hypobromite furnishes bromoform



$\alpha,\beta$ -Dibenzoyl- $\alpha$ -acetoethane (VII) furnished pyrrol ketones analogous to II, but their phenylhydrazones could not be converted to an indole in any single instance. Some of the compounds are being tested with respect to their antimalarial properties, and have been found to be antipyretic.

### Experimental

$\alpha,\alpha$ -Diacetyl- $\beta$ -benzoylethane (I) is best prepared by the following modification of March's<sup>5</sup> process.

To acetylacetone (10 g.) in absolute alcohol (50 cc.) was gradually introduced sodium ethoxide solution prepared from sodium (2.3 g.) and alcohol (20 cc.) and then bromoacetophenone (20 g.) at 5–10°. After an hour, the mixture was warmed gently until it showed neutral reaction. The cooled product poured into much ice-cold water deposited an oil, which was separated, dissolved in alcohol (*ca.* 25 cc.) and allowed to stand on ice, when a substance separated of m. p. 125° after recrystallization from alcohol; yield 2.3 g., found: C, 75.2, H, 5.8.  $C_{21}H_{20}O_4$  requires: C, 75.0; H, 6.0. This substance was the tetraketone (V). The alcoholic filtrate when treated with alcoholic copper acetate solution gave after standing for some time the copper salt of the substance I. The quickly dried copper salt decomposed by dilute sulfuric acid was extracted with ether and obtained as pale yellow needles, m. p. 58°, yield 12–15 g. Ferric chloride colors its alcoholic solution an intense red. The substance is soluble in concentrated alkali carbonate solution with a yellow color.

The substance when condensed with a primary aromatic amine furnishes the pyrrol methyl ketones of the type II. A typical experiment is described below.

The substance I (2.2 g.) and aniline (1.0 g.) were well ground and heated for two hours at 80°. The cooled product, well washed with water and dilute hydrochloric acid, was crystallized twice from alcohol, when the substance II ( $R = C_6H_5$ ), m. p. 101° was obtained (yield 2.0 g.). (Found: N, 5.10.  $C_{19}H_{17}ON$  requires N, 5.09.) The substance is soluble in benzene, chloroform, ether, methyl alcohol and acetone. It develops a yellow color with strong sulfuric acid. It is insoluble in cold hydrochloric acid but dissolves slightly on warming. The phenylhydrazone prepared in the usual way had m. p. 162° (darkening at 114°) after crystallization from hot acetic acid. (Found: N, 11.55;  $C_{28}H_{28}N_2$  requires N, 11.50.)

The following pyrrol methyl ketones analogous to II were similarly prepared.

**The Transformation of the Phenylhydrazone to the Indole III ( $R = C_6H_5$ ).**—The phenylhydrazone (2.0 g.) well ground with zinc chloride (freshly fused, 8 g.), was heated at 162° for one and one-half hours. The hard brownish mass obtained after cooling, well washed with water and dilute hydrochloric acid, was crystallized from hot acetic acid in brownish-red needles, m. p. 221°. (Found: N, 8.03;  $C_{28}H_{20}N_2$  requires N, 8.01.)

The substance is soluble in chloroform, ether and benzene. Its solution in concentrated sulfuric acid gives an intense carmine coloration; the color is discharged with

TABLE I

Reactants	M. p. of product, °C.	N analysis, %		Phenylhydrazone of product, m. p., °C.	Nitrogen analyses of phenylhydrazone	
		Found	Calcd.		Found	Calcd.
1 I + <i>o</i> -Toluidine	95	4.89	4.84	126 (dec.)	11.19	11.08
2 I + <i>m</i> -Toluidine	142	4.85	4.84	156 ( <i>ex hot alc.</i> )	11.10	11.08
3 I + <i>p</i> -Toluidine	150	4.9	4.84	167-168	11.03	11.08
4 I + Ammonium acetate	178	<i>Cf. March, loc. cit.</i>		188	14.5	14.53
5 I + <i>o</i> -Anisidine	152	4.62	4.59	174 ( <i>ex hot HAc</i> )	10.7	10.63
6 I + <i>p</i> -Anisidine	124	4.62	4.59	185	10.68	10.63
7 I + <i>o</i> -Phenetidine	100	4.44	4.38	...	...	...
8 I + $\alpha$ -Naphthylamine	128	4.40	4.30	...	...	...
9 I + $\beta$ -Naphthylamine	140	4.31	4.30	152 (dec.)	10.18	10.12
10 I + <i>o</i> -Nitraniline	170	8.82	8.75	182	13.7	13.65
11 I + <i>m</i> -Nitraniline	136	8.77	8.75	158	13.7	13.65
12 I + <i>p</i> -Nitraniline	115	8.82	8.75	...	...	...

a drop of water and a yellowish substance is precipitated. The solution in concentrated sulfuric acid gives a transient emerald-green color with isatin and also with alloxan and with benzil on warming a yellowish-brown coloration results, indicating the presence of an indole nucleus. A solution of the substance in nitric acid gives a red color which on dilution with water gives a red precipitate suspended in a yellow solution. It does not develop any color with nitrous acid.

The following indoles analogous to III were prepared from the phenylhydrazones of the substances described in Table I in a similar way.

TABLE II

Substance	M. p. of the indole, °C.	Analyses		Formula
		Found	Calcd.	
A 2 of Table I	220-221	N, 7.70	N, 7.73	C <sub>26</sub> H <sub>22</sub> N <sub>2</sub>
B 3 of Table I	224	C, 86.31	C, 86.19	
		H, 6.06	H, 6.08	C <sub>26</sub> H <sub>22</sub> N <sub>2</sub>
		N, 7.66	N, 7.73	
C 6 of Table I	228	N, 7.65	N, 7.60	C <sub>26</sub> H <sub>22</sub> ON <sub>2</sub>

Condensation of 1-*p*-Tolyl-2-methyl-3-aceto-5-phenylpyrrole II (R = *p*-C<sub>6</sub>H<sub>4</sub>CH<sub>3</sub>) with Piperonal.—The pyrrole (2.9 g.) and piperonal (1.5 g.) dissolved in alcohol were treated with a potassium hydroxide solution (0.3 g.) in water (1 cc.) and boiled on the steam-bath for one and one-half hours. The product poured in water deposited a viscous oil which solidified after standing for two hours. It crystallized from alcohol in bright yellow needles, m. p. 132° (found: N, 3.55; C<sub>28</sub>H<sub>28</sub>O<sub>3</sub>N requires N, 3.32). The substance gives with strong sulfuric acid a transient blue color which changes to red, and on dilution with water a reddish-brown mass separates, probably a sulfate. Similarly the substance II (R = C<sub>6</sub>H<sub>5</sub>) gives a piperonylidene derivative, m. p. 164° (found: N, 3.39; C<sub>27</sub>H<sub>21</sub>O<sub>3</sub>N requires N, 3.44), the salicylidene derivative, m. p. 192° (found: N, 3.77; C<sub>26</sub>H<sub>21</sub>O<sub>2</sub>N requires N, 3.69). The latter substance gives a deep red colored solution in strong sulfuric acid which deposits an orangish precipitate on dilution with water, probably a benzopyrrolinium sulfate. When hydrogen chloride is passed into an ice-cold solution of the substance in acetic acid, a deposit of scarlet needles, m. p. 135° (with dec.) is obtained. Found: N, 3.55; C<sub>26</sub>H<sub>22</sub>O<sub>2</sub>NCl requires N, 3.37. The substance is stable to boiling water but when its aqueous alcoholic solution is boiled and water added, the salicylidene derivative of m. p. 192° is recovered.

$\alpha$ -Acetyl- $\alpha,\beta$ -dibenzoylthane was prepared from benzoylacetone (8.2 g.),  $\omega$ -bromoacetophenone (10 g.) and sodium ethoxide from sodium (1.2 g.) in alcohol first at 0–5°, then by warming till neutral, and was crystallized from alcohol, m. p. 85° (yield 8 g.). The substance is soluble in alcohol, ether, chloroform and benzene. When the above substance (4.4 g.) in absolute alcohol (15 cc.) was treated with bromoacetophenone (4 g.) and sodium (0.5 g.) in alcohol (7 cc.) first at 0° and then warmed, dibenzoyldiacetylpropane m. p. 125° (colorless plates from alcohol) was produced. (Found: C, 75.2; H, 5.8.  $C_{21}H_{20}O_4$  requires C, 75.0; H, 6.0.)

$\alpha$ -Acetyl- $\alpha,\beta$ -dibenzoylthane furnished with aniline the pyrrole (formula analogous to II), m. p. 134° (from alcohol), (found: N, 4.27;  $C_{24}H_{19}ON$  requires N, 4.15), phenylhydrazone m. p. 174° (found: N, 9.76;  $C_{30}H_{25}N_3$  requires N, 9.83) but this was not converted to an indole. The foregoing substance gave with *o*-, *m*- and *p*-toluidines the pyrroles m. p. 150° (found: N, 4.08;  $C_{25}H_{21}ON$  requires N, 3.98); m. p. 156° (found: N, 4.08), m. p. 142° (found: N, 4.01), respectively.  $\alpha,\gamma$ -Dibenzoyl- $\beta,\beta$ -diacetylpropane (4.4 g.) when heated with aniline (2 g.) at 100° for four hours and the product crystallized fractionally from hot dilute alcohol gave the substance VI (R =  $C_6H_5$ ), m. p. 130° (found: C, 82.7; H, 6.0; N, 3.66.  $C_{27}H_{23}O_2N$  requires C, 82.44; H, 5.85; N 3.56). The substance is easily soluble in most solvents but is insoluble in hydrochloric acid. When treated with sodium hypobromite solution and gently warmed, bromoform is produced but the corresponding dihydropyridine-carboxylic acid could not be isolated.

We are indebted to Mr. G. S. Ahluwalia, M.Sc., for his assistance in the investigation.

### Summary

1. By the Fischer indole reaction some pyrrol methyl ketones have been converted into the corresponding indoles. The reaction is not a general one in this series.

2. The rival theories of the indole transformation do not furnish an explanation of the non-formation of the indoles in some cases.

3. A tetraketone, *e. g.*,  $\beta,\beta$ -diaceto- $\alpha,\alpha'$ -dibenzoylpropane has been prepared and converted into a pyridine derivative.

4. Some of the compounds are studied with respect to their pharmacological (antimalarial) properties. Preliminary trials indicate that they have antipyretic properties and are toxic to paramecium.

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