TABLE II

PYROLYSIS OF ACETOACETYL HYDROXAMATES

Acetoacetyl Hydroxamates	Amount Pyrolyzed, G.	Pyrolysis conditions		Product		
				Acetone	Isocyanate	
		Temp.	Pressure, mm.	Yield, %	Yield, %	B.P. (mm.)
Hexano-	5.0	400	15	45	36	48–50/14
Phenoaceto-	5.0	350	15–20	68	63	88–90/10
Benzo-	5.0	400	1	84	67	62–64/20
p-Aniso-	2.0	370–380	3	78	71	116–118/37
p-Toluo-	2.0	350	15	74	54	71–72/13
p-Chlorobenzo-	2.0	370–380	3	61	48	107–108/41

It decomposed at 149–150° with evolution of gas and gave 1-phenyl-3-*p*-methoxyphenylurea which melted at 180–185°.

Similarly, phenylcarbamyl phenylacetohydroxamate (IIb. R = $C_6H_5CH_2$—) was obtained from phenyl isocyanate and phenylacetohydroxamic acid in 82% yield, 124° dec. (recrystallized from 95% ethanol).

Anal. Calcd. for $C_{15}H_{14}N_2O_3$: C, 66.65; H, 5.22; N, 10.37. Found: C, 66.33; H, 5.15; N, 10.21.

Decomposition of IIa *in the presence of triethylamine.* A solution of 1.2 g. of IIa and 3 drops of triethylamine in 10 ml. of dry toluene was refluxed for 20 min. After cooling, the precipitate (1.0 g., 98%) of 1-phenyl-3-*p*-methoxyphenylurea was collected, m.p. 189–190°; it was recrystallized from 95% ethanol.

In a similar fashion IIb was converted into 1-phenyl-3-benzylurea in 95% yield, m.p. 169–170°; it was recrystallized from 95% ethanol.

Preparation of acetoacetyl benzohydroxamate. A solution of ketene dimer (15.0 g., 0.185 mole) in 10 ml. of ethyl acetate was added dropwise over a period of 20 min. to a suspension of benzohydroxamic acid (20.0 g., 0.165 mole) in 20 ml. of ethyl acetate at room temperature. After addition was completed, the mixture was stirred at 50° for 30 min. The solvent was subsequently removed under reduced pressure and the residual acetoacetyl benzohydroxamate was recrystallized from ethyl acetate, weighed 29.0 g. (88%). The white crystal melted at 83–84° and decomposed at 130–135°.

Anal. Calcd. for $C_{11}H_{11}NO_4$: C, 59.72; H, 5.01; N, 6.33. Found: C, 59.55; H, 5.13; N, 6.33.

Similarly, acetoacetyl phenylaceto-, *p*-toluo-, *p*-aniso-, and hexanohydroxamates were prepared from ketene dimer and corresponding hydroxamic acids. Their properties are listed in Table I.

The *p*-chlorobenzohydroxamate was prepared analogously except for the use of refluxing absolute ether (10 hr.) instead of the ethyl acetate.

Pyrolysis of acetoacetyl hydroxamates. The apparatus used for all pyrolyses consisted essentially of a vertical pyrex tube, 12 mm. or 18 mm. in diameter and 60 cm. long, equipped with standard taper joint and a side-inlet tube near the top for the exchange of air with nitrogen. This tube was packed with Pyrex chips and externally heated with electric furnace. The temperature was determined with a thermocouple located between the Pyrex tube and furnace. Before each pyrolysis the whole system was flushed for 10 min. with dry nitrogen. Pyrolysis was conducted under reduced pressure and 2.0 g. or 5.0 g. of acetoacetyl hydroxamate was dropped into the column at a rate of 0.2 g. per min. The pyrolysate was collected directly in a Claisen flask cooled in a Dry Ice acetone bath, and fractionated by distillation (Table II).

Acknowledgment. The authors wish to express their hearty thanks to Prof. Toshio Hoshino for his encouragement and to Mr. Makoto Tokizawa, Mr. Kazuyoshi Tonooka, and Mr. Mochihiro Iijima for their help during the course of this experiment. Thanks are also due to Mr. Asaji Kondo for the microanalyses.

OHOKAYAMA, MEGURO-KU, TOKYO

[CONTRIBUTION FROM THE SHELL DEVELOPMENT COMPANY]

Some Observations on the Pechmann Reaction[1]

D. E. WINKLER AND R. R. WHETSTONE

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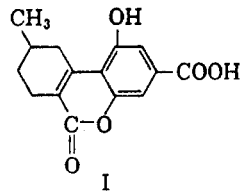
α-Resorcylic acid and 3-dimethylamino-5-pentylphenol do not undergo the Pechmann reaction with ethyl 5-methylcyclohexanone-2-carboxylate under conditions normally used. Separation of the carboxyl groups from the ring by one methylene group permits the reaction to proceed easily. An unusual ring closure between a 5-alkyl resorcinol and the above β-ketonic ester has been observed.

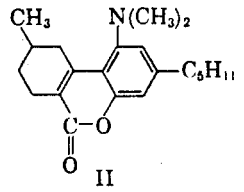
In the course of work on the condensation of ethyl 5-methylcyclohexanone-2-carboxylate with certain phenol and resorcinol derivatives, it was observed that α-resorcylic acid (3,5-dihydroxybenzoic acid) and 3-dimethylamino-5-pentylphenol would not undergo the Pechmann condensation with the above β-ketonic ester to give, respectively, the expected compounds I and II.

A number of references to the condensation of β- and γ-resorcylic acids or esters (2,4- and 2,6-dihydroxybenzoic acids, respectively) with β-ketonic

(1) This paper reports work done under contract with the Chemical Corps, U. S. Army, Washington, D. C.

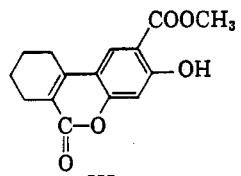


I



II

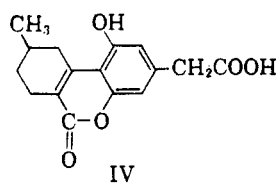
esters can be found in the literature,[2-4] but no mention is made of either positive or negative results with α-resorcyclic acid. Whether this is due to the fact that the α-resorcyclic acid is more difficult to obtain or has just not been used is not known. When methyl β-resorcylate is condensed with ethyl cyclohexanone-2-carboxylate, condensation is reported[2] to be always *para* to one of the hydroxyl groups, thus giving methyl 3-hydroxy-7,8,9,10 - tetrahydro - 6 - dibenzopyrone - 2 - carboxylate, III.



III

In the case of α-resorcylic acid, this would mean condensation *ortho* to the carboxyl group which is not likely. On the other hand, compounds in which the carboxyl group of α-resorcyclic acid is replaced by an alkyl group readily undergo the Pechmann reaction to give condensation between the two hydroxyl groups.[5-7]

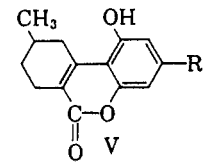
On this basis one might expect α-resorcylic acid and its esters to react; however, the replacement of a negative alkyl group by a more positive carboxyl group apparently changes the reactivity of the *para* position sufficiently to prevent reaction. All attempts to obtain reaction with α-resorcyclic acid or its methyl and butyl esters under a variety of conditions were completely unsuccessful. Separation of the carboxyl group from the ring by one methylene group is sufficient to permit reaction, for 3,5-dihydroxyphenylacetic acid has been shown to react with ethyl 5-methylcyclohexanone-2-carboxylate



IV

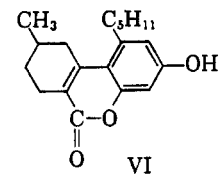
at room temperature in the presence of 80% sulfuric acid to give 1-hydroxy-9-methyl-,7,8,9,10-tetrahydro-6-dibenzopyrone-3-acetic acid, IV.

The only products isolated by Adams[6] or Russell[7] from the condensation of 5-alkyl resorcinols with ethyl 5-methylcyclohexanone-2-carboxylate in the presence of acidic catalysts have structure V.



V

They do not report the isolation of any other product. It has now been observed in these laboratories that if pentyl-3,5-dihydroxybenzene and ethyl 5-methylcyclohexanone-2-carboxylate are heated together in equimolar amounts without solvent or catalyst, a crystalline solid is obtained whose elemental analysis is identical with that of V (R = pentyl), but which melts 14° higher. It is believed to be 1-pentyl-3-hydroxy-9-methyl-7,8,9,10-tetrahydro-6-dibenzopyrone, VI.

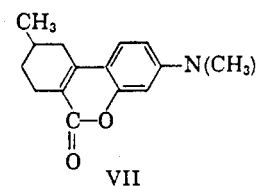


VI

An authentic sample of V was prepared according to the method of Adams and Baker[8] and when mixed with VI the melting point was lowered.

The type of condensation represented by VI, *para* to one of the hydroxyl groups in a 5-alkyl resorcinol, is contrary to what has been reported[5-7] to occur in the presence of acidic catalysts, but is in agreement with what usually occurs with 2- and 4-alkyl resorcinols.

The condensation of 3-dialkylaminophenols with β-ketonic esters in the presence of anhydrous zinc chloride has been described.[9,10] In this laboratory 3-dimethylaminophenol was condensed with ethyl 5-methyl-cyclohexanone-2-carboxylate according to the method of Long to give VII.



VII

Condensation is always written as having taken place at the position *para* to the amino group and we see no reason to question this structure.

(2) R. D. Desai, M. M. Gaitonde, S. Mehdi Hasan, and R. C. Shah, *Indian Acad. Sci.*, **25**, 345 (1947).

(3) R. C. Shah, S. M. Sethna, B. C. Banerjee, and D. Chakravarti, *J. Indian Chem. Soc.*, **14**, 717 (1937).

(4) D. B. Limaye and K. M. Kulkarni, *Rasayanam*, **1**, 251 (1943) [*Chem. Abstr.*, **38**, 4264 (1944)].

(5) S. Sethna and R. Phadke, *Org. Reactions*, **3**, 8 (1953).

(6) R. Adams, S. Loewe, C. Jelinek, and H. Wolff, *J. Am. Chem. Soc.*, **63**, 1971 (1941).

(7) P. B. Russell, A. R. Todd, S. Wilkinson, A. D. Macdonald, and G. Woolfe, *J. Chem. Soc.*, 826 (1941).

(8) R. Adams and B. R. Baker, *J. Am. Chem. Soc.*, **62**, 2401 (1940).

(9) H. Pechmann and M. Schaal, *Ber.*, **32**, 3690 (1899).

(10) R. S. Long and C. A. Sears, to American Cyanamid Company, U. S. Patent 2,647,132 (1952).

In the case of the reaction of 3-dimethylamino-5-pentylphenol with ethyl 5-methylcyclohexanone-2-carboxylate, condensation by analogy with the usual course of reaction with 5-alkyl resorcinols might be expected to occur between the hydroxyl and amino groups to give II. The other possibility is for condensation to occur *para* to the amino group as it does with 3-dimethylaminophenol, in which case one would obtain an isomer of II having the amino and amyl groups interchanged.

Several attempts were made to effect the above condensation using anhydrous zinc chloride according to the method of Long, but in every case the bulk of the starting materials was recovered plus a small amount of nondistillable residue which could hardly have been either of the possible isomers. Failure of 3-dimethylamino-5-pentylphenol to condense with ethyl 5-methylcyclohexanone-2-carboxylate is probably due to the steric effects imparted by the large groups symmetrically arranged on the phenol.

EXPERIMENTAL

α-Resorcylic acid (3,5-dihydroxybenzoic). An improved method for the preparation of this acid *via* the sulfonate was developed which eliminates the time-consuming precipitation of excess sulfate ion followed by filtration and evaporation to dryness. A solution of 244 g. (2.0 moles) of benzoic acid in 1200 g. of 30% fuming sulfuric acid was slowly heated to 230–240° and then kept at that temperature for 5 hr. The cooled product was diluted with 2 l. of water and poured into a warm solution of 1700 g. of sodium chloride in 5 l. of water. After cooling overnight in an ice bath, the precipitated sodium salt of 3,5-disulfobenzoic acid was filtered and dried. The alkali fusion was carried out in a 1200 ml. stainless steel beaker following the procedure of Weston,[11] and the product was worked up in much the same way. After recrystallization of the crude acid from 500 ml. of water, 225 g. (73% yield) of 3,5-dihydroxybenzoic acid, m.p. 236–237°, was obtained.

Attempted condensation of α-resorcylic acid with ethyl 5-methylcyclohexanone-2-carboxylate. All attempts to effect a Pechmann condensation between the above resorcinol derivative and β-ketonic ester failed. The methyl and butyl esters of α-resorcylic acid were also tried. In every case the starting materials were recovered unchanged. The conditions used include (a) standing for several days with 80% sulfuric acid, (b) refluxing with phosphorus oxychloride in benzene solution, and, (c) heating for 1 hr. at 125–130° with aluminum chloride in nitrobenzene according to the method of Sethna.[12]

3,5-Dimethoxyphenylacetic acid. 3,5-Dimethoxyphenyl methyl ketone, which had been obtained from 3,5-dimethoxybenzamide and methylmagnesium iodide by the method of Suter and Weston[13] was converted to 3,5-dimethoxyphenylacetic acid using the Kindler modification of the Willgerodt reaction as described by Newman[14] and Schwenk.[15] A mixture of 50.5 g. (0.28 mole) of 3,5-dimethoxyphenyl methyl ketone, 13.5 g. (0.42 mole) of sulfur, and 36.5 g. (0.42 mole) of morpholine was brought slowly to boiling and then refluxed 14 hr. The crude thiomorpholide was hydrolyzed by refluxing for 12 hr. with 74 g. of potassium hydroxide in 740 ml. of water. After precipitating with hydrochloric acid, the crude acid was filtered and purified by recrystallizing from water with the aid of decolorizing carbon. A 69% yield of acid melting at 100.5–101° was recovered.

Anal. Calcd. for $C_{10}H_{12}O_4$: C, 61.2; H, 6.17. Found: C 60.9; H, 6.2.

3,5-Dihydroxyphenylacetic acid. A solution of 85 g. (0.43 mole) of 3,5-dimethoxyphenylacetic acid, 440 ml. of 48% hydrobromic acid, 440 ml. of acetic acid, and 42 ml. of hydriodic acid (sp. gr., 1.7) was refluxed for 16 hr. according to the method of Levine[16] for the preparation of *o*-hydroxyphenylacetic acid. About half of the solvent was removed under vacuum and the remainder was diluted with 1 l. of water and extracted with three 1-l. portions of ether. After evaporation of the ether to dryness, an 83% yield of crude acid was obtained which could be purified by dissolving in ethyl acetate and precipitating with benzene or chloroform. The purified material melted at 128–128.5°.

Anal. Calcd. for $C_8H_8O_4$: C, 57.1; H, 4.80. Found: C, 57.2; H, 4.9.

1-Hydroxy-9-methyl-7,8,9,10-tetrahydro-6-dibenzopyrone-3-acetic acid (IV). The method of Desai[17] for the condensation of methyl β-resorcylate with ethyl cyclohexanone-2-carboxylate was used. A solution 2.0 g. of 3,5-dihydroxyphenylacetic acid and 2.0 g. of ethyl 5-methylcyclohexanone-2-carboxylate in 20 g. of 80% sulfuric acid was allowed to stand 5 days at room temperature. Upon pouring into 200 g. of ice and water, a precipitate formed which was filtered and washed. The yield was 3 g. of crude material. After three recrystallizations from 40% ethanol, 1.0 g. (32% yield) was recovered which melted at 240–241°.

Anal. Calcd. for $C_{16}H_{16}O_5$: C, 66.7; H, 5.60. Found: C, 66.4; H, 5.5.

1-Pentyl-3-hydroxy-9-methyl-7,8,9,10-tetrahydro-6-dibenzopyrone (VI). A solution of 3.6 g. (0.02 mole) of 3,5-dihydroxypentylbenzene and 3.7 g. (0.02 mole) of ethyl 5-methylcyclohexanone-2-carboxylate was heated in an oil bath for 5 hr. at 180°. The unchanged starting materials were removed under vacuum in a modified Hickman still and the residue was recrystallized once from ethyl acetate and once from 80% ethanol to yield 3 g. (50%). This material melted at 191–192° which is 14° higher than V (R = pentyl), and when mixed with an authentic sample of V (m.p. 177–177.5°) the melting point was lowered (mixed m.p. 143–152°).

Anal. Calcd. for $C_{19}H_{24}O_3$: C, 76.0; H, 8.07. Found: C, 76.0; H, 8.0.

3-Dimethylamino-9-methyl-7,8,9,10-tetrahydro-6-dibenzopyrone (VII). A solution of 14 g. (0.1 mole) of 3-dimethylaminophenol, 20.2 g. (0.11 mole) of ethyl 5-methylcyclohexanone-2-carboxylate, and 14 g. (0.1 mole) of anhydrous zinc chloride in 40 ml. of ethanol was refluxed for 20 hr. The alcohol was removed under vacuum and the product dissolved in chloroform, washed with water, and distilled in a modified Hickman still to yield 5 g. (20%). A greenish-yellow crystalline product, m.p. 122–123°, was obtained after two recrystallizations from toluene.

Anal. Calcd. for $C_{16}H_{19}O_2N$: C, 74.7; H, 7.46; N, 5.44. Found: C, 74.6; H, 7.6; N, 5.0.

3-Dimethylamino-5-pentylphenol. A mixture of 35 g. (0.194 mole) of pentyl-3,5-dihydroxybenzene, 27 g. of dimethylamine, 40 g. of water, and 12 g. of 85% phosphoric acid was shaken in a steel bomb for 12 hr. at 175°. The excess of dimethylamine was removed under vacuum, and

(11) A. W. Weston and C. M. Suter, *Org. Syntheses*, **21**, 27 (1941).

(12) S. M. Sethna, N. M. Shah, and R. C. Shah, *J. Chem. Soc.*, 208 (1938).

(13) C. M. Suter and A. W. Weston, *J. Am. Chem. Soc.*, **61**, 232 (1939).

(14) M. S. Newman, *J. Org. Chem.*, **9**, 521 (1944).

(15) E. Schwenk and E. Bloch, *J. Am. Chem. Soc.*, **64**, 3051 (1942).

(16) J. Levine, T. E. Elbe, and H. Fischbach, *J. Am. Chem. Soc.*, **70**, 1930 (1948).

(17) R. D. Desai, M. M. Gaitonde, S. Mehdi Hanson, and R. C. Shah, *Indian Acad. Sci.*, **25**, 345 (1947).

the product dissolved in 500 ml. of ether and extracted with 500 ml. of 1*N* hydrochloric acid. The 3-dimethylamino-5-pentylphenol was precipitated by adding sodium bicarbonate, extracted with ether, washed with water, and distilled to yield 20 g. (50% yield), b.p. 141–145° at 0.2 mm.

Anal. Calcd. for $C_{13}H_{21}ON$: C, 75.3; H, 10.2; N, 6.76. Found: C, 74.9; H, 9.9; N, 6.5.

Attempted condensation of 3-dimethylamino-5-pentylphenol with ethyl 5-methylcyclohexanone-2-carboxylate. When a solution of 18 g. (0.1 mole) of 3-dimethylamino-5-pentylphenol, 20.2 g. (0.11 mole) of ethyl 5-methylcyclohexanone-2-carboxylate and 14 g. (0.1 mole) of anhydrous zinc chloride in 40 ml. of ethanol was refluxed for 20 hr., the starting materials were recovered unchanged. If the same ratio of reactants was heated for 7 hr. in an oil bath at 110° in the absence of a solvent, the resulting product after removal of the zinc chloride gave only starting material and a nondistillable residue.

Acknowledgment The authors are indebted to R. E. Benson, D. D. Campbell, and R. J. Patten for their assistance in the preparative work.

EMERYVILLE, CALIF.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, FACULTY OF SCIENCE, CAIRO UNIVERSITY]

On the Reactivity of the Unsaturated System in *N*-Arylmaleimides

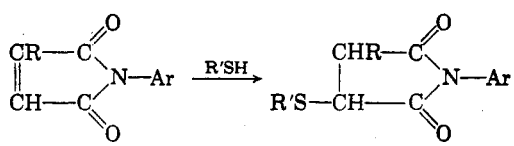
AHMED MUSTAFA, WAFIA ASKER, SAMIR KHATTAB, AND SALAH MOHAMED ABDEL DAYEM ZAYED

Received May 25, 1960

The unsaturated system in *N*-arylmaleimides (I) undergoes addition reactions with aromatic thiols and with piperidine to give the adducts (IIa–b) and (IIIa–d and IV) respectively. Similarly, addition of aromatic hydrocarbons takes place to the C=C bond in Ia–b in the presence of aluminum chloride, without opening of the hetero-ring, to yield the products Va–h, thus establishing an easy method for the preparation of substituted *N*-arylsuccinimides.

N-Arylmaleimides add a number of reagents to give substituted derivatives of *N*-arylsuccinimides. Thus, addition products are obtained with diazoalkanes[1,2] and with arylazides,[1] and they function as dienophiles in the Diels-Alder synthesis.[3]

In conjunction with a study of the pharmacological action of sulfur-containing compounds against *Belharziasis* snails, Mustafa and coworkers[4] have recently described a number of new β-nitrosulfides, prepared by the addition of aromatic thiols to ω-nitrostyrenes in the presence or absence of piperidine. We now have extended our study to the addition of aromatic thiols, *e.g.*, thiophenol and *p*-thiocresol, to *N*-phenylmaleimide (Ia) to obtain the sulfides needed for the pharmacological investigation.[4]



Ia. Ar = C_6H_5; R = H
b. Ar = *p*-$CH_3C_6H_4$; R = H
c. Ar = *p*-$CH_3OC_6H_4$; R = H
d. Ar = *p*-$C_2H_5OC_6H_4$; R = H
e. Ar = C_6H_5; R = CH_3
IIa. Ar = R' = C_6H_5; R = H
b. Ar = C_6H_5; R' = *p*-$CH_3C_6H_4$; R = H

The sulfides (IIa–b) are colorless crystalline products, obtained in good yields, and are believed to have structures like II. The addition of thiols to the double bond in Ia finds analogy with the well established addition of the same reagents to unsaturated compounds.[5,6]

Reaction of N-arylmaleimides with piperidine. We now have also investigated the addition of piperidine to the unsaturated system in *N*-arylmaleimides. Thus, when benzene solutions of Ia–e were treated with piperidine at room temperature, the piperidinium adducts (IIIa–d and IV, respectively) were obtained in good yields.

The piperidinium adducts are sharp melting crystalline compounds and are stable under normal conditions, but decompose to the original components when heated above their melting points.[7]

(1) A. Mustafa, S. M. A. D. Zayed, and S. Khattab, *J. Am. Chem. Soc.*, **78**, 145 (1956).

(2) *N*-Phenylmalemide adds diazomethane to give the corresponding pyrazoline derivative, which upon thermal decomposition yields cyclopropane-2,3-(*N*-phenyl)dicarboximide (*cf.* ref. No. 1). The latter compound was erroneously formulated by Gregory and Perkin (T. W. D. Gregory and W. H. Perkin, *J. Chem. Soc.*, 780 (1903) as hexahydropyromellitic acid di(*N*-phenyl)carboximide, and was later corrected by Perkin (W. H. Perkin, *J. Chem. Soc.*, 359 (1905); *Beilstein*, Vol. **21**, 411) as cyclopropane-2,3-(*N*-phenyl)dicarboximide.

(3) *Cf.* A. Mustafa and M. Kamel, *J. Am. Chem. Soc.*, **77**, 1328 (1955), A. Mustafa and M. I. Ali, *J. Org. Chem.*, **21**, 849 (1956); A. Mustafa, M. Kamel, and M. A. Allam, *J. Am. Chem. Soc.*, **78**, 4692 (1956).

(4) The pharmacological results will be published elsewhere.

(5) *Cf.* T. Posner [*Ber.*, **35**, 809 (1902)] and B. H. Nicolet [*J. Am. Chem. Soc.*, 3066 (1931)] in the case of α,β-unsaturated ketones; R. M. Ross and F. W. Raths [*J. Am. Chem. Soc.*, **73**, 129 (1951)] in the case of 1-cyano-1-cyclohexene; and R. M. Ross, H. L. Bushey, and R. J. Rolih [*J. Am. Chem. Soc.*, **73**, 540 (1951)] and R. M. Ross [*J. Am. Chem. Soc.*, **71**, 3458 (1949)] in the case of alkylacrylonitriles.

(6) For the addition of thioglycollic acid to Ia, *cf.* D. H. Marrian, [*J. Chem. Soc.*, 1515 (1949)]. E. Friedmann, D. H. Marrian, and Simon-Reuss [*J. Brit. J. Pharmacol.*, **4**, 105 (1949)].

(7) A. Mustafa, W. Asker, A. F. A. Shalaby, S. A. Khattab, and Z. Selim, *J. Am. Chem. Soc.*, **81**, 6007 (1959).