line-5-carboxylic acid was 352 mg. (71.3%); fine, grayish needles. m.p. 222–224° dec.

2,3-Diphenyl-7-nitroquinoxaline-5-carboxylic acid XIII. Two millimoles (394 mg.) of VIII treated with an equivalent quantity of benzil in 25 ml. of glacial acetic acid as described for VII, yielded 526 mg. (70.8%) of 2,3-diphenyl-7-nitroquinoxaline-5-carboxylic acid in the form of yellow plates, m.p. 235–236°. A sample for analysis was recrystallized from methanol.

6-Chloro-4-nitrobenzotriazole XIV. A solution of 940 mg. (5 mmoles) of 5-chloro-3-nitro-*o*-phenylenediamine in 100 ml. of hot 1*N* sulfuric acid was treated with Darco and filtered. The sulfate of the base which separated on cooling the filtrate was kept in suspension by vigorous stirring while a solution of 450 mg. of sodium nitrite in 5 ml. of water was added over a period of 10 min. Stirring was continued for 1 hr. The 6-chloro-4-nitrobenzotriazole was collected, washed with water, and recrystallized from 50% ethanol (75 ml.), m.p. 238–239°. The yield was 619 mg. (62.3%).

6-Chloro-2-methyl-4-nitrobenzimidazole XV. Three millimoles (563 mg.) of 5-chloro-3-nitro-*o*-phenylenediamine, treated with acetic anhydride and then hydrochloric acid as described for III, yielded 548 mg. (86.3%) of 6-chloro-2-methyl-4-nitrobenzimidazole; it was recrystallized from benzene, m.p. 229–230°.

7-Chloro-5-nitroquinoxaline (XVI). To a solution of 940 mg. (5 mmoles) of 5-chloro-3-nitro-*o*-phenylenediamine in 50 ml. of hot ethanol, there was added 1.5 ml. of a 30% aqueous solution of glyoxal. The solution was refluxed for 1 hr., treated with Nuchar, and filtered. On cooling the filtrate, the 7-chloro-5-nitroquinoxaline crystallized as long, yellow needles, m.p. 174–175°. The yield was 690 mg. (65.8%).

7-Chloro-2,3-dimethyl-5-nitroquinoxaline (XVII). Five millimoles (940 mg.) of 5-chloro-3-nitro-*o*-phenylenediamine in 75 ml. of 50% ethanol treated with 605 mg. (7 mmoles) of diacetyl as outlined for VI gave 815 mg. (68%) of 7-chloro-2,3-dimethyl-5-nitroquinoxaline; pale, yellow needles, m.p. 140–141°.

7-Chloro-2,3-diphenyl-5-nitroquinoxaline (XVIII). When a mixture of 563 mg. (3 mmoles) of 5-chloro-3-nitro-*o*-phenylenediamine and 700 mg. (3.3 mmoles) of benzil in 25 ml. of glacial acetic acid was processed as described for VII, a yield of 882 mg. (81.4%) of 7-chloro-2,3-diphenyl-5-nitroquinoxaline was obtained. The compound was recrystallized from ethanol: short, yellow needles, m.p. 184–185°.

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[CONTRIBUTION FROM THE RESEARCH AND DEVELOPMENT DIVISION, SMITH KLINE AND FRENCH LABORATORIES]

Synthesis of Phenothiazines. IV.[1-3] 10-Aminoalkyl Derivatives of 2-Substituted Phenothiazines and 2-Azaphenothiazines

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The present paper describes various 10-aminoalkyl derivatives of the following phenothiazines: 2-hydroxyphenothiazine, 2-methylthiophenothiazine, 2-methylsulfonylphenothiazine, 2-trifluoromethylsulfonylphenothiazine, 2-trifluoromethylthiophenothiazine, 2-azaphenothiazine, and 8-chloro-2-azaphenothiazine.

Paper II[2] of this series describes the preparation of 2-azaphenothiazine and 8-chloro-2-azaphenothiazine. Paper III describes the preparation of 2-hydroxyphenothiazine, 2-benzoyloxyphenothiazine, 2-methylthiophenothiazine, 2- and 4-trifluoromethylthiophenothiazine, 2-methylsulfonylphenothiazine, and 2-trifluoromethylsulfonylphenothiazine. In Tables I and II of the present paper are reported the preparation and physical properties of eighteen different 10-aminoalkyl derivatives of the substituted phenothiazine intermediates described in papers II and III. Biological data concerning these compounds will be published elsewhere.

EXPERIMENTAL[4]

The alkylations were carried out in the usual manner[1] with the following exceptions. The direct alkylation of 2-hydroxyphenothiazine was not attempted. Instead 2-benzoyloxyphenothiazine was alkylated using sodamide in xylene and the ester group was removed by basic hydrolysis during the workup. The alkylation of 2-trifluoromethylsulfonylphenothiazine with 3-(4-methylpiperazinyl)propyl chloride required 48 hr. instead of the usual 2 to 10 hr. The preparation of the β-acetoxyethyl compounds was accomplished as shown.

Preparation of 4-[3-(2-azaphenothiazin-10-yl)propyl]-1-piperazineethanol, acetate dimaleate. (Compound 17). A mixture of 15 g. of 2-azaphenothiazine,[2] 6.8 g. of sodamide, and 500 ml. of dry toluene was refluxed and stirred under a nitrogen atmosphere for 45 min. To the mixture was added a slurry of 21 g. of 3-chloro-1-(1-formyl-4-piperazinyl)propane hydrochloride and 300 ml. of dry toluene which had been previously azeotroped together for 1 hr. The mixture was cooled and 150 ml. of water was added. The toluene layer was extracted with dilute hydrochloric acid. The acid extracts were made alkaline and extracted with benzene. The benzene was evaporated to give 21 g. of an oil. The oil was dissolved in a solution of 250 ml. of ethanol, 60 ml. of water, and 7 ml. of 40% sodium hydroxide solution. The mixture

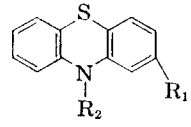
(1) Paper I. P. N. Craig *et al.*, *J. Org. Chem.* **22**, 709 (1957).

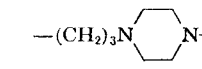
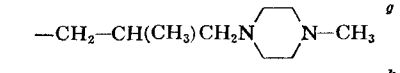
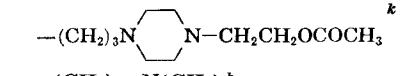
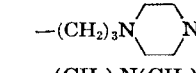
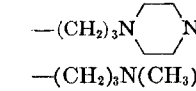
(2) Paper II. A. J. Saggiomo *et al.*, *J. Org. Chem.* **23**, 1906 (1958).

(3) Paper III. E. A. Nodiff *et al.*, *J. Org. Chem.*, **25**, 60 (1960).

(4) All melting points are uncorrected.

TABLE I



Compound Number	R_1	R_2	M.P. and B.P.	Yield, %	Molecular Formula	Analyses					
						Calcd.			Found		
						C	H	N	C	H	N
1	$-SCH_3$	$-(CH_2)_3N(CH_3)_2$[g]	220–223°/0.7 mm.[c] 149–150°[b] (lit. 160°)[g]	88%	$C_{18}H_{23}ClN_2S_2$[b]	58.91	6.32	—	58.77	6.52	—
2	$-SCH_3$	$-CH_2-CH(CH_3)CH_2N(CH_3)_2$[g]	218–221°/0.1 mm.[c] 173–174°[b]	93%	$C_{19}H_{25}ClN_2S_2$[b]	59.89	6.61	—	59.91	6.81	—
3	$-SCH_3$		239–242°/0.1 mm.[c] 224–225°[f] (lit. 220°)[g]	92%	$C_{21}H_{29}Cl_2N_3S_2$	55.01	6.38	—	55.29	6.20	—
4	$-SCH_3$		200–220°/0.03 mm.[c] 174–175°[e] (lit. 199°)[g]	44%	$C_{30}H_{37}N_3O_8S_2$[e]	57.03	5.90	6.65	56.83	5.78	6.70
5	$-SCH_3$		165–166°[e] (Lit. 173–175°)[g]	33%	$C_{32}H_{39}N_3O_{10}S_2$[e]	55.72	5.70	—	56.01	5.98	—
6	$-SO_2CH_3$	$-(CH_2)_3-N(CH_3)_2$[h]	115–116°[a] 112–115°[b] (lit. 158–168°)[h]	62%	$C_{18}H_{22}N_2O_2S_2$[a]	59.64	6.12	—	59.73	6.33	—
7	$-SO_2CH_3$	$-CH_2CH(CH_3)CH_2N(CH_3)_2$[h]	234–235°[b] (lit. 229–230°)[h] 255–260°/0.2 mm.[a]	60%	$C_{19}H_{25}ClN_2O_2S_2$[b]	55.25	6.10	—	55.50	6.12	—
8	$-SCF_3$	$-(CH_2)_3N(CH_3)_2$	153–157°/0.1 mm.[c]	64%	$C_{18}H_{19}N_2F_3S_2$[a]	56.23	4.98	7.29	56.37	5.23	7.52
9	$-SCF_3$	$-CH_2CH(CH_3)CH_2N(CH_3)_2$	153–157°/0.1 mm.[c] 158.5–159.5°[d]	54%	$C_{19}H_{21}F_3N_2S_2$[a] $C_{25}H_{24}F_3N_5O_7S_2$[d]	57.26 47.84	5.31 3.85	7.03 11.16	57.55 47.88	5.57 4.16	7.24 11.48
10	$-SCF_3$		220–223°/0.3 mm.[c] 182–183°[e]	63%	$C_{29}H_{32}F_3N_3O_8S_2$[e]	51.85	4.80	—	52.05	4.95	—
11	$-SO_2CF_3$	$-(CH_2)_3N(CH_3)_2$	235–240°/0.4 mm.[c] 174–175°[b]	15%	$C_{18}H_{20}ClF_3N_2O_2S_2$[b]	47.73	4.45	—	47.93	4.68	—
12	$-SO_2CF_3$	$-CH_2CH(CH_3)CH_2N(CH_3)_2$	182–184°/0.2 mm.[a] 203–204°[d]	19%	$C_{19}H_{21}F_3N_2O_2S_2$[a] $C_{25}H_{24}F_3N_5O_9S_2$[d]	53.01 45.52	4.92 3.67	6.51 10.62	53.06 45.84	5.12 3.76	6.71 10.06
13	$-SO_2CF_3$		249.5° dec.[f] (not distilled)	16%	$C_{21}H_{26}F_3Cl_2N_3O_2S_2$[f]	46.32	4.81	7.72	46.17	5.37	7.72
14	—OH	$-(CH_2)_3N(CH_3)_2$	220–225°/0.05 mm.[c] 90–91°[c] 132–133°[e]	49%	$C_{21}H_{24}N_2O_5S$[j]	60.56	5.81	—	60.56	5.94	—

See Table II for footnotes.

TABLE II

DERIVATIVES OF 2-AZAPHENOTHIAZINE

Compound Number	X	R	M.P. or B.P.	Yield, %	Molecular Formula	Analyses					
						Calcd.			Found		
						C	H	N	C	H	N
15	H	—$(CH_2)_3N(CH_3)_2$[b]	165–170°/0.007 mm.[c] 240.5–244.5° dec.[d]	63%	$C_{16}H_{21}Cl_2N_3S$[f]	53.63	5.91	—	53.43	5.80	—
16	H	—$CH_2CH(CH_3)CH_2N(CH_3)_2$	190–195°/0.6 mm.[e] 234–235°[f]	82%	$C_{17}H_{23}Cl_2N_3S$[f]	54.68	6.21	—	54.48	6.51	—
17	H	—$(CH_2)_3$$NCH_2CH_2OCOCH_3$	147–148°[g] dec.	9%	$C_{30}H_{36}N_4O_{10}S\cdot H_2O$[e]	54.37	5.78	—	54.40	5.78	—
18	Cl	—$(CH_2)_3N(CH_3)_2$[i]	215–220°/1 mm.[c] 249–250°[f]	66%	$C_{16}H_{20}Cl_3N_3S$·	48.92	5.13	—	48.81	5.36	—

[a] Free base. [b] Hydrochloride. [c] B.p., sausage flask distillation. [d] Picrate. [e] Dimaleate. [f] Dihydrochloride. [g] British Patent 802,725, October 8, 1958. [h] R. M. Jacob and G. L. Regnier, U. S. Patent 2,889,322, June 2, 1959. [i] P. J. C. Buisson, Canadian Patent 569,806, January 27, 1959. [j] Maleate. [k] J-P. Bourquin, *et al.*, *Helv. Chim. Acta*, **41**, 1072 (1958).

was refluxed for 2 hr. to remove the formyl protecting group. The solvents were removed under vacuum and the residual oil dissolved in benzene. The benzene solution was extracted with dilute hydrochloric acid. The acid extracts were made alkaline with 10% sodium hydroxide solution and extracted with benzene. The benzene was evaporated and the residual oil distilled at 240–270° (70–90 μ). The yield of distilled 10-[3-(1-piperazinyl)propyl]-2-azaphenothiazine was 11 g. (45%). The distilled material was dissolved in 250 ml. of methanol and refluxed for 90 min. with 1.8 g. of ethylene oxide. The solvent was evaporated under vacuum and the residue dissolved in 250 ml. of benzene. The solution was azeotroped for 1 hr., cooled, filtered, and treated with 6.5 g. of acetyl chloride followed by a reflux period of 1 hr. The solvents were evaporated under vacuum and the residual gum treated with 10% sodium hydroxide solution and benzene. The benzene was evaporated and the resulting oil dissolved in ethyl acetate. The solution was added to sufficient maleic acid, dissolved in ethyl acetate, to form a dimaleate salt. The salt was removed by filtration and recrystallized from ethanol; m.p. 147–148° dec. The overall yield of analytically pure salt based on 2-azaphenothiazine was 4.3 g. (9%).

Anal. Calcd. for $C_{30}H_{36}N_4O_{10}S\cdot H_2O$: C, 54.37; H, 5.78. Found: C, 54.44, 54.35; H, 5.70, 5.85.

Preparation of 3-chloro-1-(1-formyl-4-piperazinyl)propane. 1-Piperazinepropanol (57.6 g.) was refluxed for 1 hr. with 48.0 g. of methyl formate. After removal of excess methyl formate on the steam bath, the residue was quickly fractionated through a small Vigreux column to give 65.3 g. (95%) of an oil; b.p. 174.5–177°/1.1 mm; $n_D^{24°} = 1.5072$. Prolongation of the distillation time was accompanied by formation of gases, with a lower yield of the formamide. A solution of 42.8 g. of this oil in 300 cc. of chloroform was treated with excess gaseous hydrogen chloride to form a slurry. While

stirring the slurry, 19 g. of thionyl chloride was added and the mixture was refluxed for 0.5 hr. A further addition of 3 g. of thionyl chloride was added and refluxing was continued for 2.5 hr. Complete removal of volatile solvents *in vacuo* at room temperature left the hygroscopic crystalline hydrochloride which could be used without further purification. Recrystallization of this salt separated about 5% impurities.

Conversion of this hydrochloride to the free base, 1-formyl-4-(3-chloropropyl)piperazine, was accomplished with potassium hydroxide. Benzene extracts were distilled; approximately 60% yields were obtained of a pale yellow oil; b.p. 144.5–148.5°/0.4 mm; $n_D^{25°}$ = 1.5053, which was not further characterized.

Acknowledgment. The authors wish to express their appreciation to Dr. James W. Wilson for his help, and to Messrs. E. A. Nodiff and A. J. Saggiomo, Research Institute of Temple University, and Dr. H. Reiff, Smith, Kline and French Laboratories, for the preparation of chemical intermediates. Analyses were obtained by the Analytical and Physical Chemistry Section of Smith, Kline and French Laboratories.

PHILADELPHIA 1, PA.

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

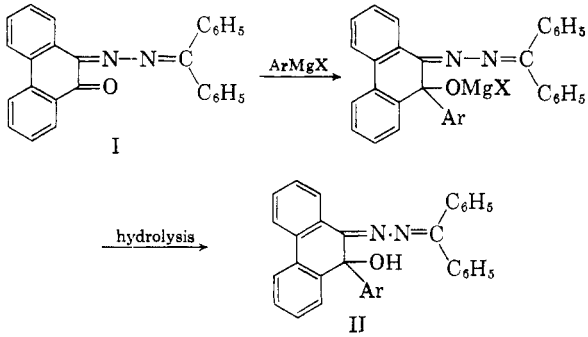
Studies of Quinoid Structures. V. Action of Grignard Reagents on Phenanthrenequinone Benzophenone Azine

WILLIAM IBRAHIM AWAD AND (MRS.) AIDA MOUSTAFA KAMEL

Received September 28, 1959

Arylmagnesium halides add preferentially to the carbonyl group of phenanthrenequinone benzophenone azine (I). When excess Grignard reagent is used, cleavage-condensation reaction takes place with the formation of 9,10-diarylphenanthrene.

In continuation of the previous study[1,2,3,4] of the action of Grignard reagents on derivatives of *ortho*-quinoid structures, the authors have now investigated the action of Grignard reagents on phenanthrenequinone benzophenone azine (I). In molecular proportion or slight excess, Grignard reagents add preferentially to the carbonyl group as it has been previously stated[1,2,3,4] (*cf.* Scheme A).



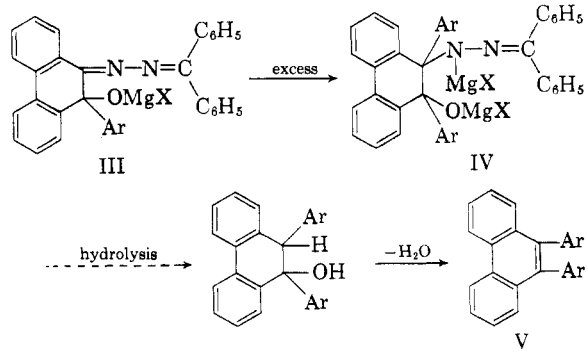
IIa. Ar = C_6H_5, IIb. Ar = $C_{10}H_7$-(α)

Scheme A

The constitution of II is based on 1) the preferential addition to the carbonyl group,[1,2,3,4,5,6a] 2) the carbonyl stretching frequency[6b] (at 1661 cm.$^{-1}$),[7] which is present in the infrared spectrum of the azine, is absent from the spectra of IIa and IIb, 3) an —OH stretching frequency at 3508 cm.$^{-1}$ appeared which was not present in the infrared spectrum of the starting material, and 4) elemental analysis.

However, excess of phenyl or anisylmagnesium bromide gave, in good yield, as a final product 9,10-diphenyl or 9,10-dianisylphenanthrene respectively as proved by 1) mixture melting point with an authentic sample of 9,10-diphenylphenanthrene,[8] and 2) elemental analysis.

It is to be noticed that the cleavage-condensation reaction takes place when acetone anil or acetophenone anil is treated with some Grignard reagents.[9] A possible series of steps for the reaction is:



Va. Ar = C_6H_5, Vb. Ar = C_6H_4—OCH_3(p)

Scheme B

(1) W. I. Awad and A. R. A. Raouf, *J. Org. Chem.*, **22**, 881 (1957).

(2) W. I. Awad and A. R. A. Raouf, *J. Org. Chem.*, **23**, 282 (1958).

(3) W. I. Awad, A. R. A. Raouf, and A. M. Kamel, *J. Org. Chem.*, **24**, 1777 (1959).

(4) W. I. Awad, A. K. Fateen, and M. A. Zayed, *J. Org. Chem.*, in press.

(5) O. Diels and F. ter Meer, *Ber.*, **42**, 1940 (1909).

(6) (a) O. Diels and J. M. Johlin, *Ber.*, **44**, 403 (1911). (b) The infrared measurements were carried out on Perkin-Elmer infracord, model 137 in nujol mulls.

(7) L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, Metheun, London, 1957, p. 114.

(8) A. Werner and A. Grob., *Ber.*, **37**, 2887 (1904).