

Upon making the appropriate substitutions the expression becomes independent of the concentration of acid HA. This is also contrary to fact.

The mechanism outlined in equations 1-5 is interesting in view of the fact that in basic solution antipyrine has been reported to give a poorer yield of 4-dimethylaminomethylantipyrine with dimethylaminomethanol than with dimethylamine and formaldehyde under similar conditions.¹⁴ This was interpreted to mean that the reaction did not proceed through the primary condensation of the amine with formaldehyde. We have repeated the experiments and have verified these results. While we do not, as yet, understand their significance to the base catalyzed transformation, it is clear that they have no bearing on our reaction carried out in acid solution. We have shown that the kinetics is unchanged when formaldehyde and dimethylamine are replaced by dimethylaminomethanol.

(14) Bodendorf and Koralewski, *Arch. Pharm.*, **271**, 101 (1933).

Summary

1. In acid solution the Mannich reaction of ethylmalonic acid, formaldehyde and dimethylamine, follows third order kinetics, first order in each of the three components.

2. The rate of reaction shows a critical dependence on pH. It passes through a maximum at about pH 3.8.

3. Under the conditions of our experiments, no reaction takes place between ethylmalonic acid and formaldehyde.

4. Smooth, third order curves are obtained for the reaction only if the amine and formaldehyde are mixed and allowed to stand for twelve hours before adding the ethylmalonic acid, but if the formaldehyde and dimethylamine are replaced by dimethylaminomethanol, the reagents may all be mixed at once.

These facts are in agreement with an ionic mechanism for the Mannich reaction of methynyl compounds, based upon a primary condensation of formaldehyde with the amine.

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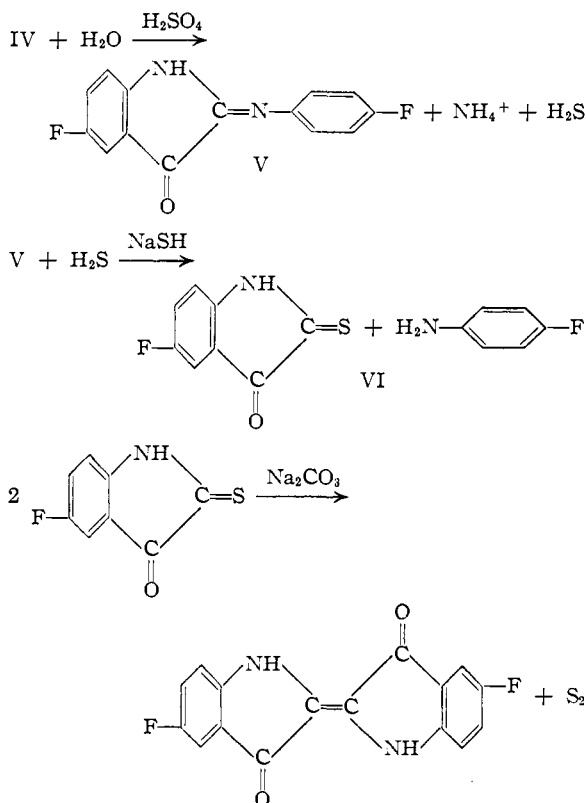
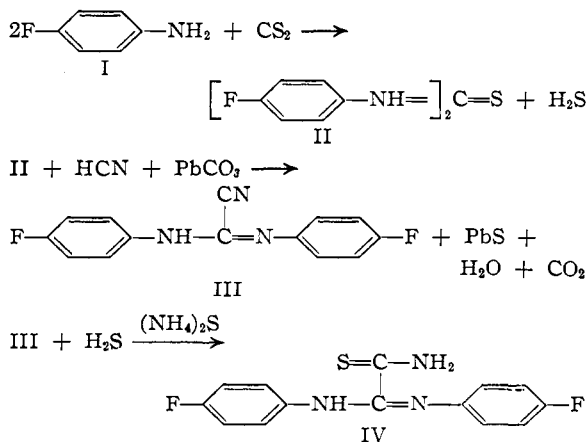
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[CONTRIBUTION FROM THE VENABLE CHEMICAL LABORATORY OF THE UNIVERSITY OF NORTH CAROLINA]

The Preparation of 5,5'- and 7,7'-Difluoroindigo

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The preparation of several fluoroindigos was undertaken as part of a study of aromatic and heterocyclic fluorine compounds being carried out in this Laboratory. The method of Sandmeyer¹ was found to be the most satisfactory way to prepare these compounds; 5,5'- and 7,7'-difluoroindigo were prepared from *p*-fluoroaniline and *o*-fluoroaniline, respectively, by this method. The preparation of 5,5'-difluoroindigo is outlined in the accompanying equations.



(1) (a) Sandmeyer, *Z. Farb. Text. Chem.*, **2**, 129 (1903); *J. Chem. Soc. Abst.*, **84**, I, 486 (1903); (b) Fierz-David, "Dye Chemistry," J. A. Churchill, London, 1921, p. 161-167.

TABLE I

Compound	Formula	M. p., °C.	Yield, %	Nitrogen, %	
				Calcd.	Found
1 <i>s</i> -Di- <i>p</i> -fluorophenylthiourea ^{2,3}	C ₁₃ H ₁₀ F ₂ N ₂ S	187.5	94	10.6	10.7
2 <i>s</i> -Di- <i>o</i> -fluorophenylthiourea	C ₁₃ H ₁₀ F ₂ N ₂ S	188	97	10.6	10.6
3 N,N'-bis-(<i>p</i> -Fluorophenyl)-cyanoforamidine	C ₁₄ H ₉ F ₂ N ₃	128	99	16.3	16.3
4 N,N'-bis-(<i>o</i> -Fluorophenyl)-cyanoforamidine	C ₁₄ H ₉ F ₂ N ₃	128	98	16.3	16.3
5 α -(N,N'-Di- <i>p</i> -fluorophenylguanyl)-thioformamide	C ₁₄ H ₁₁ F ₂ N ₃ S	119	73	14.4	14.5
6 α -(N,N'-Di- <i>o</i> -fluorophenylguanyl)-thioformamide	C ₁₄ H ₁₁ F ₂ N ₃ S	106	98	14.4	14.6, 14.7
7 5,5'-Difluoroindigo	C ₁₆ H ₈ F ₂ N ₂ O ₂	...	28 ^a	9.4	9.3, 9.4
8 7,7'-Difluoroindigo	C ₁₆ H ₈ F ₂ N ₂ O ₂	...	37 ^b	9.4	9.3

^a Yield based on compound (5). ^b Yield based on Compound (6).

The attempted preparation of 4,4'- or 6,6'-difluoroindigo starting with *m*-fluoroaniline was not possible because *m*-fluoroaniline would not react with carbon disulfide to form a difluorodiphenylthiourea; after one hundred and fifty hours refluxing the *m*-fluoroaniline was recovered almost quantitatively. The reaction of carbon disulfide with *o*- and *p*-fluoroaniline was complete in forty and seventy hours, respectively.

The *s*-di-*p*-fluorophenylthiourea formed by the action of carbon disulfide on *p*-fluoroaniline is not a new compound; conflicting reports of its melting point appear in the literature, however. Browne and Dyson² prepared it from *p*-fluoroaniline and thiocarbonyl chloride, and reported a melting point of 145°; Lubs and Fox³ prepared it by the reaction of *p*-fluorophenyl isothiocyanate with *p*-fluoroaniline and report a melting point of 186.5–188°. The third synthesis here reported gives a product melting at 187.5°.

Attempts to prepare 5,5'-difluoroindigo by Baeyer's method⁴ were not too successful. The preparation of 5-fluoro- α -isatin chloride from *p*-fluoroaniline was accomplished satisfactorily; attempted conversion of this to the fluoroindigo, however, resulted in the formation of large amounts of a difluoroindirubin contaminated with traces of 5,5'-difluoroindigo.

Attempts to use the Heumann method⁵ starting with *p*-fluorophenylglycine were not too satis-

factory; very poor yields of 5,5'-difluoroindigo were obtained in this way.

A comparison of the two new difluoroindigos with 5,5'-dibromoindigo⁶ was made. No difference in the ease of vatting with hydrosulfite and the stability of the reduced form of the three dyes was noted. The dibromoindigo was absorbed on cotton cloth more rapidly than either of the difluoroindigos; both difluoroindigos were markedly more light-fast than was the dibromo derivative, however.

Experimental⁶

Directions given^{1a,b} for the preparation of indigo were followed in the synthesis of 5,5'- and 7,7'-difluoroindigo; compounds involved in the synthesis which were stable enough to be analyzed are shown in the table below along with the final products. The fluoroanilines used as starting materials were prepared by the Schiemann reaction.⁷

Vatting of the dyes was carried out as follows: 0.15 g. of the dye was placed in a beaker with 100 ml. of 10% sodium hydroxide and the solution warmed to about 90°; 1 g. of sodium hydrosulfite was added with stirring. The dyes went into solution immediately, forming a light yellow solution.

Summary

The synthesis of 5,5'- and 7,7'-difluoroindigo is reported.

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- (2) Browne and Dyson, *J. Chem. Soc.*, 3285 (1931).
 (3) Lubs and Fox, U. S. Patent 2,061,243 (1937); *C. A.*, **31**, 885 (1937).
 (4) Baeyer, *Ber.*, **3**, 514 (1870); **11**, 1296 (1878); **12**, 456 (1879).
 (5) Heumann, *ibid.*, **23**, 3043 (1890).

- (6) A sample of 5,5'-dibromoindigo was kindly furnished by E. I. du Pont de Nemours and Company.
 (6) All melting points are corrected.
 (7) Balz and Schiemann, *Ber.*, **60**, 1186 (1927).