[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF COLUMBIA UNIVERSITY]

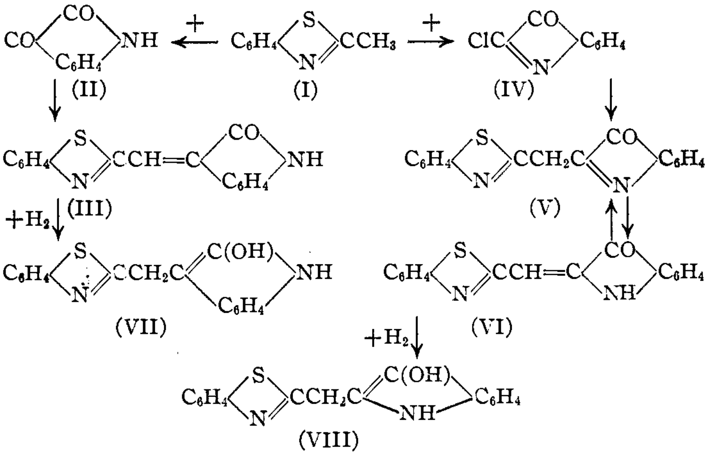
Researches on Thiazoles. XXI. The Synthesis of Indirubin Types by Condensation of 2-Methylbenzothiazoles with Isatins[1]

BY BARNET NAIMAN AND MARSTON TAYLOR BOGERT

The reactivity of the methyl group in 2-methylbenzothiazoles (I) is in entire agreement with the structure assigned to them, as was noted by those investigators who were the first to prepare and study these compounds.[2]

Bearing in mind this reactivity, it was decided to attempt the condensation of such thiazoles with isatins, in the belief that the indirubin types so produced might possess interesting tinctorial properties. As initial materials, both 2-methyl- and 2-methyl-6-bromobenzothiazoles were employed, with isatin, its 5-bromo-, 5,7-dibromo- or 5-nitro-derivatives.

FLOW SHEET



The condensation was effected quite easily by heating an intimate mixture of the thiazole and the isatin, with or without the addition of anhydrous zinc chloride, and crystallization of the crude product from glacial acetic acid. With isatin itself, the product formed deep-red long needles which, on reduction, yielded a colorless leuco-base, stable in the dry state, but rapidly reoxidizing in solution. As a vat dye, however, it was not satisfactory. Its sulfonic acid dyed wool a brilliant yellow, quite stable to light, but not to washing.

The condensation product obtained from 2-methylbenzothiazole and 5-bromoisatin was dark red, from 5,7-dibromoisatin an orange-red, and from 5-nitroisatin a yellowish-brown; from 2-methyl-6-bromobenzothiazole and isatin, it was a reddish-brown.

As is well known, isatin (II) generally condenses with its beta-CO group, to form indirubin types (III). On the other hand, isatin alpha-chloride or alpha-anil condenses in the alpha-position to isomeric compounds (V or VI). We were somewhat surprised, therefore, when a solution of the isatin alpha-chloride in methylbenzothiazole was heated, to obtain the same product as when isatin itself was used. A similar thing happened when 5-bromoisatin was used in place of isatin. Because the products obtained in these four cases all refused to form oximes, it seemed probable that they must all have been of indirubin type, and that in some way a rearrangement of the alpha-chloride had occurred, or that isatin itself had been set free and then underwent the normal beta-condensation. That the products were actually from beta-condensations was supported also by the successful preparation of the isomeric alpha-condensation product (V) by the careful heating of a benzene solution of isatin alpha-chloride with 2-methylbenzothiazole and a few drops of piperidine.[3] This compound differed from its isomer in melting point, as well as in its appearance.

The leuco-bases of the beta- and alpha-condensation products are believed to possess the structures (VII) and (VIII) shown in the Flow Sheet, or tautomeric forms thereof.

2-Methylbenzothiazole added bromine, in glacial acetic acid solution, with formation of an un-

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(2) (a) Jacobsen and Reimer, *Ber.*, **16**, 2602 (1883); (b) Hofmann, *ibid.*, **20**, 2264 (1887); (c) Jacobson, *ibid.*, **21**, 2629 (1888); (d) Mills and Smith, *J. Chem. Soc.*, **121**, 2724 (1922); (e) S. R. H. Edge, *ibid.*, **123**, 2330 (1923); (f) Koenig, *Ber.*, **61**, 2068 (1928); (g) Schuloff, Pollak, Riesz and Hopmayer, *ibid.*, **61**, 2538 (1928).

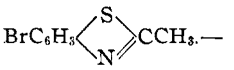
(3) (a) Friedlaender, *Monatsh.*, **29**, 359, 375, 387 (1908); (b) Wahl and Bagard, *Bull. soc. chim.*, [4] **5**, 1033 (1910).

stable bromine derivative[4] which, when heated, rearranged to the 2-methyl-6-bromobenzothiazole. Both the latter and the 2-alpha-pyrrylbenzothiazole exhaled odors recalling that of 2-phenylbenzothiazole.

Experimental

2-Methylbenzothiazole (I).—A mixture of 12.6 g. of zinc *o*-aminothiophenolate, 9 cc. of acetic anhydride and 25 cc. of glacial acetic acid was refluxed for two hours and then allowed to cool and stand for several hours. A large quantity of zinc acetate crystallized out and was removed. The mother liquor was distilled. Most of the liquid came over at 100–130°, and the temperature then rose rapidly to about 230°. Between 235–239° a colorless fraction was collected of quinoline odor; yield, 75–80%. Hofmann,[5] who prepared this compound by a somewhat different method, recorded its b. p. as 238°.

Action of Bromine upon 2-Methylbenzothiazole: 2-Methyl-6-bromobenzothiazole,



$\mathrm{BrC_6H_3}\left\langle\begin{matrix}\mathrm{S}\\ \mathrm{N}\end{matrix}\right\rangle\mathrm{CCH_3}$.—When an ice-cooled solution of 1.1 g. of 2-methylbenzothiazole in 100 cc. of glacial acetic acid was treated very slowly with 0.4 cc. of bromine, a red oil separated which soon congealed to a deep red crystalline mass. This mass was removed, washed with glacial acetic acid and dried *in vacuo* over solid potassium hydroxide. The red crystals thus obtained turned brown on long standing, or decomposed when heated gently (50–60°), evolving bromine and hydrogen bromide, changing to a yellow mass and then charring completely.

In another experiment, an ice-cooled solution of 1 g. of the thiazole in 50 cc. of glacial acetic acid was treated gradually with 1.2 g. of bromine. A deep red heavy oily layer separated. When this mixture was warmed at 40° for about five minutes, it formed a clear red solution which on cooling deposited large red crystals of a product believed to be a tetrabromo addition product. These were collected, washed and dried *in vacuo*. They decomposed on standing.

But when the original glacial acetic acid solution was warmed at 100° for about an hour, its red color changed to yellow and cooling then precipitated yellow crystals. More of these yellow crystals were recovered by concentrating the mother liquor. Recrystallized from glacial acetic acid, they formed large yellow crystals which began to darken at about 190° and decomposed completely at 220°. They possessed a pronounced geranium type of odor.

Anal. Calcd. for C_8H_6NSBr: S, 14.03; Br, 35.05. Found: S, 14.55; Br, 34.59.

In the light of the experimental work of Bogert and Abrahamson,[4a] and of Hunter,[4b,6] in the thiazole field, of Fromm and Martin[7] in the case of the analogous selenazoles, and of Baczynski and Niementowski[8] on the benzimidazoles, we believe that we are justified in assigning to this product the structure of 2-methyl-6-bromobenzothiazole.

Condensation of 2-Methyl-benzothiazole with Isatin. 3-[(2-Benzothiazolyl)methylene]-oxindole (III).—An intimate mixture of 1.5 g. of the thiazole, 1.5 g. of isatin and 0.5 g. of fused zinc chloride, was heated at about 150° for two hours. A deep red melt resulted which congealed to a mass of red crystals as it cooled. Recrystallized repeatedly from glacial acetic acid, they formed fine red needles, m. p. 262–263° (corr.); yield, about 55%.

Anal. Calcd. for $C_{16}H_{10}ON_2S$: C, 69.04; H, 3.62; S, 11.51. Found: C, 69.07; H, 3.82; S, 11.71.

Sulfonation.—A small amount (0.1 g.) of this product was treated with concentrated sulfuric acid (5 cc.) at 0°. The deep red solution was kept at room temperature for an hour and then warmed at 100° for thirty minutes, cooled, poured upon cracked ice, the orange-red precipitate collected, washed with a small amount of water and dried at about 35°. This product was dissolved in warm water, a few strands of wool suspended in the solution, salt added to saturation, and the whole heated for an hour at 100°. The wool was colored red at first, but this soon changed to a bright yellow, and a yellow flocculent amorphous precipitate separated in the dye bath, which was difficult to filter or purify, and so was not further investigated. Exposed to direct sunlight for three days, the wool lost none of its color or brightness, but bled when washed in warm water.

When this compound (III) was boiled with dilute nitric acid, isatin was regenerated.

Action of Caustic Alkali.—Following up the interesting studies of Friedlaender and his co-workers[9] on the action of alkalies on indigoids, the thiazole isatin condensation product (2 g.) was covered with 25 cc. of a 40% potassium hydroxide solution and warmed at 100° for about an hour. It dissolved partially to a wine-red or purplish solution, which was filtered from the undissolved initial compound. This solution had a fine grape-like aroma, recalling that of certain anthranilic esters. When acidified with glacial acetic acid, the purple color vanished and a yellow precipitate separated, which crystallized from alcohol in lustrous yellowish-green plates, m. p. 93° (corr.). Mixed with some pure *o*-aminophenyl disulfide, the melting point was unchanged. Investigation of the original purplish alkali solution yielded only gummy products which could not be identified. Neither anthranilic acid nor a 2-formylbenzothiazole was detected in any of these experiments.

Reduction of the Isatin Condensation Product: 3-[(2-Benzothiazolyl)methyl]-2-indolol (VII).—The isatin condensation product (III) (0.3 g.) was dissolved in glacial acetic acid (15 cc.) and reduced hot by adding zinc dust in small amounts until the color of the solution was discharged. It was then diluted largely (6 volumes) with water, protected from oxidation and allowed to cool thoroughly. The excess of zinc dust and the white foamy solid were removed and extracted with hot alcohol. The alcohol extract as it cooled deposited colorless crystals, which, when recrystallized from dilute alcohol, formed colorless flakes, m. p. 171° (corr.); yield, about 50%.

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(4) (a) Bogert and Abrahamson, This Journal, **44**, 830 (1922); (b) Hunter, *J. Chem. Soc.*, 125 (1930).

(5) Hofmann, *Ber.*, **13**, 16 (1880).

(6) (a) Hunter, *J. Chem. Soc.*, **127**, 1318 (1925); (b) *Muslim Assoc. Adv. Sci.*, Dec., 1931.

(7) Fromm and Martin, *Ann.*, **401**, 178 (1913).

(8) Baczynski and Niementowski, *Bull. Acad. Sci. Cracow*, **1902**, 421–435; *J. Chem. Soc.*, **84**, 124 (1903).

(9) (a) Friedlaender, *Ber.*, **41**, 1035 (1908); (b) Friedlaender and Schwenk, *ibid.*, **43**, 1971 (1910); (c) Friedlaender and Kielbasinski, *ibid.*, **44**, 3098 (1911).

Anal. Calcd. for $C_{16}H_{12}ON_2S$: S, 11.44. Found: S, 11.42.

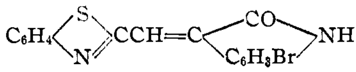
This product was practically insoluble in water, dilute sodium hydroxide or dilute hydrochloric acid, but dissolved in concentrated hydrochloric acid and in most of the usual neutral organic solvents. In the solid state, it was stable in the air, but in glacial acetic acid solution readily reoxidized to the original red compound, but not so rapidly as does reduced indigo. It could be neither acetylated nor benzoylated by the ordinary methods, whereas indigo white is easily acylated.

Condensation of 2-Methylbenzothiazole with Isatin Alpha-Chloride.—A mixture of 0.1 g. of isatin alpha-chloride and 0.1 g. of the thiazole was heated at 110° for an hour, the mass cooled and crystallized from glacial acetic acid. Deep red needles were obtained, m. p. 263° (corr.), apparently identical with the product obtained from isatin itself; yield, 35%. An intimate mixture of the two melted at 262° (corr.).

2 - [(2 - Benzothiazolyl)methylene] - pseudoindoxyl (VI).—To a solution of 1 g. of isatin in 10 cc. of dry benzene, there was added 7 g. of phosphorus pentachloride and the mixture was refluxed for about four hours, when the evolution of hydrogen chloride had ceased. Then there were added 1 cc. of 2-methylbenzothiazole and two drops of piperidine. After a further refluxing of four hours, the mixture was filtered hot and the filtrate allowed to cool. The red crystals which separated were washed thrice with petroleum ether and then crystallized twice from benzene. The product formed small red needles, with a bright greenish sheen, and melted at 223.5-224° (corr.); yield, 20%, calculated to the isatin used.

Anal. Calcd. for $C_{16}H_{10}ON_2S$: C, 69.04; H, 3.62. Found: C, 69.51; H, 3.93.

In glacial acetic acid solution this product was reduced by zinc dust with formation of a nearly colorless solution, just as in the case of its beta-isomer and, like the latter, this leuco-base was rapidly reoxidized by air to the original compound.

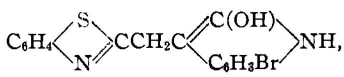


$\mathrm{C_6H_4}\left<\begin{matrix}\mathrm{S}\\ \mathrm{N}\end{matrix}\right>\mathrm{CCH{=}C}\left<\begin{matrix}\mathrm{CO}\\ \mathrm{C_6H_3Br}\end{matrix}\right>\mathrm{NH}$,

3-[(2-Benzothiazolyl)methylene]-5-bromooxindole.—After heating a mixture of 3 g. of 2-methylbenzothiazole with 2.2 g. of 5-bromoisatin for two hours at 160°, it was permitted to cool and the cold mass was then dissolved in hot glacial acetic acid, from which solution the condensation product separated on cooling. Recrystallized from the same solvent, it formed orange-red needles, m. p. 315-317° (corr.); yield, about 50%.

Anal. Calcd. for $C_{16}H_9ON_2SBr$: S, 8.98; Br, 22.38. Found: S, 9.08; Br, 22.10.

The same compound resulted when 5-bromoisatin-alpha-chloride was condensed with 2-methylbenzothiazole. The crude product, crystallized twice from glacial acetic acid, melted at 317-318° (corr.), and this melting point was not appreciably reduced when this product was mixed with that obtained from 5-bromoisatin itself; yield, 35%.

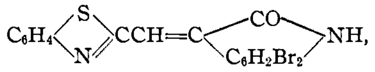


$\mathrm{C_6H_4}\left<\begin{matrix}\mathrm{S}\\ \mathrm{N}\end{matrix}\right>\mathrm{CCH_2C}\left<\begin{matrix}\mathrm{C(OH)}\\ \mathrm{C_6H_3Br}\end{matrix}\right>\mathrm{NH}$,

3-[(2-Benzothiazolyl)methyl]-5-bromo-2-indolol.—The foregoing condensation product (0.5 g.) was dissolved in 50 cc. of hot glacial acetic acid and reduced with zinc dust, as described for the unbrominated isatin condensation product. The crude compound crystallized from dilute alcohol in colorless flakes, which turned yellow at 200° and melted at 210° (corr.) to a red liquid, which resolidified on cooling and then slowly remelted above 210° (corr.); yield, 50%.

Anal. Calcd. for $C_{16}H_{11}ON_2SBr$: S, 8.91; Br, 22.22. Found: S, 9.01; Br, 22.37.

In general the properties of this compound resembled those of the unbrominated analog already described.



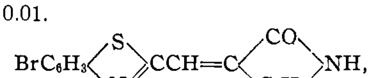
$\mathrm{C_6H_4}\left<\begin{matrix}\mathrm{S}\\ \mathrm{N}\end{matrix}\right>\mathrm{CCH{=}C}\left<\begin{matrix}\mathrm{CO}\\ \mathrm{C_6H_2Br_2}\end{matrix}\right>\mathrm{NH}$,

3-[(2-Benzothiazolyl)methylene] - 5,7 - dibromooxindole, was prepared as outlined for the analogous compounds. The crude substance crystallized from glacial acetic acid in orange-yellow needles, m. p. 300-304° (corr.); yield, 40%.

Anal. Calcd. for $C_{16}H_8ON_2SBr_2$: Br, 36.66; S, 7.36. Found: Br, 36.41; S, 7.49.

3 - [(2 - Benzothiazolyl)methylene] - 5 - nitrooxindole, prepared similarly, crystallized from glacial acetic acid in mustard yellow crystals, which darkened at 295° and melted with decomposition at 316-320° (corr.).

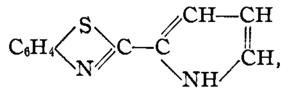
Anal. Calcd. for $C_{16}H_9O_3N_3S$: S, 9.92. Found: S, 10.01.



$\mathrm{BrC_6H_3}\left<\begin{matrix}\mathrm{S}\\ \mathrm{N}\end{matrix}\right>\mathrm{CCH{=}C}\left<\begin{matrix}\mathrm{CO}\\ \mathrm{C_6H_4}\end{matrix}\right>\mathrm{NH}$,

3-[(6-Bromo-2-benzothiazolyl)methylene]-oxindole.—An intimate mixture of 2-methyl-6-bromobenzothiazole (1 g.) with isatin (0.65 g.) was suspended in nitrobenzene (5 cc.) and the whole heated at 135-140° for four hours. The crude deep red product crystallized from glacial acetic acid in reddish-brown crystals, which darkened at 298° and melted with decomposition at 320-324° (corr.).

Anal. Calcd. for $C_{16}H_9ON_2SBr$: S, 8.98; Br, 22.38. Found: S, 8.62; Br, 22.09.



$\mathrm{C_6H_4}\left<\begin{matrix}\mathrm{S}\\ \mathrm{N}\end{matrix}\right>\mathrm{C{-}C}\left<\begin{matrix}\mathrm{{=}CH{-}CH}\\ \Vert\\ \mathrm{NH{-}CH}\end{matrix}\right.$,

2-Alpha-pyrryl-benzothiazole.—A suspension of 4 g. of zinc *o*-aminothiophenolate in about 75 cc. of boiling glacial acetic acid was treated with hydrogen sulfide and the zinc sulfide filtered from the hot solution. To the hot filtrate there was added 4 g. of alpha-pyrroyl chloride and the yellow solution was refluxed for about fifteen minutes. It was then made weakly alkaline by the addition of sodium hydroxide solution. The whole solution clouded immediately and as it cooled deposited brownish-yellow needles, which were crystallized and decolorized by Norite in alcoholic solution, when they appeared as yellowish-green needles, melting with decomposition at 130-133° (corr.) and having an aroma similar to that of 2-phenylbenzothiazole, but not sufficient pure material was secured for an analysis.

Summary

1. Isatin and certain of its derivatives have been condensed with 2-methyl and 2-methyl-6-bromo benzothiazoles to compounds of indirubin type.

2. With isatin alpha-chlorides, either alpha or beta-condensations were obtained, depending upon the experimental conditions.

3. As dyes, these products proved to be of little value.

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[CONTRIBUTION FROM THE CHEMISTRY LABORATORY OF THE UNIVERSITY OF MICHIGAN]

The Exchange Reaction between Acetone and Deuterium Oxide. Kinetics and Equilibrium

BY J. O. HALFORD, LEIGH C. ANDERSON, JOHN R. BATES AND R. D. SWISHER

The direct introduction of deuterium atoms into acetone by means of the reaction between acetone and dilute deuterium oxide, using an alkaline catalyst, has been reported independently by several investigators.[1] In the original communication from this Laboratory, the exchange in the presence of potassium carbonate was described as rapid, and the equilibrium constant of the reaction

$$CH_3COCH_3 + DOH = CH_3COCH_2D + HOH \quad (1)$$

was estimated to be approximately two.

This paper presents the results of a study of the kinetics at 35 and 40°, and of the equilibrium at temperatures from 35 to 80°. The reaction is actually very slow at room temperature and only moderately rapid at the boiling point of the acetone–water solution.

Experimental

The deuterium content of the acetone was calculated from the decrease in density of the water, measured by the "plummet" method to within 20 parts per million. The quantitative separation of acetone and water was the principal experimental problem. For this purpose a 90-cm. vacuum-jacketed fractionating column was found to be satisfactory, as demonstrated by the ready recovery of water of normal density from an acetone–water solution. In the determinations at the boiling point of the solution, in which potassium carbonate was present during the entire separation, no difficulty was encountered in obtaining water free from organic impurities. When the reaction was studied at lower temperatures, it was necessary to neutralize the catalyst with phosphoric acid before distilling. The water fraction obtained from the acid solution contained traces of an organic impurity, presumably diacetone alcohol, which interfered with the density determination. The impurity was removed as acetone by redistilling the water from potassium carbonate. The water fraction constituted 60–70% of the amount originally introduced into the reaction, the remainder being divided about equally between rejected initial and final fractions, thus ensuring that the density measurement would be representative.

The acetone was obtained by fractional distillation of a good grade of c. p. acetone, using the 90-cm. column. A middle fraction boiling well within 0.1° and constituting 50–70% of the total was retained. It was decided that purity of the acetone could best be tested by mixing it with a deuterium oxide solution, without the catalyst, and then examining the water for decrease of deuterium content after the separation by distillation. The deuterium content of a sample of water, on treatment with twice its volume of acetone, was decreased from 4.17 to 4.09%. If the effect is due entirely to dilution by water in the acetone, its concentration is calculated to be 1.0% by volume or 3.15 mole per cent. Reaction without the catalyst, as indicated by the velocity data, would be expected to be negligible. In calculating the concentrations at equilibrium a correction for the water content of the acetone has been made.

Recovery of Deuterium Oxide by Combustion.—A sample of 12.05% deuterium oxide was decreased to 5.19% by the exchange reaction with twice its volume of acetone. The acetone fraction was dried with powdered fused potassium hydroxide, carefully redistilled, and the middle fraction burned in a small lamp with an asbestos wick. The gases from the combustion were passed through a tube containing hot cupric oxide, to produce water containing 4.60% deuterium oxide. This is to be compared with 4.64% calculated from the decrease in deuterium content of the water.

Kinetics

The kinetics of reaction 1, which is found to be pseudo-unimolecular, are consistent with any one of several postulated mechanisms, including the mechanism which assumes an intermediate enolization of the acetone. It is therefore not possible to say definitely that enolization is responsible for the reaction, or to obtain from the temperature coefficient the energy necessary to convert the keto to the enol form. However, this mechanism is by no means excluded.

Each experiment was performed with a solution made up of 20 cc. of 2.55% deuterium oxide, 40 cc. of acetone, and a weighed amount of anhydrous potassium carbonate. After the solution

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[1] Halford, Anderson and Bates, THIS JOURNAL, **56**, 491 (1934); Bonhoeffer and Klar, *Naturwissenschaften*, **22**, 45 (1934); Schwarz and Steiner, *Z. physik. Chem.*, **B25**, 153 (1934); Klar, *ibid.*, **B26**, 335 (1934).