[CONTRIBUTION FROM THE COURTAULD INSTITUTE OF BIOCHEMISTRY, MIDDLESEX HOSPITAL, LONDON, W.1.]

Separation of Isomeric Isatins

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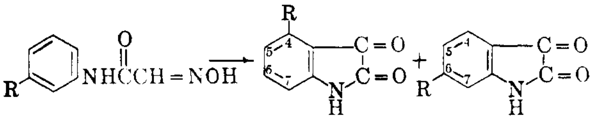
Many *m*-substituted *iso*nitrosoacetanilides (I) undergo ring closure in hot concentrated sulphuric acid to give, in varying proportions, isomeric mixtures of 4- and 6- substituted isatins (II) and (III) respectively.[1]



I II III

These often form mixed crystals and separation by fractional crystallization is unsatisfactory, but in most cases a complete and rapid separation may be effected by treating an aqueous solution of the sodium isatinates with glacial acetic acid, which results in the precipitation of the 4-isomer (usually as red needles). The 6-isomer can subsequently be precipitated (usually as yellow plates) on the addition of concentrated hydrochloric acid.[2]

Alternative but less efficient methods of separation have been used. Baker, *et al.*,[3] separated the isomeric mixture of 4,5- and 5,6-dimethylisatins by fractional precipitation with hydrochloric acid. The first three portions collected were the crude 4,5-dimethylisatin, while the last portion on strong acidification gave the 5,6-isomer. Another method is exemplified by the partial separation of 4- and 6-methylisatins by Mayer and Shulze,[4] who poured the hot sulphuric acid reaction mixture containing the two isomers into water, the impure 4-isomer being precipitated first, followed by the 6-isomer in a crude state.

The two isomers form in varying relative proportions according to the substituent as shown in Table I.

Ring closure of the *iso*nitrosoacetanilides can occur either *o*- or *p*- to the substituent R, and from the data quoted it would seem that the reaction is analogous to nitration of the corresponding acetanilide. Where R is the nitro group both *o* and *p* positions are deactivated to such an extent that ring closure does not occur, whereas *o*-nitro-*iso*nitrosoacetanilide ring closes in the *m*-position to give a 60% yield of 7-nitroisatin.

If R is the methoxy group, this forms a positive oxonium ion in the presence of sulfuric acid which deactivates the *o*-position and permits ring closure only in the *p*-position to give the rather low yield of 6-methoxyisatin quoted above. Ring closure occurs with equal facility in both *o*- and *p*-positions if R = CH_3. The low yields recorded are presumably due, as in the methoxy-compounds, to the sensitivity of the products to the drastic reaction medium and not to resistance to ring closure.

In the halogen series the percentage of 4-isomer increases with decreasing electronegativity of R as indicated in the table. The very small yield of the 4-fluoroisatin can be explained by the very powerful *ortho* inductive effect of the fluorine, which by withdrawing electrons from the *o*-position causes almost exclusive *p* ring closure.

The last example quoted (R = CF_3) is not readily explicable as the inductive effect of the highly electronegative grouping should strongly deactivate the *o*-position. That this is not so is shown by only the 4-trifluoromethylisatin being formed. However, the analogy to nitration still holds good as *m*-trifluoromethylacetanilide nitrates *o*- to the trifluoromethyl group and *p*- to the anilide to give 2-nitro-5-acetaminobenzotrifluoride as the main product[5]; Jones[6] claims this to be the only product.

It is of interest to note that 4-iodoisatin undergoes alkaline peroxide oxidation to give 6-iodoanthranilic acid, a compound that Baker, *et al.*[7]

TABLE I

RELATIVE PROPORTION OF ISOMERIC ISATINS WITH SUBSTITUENT

	NO_2	CH_3O	CH_3	F	Cl	Br	I	CF_3
4-Isomer, %	0	0	16.3	trace	33.0	46.0	44.7	17.0
6-Isomer, %	0	23.0	14.0	69.3	35.0	29.3	14.7	0

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(1) Sandmeyer, *Helv. Chim. Acta*, **2**, 234 (1919).

(2) von Braun, *Ann.*, **451**, 1 (1927).

(3) Baker, Schaub, Joseph, McEvoy, and Williams, *J. Org. Chem.*, **17**, 149 (1952).

(4) Mayer and Shulze, *Ber.*, **58**, 1465 (1925).

(5) Pondermann and Giradet, *Helv. Chim. Acta*, **30**, 107 (1947).

(6) Jones, *J. Am. Chem. Soc.*, **69**, 2346 (1947).

(7) Baker, Schaub, Joseph, McEvoy, and Williams, *J. Org. Chem.*, **17**, 164 (1952).

were unable to obtain by either chemical or catalytic reduction of 6-iodo-2-nitrobenzoic acid.

EXPERIMENTAL

TABLE II

(m-SUBSTITUTED ISONITROSOACETANILIDES[a])

Substituents	Refluxing time (mins.)	Yield, %	M.P., °C.	Lit. M.P., °C.
Cl	0	40	146	154 (1)
Br	15	55	165	165 (8)
F	0	87	175	[b]
I	0	74	157	[c]
CF_3	30[e]	83	140	143 (9)
CH_3	0	90	145	146 (1)
CH_3O	0	42	172	[d]
NO_2	0	48	168	172 (10)

[a] All these compounds were prepared by the method employed for the parent *iso*nitrosoacetanilide[11] with the exceptions noted. [b] *Anal.* Calc'd for $C_8H_7FN_2O_2$: C, 52.8; H, 3.9. Found: C, 53.0; H, 3.7. [c] *Anal.* Calc'd for $C_8H_7IN_2O_2$: C, 33.1; H, 2.4. Found: C, 32.9; H, 2.4. [d] *Anal.* Calc'd for $C_9H_{10}N_2O_3$: C, 55.7; H, 5.1. Found: C, 55.9; H, 5.0. [e] Double the usual volume of water used.

TABLE III

SUBSTITUTED ISATINS[a]

Substituents	Color	M.P., °C.	Lit. M.P., °C.
4-Cl	Orange-red needles[c]	256	256.5–258 (12)
6-Cl	Yellow plates[c]	263	258–259 (12)
4-Br	Orange-red needles[c]	267	259 (13)
6-Br	Yellow plates[c]	270	263 (13)
4-I	Red needles[c]	260	[e]
6-I	Yellow plates[c]	274	[f]
4-F	Orange plates[d]	212	[g]
6-F	Yellow needles[c]	197	[h]
4-CF_3	Yellow plates[c]	224	224 (7)
4-CH_3	Red needles[b,d]	193	189 (4)
6-CH_3	Orange needles[b,d]	189	187 (14)
6-CH_3O	Amber plates[b,d]	230	229–230 (15)

[a] Compounds prepared by concentrated sulfuric acid ring closure (90–95°, $^1/_2$ hr.) of the *iso*nitrosoacetanilides of Table II. [b] 90% sulfuric acid, 60/70°, $^1/_2$ hr. [c] Recrystallised from acetic acid. [d] Recrystallized from ethanol. [e] *Anal.* Calc'd for $C_8H_4INO_2$: C, 35.2; H, 1.5; N, 5.1. Found: C, 35.2; H, 1.6; N, 5.1. [f] *Anal.* Calc'd for $C_8H_4INO_2$: C, 35.2; H, 1.5; N, 5.1. Found: C, 34.9; H, 1.4; N, 4.9. [g] *Anal.* Calc'd for $C_8H_4FNO_2$: C, 58.2; H, 2.4; N, 8.5. Found: C, 58.1; H, 2.4; N, 8.4. [h] *Anal.* Calc'd for $C_8H_4FNO_2$: C, 58.2; H, 2.4; N, 8.5. Found: C, 58.0; H, 2.3; N, 8.7.

6-Iodoanthranilic acid. To a warm solution of 11 g. of 4-iodoisatin in 80 cc. of *N* sodium hydroxide was added 10 cc. of hydrogen peroxide (100 vol.) over a period of 45 mins. The mixture then was cooled, neutralized and filtered (charcoal). The filtrate on acidification gave 7.3 g. of white crystals which, after recrystallization from water, had a melting point of 149°.

Anal. Calc'd for $C_7H_6INO_2$: C, 32.0; H, 2.3. Found: C, 32.2; H, 2.3.

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(8) Inagaki, *J. Pharm. Soc. Japan.*, **58**, 961 (1938).

(9) Maginnity and Gaulin, *J. Am. Chem. Soc.*, **73**, 3579 (1951).

(10) Rupe and Kersten, *Helv. Chim. Acta*, **9**, 578 (1926).

(11) Marvel and Hiers, *Org. Syntheses*, Coll. Vol. I, 2nd ed., 327 (1941).

(12) Senear, Sargent, Mead, and Koepfli, *J. Am. Chem. Soc.*, **68**, 2695 (1946).

(13) Ettinger and Friedländer, *Ber.*, **45**, 2081 (1912).

(14) Mayer, Schafer, and Rosenbach, *Arch. Pharm.*, **267**, 571 (1929).

(15) Giovanni and Portman, *Helv. Chim. Acta*, **31**, 1375 (1948).