HETEROCYCLIC COMPOUNDS

Part I. Experiments in Isatins

BY K. N. MENON, F.A.SC. AND P. S. RAMAN

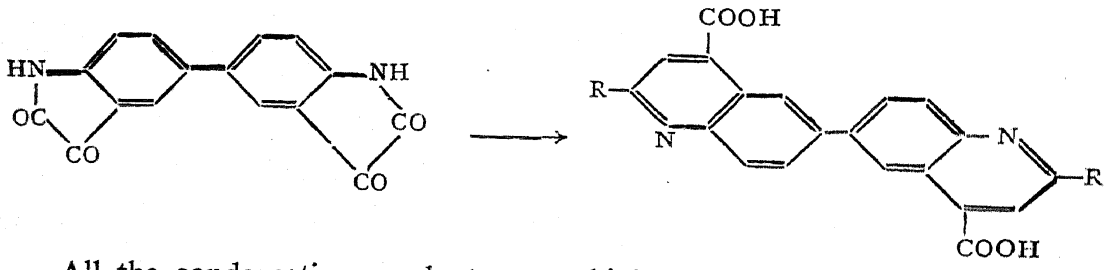
(Maharaja's College, Ernakulam and Madras University Laboratory, Guindy)

Received September 13, 1952

THE very important Sandmeyer reaction[1] for the preparation of isatin from aniline has recently been extended by Dethloff and Mix[2] for the preparation of di-isatin from benzidine. The *bis* iso-nitroso compound formed from benzidine, chloral hydrate and hydroxylamine hydrochloride with hydrochloric acid, on treatment with concentrated sulphuric acid at 90–95°, gives di-isatin (5, 5′).

Some of the important reactions of isatin is due to its lactam structure which opens out under the influence of alkali to yield a very reactive α-keto-*o*-amino-carboxylic acid. If the latter is allowed to react with reactive aldehydes and ketones under the influence of alkali, condensation takes place yielding quinoline-4-carboxylic acids.[3] Some of these condensation products, *e.g.*, Atophan from acetophenone and isatin are of importance in chemotherapy.

In view of the great importance of this important reaction, it was considered desirable to investigate it in the field of di-isatins. This report deals with the condensation of di-isatin with some reactive ketones: condensation with acetone, acetophenone, cyclohexanone and α-tetralone all gave diquinoline carboxylic acids according to the following general reaction.



All the condensation products were high melting substances, insoluble in common organic solvents and so could not be purified as such. As an alternative, purification after esterification was tried. The *bis*- (2-methyl cinchoninic acid) and the *bis*-(2-phenyl cinchoninic acid), obtained from di-isatin and acetone and acetophenone respectively, were esterified by

alcohol-sulphuric acid and the esters obtained in a pure form. The *bis*-(tetrahydro acridine-9-carboxylic acid) and the *bis*-(benz-dihydro acridine-9-carboxylic acid), obtained from di-isatin and cyclohexanone and α-tetralone respectively, could not be esterified. This difficulty in esterifying these acids can probably be due to steric hindrance. Jensen and Rethurisch[4] have reported that acridine-9-carboxylic acid cannot be esterified by alcohol-acid method. Borshe[5] has recorded a similar difficulty in esterifying tetrahydro-acridine-9-carboxylic acid. The condensation product of di-isatin with acetoacetic ester could not be obtained pure.

Experimental

The di-isatin was purified by dissolving it in 5% aqueous alkali, just neutralising with glacial acetic acid, filtering off the dark material that separated, and acidifying the solution with hydrochloric acid.

I. *Condensation with acetone.*—2 gm. of di-isatin were dissolved in 22 c.c. of 10% potassium hydroxide and 10 c.c. of acetone added. After distilling off the excess of acetone, the solution was acidified with acetic acid. The precipitated brownish-red solid (2·3 gm.) was soluble in bicarbonate solution and in dilute hydrochloric acid, but insoluble in common organic solvents.

For esterification, 2 gm. of the dry, powdered condensation product was added to a mixture of 50 c.c. of absolute methyl alcohol and 4 c.c. of concentrated sulphuric acid. The resulting solution, after standing overnight at room temperature, was refluxed on the water-bath for 4 hours, cooled and poured on to dilute ammonia and ice. The yellowish solid was stirred into cold, dilute bicarbonate, collected and washed with water. The crude product was refluxed with benzene, the solution filtered free of a dark insoluble matter, and the solvent removed. The residue crystallised in yellowish plates from methyl alcohol and melted at 229–31°. The ester shows a greenish blue fluorescence in benzene and methyl alcohol (Found: C, 71·81; H, 5·18. $C_{24}H_{20}O_4N_2$ requires C, 72·00, H, 5·00).

II. *Condensation with acetophenone.*—3 gm. of di-isatin were dissolved in 35 c.c. of 10% aqueous alcoholic potash, 3 c.c. of acetophenone added, the mixture refluxed for 5 hours, diluted and acidified with acetic acid. The resulting yellow solid (4·2 gm.) was soluble in bicarbonate but insoluble in dilute hydrochloric acid and in common organic solvents.

One gm. of the dry powdered substance was treated with 50 c.c. of absolute alcohol containing 25 c.c. of concentrated sulphuric acid. The substance dissolved with a green fluorescence. The solution was kept at

room temperature for 40 hours, then refluxed on the water-bath for 7 hours, cooled, poured on to ice and basified with ammonia. The yellow solid was immediately filtered and washed with water. The ester was dissolved in benzene and clarified with charcoal, and the solvent removed. The residue crystallised from acetic acid in glistening yellow plates melting at 249–51°. (Found: C, 77·96; H, 5·39. $C_{36}H_{28}N_2O_4$ requires C, 78·27, H, 5·07).

III. *Other condensations.*—Condensation of di-isatin with cyclohexanone and α-tetralone was carried out as given for acetophenone. The products were soluble in bicarbonate solution but all attempts at purification gave no encouraging results. Esterification also failed.

SUMMARY

The Pfitzinger condensation of di-isatin with some ketones is reported.

REFERENCES

1. Sandmeyer .. *Helv.*, 1919, **2**, 234.
Marvel and Hiess .. *Organic Synthesis, Collective Volume I*, 327.
Wibaut and Gearling .. *Rec. trav. Chim.*, 1931, **50**, 41.
2. Dethloff and Mix .. *Ber.*, 1949, **82**, 534.
3. Pfitzinger .. *J. prakt. Chem.*, 1886, **33**, 100; 1888, **38**, 583; 1897, **56**, 283.
4. Jensen and Rethurisch .. *J. Amer. Chem. Soc.*, 1928, **50**, 1144.
5. Borsche .. *Annalen*, 1910, **377**, 70.