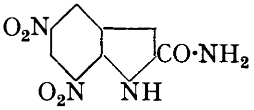
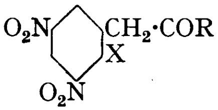
120. *Strychnine and Brucine. Part XXIV.*[*] *Synthesis of Dinitrostrycholamide.*

By Peter Hill and Robert Robinson.

The validity of the recognition of dinitrostrycholcarboxylic acid as 5 : 7-dinitroindole-2 : 3-dicarboxylic acid (Menon and Robinson, J., 1931, 773) has now been confirmed by the synthesis of the amide of dinitrostrychol (I), a substance which is correctly described as 5 : 7-*dinitroindole*-2-*carboxyamide*. After attempts to nitrate suitable indole derivatives in the 5 : 7-positions had failed, attention was directed to a method involving indole ring-closure by a new process peculiarly adapted to the synthesis of 5 : 7-dinitroindole derivatives. It was thought that substances of the form II (X = Cl or OMe) would afford the indoles (III) by the action of ammonia and it is evident that the acid (IV) would be the appropriate intermediate for the synthesis of 5 : 7-dinitroindole-2-carboxylic acid (dinitrostrychol) by this method.

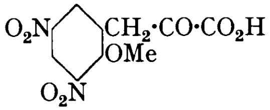


(I.)



(II.)

(III.)



(IV.)

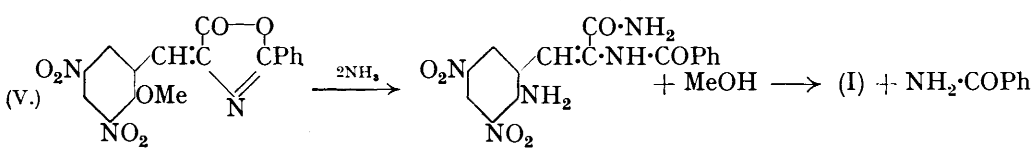
A substituted phenylpyruvic acid such as (IV) should be obtainable from the product of the condensation of 3 : 5-*dinitro*-2-*methoxybenzaldehyde* and hippuric acid.

All attempts to dinitrate *o*-chlorobenzaldehyde and 2-methoxybenzaldehyde were fruitless, but the required aldehyde was obtained by methylating dinitrosalicylaldehyde with diazomethane; other methods of methylation did not succeed.

On condensation with hippuric acid, in the usual manner, 2-*phenyl*-4-(3′ : 5′-*dinitro*-2′-*methoxybenzylidene*)*oxazolone* (V) was obtained. Hydrolysis by means of aqueous-alcoholic sodium hydroxide opened the oxazolone ring but at the same time affected the methoxyl group and, as 2 : 4-dinitrophenol is not readily convertible into dinitroaniline, it was necessary to employ a less energetic reagent.

The action of methyl-alcoholic ammonia on (V) in a sealed tube at 100° led to the production of a neutral substance which from its properties, the analytical data, and the method of formation was evidently 5 : 7-dinitroindole-2-carboxyamide (I). Possible stages of the synthesis are represented below and some alternatives, not affecting the final interpretation, will be apparent. Theoretically the reaction might have yielded 6 : 8-dinitro-3-amino-2-hydroxyquinoline (isomeric with I), but this substance has been obtained by an unambiguous method (Menon and Robinson, J., 1932, 781) and it is quite different from the compound under consideration.

Dinitrostrychol was then converted into its amide by way of the acid chloride, and this derivative proved to be identical with the synthetic specimen.



Experimental.

3 : 5-*Dinitro*-2-*hydroxybenzaldehyde* (*Dinitrosalicylaldehyde*).—The mixture of mononitrosalicylaldehydes was prepared by von Miller's method (*Ber.*, 1887, **20**, 1928) (yield, 85% and not theoretical as claimed). The dinitration following Lovett and Roberts (J., 1928, 1978) gave a crude product in 75% yield (from salicylaldehyde); this was crystallised from C_6H_6 (63% yield of product, m. p. 55·5—58·5°, used for the next stage), then twice more from C_6H_6 and from aq.

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[*] Parts XXI, XXII, and XXIII of this series have been published in the Journal of the Polish Chemical Society (O. Achmatowicz, *Rocz. Chem.*, 1932, **12**, 862, 936; 1933, **13**, 25).

AcOH; pale yellow, rhombic plates, m. p. 62—63° (Lovett and Roberts give 58—60°) (Found : C, 39·9; H, 2·2; N, 13·2. Calc. for $C_7H_4O_6N_2$: C, 39·6; H, 1·9; N, 13·2%). The vigorous reaction between dinitrosalicylaldehyde (0·5 g.) and HNO_3 (2 c.c., *d* 1·5) led to the formation of picric acid (0·43 g.), m. p. 122°, undepressed on admixture with an authentic specimen.

Dinitrosalicylaldehyde resembles picric acid in many of its properties and it forms a well-crystallised (needles), bright yellow pyridine salt.

The *phenylhydrazone* crystallises from EtOH in long, glistening, brown rods, m. p. 228° (decomp.) (Found : N, 18·6. $C_{13}H_{10}O_5N_4$ requires N, 18·6%).

The *semicarbazone* in its crude state has m. p. 237° (decomp. and variation with rate of heating) and crystn. from EtOH effected the separation of two modifications, (a) stout yellow prisms which redden at 225° (*ca.*) and decomp. 231°, and (b) orange-red needles, more readily sol. than the prisms, decomp. 239° after sintering at 225°. From MeOH a mixture of pale orange, feathery needles and pale orange prisms separated; these became orange-red at 190°, m. p. 225—227° (decomp.) (Found : N, 26·3. $C_8H_7O_6N_5$ requires N, 26·0%).

2-*Phenyl*-4-(3′ : 5′-*dinitro*-2′-*hydroxybenzylidene*)*oxazolone*.—A mixture of powdered anhyd. NaOAc (8 g.), hippuric acid (18 g.), and dinitrosalicylaldehyde (21·2 g.) with Ac_2O (55 c.c.) was heated on the steam-bath for 10 min. and well stirred. The yellow mass became at first semi-liquid and later solidified with a sudden change of colour to bright red. The solid was isolated after the addition of EtOH and then treated with boiling H_2O (500 c.c.) until the ppt. became clear yellow (yield, 30·1 g.). The very sparingly sol. substance separated from its red solution in pyridine in small, quadrilateral, buff plates, m. p. 302—303° (decomp.) after washing with EtOH (Found : C, 54·4; H, 2·7; N, 11·7. $C_{16}H_9O_7N_3$ requires C, 54·1; H, 2·6; N, 11·8%).

3 : 5-*Dinitro*-2-*methoxybenzaldehyde*.—Methylation of dinitrosalicylaldehyde by the Me_2SO_4–xylene–K_2CO_3 method was tried, but the results were not consistent and the process was quite unsatisfactory.

The dinitrosalicylaldehyde (21·8 g.), suspended in dry Et_2O (100 c.c.), was gradually treated with CH_2N_2 (from 25 c.c. of nitrosomethylurethane; cf. Gadamer, *Arch. Pharm.*, 1911, **249**, 658) in Et_2O. The evolution of N slackened and on removal of the solvent a clear viscous, amber liquid remained (24·8 g.). The substance crystallised from MeOH in very pale yellow rosettes of needles, m. p. 86—87°, subliming at 80° in a high vac. (Found in material dried at room temp. in high vac. : C, 42·1, 42·2; H, 3·3, 3·2; N, 11·7. $C_8H_6O_6N_2$,0·5MeOH requires C, 42·1; H, 3·3; N, 11·6%. Found : MeO, 17·5%, which is intermediate between the requirements for $C_8H_6O_6N_2$ and $C_8H_6O_6N_2$,0·5MeOH. Evidently the MeOH does not yield MeI in stoicheiometric amount). The substance is readily sol. in $CHCl_3$, acetone, EtOAc and C_6H_6, moderately readily sol. in the simple alcohols, and sparingly sol. in light petroleum.

The *phenylhydrazone* crystallised from EtOH in brick-red, stout prisms, m. p. 214° (decomp.) (Found : N, 17·6. $C_{14}H_{12}O_5N_4$ requires N, 17·7%).

The *semicarbazone* crystallised from EtOH in yellow rods, m. p. 205° (decomp.) (Found : C, 38·5, 38·5; H, 3·2, 3·2; N, 24·5; MeO, 11·0, 11·0. $C_9H_9O_6N_5$ requires C, 38·1; H, 3·2; N, 24·7; MeO, 11·0%).

2-*Phenyl*-4-(3′ : 5′-*dinitro*-2′-*methoxybenzylidene*)*oxazolone* (V).—The once-cryst. dinitrosalicylaldehyde methyl ether (13·2 g.) was heated for 10 min. on the steam-bath with powdered dry NaOAc (5·4 g.), hippuric acid (12·0 g.), and Ac_2O (30 c.c.); the product then crystallised in orange needles, isolated after washing with EtOH and H_2O (13·9 g., m. p. 184°, pure enough for the next stage). The *lactone* crystallised from EtOAc in pale orange needles, m. p. 185·5° (Found : C, 55·2; H, 2·9; N, 11·2. $C_{17}H_{11}O_7N_3$ requires C, 55·3; H, 3·0; N, 11·4%).

In one expt. using *crude* dinitrosalicylaldehyde methyl ether, a product was obtained which was fractionated by means of Ac_2O and EtOAc. The results need not be detailed, but the original reaction mother-liquor deposited pale lemon-yellow needles (2·2 g. from 25 g. of crude aldehyde), recryst. from Ac_2O, m. p. *ca.* 215° with softening at 205° (decomp.) (Found : C, 58·6; H, 3·3; N, 10·3. $C_{20}H_{13}O_7N_3$ requires C, 59·0; H, 3·2; N, 10·3%). This *substance* is insol. in Na_2CO_3 aq. and gives no $FeCl_3$ reaction.

3 : 5-*Dinitro*-2-*hydroxy*-α-*benzamidocinnamic Acid*.—The phenyldinitromethoxybenzylideneoxazolone (1 g.) was heated for 2 hr. on the steam-bath with EtOH (25 c.c.) and NaOH aq. (10 c.c. of 10%); some NH_3 was evolved. The granular ppt. obtained on addition of HCl aq. was dissolved in BuOH (charcoal) and crystallised therefrom in lemon-yellow needles, darkening at about 200°, softening at 216° and m. p. 218° (decomp.), a behaviour unchanged by recrystn. from EtOAc (Found : C, 51·5; H, 3·1; N, 11·2. $C_{16}H_{11}O_8N_3$ requires C, 51·5; H, 3·0; N, 11·3%). The m. p. depends to some extent on the rate of heating.

5 : 7-*Dinitroindole*-2-*carboxyamide* (I).—Phenyldinitromethoxybenzylideneoxazolone (1 g.)

was heated with MeOH–NH_3 (25 c.c. sat. at 0°) in a sealed tube at 100° for 24 hr. The product (theo. yield) was isolated after addition to dil. HCl aq. and was crystallised from AcOH (charcoal) and finally from EtOH, forming cream-yellow needles, m. p. 263° (decomp.), partly subliming at 240—250° (Found : loss at 110° in high vac. over P_2O_5, 3·4, 3·7, 3·3. Found in anhyd. material : C, 43·8, 43·5; H, 2·7, 2·5; N, 22·0, 22·1. $C_9H_6O_5N_4,0{\cdot}5H_2O$ requires H_2O, 3·5%. $C_9H_6O_5N_4$ requires C, 43·2; H, 2·4; N, 22·4%). The neutral substance is feebly pseudo-acidic, sol. in warm NaOH aq. to a yellow solution. Reduction with Zn dust and aq.-alc. HCl gives a colourless, blue-violet fluorescing solution which becomes brownish-red on addition of $FeCl_3$; the reaction resembles that given by dinitrostrychol.

Dinitrostrycholamide (I).—PCl_5 was added in excess to a suspension of dinitrostrychol in $CHCl_3$, and the reaction completed by heating on the steam-bath for 30 min. The solution was then poured slowly into a large excess of dil. NH_3 aq. and the bright yellow solid was collected (yield, theo.). The crude *amide* softened at 256°, m. p. 263°; recryst. from EtOH, m. p. 263° and at the same temperature when mixed with the synthetic specimen (Found : loss at 110° in high vac. over P_2O_5, 3·4. Found in anhyd. material : C, 42·9; H, 2·7; N, 22·5%). All the properties of the synthetic specimen and the specimen prepared from strychnine were found to be identical; the colour reactions, solubilities in AcOH and EtOH, habit of crystn., and shape of crystals were compared.

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