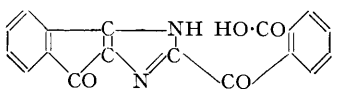
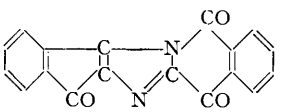
NOTES.

Studies on Indene Derivatives. Part VI. Some New Derivatives of Triketoindane Hydrate ("Ninhydrin").

By RADWAN MOUBASHER.

RUHEMANN (*J.*, 1910, **97**, 1447), by the action of aqueous ammonia on ninhydrin (VIII), obtained a scarlet substance, believed to be 2-*o*-carboxybenzoylindonoglyoxaline (I). This substance, when heated alone or with glacial acetic acid or acetic anhydride, gives a red compound, possibly (II), but structures (III) and (IV) are possible instead of (I) and (II). The acid (I) or (III) reacts with diazomethane giving the *methyl* ester.

(I.) 



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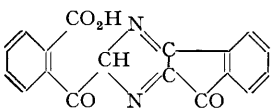
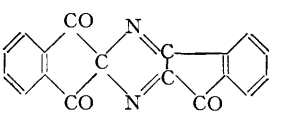
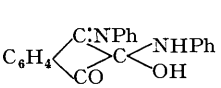
(III.) 



(IV.)

Ninhydrin (VIII) condensed with aniline to give an orange *product* (Ruhemann, *loc. cit.*), but this was not analysed; it could have structure (V) or (VI). *p*-Aminobenzoic acid and *p*-aminophenol react with



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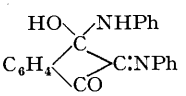

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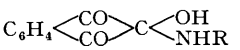
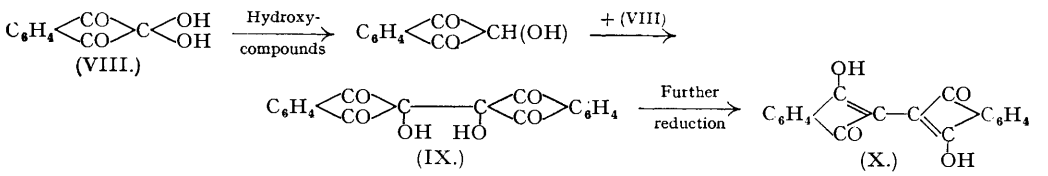


(VII.)

ninhydrin to form 2-p-*carboxy*- and 2-p-*hydroxy-anilino*-2-*hydroxy*-1 : 3-*diketoindane* (VII; R = C_6H_4·CO_2H and R = C_6H_4·OH, respectively). This reaction is similar to that of *peri*naphthindane-1 : 2 : 3-trione hydrate with amines (Moubasher and Mostafa, *J.*, 1947, 130).

Ninhydrin when treated with certain hydroxy-compounds (*e.g.*, glycerol, ethylene glycol, or some sugars) gives a characteristic violet coloration (Hall, Loewenstein, and Pribrim, *Biochem. Z.*, 1913, **55**, 357), hydrindantin (IX) * being an intermediate product. The mechanism of this reaction has not yet been explained, but the violet coloration is due to bis-1 : 3-diketoindanyl (enol form) (X), which has been isolated from the mixture.



(VIII.) (IX.) (X.)

Hydrindantin when heated in a vacuum yields (X), and in presence of selenium and oxygen it gives phthalic anhydride.

To ninhydrin, freshly crystallised (0·5 g.), dissolved in hot water (25 c.c.), and cooled; excess of aqueous ammonia was added; a violet solution was obtained, and after 5 minutes at room temperature this was filtered and acidified with concentrated hydrochloric acid. The resulting red gelatinous precipitate of the glyoxaline (I) was filtered off, washed with hot water, dried, and crystallised from alcohol, forming scarlet prisms (0·3 g.); at *ca.* 250° these change to an orange solid, and melt at 345° (brown-red melt).

* For alternative (dihydrated) formula, see Schönberg and Moubasher, *J.*, 1949, 212.

The glyoxaline is soluble in cold aqueous ammonia and is reprecipitated by acids (Found : C, 67·8; H, 2·7; N, 8·6. Calc. for $C_{18}H_{10}O_4N_2$: C, 67·9; H, 3·1; N, 8·8%).

When 0·2 g. of powdered (I) was suspended in dry ether (20 c.c.) and treated with excess of ethereal diazomethane (prepared according to Arndt and Amende, *Z. angew. Chem.*, 1930, **45**, 444), a vigorous reaction took place at room temperature. The mixture was left overnight, and the red precipitate was filtered off and recrystallised from methyl alcohol, forming red needles (0·2 g.), m. p. 245° (red-violet melt), insoluble in alkali but soluble in hot acetic acid, benzene, and alcohols (Found : C, 68·5; H, 3·6; N, 8·4. $C_{19}H_{12}O_4N_2$ requires C, 68·1; H, 3·2; N, 8·1%). The methyl ester gives an orange colour with concentrated sulphuric acid.

The *anhydride* of (I) was prepared by boiling 0·2 g. with acetic anhydride (50 c.c.) or glacial acetic acid (100 c.c.) for 10 minutes. On cooling, a crystalline orange deposit was formed; this was filtered off and crystallised from glacial acetic acid in orange needles (0·18 g.), m. p. 345° (red melt), insoluble in cold or hot ammonia solution and unchanged when refluxed with alcoholic potassium hydroxide (Found : C, 71·8; H, 2·6; N, 9·3. $C_{18}H_8O_3N_2$ requires C, 72·0; H, 2·6; N, 9·3%). It gives an orange-red coloration with concentrated sulphuric acid. The same substance can also be obtained when (I) is heated in a vacuum at 350° (bath temp.)/4 mm.

Action of Aniline on Ninhydrin.—Ninhydrin, freshly crystallised (0·6 g.), was dissolved in water (30 c.c.), and freshly distilled aniline (0·6 g.) was added in portions at room temperature, with shaking. A violet solution was obtained, giving an orange crystalline substance, which was filtered off, washed with water, and recrystallised from 50% aqueous alcohol; orange needles (0·8 g.) were formed, m. p. 99° (decomp.), depending on rate of heating (Found : C, 76·9; H, 4·8; N, 8·5. $C_{21}H_{16}O_2N_2$ requires C, 76·8; H, 4·7; N, 8·5%).

When this compound (V or VI) (0·5 g.) was boiled for 5 minutes with concentrated hydrochloric acid (15 c.c.), a yellow solution was obtained. This was cooled and extracted several times with small amounts of ether. The combined ethereal solutions were evaporated to dryness. The residue formed colourless crystals of ninhydrin (m. p., mixed m. p., and colour reactions). The aqueous layer contained aniline hydrochloride (formation of benzeneazo-β-naphthol).

Action of p-*Aminobenzoic Acid on Ninhydrin.*—Ninhydrin (1 g.) was dissolved in hot benzene (50 c.c.), and a hot benzene solution of *p*-aminobenzoic acid (1·5 g. in 50 c.c.) added. The mixture was heated under reflux for 3 hours; a deep violet coloration was immediately observed, which changed to orange, and an orange precipitate began to form. After cooling, this was filtered off, and when recrystallised from ethyl alcohol afforded orange needles (1·6 g.), m. p. 230° (decomp.; brown melt) (Found : C, 64·8; H, 3·7; N, 4·8. $C_{16}H_{11}O_5N$ requires C, 64·6; H, 3·7; N, 4·7%). The substance (VII; R = $C_6H_4{\cdot}CO_2H$) is soluble in alkali and in alcohols, giving red solutions, but difficultly soluble in ether; with sodium hydrogen carbonate solution it evolves carbon dioxide and gives a red solution.

When this product (0·5 g.) was treated with 18N-sulphuric acid (20 c.c.), the colour disappeared immediately; after 10 minutes at room temperature the mixture was heated on a steam-bath for 3 minutes, then cooled and diluted with water (50 c.c.); a colourless solid separated and was proved to be *p*-aminobenzoic acid (m. p. and mixed m. p.), and the solution contained ninhydrin (extracted with ether and identified by m. p., mixed m. p., and properties).

Action of p-*Aminophenol on Ninhydrin.*—Ninhydrin (0·5 g.), dissolved in acetic acid (20 c.c.), and *p*-aminophenol (0·7 g.), dissolved in acetic acid (50 c.c.), were heated together on a steam-bath for 30 minutes; on concentration and cooling, a precipitate was formed, and after separation this crystallised from absolute methyl alcohol in dark reddish crystals (0·2 g.), m. p. 210° (decomp.) (Found : N, 5·0. $C_{15}H_{11}O_4N$ requires N, 5·2%). These gave a beautiful red coloration with concentrated sulphuric acid, and an intense blue with sodium hydroxide solution.

Action of Hydroxy-compounds on Hydrindantin.—Hydrindantin (0·5 g.) was treated with 95% ethyl alcohol (100 c.c.), *iso*propyl alcohol (50 c.c.), glycerol (50 c.c., mixed with 50 c.c. of water), or glucose (2 g. in 100 c.c. of water) and heated under reflux for about 3 hours; the colour gradually became red then intensely violet, and a violet precipitate was formed; after dilution with water, this was filtered off, dried, and recrystallised from benzene, forming violet needles, m. p. 297° (decomp.), of bis-1 : 3-diketoindanyl (m. p., and mixed m. p., and properties). The yield in all these cases was about 80%.

Action of Heat on Hydrindantin.—(a) *In a vacuum* (experiment by William Awad). 0·5 G. of hydrindantin was placed in a pyrolysis flask and heated in a vacuum (10 mm.) at 280—300° (bath temp.) for ½ hour; violet crystals were formed on the cold parts of the flask, and after recrystallisation from benzene, these were identified as bis-1 : 3-diketoindanyl (m. p., 297°, mixed m. p., and pink colour with sulphuric acid).

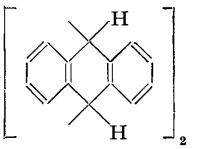
(b) *In presence of selenium and oxygen.* 0·5 G. of hydrindantin was mixed with powdered selenium (Kahlbaum; 4 g.), placed in a dry test-tube, and heated in a metal-bath at 290° for an hour, a current of oxygen being passed through the tube. The colourless sublimate formed was returned to the tube, and the heating repeated for 10 minutes. The colourless needles formed on the cold parts of the tube were proved to be phthalic anhydride (m. p., 131°, and mixed m. p.).—Fouad I University, Faculty of Science, Cairo, Egypt. [*Received, July 24th*, 1948.]

Photochemical Reactions. Part XIV. The Action of Sunlight on Some Carcinogenic Hydrocarbons.

By Alexander Schönberg and Ahmed Mustafa.

Previously (*J.*, 1948, 2126), we showed that 1 : 2-benzanthracene, which is closely related to substances showing strong carcinogenic action, forms a photo-dimer under the influence of sunlight. We now find that 5-methyl-1 : 2-benzanthracene, 20-methylcholanthrene, and 4′-methyl-1 : 2-benzanthracene [of which the first two are strongly carcinogenic (Cook, Robinson, and Goulden, *J.*, 1937, 393; Cook and Haslewood, *J.*, 1934, 430)] similarly form polymers, which, by analogy with dianthracene (I), are

believed to be dimeric and to have a constitution similar to (I). These photo-products are colourless or nearly so, and regenerate the monomers under the influence of heat, thus behaving like (I).



(I.)

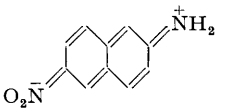
To our previous discussion (*loc. cit.*) of the possible connexion between carcinogenicity and photo-activity, we now add the conception that photo-activated (biologically highly active) compounds may be produced within the body if normal biochemical reactions are accompanied by chemi-luminescence.

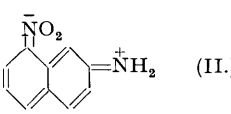
Polymerisations.—5-Methyl-1 : 2-benzanthracene, dissolved in benzene, was exposed in a sealed " Monax " tube (filled with CO_2) to the action of sunlight during 15 days (November); the colourless *photo-dimer* which separated was washed several times with hot benzene to remove the unchanged material and then melted at about 185° (Found : C, 94·3; H, 5·7. $C_{38}H_{28}$ requires C, 94·2; H, 5·8%). 4-Methyl-1 : 2-benzanthracene similarly gave a colourless *photo-dimer*, m. p. about 230° (Found : C, 94·2; H, 5·7%). 20-Methylcholanthrene, in benzene, was exposed as described above in a " Pyrex " tube for 30 days (December—January). The almost colourless *photo-dimer* was washed with hot benzene (in which it was difficultly soluble) and crystallised from a large amount of xylene; it was insoluble in aqueous potassium hydroxide and melted between 295° and 305° (Found : C, 94·1; H, 5·9. $C_{42}H_{32}$ requires C, 94·0; H, 6·0%).

Action of Heat.—The photo-dimers were heated for 30 minutes in a stream of CO_2; in all cases a crystalline sublimate of the respective monomer was obtained and identified by m. p. and mixed m. p. Bath-temperatures used were : 20-methylcholanthrene, 360°; 5- and 4′-methyl-1 : 2-benzanthracene, 270°.—Faculty of Science, Fouad I University, Abbassia, Cairo. [*Received, July 10th*, 1948.]

The Separation of 6- *and* 8-*Nitro*-2-*naphthylamine.* By Herbert H. Hodgson and John Ratcliffe.

6- and 8-Nitro-2-naphthylamine can resonate into the quinonoid structures (I) and (II), of which (I) is by far the more stable and makes a greater contribution to its resonance hybrid. In consequence the 8-nitro- will be more basic than the 6-nitro-isomeride, and a separation is now reported from their mixture which depends on this property, *viz.*, the prior solubility of the 8-nitro-2-naphthylamine in very dilute hydrochloric acid; this appears to be more complete and much less tedious than the fractional crystallisation processes of previous workers (cf. Veselý and Jakes, *Bull. Soc. chim.*, 1923, **33**, 942; Saunders and Hamilton, *J. Amer. Chem. Soc.*, 1932, **52**, 638).

(I.) 

 (II.)

Experimental.—The mixture (140 g.) of 1-, 6-, and 8-nitroaceto-2-naphthalides, obtained by nitration of the acet-β-naphthalide from β-naphthylamine (120 g.) *via* the procedure of Hartman and Smith (*Org. Synth.*, Coll. Vol. II, p. 438) or that of Saunders and Hamilton (*loc. cit.*), was refluxed for 20 minutes with benzene (800 c.c.), and the mixture cooled to 40° and filtered. The filtrate afforded the 1-nitroaceto-2-naphthalide (70—75 g.), while the insoluble portion (50—55 g., m. p. 140—150°), which contained approximately equal amounts of the three isomerides, was refluxed for 1 hour with a solution of ethanol (200 c.c.) and hydrochloric acid (50 c.c., *d* 1·18), and filtered hot. The deposit *A*, which had formed during the reflux period, was almost exclusively a mixture of 6- and 8-nitro-2-naphthylamine hydrochlorides, but at room temperature the further deposit *B* contained, in addition, substantial amounts of the 1-nitro-isomeride. On addition of water to the filtrate from *B*, the precipitate *C* (13 g.) was mainly the 1-nitro- with a little of the 6-nitro-2-naphthylamine. The final filtrate when rendered alkaline with ammonia, gave a precipitate *D*, which consisted mainly of 8-nitro-2-naphthylamine contaminated with a small amount of an unidentified impurity. 8-Nitro-2-naphthylamine was removed completely from the precipitates *A*, *B*, and *D* by several extractions with cold dilute hydrochloric acid (containing 1 c.c. of acid, *d* 1·18, per 100 c.c. of water), *ca.* 6 l. being used in all. The combined filtrates, when just basified with ammonia, at 0°, afforded micro-crystals of almost pure 8-nitro-2-naphthylamine (10—12 g.), m. p. 98—102°, which crystallised from ethanol in red needles, m. p. 104·5—105° (lit., m. p. 103·5°). The residues from *A* and *B*, together with *C*, were extracted by boiling ethanol (100 c.c.), and the extract cooled rapidly and filtered before crystallisation began; the insoluble 6-nitro-2-naphthylamine (10—12 g., m. p. 203—205°) crystallised from ethanol in thin yellow-orange plates, m. p. 207—207·5° (lit., m. p. 203°). The hot filtrate (above) deposited 1-nitro-2-naphthylamine, which crystallised from ethanol in thick red needles, m. p. 126—127°. The approximate ratio now obtained of 1 : 1 for the amounts of the 6- and the 8-nitro-2-naphthylamine, agrees with that of Veselý and Jakes (*loc. cit.*) but differs from the 1 : 3 ratio reported by Saunders and Hamilton (*loc. cit.*).—Technical College, Huddersfield. Technical College of South-East Essex, Dagenham. [*Received, October 1st*, 1948.]

A Synthesis of DL-*Valine from Ethyl Acetamidomalonate.* By R. O. Atkinson and P. A. A. Scott.

Valine has been prepared by the Strecker (Lipp, *Annalen*, 1880, **205**, 9, 18) and halogen-acid (*Org. Synth.*, 1940, **20**, 106) methods, and by a variation of the Sörensen method, namely the reaction of *iso*propyl iodide with ethyl benzamidomalonate (Redeman and Dunn, *J. Biol. Chem.*, 1939, **130**, 346). Its preparation by the reaction of *iso*propyl bromide with ethyl acetamidocyanoacetate (Albertson and Tuller, *J. Amer. Chem. Soc.*, 1945, **67**, 502) has been claimed.

It has been reported by Snyder, Shekleton, and Lewis (*J. Amer. Chem. Soc.*, 1945, **67**, 310) that attempts to prepare *iso*leucine and valine by alkylation of ethyl acetamidomalonate with *sec.*-butyl bromide and *iso*propyl bromide, respectively, were unsuccessful, and they suggested that secondary halides are of little use in this or any of the variations of the Sörensen method.

We have found this to be the case for *sec.*-butyl bromide, but we have prepared valine by this method in 31·5% overall yield. The alkylation proceeds very slowly, and a reaction period of 72 hours is necessary for maximum yield. This time, however, can be halved by using the corresponding iodide.

Experimental.—Ethyl α-acetamido-α-carbethoxyisovalerate. To a solution of sodium (23 g.) in specially-dried ethyl alcohol (1500 ml.) ethyl acetamidomalonate (217 g.; 1 mole) was added. *iso*Propyl bromide (123 g.; 1 mole) was added to the resultant solution with stirring. The mixture was boiled under reflux for 72 hours, and the alcohol was then removed by distillation. The product was extracted from the residue with ether, and the extract concentrated to a pale brown syrup which crystallised on cooling to give ethyl α-acetamido-α-carbethoxy*iso*valerate (92 g.; 37%), m. p. 73° (uncorr.) (Found : C, 55·4; H, 8·14; N, 5·32. Calc. for $C_{12}H_{21}O_5N$: C, 55·6; H, 8·17; N, 5·40%).

DL-*Valine.*—A mixture of ethyl α-acetamido-α-carbethoxy*iso*valerate (50 g.) and 48% hydrobromic acid (250 ml.) was heated under reflux for 18 hours. The hydrobromic acid was then removed by distillation under reduced pressure, and the residue was dissolved in water, treated with charcoal, and filtered. The filtrate was adjusted to pH 6 with ammonia, and an equal volume of methanol was added. The mixture was chilled overnight, and valine filtered off, washed free of bromide with methanol, and recrystallised from aqueous alcohol (yield, 20 g.; 85%) (Found : N, 11·8. Calc. for $C_5H_{11}O_2N$: N, 11·9%).

We wish to thank the Board of Directors of the British Drug Houses Ltd., for permission to publish this note.—Amino Acids Department, The British Drug Houses Ltd., London, N.1. [*Received, August 12th*, 1948.]