

Studies on Some New Indazole and Benzimidazole Derivatives

By M. KAMEL, M. A. ALLAM, F. I. ABDEL HAY and (in part) M. A. OSMAN

Summary

Alkylation of 5-nitroindazole (I) with dimethyl sulphate and/or diethyl sulphate in presence of sodium hydroxide yields mixtures containing more 2-alkylated than 1-alkylated products. The action of diazomethane on 5-nitro (I) and 6-nitro-indazole (IV) was investigated. Reduction of nitroindazoles with hydrogen on Pd/charcoal proceeds smoothly. The synthesis of several new benzimidazole and indazole dye intermediates is also described.

In the course of investigations[†] carried out in this laboratory to prepare new intermediates and dyestuffs containing the indazole and benzimidazole moieties, several novel results were obtained. The present communication gives a brief description of these findings.

AUWERS and DÜESBERG¹⁾ formulated the rule that alkylation of indazole by alkyl iodides in presence of sodium alkoxides, takes place mainly in the 1-position. Exceptions to the rule are known, for example, the methylation of indazole-3-methylcarboxylate using either methyl iodide and sodium methoxide or dimethyl sulphate and sodium hydroxide leads to the formation of 2-methyl-3-methylcarboxylate²⁾. BARCLAY, CAMPBELL and DODDS³⁾ found other exceptions in the methylation of 6-nitroindazole and 3-bromo-6-nitroindazole and were inclined to doubt the general validity of this rule.

DAVIES⁴⁾ studied the methylation of 6- and 7-nitroindazoles with dimethyl sulphate and sodium hydroxide, and reported that the reaction gave about equal parts of 1- and 2-isomers. It is now shown that the reaction of 5-nitroindazole (I) and dimethyl sulphate under the same experimental conditions outlined by the above author gives 2-methyl (IIa) and 1-methyl-5-nitroindazole (IIIa) in the proportion 2.5:1. In this connection it is inter-

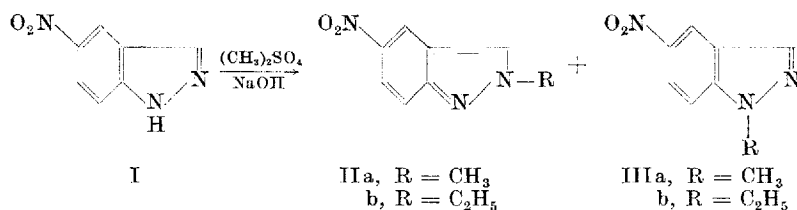
¹⁾ K. V. AUWERS and M. DÜESBERG, Ber. dtsh. chem. Ges. **53**, 1179 (1920).

²⁾ K. V. AUWERS and R. DERESER, Ber. dtsh. chem. Ges. **52**, 1340 (1919).

³⁾ I. M. BARCLAY, N. CAMPBELL and G. DODDS, J. chem. Soc. London **1941**, 113.

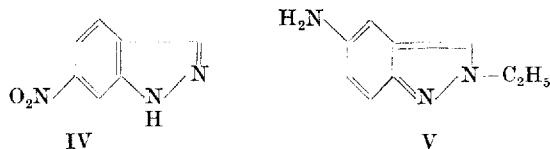
⁴⁾ R. R. DAVIES, J. chem. Soc. London **1955**, 2412.

esting to mention that AUWERS et al. and later FRIES and TAMPKE⁵⁾ obtained higher yields of the 1-isomer when the methylation of nitroindazoles was carried out using potassium hydroxide and dimethyl sulphate.



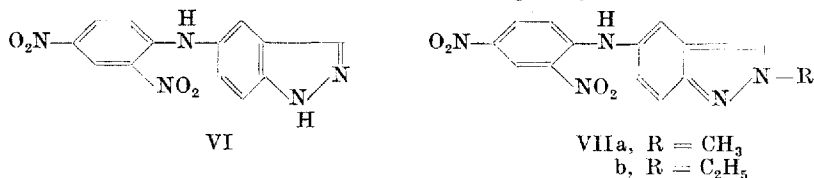
Similarly, (I) reacts with diethyl sulphate and sodium hydroxide to yield a mixture of two separable isomers in which the 2-isomer is in excess. The elucidation of the structure of IIb and IIIb is inferred from the difference in colour and melting points and solubility (2-isomer is orange whereas the 1-isomer is yellow; 2-isomer has a higher m.p. and is less soluble than the 1-isomer (cf. 4, 5)).

Nothing has been reported in literature on the action of diazoalkanes on nitroindazoles. It is now found that I and IV react with diazomethane to yield a mixture of the corresponding methylated products in which the proportion of the 2-isomer to the 1-isomer is nearly 2:1.



Reduction of nitroindazoles was normally carried out either by iron in water or alcohol, or by hydrogenation in presence of RANEY nickel^{4,6)}. It is now shown that the reduction can be easily effected with hydrogen using palladium-charcoal catalyst in excellent yields. 2-Ethyl-5-aminoindazole (V) has as yet not been prepared.

5-Aminoindazole, 2-methyl-5-aminoindazole and 2-ethyl-5-aminoindazole (V) condense with 1-chloro-2,4-dinitrobenzene to give the corresponding anilino derivatives (VI), (VIIa), and (VIIb) in good yields⁷⁾.

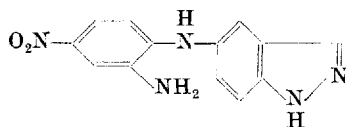


⁵⁾ K. FRIES and H. TAMPKE, *Liebigs Ann. Chem.* **453**, 307 (1927).

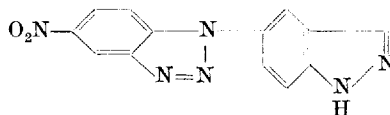
⁶⁾ C. E. KWURLER and P. LUCAS, *J. Amer. chem. Soc.* **65**, 1804 (1943).

⁷⁾ E. NOELTING, *Ber. dtsh. chem. Ges.* **37**, 2556 (1904).

When 5(2',4'-dinitroanilino-)indazole (VI) was reduced with sodium sulphide in alcohol, partial reduction took place and 5(2'-amino-4'-nitroanilino-)indazole (VIII) was obtained. The structure of this product is based on the fact that it gives correct analytical figures and undergoes cyclization to the corresponding benzotriazole derivative (IX) upon treatment with nitrous acid, indicating that it is an o-diamino compound.



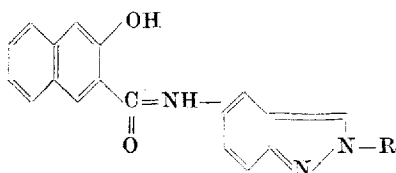
VIII



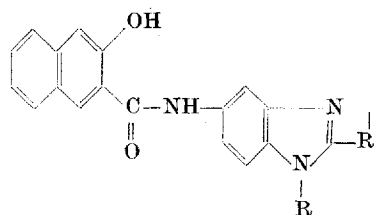
IX

Heterocyclic rings containing oxygen, nitrogen, and sulphur were found to be favourable to substantivity of the naphthols⁸⁾. The examples of Naphthol AS—L 4 G, AS—SG and AS—SR have been quoted; and there are numerous patents in which substantivity is thought to be increased by the introduction of hetero elements in the ring systems, especially in attempts to produce substantive β -ketic acid arylamides for yellow shades.

In view of the above considerations, we have now proceeded to prepare several new azoic coupling components containing the indazole and benzimidazole nuclei.



X a, R = CH₃
b, R = C₂H₅



XI a, R = H, R' = H
b, R = H, R' = CH₃
c, R = CH₃, R' = H
d, R = R' = CH₃

Preparation of 3-hydroxy-N-(5'-indazolyl)-2-naphthamide derivatives (Xa, b) and 3-hydroxy-N-(5'-benzimidazolyl)-(XIa—d) was carried out by refluxing equimolecular quantities of 3-hydroxy-2-naphthoyl chloride and the corresponding amino derivatives in a suitable solvent. In this connection it is interesting to mention that aminoindazoles are condensed with 3-hy-

⁸⁾ K. VENKATARMAN, "The chemistry of Synthetic Dyes", Academic Press Inc., Publisher, New York, 1952, Vol. I, p. 678.

droxy-2-naphthoic acid in the presence of Pcl_3 in a hydrocarbon solution to give similar compounds to our indazole derivatives⁹⁾.

Acetoarylides containing the indazole and benzimidazole nuclei are hitherto unknown. It is now shown that aminobenzimidazoles and indazoles condense readily with ethylacetoacetate to yield the corresponding acetoarylides in reasonable yields.

Details on the use of the above compounds as azoic couplers and their dyeing and fastness properties will be published elsewhere.

Experimental

Methylation of 5-nitroindazole (I): 2-methyl-5-nitro-indazole (IIa) and 1-methyl-5-nitroindazole (IIIa)

To 5-nitroindazole (6 g.) dissolved in water (140 ml.) and 32% sodium hydroxide solution (20 ml.) at 80°, dimethyl sulphate (13.2 g.) was added while the temperature was allowed to fall to 65° during 1/2 hour. The mixture was stirred at 60–65° for 2 hours, filtered off and dried. Separation of the 2 isomers was effected using Fries procedure⁵⁾ to give 1-methyl-5-nitroindazole (IIIa) as pale yellow needles, m. p. 129°, yield 25% and 2-methyl-5-nitroindazole (IIa) as red crystals, m. p. 163°, yield 62.5%. The m. p. of (IIIa) and (IIa) were undepressed when admixed with samples of the same compounds prepared according to Fries.

Ethylation of 5-nitroindazole (I): 2-ethyl-5-nitroindazole (IIb) and 1-ethyl-5-nitroindazole (IIIb)

A similar procedure to the above was adopted using 15 g. of (I) dissolved in water (350 ml.) and 32% sodium hydroxide solution (50 ml.) and diethyl sulphate (40 g.). The viscous product that formed solidified to a brown solid on cooling. The latter was filtered off and dried. Yield 90%.

The mixture was separated into its two components by repeated fractional crystallization from ethyl alcohol, whereby, the comparatively less soluble 2-isomer separated out and the 1-isomer remained in solution.

2-Ethyl-5-nitroindazole (IIb) was crystallized from ethyl alcohol, in orange crystals, m. p. 154–155°, yield 60%. Found: C 56.60; H 4.82; N 22.45. $\text{C}_9\text{H}_9\text{O}_2\text{N}_3$ requires C 56.54; H 4.70; N 21.99%.

(IIb) is readily soluble in hot ethyl alcohol, acetic acid, benzene, sparingly soluble in ether and light petrol. It gives a reddish brown colour with concentrated sulphuric acid.

Addition of water to the combined alcohol filtrates gave 1-ethyl-5-nitroindazole (IIIb), which was crystallized from light petrol (60–80°) to give pale yellow needles, m. p. 70°; yield 15.5%. Found: C 56.62; H 4.70; N 22.30. $\text{C}_9\text{H}_9\text{O}_2\text{N}_3$ requires C 56.54; H 4.70; N 21.99%.

⁹⁾ D. A. W. ADAMS, E. G. BAINBRIDGE, H. B. BRADELY and R. R. DAVIES, Brit. Pat. 707, 897 (1954).

(IIIb) is readily soluble in alcohol, ether, benzene, light petrol and acetic acid. It gives no colour with concentrated sulphuric acid.

Methylation of 5-nitroindazole (I) with diazomethane

A solution of (0.55 g.) diazomethane in ether was added gradually to 5-nitroindazole (5 g.) in the same solvent. The mixture was allowed to stay for 5 days in an ice-chest. Evaporation of the ethereal solution gave a mixture (5 g.) of the 1- and 2-isomers. Separation was effected by the method described above to give IIIa; yield 20% and IIa; yield 42% respectively.

Methylation of 6-nitroindazole (IV) with diazomethane: (1-methyl-6-nitroindazole and 2-methyl-6-nitroindazole)

The reaction was carried out as described above for (I) followed by separation by BARCLAY, CAMPBELL and DODDS' method⁹); fractionation from methyl alcohol gave I-methyl-, m. p. 125°; yield 22.5% and 2-methyl-6-nitroindazole, m. p. 160°; yield 54% respectively.

Reduction of Nitroindazoles and Nitrobenzimidazoles

Reduction of nitroindazoles and nitrobenzimidazoles was advantageously carried by reduction with hydrogen using 10% palladium on charcoal catalyst¹⁰). An apparatus similar to that described by VOGEL¹¹) was used. The flask was evacuated and filled with hydrogen several times. The nitro compounds were reduced in alcoholic solutions and after reduction has been completed, the solutions were filtered off and concentrated under reduced pressure.

2-Ethyl-5-aminoindazole (V)

It is prepared from 2-ethyl-5-nitroindazole (10 g.), ethyl alcohol (600 ml.) and palladium on charcoal catalyst (1 g.). It was crystallized from light petrol (70–80°) in brownish-yellow needles, m. p. 99–100°, yield 70%. Found: C 67.04; H 6.82; N 25.81. $C_9H_{11}N_3$ requires C 67.08; H 6.83; N 26.09%. (V) is readily soluble in ethyl alcohol, acetic acid, ether and benzene, but sparingly soluble in petroleum ether.

5-(2',4'-Dinitroanilino-) indazole (VI–VIIa, b)

General method of preparation: Aminoindazole (0.8 g.), 1-chloro-2,4-dinitrobenzene (1.1 g.) in the least amount of ethyl alcohol and 0.3 g. of anhydrous sodium acetate were refluxed for ca. 20 minutes on a water-bath. The dinitroanilino indazole derivatives separated out usually as crystalline products.

5-(2',4'-Dinitroanilino-) indazole (VI)

5-(2',4'-Dinitroanilino-) indazole (VI) was prepared from 5-aminoindazole and 1-chloro-2,4-dinitrobenzene. It was crystallized from ethyl alcohol or acetic acid in orange crystals,

¹⁰) R. MOZINGO, *Org. Synth.* **26**, 77 (1948).

¹¹) A. I. VOGEL, *Text Book of Practical Organic Chemistry Including Quantitative Organic Analysis*, Longmans, Green and Co., New York 1948, p. 459.

m. p. 250°, yield 74%. Found: C 52.14; H 3.21; N 23.44. $C_{13}H_9O_4N_5$ requires C 52.17; H 3.01; N 23.40%. (VI) is readily soluble in ethyl alcohol, acetic acid, but sparingly soluble in benzene and light petrol. It gives a yellow-orange colour with concentrated sulphuric acid.

5-(2',4'-Dinitroanilino)-2-methylindazole (VIIa)

Similarly prepared from 2-methyl-5-aminoindazole and 1-chloro-2,4-dinitrobenzene. It was crystallized from ethyl alcohol in yellowish brown needles, m. p. 252°, yield 66%. Found: C 54.28; H 3.86; N 22.25. $C_{14}H_{11}O_4N_5$ requires C 53.67; H 3.51; N 22.36%. (VIIa) is soluble in ethyl alcohol, acetic acid, hot benzene, but sparingly soluble in light petrol. It gives a yellow-orange colour with concentrated sulphuric acid.

5-(2',4'-Dinitroanilino) 2-ethylindazole (VIIb)

(VIIb) was prepared from 2-ethyl-5-aminoindazole and 1-chloro-2,4-dinitrobenzene. It was crystallized from ethyl alcohol in golden yellow needles, m. p. 190–191°, yield 60%. Found: C 54.31; H 4.10; N 21.76. $C_{15}H_{13}O_4N_5$ requires C 55.0; H 3.97; N 21.40%. (VIIb) is soluble in ethyl alcohol, acetic acid, hot benzene, sparingly soluble in petroleum ether. It gives a golden yellow colour with concentrated sulphuric acid.

5-(2'-Amino-4'-nitroanilino-) indazole (VIII)

A freshly prepared concentrated solution of sodium sulphide (prepared from 2 g. sodium hydroxide saturated with hydrogen sulphide) was added gradually with shaking to 5-(2',4'-dinitroanilino-) indazole (5 g.) in ethyl alcohol. The colour of the solution changed gradually from orange to red. The heating was then continued for two hours, at the end of this period it was filtered and concentrated. On addition of water a red precipitate was formed (3 g.). The latter was crystallized from dilute ethyl alcohol, in red brown crystals, m. p. 215–216°. Found: N 26.19. $C_{13}H_{11}O_2N_5$ requires N 26.02%. (VIII) is soluble in ethyl alcohol, acetic acid, but sparingly soluble in ether, benzene, and light petrol. It gives a brown colour with concentrated sulphuric acid.

5-(5'-Nitro-1-benzotriazolyl-) indazole (IX)

5-(2'-amino-4'-nitroanilino-) indazole (2 g.) was diazotised with nitrous acid (0.5 g. sodium nitrite), the pale yellow precipitate that separated (0.9 g.) was crystallized from ethyl alcohol in pale yellow crystals, m. p. 301–303°. Found: C 55.14; H 3.01; N 30.1. $C_{13}H_8O_2N_6$ requires C 55.71; H 2.86; N 30.0%. (IX) is sparingly soluble in ethyl alcohol, acetic acid, and nearly insoluble in benzene, light petrol and ether.

3-Hydroxy-N-(5'-indazolyl)-2-naphthamides (Xa, b) and 3-Hydroxy-N-(5'-benzimidazolyl)-2-naphthalamides (XIa–d)

Preparation of these compounds is exemplified by the preparation of 3-Hydroxy-N-(2'-methyl-5'-indazolyl)-2-naphthamide (Xa):

To a solution of 2-methyl-5-aminoindazole (0.01 mole) in xylene, 3-hydroxy-2-naphthoyl chloride (0.01 mole) was added and the mixture boiled for one hour. The precipitated product was filtered off, and washed with hot water to remove all traces of the unreacted

amine. Removal of any trace of 3-hydroxy-2-naphthoic acid formed by hydrolysis, was effected by suspending the precipitate in a sodium carbonate solution and boiling. After another washing with water, the product was crystallized from benzene and then from ethyl alcohol to give colourless crystals, m. p. 254°, yield 66%. Found: C 72.02; H 4.80; N 13.46. $C_{19}H_{15}O_2N_3$ requires C 71.92; H 4.73; N 13.24%.

3-Hydroxy-N-(2'-methyl-5'-indazolyl)-2-naphthamide is insoluble in water but soluble in ethyl alcohol and sodium hydroxide solution giving a yellow colour. It gives a yellow colour with concentrated sulphuric acid.

3-Hydroxy-N-(2'-ethyl-5'-indazolyl)-2-naphthamide (Xb)

It was prepared similarly from 2-ethyl-5-aminoindazole (V) and 2-hydroxy-3-naphthoyl chloride. It crystallized from ethyl alcohol in colourless crystals, m. p. 225°, yield 70%. Found: C 72.23; H 5.40; N 12.63. $C_{20}H_{17}O_2N_3$ requires C 72.50; H 5.13; N 12.68%.

(Xb) is insoluble in water, but readily soluble in ethyl alcohol and sodium hydroxide solution with a yellow colour. It gives a yellow colour with concentrated sulphuric acid.

3-Hydroxy-N-(5'-benzimidazolyl)-2-naphthamides (XIa—d)

These four compounds were prepared in a similar manner to (Xa) except that chloroform was used instead of xylene as a reaction medium. After removal of the unreacted amines and 3-hydroxy-2-naphthoic acid as described above, the precipitates were dissolved in dilute sodium hydroxide solution (5%) containing little alcohol, and the solutions treated with animal charcoal, filtered and acidified with dilute HCl.

3-Hydroxy-N-(5'-benzimidazolyl)-2-naphthamide (XIa)

(XIa) was prepared from 5-aminobenzimidazole and 3-hydroxy-2-naphthoyl chloride. It was crystallized from acetic acid in colourless crystals, m. p. 291° (decomp.). Yield 76%. Found: C 71.06; H 4.20; N 3.41. $C_{18}H_{13}O_2N_3$ requires C 71.27; H 4.32; N 13.85%. (XIa) is insoluble in water and benzene, sparingly soluble in ethyl alcohol but easily soluble in acetic acid. It dissolves in both concentrated sulphuric acid and sodium hydroxide solution giving yellow colours.

3-Hydroxy-N-(2'-methyl-5'-benzimidazolyl)-2-naphthamide (XIb)

From 5-amino-2-methylbenzimidazole and 3-hydroxy-2-naphthoyl chloride. It was crystallized from acetic acid or dilute ethyl alcohol in colourless crystals, m. p. 305° (charring). Yield 79%. Found: C 71.57; H 4.85; N 13.52. $C_{19}H_{15}O_2N_3$ requires C 71.92; H 4.73; N 13.24%. (XIb) is insoluble in water, chloroform and benzene, but soluble in acetic and ethyl alcohol. It dissolves in both concentrated sulphuric acid and sodium hydroxide solution giving yellow colours.

3-Hydroxy-N-(1'-methyl-5'-benzimidazolyl)-2-naphthamide (XIc)

From 5-amino-1-methylbenzimidazole and 3-hydroxy-2-naphthoyl chloride. It was crystallized from ethyl alcohol as colourless crystals. m. p. 237°. Yield 85%. Found:

C 71.54; H 4.53; N 13.74. $C_{16}H_{15}O_2N_3$ requires C 71.90; H 4.76; N 13.24%. (XIc) was found to be insoluble in water, benzene, and chloroform, but soluble in acetic acid and ethyl alcohol. It dissolves in concentrated sulphuric acid giving a yellow solution. It is partially soluble in sodium hydroxide solution.

3-Hydroxy-N-(1',2'-dimethyl-5'-benzimidazolyl)-2-naphthamide (XI d)

From 5-amino-1,2-dimethylbenzimidazole and 3-hydroxy-2-naphthoyl chloride. It was crystallized from acetic acid as colourless crystals. m. p. 282° (decomp.). Yield 85%. Found: C 72.42; H 5.18; N 12.69. $C_{20}H_{17}O_2N_3$ requires C 72.30; H 5.10; N 12.68%.

(XI d) is insoluble in water, chloroform, benzene and xylene, but soluble in ethyl alcohol and acetic acid. It is soluble in concentrated sulphuric acid and partially soluble in sodium hydroxide solution giving yellow solutions.

Acetacetamido-indazoles and benzimidazoles

These derivatives were prepared by heating together equimolecular quantities of the corresponding amines and freshly distilled ethyl acetoacetate in an open vessel for 15 minutes at 160° (internal temperature). The reaction mixture was then left to cool down to room temperature. The acetacetamido derivatives were usually obtained as oily products which solidify on crystallisation.

5-Acetacetamidoindazole

Prepared from 5-aminoindazole (0.01 mole) and ethylacetoacetate (0.01 mole). It was obtained as colourless crystals, by crystallisation from ethyl alcohol-benzene (charcoal); m. p. 184° (decomp.), yield 40%. Found: C 60.39; H 5.18; N 19.25. $C_{11}H_{11}O_2N_3$ requires C 60.83; H 5.07; N 19.36%.

It is insoluble in water, soluble in ethyl alcohol and in sodium hydroxide solution giving a faint orange solution.

6-Acetacetamidoindazole

Similarly prepared from 6-aminoindazole and ethylacetoacetate. It was obtained as colourless crystals, by crystallisation from ethyl alcohol, m. p. 211° (decomp.). Yield 60%. Found: C 60.57; H 5.19; N 19.27. $C_{11}H_{11}O_2N_3$ requires C 60.83; H 5.07; N 19.36%.

It is insoluble in water, soluble in ethyl alcohol and in sodium hydroxide solution giving a yellow solution.

5-Acetacetamido-2-methylindazole

Similarly prepared from 2-methyl-5-aminoindazole and ethylacetoacetate. It was obtained as colourless crystals, by crystallisation from benzene-light petrol. m. p. 130–131°. Yield 22%. Found: C 62.25; H 5.86; N 17.63. $C_{12}H_{13}O_2N_3$ requires C 62.33; H 5.65; N 18.18%.

It is soluble in water, ethyl alcohol and sodium hydroxide giving a colourless solution.

5-Acetacetamido-1,2,-dimethylbenzimidazole

Prepared from 5-amino-1,2-dimethylbenzimidazole and ethylacetoacetate. It crystallizes from chloroform in colourless crystals, m. p. 220°. Yield 30%. Found: C 63.31; H 6.02; N 17.35. $C_{13}H_{15}O_2N_3$ requires C 63.65; H 6.16; N 17.13%.

It is insoluble in water, benzene and ether but soluble in chloroform, ethyl alcohol and acetic acid. It dissolves in concentrated sulphuric acid giving a colourless solution.

Dokki, Cairo (UAR), Dyestuffs Unit, Textile Research Centre.

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