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HYDROXYPYRIDOCARBAZOLES

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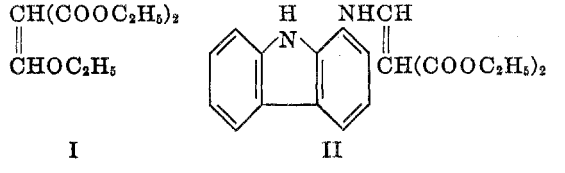
The condensation of ethoxymethylenemalonic ester with aromatic amines followed by cyclization of the resulting α-carbethoxy-β-arylaminoacrylates and decarbethoxylation is a general method for the synthesis of 4-hydroxyquinolines which was devised in 1939 (1). In attempts to synthesize pyridocarbazoles of the quinoline series we applied the ethoxymethylenemalonic ester synthesis to three aminocarbazoles. The hydroxypyridocarbazoles III and V or VI (R = X = H) were successfully obtained but elimination of the hydroxyl groups could not be accomplished.

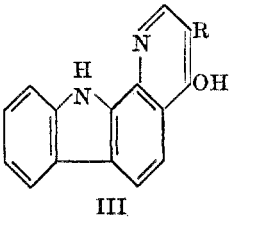
The nitration of carbazole (2) leads to a mixture of 1- and 3-nitrocarbazole with the latter predominating. Menon, Menon, and Peacock (3) reported that 9-*p*-toluenesulfonylcarbazole is nitrated in the 1-position exclusively and this appeared to be a good preparative method for 1-nitrocarbazole in view of the fact that 9-*p*-toluenesulfonylcarbazole is readily hydrogenolyzed to carbazole with lithium aluminum hydride. However, all attempts to nitrate N-*p*-toluenesulfonylcarbazole under the conditions reported were unsuccessful. In each case only the starting material was recovered.

The α-carbethoxy-β-carbazolylaminoacrylates (II and IV), which were obtained by warming 1- (4) and 3-aminocarbazole (5) with ethoxymethylenemalonic ester (I), were cyclized by heating under reflux in diphenyl ether. The resulting esters were hydrolyzed with aqueous alkali and the acids decarboxylated to the corresponding hydroxypyridocarbazoles. While ethyl α-carbethoxy-β-(1-carbazolylamino)acrylate (II) cyclizes to 3-carbethoxy-4-hydroxy-11*H*-

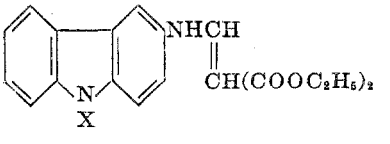


I

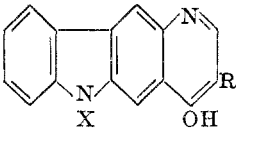
II



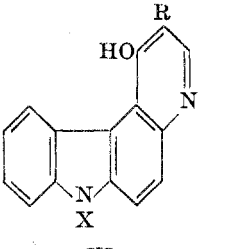
III



IV



V



VI

pyrido[2,3-*a*]carbazole (III) unambiguously, ethyl α-carbethoxy-β-(3-carbazolylamino)acrylate (IV, X = H) can theoretically undergo ring closure in two directions to form 3-carbethoxy-4-hydroxy-6*H*-pyrido[3,2-*b*]carbazole (V, R = —$COOC_2H_5$, X = H) and 1-hydroxy-2-carbethoxy-7*H*-pyrido[2,3-*c*]carbazole (VI, R = —$COOC_2H_5$, X = H). Actually only one compound was formed but all attempts to orientate it by conversion to the known 6*H*-pyrido[3,2-*b*]- or 7*H*-pyrido[2,3-*c*]-carbazole (6) were unsuccessful.

The decarbethoxylation of this compound to V or VI (R = X = H) followed by distillation with zinc dust in an inert atmosphere yielded no pyridocarbazole. The treatment of V or VI (R = X = H) with phosphorus oxychloride gave resinous material and no chloropyridocarbazole. Attempts to reduce V or VI (R = X = H) with sodium and amyl alcohol or hydrogen iodide and red phosphorus did not yield products which could be dehydrogenated to a pyridocarbazole. This hydroxypyridocarbazole (V or VI, R = X = H) remained unaltered after exposure to catalytic hydrogenation under a variety of conditions. This resistance of the hetero ring to hydrogenation has also been encountered in the case of other 4-hydroxyquinolines (1, 7).

In order to determine the influence of a blocking group in ethyl α-carbethoxy-β-(3-carbazolylamino)acrylate (IV, X = H) on the course of cyclization, 3-amino-9-*p*-toluenesulfonylcarbazole was condensed with I and the resulting acrylate (IV, X = *p*-$CH_3C_6H_4SO_2$—) cyclized. The product (V or VI) R = —$COOC_2H_5$, X = *p*-$CH_3C_6H_4SO_2$—) on alkaline hydrolysis followed by decarboxylation yielded the same hydroxypyridocarbazole (V or VI, R = X = H) as was obtained from 3-aminocarbazole by the same series of reactions. This shows that (IV, X = H) and its toluenesulfonyl derivative (IV, X = *p*-$CH_3C_6H_4SO_2$—) undergo cyclization in the same direction.

The authors are indebted to A. E. Ledingham and R. Mills for the microanalyses.

EXPERIMENTAL

3-Amino-9-p-toluenesulfonylcarbazole. To a suspension of 3-nitro-9-*p*-toluenesulfonylcarbazole (3) (7.0 g.) in ethyl acetate (125 cc.) and ethanol (50 cc.) was added Raney nickel catalyst (about 5 g.) and the reaction mixture was shaken under 40 lbs. of hydrogen pressure for 15 hours. The catalyst and solvent were removed by filtration and distillation respectively and the residue was crystallized from ethanol. The yield of white needles melting at 157–158° was 5.3 g. or 80%.

Anal. Calc'd for $C_{19}H_{16}N_2O_2S$: C, 67.86; H, 4.65; N, 8.34.
Found: C, 68.29, 67.49; H, 4.92, 4.75; N, 8.13.

The *hydrochloride* of this amine was only very sparingly soluble in water.

Ethyl α-carbethoxy-β-(1-carbazolylamino)acrylate (II). 1-Aminocarbazole (4) (3.0 g.) and ethoxymethylenemalonic ester (5 cc.) were heated on the steam-bath for one hour. The solid cake was pulverized, washed with methanol, and crystallized from ethyl acetate. The yield of yellow prisms melting at 229–230° was 4.5 g. or 82%.

Anal. Calc'd for $C_{20}H_{20}N_2O_4$: C, 68.18; H, 5.69; N, 7.95.
Found: C, 68.37; H, 5.46; N, 8.04.

Ethyl α-carbethoxy-β-(3-carbazolylamino)acrylate (IV, X = H) was prepared in the same manner as II. The yield of light tan crystals after crystallization from ethyl acetate was 95%, m.p. 183–184°.

Anal. Calc'd for $C_{20}H_{20}N_2O_4$: C, 68.18; H, 5.69.

Found: C, 68.09, 68.08; H, 5.73, 5.77.

Ethyl α-carbethoxy-β-(9-p-toluenesulfonyl-3-carbazolylamino)acrylate (IV, X = *p*-$CH_3C_6H_4SO_2$—). This was prepared in the same manner as II. The yield of white, needle-like crystals after crystallization from benzene containing a little ethanol was 90%, m.p. 165–166°.

Anal. Calc'd for $C_{27}H_{26}N_2O_6S$: C, 64.03; H, 5.14; N, 5.53.

Found: C, 64.07, 64.36; H, 4.95, 4.88; N, 5.71.

3-Carbethoxy-4-hydroxy-11H-pyrido[2,3-a]carbazole (III, R = —$COOC_2H_5$). Ethyl α-carbethoxy-β-(1-carbazolylamino)acrylate (II) (4.0 g.) was added to boiling diphenyl ether (75 cc.) and the reaction mixture was heated under reflux for one hour. The precipitated brown solid (3.5 g.) was filtered from the cooled reaction mixture, washed with methanol and crystallized from acetic acid to yield light tan crystals, m.p. 316–317° dec.

Anal. Calc'd for $C_{18}H_{14}N_2O_3$: C, 70.59; H, 4.57.

Found: C, 70.59; H, 4.88.

4-Hydroxy-11H-pyrido[2,3-a]carbazole (III, R = H). The crude 3-carbethoxy-4-hydroxy-11*H*-pyrido[2,3-a]carbazole (III, R = —$COOC_2H_5$) (2.5 g.) and 2 *N* sodium hydroxide (200 cc.) were heated under reflux for seven hours. The cooled reaction mixture was filtered and the filtrate added to excess dilute hydrochloric acid. This was brought to *p*H 7 by addition of sodium carbonate, then heated on the steam-bath in order to coagulate the gelatinous precipitate. The filtered and washed brown soild was heated at 280° in an atmosphere of nitrogen for one hour and then sublimed at 0.3 mm. The sublimate on crystallization from quinoline yielded light tan microscopic crystals (0.25 g.) m.p. 445–447°.

Anal. Calc'd for $C_{15}H_{10}N_2O$: C, 76.93; H, 4.27; N, 11.97.

Found: C, 77.27; H, 4.25; N, 11.80.

3-Carbethoxy-4-hydroxy-6-p-toluenesulfonyl-6H-pyrido[3,2-b]carbazole (V, R = —$COOC_2H_5$, X = *p*-$CH_3C_6H_4SO_2$—) *or 2-carbethoxy-1-hydroxy-7-p-toluenesulfonyl-7H-pyrido[2,3-c]carbazole* (VI, R = —$COOC_2H_5$, X = *p*-$CH_3C_6H_4SO_2$—) was prepared from ethyl α-carbethoxy-β-(9-*p*-toluenesulfonyl-3-carbazolylamino)acrylate (IV, X = *p*-$CH_3C_6H_4SO_2$) in the same manner as was III (R = —$COOC_2H_5$) (see above). The yield of white needles after crystallization from pyridine was 75%, m.p. 257–260°.

Anal. Calc'd for $C_{25}H_{20}N_2O_5S$: C, 65.22; H, 4.35; N, 6.09.

Found: C, 65.31, 65.07; H, 4.49, 4.68; N, 6.22.

4-Hydroxy-6H-pyrido[3,2-b]carbazole (V, R = X = H) *or 1-hydroxy-7H-pyrido[2,3-c]carbazole* (VI, R = X = H). (*a*). *From ethyl α-carbethoxy-β-(3-carbazolylamino) acrylate* (IV, X = H). This acrylate was cyclized and the resulting crude pyridocarbazole (V or VI, R = —$COOC_2H_5$, X = H) was decarbethoxylated in the same way as described in the preparation of III (R = H). The yield of yellow prisms of the hydroxypyridocarbazole after crystallization from ethanol was 55%, m.p. 301–303°.

Anal. Calc'd for $C_{15}H_{10}N_2O$: C, 76.93; H, 4.27; N, 11.97.

Found: C, 76.62, 76.51; H, 4.42, 4.51; N, 11.74.

(*b*) *From 3-carbethoxy-4-hydroxy-6-p-toluenesulfonyl-6H-pyrido[3,2-b]carbazole* (V, R = —$COOC_2H_5$, X = *p*-$CH_3C_6H_4SO_2$—) *or 2-carbethoxy-1-hydroxy-7-p-toluenesulfonyl-7H-pyrido[2,3-c]carbazole* (VI, R = —$COOC_2H_5$, X = *p*-$CH_3C_6H_4SO_2$—). This compound was subjected to alkaline hydrolysis followed by decarboxylation under the same conditions as described for the preparation of III (R = H) above. The product melted at 300° alone or in admixture with that obtained in (*a*).

Hydrogenolysis of 9-p-toluenesulfonylcarbazole. A reaction mixture of lithium aluminum hydride (1.5 g.), tetrahydrofuran (50 cc.), and 9-*p*-toluenesulfonylcarbazole (3) (2.0 g.) was heated under reflux for 25 hours. The excess lithium aluminum hydride was decomposed with wet ether and the reaction mixture was washed with dilute hydrochloric acid, with water, and with dilute alkali. The organic solvent mixture was removed by distillation and the residue was crystallized from ethanol yielding white plates (0.90 g. or 90%) which melted at 243–245° alone or in admixture with carbazole. The alkali washings on acidification yileded a solid (0.7 g. or 90%) melting at 43–44°. *p*-Thiocresol melts at 44°.

SUMMARY

1. 4-Hydroxy-11*H*-pyrido[2,3-*a*]- and 4-hydroxy-6*H*-pyrido[3,2-*b*]- or 1-hydroxy-7*H*-pyrido[2,3-*c*]-carbazole have been prepared by means of the ethoxymethylenemalonic ester synthesis.

2. Attempts to dehydroxylate the latter compound by various methods in order to orientate it were not successful.

3. 3-Aminocarbazole and 3-amino-9-*p*-toluenesulfonylcarbazole yielded the same hydroxypyridocarbazole in the ethoxymethylenemalonic ester synthesis.

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