ACETALS OF LACTAMS AND ACID AMIDES.

60.* NOVEL APPROACH TO THE SYNTHESIS OF γ-CARBOLINES

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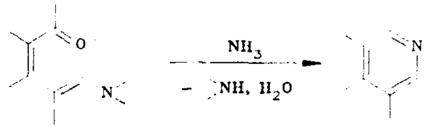
N-Alkylation of 2-methyl-5-nitroindole followed by the Vilsmeyer reaction has given some 2-methyl-3-formyl-5-nitro-N-alkylindoles, which on reaction with DMF diethyl acetal afford 2-(β-dimethylamino)vinylindoles. Heating the latter with ammonia provided a novel synthesis of γ-carbolines. Condensation of 1,2-dimethyl-3-formyl-5-nitroindole with dimethylacetamide diethyl acetal gave 2-dimethylamino-6-nitro-9-methylcarbazole.

Compounds which contain a dienaminocarbonyl grouping [2-4] constitute convenient five-carbon components for the construction of the pyridine ring, by reaction with ammonia or primary amines



For this reason, it was of interest to attempt to utilize for the synthesis of carbolines compounds in which the dienaminocarbonyl moiety was partially incorporated into an indole ring. The starting material selected for this study was 2-methyl-5-nitroindole (I) [5]. Vilsmeyer formylation of (I) afforded high yields of the 3-aldehyde (IIa), obtained earlier [6] in lower yields by nitration of 2-methyl-3-formylindole. N-Alkylation of the formylindole (IIa) with methyl or ethyl iodide in DMF in the presence of potassium carbonate proceeded smoothly to give near-quantitative yields of 1-methyl- (IIb) and 1-ethyl-2-methyl-5-nitro-3-formylindole (IIc). Compound (IIb), and the 1-benzyl derivative (IId), were also obtained by alkylating the indole (I) with methyl iodide (or dimethyl sulfate) or benzyl chloride followed by formylation of the resulting 1-methyl- and 1-benzyl-2-methyl-5-nitroindoles (IIIa, b). It is noteworthy that reaction of the N-unsubstituted indole (IIa) with dimethyl sulfate in acetone in the presence of caustic alkali results not only in N-methylation, but also condensation at the acetone methyl group to give 1,2-dimethyl-3-(β-acetyl)vinyl-5-nitroindole (IV). This compound (IV) was also obtained by heating (IIb) with acetone under the same conditions. The PMR spectrum of this compound in DMSO-D$_6$ showed signals at 2.37 (s, β-COCH$_3$), 2.62 (s, 2-CH$_3$), 3.82 (s, N–CH$_3$), 6.63 and 7.83 (two d, J = 12 Hz, vinyl), 8.68 (d, 4-H, J_{46} = 2.4 Hz), and 8.13 ppm (d.d, 6-H, J_{46} = 2.4, J_{67} = 9 Hz), thus proving the structure unambiguously.

The presence of two powerful electron-acceptor substituents (CHO and NO$_2$) in (IIa-d) results in activation of the 2-methyl group sufficient for it to condense with amide acetals. On heating (IIa) with DMF diethyl acetal (V), in addition to condensation N-ethylation occurred, with the formation of 1-ethyl-2-(β-dimethylamino)vinyl-3-formyl-5-nitroindole (VIc). The PMR spectrum of (VIc) in DMSO-D$_6$ showed signals at 1.27 and 4.27 ppm (t and q, N–CH$_2$CH$_3$), as well as signals at 3.04 (N–Me$_2$), 5.21 and 7.53 (two d, J = 13 Hz, vinyl fragment), 8.88 (d, 4-H, J_{46} = 2.5 Hz), 8.04 (d.d, 6-H, J_{46} = 2.5, J_{67} = 9 Hz), 7.6 (d, 7-H, J_{67} = 9 Hz), and 9.79 ppm (s, CHO). The same compound was obtained by condensing the 1-ethyl compound (IIc) with the acetal (V). So far as we are aware, this is the first reported instance of the N-alkylation of an indole with

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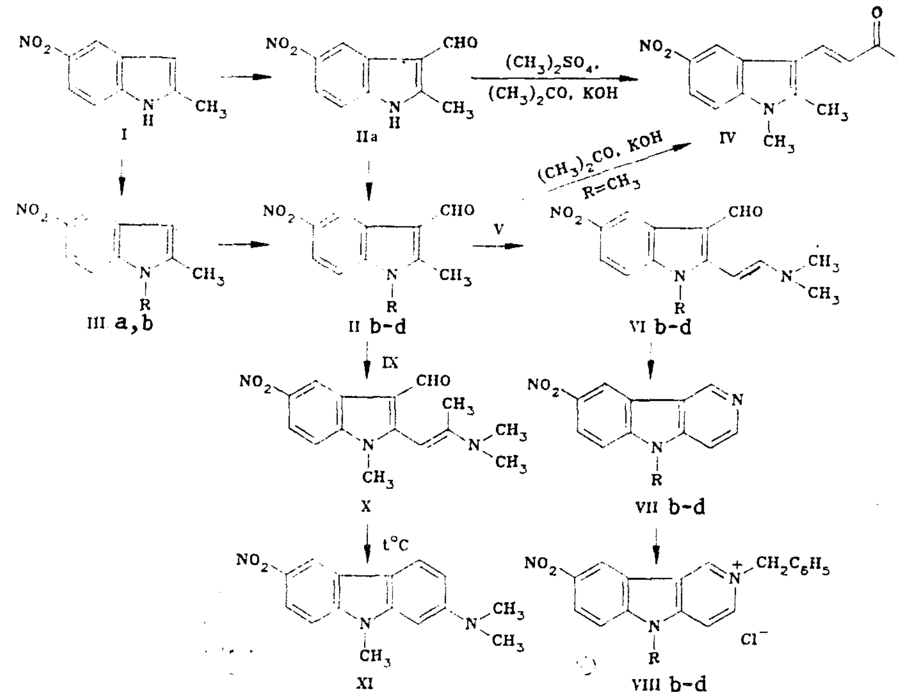
an amide acetal (other types of compounds, such as carboxylic acids, phenols, CH-acids, and pyrimidines are known to undergo alkylation [7]). Condensation of the acetal (V) at the 2-methyl group in (IIb, d) also proceeds with the formation of the enamines (VIb, d). Transamination of these compounds (VIb-d) by heating with ammonia resulted in pyridine cyclization to give good yields of the γ-carbolines (VIIb-d). The latter were readily and almost quantitatively benzylated with benzyl chloride to give the quaternary ammonium salts (VIIIb-d).

The possibilities opened up for heterocyclic synthesis consequent upon the preparation of the indole enaminoaldehydes (VI) are of course not restricted to the reactions described. In particular, the use of a homolog of acetal (V), namely dimethylacetamide diethyl acetal (IX), provided a novel approach to the synthesis of carbazoles. Brief heating of the indole (IIb) with the acetal (XI) in DMF gave the enamine (X), while prolonged reaction under these conditions resulted in cyclization to give 2-dimethylamino-6-nitro-9-methylcarbazole (XI). It is important to note that in the PMR spectrum of (X) (see Experimental), the signal for the α-vinyl proton is shifted to lower field by approximately 0.6 ppm as compared with the analogous signals for (VIb, c), evidently indicating steric hindrance to conjugation of the dimethylamino-group in the α-dimethylaminovinyl moiety in the enamine (X).



III a $R=CH_3$, b $R=CH_2C_6H_5$; II, VI, VII, VIII b $R=CH_3$, c $R=C_2H_5$, d $R=CH_2C_6H_5$

EXPERIMENTAL

PMR spectra were obtained on a Varian XL-200, internal standard TMS. The reactions were followed and the purity of the products checked by chromatography on Silufol UV-254 plates in the systems benzene–methanol (9:1), 2-propanol–ammonia–ethyl acetate (3:1:5), and chloroform–acetone (1:1), visualized in UV.

The elemental analyses and mass numbers of the compounds obtained were in agreement with the calculated values.

2-Methyl-3-formyl-5-nitroindole (IIa, $C_{10}H_8N_2O_3$). A solution of 3.2 g (185 mmoles) of the indole (I) in 20 ml of DMF was added dropwise with stirring and cooling to a mixture of 3 ml of phosphoryl chloride and 7.5 ml of DMF. The mixture was stirred for 30 min at 20°C and 1 h at 50°C, following which 50 g of ice and 40 ml of 30% aqueous NaOH were added, and the mixture heated to the boil and cooled. The solid which separated was filtered off, washed with water, and dried to give 3.56 g (96%) of the formylindole (IIa), mp 322-324°C (from alcohol) [6].

1,2-Dimethyl-3-formyl-5-nitroindole (IIb, $C_{11}H_{10}N_2O_3$). A mixture of 1 g (5 mmoles) of the formylindole (IIa), 2.8 g (20 mmoles) of methyl iodide, and 2.8 g of anhydrous potassium carbonate in 20 ml of DMF was heated for 3 h at 60°C, cooled, poured into water, and the solid filtered off, washed with water, and dried. The yield of (IIb) was 1.1 g (96%), mp 206-208°C (from alcohol). Compound (IIb) was obtained in 95% yield by formylating the indole (IIIa) as described in [6]. A mixed melting point of the compounds obtained gave no depression.

1-Ethyl-2-methyl-3-formyl-5-nitroindole (**IIc**, $C_{12}H_{12}N_2O_3$) was obtained by alkylating the indole (IIa) with ethyl iodide as for (IIb). Yield 94%, mp 199-201°C (from alcohol).

1-Benzyl-2-methyl-3-formyl-5-nitroindole (**IId**, $C_{17}H_{14}N_2O_3$) was obtained as in [6] by formylation of the indole (IIIb). Yield 92%, mp 182-185°C (from alcohol).

1,2-Dimethyl-5-nitroindole (**IIIa**, $C_{10}H_{10}N_2O_2$). **A.** To a solution of 5.28 g (30 mmoles) of the indole (I) in 50 ml of acetone was added with stirring at 20°C 50% aqueous potassium hydroxide (6.9 g in 10 ml of water), and the mixture stirred for 10 min, followed by the dropwise addition of 6 g (7 mmoles) of dimethyl sulfate. The mixture was stirred for 5 h at 20°C, poured into water, the solid filtered off, washed with water, and dried. The yield of the indole (IIIa) was 5.13 g (90%), mp 129-130°C (methanol–ethyl acetate, 5:1).

B. Compound (IIIa) was obtained in 86% yield by heating the indole (I) with methyl iodide in the presence of potassium carbonate in DMF at 60°C. The (IIIa) obtained gave no depression of melting point when mixed with a sample obtained by method **A**.

1-Benzyl-2-methyl-5-nitroindole (**IIIb**, $C_{16}H_{14}N_2O_2$). A mixture of 1.76 g (10 mmoles) of the indole (I), 2.52 g (20 mmoles) of benzyl chloride, and 5.6 g of potassium carbonate in 20 ml of DMF was boiled for 3 h. The mixture was cooled and poured into water, the solid filtered off, washed with water, and dried. The yield of the benzylindole (IIIb) was 2.13 g (82%), mp 156-158°C (from ethanol).

1,2-Dimethyl-3-(β-acetyl)vinyl-5-nitroindole (**IV**, $C_{14}H_{14}N_2O_3$). To a mixture of 6 g (30 mmoles) of (IIa) in 100 ml of acetone was added with stirring a solution of 26.4 g of potassium hydroxide in 330 ml of water, and the mixture stirred for 30 min. To the resulting solution was added over 40 min 26.4 g (20 ml) of dimethyl sulfate, and the mixture stirred for 6 h. The solid was filtered off, washed with water, and dried to give 5.7 g (75%) of (IV), mp 253-255°C (alcohol–DMF). The same compound was obtained in 74% yield by reacting (IIb) with acetone in aqueous KOH for 6 h at 40°C. A mixed melting point of the products obtained showed no depression.

1-Ethyl-2-(β-dimethylamino)vinyl-3-formyl-5-nitroindole (**VIc**, $C_{15}H_{17}N_3O_3$). A mixture of 1 g (5 mmoles) of (IIa) and 2 ml (15 mmoles) of the acetal (V) in 15 ml of DMF was boiled for 8 h. The product which separated on cooling was filtered off, washed with alcohol, and dried. The yield of (VIc) was 1 g (78%), mp 225-227°C (from alcohol–DMF). The same compound was obtained in 80% yield by reacting the indole (IIc) with the acetal (V). A mixed melting point of the products obtained showed no depression.

1-Methyl-2-(β-dimethylamino)vinyl-3-formyl-5-nitroindole (**VIb**, $C_{14}H_{15}N_3O_3$) was obtained in 78% yield by boiling the indole (IIb) with the acetal (V), mp 234-236°C (from alcohol–DMF).

1-Benzyl-2-(β-dimethylamino)vinyl-3-formyl-5-nitroindole (**VId**, $C_{20}H_{19}N_3O_3$) was obtained in 74% yield by boiling the indole (IId) with acetal (V), mp 183-185°C (from alcohol).

6-Nitro-9-methyl-γ-carboline (**VIIb**, $C_{12}H_9N_3O_2$). A mixture of 2.7 g (10 mmoles) of (VIb) and 60 ml of a saturated solution of ammonia in alcohol was heated in an autoclave for 5 h at 110-120°C. After cooling, the solid was filtered off, washed with 10 ml of alcohol, and dried to give 1.87 g (85%) of the carboline (VIIb), mp 193-195°C (from alcohol).

6-Nitro-9-ethyl- (**VIIc**, $C_{13}H_{11}N_3O_2$) **and 6-Nitro-9-benzyl-γ-carboline** (**VIId**, $C_{18}H_{13}N_3O_2$) were obtained as for (VIIb), from (VIc, d), in yields of 79 and 81%, mp 203-205°C (from alcohol–DMF) and 187-190°C (from alcohol), respectively.

Quaternary Salts of Carbolines (VIIb-d) with Benzyl Chloride (**VIIIb-d**, $C_{19}H_{16}ClN_3O_2$, $C_{20}H_{18}ClN_3O_2$, $C_{25}H_{20}ClN_3O_2$) were obtained by heating the carbolines (VIIb-d) with benzyl chloride in DMF at 100°C. The yields of salts (VIIIb-d) were 95-98%, mp >300°C (from DMF).

1-Methyl-2-(β-dimethylamino-β-methyl)vinyl-3-formyl-5-nitroindole (**X**, $C_{15}H_{17}N_3O_3$). A mixture of 1.1 g (5 mmoles) of (IIb) and 1.6 g (10 mmoles) of the acetal (IX) in 10 ml of DMF was boiled for 2.5 h. After cooling, the solid was filtered off, washed with 10 ml of alcohol, and dried to give 1.1 g (83%) of (X), mp 239-241°C (from DMF–alcohol). PMR spectrum (DMSO-D_6): 2.07 (3H, s, $=C-CH_3$), 3.06 [6H, s, $N(CH_3)_2$], 3.72 (3H, s, 1-CH_3), 7.55 (1H, d, 7-H, $J_{67} \approx 9$ Hz), 8.07 (1H, d.d, 6-H, $J_{68} \approx 9$, $J_{64} \approx 2$ Hz), 8.12 (1H, s, $C_{(2)}-CH=$), 8.92 (1H, d, 4-H, $J_{46} \approx 2$ Hz), 9.72 ppm (1H, s, CHO).

2-Dimethylamino-6-nitro-9-methylcarbazole (**XI**, $C_{15}H_{15}N_3O_2$). A mixture of 1.1 g (5 mmoles) of the indole (IIb) and 1.6 g (10 mmoles) of the acetal (IX) in 10 ml of DMF was boiled for 12 h. After cooling, the solid was filtered off, washed with 10 ml of alcohol, and dried to give 1 g (75%) of the carbazole (XI), mp 193-195°C (from alcohol).

The same compound was obtained in 80% yield by boiling (X) in DMF for 10 h. A mixed melting point of the carbazoles showed no depression.

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ACETALS OF LACTAMS AND ACID AMIDES.

61.* SYNTHESIS AND TRANSAMINATION OF INDOXYLS AND PYRROL-2-IN-4-ONES

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Reaction of N-acetylindoxyl and 2-methyl-3-ethoxycarbonylpyrrol-2-in-4-one with acetals of N,N-dimethylformamide and N-formylpiperidine has given the enaminoketones. Hydrolysis and transamination of these enaminoketones has been studied. The structures of the products were established by IR, PMR, and ^{13}C NMR spectroscopy.

A vigorously developing area of the chemistry of amide and lactam acetals is the study of their reactions with compounds with an active methylene group, and the heterocyclization of the resulting enamines [2-4]. In order to extend the range of uses of these reactions, it is necessary to use unconventional compounds containing the amide acetal groupings required for condensation. These include cyclic ketones, the enol forms of which are hydroxylated heteroaromatic systems. The aim of the present work was to examine the reactions of N-acetylindoxyl (I) and 2-methyl-3-ethoxycarbonylpyrrol-2-in-4-one (II) with N,N-DMF acetal (III) and N-formylpiperidine acetal (IV), and to examine the properties and reactions of the resulting enaminoketones, which are of interest as synthons for novel heterocyclization reactions.

Reaction of N-acetylindoxyl (I) with the acetal (III) in benzene was accompanied by side reactions, rendering isolation of the required enaminoketone [1-acetyl-2-dimethylaminomethyleneindolin-3-one (V)] extremely laborious [the isolated yield of (V) was ~20%]. Study of this reaction showed, however, that brief treatment of the reaction mixture with dilute HCl resulted in hydrolysis of the enaminoketone (V) to give 1-acetyl-2-formyl-3-hydroxyindole (VI), which was isolated in ~60% yield. In contrast to this, on reaction of the ketone (I) with the acetal (IV) there were no problems with the isolation of the product, and

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