Acyl Indoles. III (1). The Synthesis of [1,4]Diazepino[6,5-*b*]indoles

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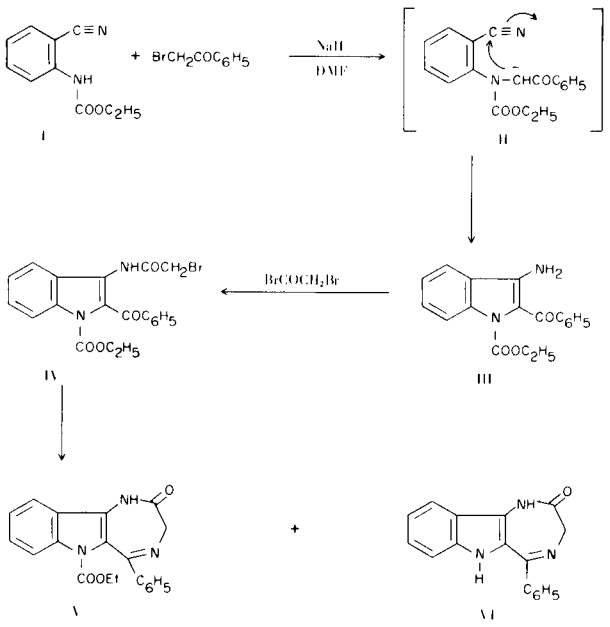
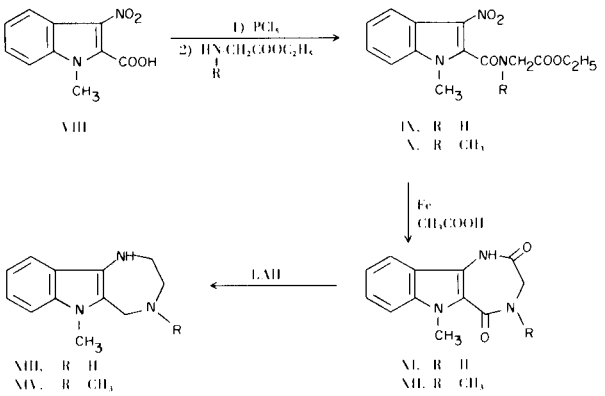
The synthesis of 1,3,4,6-tetrahydro-6-methyl-2*H*,5*H*-[1,4]diazepino[6,5-*b*]indole-2,5-diones and 5-phenyl-3,6-dihydro[1,4]diazepino[6,5-*b*]indole-2(1*H*)one is described. Also detailed is the preparation of a 3-amino-2-benzoylindole.

As a logical extension of our interest in 1,4-diazepines containing an indole moiety (2), we have prepared a series of 1,4-diazepino[6,5-*b*]indoles.

Our first objective in this area was a synthetic route to a 5-phenyl substituted [1,4]diazepino[6,5-*b*]indole-2-one. The obvious precursor for such a substance was the previously unknown 3-amino-2-benzoylindole (3). We have found that the requisite aminoketone can be readily prepared from anthranilonitrile. When *N*-carbethoxyanthranilonitrile (I) was treated with sodium hydride and phenacyl bromide in DMF (4) the aminobenzoylindole III was obtained in good yield. We propose that this cyclization occurs *via* an initial alkylation of the amide nitrogen followed by intramolecular addition of the methine carbanion II across the nitrile function to yield, after a final proton shift, compound III. In a straightforward fashion III was bromoacetylated to IV and this in turn was cyclized with ammonia to a mixture of diazepinones V and VI.



Also of interest to us was the synthesis of [1,4]-diazepino[6,5-*b*]indole-2,5-dione derivatives. Starting from 3-nitroindole-2-carboxylic acid (VII), we initially considered utilizing the now classical method of 1,4-diazepinedione synthesis, *i.e.* amine → bromoacetamido derivative → diazepinedione (5). However, catalytic reduction of VII gave an intractible, dark gum, which was obviously the result of autoxidation (6) of the desired amine. In view of this result, the synthesis was then approached by a method which involved reducing the nitro group at a stage whereby the resultant amine could be stabilized by formation of a cyclic amide. To this end, the more soluble *N*-methylindole derivative VIII was converted by reaction of its acid chloride with glycine ethyl ester and sarcosine ethyl ester to the corresponding indole-2-carboxamides IX and X, respectively. Treatment of IX and X with iron and acetic acid effected the desired dual sequence of reduction and cyclization to yield the diones XI and XII in 70 to 90% yields. Lithium aluminum hydride reduction of XI and XII gave the hexahydrodiazepines XIII and XIV (7).



EXPERIMENTAL

All melting points are corrected. Ir spectra were determined using a Beckman IR-9 spectrophotometer, mass spectra with a CEC 21-100 spectrometer and uv spectra, in 2-propanol, with a Cary Model 14 spectrophotometer.

3-Amino-2-benzoyl-1-carbethoxyindole (III).

To an ice-cooled, stirred solution of 38 g. (0.2 mole) of *N*-carbethoxy anthranilonitrile (I) in 400 ml. of DMF was added portionwise 8.4 g. (0.2 mole) of 57% sodium hydride. After stirring in ice for an additional 15 minutes, 40 g. (0.2 mole) of phenacyl bromide was added portionwise. The solution was stirred overnight at room temperature, poured into ice-water and extracted with ethyl acetate. The organic layer was separated, washed with brine and concentrated to yield a yellow solid. The solid was covered with 1800 ml. of ether, evaporated on the steam bath to *ca.* 1 l. and filtered while hot to remove suspended starting material. Further evaporation to *ca.* 600 ml. and cooling gave yellow crystals which were collected. The filtrate was treated with additional ether to a volume of 1 l., warmed and filtered while hot to remove additional starting material. Evaporation of the filtrate to *ca.* 500 ml. yielded more yellow crystals. The yellow crystals were combined to give 27.2 g. (44%) of III, m.p. 131-133°. Recrystallization from acetonitrile gave yellow prisms, m.p. 131-133°; ir (chloroform): 3490, 3350 cm^{-1} (-NH_2), 1725 cm^{-1} (-COOEt), 1625 (COϕ).

Anal. Calcd. for $C_{18}H_{16}N_2O_3$: C, 70.11; H, 5.23; N, 9.09. Found: C, 70.02; H, 5.19; N, 9.09.

2-Benzoyl-3-(2-bromoacetamido)-1-carbethoxyindole (IV).

To a stirred solution of 15.4 g. (0.05 mole) of III in 300 ml. of benzene was added dropwise 11.1 g. (0.055 mole) of bromoacetyl bromide. After heating under reflux for 3.5 hours, the mixture was cooled to room temperature and concentrated to a viscous oil. The oil was triturated successively with 150 ml. of ether and 75 ml. of ethanol to give IV as an off-white solid (16.5 g., 76%), m.p. 114-115°. Recrystallization from ethanol gave white rods, m.p. 115-116°.

Anal. Calcd. for $C_{20}H_{17}BrN_2O_4$: C, 55.96; H, 3.99; N, 6.52. Found: C, 55.91; H, 4.14; N, 6.37.

5-Phenyl-3,6-dihydro[1,4]diazepino[6,5-*b*]indole-2(1*H*)one (VI) and 6-Carbethoxy-5-phenyl-3,6-dihydro[1,4]diazepino[6,5-*b*]indole-2(1*H*)one (V).

A solution of 32 g. (0.075 mole) of IV in 400 ml. of dichloromethane was added dropwise to 400 ml. of liquid ammonia being stirred in a flask equipped with a dry ice-condenser. After stirring overnight to evaporate the excess ammonia, the suspension was filtered and the solid filter cake washed with dichloromethane. The filtered solid was then washed thoroughly with water and dried at 80° to give 10.7 g. of VI, m.p. 320-325° dec. Recrystallization from a large volume of THF gave white prisms, m.p. 320-322° dec.

Anal. Calcd. for $C_{17}H_{13}N_3O$: C, 74.16; H, 4.76; N, 15.26. Found: C, 74.18; H, 4.99; N, 15.11.

The dichloromethane filtrate was concentrated to small volume and adsorbed on Florisil. Elution with dichloromethane gave upon evaporation, an oily solid which was triturated with ethyl acetate to yield 0.8 g. of off-white crystals (9). Recrystallization from acetonitrile gave 6-carbethoxy-5-phenyl-3,6-dihydro[1,4]diazepino[6,5-*b*]indole-2(1*H*)one (V) as white plates, m.p. 254-255°; mass spectrum: molecular ion at 347.

Anal. Calcd. for $C_{20}H_{17}N_3O_3$: C, 69.15; H, 4.93; N, 12.10. Found: C, 69.45; H, 4.85; N, 12.40.

3-Nitroindole-2-carboxylic Acid (VII).

Seventy percent nitric acid (30 ml., 28.5 g., 0.45 mole) was added dropwise to 300 ml. of acetic anhydride with stirring at 25-30°. The mixture was then cooled in an ice-salt bath and 48.3 g. (0.3 mole) of indole-2-carboxylic acid was added at such a rate that the temperature never reached 15°. After stirring for an additional 15 minutes, the suspension was filtered and the filter cake washed with dichloromethane and air-dried. The yield of VII, a yellow solid, was 30.1 g. (49%), m.p. 225-230° (lit. (8), m.p. 225-233°).

1-Methyl-3-nitroindole-2-carboxylic Acid (VIII).

To a solution of 45.4 g. (0.22 mole) of VII in 440 ml. (0.44 mole) of *N* sodium hydroxide was added dropwise 27.8 g. (20.5 ml., 0.22 mole) of dimethyl sulfate. After stirring at room temperature for 30 minutes, the mixture was filtered to remove some insoluble material (discarded) and the filtrate treated with 3*N* hydrochloric acid until strongly acidic. The mixture was stirred until the orange gum crystallized and then filtered. After washing with water, the solid was recrystallized from ethyl acetate-petroleum ether to give VIII as yellow crystals, m.p. 179-181°.

Anal. Calcd. for $C_{10}H_8N_2O_4$: C, 54.55; H, 3.66; N, 12.72. Found: C, 54.50; H, 3.65; N, 12.59.

1-Methyl-3-nitro-*N*-carbethoxymethylindole-2-carboxamide (IX).

A mixture of 28.5 g. (0.12 mole) of 1-methyl-3-nitro-indole-2-carbonyl chloride (prepared by adding a slight excess of phosphorus pentachloride to a suspension of VIII in benzene and then, after stirring at room temperature for 1 hour, cooled and precipitated by adding petroleum ether), and 33.6 g. (0.24 mole) of glycine ethyl ester hydrochloride in 570 ml. of benzene was stirred and treated dropwise with 36.4 g. (0.36 mole) of triethylamine. After stirring at room temperature for 30 minutes, the benzene suspension was washed in succession with water, dilute hydrochloric acid, water, saturated sodium bicarbonate, and then dried over sodium sulfate. The residue remaining after evaporation of the solvent was stirred with a little ethyl acetate and filtered to give 15.5 g. (42.5%) of IX as tan prisms, m.p. 154-159°. Recrystallization from ethyl acetate-dichloromethane gave yellow prisms, m.p. 159-160°.

Anal. Calcd. for $C_{14}H_{15}N_3O_5$: C, 55.08; H, 4.95; N, 13.76. Found: C, 55.27; H, 4.77; N, 13.71.

N,1-Dimethyl-3-nitro-*N*-carbethoxymethylindole-2-carboxamide (X).

A solution of 19.5 g. (0.083 mole) of 1-methyl-3-nitroindole-2-carbonyl chloride (prepared as in the procedure for IX) in 400 ml. of benzene was treated with 10 g. (0.085 mole) of sarcosine ethyl ester in 85 ml. of benzene and then 8.4 g. (0.085 mole) of triethylamine was added dropwise with stirring. After an additional 30 minutes at room temperature, the mixture was washed successively with water, dilute hydrochloric acid, water, saturated sodium bicarbonate and water. After drying and removing the solvent, the residue was triturated with ether to yield X as an off-white solid (19 g., 72%), m.p. 158-160°. Recrystallization from ethyl acetate-petroleum ether gave off-white plates, m.p. 162-164°.

Anal. Calcd. for $C_{15}H_{17}N_3O_5$: C, 56.42; H, 5.36; N, 13.15. Found: C, 56.36; H, 5.47; N, 13.14.

1,3,4,6-Tetrahydro-4,6-dimethyl-2*H*,5*H*-[1,4]diazepino[6,5-*b*]indole-2,5-dione (XII).

In a 500 ml. 3-necked flask fitted with a thermometer, stirrer and condenser, protected by a Drierite drying tube, was placed

a solution of 14 g. (0.044 mole) of X in 70 ml. of glacial acetic acid. While stirring and being heated on the steam bath, 14 g. of iron powder was added in portions during 5 minutes. The temperature rose to 98° during this addition. After an additional 1.5 hours of heating (temperature dropped to 85°), 20 ml. of hot water was added and the stirring and heating continued for a further 15 minutes. After being cooled to room temperature, 150 ml. of water was added, and the mixture was extracted with dichloromethane, and then filtered to remove iron salts. The organic layer was then separated and washed with sodium bicarbonate. After drying, evaporation of the solvent gave a gum which solidified upon cooling. The solid was triturated with ether and filtered to yield 9.6 g. (89%) of XII, m.p. 208-210°. Recrystallization from ethyl acetate gave white prisms, m.p. 215-216°; uv max 210 nm (ϵ, 16,500), 239 (33,000), 290 (infl. 10,000), 300 (12,600), and 323 (7,200).

Anal. Calcd. for $C_{13}H_{13}N_3O_2$: C, 64.18; H, 5.39; N, 17.28. Found: C, 64.17; H, 5.72; N, 17.25.

1,3,4,6-Tetrahydro-6-methyl-2*H*,5*H*-[1,4]diazepino[6,5-*b*]indole-2,5-dione (XI).

A solution of 12.3 g. (0.04 mole) of IX in 125 ml. of acetic acid was treated with 12.3 g. of iron powder as in the preceeding experiment. After heating and adding 25 ml. of water, the mixture was filtered hot and the filtrate diluted with *ca.* 150 ml. of water, cooled in ice and filtered. The resultant tan solid was stirred with 25 ml. of methanol and filtered. After washing with some additional methanol, air drying gave 7.3 g. (79%) of XI as a beige solid, m.p. 278-284°. Recrystallization from acetonitrile-methanol-ether gave tan platelets, m.p. 284-286° dec.; uv max 237 nm (ϵ, 31,400), 290 (infl. 9,200), 300 (11,800), and 326 (7,000).

Anal. Calcd. for $C_{12}H_{11}N_3O_2$: C, 62.87; H, 4.84; N, 18.33. Found: C, 63.14; H, 4.83; N, 18.20.

4,6-Dimethyl-1,2,3,4,5,6-hexahydro[1,4]diazepino[6,5-*b*]indole Dihydrochloride 2/3 Hydrate (XIV).

Under an atmosphere of nitrogen, 4.7 g. (0.123 mole) of lithium aluminum hydride in 235 ml. of dry THF was stirred and treated portionwise with 10 g. (0.041 mole) of XII. After stirring at room temperature for 5 hours, the mixture was heated under reflux for 20 hours and then cooled in ice. The resultant suspension, after being hydrolyzed by the cautious addition of 8 ml. of water and 5 ml. of 20% sodium hydroxide solution, was then filtered immediately through a bed of Celite into a flask containing methanol previously saturated with hydrogen chloride. Evaporation of the solvent gave a red-brown solid which was treated twice with 50 ml. of ethanol and concentrated *in vacuo*. Filtration with the aid of ethanol gave 9.6 g. (81%) of XIV as beige crystals, m.p. 165-170° dec. The product was recrystallized by solution in hot methanol and dilution with ethyl acetate to give greenish crystals which when dried at 100° became beige in color, m.p. 165-170° dec.; mass spectrum, molecular ion at 215, very weak peak at 231.

Anal. Calcd. for $C_{13}H_{17}N_3 \cdot 2HCl \cdot 2/3H_2O$: C, 52.00; H, 6.66; N, 14.00. Found: C, 51.97; H, 6.80; N, 13.84.

6-Methyl-1,2,3,4,5,6-hexahydro[1,4]diazepino[6,5-*b*]indole Hydrochloride 2/3 Hydrate (XIII).

Using the same method employed for the preparation of XIV, a solution of 1.1 g. (5 mmoles) of XI in 30 ml. of THF was reduced with 0.6 g. (15 mmoles) of LAH. Ether was added to the THF-methanolic hydrogen chloride mixture to complete precipitation of the product. Filtration gave 0.6 g. (45%) of XIII as a tan solid. Recrystallization from methanol-ether yielded tan needles, m.p. 160-200° dec.; mass spectrum: moelcular ion at 201, later scans show decomposition.

Anal. Calcd. for $C_{12}H_{15}N_3 \cdot HCl \cdot 2/3H_2O$: C, 57.60; H, 6.64; N, 16.80. Found: C, 58.05; H, 6.71; N, 16.92.

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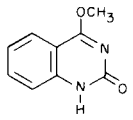

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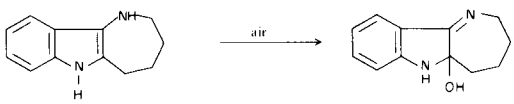
(5) For a review of 1,4-diazepinedione syntheses see: G. A. Archer and L. H. Sternbach, *Chem. Rev.*, 68, 764 (1968).

(6) For examples of the autoxidation of 3-aminoindoles see "The Chemistry of Indoles," R. J. Sundberg, Academic Press, New York, N. Y., 1970, p. 290.

(7) To avoid oxidation of these amines, V and VI were immediately converted to their hydrochlorides. The facile oxidation if ii → iii has been reported by J. B. Hester, Jr., *J. Org. Chem.*, 32, 3804 (1967).



ii iii

(8) W. E. Noland and K. R. Rush, *ibid.*, 31, 70 (1966).

(9) Further elution of the Florisil with ethyl acetate gave a mixture which could not be further separated.