# SYNTHESIS AND PROPERTIES OF NOVEL DIBENZ[b,f]AZOCINES

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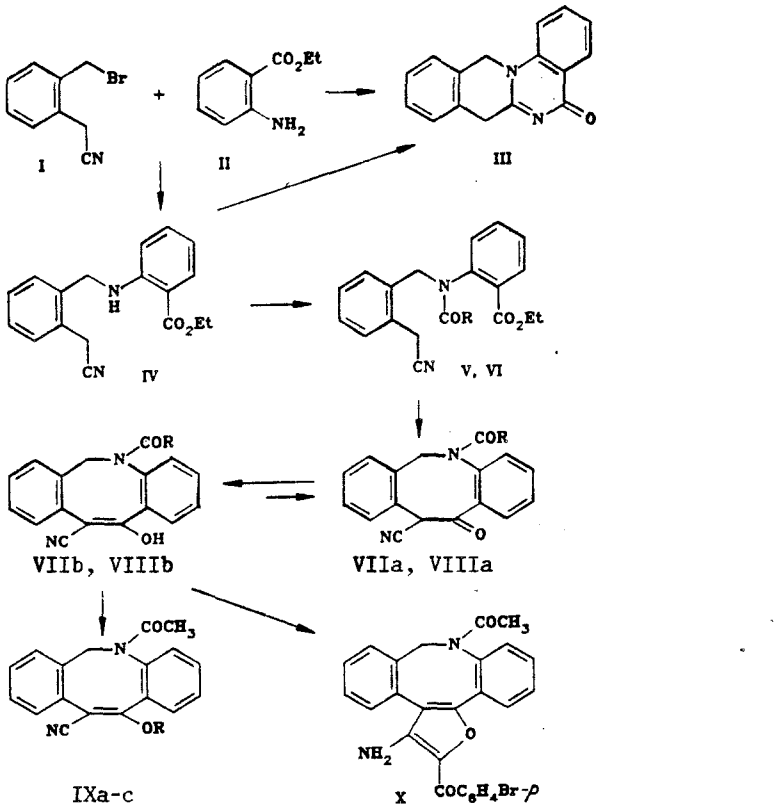
*5-Acetyl- and 5-trifluoroacetyl-12-hydroxy-11-cyano-5,6-dihydrodibenz[b,f]azocines have been synthesized by intramolecular cyclocondensation of ethyl N-acetyl and N-trifluoroacetyl-N-[1-(cyanomethyl)benzyl]-anthranilates. Spectral data show that the hydroxyl group in 5-acetyl-12-hydroxy-11-cyano-5,6-dihydrodibenz[b,f]azocine takes part in transannular hydrogen bond formation with the acetamide group carbonyl oxygen. A study of the chemical properties of this compound has shown that its alkylation by p, ω-dibromoacetophenone is accompanied by a Thorpe reaction to form 11-amino-5-acetyl-12-(p-bromo-benzoyl)-5,6-dihydro[b,f]dibenzofuro[2,3-d]azocine.*

We have previously shown [1] that the reaction of o-(bromomethyl)phenylacetonitrile (I) with ethyl anthranilate (II) leads to formation of 7,12-dihydro-5H-isoquino[2,3-*a*]quinazolin-5-one (III). Subsequent studies of this reaction have shown that it can lead exclusively to ethyl N-[2-(cyanomethyl)benzyl]anthranilate (IV) in high yield when it is carried out in the presence of hydrogen bromide acceptors (the most suitable being sodium acetate). In this structure the presence of ester and activated




V, VII R=$CH_3$; VI, VIII R=$CF_3$; IX a R=$CH_3$, b R=$COOCH_3$, c R=$SO_2C_6H_4CH_3$-*p*

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TABLE 1. Spectral Characteristics for Dibenzazocines in VII-IX

| Compound | IR spectrum, ν, | | | PMR Spectra*[1] | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | C≡N | C=O | O–H | solvent | δ, ppm | | | | | $\delta_A-\delta_B$ | $T_K$, K*[4] |
| | | | | | 5-$COCH_3$ | 12-OR | 6-$H_2$*[2] | 6-$H_A$*[3] | 6-$H_B$*[3] | | |
| VII | 2200 | 1620 | 3100 | DMSO-$D_6$ | 1,71 | 12,19 | 4,74 | 5,08 | 4,41 | 0,67 | 360 |
| VIII | 2220 | 1690 | 3000 | DMSO-$D_6$ | — | 13,28 | 4,84 | — | — | — | — |
| | | | | $CDCl_3$ | — | — | — | 4,92 | 4,53 | 0,39 | — |
| IXa | 2210 | 1650 | — | DMSO-$D_6$ | 1,76 | 3,73 | 4,67 | 4,91 | 4,53 | 0,38 | 350 |
| | | | | $CDCl_3$ | 1,86 | 3,84 | — | 5,05 | 4,61 | 0,44 | — |
| IXb | 2220 | 1785 | — | DMSO-$D_6$ | 1,66 | 2,35 | 4,84 | 4,97 | 4,62 | 0,35 | 317 |
| | | 1650 | | $CDCl_3$ | 1,82 | 2,31 | 4,92 | 5,11 | 4,81 | 0,30 | 320 |
| IXc | 2220 | 1650 | — | DMSO-$D_6$ | 1,82 | 2,46 | 4,74 | — | — | — | — |
| | | | | $CDCl_3$ | 1,99 | 2,49 | 4,81 | 4,86 | 4,69 | 0,17 | 270 |

*[1]The aryl proton multiplets are hard to interpret and are not recorded.

*[2]The chemical shifts of 6-H are recorded at a temperature of rapid exchange (above the coalescence temperature.

*[3]The chemical shift for 6-H is given in the region of slow exchange (below the coalescence temperature).

*[4]$T_K$) coalescence temperature.

methylene groups in positions suitable for intramolecular condensation offers a route to synthesis of the dibenz[b,f]azocine heterocyclic system.* The proposed method shows promise in facilitating the preparation of substituted versions of this system. These are urgently needed in light of literature data on the biological activity of dibenzazocines [3].

A necessary condition for this synthesis is the protection of the secondary amino group in the aminonitrile IV, since an alternate intramolecular reaction can also occur involving the nitrile and amino groups, catalyzed by strong base. In fact, the behavior of IV in the presence of alkali metal alcoholates is ambiguous and even the action of an alcoholic solution of sodium methiodide on an alcoholic solution of IV, gives only a moderate yield of the isoquinoquinazolinone III among a complex product mixture (according to TLC data). As protecting groups we have used acetyl and trifluoroacetyl which can be readily introduced by use of acetyl chloride or trifluoroacetic anhydride on aminonitrile IV in the presence of sodium acetate. The products are the ethyl N-acetyl- and N-trifluoroacetyl-N-[2-(cyanomethyl)benzyl]anthranilates (V or VI) which undergo cyclization to the dibenz[b,f]azocines VII and VIII using potassium tert-butoxide in tert-butanol. Both of these compounds can exist in two tautomeric forms – the ketone (a) and enol (b). A choice between these can be made using IR and PMR spectra. Thus, the IR spectrum of VII shows absorption bands for the nitrile group at 2200 $cm^{-1}$, characteristic of conjugated nitriles [4], a hydroxyl group at 3100 $cm^{-1}$, and just one band in the carbonyl absorption region at 1620 $cm^{-1}$ (assigned to the acetamide $\nu_{C=O}$). The PMR spectrum of this compound shows no $sp^3$ hybridized methine proton which would be expected for the ketone form VIIa, but there is observed a broad signal for the hydroxyl proton at 12.19 ppm which exchanges with $D_2O$. Similar data (Table 1) are recorded for the trifluoroacetyl dibenzazocine VIII. Hence, the spectral data for VII and VIII show that, both in the solid state and in DMSO solution, these compounds exist as the 5-acetyl- and 5-trifluoroacetyl-12-hydroxy-11-cyano-5,6-dihydrodibenz[b,f]azocines (VIIb and VIIIb) (see scheme above).

The chemical properties of VII also confirm the enol structure. It does not take part in condensation with 2,4-dinitrophenylhydrazine in conditions even more stringent than those for obtaining the 2,4-dinitrophenylhydrazones of carbonyl compounds are used. By contrast it is readily alkylated, acetylated, and tosylated at the hydroxyl group by the corresponding agents. An alternative structure based on C-11 addition of the R group was excluded because of the inertness of IX to the 2,4-dinitrophenylhydrazine reagent, the characteristic conjugated nitrile band, and the absence of a ketonic carbonyl band in the IR spectra. A characteristic feature both of the 12-RO- and 12-hydroxy dibenzazocines VII-IX is the low conformational mobility

*See also our short communication [2].

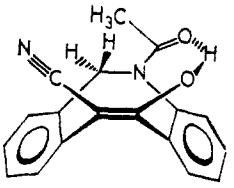

Fig. 1. Proposed transannular hydrogen bond in the preferred conformation of dibenzazocine VII.

of the azocine ring which gives rise to separate signals for the 6-H protons as an AB-spin system in the majority of cases (depending on the solvent used). Increasing the sample temperature leads to coalescence of these signals due to rapid inversion of the azocine ring on the NMR time scale. Where these coalescence temperatures occur in an experimentally convenient range they are reported in Table 1.

Alkylation of dibenzazocine VII with p, ω-dibromoacetophenone is accompanied by further Thorpe-type cyclization to give 11-amino-5-acetyl-12-(p-bromobenzoyl)-5,6-dihydro[b,f]dibenzofuro[2,3-d]azocine (X), which is a novel heterocyclic derivative. The presence of the tetracyclic system in the product is supported by the absence of nitrile group absorption in the IR spectrum and the presence of symmetric and asymmetric amino vibrations.

The position and nature of the hydroxyl group peaks in the IR and PMR spectra of dibenzazocine VII point to the existence of an intramolecular hydrogen bond, this being most unlikely in the linear 11-nitrile structure. A comparison of the position of the acetyl carbonyl group absorption bands in the IR spectra of V, VII, and IX suggests the occurrence of a transannular hydrogen bond with the carbonyl oxygen atom. It was shown that cyclization of acetamide V to dibenzocine VII gives a 40 $cm^{-1}$ shift of the carbonyl band to low frequency. More importantly, the position of this band is extremely sensitive to change of the hydroxyl group proton in VII to methyl, acetyl, or p-toluenesulfonyl. The result is a high-frequency shift of 30 $cm^{-1}$. An obvious consequence of establishing the transannular H-bond in the dibenzazocine VII is conformational fixing of the 5-acetyl group. Together with the low conformational mobility of the azocine ring, this leads to a large separation in chemical shift for the 6-H protons giving two doublets at 5.08 and 4.41 ppm with a geminal spin-spin coupling of 14 Hz. In compound IX, where the hydrogen bond is impossible, the chemical shift difference for these protons is approximately halved (entry $\delta_A$–$\delta_B$ in Table 1).

Analysis of a molecular model of the dibenzazocine VII shows the most stable conformation for the azocine ring to be a boat (Fig. 1). In spite of the loss of the conjugation of π-electrons in the double bond with the π-electron system of the benzene ring (because of the noncoplanar molecular structure), such a conformation is evidently preferred. In this conformation there are favored steric grounds for occurrence of the trans-annular hydrogen bond. A similar relationship might also be expected in the dibenzazocine VIII; however, the tendency of the carbonyl oxygen in the trifluoroacetyl group to take part in hydrogen bonding is expected to be less because of the large –I effect of the trifluoromethyl group (leading to a decrease in the excess negative charge on the oxygen atom). In fact, the carbonyl band is not changed in position from the precursor VI to the dibenzazocine VIII. However, the position of the broad hydroxyl signal at 13.28 ppm in the PMR spectrum of VIII does point to the presence of the hydrogen bond.

## EXPERIMENTAL

Melting points were determined on a Boetius heating block. IR spectra were taken for pressed KBr tablets on a Pye-Unicam SP3-300 instrument. PMR spectra were recorded on a Bruker WP-100 (100.13 MHz) instrument using TMS as internal standard. Chemical shifts were determined with an accuracy of 0.01 ppm and quoted on the δ scale. All newly synthesized materials were purified by recrystallization from 2-propanol. Elemental analytical data for C, H, Br, F, and N agreed with those calculated.

**Ethyl N-[2-(cyanomethyl)benzyl]anthranilate (IV, $C_{18}H_{18}N_2O_2$).** A mixture of o-(bromomethyl)phenylacetonitrile (16.8 g, 80 mmoles), ethyl anthranilate (13.8 g, 80 mmoles), and sodium acetate (19.4 g, 240 mmoles) in 2-propanol (150 ml) was refluxed for 1.5 h, filtered hot, and the precipitated salt washed on the filter with a small quantity of hot solvent. The combined, cooled filtrates gave colorless crystals which were filtered, washed with 2-propanol, and dried to give IV (17.7 g, 75%) with mp 96°C. IR spectrum: 3350 (N–H), 1675 (C=O), 2240 $cm^{-1}$ (C≡N). PMR spectrum ($CDCl_3$): 1.36 (3H, t, J = 7 Hz, $OCH_2CH_3$), 4.29 (2H, q, J = 7 Hz, $OCH_2CH_3$), 3.81 (2H, s, $CH_2CN$), 4.41 (2H, s, $CH_2N$), 6.5-8.0 ppm (8H, m, arom. protons).

**Ethyl N-acetyl-N-[2-(cyanomethyl)benzyl]anthranilate (V, $C_{20}H_{20}N_2O_3$).** A mixture of IV (14.3 g, 50 mmoles), acetyl chloride (13 ml, 150 mmoles), and sodium acetate (10.8 g, 150 mmoles) in dioxane (80 ml) was heated for

15 min, cooled, diluted with water to 300 ml, and the precipitate filtered and washed with water to give V (15.6 g, 92.5%) with mp 120°C. IR spectrum: 1660, 1720 (C=O), 2240 $cm^{-1}$ (C≡N). PMR spectrum (DMSO-$D_6$: 1.24 (3H, t, J = 7 Hz, $CH_2CH_3$), 1.73 (3H, s, $COCH_3$), 3.99 (2H, s, $CH_2CN$), 4.15 (2H, q, J = 7 Hz, $CH_2CH_3$), 4.50 and 5.11 (each 1H, J = 15 Hz, N-$CH_2$), 6.8-7.9 ppm (8H, m, arom. protons).

**Ethyl N-trifluoroacetyl-N-[2-(cyanomethyl)benzyl]anthranilate (VI, $C_{20}H_{18}F_3N_2O_3$)** was obtained similarly to V using trifluoroacetic anhydride as acylating agent and gave a yield of 86% with mp 103°C. IR spectrum: 1690, 1720 (C=O), 2250 $cm^{-1}$ (C≡N). PMR spectrum ($CDCl_3$): 1.34 (3H, t, J = 7 Hz, $CH_2CH_3$), 4.27 (2H, q, J = 7 Hz, $CH_2CH_3$), 3.76 (2H, s, $CH_2CN$), 4.51 and 5.42 (each 1H, d, J = 14 Hz, N–$CH_2$), 6.8-8.15 ppm (8H, m, arom. protons).

**5-Acetyl-12-hydroxy-11-cyano-5,6-dihydrodibenz[b,f]azocine (VII, $C_{18}H_{14}N_2O_2$).** The acetyl derivative V (13.45 g, 40 mmoles) was added to a solution of potassium tert-butoxide which had been prepared from potassium (4.7 g, 120 mmoles) in tert-butanol (50 ml). The mixture was refluxed for 1 h, cooled, diluted with water to 150 ml, neutralized with 2N HCl, and the precipitate filtered, washed with water and alcohol to give 8.45 g (73%) with mp 243°C.

**5-Trifluoroacetyl-12-hydroxy-11-cyano-5,6-dihydrodibenz[b,f]azocine (VIII, $C_{18}H_{11}F_3N_2O_3$)** was obtained similarly to VII from the trifluoroacetyl compound VI in 38% yield with mp 264°C.

**5-Acetyl-12-methoxy-11-cyano-5,6-dihydrodibenz[b,f]azocine (IX, $C_{19}H_{16}N_2O_2$).** A mixture of VII (0.58 g, 2 mmoles), dimethylsulfate (0.3 ml, 0.38 g, 3 mmoles), and potassium carbonate (1.1 g, 8 mmoles) in acetone (15 ml) was refluxed for 2 h, cooled, filtered, the filtrate evaporated on a rotary evaporator, and the residue treated with water. The solid product was filtered off and washed with water and alcohol to give 0.37 g (61%) with mp 243°C.

**5-Acetyl-12-acetoxy-11-cyano-5,6-dihydrodibenz[b,f]azocine IXb, $C_{20}H_{16}N_2O_3$)** was obtained similarly to V from dibenzazocine VII and acetyl chloride to give an 88% yield with mp 228°C.

**5-Acetyl-12-(p-tosyloxy)-11-cyano-5,6-dihydrodibenz[b,f]azocine (IXc, $C_{25}H_{20}N_2SO_4$)** was obtained similarly to V from VII and p-toluenesulfonyl chloride to give a 91% yield with mp 254°C.

**11-Amino-5-acetyl-12-(p-bromobenzoyl)-5,6-dihydro[b,f]dibenzofuro[2,3-d]azocine (X, $C_{26}H_{19}BrN_2O_3$).** A mixture of dibenzazocine VII (0.73 g, 2.5 mmoles), p, ω-dibromoacetophenone (0.7 g, 2.52 mmoles), and potassium carbonate (1.05 g, 7.5 mmoles) in acetone (30 ml) was refluxed for 10 h, the precipitated salt filtered off, washed on the filter with hot solvent, and the combined filtrate evaporated on a rotary evaporator. The residue was triturated with ethanol and the solid material filtered to give 0.28 g (23%) with mp 249°C. IR spectrum: 1620, 1660 (C=O), 3300, 3450 $cm^{-1}$ (N–H). PMR spectrum (DMSO-$D_6$): 1.43 (3H, s, $COCH_3$), 4.62 and 5.70 (each 1H, very broad doublet, J = 14 Hz, N-$CH_2$), 6.81 (2H, s, $NH_2$), 7.30-8.00 ppm (12H, m, arom. protons).

**Reaction of IV with Sodium Methoxide.** A solution of sodium methoxide (0.76 g, 15 mmoles) and IV (1.43 g, 5 mmoles) in methanol (20 ml) was heated for 2 h, the solvent evaporated on a rotary evaporator, the residue treated with water, and the solid filtered and recrystallized from 2-propanol. The product purity was monitored by TLC (Silufol plates, eluent benzene–ethanol, 9:1). After three recrystallizations just the isoquinoquinazolinone III was obtained (0.19 g, 15%). Its identity was confirmed by comparison with an authentic sample prepared directly from bromonitrile I and ethyl anthranilate [1]. Their spectral characteristics were in full agreement and there was no depression of melting point in a mixed sample.

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