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Synthesis and Cytostatic Activity of 4-Substituted Derivatives of Isoxazolyltriazenes

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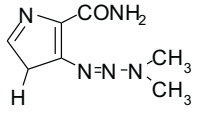
4-(3,3-Alkyltriazeno)-5-benzoylisoxazole-3-carboxamides hydrochloride **6a–h** and 7-benzoyl-3,4-dihydroisoxazolo[4,3-d]-[1,2,3]-triazyne-4-one **10** have been synthesized from 4-diazo-5-benzoylisoxazole-3-carboxamide chloride **5**. Some from the triazenes were examined for cytostatic activity in comparison with Dacarbazine.

Key words: triazenes, isoxazolo[4,3-d]-*v*-triazyne, 4-dialkylamino isoxazoles

Although triazenes were extensively studied prior to 1950 [1], and 5-triazenoimidazoles to 1970 [2], their versatility in organic synthesis has been greatly expanded during the next years. Triazenes are very useful in pharmacology, total synthesis, polymer technology and the construction of novel ring system [3]. A number of triazenes have been made and tested, particularly for antitumor activity [2,4]. The most of triazenes are prepared from the corresponding amines in the usual manner as 1-aryl-3,3-dialkyltriazenes [5–7]. Their biological activity derives from their ability to form methyl (alkyl) carbocation rather than diazonium salts, that can alkylate DNA [4,8]. Another class of triazenes, which show potent antitumor activity so 1,3-dialkyl-3-acyl triazenes [9], for example 1-(chloroethyl)-3-methyl-3-methylcarbamoyl)triazene shows cytotoxity against of leukemia and melanoma [10].

However, from all triazenes only Dacarbazine **1** 5-(3,3-dimethyl-1-triazenyl)-1H-imidazole-4-carboxamide (DTIC) is a clinically used triazene, and is active against L 1210 leukaemia and malignant melanoma [11]. The triazenes with ortho-carbalkoxy [12,13] or ortho-carboxamide [14–16] groups readily undergoe intramolecular cyclization in solution at the 7–14 pH range to give corresponding 1,2,3-triazines [17]. Dacarbazine and another 5-triazenoimidazole-4-carboxamides cyclize to 2-azahypoxanthine **2** {imidazo[4,5-d]-[1,2,3]-triazines} in basic solutions. The 2-azahypoxanthine have shown activity as inhibitors of neoplastic cells [18].



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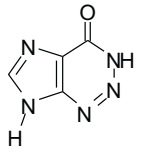

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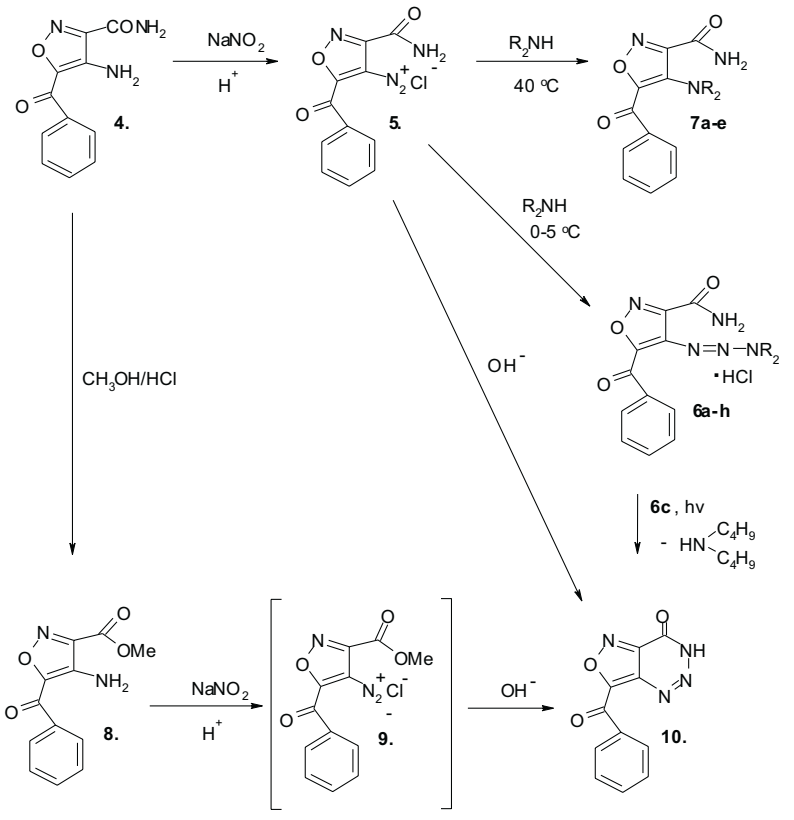
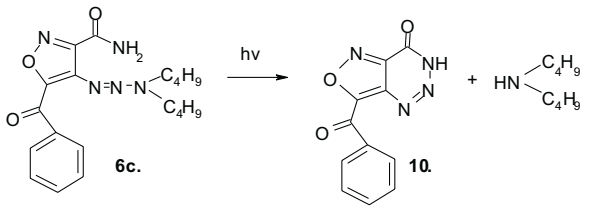
Numerous triazenes containing other heterocyclic systems pyrimidine [19], isoxazole [20] and carbazole [21], have been investigated. In this paper we report the synthesis of new analogues of Dacarbazin containing isoxazole ring instead of imidazole. The triazenes have been obtained from product of diazotization of 4-amino-5-benzoylisoxazole-3-carboxamide **4**. The diazonium salt **5** was isolated in 54% yield as a crystalline solid, which decomposes explosively at 132°C, gives a positive Bratton-Marshall test (indicative of an aromatic diazonium group by colour coupling reaction with N-(1-naphtyl)ethylenediamine) [22]. The diazonium salt **5** can be stored in a refrigerator under anhydrous conditions for long of time. Compound **5** reacts with dialkylamines to form 1,1-dialkyl-3-aryltriazenes **6a–h**. Analogously reacted cyclic amines and mono alkylamines.

Scheme 1



a	b	c	d	e	f	g	h
$-NMe_2$	$-NEt_2$	$-NBu_2$	$-N(CH_2CH_2)_2O$	$-N(CH_2CH_2)_2NMe$	$-NHCH_2CH_2NMe_2$	$-NH-N(CH_2CH_2)_2O$	$-NH-NMe_2$

These reactions were conducted at 0–5°C in anhydrous methanol in the absence of light. The same reactions carried out at above 40°C evolved nitrogen and led to the 4-dialkylaminoisoxazoles **7a–e**. Diazonium salt (**5**) was readily converted by 1N aqueous ammonia into isoxazolo[4,3-d]-1,2,3-triazine-4-one **10** in 83% yield. Compound **10** was prepared also from methyl 4-amino-5-benzoylisoxazole-3-carboxylate **8** after diazotization and reaction with 1N aqueous ammonia. Solution of triazenes hydrochloride in ethanol were stable in absence of light for at least forty-eight hours. Exposition of solution of **6c** to ambient light for two days resulted in the formation of compound **10** in 32% yield**.**



Compounds **6a** and **6c** were assayed about their antitumor activity.

Biological activity. The synthesized compounds **6a** and **6c** were screened for their cytostatic activity on mouse P-388 leukemia cell lines with the reference drug, Dacarbazin. In conclusion, the results obtained on P-388 leukemia cells show that the activity of compounds **6a** and **6c** in the dose 25 mg/kg and 50 mg/kg respectively is similar to Dacarbazine (25 mg/kg and 50 mg/kg).

EXPERIMENTAL

Melting points were determined with a Digital Melting Point Apparatus Electrothermal IA 9100. ^{1}H NMR spectra were recorded in $CDCl_3$ and DMSO on a Bruker DRX 300 spectrometer: ^{1}H NMR (300 MHz). Chemical shifts (δ) are given in ppm relative to TMS. IR spectra were recorded on a Specord M80 spectrometer (KBr discs). Mass spectra were recorded on a Finnigan MAT 95. Elemental analyses were performed on a Carbo Erba NA 1500 analyzer.

4-Diazo-5-benzoylisoxazole-3-carboxamide chloride (5). A stirred solution of 8.3 g (0.12 mole) of sodium nitrite in 60 ml of water was maintained at 0–5°C while a solution of 23.1 g (0.1 mole) of 4-amino-5-benzoylisoxazole-3-carboxamide (**4**) [23] in 150 ml THF and 23.5 ml conc. hydrochloric acid was introduced in small portions and diazotized to a starch-iodide end-point. Stirring was continued for one hour. Then organic layer was separated, concentrated to 50 ml under reduced pressure at room temperature, and chilled. The precipitated product was collected by filtration, washed with a solvent and dried in vacuo over phosphorus pentoxide. The precipitate of faintly yellow needles amounted to a yield of 75%. A sample of the diazo **5** that have been recrystallized from methanol-ether was submitted for analysis. The compound **5** gave a positive Bratton-Marshall test [22], decomposed explosively near 132°C, and produced a diazo absorption band at 2090 cm^{-1}. Anal. Calcd. For $C_{11}H_7N_4O_3Cl$ (278.65): C, 47.41; H, 2.53; N, 20.11. Found: C, 47.23; H, 2.42; N, 19.95. IR (KBr): ν 3200, 3100 ($CONH_2$), 2090 ($-N_2^+Cl^-$), 1695, 1660 (C=O), 1600 (C=N), 700 cm^{-1} (Ar^-).

Preparation of hydrochlorides of 4-substituted-triazeno-5-benzoylisoxazole-3-carboxamides (6a–h). Into a stirred, cooled (0°C) solution of 2.8 g (10 mmoles) of 4-diazo-5-benzoylisoxazole-3-carboxamide chloride (**5**) in 20 ml of anhydrous methanol were introduced dropwise 9 mmoles of corresponding anhydrous amine in 5 ml anhydrous methanol. The reaction mixture was kept under nitrogen

and was protected from atmospheric moisture. A crystalline precipitate began to form after a fifteen minutes. The reaction mixture was stirred and cooled for 2 h. The crystalline product was collected by filtration, washed with cold methanol and dried. During all operations involved in the preparation purification and recrystallization of hydrochlorides of the triazenes, they were protected from light as much as possible by wrapping the reaction flasks, filter funnels, or other equipment used to contain the triazenes with aluminium foil. The following compounds were obtained:

4-(3,3-Dimethyltriazeno)-5-benzoylisoxazole-3-carboxamide hydrochloride (6a). Yield 35%. Dark yellow needles (anhydrous methanol) explosive decomposition 108°C. IR (KBr): ν 3200, 3100 ($CONH_2$), 2700 (NH^+), 1690, 1660 (C=O), 1530, 1430, 1270, 700 cm^{-1}. ^1H NMR: 2.35 (s, 6H, 2xCH_3), 7.05 (s, 1H, N^+H), 7.54 (d, 2H, $CONH_2$), 7.75–7.88 (m, 3H, ArH), 8.09–8.21 (m, 2H, ArH). Anal. Calcd. for $C_{13}H_{14}N_5O_3Cl$ (323.75); C, 48.23; H, 4.36; N, 21.63. Found C, 48.00; H, 4.2; N, 21.42.

4-(3,3-Diethyltriazeno)-5-benzoylisoxazole-3-carboxamide hydrochloride (6b). Yield 8%. Dark yellow needles (anhydrous methanol) explosive decomposition, 94.6°C. IR (KBr): ν 3200, 3100 ($CONH_2$), 2710 (N^+H), 1690, 1665 (C=O), 1530 ($CONH_2$), 1435, 1270, 700 cm^{-1}(ArH). ^1H NMR: 1.12 (t, J = 7.6, 6H, 2xCH_3), 2.93 (q, J = 7.6, 4H, 2xCH_2), 7.01 (s, 1H, N^+H), 7.56 (d, 2H, $CONH_2$), 7.73–7.91 (m, 3H, ArH), 8.11–8.21 (m, 2H, ArH). Anal. Calcd. for $C_{15}H_{18}N_5O_3Cl$ (351.79); C, 51.21; H, 5.16; N, 19.91. Found C, 51.32; H, 4.95; N, 20.1.

4-(3,3-Dibutyltriazeno)-5-benzoylisoxazole-3-carboxamide hydrochloride (6c). Yield 75%. Dark yellow prisms, (anhydrous methanol) m.p. 115–6°C dec. IR (KBr): ν 3205, 3105 ($CONH_2$), 2700 (N^+H), 1690, 1665 (C=O), 1530, 1420, 1270, 700 cm^{-1} (ArH). ^1H NMR: 0.92 (t, J = 7.6, 6H), 1.11–1.91 (m, 8H), 3.82 (t, J = 7.4, 4H), 7.02 (s, 1H, N^+H), 7.52 (d, 2H, $CONH_2$), 7.65–7.78 (m, 3H, ArH), 7.95–8.05 (m, 2H, ArH). Anal. Calcd. for $C_{19}H_{26}N_5O_3Cl$ (407.91); C, 55.94; H, 6.41; N, 17.17. Found C, 56.02; H, 6.28; N, 17.39.

4-Morpholinoazo-5-benzoylisoxazole-3-carboxamide hydrochloride (6d). Yield 43%. Yellow prisms, (anhydrous ethanol) m.p. 83–5°C dec. IR (KBr): ν 3200, 3100 ($CONH_2$), 2800 (N^+H), 1685, 1655 (C=O), 1530, 1290, 700 cm^{-1} (ArH). ^1H NMR: 2.58–2.92 (m, 4H), 3.61–3.83 (m, 4H), 7.03 (s, 1H, N^+H), 7.51 (2H, $CONH_2$), 7.73–7.89 (m, 3H, ArH), 7.94–8.13 (m, 2H, ArH). Anal. Calcd. for $C_{15}H_{16}N_5O_4Cl$ (365.78); C, 49.25; H, 4.49; N 19.14. Found C, 49.45; H, 4.34; N, 19.18.

4-(4-Methyl-1-piperazino)azo-5-benzoylisoxazole-3-carboxamide hydrochloride (6e). Yield 48%. Yellow prisms (anhydrous methanol), m.p. 154–5°C dec. IR (KBr): ν 3200, 3090 ($CONH_2$), 1680, 1660 (C=O), 1550, 1280, 700 cm^{-1} (ArH). ^1H NMR: 2.3 (s, 3H, CH_3), 2.6–2.8 (m, 4H), 3.5–3.8 (m, 4H), 7.12 (s, 1H, N^+H), 7.52 (d, 2H, $CONH_2$), 7.71–7.82 (m, 3H, ArH), 7.93–8.13 (m, 2H, ArH). Anal. Calcd. for $C_{16}H_{19}N_6O_3Cl$ (378.83); C, 50.72; H, 5.05: N, 22.18. Found C, 50.55; H, 5.15; N, 22.36.

4-β-Dimethylaminoethyltriazeno-5-benzoylisoxazole-3-carbamide hydrochloride (6f). Yield 36%. Dark yellow prisms (anhydrous methanol), m.p. 97–8°C dec. IR (Kbr): ν 3380 (NH), 3200, 3100 ($CONH_2$), 2700, 1685, 1655 (C=O), 1435, 1285, 700 cm^{-1} (ArH). ^1H NMR: 2.25 (s, 6H, 2xCH_3), 2.36 (t, 2H, CH_2), 2.93 (t, 2H, CH_2), 7.05 (s, 1H, N^+H), 7.61 (d, 2H, $CONH_2$), 7.70–7.81 (m, 3H, ArH), 7.94–8.12 (m, 2H, ArH). Anal. Calcd. for $C_{15}H_{19}N_6O_3Cl$ (366.81); C, 49.11; H, 5.22; N, 22.91. Found C, 48.92; H, 4.83; N, 22.70.

4-(4-Morpholino)triazeno-5-benzoylisoxazole-3-carboxamide hydrochloride (6g). Yield 38%. Dark yellow prisms (anhydrous methanol), m.p. 168–9°C dec. IR (KBr): ν 3400 (NH), 3200, 3080 ($CONH_2$), 2600, 1680, 1660 (C=O), 1530, 1430, 1270, 710 cm^{-1} (ArH). ^1H NMR: 2.91 (m, 4H), 3.72 (m, 4H), 7.15 (s, 1H, N^+H), 7.48–7.60 (m, 3H, ArH), 8.04–8.26 (m, 2H, ArH), 11.65 (s, 1H, NH). Anal. Calcd. for $C_{15}H_{17}N_6O_4Cl$ (380.79); C, 47.31; H, 4.50, N, 22.07. Found C, 47.09; H, 4.35; N, 22.27.

4-Dimethylaminotriazeno-5-benzoylisoxazole-3-carboxamide hydrochloride (6h). Yield 42%. Dark yellow needles (anhydrous ethanol), m.p. 68–9°C dec. IR (KBr): ν 3300 (NH), 3200, 3095 ($CONH_2$), 2760, 1690, 1660 (C=O), 1430, 1280, 700 cm^{-1} (ArH). ^1H NMR: 3.72 (s, 6H), 7.13 (1H, N^+H), 7.66–7.81 (m, 3H, ArH), 8.02–8.28 (m, 2H, ArH), 11.8 (s, 1H, NH). Anal. Calcd. for $C_{13}H_{15}N_6O_3Cl$ (338.76); C, 46.09; H, 4.46: N, 24.81. Found C, 45.92; H. 4.22; N, 24.72.

Procedures for preparation of 5-benzoyl-4-alkylaminoisoxazole-3-carboxamides (7a–e). To a warm (45°C) solution of 1.39 g (5 mmoles) of **5** in 10 ml of absolute methanol corresponding amine (12 mmoles) was added. The reaction mixture was stirred for one hour and then into 50 ml of water was poured. After cooling the suspension was filtered and the precipitate was filtered and washed with water.

Corresponding compounds were obtained:

5-Benzoyl-4-dimethylaminoisoxazole-3-carboxamide (7a). Yield 81%. Pale yellow needles (95% ethanol), m.p. 248–9°C. IR (KBr): ν 3210, 3100 ($CONH_2$), 1695, 1660 (C=O), 1530, 1550 (C=N), 1280, 700 cm^{-1} (ArH). ^{1}H NMR: 2.33 (s, 6H, 2xCH_3), 7.61 (d, 2H, $CONH_2$), 7.69–7.85 (m, 3H, ArH), 8.08–8.17 (m, 2H, ArH). EI MS: m/z (%) 259(M^+, 13), 244(10), 241(3), 231(5), 215(11), 182(4), 154(20), 138(3), 105(80), 77(32). Anal. Calcd. for $C_{13}H_{13}N_3O_3$ (259.27); C, 60.23; H, 5.05; N, 16.21. Found C, 59.98; H, 5.04; N, 16.3.

5-Benzoyl-4-diethylaminoisoxazole-3-carboxamide (7b). Yield 84%. Pale yellow needles (ethanol), m.p. 257–8°C. IR (KBr): ν 3230, 3085 ($CONH_2$), 1700, 1660 (C=O), 1530, 1350 (C–N), 1280, 710 cm^- (ArH). ^{1}H NMR: 1.53 (t, J = 7.6, 6H), 3.23 (q, J = 7.6, 4H), 7.52 (d, 2H, $CONH_2$), 7.68–7.82 (m, 3H, ArH), 8.06–8.15 (m, 2H, ArH). EI MS: m/z (%) 287(M^+, 9), 259(5), 258(8), 243(21), 210(12), 182(12), 166(3), 105(75), 77(28). Anal. Calcd. for $C_{15}H_{17}N_3O_3$ (287.32);C, 62.71; H, 5.96; N, 14.62. Found C, 62.78; H, 6.02; N, 14.78.

5-Benzoyl-4-dibutylaminoisoxazole-3-carboxamide (7c). Yield 78%. The ivory micro-crystalline product was recrystallized from n-propanol, m.p. 198–9°C. IR (KBr): ν 3220, 3085 ($CONH_2$), 1700, 1660 (C=O), 1520, 1340 (C–N), 1270, 710 cm^{-1} (ArH). ^{1}H NMR: 0.95 (t, J = 7.6, 6H), 1.21–1.82 (m, 8H), 3.82 (t, J = 7.4, 4H), 7.91 (d, 2H, $CONH_2$), 7.65–7.81 (m, 3H, ArH), 8.02–8.15 (m, 2H, ArH). EI MS: m/z (%) 343 (M^+, 10), 299(18), 286(8), 266(22), 238(20), 210(15), 105(65), 77(25). Anal. Calcd. for $C_{19}H_{25}N_3O_3$ (343.43); C, 66.45; H, 7.34; N, 12.24. Found C, 66.28; H, 7.15; N, 12.08.

5-Benzoyl-4-morpholinoisoxazole-3-carboxamide (7d). Yield 51%. Yellow needles (ethanol), m.p. 268–9°C. IR (KBr): ν 3200, 3100 ($CONH_2$), 1700, 1650 (C=O), 1270, 1120 (C–O–C), 700 cm^{-1} (ArH). ^{1}H NMR: 2.62–2.96 (m, 4H), 3.62–3.88 (m, 4H), 7.60 (d, 2H, $CONH_2$), 7.68–7.80 (m, 3H, ArH), 8.05–8.18 (m, 2H, ArH).). EI MS: m/z (%) 301 (M^+, 4), 273(25), 255(5), 215(3), 187(30), 153(10), 135(16), 116(10), 105(45), 77(24). Anal. Calcd. for $C_{15}H_{15}N_3O_4$ (301.30); C, 59.80; H, 5.02; N, 13.95. Found C, 59.61; H, 5.07: N, 13.76.

5-Benzoyl-4-(4-methyl-1-piperazin)isoxazole-3-carboxamide (7e). Yellow prisms (95% ethanol), m.p. 239–40°C. IR (KBr): ν 3200, 3150 ($CONH_2$), 1690 (CO), 1660, 700 cm^{-1} (ArH). ^{1}H NMR: 3.01 (s, 3H, CH_3), 3.05–3.21 (m, 4H, CH_2), 3.41–3.52 (m, 4H, CH_2), 7.52 (d, 2H, $CONH_2$), 7.66–7.83 (m, 3H, ArH). 7.8–9.05 (m, 2H, ArH). EI MS: m/z (%) 314 (M^+, 5), 286(25), 271(5), 242(3), 187(30), 181(5), 165(3), 105(20). Anal. Calcd. for $C_{16}H_{18}N_4O_3$ (314.35); C, 61.14; H, 5.77; N, 17.82. Found C, 61.28; H, 5.89; N, 17.64.

Methyl 4-amino-5-benzoylisoxazole-3-carboxylate (8). A solution of 4-amino-5-benzoylisoxazolo-3-carboxamide (**4**) (11.55 g, 50 mmoles) in 200 ml absolute methanol was heated to reflux and gaseous hydrogen chloride was bubbled into the solution for 3 h. Refluxing was continued for 30 h with more hydrogen chloride being added periodically during this period. After the methanol was removed by distillation, the residue was dissolved in 60 ml of water. The aqueous solution was neutralized by the careful addition of solid sodium bicarbonate and then the crystalline reaction product was filtered. After four recrystallizations from methanol and isopropanol the product formed yellow needles melting at 203–4°C (6.27 g, 51%). IR (KBr): ν 3490, 3360 (NH_2), 1715, 1660 (C=O), 700 cm^{-1} (Ar). ^{1}H NMR: 3.85 (s, 3H, CH_3), 6.32 (s, 2H, NH_2), 7.52–7.65 (m, 3H, ArH), 7.98–8.12 (m, 2H, ArH). Anal. Calcd. for $C_{12}H_{10}N_2O_4$ (246.21); C, 58.54; H, 4.09; N, 11.38. Found C, 58.61; H, 3.96; N, 11.22.

7-Benzoyl-3,4-dihydroisoxazolo[4,3-d]-1,2,3-triazine-4-one (10).

Method A. From compound **6c**. A solution of 1.02 g (2.5 mmoles) of the 4-(dibutyltriazeno)-5-benzoylisoxazolo-3-carboxamide hydrochloride **(6c)** in 30 ml of ethanol was neutralized by 1N sodium hydroxide. The solution was stirred in the presence of light for 2 days, the ethanol was removed under reduced pressure. The formed crystals were filtered and washed with water. After recrystallization from ethanol, colorless prisms (0.19 g, 32%) were obtained explosive decomposition at 245°C. This product did not give a positive Bratton-Marshall test, had no distinct absorption bands in the 2300–2000 cm^{-1} region of its infrared spectrum. IR (KBr): ν 3300 (NH), 1690, 1670 (C=O), 1600 (C=N), 1480 (N=N), 700 cm^{-1} (Ar^-). ^{1}H NMR: 7.48–7.56 (m, 3H, ArH), 7.94–8.05 (m, 2H, ArH), 8.45 (s, 1H, NH).). EI MS: m/z (%) 342 (M^+, 22), 214(18), 211(15), 197(4), 171(3), 165(46), 137(20), 109(15), 105(80), 77(40), 38(25). Anal. Calcd. for $C_{11}H_6N_4O_3$ (242.18): C, 54.55; H, 2.5; N, 23.13. Found C, 54.35; H, 2.61; N, 22.96.

Method B. From compound **5**. A mixture of 2.78 g (10 mmoles) 5-benzoyl-4-diazoisoxazolo-3-carboxamide chloride, 40 ml of ethanol and 20 ml of 1N ammonia was allowed to stand overnight. The

mixture was evaporated to 10 ml under diminished pressure and chilled. The formed crystals were filtered and washed with cold water, after recrystallization from ethanol was identical with compound obtained method A. Weight, 2.0 g (83% yield).

Method C. From compound **8**. A stirred solution of 1.73 g (25 mmoles) of sodium nitrite in 40 ml of water was maintained at 0–5°C while a solution of 4.92 g (20 mmoles) of methyl 4-amino-5-benzoylisoxazole-3-carboxylate **(8)** in 50 ml of cold 1N hydrochloric acid was added dropwise. Stirring was continued for one hour and 60 ml of 1N ammonia was added into the stirred solution, and was allowed to stand overnight. The mixture was filtered and the white solid was washed with water. After recrystallization from ethanol it was identical with compound obtained by method A. Weight, 1.91 g (40% yield).

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