SYNTHETIC ROUTES TO 3,4,5-TRIMETHOXYBENZALDEHYDE (REVIEW)

Yu. V. Erofeev, V. L. Afanas'eva, and R. G. Glushkov

UDC 615.31:547.571].012.1

3,4,5-Trimethoxybenzaldehyde (I) is a key intermediate in the synthesis of trimethoprim[2,4-diamino-5-(3,4,5-trimethoxybenzyl)pyrimidine], which, in addition to its antibacterial activity [9], possesses the property of significantly strengthening the bactericidal activity of sulfanilamide preparations; it is widely used in combination with the latter in medical practice [9, 47].

The raw materials for the preparation of I are mainly vanillin (II) and 3,4,5-trimethoxybenzoic acid (TMBA), obtained in turn from gallic acid. Judging by the volume of publications over the last 20 years, I is more frequently prepared from TMBA and its derivatives. However, as regards the accessibility of raw material resources (chemical synthesis and products obtained by treatment of wood), vanillin has the highest potential; its yearly world production at present reached the level of 7400 tons [61] in 1982.

There is the possibility of using other forms of raw materials for the synthesis of I on an industrial scale with one or another degree of restriction.

1. SYNTHESIS OF HALOGEN-CONTAINING INTERMEDIATES TO I

1.1. Halogenated Vanillin

1.1.1. 5-Bromovanillin was developed in 1909 as an intermediate by the direct bromination of vanillin [55], providing high yields of 5-bromovanillin (5BV, III) [63]. Vanillin is brominated in AcOH [48, 71], containing sodium acetate [62], and also in 48% HBr [21, 53] or chlorinated hydrocarbons [21], using an excess of bromine (5-15 mole %) over the stoichiometric quantity. The escaping HBr is not utilized, and the decomposition of unreacted bromine usually by the use of different reducing agents is recommended [62].

Among the insufficiencies of these methods is the related irrational expenditure of difficultly available raw materials (Br_2, HBr). Furthermore, the 5BV formed contains about 3% vanillin and thus requires extensive purification. In the present case, the desired product (I) occurs in undesirable admixture with veratryl and 5-bromoveratryl aldehyde [81].

The indicated insufficiencies in the synthesis of III significantly depresses the usage of the oxidative bromination reaction. Information on the yield of this reaction abroad (patents by Rhone-Poulenc) first appeared in 1986 [32, 35]. Simultaneously and independently, the oxidative bromination reaction of vanillin was subjected to intense study with the aim of identification of constituents to explain the mechanism of the process and the character of the side reactions taking place [1].

The overall oxidative bromination reaction (using the most common oxidant, H_2O_2) is described by the equation [1, 32, 35]:

$$II+0.5Br_2+0.5H_2O_2\rightarrow III+H_2O$$

The maximum values for the conversion of vanillin (not less than 92%), and the yield of III (now lower than 91%) occur in homogeneous (AcOH [35] or AcOH + Ac_2O [32]) and in heterogeneous media such as two-phase systems of organic solvents ($CHCl_3$ [32], C_2H_4Cl [1]) and mineral acid solutions (HBr [32], H_2SO_4 [1, 32]). Although the patents [32, 35] do not indicate the contents of the mixtures of vanillin in 98% III, published data [1] indicate that the observance of optimal conditions for the oxidative bromination gives a final

S. Ordzhonikidze All-Union Scientific Research Institute of Pharmaceutical Chemistry, Moscow. Translated from Khimiko-farmatsevticheskii Zhurnal, Vol. 24, No. 7, pp. 50-56, July, 1990. Original article submitted November 28, 1989.

0091-150X/90/2407- 0501$12.50

content of the starting vanillin and minor components (3-bromo-4,5-dihydroxy-2,3-dibromo-4,5-dihydroxy-, and 2,5,6-tribromo-3,4-dihydroxybenzaldehyde; di- and tribromo-substituted-2-methoxyphenols) in III of less than 1%. The consumption of bromine is 0.58 g per 1 g of vanillin [1].

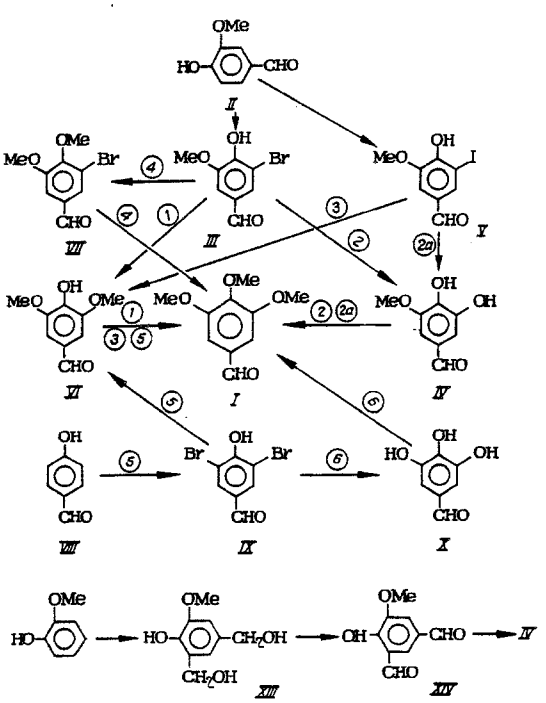
Another previously patented [33] means of preparing III consists of adding to a mixture of vanillin, KBr, and succinimide in a two-phase system of dichloroethane/H_2O, bromine at first and then chlorine gas to the appearance of Br_2 which is destroyed with sodium sulfite. The bromine consumption is 0.5 g per 1 g of vanillin. The overall yield of III (including that isolated from the mother liquor) is satisfactorily high: 90.7% [33]. However, the melting point of III prepared by this method, according to [33] is 3-4°C lower than the "standard" 98-99% III.

It should be noted that the use of other oxidants (for example NaOCl, or a mixture of HNO_3 and HNO_2) in the oxidative bromination of vanillin leads, as is known, to a lowering of the yield of the desired product [32]. In addition, hydrogen peroxide as oxidant is obviously important from the point of view of the protection of the environment [4].

The potential possibilities for III as raw material for I have practically not been realized even after 70 years, and it was used in the framework of the classical scheme [through 5-hydroxyvanillin (IV)], considerably more rare than 5-iodovanillin (V). The reason, apparently, lies in the necessarily more strenuous conditions for the substitution of Br (compared to I) for the OH-group in aqueous basic medium. Further, the resultant basic hydrolysis of III correspondingly depends on the quantity and chemical composition of the metals used as catalysts (powdered copper or its alloys) [21, 49, 52, 66]. The latter case naturally impairs reproducibility of the method. It is impossible to take into account the tendency of III to enter into the Canizzaro reaction [59, 63]. However, some workers establish the synthetically equivalent method of substituting halogen in III or in 5-iodovanillin by an hydroxy or an alkoxy group in the 5-position [3]. Among these is the methoxylation of III by analogy with 5-iodovanillin [52] leading to the formation of a mixture of products including predominantly 5-bromovanillyl alcohol and its derivatives [62].

Thus there has appeared in recent years a catalyst for the methoxylation of bromoaromatic aldehydes [71, 80] indicated mainly by the more technological schemes (1) as compared with the classical schemes (2).

Scheme



1.1.2. 5-Iodovanillin. 5-Iodovanillin, obtained by the iodination of vanillin with I_2 in the presence of KI in aqueous solution of salts [77] or base [49] in a yield of 91%, is significant only for the preparative synthesis of I by the hydrolysis of the Ar-I bond through 5-hydroxyvanillin (Scheme, 2a) [49] or by methoxylation through syringaldehyde (VI) (Scheme, 3) [67].

1.1.3. 5-Bromo-3,4-dimethoxybenzaldehyde. Dimethylsulfate methylation of III in basic medium with a yield of at least 80% gives 5-bromo-3,4-dimethoxy-benzaldehyde (VII) [76], which may be considered [34] as a potential byproduct in the preparation of I (Scheme, 4) [69].

1.2. Halogen Derivatives of 4-Hydroxybenzaldehyde.

This group of synthates presents rare examples of the preparation of I through 3,5-dibromo-4-hydroxybenzaldehyde (IX) based on 4-hydroxybenzaldehyde (VIII), in two steps (Scheme, 5) with an overall yield of 65.5%; the process proceeds under conditions analogous to the corresponding oxidative bromination of vanillin and the methoxylation of III [33]; and in three steps (Scheme, 6) with the isolation of 3,4,5-trihydroxybenzaldehyde (X) with an overall yield of 28.4% [17].

Using a highly-selective method for monobromination of aldehyde VIII [80] [yield of 3,5-dibromo-4-hydroxybenzaldehyde (IX) = 4.5%; of 3-bromo-4-hydroxybenzaldehyde (XI) = 90%], bromide XI may give I according to the hypothetical scheme VIII → XI → II (84% from IV [80]) → I. However, since aldehyde VIII remains more difficultly accessible and expensive compared to vanillin, the chances of its usage in large-scale synthesis of I, including the method of [33], are small.

2. SYNTHESIS OF HYDROXYBENZALDEHYDES — IMMEDIATE PRECEDENTS TO I.

Hydroxybenzaldehydes — 5-hydroxyvanillin (IV) and syringaldehyde (VI) — are key intermediates in the synthesis of I according to the Scheme: $Ar^1CHO \rightarrow Ar^2CHO$, and are not expensive aldehyde groups. The least significant of this series, 3,4,5-trihydroxybenzaldehyde (X) is referred to in Division 1.2. (cf. also [30]).

2.1. 5-Hydroxyvanillin.

2.1.1. Preparation of 5-Hydroxyvanillin by Basic Hydrolysis of 5-Halovanillin. The hydrolysis of 5-halovanillin takes place by heating the starting ArX (X = Br, I) in dilute aqueous basic solution in the presence of a copper catalyst. Typical examples of this hydrolysis are given in Table 1. The result of the hydrolysis to a significant degree is determined by the characteristics of the copper catalyst. Also, according to [66], the substitution of copper bronze by 'active copper catalyst' [46] leads to the formation of a mixture of VI, guaiacol, II, vanillic acid (XII), and 5-bromo-XII.

The process of hydrolysis of the less reactive III is intensified at the expense of the use of increased temperature and pressure, and also a significant quantity of catalyst.

There exists the possibility under hydrolysis conditions of a side reaction of reductive dehalogenation of ArX taking place with the formation of vanillin, which depends on the ratio of catalyst to ArX [21].

The mechanism of action of the copper catalyst similarly has not been studied. On the character of the transformation of CuO it might be noted, for example, that the accomplishment of hydrolysis with quantitative yield also resulted in the isolation of Cu_2O [19].

The preparation of IV without the use of high pressure is possible only in case of 5-iodovanillin. Removal of difficulties connected with the nonreproducibility of catalytic activity of different metallic copper catalysts in the hydrolysis of 5-iodovanillin is possible by using salts of Cu(2+) [24] or freshly-prepared 'active copper catalyst' [46], obtained by treatment of copper sulfate solutions with zinc dust. However, the yield of aldehyde IV in this case does not exceed 68-70% [49] (cf. Table 1). Further, this reaction leads to considerable excess base in the highly dilute solutions [49], as a result of which the expected product IV with a single system becomes the method low. The presence in the reaction mixture of traces of iodine (introduced with the starting 5-iodovanillin, or possibly formed as a result of the reaction: $ArI + I^- + H_2O \rightarrow ArH + I_2 + OH^-$) leads to

TABLE 1. Basic Hydrolysis of Halovanillins ArX (III, V)

X	Hydrolysis conditions				Catalysts			Yield, %	Indication of quality of IV	Special conditions	Literature reference
	NaOH conc., %	mole ratio, NaOH:ArX	temperature, °C	duration, hr	characteristics	preparation (producer)	gravimetric ratio; Cu_{cat}:ArX				
Br	7,5	7	Boiling point of reaction mixture	27	Powdered copper	Alliend Chem. Corp. (No.1618)	0,01—0,1	83,3	mp = 132-134°C	Inert atmosphere (nitrogen)	[21]
Br	15	7	100—102	27	$CuSO_4$+NaOH	At 50°C in situ	0,016*	91,4	Target material content = 99.5%	The same (hydrogen)	[29]
Br	8	10	200—210	1	Copper bronze		0,387	86	mp = 129-131°C	Autoclave	[52]
Br	8	10	200—210	1	Commercial copper bronze: 'Bronze Pigment Copper Brilliant 104'	Crescent Bronze Powder Co.	0,39	The same	The same	The same	[66]
Br	7,9	4	150	2	Powdered copper		0,016	80**	—***	The same	[19]
I	20	17	Boiling point of reaction mixture	4	The same		0,375	93	mp = 120—127 °C		[69]
I	14	30	105	4,5	$CuSO_4 \cdot 5H_2O$+NaOH	In situ	0,143	68	mp = 128—129 °C	Inert atmosphere (nitrogen)	[49]

*As copper.
**Contains about 14% vanillin (calculations based on results from the methylation step).
***Process carried out without isolation of VI.

deterioration of quality of the desired product and a decreasing yield of IV. In its own turn, the isolation of IV from the reaction mixture (after acidification) requires a many-step extraction, involving the use of significant quantities of flammable organic solvents such as ethyl acetate, ether [49], or toluene [21] at high temperatures [21].

Thus, even with conditions for the regeneration of scarce and expensive I_2 (and KI) the known means of obtaining IV by basic hydrolysis of 5-halovanillin from a technological point of view is not optimal.

2.1.2. Preparation of 5-Hydroxyvanillin Based on Guaiacol. The patented method for obtaining aldehyde IV from guaiacol according to the scheme [30], includes 2 stages of selective oxidation: the bisoxymethyl compound XIII (under platinum catalysis) and dialdehyde XIV (with hydrogen peroxide as oxidant; yield in the steps = 94%).

2.2 Syringic Aldehyde (SA)*

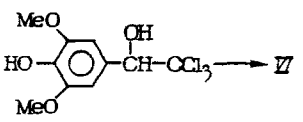
2.2.1. Methoxylation of 5-Halovanillin in the NaOMe–MeOH System. The failure of experiments on the methoxylation of 5-BV at 163-205°C under pressure in the presence of copper shavings [62] dominated for a long time the opinions on the use of 5-iodovanillin in the synthesis of SA (the latter formed under the action of a 4-fold excess of powdered copper catalyst in an autoclave at 124-128°C to give a yield of 85.5% [67]), which we duplicated in our recent work [5]. The situation changed after that, however, as a result of Japanese studies [80] at Upjohn Company for the methoxylation of III which suggested the catalyst system $CuCl_2$–MeONa–MeOH–DMF [71]. The yield of SA ranged from 83 [71] to 99% (upon carrying out the reaction in a sealed ampule at 120°C) [69].

In accord with recommendations [71], it is necessary to provide effective removal of the MeOH in the methoxylation process. Comparative study of the methoxylation of III with removal of MeOH at a temperature of about 100°C, using CuCl, $CuCl_2$, and $CuCl_2 \cdot 3Cu(OH)_2$ showed that under the above conditions the catalytically active form is preferably the Cu(1+) ion [2].

For the preparation of SA (without isolation in the form of the Na-salt) from III a significantly more complex catalyst system containing the following components: $Cu(OAc)_2$–MeONa–MeOH–DMA–ethylenediaminetetraacetic acid–trimethyl phosphite–lysine hydrochloride–morpholine also has been used [33].

The use of DMF as a component of catalytic systems was discovered as a new possibility for the classical type of catalyst from powdered copper. The results of special studies [51] have established that even a 10% concentration of DMF in the reaction mixture with high surface area copper dust (particle size about 4 μm) for 2 h at 120°C provides more than 90% conversion of III. Promotion by the addition of CuI increases the rate of reaction. Repeated use of the catalyst is not recommended because intense side reactions take place.

2.2.2. Other Methods for the Preparation of SA. Also worthy of mention is the existence of an earlier industrial means of preparing SA with a yield of 75% according to the scheme [64]:

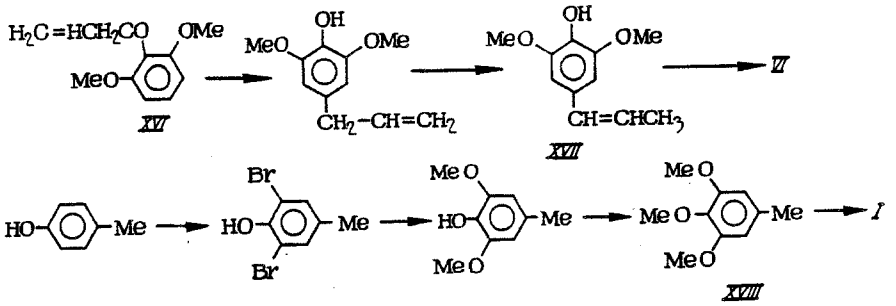


XV

as well as a variant of the Claisen rearrangement with overall yield of SA of from 67.5 to 72% with subsequent oxidation of compound XVII in the system nitrobenzene–50% aqueous base [65] (see scheme on following page).

Oxidation of olefins of the type XVII in the indicated reaction may also employ $KMnO_4$ in the presence of H_5IO_5 on a solid carrier (Al_2O_3). The yield of aldehyde was from 20 to 79% [82].

*The preparative synthesis of SA by the demethylation of I under the action of various agents is not considered in this review.



Common to both reactions [64, 65] is the possibility of obtaining both the carbinol XV and 2-allyloxy-1,3-dimethoxybenzene (XVI) from pyrogallol.

3. OBTAINING 1-METHOXYLATEDHYDROXYBENZALDEHYDE

Methylation of hydroxybenzaldehyde IV [21, 29, 38, 40, 48] and VI [20, 69] with dimethyl sulfate by heating in an organic solvent (usually acetone) in the presence of a basic agent leads easily to a high yield. Besides dimethyl sulfate, trimethyl phosphite [24, 35, 31] or dimethyl sulfite [24, 25] can be used. In a heterophasic system the "liquid–liquid" process is catalyzed by quaternary ammonium chloride salts [33], since in the methyl trialkyl series (C_8-C_{10}) of amine hydrochlorides ("Adogen 464") the methoxylation of VI proceeds at ordinary temperatures with yields of 96% [71].

4. OBTAINING I BY OXIDATION OF 3,4,5-TRIMETHOXYTOLUENE

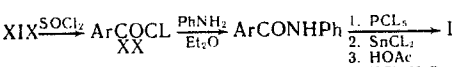
In the last decade the synthesis of I by the selective oxidation of 3,4,5-trimethoxytoluene (XVIII) according to the scheme [39] underwent intensive development in Japan, which apparently explains the leading position of the Japanese firm in the world production of synthetic p-cresol [7], from which XVIII can be prepared in 3 steps with overall yield of 85% [39]*. In the beginning of the 1980's the electrochemical oxidation of XVIII [60, 74] was adopted on an industrial scale, but a less energetic catalytic oxidation with oxygen in the liquid or vapor phase was shown later. Concrete examples are given in Table 2.

It is indicated that compatible usages of Cu- and Co-catalysts allow the accomplishment of the low-temperature oxidation of XVIII in methanolic solution with NaOH with high selectivity [42].

5. OBTAINING I BASED UPON GALLIC ACID

Gallic (3,4,5-trihydroxybenzoic) acid (GA) is a widely-available natural compound, that occurs mainly in the form of glycosides in many higher plants. Industrially significant sources of GA are mainly four in number: Gallae turcicae, Quercus lusitanica (beech fam.), Gallae Chinensis, and Rhus Semialata (sumac fam.) [16]. However, because of the limited area of vegetation of the above-mentioned plants [6], GA obtained from natural sources does not satisfy the requirements of large tonnage production. It is known that the means of preparing [72, 75] synthetic GA based upon 4-hydroxybenzoic acid is awkward and difficult. In addition, the number of steps in the synthesis of I starting from GA is larger compared with the Schemes described in Parts 1-4. In confirmation of this, chemical schemes are provided below beginning with the key intermediate: 3,4,5-trimethoxybenzoic acid (XIX):

Scheme *a* [57]:



Ar = 3,4,5-trimethoxyphenyl (here and later).

*It is interesting to note that in a 1978 publication [78] the Japanese investigated the use of gallic acid as a raw material for the synthesis of XVII.

TABLE 2. Catalytic Oxidation of XVIII

Catalyst	Solvent	Temperature, °C	Time for Oxidation, h	Type of Apparatus	Yield of Aldehyde, %	Literature Reference
$Ce(OAc)_3$ and/or Pd-catalyst	MeOH	100	3	Autoclave	94	[43]
$NaVO_3$ + C_3NO_3, promoted by Cu, Ag, Pb, Sb, Bi	-	400		Column with continuous flow of a mixture of 1% XVIII and 99% air (oxygen).	70 Conversion = 95%	[41]
Oxides of Cs/V, Wt ratio = 0.4	-	400		The same		[45]
Acetates of Co and Ce	-	140 (0-3 atm)	2	Reactor	84	[44]
Acetates of Cu and Co	MeOH + H_2O, NaOH	65		Large scale reactor (800 volumes/min)	Conversion = 98%	[42]

Scheme b (McFadyen–Stevens Reaction) [79]:

$$XIX \xrightarrow[2.\ N_2H_4\cdot H_2O]{1.\ ROH} ArCONHNH_2 \xrightarrow{PhSO_2Cl} \underset{XXI}{} \rightarrow ArCONHNHSO_2Ph \xrightarrow[150-160\ ^\circ C]{Na_2CO_3} I$$

R = Me, Et.

Scheme c (Oxidation of Hydrazide XXI):

$$XXI \rightarrow I$$

Oxidant: oxygen/air gas in butylamine [50], potassium hexacyanoferrate(3+) [8, 12, 13, 15, 36].

Scheme d (oxidation of carbinol XXII):

$$\underset{XXII}{ArCH_2OH} \rightarrow I$$

Oxidant: sodium hypochlorite under PTC ('Aliquat 336') [23], CrO_3 in glacial AcOH [11, 23], MnO_2, $K_2Cr_2O_7$ [56], pyridinium chlorochromate [58], tetrabutylammonium chromate [54], air/oxygen in aqueous base in the presence of metals of the platinum group [37].

Carbinol XXII may be obtained by catalytic hydrogenation of the mixed anhydride ArCOOCOOR, where R = ET or iso-Bu [10, 11, 23, 22].

Scheme e (Rosenmund eduction of chloroanhydride XX) [18, 27, 28, 68, 70, 83]:

$$XX \xrightarrow{H_2Pd} I$$

A variation of this scheme is the reduction of the mixed anhydride [18]:

$$ArCOOCOOEt \xrightarrow{H_2Pd} I$$

Scheme f (reduction of the ester XIX with a complex of medal hydrides with isolated I in the form of the butyl sulfite derivative [14]):

$$ArCOOR \xrightarrow[\substack{2.\ Morpholine \\ 3.\ HCl}]{1.\ Na(MeOCH_2CH_2OEt)_2AlH_2} I$$

In addition, the Reissert synthesis of I starting from chloroanhydride XX also has been described [73].

On the basis of the examination of these materials it can be concluded that the most promising industrial routes for the production I are from 5-bromovanillin through syringic acid, and the route through the oxidation of XVIII.

LITERATURE CITED

1. V. L. Afanas'eva, A. V. Lyubeshkin, S. S. Kovaleva, et al., Khim.-farm. Zh., No. 1, 1367-1371 (1987).
2. V. L. Afanas'eva, L. V. Vlasenko, S. S. Kovaleva, and Yu. V. Erofeev, Catalysis and Catalytic Processes of Chemical Pharmaceutical Production [in Russian], Part 2, Moscow (1989), pp. 45-46.
3. K. M. Dyumaev and I. S. Belostotskaya, Zh. Obshch. Khim., 32, 2661-2663 (1962).
4. O. A. Ermakov, Khim. Prom., No. 2, 93-95 (1989).
5. G. F. Zakis and B. Ya. Neiberte, Khim. Drevesini, No. 5, 76-80 (1985).
6. I. E. Korobeinikova, Z. D. Kanchabeli, and B. G. Yasnitskii, Collected Scientific Transactions, All-Union Pharmaceutical Chemistry Research Institute [in Russian], Issue 6, Part 1 (1976), pp. 115-117.
7. Handbook of Large Chemical Companies in Capitalistic Countries [in Russian], Moscow (1980).
8. N. I. Kydryashova, L. R. Davidenko, and N. V. Khromov-Borisov, Zh. Obshch. Khim., 29, 1885-1888 (1959).
9. M. D. Mashkovskii, Drug Materials [in Russian], Vol. 2, Moscow (1984), pp. 289-290.
10. Belgian Patent 873,645, Chem. Abstr., 91, 192,992 (1979).
11. Belgian Patent 873, 647, ibid., 91, 123,559 (1979).

12. Hungarian Patent 181,148, ibid., 98, 178,943 (1983).
13. Hungarian Patent 23,214, ibid., 178,943.
14. Hungarian Patent 23,998, ibid., 99, 53,359 (1983).
15. Hungarian Patent 40,604, ibid., 107, 154,072 (1987).
16. East German Patent 55,673, ibid., 67, 89,817 (1967).
17. Polish Patent 126,462, ibid., 102, 148,882 (1985).
18. Romanian Patent 79,123, ibid., 101, 151,585 (1984).
19. Romanian Patent 90,635, ibid., 108, 55,651 (1988).
20. Romanian Patent 90,836, ibid., 107, 217,224 (1987).
21. US Patent 3,855,306, Ref. Zh., 23057P (1975).
22. US Patent 4,240,984, Chem. Abstr., 91, 123,559 (1979).
23. US Patent 4,239,702, ibid., 94, 174,653 (1981).
24. US Patent 4,453,004, ibid., 100, 22,403 (1984).
25. US Patent 4,453,017, ibid., 101, 54,713 (1984).
26. US Patent 4,453,018, ibid., 54,712.
27. West German Patent 2,046,105, ibid., 77, 101,184 (1972).
28. West German Patent 3,129,273, ibid., 98, 143,122 (1983).
29. Czechoslovakian Patent 216,633, ibid., 102, 148,882 (1985).
30. European Patent Declaration 44,260, ibid., 96, 162,325 (1982).
31. European Patent Declaration 91,022, ibid., 100, 22,403 (1984).
32. European Patent Declaration 149,952, ibid., 104, 148,504 (1986).
33. European Patent Declaration 155,335, Ref. Zh., 13043P (1986).
34. European Patent Declaration 277,894, Chem. Abstr., 109, 210,701 (1988).
35. French Patent Declaration 2,557,098, ibid., 104, 109,218 (1986).
36. Japanese Patent Declaration 7,428,184, ibid., 82, 125,092 (1975).
37. Japanese Patent Declaration 7,831,607, ibid., 93, 185,964 (1980).
38. Japanese Patent Declaration 80,162,731, ibid., 95, 80,482 (1981).
39. Japanese Patent Declaration 8,168,635, ibid., 132,491.
40. Japanese Patent Declaration 81,150,094, ibid., 96, 103,857 (1982).
41. Japanese Patent Declaration 85,233,027, ibid., 104, 168,136 (1986).
42. Japanese Patent Declaration 8,626,535, ibid., 105, 60,418 (1986).
43. Japanese Patent Declaration 86,268,645, ibid., 107, 6,927 (1987).
44. Japanese Patent Declaration 8,827,452, ibid., 109, 110,021 (1988).
45. PCT Int. Appl. WO 8,606,715, ibid., 106, 119,449 (1987).
46. Organic Syntheses [Russian translation], Coll. Vol. 2, Moscow (1949), p. 371.
47. T. D. Skalaban, N. M. Kalenik, L. I. Volkova, et al., Antimicrobial Sulfanilamides in Single-Component and Combined Drug Materials, Deposited in TsBNTI Medbioprom. No. 50, MP/MB. Dept. Nauch. Raboty, No. 2, 112 (1989).
48. J. Asakawa, K. Tanikana, and T. Aratani, Phytochemistry, 15, No. 6, 1057-1059 (1976).
49. S. K. Banerjee, M. Manolopoulo, and J. M. Pepper, Can. J. Chem., 40, 2175-2177 (1962).
50. G. Barta-Szalai and K. Lempert, Period. Polytech. Chem. Eng., 24, No. 4, 253-258 (1980).
51. H. V. Borgaonkar and S. B. Chandalia, J. Chem. Tech. Biotechnol., 34A, No. 8, 446-452 (1984).
52. W. Bradley, R. Robinson, and G. Schwarzenbach, J. Chem. Soc., 793-817 (1930).
53. M. Brink, Acta Univ. Lund, Sect. 2, No. 6, 3-17 (1965).
54. S. Cacchi, F. La Torre, and D. Misiti, Synthesis, No. 5, 356-359 (1979).
55. H. D. Dakin, Am. Chem. J., 42, 493 (1909).
56. A. DeSotgiu, Corriere Farm., 22, No. 7, 196-200 (1967). Chem. Abstr., 68, 49,247 (1968).
57. P. Dessi, Arch. Ital. Sci. Farmacol., 3, No. 2, 376-383 (1952).
58. F. S. Guziec and F. Luzzio, J. Org. Chem., 47, No. 2, 1787-1789 (1982).
59. R. Jones and R. Robinson, J. Chem. Soc., 111, 921 (1917).
60. N. Kitajima, K. Takemura, Y. Moro-Oka, et al., Bull. Chem. Soc. Jpn., 61, No. 3, 1035-1037 (1988).
61. H. I. Kvisgaard, Wood, Versatile and Renewable Chemical Feedstock, Oslo (1982).
62. R. A. McIvor and I. A. Pepper, Can. J. Chem., 31, 298-302 (1953).
63. F. Misani and M. T. Bogert, J. Org. Chem., 10, 347-365 (1945).
64. H. Pauly and L. Strasberger, Chem. Ber., 62, 2277-2284 (1929).
65. I. A. Pearl, J. Am. Chem. Soc., 70, 1746-1748 (1948).
66. I. A. Pearl and D. L. Beyer, ibid., 74, 4262-4263 (1952).
67. I. M. Pepper and I. A. MacDonald, Can. J. Chem., 31, 476-483 (1953).
68. I. A. Peters and H. VanBekkum, Rec. Trav. Chim. Pays-Bas., 100, No. 1, 21-24 (1981).

69. S. C. Puri, S. M. Anand, and C. K. Atal, Indian J. Chem., Sect. B, 24, 294-295 (1985).
70. A. J. Rachlin, H. Gurien, and D. P. Wagner, Org. Syn., 51, 8-11 (1971).
71. D. V. Rao and F. A. Stuber, Synthesis, No. 4, 308 (1983).
72. K. A. Reddy, East. Pharm., 21, 37-40 (1978).
73. A. Schwarts, J. Org. Chem., 47, No. 11, 2213-2214 (1982).
74. K. Shimizu, K. Kizawa, T. Yoshimota, et al., J. Jpn. Petrol. Inst., 25, 7 (1982).
75. M. T. Shipchandler, C. A. Peters, and C. D. Hurd, J. Chem. Soc., Perkin I, No. 14, 140 (1975).
76. R. L. Shriner and P. McCutchan, J. Am. Chem. Soc., 51, 2193-2195 (1929).
77. P. Smith, J. Chem. Soc., 3740-3741 (1958).
78. H. Sugihara, M. Wanatabe, Y. Kawamatsu, and H. Morimoto, Liebigs Ann. Chem., 763, 109-120 (1972).
79. Bu Tianheng, et al., Jinan Liyi Xuebao, No. 1, 70-74 (1986). Chem. Abstr., 106, 84,088 (1987).
80. S. Torii, H. Tanaka, T. Siroi, et al., J. Org. Chem., 44, No. 19, 3305-3310 (1979).
81. 3,4,5-Trimethoxybenzaldehyde (TMBA) Data Sheet, Rhone-Poulenc Specialities Chimiques, Paris (1987).
82. D. Villemin and M. Picard, Nouv. J. Chem., No. 3, 185-189 (1984).
83. D. P. Wagner, H. Gurien, and A. J. Rachlin, Ann. N.Y. Acad. Sci., 172, No. 9, 186-193 (1970).

REACTION OF AROMATIC DIAZO DERIVATIVES WITH GLYCINE AND GLYCINE METHYLAMIDE*

V. I. Nifontov, N. P. Bel'skaya,
O. A. Bagaeva, L. V. Krupnova,
N. M. Khvorova, and M. A. Bobarykina

UDC 615.277.3:547.236.1].012.1

We have previously shown [1, 3] that when the pH, temperature and ionic strength of the solution correspond to the biological values (pH 7.4, 37°C and μ = 0.178), free amino acids and also terminal basic amino groups of peptides can take part in the formation of unstable disubstituted triazenes with aryldiazo derivatives, which subsequently undergo rapid transformation into 1,3-diaryltriazenes.

In continuation of the investigations carried out in [3], the present work is devoted to a kinetic study of the reactivity of aryldiazo derivatives (I-III) in reaction with glycine and glycine methylamide, similar to the chemical model of the glycine target of natural proteins and peptides.

EXPERIMENTAL (CHEMICAL)

The course of the reactions, the composition of the reaction mixtures and the purity of the synthesized compounds were monitored chromatographically on "Silufol UV-254" plates in the systems of PrOH – 0.2 N ammonia (3:1), R_{f_1}, $CHCl_3$ – EtOH (6:1), R_{f_2} BuOH–AcOH–water (4:1:1) R_{f_3}. The UV spectra were taken on a "Beckman" spectrometer, model 26 "Kinetic" (USA), the IR spectra on a UR-20 spectrophotometer in KBr tablets, and the PMR spectra on a "Bruker" WH-80 spectrometer (90 MHz) with tetramethylsilane as internal standard.

The diazo derivatives I-III were synthesized according to [4]. The results of the elemental analyses corresponded to the calculated values.

*Communication IX; for VIII see [3].

S. M. Kirov Ural' Polytechnical Institute, Sverdlovsk. Translated from Khimiko-farmatsevticheskii Zhurnal, Vol. 24, No. 7, pp. 56-57, July, 1990. Original article submitted June 6, 1989.

 0091-150X/90/2407-0510 $12.50