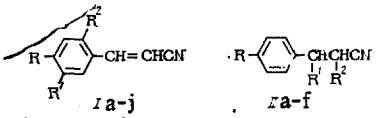
RADIOPROTECTANT ACTIVITY OF CINNAMO- AND HYDROCINNAMONITRILES

S. A. Bol'shakova, Zh. A. Goloshchapova,
T. N. Tuzhilkova, A. D. Grebenyuk, and
V. M. Myakishev

UDC 615.849.1.015.25:547.586.73

Cyano compounds are known to exhibit antiactinic properties. In the search for new radioprotectants, we have synthesized and examined the toxic and radioprotectant properties of some nitriles of substituted cinnamic (Ia-k) and hydrocinnamic (IIa-f) acids



I a-j II a-f

Ia: $R = R^1 = R^2 = H$; Ib: $R^1 = R^2 = H$, $R = OCH_3$; Ic: $R^1 = R^2 = H$, $R = NO_2$; Id: $R^1 = R^2 = H$, $R = Cl$; Ie: $R^1 = R^2 = H$, $R = Br$; If: $R^1 = R^2 = H$, $R = CH_3$; Ig: $R = R^2 = H$, $R^1 = NO_2$; Ih: $R = R^1 = H$, $R^2 = NO_2$; Ii: $R^1 = R^2 = H$, $R = COOH$; Ij: $R = R^2 = H$, $R^1 = OCH_3$;
IIa: $R^1 = H$, $R^2 = Cl$, $R = NO_2$; IIb: $R^1 = H$, $R^2 = Cl$, $R = OCH_3$; IIc: $R^2 = H$, $R = Cl$, $R^1 = CH_3$; IId: $R^1 = R^2 = H$, $R = OCH_3$; IIe: $R = R^2 = H$, $R^1 = C_6H_5$; IIf: $R^2 = H$, $R = Cl$, $R^1 = C_6H_5$.

Nitriles (Ia-k) were obtained by dehydrochlorination of the corresponding α-chlorocinnamonitriles, which were prepared by the Meerwein reaction from acrylonitrile and the appropriate diazonium chloride. Nitriles (IIa-b) were obtained by the Meerwein reaction. Nitriles (IIc-f) were synthesized by cyanoalkylation of the aromatic nucleus in the presence of aluminum chloride. The synthesis and properties of (Ia-h), (IIa-b), and (IIe-f) have been described in [1, 2], (IIc-d) in [3], and (IIf) in [4].

EXPERIMENTAL BIOLOGY

Tests were carried out using male mice of the C57B1/6 strain weighing 23-25 g. Irradiation was carried out in an IGUR gamma unit in a dose of $LD_{95-99/30}$ (810 cGy) at a dose rate of 1.23 cGy/sec. The compounds were administered intraveously 15 min before irradiation. All the test compounds were insoluble in water, and they were therefore administered as aqueous suspensions with Tween-80 in a dose of 0.2 ml per mouse. The toxic doses of the compounds were calculated by Litchfield and Wilcoxon's method [5].

The toxicities of the compounds (Table 1) show that the CD_{50} value for these compounds range from 35 to 1000 mg/kg, i.e., these nitriles include highly, moderately, and slightly toxic compounds. Most of them are of moderate toxicity (CD_{50} 200-1000 mg/kg). It will be seen that these compounds contain a variety of substituents in the p-, m-, and o-positions of the benzene ring, namely, methoxy, nitro, carboxy, or methyl. In these instances in which the benzene ring contains no substituent, the compound is of high toxicity (for example, Ia). Thus, the introduction into the nitrile molecule of a variety of groups may moderate its toxic effects.

A study of the radioprotectant properties showed (Table 1) that three of the compoounds possessed radioprotectant properties, namely, p-methoxycinnamonitrile (Ib), p-nitrocinnamonitrile (Ic), and α-chloro-p-methoxyhydrocinnamonitrile (IIb). These compounds ensured the survival of 43-58% of the irradiated mice when the control survival rate was 6%. It will be seen that these compunds contain a methoxy or nitro group in the p-position of the benzene ring. Replacement of these groups by other groups (Id-f and Ii), or moving the group from the p- to the m-position (Ig and Ij) or the o-position (Ih), results in the loss of radioprotectant activity. Likewise inactive is (Ia), which contains no substituents.

Thus, from the compounds studied it will be seen that radioprotectant activity in nitriles is dependent not only on the presence of the nitrile group, but also other groups, the types and positions of which should be fully defined. It is no coincidence, therefore, that

Translated from Khimiko-farmatsevticheskii Zhurnal, Vol. 17, No. 7, pp. 795-797, July, 1983. Original article submitted December 7, 1982.

 0091-150X/83/1707-0474$07.50

TABLE 1. CD_{50} and Ratioprotectant Properties of Substituted Cinnamo- and Hydrocinnamonitriles

Compound	CD_{50}, mg/kg	Radioprotectant activity		
		No. of animals	dose, mg/kg	survival to day 30, %
Ia	35	14	10	7 ±6,9
Ib	218	34	69	56±8,5*
Ic	800	24	250	58±10,1*
Id	78	18	32	0
Ie	136	18	62	0
If	760	17	370	7 ±6,2
Ig	510	18	170	0
Ih	330	18	135	16±8,7
Ii	645	20	293	10±6,7
Ij	720	18	305	23±9,8
IIa	100	14	30	7 ±6,9
IIb	125	14	40	43±13,2*
IIc	220	14	70	14±9,3
IId	450	14	150	29±12,1
IIe	1000	14	300	14±9,3
IIf	>1000	14	300	14±9,3
Control irradiation	—	54	—	6±3,2

*Significant difference from controls ($P \leqslant 0.05$).

of 40 nitriles described in the literature [6], radioprotectant activity is shown only by malononitriles with a hydroxyl group or chlorine ion in the p-position of the benzene ring.

This study has therefore revealed radioprotectant activity in a series of cinnamo- and hydrocinnamonitriles. These compounds (p-methoxy- and p-nitrocinnamonitrile and α-chloro-p-methoxyhydrocinnamonitrile), when administered 15 min before irradiation, ensure the survival of an average of 50% of lethally irradiated animals. It is clear that the search for radioprotectants in this series should continue.

EXPERIMENTAL CHEMISTRY

Compounds (Ii) and (Ij) were prepared as described in [7].

p-Carboxycinnamonitrile (Ii). p-Aminobenzoic acid (13.7 g, 0.1 mole) was dissolved with warming in 18% hydrochloric acid. The solution was cooled to 5°C, and diazotized by adding a saturated aqueous solution of sodium nitrite (6.9 g). To the resulting solution was added 15 ml of acetone, 23 ml of acrylonitrile, and 0.3 g of cupric chloride, and the mixture was stirred for 3 h at 25°C, then kept overnight. The precipitated α-chloro-p-carboxyhydrocinnamonitrile was washed with water and dried. Elimination of hydrogen chloride was effected by boiling the compound with 35 ml of triethylamine for 6 h. The cooled solution was poured into 10% sulfuric acid, and the resulting nitrile (Ii) was twice reprecipitated from its solution in sodium carbonate. Yield 8.5 g (50.9%), mp 256-257°C.

m-Methoxycinnamonitrile (Ij). m-Anisidine (15 g, 0.12 mole), purified by distillation, was dissolved in 88 ml of hydrochloric acid (sp. gr. 1.18), and diazotized at 0°C with a saturated aqueous solution of sodium nitrite (9 g). To the resulting solution was added an ice-cold solution of acrylonitrile (9 ml) in acetone (70 ml), followed by the dropwise addition of an aqueous solution of 3.4 g of cupric chloride. When the reaction was complete, the mixture was neutralized with sodium carbonate solution, and the oil was extracted with benzene, washed with water, and dried over sodium sulfate. Dehydrochlorination of the resulting nitrile was carried out by boiling 15 g of the compound with 40 ml of triethylamine for 6 h. The solution obtained was poured into 10% sulfuric acid, and the oil was extracted with ether and dried over sodium sulfate. Yield of (Ij), 2.2 g (18%), bp 132-135°C (14 mm).

LITERATURE CITED

1. A. V. Dombrovskii, B. S. Fedorov, and Zh. V. Belitskaya, in: Problems in the Preparation of Intermediates in Industrial Organic Synthesis [in Russian], Leningrad (1967), pp. 173-174.

2. A. D. Grebenyuk, V. I. Vinogradova, and É. L. Kristallovich, Zh. Org. Khim., 9, 85-89 (1973).
3. A. D. Grebenyuk, A. Kobilov, and L. N. Breslavskaya, Nauchn. Tr. Tashkent Univ.: Vopr. Khim., No. 435, 91-95 (1973).
4. I. P. Tsukervanik and A. D. Grebenyuk, Dokl. Akad. Nauk SSSR, 76, 223-225 (1951).
5. M. L. Belen'kii, Fundamentals of the Quantitative Measurement of Pharmacological Activity [in Russian], Leningrad (1963), p. 62.
6. V. G. Yashunskii, Usp. Khim., 44, 531-574 (1975).
7. French Pat. No. 7328972; Ref. Zh. Khim., No. 16, No. N285P (1976).

SYNTHESIS AND BIOLOGICAL ACTIVITY OF SOME 5-HETEROMERCAPTO-1,2,4-TRIAZOLES

E. G. Knysh, I. A. Mazur, N. N. Savenkova, V. R. Smets, and A. A. Martynovskii

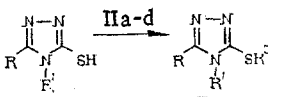
UDC 616.28+616.276]:547.791].012.1

Derivatives of 1,2,4-triazole, 5-pyrazolone, benzimidazole, quinoline, and acridine are widely used in medical practice as antimicrobial, antimalarial, analgesic, and antiinflammatory agents [1].

Recently, derivatives of 1,2,4-triazole have been reported to possess analeptic [2], neuroleptic [2, 3], diuretic [2], spasmolytic [4], hypoglycemic [5], antispasmodic [6], analgesic [7], antiinflammatory [7], antimicrobial [8], and antiviral activity [9].

It is of special interest, therefore, to investigate the pharmacological properties of some new compounds consisting of a triazole ring with a 5-pyrazolone, benzimidazole, quinoline or acridine group linked to the triazole ring by means of a sulfur atom.

The synthesis of the 5-heteromercapto-1,2,4-triazoles (Ia-d) was accomplished by reacting the substituted 5-mercapto-1,2,4-triazoles (Ia-d) with 4-bromoantipyrine (IIa), 2-chloromethylbenzimidazole (IIb), 2-chloroquinoline (IIc), 5-nitro-8-chloroquinoline (IId), and 2-ethoxy-6-nitro-9-chloroacridine (IIe) (see Table 1).



Ia-d IIa-h

Ia: $R=CH_3$; $R^1=H$; Ib: $R=CH_2C_6H_5$, $R^1=H$; Ic: $R=R^1=C_2H_5$; Id: $R=$ =4-pyridyl, $R^1=C_6H_5$; IIIa: $R=CH_3$, $R^1=H$, $R^2=$ 4-antipyryl; IIIb: $R=$ $=CH_2C_6H_5$, $R^1=H$, $R^2=$ 4-antipyryl; IIIc: $R=CH_3$, $R^1=H$, $R^2=$2-benzimidoazolylmethyl; IIId: $R=R^1=C_6H_5$, $R^2=$ 2-benzimidoazolylmethyl; IIIe: $R=CH_3$, $R^1=H$, $R^2=$ 2-quinolyl; IIIf: $R=R^1=C_6H_5$, $R^2=$5-nitro-8-quinolyl; IIIg: R=4-pyridyl, $R^1=C_6H_5$, $R^2=$5-nitro-8-quinolyl; IIIh $R=$ =4-pyridyl, $R^1=C_6H_5$, $R^2=$2-ethoxy-6-nitro 9-acridinyl.

Compounds IIIa-e were isolated as salts; use of IId and e as starting components led to the formation of the bases IIIf-h. The synthesized compounds were white (IIIa-d), yellow (IIId-g), or brown (IIIh) substances, insoluble in water (with the exception of IIIa-c), and soluble in organic solvents. The structures of compounds IIIa-h were confirmed by IR spectroscopy. The IR spectra of the compounds have absorption bands at 1630-1650 cm^{-1} (C–N, bending), and also at 3200-3500 cm^{-1} (N–H, stretching) for compounds IIIa-e).

Tests for pharmacological activity showed that compounds IIIa-h possess neuroleptic, analgesic, and antiinflammatory activity (Tables 2 and 3). Moreover, the extent and nature of the activity varies both with the substituent in the triazole ring and with the hetero radical.

Compounds with a methyl group at position 3 of the triazole ring (IIIa, c, and e) exhibit neuroleptic, antiinflammatory, and analgesic activity. Replacement of the methyl group by a benzyl group leads to the disappearance of neuroleptic action (IIIb), and a similar substitution at position 5 leads to a sharp increase in toxicity. Introduction of the benzimida-

Zaporazhye Medical Institute. Translated from Khimiko-farmatsevticheskii Zhurnal, Vol. 17, No. 7, pp. 798-801, July, 1983. Original article submitted October 11, 1982.

 0091-150X/83/1707-0476$07.50