80. A parallel test was carried out with phenylbutazone at the same dose. The test compound showed antiinflammatory activity comparable with that of phenylbutazone.

Hypotensive activity was assessed by the effects of the compound on arterial pressure in intact rats in an acute test. The tests were carried out with 12 white rats of both sexes, weighing 200-300 g, as described in [1]. The compound (VIII) was administered intravenously as the 1% aqueous solution in doses of 5, 10, and 20 mg/kg. The arterial pressure fell immediately following administration of the solution, the maximum reduction being reached after 15-20 sec, followed by restoration of the pressure to its original levels after 1-1.5 min. The maximum reduction in the arterial pressure was 40-45% (at a dose of 5 mg/kg) of the original value. The $LD_{50}$ of (VIII) by the intraperitoneal route in white mice was 1300 mg/kg, using the method described in [3].

This group of compounds is therefore promising in the search for antiphlogistic agents, and for drugs with hypotensive activity.

## LITERATURE CITED


1. V. V. Bolotov, V. V. Drugovina, S. M. Drogovoz, et al., Khim.-farm. Zh., No. 1, 58-61 (1982).
2. V. V. Bolotov, S. M. Drogovoz, L. V. Yakovleva, et al., ibid., No. 9, 1060-1063 (1983).
3. V. V. Bolotov, A. Nambelbai, S. M. Drogovoz, et al., ibid., No. 5, 552-554 (1984).
4. P. A. Petyunin, Zh. Obshch. Khim., 22, No. 6, 975-979 (1952).
5. Sh. A. Samsonya, N. L. Targamadze, L. G. Tret'yakova, et al., Khim. Geterotsikl. Soedin., No. 7, 938-944 (1977).


# SYNTHESIS AND STUDY OF CARDIOVASCULAR ACTIVITY OF 6-NITRO-7-OXO-4,7-DIHYDROAZOLO[1,5-a]PYRIMIDINE DERIVATIVES


V. L. Rusinov, A. Yu. Petrov,
T. L. Pilicheva, O. N. Chupakhin,
G. V. Kovalev, and E. R. Komina



UDC 615.214:547.792


Derivatives of 7-oxo-4,7-dihydro-1,2,4-triazolo[1,5-c] [1, 2, 11] triazine [7] and 7-alkylamino-1,2,4-triazolo[1,5-a]pyrimidine [5, 6, 8, 9] with a vasodilating and antisclerotic action are well known. 5-Methyl-7-diethylamino-1,2,4-triazolo[1,5-a]pyrimidine, under the name "Trapidyl" is used for treating atherosclerosis [3, 4]. These data indicate good prospects for the search for compounds with cardiovascular activity in the azolo[1,5-a]pyrimidine (Ia-l) class of compounds.

The increased $\pi$-deficiency of the azolo[1,5-a]pyrimidine system, the formation of cations with $HNO_3$, and also the limited availability of the reagents complicates the preparation of nitro derivatives by direct nitration [10, 12]. In the present work, the nitropyrimidine ring was built by means of aliphatic nitrosyntone, ethyl ethoxymethylenenitroacetate (II). The formation of 5-nitrouracil [13] and 6-nitropyrido[1,2-a]pyrimidine [15] in the condensation of ester II with urea and 2-aminopyridine is known.

We found that aminoazoles do not react with ethoxymethylenenitroacetic ester when heated in alcohols, benzene, DMFA, or acetic acid under the conditions of condensation of the ester with aromatic amines and 2-aminopyridine [1, 15]. We were able to condense 5-aminopyrazoles and 5-amino-1,2,4-triazoles with compound II by heating without a solvent. Esters of 2-nitro-3-azolylaminoacrylic acid III were thus obtained. Products IIIa-d,f,g were isolated and identified, and the remaining azoloamino-acrylates were used for cyclization without isolation from the reaction mixture.

Absorption bands of the nitro group, carbonyl and amino groups were observed in the IR spectra of compounds IIIa-d,f,g (Table 1). The chemical shifts and the multiplicity of the


S. M. Kirov Ural' Polytechnical Institute, Sverdlovsk. Volgograd Medical Institute.


Translated from Khimiko-farmatsevticheskii Zhurnal, Vol. 20, No. 2, pp. 178-182, February, 1986. Original article submitted January 21, 1985.

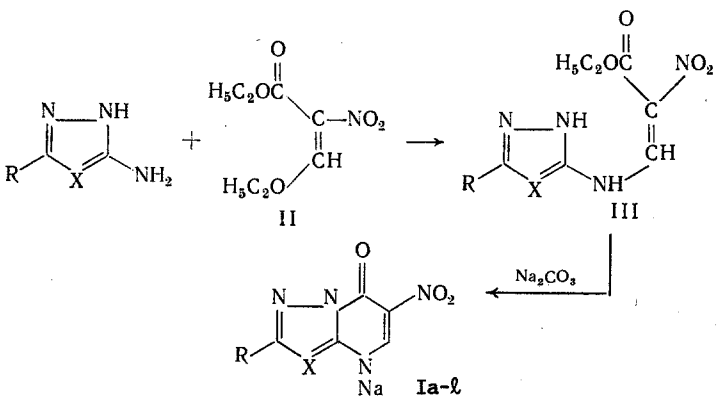
TABLE 1. Physicochemical Properties of Compounds Synthesized

| Compound | Yield % | Mp, °C | Found, % | | | Empirical formula | Calculated, % | | | Spectral data[e] | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | IR spectrum, $cm^{-1}$ | | | |
| | | | C | H | N | | C | H | N | $\nu_{NO_2}$ | $\nu_{C=O}$ | $\nu_{NH}$ | PMR spectrum, δ, ppm |
| IIIa | 95 | 201–202[a] | 42.1 | 4.4 | 24.5 | $C_9H_{10}N_4O_4$ | 42.5 | 4.4 | 24.8 | 1330<br>1490 | 1725 | 3130<br>3250 | 1,30 (3H, t, $CH_3$), 4,35 (2H, q, $CH_2$), 6,62 (1H, d, 4-H), 8,00 (1H, d, 3-H), 9,25 & 9,65 (1H, br.s =CH–) |
| IIIb | 95 | 199–201[a] | 44,9 | 4,8 | 23,5 | $C_9H_{12}N_4O_4$ | 45,0 | 5,0 | 23,3 | 1330<br>1490 | 1725 | 3130<br>3260 | 1,30 (3H, t, $CH_3$), 2,30 (3H, s, $CH_3$), 4,35 (2H, q, $CH_2$), 6,35 (1H, s, 4-H), 9,20 & 9,65 (1H, br.s, =CH–) |
| IIIc | 80 | 175–177[a] | 56,0 | 4,3 | 18,5 | $C_{14}H_{14}N_4O_4$ | 55,6 | 4,6 | 18,5 | 1325<br>1485 | 1720 | 3130<br>3260 | 1,27 (3H, t, $CH_3$), 4,30 (2H, q, $CH_2$), 6,57 (1H, s, 4-H), 7,85-8,15 (5H, wk. mult. $C_6H_5$), 9,25 and 9,70 (1H, br.s. =CH–) |
| IIId | 90 | 270–275[b] | 37,2 | 4,2 | 30,6 | $C_7H_8N_5O_4$ | 37,2 | 4,0 | 30,8 | 1310<br>1480 | 1720 | 3120<br>3220 | 1,28 (3H, t, $CH_3$), 4,30 (2H, q, $CH_2$), 8,54 (1H, s, 2-H), 8,75 & 9,05 (1H, br.s, =CH–) |
| IIIe | 85 | 265–266[b] | 40,0 | 4,4 | 28,8 | $C_8H_{11}N_5O_4$ | 39,8 | 4,6 | 29,0 | 1315<br>1480 | 1720 | 3125<br>3225 | 1,30 (3H, t, $CH_3$), 2,35 (3H, s, $CH_3$), 4,30 (2H, q, $CH_2$), 8,75 & 9,05 (1H, br.s. =CH–) |
| Ia | 90 | >300 c | 35,4 | 1,8 | 27,4 | $C_6H_3N_4NaO_3$ | 35,6 | 1,5 | 27,7 | 1345<br>1535 | 1680 | — | 6,60 (1H, d, 3-H), 8,25 (1H, d, 2-H), 9,00(1H, s, 5-H) |
| Ib | 85 | >300 c | 38,6 | 2,6 | 25,8 | $C_7H_5N_4NaO_3$ | 38,8 | 2,3 | 25,9 | 1340<br>1535 | 1680 | -- | 2,28 (3H, s, $CH_3$), 6,21 (1H, s, 3-H), 9,01 (1H, s, 5-H) |
| Ic | 80 | 289–292 c | 51,3 | 2,8 | 19,9 | $C_{12}H_7N_4NaO_3$ | 51,8 | 2,5 | 20,1 | 1345<br>1530 | 1680 | — | 6,95 (1H, s, 3-H), 7,55–8,30 (5H, m, $C_6H_5$), 9,10 (1H, s, 5-H) |
| Id | 80 | >300 d | 38,9 | 2,8 | 20,0 | $C_8H_7N_4NaO_3$ | 39,4 | 2,5 | 20,4 | 1345<br>1535 | 1680<br>1720 | — | 1,33 (3H, t, $CH_3$), 4,35 (2H, q $CH_2$), 8,40 (1H, s, 2-H), 9,12 (1H, s, 5-H) |
| Ie | 80 | >300[d] | 37,2 | 2,5 | 17,1 | $C_{10}H_9N_4NaO_5S$ | 37,5 | 2,8 | 17,5 | 1350<br>1535 | 1680<br>1720 | — | 1,30 (3H, t, $CH_3$), 2,60 (3H, s, $CH_3$), 4,40 (2H, q, $CH_2$), 9,41 (1H, s, 5-H) |
| If | 90 | >300 [d] | 29,1 | 1,4 | 34,2 | $C_5H_2N_5NaO_3$ | 29,5 | 1,0 | 34,5 | 1340<br>1535 | 1680 | — | 8,75 (1H, s, 2-H), 9,30 (1H, s, 5-H) |
| Ig | 85 | >300 [d] | 33,0 | 2,0 | 32,1 | $C_6H_4N_5NaO_4$ | 33,2 | 1,8 | 32,2 | 1340<br>1530 | 1680 | — | 2,50 (3H, s $CH_3$), 9,36 (1H, s 5-H) |
| Ih | 90 | >300 [d] | 47,0 | 2,6 | 24,8 | $C_{11}H_6N_5NaO_3$ | 47,3 | 2,2 | 25,1 | 1350<br>1535 | 1675 | - | 7,65–8,35 (5H, m, $C_6H_5$), 9,20 (1H, s, 5-H) |
| Ii | 80 | 285–290 d | 28,6 | 2,0 | 28,0 | $C_6H_4N_5NaO_3S$ | 28,9 | 1,6 | 28,1 | 1325<br>1530 | 1685 | -- | 2,65 (3H, s, $CH_3$), 9,40 (1H, s, 5-H) |
| Ij | 75 | >300 d | 40,2 | 1,8 | 26,0 | $C_{11}H_5N_6NaO_5$ | 40,6 | 1,6 | 25,8 | 1325<br>1525 | 1680 | - | 8,40 (2H, d, $C_6H_4$), 8,60 (2H, d, $C_6H_4$), 9,10 (1H, s, 5-H) |
| Ik | 70 | >300 d | 40,3 | 1,5 | 26,0 | $C_{11}H_5N_6NaO_5$ | 40,6 | 1,6 | 25,8 | 1340<br>1540 | 1680 | — | 7,80–9,10 (4H, m, $C_6H_4$), 9,35 (1H, s, 5-H) |
| Il | 70 | >300 d | 42,5 | 1,5 | 29,7 | $C_{10}H_6N_6NaO_3$ | 42,8 | 1,8 | 30,0 | 1340<br>1540 | 1680 | -- | |

[a]From ethanol. [b]From acetic acid. [c] From methanol. [d]From water. [e]UV spectrum, $\lambda_{max}$, nm (log ε): If, 253 (3.95), 349 (3.99); Ig 250 (3.78), 350 (3.97); Ih 256 (4.20), 354 (3.94); Ii, 253 (4.08) 353 (3.98); Ij, 253 (4.30), 353 (3.95); Ik, 253 (4.30), 352 (3.94); I1 260 (4.25), 350 (3.95).

signals in the PMR spectra correspond to structure III. The presence of two broadened 3CH signals of the acrylic fragment proton can be explained in analogy to the case of arylaminoacrylates [1], by the presence of Z and E-isomers in a DMSO-$d_6$ solution.

Sodium salts of 6-nitro-7-oxo-4,7-dihydroazolo[1,5-a]pyrimidines Ia-l were prepared by the action of aqueous solutions of sodium carbonate or alkali on compounds III




Ia-ℓ

a: R = H, X = CH; **b**: R = $CH_3$, X = CH; **c**: R = $C_6H_5$, X = CH; **d**: R = H, X = $CCOOC_2H_5$; **e**: R = $SCH_3$, X = $CCOOC_2H_5$; **f**: R = H, X = N; **g**: R = $CH_3$, X = N; **h**: R = $C_6H_5$, X = N; **i**: R = $SCH_3$, X = N; **j**: R = 4-$NO_2C_6H_4$, X = N; **k**: R = 3-$NO_2C_6H_4$, X = N; **l**: R = 4-**pyridyl** X = N.

Most of azoloamino-acrylates III cyclize at room temperature, but in the presence of acceptor substituents in the azole fragment (compounds IIId,e,j-l), heating to 100°C is necessary.

In the IR spectra of sodium salts Ia-l (see Table 1), there are characteristic bands of vibrations of the nitro and carbonyl groups. The PMR spectra of compounds Ia-l confirm the attributed structure. The cyclization of ethyl 2-nitro-3-(1,2,4-triazolyl-5-amino)acrylates IIIf-l may proceed at the N(1) or N(4) atoms of the triazole ring with the formation of triazolo[1,5-a]- or triazolo[4,3-a]pyrimidines. It was shown in [11, 14] that the position of the signal of the triazole proton in the condensed triazole derivatives can serve as an indicator of the nature of the ring fusion: in 7-oxo-4,7-dihydro-1,2,4-triazolo[1,5-a]pyrimidine (IV) it is equal to 8.84 ppm, and in the corresponding [4,3-a]isomer (V) 9.24 ppm. Comparison of the spectra of 6-nitro-7-oxo-4,7-dihydro-1,2,4-triazolo[1,5-a]pyrimidine (the δ of the triazole proton is 8.85 ppm) obtained by treating the sodium salt. Compound if with 40% $H_2SO_4$, with the spectra of model compounds IV and V indicates a [1,5-a]-fusion of the triazole and pyrimidine fragments in compound If. The similarity of the UV spectra of salts If-l confirms the formation of [1,5-a]-isomers also when substituted triazoles are used.

## EXPERIMENTAL (CHEMICAL)

The UV spectra of the aqueous solutions were recorded on a "Specord UV-VIS" spectrophotometer (GDR) and the IR spectra in mineral oil on a UR-20 spectrophotometer (GDR). The PMR spectra of solutions in DMSO-$d_6$ were obtained on a "Perkin-Elmer R-12B" spectrometer (Great Britain, 60 MHz), using hexamethyldisilane as internal standard.

Ethyl 2-Nitro-3-azolylaminoacrylates (IIIa-d,f,g). A mixture of 0.01 mole of the corresponding amino-azole and 1.5 ml of ethyl ethoxymethylenenitroacetate is heated at 50-60°C for 30 min, and cooled, and the precipitate is filtered and recrystallized.

Sodium Salts of 6-Nitro-7-oxo-4,7-dihydroazolo[1,5-a]pyrimidines (Ia-l). A mixture of 0.01 mole of aminoazole and 1.5 ml of ethyl ethoxymethylenenitroacetate is heated at 50-60°C for 30 min. A 10-ml portion of 20% $Na_2CO_3$ solution is added, and the mixture is held for 1 h at 20°C (for compounds (Ia-c, f, h), or at 100°C (for compounds Id,e, j-l). When cool, the precipitate is filtered and recrystallized. The sodium salts Ia-d,f,g were also obtained by treating the azolylaminoacrylates IIIa-d,f,g with a 20% sodium carbonate solution under the same conditions.

TABLE 2. Hypotensive Action of Sodium Salts of 6-Nitro-7-oxo-4,7-dihydroazolo[1,5-a]pyrimidines

| Compound | Dose, mg/kg | Decrease in SAP, % of initial arterial pressure | | | |
|---|---|---|---|---|---|
| | | after 5 min | after 15 min | after 30 min | after 60 min |
| Id | 10 | — | — | —5 | — |
| | 25 | —8 | —8 | —9 | —9 |
| | 50 | —9 | —9 | —9 | —3 |
| Ie | 10 | —7 | —7 | —7 | —7 |
| | 25 | —8 | —9 | —8 | —8 |
| | 50 | —8 | —9 | —7 | —8 |
| Ig | 10 | —20 | —8 | —8 | —5 |
| | 25 | —9 | —9 | —8 | —8 |
| | 50 | —8 | —8 | —7 | —7 |
| Ih | 10 | —7 | —7 | — | — |
| | 25 | —11 | —10 | —8 | —7 |
| | 50 | —16 | —11 | —9 | —7 |
| Ii | 10 | —5 | —8 | —11 | —26 |
| | 25 | —12 | —12 | —15 | —23 |
| | 50 | —17 | —19 | —26 | —25 |
| Ij | 10 | —15 | —12 | —10 | —5 |
| | 25 | —3 | —9 | —9 | —11 |
| | 50 | —13 | —13 | —11 | —15 |
| Ik | 10 | —8 | —7 | —4 | —7 |
| | 25 | —18 | —15 | —13 | —17 |
| | 50 | —17 | —15 | —12 | —12 |
| Il | 10 | —2 | —2 | — | — |
| | 25 | —9 | —9 | —9 | —9 |
| | 50 | —11 | —11 | —11 | —11 |

## EXPERIMENTAL (PHARMACOLOGICAL)

The influence of compounds Id,e,g-l on the level of the arterial pressure was studied. The experiments were carried out on white rats of both sexes weighing 200-250 g each under Nembutal-induced narcosis (50 mg/kg). The systemic arterial pressure (SAP) was recorded in the main carotid artery in the conventional way. The compounds studied were administered intravenously into the exterior jugular vein in doses of 10, 25, and 50 mg/kg.

Compounds Id,e,g,h,k,l caused a weak decrease in the SAP level; increase in the dose of each introduced compound did not generally intensify the hypotensive effect (Table 2). The sodium salts of 2-methylthio- and 2-(4-nitrophenyl)-6-nitro-7-oxo-4,7-dihydro[1,5-a]pyrimidine (Ii, j) were the most active. For these two compounds, a tentative $LD_{50}$ dose was determined, characterizing their acute toxicity. The experiments were carried out on white nonpedigree mice weighing 16-20 g each, and the animals were observed for 24 h. The compounds were administered intraperitoneally. The acute toxicity ($LD_{50}$) of salt Ij was within 500 to 1000 mg/kg, and that of Ii was more than 1000 mg/kg.

In separate series of experiments, the influence of Ii, the most interesting compound in the series studied, on the central hemodynamic indexes was studied on cats. The minute volume of blood (MVB) was determined by the thermal dilution method [2], the frequency of heart contractions (FHC) was computed from ECG, the stroke volume (SV), the peripheral resistance (PR) and the work-load of the left ventricle (WLV) were determined by calculation.

The introduction of the sodium salt of Ii in a dose of 50 mg/kg practically did not change the SAP. In a dose of 100 mg/kg, it caused a short-term increase in SAP (by 10 mm Hg) compared with the initial level, and then a 12% decrease in the arterial pressure for 60 min. The MVB thus decreased by 15%, due to a 10% decrease in FHC and 13% decrease in SV. The PR increased at the end of the first hour by 28%, and WLV decreased inappreciably.

Thus, in experiments on cats, compound Ii had a weak hypotensive action with inappreciable change in the central hemodynamic indexes. The more pronounced hypotensive effect of the preparation in experiments on rats is clearly explained by the species sensitivity of these animals to this group of compounds.

## LITERATURE CITED

1. V. I. Bakhmutov, K. K. Babievskii, and É. I. Fedin, Izv. Akad. Nauk SSSR, Ser. Khim., No. 9, 2029-2037 (1982).

2. M. I. Gurevich, S. A. Bronshtein, D. A. Golov, et al., Fiziol. Zh. SSSR, 53, 350-354 (1967).
3. Japanese Patent No. 57-38715 (1980); Ref. Zh. Khim., No. 8 (P), No. 8 O 259 (1981).
4. Japanese Patent No. 57-7417 (1982); Ref. Zh. Khim., No. 3 (P) O 275 (1983).
5. Japanese Patent No. 57-35592 (1981); Ref. Zh. Khim., No. 4 (P), No. 4 O 200 (1983).
6. East German Patent No. 61269 (1968); Ref. Zh. Khim., No. 1(P), No. 1 O 208 (1976).
7. East German Patent No. 110662 (1975); Ref. Zh. Khim., No.1(P), No. 1 O 201 (1976).
8. East German Patent No. 165881 (1976); Ref. Zh. Khim., No. 3(P), O 110 (1977).
9. East German Patent No. 155068 (1982); Ref. Zh. Khim., No. 12(P), No. 12 O 177 (1983).
10. V. L. Rusinov, A. Yu. Petrov, and O. N. Chupakhin, Khim. Geterotsikl. Soedin., No. 2, 147-165 (1985).
11. V. L. Rusinov, A. Yu. Petrov, and I. Ya. Postovskii, Khim. Getrotsikl. Soedin., No. 9, 1283-1285 (1980).
12. J. Makisumi, Chem. Pharm. Bull., 9, 873-877 (1961).
13. M. Prustas and Y. Gut, Collect. Czech. Chem. Commun., 28, 2501-2509 (1963).
14. H. Reimlinger and M. A. Peiren, Chem. Ber., 103, 3266-3277 (1970).
15. O. S. Wolfbeis, Chem. Ber., 110, 2480-2493 (1977).

# SYNTHESIS AND PROPERTIES OF 4-OXO-3,4-DIHYDROBENZO[g]PTERIDINE-2-CARBOXYLIC ACID AND ITS DERIVATIVES

I. S. Musatova, V. I. Pol'shakov, G. G. Dvoryantseva, V. V. Chistyakov, and A. S. Elina

UDC 547.859.29.66.091:543.422.25

There has recently developed considerable interest in condensed heterocyclic systems with a view to the synthesis and biological study of analogs of the highly active antibacterial drugs nalidixic and oxolinic acids. The subject of the present investigation was the synthesis of some benzo[g]pteridines containing hydroxy, N-alkyl, carboxy, or carboxamido groups in the pyrimidine moiety of the molecule. These substituents are characteristic of the above-mentioned drugs and compounds of similar structure.

The key compound was ethyl 4-oxo-3,4-dihydrobenzo[g]pteridine-2-carboxylate (I), obtained from 2-amino-3-carboxamidoquinoxaline (II), which was in turn obtained by hydrolyzing the nitrile group in 2-amino-3-cyanoquinoxaline di-N-oxide (III), followed by N-deoxidation of the resulting 2-amino-3-carboxamidoquinoxaline di-N-oxide (IV).

The preparation of the dioxide (IV) was complicated by the lability of the nitrile and carboxamide groups adjacent to the N → O function. For example, we have found that dioxides (III) and (IV) in dilute caustic alkali are converted at temperatures as low as 0-5°C into 2-amino-3-hydroxyquinoxaline dioxide (V).

Conversion of the nitrile (III) into the amide (IV) was effected by acidic hydrolysis, by heating (III) in conc. sulfuric acid as described in the patent literature [4]. Closer examination of this reaction showed that high yields of (IV) of good quality were obtained only when the temperature range was closely controlled (65-68°C). Even at this temperature, the reaction products, in addition to the principal product, contained chromatographically detectable traces of 2-amino-3-hydroxyquinoxaline 1-N-oxide (VI), formed by replacement of the carboxamide group in the dioxide (IV) by hydroxyl, and deoxidation of the neighboring cyclic nitrogen atom ($N_4$). As the temperature was raised, the amount of the mono-oxide (VI) increased, and at 85-95°C it became the principal product (96.6%). However, the nitrile group in the dioxide (III) was found to be stable in dilute sulfuric acid and on prolonged heating in 2 N sulfuric acid (96-100°C) it remained virtually unchanged. The reaction mixture, however, contained traces of the mono-oxide (VI) and 2,3-dihydroxyquinoxaline 1-N-oxide (VII), which is formed in small amounts under these conditions. This assumption was confirmed by heating the amide (IV) in sulfuric acid of the same concentration at 85-90°C, when the presence

S. Ordzhonikidze All-Union Scientific-Research Institute for Pharmaceutical Chemistry, Moscow. Translated from Khimiko-farmatsevticheskii Zhurnal, Vol. 20, No. 2, pp. 182-187, February, 1986. Original article submitted December 6, 1984.

0091-150X/86/2002-0117$12.50  