

STUDIES ON POTENTIAL ANTITUMOR AGENTS (III).

Synthesis of 4-Arylcyclophosphamides.

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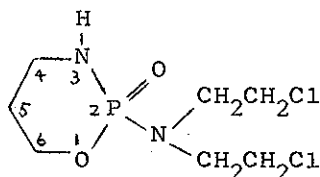
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Nine cis-trans pairs of 4-arylcyclophosphamides have been synthesized from benzaldehydes in three steps. Structures were assigned based on infrared spectra.

Cyclophosphamide, 2-bis(2-chloroethyl)aminotetrahydro-2H-1,3,2-oxazaphosphorinane 2-oxide (I), is an antitumor agent now used in the treatment of various kinds of human cancer. The mechanism of action has been well studied in recent years. It has been shown that the in vivo degradation of this alkylating agent involved, as the first step, oxidation at the C-4 position on the 1,3,2-oxazaphosphorinane ring.¹⁻³



I

This synthetic study concerns structural modification at the C-4 position. An aryl group at this position is expected, from the electronic point of view, to facilitate the oxidation and thus to modify its pharmacological activity, although the steric consideration would predict retarded oxidation.

4-Arylcyclophosphamides (cpds. 20-28) have now been synthesized starting from benzaldehydes. The aldehydes were condensed with equimolar amounts of malonic acid in refluxing ethanol in the presence of two mole equivalents of ammonium acetate to form 3-aryl-3-aminopropionic acids⁴ (cpds. 1-9) in 32.1-96.7% yields (Table I).

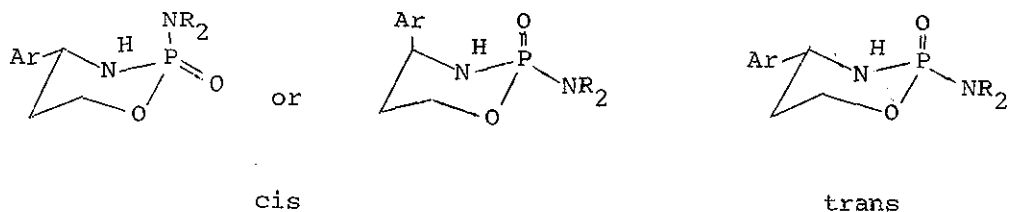
The amino acids were then reduced with 2.5 mole equivalents of lithium aluminum hydride in refluxing dry tetrahydrofuran to form 3-aryl-3-aminopropanols⁵ (cpds. 10-18) in high yields (61.1-97.0%)(Table II).

Bis(2-chloroethyl)phosphoramidic dichloride (cpd. 19) was prepared by the reaction of phosphorus oxychloride with bis(2-chloroethyl)amine hydrochloride by the known procedure.⁶

The nine amino alcohols (cpds. 10-18) were allowed to react at room temperature with equimolar amounts of cpd. 19 in the presence of 2 mole equivalents of triethylamine in ethyl acetate.⁷ The reaction mixture was stirred for 48 hours, and filtered to remove triethylamine hydrochloride. The clear solution was rotary evaporated and the residue was chromatographed on silica

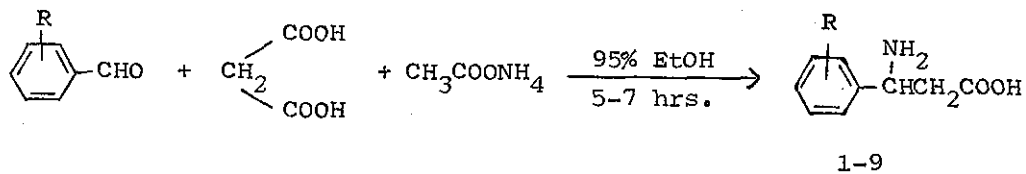
gel, eluting with benzene containing 5-15% ethyl acetate. Two isomers (fast migrating A and slow migrating B according to their relative mobilities on column chromatography) were obtained in nearly equal amounts in each case. The two isomers in each pair have the same mass spectra but different crystalline forms, mp, infrared spectra, and proton nmr spectra. Relevant data were shown in Table III and IV.

Table III shows each compound of the B class exhibits a lower P=O stretching band absorption ($1210-1218\text{ cm}^{-1}$) than the corresponding isomer of the A class ($1228-1235\text{ cm}^{-1}$); this contrast is very similar to that of 4-methylcyclophosphamides (slow B 1218 cm^{-1} , fast A 1231 cm^{-1}).⁸ Thus, it is possible to assign the relative configuration of these 4-arylcyclophosphamide isomers based on the 4-methylcyclophosphamide isomers: the fast migrating A is cis with the spatial arrangement of 4-Ar(eq)-2-NR₂(ax) or 4-Ar(ax)-2-NR₂(eq), and the slow migrating B is trans with the spatial arrangement of 4-Ar(eq)-2-NR₂(eq). The cis-trans isomerism is defined with respect to the relative orientation of the 4-aryl substituent and the oxygen atom of the P=O bond.



The proton nmr data in Table IV were consistent with the structures, especially when compared with the data for the parent, cyclophosphamide.⁹ Thus, signals for C-5(2H), NR₂(8H), and C-6(2H) of these new 4-arylcyclophosphamides fell in the same ranges, respectively, as those for cyclophosphamide; the NH signals were identified by D₂O exchange experiments; and the signals for C-4(1H) moved downfield from that in cyclophosphamide owing to the 4-aryl substituents. The following characteristics were observed when cis and trans isomers were compared. Thus, C-5(2H) signal in cis A is downfield from that in trans B; NH signal in cis A is downfield(broad) from that in trans B(sharp); and the signal positions of NR₂(8H) and aryl protons are essentially unaffected by the cis-trans isomerism.

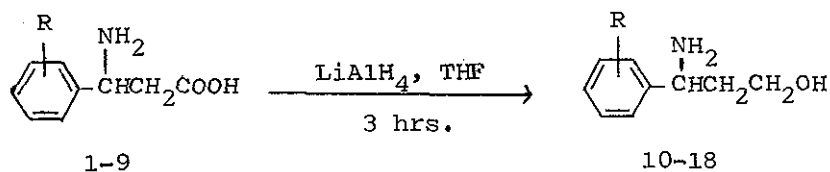
Table I. 3-Aryl-3-aminopropionic Acids



| Compd. | R | mp(°C, obs.) mp(°C, lit.) | % Yield | Mass Spectra(M ⁺) |
|----------------|--------------------|------------------------------|---------|-------------------------------|
| 1 | H | 220.5-221 216(4) | 52.5 | 165 |
| 2 | 2-CH ₃ | 237-238 242(10) | 32.1 | 179 |
| 3 | 3-CH ₃ | 221-222 225(10) | 63.2 | 179 |
| 4 | 4-CH ₃ | 221-221.5 226(10) | 96.2 | 179 |
| 5 | 3-OCH ₃ | 213-214 216(11) | 56.3 | 195 |
| 6 | 4-OCH ₃ | 237-239 243(11) | 92.2 | 195 |
| 7 | 2-Cl | 246-247 245(12) | 91.2 | 199, 201 |
| 8 ^a | 3-Cl | 242-243 | 90.3 | 199, 201 |
| 9 | 4-Cl | 242.5-243 245(12) | 96.7 | 199, 201 |

a. New compound.

Table II. 3-Aryl-3-aminopropanols

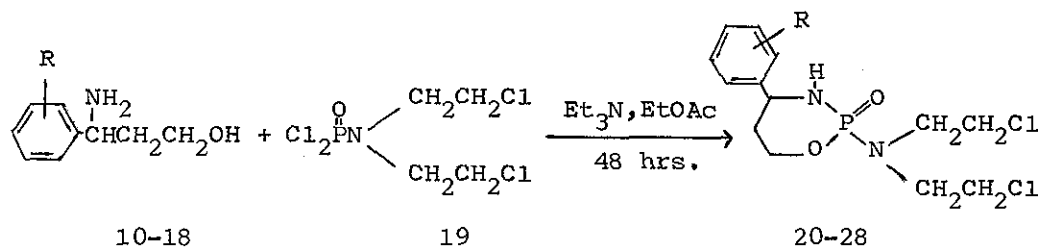


| Compd. | R | mp(°C, obs.) mp(°C, lit.) | bp(°C/mm Hg, obs.) bp(°C/mm Hg, lit.) | % Yield | Mass Spectra(M ⁺) |
|-----------------|--------------------|------------------------------|--|------------|----------------------------------|
| 10 | H | 71-72 73(13) | 132-134/4 | 86.1 | 151 |
| 11 | 2-CH ₃ | 46-47 b(14) | 155/8 | 88.9 | 165 |
| 12 ^a | 3-CH ₃ | 50-53.5 | 139.5/8 | 91.7 | 165 |
| 13 ^a | 4-CH ₃ | 81-81.5 | | 94.0 | 165 |
| 14 | 3-OCH ₃ | 41-45(15) | 167-169/8 105-115/0.05(15) | 61.1 | 181 |
| 15 | 4-OCH ₃ | 82-83 85(13) | | 96.9 | 181 |
| 16 | 2-Cl | 65-67 b(14) | | 88.2 | 185,187 |
| 17 | 3-Cl | 61-63 63-65(15) | | 73.7 | 185,187 |
| 18 ^a | 4-Cl | 84.5-86.5 | | 97.0 | 185,187 |

a. New compounds.

b. We have no access to the original article.

Table III. 4-Arylcyclophosphamides



| Compd. ^a | R | mp (°C) | Mass Spectra(M ⁺) | ir cm ⁻¹ (ν _{P=O}) ^b | % Yield ^c |
|---------------------|--------------------|-----------|-------------------------------|--|----------------------|
| 20A | H | 130.5-132 | 336,338 | 1230 | 33.5 |
| 20B | H | 114-116 | 336,338 | 1212 | 28.0 |
| 21A | 2-CH ₃ | 128.5-130 | 350,352 | 1234 | 36.8 |
| 21B | 2-CH ₃ | 152-153 | 350,352 | 1214 | 31.7 |
| 22A | 3-CH ₃ | 84-86 | 350,352 | 1232 | 36.5 |
| 22B | 3-CH ₃ | 126-127.5 | 350,352 | 1210 | 32.1 |
| 23A | 4-CH ₃ | 106-107.5 | 350,352 | 1229 | 29.1 |
| 23B | 4-CH ₃ | 150.5-152 | 350,352 | 1212 | 28.2 |
| 24A | 3-OCH ₃ | 73.5-74.5 | 366,368 | 1228 | 48.6 |
| 24B | 3-OCH ₃ | 79-80.5 | 366,368 | 1211 | 43.2 |
| 25A | 4-OCH ₃ | 96.5-98 | 366,368 | 1234 | 35.0 |
| 25B | 4-OCH ₃ | 102-103.5 | 366,368 | 1216 | 21.6 |
| 26A | 2-Cl | 119-120.5 | 370,372 | 1232 | 23.8 |
| 26B | 2-Cl | 127-129 | 370,372 | 1217 | 17.7 |
| 27A | 3-Cl | 92-93.5 | 370,372 | 1235 | 29.8 |
| 27B | 3-Cl | 124-126 | 370,372 | 1218 | 17.5 |
| 28A | 4-Cl | 104-105.5 | 370,372 | 1230 | 34.0 |
| 28B | 4-Cl | 163-165 | 370,372 | 1212 | 48.5 |

a. All new compounds with satisfactory elementary analysis.

b. Recorded by a Perkin Elmer IR Model 297 Infrared Spectrophotometer using KBr tablets, carbon disulfide solutions, and mixtures with liquid paraffin. These compounds are practically insoluble in carbon tetrachloride.

c. Crude yields from chromatography.

Table IV. Proton nmr Spectra of 4-Arylcyclophosphamides^a

| Compd. | R | C-5(2H) | N-H ^c | NR ₂ -H(8H) | C-6(2H) | C-4(1H) | Aryl group | |
|------------------------------------|--------------------|-----------|------------------|------------------------|-----------|-----------|------------|------|
| | | | | | | | Aromatic H | R-H |
| 20A | H | 2.11(q) | 3.08-3.17 | 3.35-3.75 | 4.15-4.45 | 4.50-4.66 | 7.25-7.53 | |
| 20B | H | 1.81-1.95 | 2.82 | 3.42-3.65 | 4.04-4.44 | 4.52-4.72 | 7.28-7.35 | |
| 21A | 2-CH ₃ | 2.06(q) | 2.88-3.02 | 3.40-3.73 | 4.16-4.47 | 4.71-4.96 | 7.10-7.86 | 2.34 |
| 21B | 2-CH ₃ | 1.77-1.94 | 2.63 | 3.45-3.66 | 4.07-4.60 | 4.85-4.99 | 7.11-7.52 | 2.34 |
| 22A | 3-CH ₃ | 2.10(q) | 2.94-3.04 | 3.40-3.73 | 4.16-4.45 | 4.52-4.63 | 7.08-7.31 | 2.36 |
| 22B | 3-CH ₃ | 1.82-1.96 | 2.79 | 3.47-3.65 | 4.04-4.44 | 4.52-4.70 | 7.06-7.28 | 2.36 |
| 23A | 4-CH ₃ | 2.08(q) | 2.98-3.10 | 3.33-3.72 | 4.14-4.40 | 4.44-4.58 | 7.13-7.42 | 2.33 |
| 23B | 4-CH ₃ | 1.81-1.96 | 2.78 | 3.45-3.71 | 4.04-4.47 | 4.54-4.71 | 7.07-7.28 | 2.34 |
| 24A | 3-OCH ₃ | 2.13(q) | 2.91-3.02 | 3.41-3.67 | 4.15-4.49 | 4.51-4.74 | 6.80-7.38 | 3.83 |
| 24B | 3-OCH ₃ | 1.83-1.99 | 2.74 | 3.47-3.73 | 4.05-4.48 | 4.57-4.73 | 6.78-7.60 | 3.82 |
| 25A | 4-OCH ₃ | 2.08(q) | 2.91-3.03 | 3.40-3.73 | 4.14-4.42 | 4.45-4.68 | 6.86-7.46 | 3.80 |
| 25B | 4-OCH ₃ | 1.81-1.95 | 2.72 | 3.46-3.65 | 4.03-4.47 | 4.52-4.70 | 6.85-7.31 | 3.80 |
| 26A | 2-C1 | 2.08(q) | 2.83-2.99 | 3.40-3.72 | 4.06-4.48 | 4.92-5.24 | 7.27-8.15 | |
| 26B | 2-C1 | 1.72-1.90 | 2.83 | 3.49-3.67 | 4.06-4.62 | 5.05-5.26 | 7.21-7.68 | |
| 27A | 3-C1 | 2.09(q) | 3.02-3.16 | 3.40-4.73 | 4.15-4.43 | 4.47-4.76 | 7.27-7.58 | |
| 27B | 3-C1 | 1.81-1.94 | 2.98 | 3.42-3.72 | 4.05-4.47 | 4.55-4.73 | 7.28-7.34 | |
| 28A | 4-C1 | 2.09(q) | 3.05-3.17 | 3.31-3.68 | 4.16-4.43 | 4.47-4.77 | 7.28-7.53 | |
| 28B | 4-C1 | 1.82-1.93 | 2.77 | 3.47-3.71 | 4.07-4.49 | 4.55-4.73 | 7.28-7.33 | |
| Cyclo- phosphamide ^b | | 1.85-1.95 | variable | 3.3-3.65 | 4.2-4.5 | 3.1-3.3 | | |

- a. Recorded on a JEOL FX-100 High Resolution NMR Instrument using CDCl₃ as solvent. The chemical shifts are reported in ppm downfield from internal TMS.
- b. Ref. 9.
- c. Identified by D₂O exchange experiment: broad in A and sharp in B.

REFERENCES

- 1 N. Brock and H. J. Hohorst, Arziem.-Forsch., 1963, 13, 1021.
- 2 D. L. Hill, M. C. Kirk, and R. R. Struck, J. Am. Chem. Soc., 1970, 92, 3207.
- 3 A. Takamizawa, Y. Tochino, Y. Hamashima, and T. Iwata, Chem. Pharm. Bull., 1972, 20, 1612.
- 4 T. B. Johnson and J. E. Livak, J. Am. Chem. Soc., 1936, 58, 301.
- 5 V. M. Rodinov and V. V. Kiseleva, Izvest. Akad. Nauk. SSSR., Otdel. Khim. Nauk. 1956, 575; Chem. Abstr., 1957, 51, 1885f.
- 6 O. M. Friedman and A. M. Seligman, J. Am. Chem. Soc., 1954, 76, 655.
- 7 S. M. Ludeman and G. Zon, J. Med. Chem., 1975, 18, 1251.
- 8 R. Kinas, K. Pankiewicz, and W. J. Stec, J. Org. Chem., 1977, 42, 1650.
- 9 W. Egan and G. Zon, Tetrahedron Letters, 1976, No. 11, 813.
- 10 T. Posner and G. Schreiber, Ber., 1924, 57, 1129.
- 11 V. M. Rodinov and A. M. Fedorova, Arch. Pharm., 1928, 266, 120; Chem. Abstr., 1928, 22, 4462.
- 12 N. K. Richtmyer, J. Am. Chem. Soc., 1946, 68, 1136.
- 13 L. Birkofer and L. Erlenbach, Chem. Ber., 1958, 91, 2383.
- 14 H. W. Schubert and O. Behner, Arch. Pharm., 1968, 301, 750; Chem. Abstr., 1969, 70, 47380j.
- 15 Farbenfabriken Bayer A.-G. Belg. 634,554, Jan. 6, 1964.

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