HETEROCYCLIC ANALOGS OF PLEIADIENE

XI.* SYNTHESIS OF 1-(β-DIALKYLAMINOALKYL)- AND 2-AMINOPERIMIDINES

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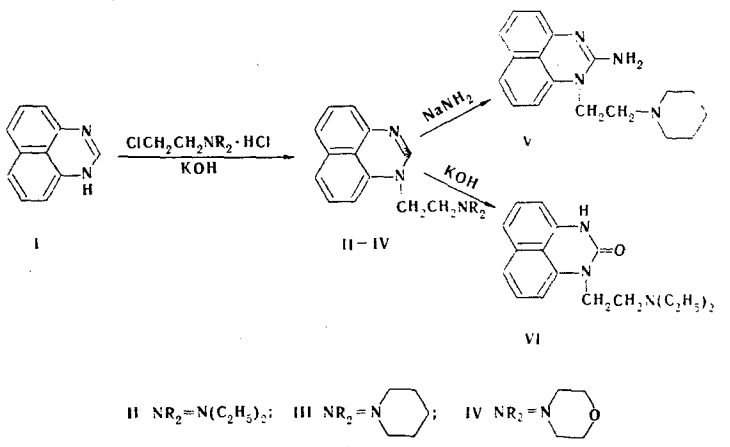
The corresponding 1-β-dialkylaminoethylperimidines were obtained by the action of β-dialkylaminoethyl chloride hydrochlorides on perimidines in alkaline media. Some of the compounds obtained form substituted 2-aminoperimidines and 2-perimidone on reaction with sodium amide or alkali. 2-Morpholino- and 2-piperidino-1-methylperimidines are obtained from 1-methyl-2-chloroperimidine and morpholine or piperidine. The synthesized compounds have weak bacteriostatic, fungistatic, and tuberculostatic activity.

Almost all simple derivatives of perimidine have weak or moderate bacteriostatic and fungistatic activity [2]. In the present research we have synthesized perimidine derivatives containing β-diethylamino, β-piperidino, and β-morpholinoethyl groups in the 1 position and morpholine and piperidine residues in the 2 position; the products were also subjected to microbiological tests. The introduction of the above groupings frequently intensifies the toxic effect of a preparation, apparently due to interaction of the unshared electron pair of the amine nitrogen with the biological receptors [3].

1-Substituted perimidines II-IV were obtained as a result of the reaction of perimidine with the appropriate β-dialkylaminoethyl chloride hydrochlorides in alcoholic alkali in an inert atmosphere (because of the high oxidizability of the N-anion of perimidine [4]). In connection with the appreciable resinification of the reaction mixture, the isolation and purification of II-IV present definite difficulties (see the experimental section of this paper). Caution should be excercised in work with perimidines II-IV, inasmuch as they cause pronounced irritation of the skin and mucous membranes that lasts for 30-60 min.



* See [1] for communication X.

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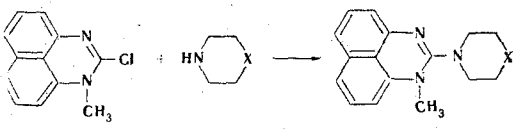
In the amination of II-IV by means of sodium amide, we were able to isolate a 2-amino derivative (V) in 52% yield only in the case of perimidine III. In the case of II, the formation of a certain amount of amine was proved by means of IR spectroscopy. Hydroxylation of 1-(β-diethylaminoethyl)perimidine II with solid alkali leads to perimidone VI (in 30% yield).

We also obtained 2-piperidino- and 2-morpholino-1-methylperimidines VII and VIII as a result of the facile reaction of 2-chloro-1-methylperimidine with piperidine and morpholine.



VII, VIII

VII $X=CH_2$; VIII $X=O$

Microbiological tests* showed that II-IV and VII and VIII have weak tuberculostatic and fungistatic activity. In addition, preparation III displays weak bacteriostatic activity with respect to staphylococcus, the diphtheria bacillus, and anthranoid spores.

EXPERIMENTAL

1-(β-Diethylaminoethyl)perimidine (II). A solution of 6.6 g (0.12 mole) of potassium hydroxide in 40 ml of alcohol was added dropwise, with continuous passage of nitrogen through the system, to a well stirred and ice-cooled suspension of 8.4 g (0.05 mole) of perimidine in 50 ml of ethanol. An alcohol solution of 9.4 g (0.055 mole) of diethylaminoethyl chloride hydrochloride was then added dropwise. The reaction mixture was held in the cold for another 30 min, after which it was refluxed under nitrogen for 3 h. The alcohol was removed by distillation, and the residue was extracted with chloroform (250-300 ml) to obtain perimidine II. The extract was dried with sodium sulfate, evaporated to 50 ml, and passed through a column filled with 300 g of aluminum oxide. The leading zone containing perimidine II was collected. The chloroform was removed by distillation, and the resulting oil was purified by one of two methods.

A) Perimidine II was extracted with hot hexane until a new portion of hexane no longer became colored. The solution was evaporated with charcoal two to three times, and the solvent was removed by distillation to give 4.8 g (37%) of a light-yellow oil.

B) The oil was dissolved in ethanol, and a saturated alcohol solution of picric acid was added. The yield of dipicrate was 17.7 g (86%); recrystallization gave 13.7 g (62%) of light-yellow crystals with mp 216° (from acetic acid). Found: C 48.1; H 3.7; N 17.8%. $C_{17}H_{21}N_3 \cdot 2C_6H_3N_3O_7$. Calculated: C 48.0; H 3.7; N 17.4%.

A solution of 13.7 g of the picrate in 200 ml of liquid ammonia was evaporated at room temperature to 50-70 ml, 130-150 ml of anhydrous chloroform was added, and the residual ammonia was evaporated. The ammoniated picrate was removed by filtration, the filtrate was decolorized with activated charcoal, and the chloroform was removed by distillation to give 4.5 g (35% based on the starting perimidine) of chromatographically pure perimidine II. Found: C 75.5; H 7.8; N 15.2%. $C_{17}H_{21}N_3$. Calculated: C 46.4; H 7.8; N 15.7%. The hydrochloride was obtained by passing dry HCl into a benzene solution of amine II. Workup gave 4.3 g (78%) of light-yellow crystals with mp 260° (dec., from alcohol–ether). Found: C 58.3; H 6.5; Cl 19.8; N 12.3%. $C_{17}H_{21}N_3 \cdot 2HCl \cdot 0.5H_2O$. Calculated: C 58.4; H 6.8; Cl 20.3; N 12.0%.

1-(β-Piperidinoethyl)perimidine (III). This compound was obtained in analogy with the synthesis of II. After column separation, the yield of crude perimidine III was 70%. It was more conveniently purified by method A. The light-yellow crystals (44%) had mp 81.5-82° (from hexane). Found: C 78.3; H 7.6; N 14.9%. $C_{18}H_{21}N_3$. Calculated: C 77.4; H 7.5; N 15.0%. The hydrochloride was obtained by bubbling dry HCl into a benzene solution of III or into the hexane extract of this compound obtained during purification by method A. The light-yellow crystals (65% yield) had mp 277° (dec., from alcohol). Found: C 59.4; H 6.3; Cl 19.5; N 11.0%. $C_{18}H_{21}N_3 \cdot 2HCl \cdot 0.5H_2O$. Calculated: C 59.9; H 6.6, Cl 19.6; N 11.6%.

1-(β-Morpholinoethyl)perimidine (IV). This compound was obtained by the method used to synthesize amine II. After purification by method A the yield was 42%. The light-yellow crystals had mp 117-118°

* The tests were performed in the chemotherapy branch of the All-Union Scientific-Research Pharmaceutical-Chemistry Institute under the supervision of G. N. Pershin.

(from hexane). Found: C 72.2; H 6.8; N 15.1%. $C_{17}H_{19}N_3O$. Calculated: C 72.6; H 6.8; N 14.9%. The hydrochloride was obtained by passing dry HCl into a benzene solution of IV or into a hexane extract of this compound, which was obtained during purification by method A. The light-yellow crystals (70%) had mp 280° (from alcohol–ether). Found: C 56.3; H 6.3; Cl 19.2; N 11.6%. $C_{17}H_{19}N_3O \cdot 2HCl \cdot 0.5H_2O$. Calculated: C 56.2; H 6.1; Cl 19.5; N 11.5%.

2-Amino-1-(β-piperidinoethyl)perimidine (V). A solution of 2.8 g (0.01 mole) of perimidine III in 10 ml of absolute dimethylaniline was added with stirring at 70–80° in a stream of nitrogen to a finely ground suspension of 1.9 g (0.05 mole) of sodium amide in 3 ml of absolute dimethylaniline. The mixture was held at 150° until hydrogen evolution ceased (~2 h). The sodium derivative was cooled and treated with 20 ml of water in an intense stream of nitrogen. The light-green crystals had mp 206–207° (from alcohol). IR spectrum in $CHCl_3$: 3455, 3230–3280 cm^{-1} (N–H). Found: C 73.3; H 7.7; N 19.0%. $C_{18}H_{22}N_4$. Calculated: C 73.5; H 7.5; N 19.0%.

1-(β-Diethylaminoethyl)-2-perimidone (VI). A 2.67 g (0.01 mole) sample of II was fused with 2.24 g (0.04 mole) of finely ground anhydrous potassium hydroxide [5] at 200–210° for 1.5 h. The mass was then cooled and treated with 100 ml of 5% hydrochloric acid, after which it was neutralized with concentrated ammonium hydroxide. The dark-gray precipitate was extracted with 120 ml of chloroform, and the extract was dried with sodium sulfate, concentrated to 20 ml, and passed through a column filled with aluminum oxide (100 g). The column was eluted with chloroform, and the first fraction was collected. Removal of the chloroform by distillation gave 0.85 g (30%) of a gray substance. The colorless needles (from aqueous alcohol) had mp 137°. IR spectrum in $CHCl_3$: 1685 cm^{-1} (C=O), 3440 cm^{-1} (N–H). Found: C 71.9; H 7.4; N 14.7%. $C_{17}H_{21}N_3O$. Calculated: C 72.0; H 7.4; N 14.8%.

1-Methyl-2-piperidinoperimidine (VII). A solution of 2.1 g (0.01 mole) of 1-methyl-2-chloroperimidine in 2 ml (0.02 mole) of piperidine was refluxed for 3–5 min until a precipitate began to form. The mixture was then cooled, and the precipitated yellowish VII was removed by filtration and washed with water to give a quantitative yield of product. After crystallization from petroleum ether it had mp 121–122°. Found: C 76.5; H 7.2; N 15.6%. $C_{17}H_{19}N_3$. Calculated: 76.7; H 7.3; N 15.8%. The hydrochloride was obtained as colorless prisms with mp 236–237° (from alcohol–ether). Found: C 67.3; H 6.6; Cl 11.5; N 13.7%. $C_{17}H_{19}N_3 \cdot HCl$. Calculated: C 67.6; H 6.7; Cl 11.8; N 14.0%.

1-Methyl-2-morpholinoperimidine (VIII). This compound was obtained as in the preceding experiment. The yield was quantitative. The colorless needles had mp 146–147° (from petroleum ether). Found: C 71.5; H 6.2; N 15.4%. $C_{16}H_{17}N_3O$. Calculated: C 71.8; H 6.4; N 15.7%. The hydrochloride was obtained as colorless needles with mp 239–240° (from alcohol–ether). Found: C 63.0; H 5.6; Cl 11.3; N 13.5%. $C_{16}H_{17}N_3O \cdot HCl$. Calculated: C 63.3; H 6.0; Cl 11.6; N 13.8%.

LITERATURE CITED

1. V. I. Sokolov, B. A. Ardashev, I. S. Kashparov, and A. F. Pozharskii, Khim. Geterotsikl. Soedin., 849 (1973).
2. G. N. Pershin, A. F. Pozharskii, I. S. Kashparov, N. S. Bogdanova, N. A. Novitskaya, and A. L. Mikerina, Khim.-Farmats. Zh., 2, 5 (1973).
3. A. Albert, Selective Toxicity and Related Topics, 4th ed., Methuen (1968).
4. A. F. Pozharskii and I. S. Kashparov, Khim. Geterotsikl. Soedin., 111 (1970).
5. A. F. Pozharskii and A. M. Simonov, Chichibabin Amination of Heterocycles [in Russian], Izd. RGU, Rostov-on-Don (1971), p. 72.