SYNTHESIS OF SOME QUATERNARY GRANATANOL ESTERS OF PHARMACOLOGICAL ACTIVITY

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In order to clear up the nature of the correlation between pharmacological activity and stereostructure in the case of the esters of such compounds of granatane skeleton where the ring is longer by a methylene group than that of the group of alkaloids of tropane skeleton, certain granatanol esters were prepared which were isomeric as regards the configuration of the C(3) atom. The comparative study of these compounds, together with that of other derivatives, is expected to result in valuable data, complementing our knowledge of stereo-structure and pharmacological effect.

Of the tropan alkaloids, many compounds of intensive pharmacological activity are known. These can be classified, in essence, in three main groups, according to the representative members of outstanding effect which occur in nature: 1) the group of atropine and ist derivatives, 2) hyoscine and its derivatives and 3) cocaine and the group of substances derivable from it or being in close relation to it.

Differences exist also in the pharmacological activities of the members of these groups [1].

Quaternary tropan esters are similarly discussed in literature in detail.

The quaternary methylate of atropine has been prepared already in 1869 [2]. The curare-like effect of these substances was reported by HILDEBRAND [3]. Studies in detail were carried out by ISSEKUTZ and associates [4, 5, 6] with the scope to clear up the curare-like effect of quaternary tropeins. In the case of quaternary tropeins of the atropine group, ganglion blocking action was observed by GYERMEK and SZTANYIK [7]. The investigations of other authors [8] in the field of the quaternary derivatives of the hyoscine group resulting in discovering important therapeutics such as butyl scopolammonium bromide.

Aliphatic tropin esters proved to show a parasympathicomimetic activity.

The afore-mentioned observations, together with the synthesis of a great number of compounds of tropan skeleton made possible to disclose in detail the correlation of pharmacological activity and chemical structure. It appears practical to mention here only a few of these observations. It was found *e. g.* that the characteristic effect of atropine on ganglions is due to the ester nature of the compounds. Another observation of interest is that in the groups

of atropine and hyoscine, respectively, the activity is reduced to 1/8 by converting the substances into norcompounds.

According to the mentioned authors, *e. g.* the quaternary nitrogen of hyoscine is, from the aspect of activity, more essential than the epoxy group, in that the effectiveness was in some cases reduced by introducing an epoxy group [9].

The hydroxyl group on the C(3) atom of the tropan skeleton may be either cis (β) or trans (α) positioned with respect to the methyl group on the nitrogen atom of the ring. In order to secure the pharmacological activity of atropine, an optimum distance between the nitrogen and oxygen atoms is essential [10]. Whilst this is present in the case of α-tropine, the β-isomer is lacking that property [1], and this is the cause why the activities of both isomers are different. The ganglion blocking and the curare-like effects are not influenced by the steric position of hydroxyl group 3. From the aspect of the local anesthetic effect of cocaine, the steric position of the C(2)-carbomethoxy group of cocaine has no essential role. Moreover, the presence of the carbomethoxy group is not necessary at all for securing a local anesthetic activity [1].

The steric position of the substituent groups of the C(3) atom is, in turn, of appreciable importance from the point of view of ganglion blocking effect. In this aspect, α-tropine esters proved to possess lower activities than β-tropine esters. The effect is, in general, reduced in these cases by quaternization. However, quaternary derivatives disclose certain favourable properties in that they dissolve and are assimilated more readily.

We carried out experiments in the first line with alkaloids of granatane skeleton, *i. e.* alkaloids possessing a ring system longer by a methylene group than that of the tropan skeleton. The scope of our investigations was on one hand to clear up the configuration of the hydroxyl group of the C(3) atom with respect to the methyl group of the N atom, and, on the other hand, to prepare ecgonine analogs on the granatane skeleton [11]. At the same time, also a group of salts of granatanium esters were produced. These latter seem to be promising in studies into the various effects of α- and β-esters.

Experimental

Acetone dicarboxylic acid was prepared according to Organic Syntheses Coll. Vol. I [12].

Glutaric aldehyde dioxime was prepared according to the prescriptions by COPE and associates [13].

Pseudo-pelletierine. Glutaric aldehyde required for condesation was prepared from glutaric aldehyde dioxime according to COPE and associates [13] and applied without isolation. Condensation was carried out by the ZIEGLER and WILMS method [14]. The obtained crude product was distilled under reduced pressure. B. $p._{4\,mmHg}$: 98—100 °C. Yield 54 %.

Pseudo-pelletierine was quantitatively determined in form of its reineckate. On applying a 1 % solution of Reinecke's salt in an excess of 30 %,

pseudopelletierine was quantitatively precipitated as a violet crystalline powder, m. p. 193—194 °C.

Prior to analysis, the product was dried for 4 hours at 78 °C under reduced pressure.

$C_{13}H_{22}ON_7S_4Cr$ (472,53)

Calcd. C 33,01; H 4,69; N 20,75; Cr (as Cr_2O_3) 16,09 %.

Found C 32,81; H 5,05; N 21,12; Cr 16,30 %.

The precipitation of pseudo-pelletierine as reineckate lends itself as well to the quantitative determination of aminoketone of the reaction mixture [15].

Granatan—3 β-ol. Prepared according to CIAMICIAN and SILBER (16), and, respectively, to ALDER and DORTMANN (17). The prescriptions were slightly modified in that the crude crystalline granatane—3 β-ol obtained on processing the reduction mixture was extracted with benzene, the benzene solution dried with $MgSO_4$ *siccum*, evaporated and distilled under reduced pressure.B. p. 8 mm Hg: 128—130 °C. On crystallizing the distillate from the mixture of 2 parts by weight of anhydrous benzene and 4 parts by weight of petroleum ether, yield 80 % of perfectly pure granatane—3 β-ol, m. p. 99—100 °C.

$C_9H_{17}ON$ (155,2)

Calcd. C 69,63; H 11,04; N 9,02 %

Found C 69,50; H 11,20; N 8,70 %.

The picrate, m. p. 264—265 °C (from water)

$C_9H_{17}ON \cdot C_6H_3O_7N_3$ (384,3)

Calcd. C 46,87: H 5,25; N 14,58 %

Found C 47,10; H 5,43; N 14,40 %.

Granatane—3 β-ol. Prepared by reduction with Raney-nickel, as prescribed by ALDER and associate (18). The substance is extremely hygroscopic.

$C_9H_{17}On$ (155,2)

Calcd. C 69,63; H 11,04; N 9,02 %

Found C 69,60; H 11,15; N 9,20 %.

The picrate, on recrystallisation from ethanol, showed m. p. 275—276 °C.

$C_9H_{17}ON \cdot C_6H_3O_7N_3$ (384,3)

Calcd.: C 46,87; H 5,25; N 14,58 %

Found: C 47,01; H 5,43; N 14,70 %.

O-acetyl—3 β-granatanol. Prepared by dissolving 1 mole of 3 β-granatanol in 20 moles of acetic anhydride and refluxing the solution for 5 hours in a Babo funnel. On removing excess glacial acetic acid by distillation under

reduced pressure, the residue was treated with double volume of distilled water and processed with potassium carbonate. After extraction with 5—6 portions of 50—100 ml of ether, the ethereal solutions were dried with $MgSO_4$ *siccum*, evaporated and the obtained O-acetyl compound distilled from oil bath under reduced pressure. Straw-yellow viscous liquid, b. p. 9 mm Hg: 135—150 °C.

$C_{11}H_{19}O_2N$ (197,27) n_D^{25}: 1,4849

Calcd.: C 66,66; H 9,62; N 7,19 %

Found: C 66,50; H 9,27; N 7,11 %.

The picrate showed m. p. 201 °C.

$C_{11}H_{19}ON \cdot C_6H_3O_7N$ (410,38)

Calcd.: C 49,75; H 5,40; N 13,65 %

Found: C 49,66; H 4,94; N 13,61 %.

O-acetyl—3 β-granatanol. Prepared by refluxing for 5 hours the solution of 1 mole of freshly distilled 3 α-granatanol in 2 moles of acetic anhydride. Excess glacial acetic was removed by distillation under reduced pressure. On treating the residue with double volume of distilled water, the aqueous solution was saturated with potassium carbonate and the alkaline solution extracted with 5—6 portions of 50—100 ml of ether. The combined ethereal solutions were dried with $MgSO_4$ *siccum*, the solvent removed by distillation under reduced pressure and the obtained viscous residue distilled on the oil bath under reduced pressure. Light yellowish liquid, b. p. 10 mm Hg: 172—190 °C.

$C_{11}H_{19}O_2N$ (197,27) n_D^{25}: 1,4849

Calcd.: C 66,66; H 9,62; N 7,19 %

Found: C 66,06; H 9,56; N 7,17 %.

The picrate disclosed m. p. 204 °C.

$C_{11}H_{19}O_2N \cdot C_6H_3O_7N_3$ (410,38)

Calcd.: C 49,75; H 5,40; N 13,65 %

Found: C 50,02; H 5,06; N 13,58 %.

O-α-acetyl-N-dimethyl granatanium iodide. Prepared by treating the solution of 1 mole of O-acetyl-3 α-granatanol in 100 ml of anhydrous ethanol with one mole of methyl iodide. On allowing the mixture to stand for a short time, the crystalline product quantitatively precipitated, m. p. 329 °C

$C_{12}H_{22}O_2NI$ (339,22)

Calcd.: C 42,48; H 6,53; $I^{(-)}$ 37,01 %

Found: C 42,72; H 6,24; $I^{(-)}$ 37,21 %.

O-α-acetyl-N-methyl-ethyl granatanium iodide. Prepared by processing one mole of O-acetyl—3 α-granatanol, dissolved in 10 ml of anhydrous ethanol, with one mole of ethyl iodide [18]. Allowing the mixture to stand for 24 hours in a dark place, the quaternary iodide crystallised almost quantitatively, m. p. 337,5 °C.

$C_{13}H_{24}O_2NI$ (353,25)

Calcd.: C 44,19; H 6,85; $I^{(-)}$ 35,82 %

Found: C 43,96; H 7,02; $I^{(-)}$ 36,18 %.

O-α-acetyl-N-methyl-propyl granatanium iodide. Prepared by quaterneration of one mole of O-acetyl—3 α-granatanol with one mole of propyl iodide [18] in the previously described way. On allowing the mixture to stand for several days, the quaternary salt crystallized. On filtering and washing with anhydrous ethanol, m. p. 240 °C.

$C_{14}H_{26}O_2NI$ (367,28)

Calcd.: C 45,76; H 7,01; $I^{(-)}$ 34,54 %

Found: C 45,66; H 7,17; $I^{(-)}$ 34,24 %.

O-β-acetyl-N-dimethyl granatanium iodide. Prepared by processing the solution of one mole of O-acetyl—3 β-granatanol in anhydrous ethanol with one mole of methyl iodide. The formed quaternary salt immediately precipitates and can be filtered, m. p. 331 °C, The reaction is quantitative.

$C_{12}H_{22}O_2NI$ (339,22)

Calcd.: C 42,48; H 6,24; $I^{(-)}$ 37,01 %

Found: C 42,62; H 6,53; $I^{(-)}$ 37,14 %.

O-β-acetyl-N-Methyl-ethyl granatanium iodide. Prepared by processing one mole of O-acetyl—3 β-granatanol with one mole of ethyl iodide. Allowing the mixture to stand for several days, the crystalline product almost quantitatively precipitates. On filtering and drying, m. p. 289,5 °C.

$C_{13}H_{24}O_2NI$ (353,25)

Calcd.: C 44,19; H 6,85; $I^{(-)}$ 35,92 %

Found: C 44,06; H 7,05; $I^{(-)}$ 35,76 %.

O-β-acetyl-N-methyl-propyl granatanium iodide. Prepared by treating one mole of O-acetyl—3 β-granatanol with one mole of propyl iodide in the afore-mentioned way. On allowing the mixture to stand for some days, the precipitated crystals are filtered. The product is obtained in theoretical yield. On recrystallisation from anhydrous ethanol, m. p. 290 °C.

$C_{14}H_{26}O_2NI$ (367,28)

Calcd.: C 45,90; H 7,14; $I^{(-)}$ 34,42 %

Found: C 45,50; H 7,10; $I^{(-)}$ 34,60 %.

References

[1] *Gyermek, L., K. Nádor:* J. Pharm. Pharmacol. **9**, 209 (1957).
[2] *Crum Brown, Faser:* Trans. Roy. Soc., Edinburgh **25**, 151, 693 (1869).
[3] *Hidebrandt, F.:* Arch. exp. Path. Pharmak. **56**, 73 (1905).
[4] *Issekutz, B.:* Z. exp. Path. **19**, 99 (1918).
[5] *Issekutz, B., K. Nádor:* Acta Physiol. Acad. Sci. Hung. Suppl. **1**, (1951).
[6] *Gyermek, L., L. Sztanyik:* Acta Physiol. Acad. Sci. Hung. **2**, 41 (1951).
[7] *Gyermek, L., K. Nádor:* Acta Physiol. Acad. Sci. Hung. **3**, 183 (1952).
[8] *Wick, C.:* Arch. exp. Path. Pharmak. **213**, 485 (1951).
[9] *Gyermek, L.:* Acta Physiol. Acad. Sci. Hung. **2**, 511 (1951).
[10] *Pfeiffer, S. C.:* Science **107**, 94 (1948).
[11] *Weisz, I., M. Halmos, B. Matkovics:* Naturwiss. **45**, 568 (1958).
[12] Organic Synthesis, (John Wiley and Sons Inc., New York, 1941), Coll. Vol. 1., p. 10.
[13] *Cope, A. C., H. L. Dryden Jr., C. A. Overberger, A. A. D'Addiew:* J. Amer. Chem. Soc. **73**, 3416 (1951).
[14] *Ziegler, K., H. Wilms:* Ann. **567**, 1 (1950).
[15] *Gál, Gy., I. Simonyi, G Tokár:* Magy. Kém. Foly. **61**, 74 (1955).
[16] *Ciamician, A., P. Silber:* Chem. Ber. **25**, 1062 (1892).
[17] *Alder, K., H. A. Dortmann:* Chem. Ber, **86**, 1544 (1953).
[18] *Vogel, A. I.:* Practical Organic Chemistry (Longmans, Green and Co. 1957).