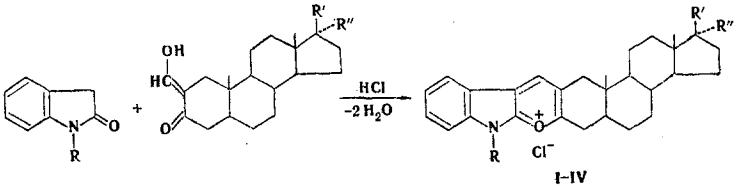
STEROIDO[3,2-b](CARBAZOLE-1-OXONIUM) SALTS

G. I. Zhungietu, B. P. Sukhanyuk,
F. N. Chukhrii, and L. N. Volovel'skii

UDC 547.756'816'924

The reaction of 2-hydroxymethylene-3-ketosteroids with 2-ketoindoline in the presence of hydrogen chloride gives steroido[3,2-b](carbazole-1-oxonium) chlorides, which split out a 2-ketoindoline molecule under the influence of phenylhydrazine and are converted to steroido[3,2-c]-1'-phenylpyrazoles.

Of the modified steroids, particular attention has been directed to those that contain heterocyclic residues that have a substantial effect on the physiological activity of the system as a whole [1]. Continuing our research on the synthesis of pyrylium derivatives of steroids [2-4], we have found that 2-hydroxymethylene-3-ketosteroids form steroidopyrylium salts I-IV with 2-ketoindoline on saturation of solutions of equimolecular amounts of the reagents in methanol, ethanol, or ether with hydrogen chloride.



I-IV

I R=R''=H, R'=OH; II R=CH_3, R'=OH, R''=H; III R=H, R'=OH, R''=C_2H_5; IV R=CH_3, R'=C_8H_{17}, R''=H

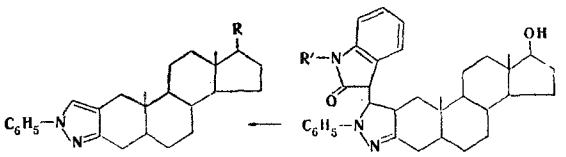
The IR spectra of I-IV do not contain carbonyl group absorption, but the stretching vibrations of the C=C bonds of the pyrylium cation [5] appear as two intense absorption bands at 1650 and 1570 cm^{-1}.

The compounds that we obtained are of definite interest, since it is assumed that steroids that contain an indole residue together with a hormone residue should also have directed psychotonic activity [6]. In addition, the presence of a pyrylium ring makes it possible to use these compounds for a number of additional transformations and for the preparation of new derivatives. In [2-4], pyrylium derivatives of steroids were converted to steroidopyridines by treatment with ammonia. However, salts I-IV could not be converted to pyridine bases; prolonged refluxing with ammonium acetate in acetic acid gave a complex mixture of products from which not even one could be isolated in the crystalline state by chromatography with a column filled with aluminum oxide. It is possible that there is a certain analogy between the behavior of these salts and that of benzopyrylium salts in which the oxygen is bonded directly to the aromatic ring (as a rule, these compounds also are not converted to pyridines [7]).

Interesting results are obtained when salts I-IV are treated with phenylhydrazine. 17β-Hydroxyandrostano[3,2-b](carbazole-1-oxonium) chloride (I) on refluxing with phenylhydrazine in alcohol is apparently converted to pyrazoline V, which splits out a 2-ketoindoline residue to give 17β-hydroxyandrostano-[3,2-c]-1'-phenylpyrazole (VI), while, under similar conditions, its N-methyl derivative (II) is converted to pyrazoline VII in analogy with many other examples of the formation of pyrazolines from pyrylium salts (for example, see [8, 9]):

Institute of Chemistry, Academy of Sciences of the Moldavian SSR, Kishinev. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 2, pp. 219-221, February, 1973. Original article submitted January 4, 1972.

© 1975 Consultants Bureau, a division of Plenum Publishing Corporation, 227 West 17th Street, New York, N. Y. 10011. No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, microfilming, recording or otherwise, without written permission of the publisher. A copy of this article is available from the publisher for $15.00.



VI, VIII, IX V, VII

VI R=OH; VIII R=$OCOCH_3$; IX R=C_8H_{17}; V R'=H; VII R'=CH_3

Intense absorption bands of a carbonyl group (1690 cm^{-1}) and of a C=C double bond (1600 cm^{-1}) appear in the IR spectrum of pyrazoline VII. On brief refluxing in acetic acid, this compound gives 17β-acetoxyandrostano[3,2-c]-1'-phenylpyrazole (VIII) as a result of splitting out of a 2-ketoindoline residue and simultaneous acetylation of the secondary hydroxyl group. Saponification of acetate VIII with aqueous alcoholic alkali leads to pyrazole VI. The conversion of salts of the I-IV type to pyrazoles of the VI type can also be carried out without the isolation of the intermediate compounds. For example, pyrylium salt IV forms pyrazole IX on more prolonged refluxing with phenylhydrazine in alcohol.

The formation of steroido[3,2-c]-1'-phenylpyrazoles from salts I-IV may be of definite interest, since it is known that the direct reaction of 2-hydroxymethylene-3-ketosteroids with phenylhydrazine does not make it possible to obtain these products in the pure state in good yields but, as a rule, gives primarily 2'-phenylpyrazoles [10, 11]. The absorption maxima in the UV spectra of pyrazoles VI, VIII, and IX are found at 260 nm [10-12].

We were unable to isolate the expected pyrylium salts on numerous attempts to condense 2-ketoindoline and 1-methyl-2-ketoindoline with 16-hydroxy methylene-17-ketosteroids; as in the preceding papers [2-4], we explain this in terms of the known strained character of the cyclopentane ring.

EXPERIMENTAL

The IR spectra of mineral oil pastes were recorded with a UR-10 spectrometer. The UV spectra of methanol solutions were recorded with a Specord spectrophotometer. The melting points were determined with a Kofler block and were not corrected. The individuality of all of the compounds was verified by chromatography on plates with a thin layer of aluminum oxide.

17-β-Hydroxyandrostano[3,2-b](carbazole-1-oxonium) Chloride (I). A solution of 0.63 g (2 mmole) of 2-hydroxymethylenedihydrotestosterone and 0.27 g (2 mmole) of 2-ketoindoline in 15 ml of methanol was cooled with ice and saturated with dry hydrogen chloride, after which the mixture was allowed to stand in a refrigerator for a few hours. The resulting crystalline precipitate was removed by filtration, washed thoroughly with absolute ether, and recrystallized from methanol to give 0.45 g (46%) of a product with mp 226°. Found,%: C 71.8; H 7.8; Cl 7.0; N 3.0. $C_{28}H_{34}ClNO_2 \cdot CH_3OH$. Calculated,%: C 72.0; H 7.9; Cl 7.3; N 2.9.

The following compounds were similarly obtained: 17β-hydroxyandrostano[3,2-b](9-methylcarbazole-1-oxonium) chloride (II) (96% yield, mp 243°. Found,%: C 68.0; H 7.9; N 2.5. $C_{29}H_{36}ClNO_2 \cdot 3CH_3OH$. Calculated,%: C 68.3; H 8.5; N 2.5). 17α-ethyl-17β-hydroxyandrostano[3,2-b](carbazole-1-oxonium)chloride (III) (52% yield, mp 188-189°. Found,%: C 75.2; H 7.9; Cl 7.6; N 3.1. $C_{30}H_{38}ClNO_2$. Calculated,%: C 75.1; H 7.9; Cl 7.4; N 2.9) and cholestano[3,2-b](9-methylcarbazole-1-oxonium) chloride (IV) [92% yield, mp 147-148° (from aqueous alcohol). Found,%: C 76.0; H 9.3; Cl 6.3; N 2.5. $C_{37}H_{52}ClNO \cdot H_2O$. Calculated,%: C 76.6; H 9.3; Cl 6.1; N 2.4].

17β-Hydroxyandrostano[3,2-c]-1'-phenylpyrazole (VI). A solution of 1.03 g (2 mmole) of chloride I and 0.4 g (4 mmole) of phenylhydrazine in 20 ml of methanol was refluxed for a few hours, after which it was cooled and poured into water. The product was extracted in the usual way to give 0.35 g (45%) of a product with mp 238° (from benzene–petroleum ether). λ_{max}, nm (log ε): 212 (4.30), 268 (4.82). Found,%: C 79.7; H 8.9; N 7.2. $C_{26}H_{34}N_2O$. Calculated,%: C 80.0; H 8.7; N 7.2.

17β-Hydroxyandrostano[3,2-c]-1'-phenyl-5'-(1-methyl-2-keto-3-indolinyl)-Δ^2-pyrazoline (VII). This compound was similarly obtained in 67% yield and had mp 184°. Found,%: C 78.1; H 8.1. $C_{36}H_{43}N_3O_2$. Calculated,%: C 78.2; H 8.0.

17β-Acetoxyandrostano[3,2-c]-1'-phenylpyrazole (VIII). A solution of 1.1 g (2 mmole) of pyrazoline VII in 10 ml of acetic acid was refluxed for 2 h, after which the solvent was removed by distillation at reduced pressure, and the residue was crystallized from benzene–petroleum ether to give 0.8 g (93%) of a

product with mp 229°. λ_{max}, nm (log ε): 270 (4.63), 212 (4.43). Found,%: C 77.6; H 8.3; N 6.0. $C_{28}H_{36}N_2O$. Calculated,%: C 77.8; H 8.3; N 6.5. Pyrazole VI was formed in quantitative yield when acetate VIII was refluxed in aqueous alcoholic alkali.

Cholestano[3,2-c]-1'-phenylpyrazole (IX). A solution of 5.8 g (10 mmole) of chloride IV and 2.16 g (20 mmole) of phenylhydrazine in 20 ml of methanol was refluxed for a few hours, after which it was poured into water. The product was extracted in the usual way and crystallized from benzene–petroleum ether to give 3.2 g (66%) of a product with mp 137-138°. λ_{max}, nm (log ε): 270 (4.83), 212 (4.60). Found,%: C 84.0; H 10.5. $C_{34}H_{50}N_2$. Calculated,%: C 84.0; H 10.3.

LITERATURE CITED

1. G. I. Zhungietu and G. N. Dorofeenko, Usp. Khim., 36, 48 (1967).
2. G. I. Zhungietu, G. N. Dorofeenko, and G. V. Lazur'evskii, Dokl. Akad. Nauk SSSR, 163, 372 (1965).
3. G. I. Zhungietu, G. N. Dorofeenko, L. N. Volovel'skii, and G. V. Lazur'evskii, Khim. Geterotsikl. Soedin., 318 (1965).
4. G. N. Dorofeenko, L. N. Volovel'skii, and B. M. Savin, Zh. Obshch. Khim., 39, 659, 676 (1969).
5. A. T. Balaban, G. Mateescu, and M. Elian, Tetrahedron, 18, 1083 (1962).
6. M. G. Lester, V. Petrow, and O. Stephenson, Tetrahedron, 21, 1761 (1965).
7. K. Dimroth, Angew. Chem., 72, 331 (1960).
8. G. N. Dorofeenko, A. N. Narkevich, and Yu. A. Zhdanov, Khim. Geterotsikl. Soedin., 1130 (1967).
9. A. T. Balaban, Tetrahedron, 24, 5059 (1968).
10. R. O. Clinton, A. J. Manson, F. W. Stonner, H. C. Neumann, R. G. Christiansen, R. L. Clarke, J. H. Ackerman, D. F. Page, J. W. Dean, W. B. Dickinson, and C. Carabateas, J. Am. Chem. Soc., 83, 1478 (1961).
11. R. Hirschmann, N. G. Steinberg, P. Buchschacher, J. H. Fried, G. J. Kent, and M. Tishler, J. Am. Chem. Soc., 85, 120 (1963).
12. N. J. Doorenbos and L. Milewich, J. Org. Chem., 31, 3193 (1966).