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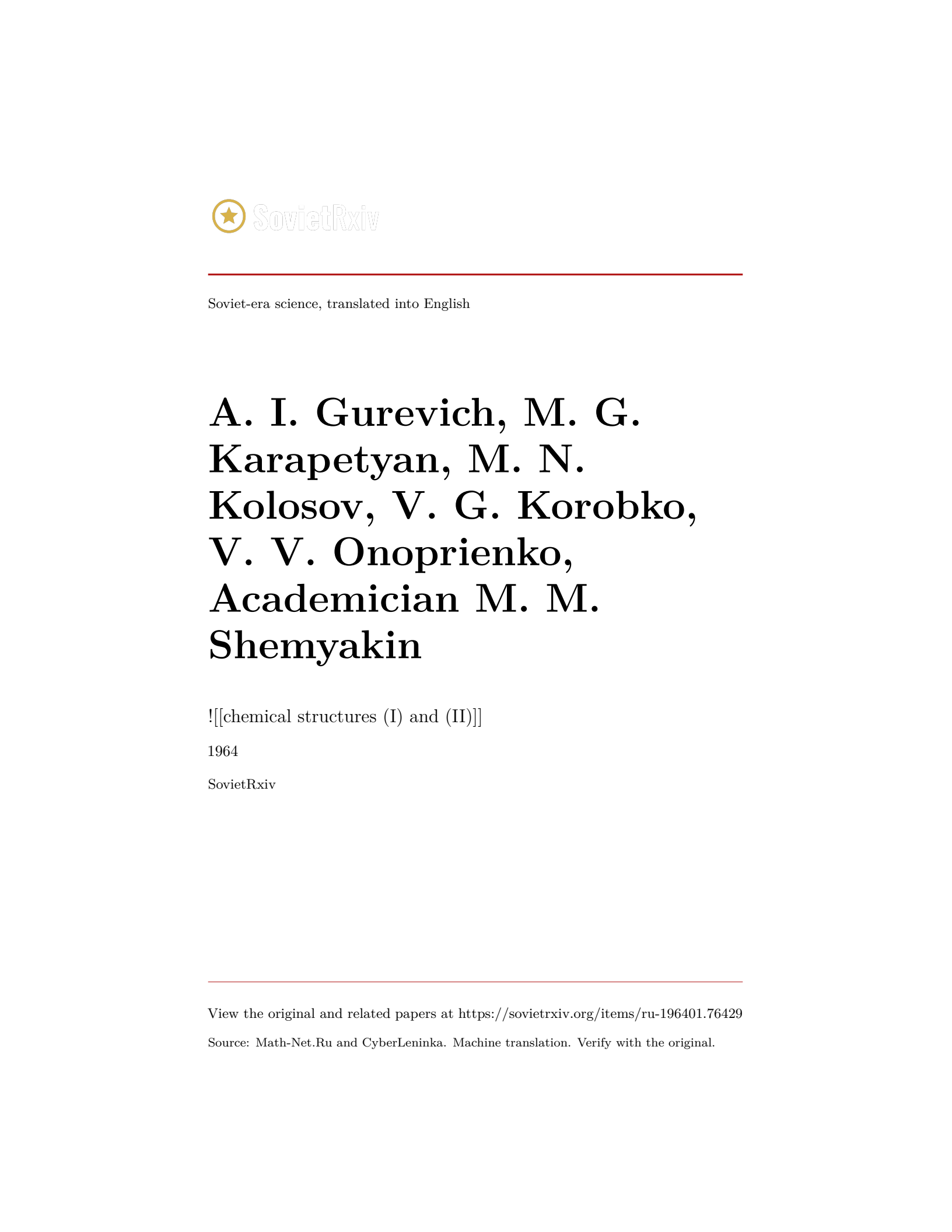

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Abstract

Full Text

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SYNTHESIS OF HYDRONAPHTHACENES RELATED TO ANHYDROTETRACYCLINES

Thanks to the discovery of the reaction of photochemical C_6-hydroxylation of anhydroaureomycin ([1]), 5a,6-anhydrotetracyclines (I) have acquired importance as intermediates for obtaining natural tetracyclines (II). In this connection we undertook investigations in a series of anhydrotetracyclines with the aim of finding rational routes for their synthesis. First of all, we carried out the synthesis of hydronaphthacene triketoamides of type (XVI), which created the prerequisites for accomplishing the total synthesis of the 5a,6-anhydrotetracyclines themselves.

[[chemical structures (I) and (II)]]

The key compounds in our synthesis were 2,3-unsaturated 4-ketones (VI) and (VIII), of which the first had been described earlier ([2]), while the second was obtained by the following route (constants and analytical data of the synthesized –

Table 1

Compound	M.p., °C (solvent for crystallization)	λ_{max}^{EtOH}, mμ (lg ε)	ν_{max}^{nujol}, cm^{-1}	Found, % C	Found, % H	Calculated, % C	Calculated, % H
IIIb	165–166 (EtOH)	225, 258, 313 (4.48; 4.02; 3.57)	1589, 1686, 1723, 1731	71.84	5.87	71.41	5.75
IV	173–175 (benzene)	277, 283 (3.19; 3.16)	1590, 1707, 1724, 3400	70.94	6.41	71.07	6.20

Compound	M.p., °C (solvent for crystallization)	λ_{max}^{EtOH}, mμ (lg ε)	ν_{max}^{nujol}, cm^{-1}	Found, % C	Found, % H	Calculated, % C	Calculated, % H
Va	148–149 (EtOH)	278, 284 (3.36; 3.36)	1586, 1602, 1727	74.96	6.45	74.98	6.29
Vb	163–164 (EtOH)	276, 284 (3.42; 3.41)	1592, 3040, 3320, 3340	78.19	6.25	78.48	6.59
VII	164–165 (EtOH)	242, 352 (3.84; 4.12)	1595, 1665, 1720, 1733, 1753, 3420, 3460	71.13	6.61	70.71	6.55
VIII	131–132 (EtOH)	258, 276, 284 (3.06; 3.33; 3.33)	1585, 1673, 3385	78.55	5.85	78.85	6.14
IX	97–98 (EtOH)	242, 352 (3.93; 4.16)	1590, 1662, 1730, 3480	70.78	6.58	70.71	6.55
Xa	114–115 (EtOH)	219, 263, 309, 320, 372 (4.52; 4.57; 3.69; 3.58; 3.64)	1628, 1699, 1727, 1748	73.09	6.04	73.02	6.13

Compound	M.p., °C (solvent for crystallization)	λ_{max}^{EtOH}, mμ (lg ε)	ν_{max}^{nujol}, cm^{-1}	Found, % C	Found, % H	Calculated, % C	Calculated, % H
Xb	128–130 (EtOH)	222, 261, 308, 319, 372 (4.53; 4.63; 3.76; 3.66; 3.76)	1585, 1622, 1696, 1726	73.24	6.53	73.40	6.37
XI	139–140 (EtOH)	242, 348 (3.85; 4.15)	1572, 1607, 1682, 1757	74.17	6.58	73.92	6.38
XIIa*	145 (AcOEt)	242, 301, 312, 327 (4.61; 3.73; 3.56; 3.20)	1574, 1600, 1706, 1738, 3320	69.18	5.98	69.32	5.82
XIIb	144–145 (50% EtOH)	236, 302, 315, 329 (4.71; 3.87; 3.74; 3.45)	1575, 1595, 1708, 3460	71.50	5.66	71.41	5.75
XIIIa	171–172 (EtOH)	242, 292, 300, 326 (4.67; 3.74; 3.77; 3.26)	1577, 1600, 1712, 3300	76.39	6.18	76.22	6.12

Compound	M.p., °C (solvent for crystallization)	λ_{max}^{EtOH}, mμ (lg ε)	ν_{max}^{nujol}, cm^{-1}	Found, % C	Found, % H	Calculated, % C	Calculated, % H
XIIIb	159–160 (benzene)	238, 292, 303, 316, 330 (4.67; 3.75; 3.85; 3.68; 3.26)	1575, 1596, 1710, 3460	76.38	6.29	76.57	6.43
XIVa	163–165 (AcOEt)	220, 261, 307, 320, 370 (4.49; 4.47; 3.70; 3.59; 3.57)	1572, 1600, 1627, 1684, 1706	76.42	5.58	76.65	5.59
XIVb	193–194 (AcOEt)	223, 260, 309, 320, 372 (4.54; 4.60; 3.74; 3.64; 3.74)	1582, 1616, 1681, 1700	77.10	6.13	76.98	5.92

Compound	M.p., °C (solvent for crystallization)	λ_{max}^{EtOH}, mμ (lg ε)	ν_{max}^{nujol}, cm^{-1}	Found, % C	Found, % H	Calculated, % C	Calculated, % H
XVa	147–149 (EtOH)	219, 263, 308, 320, 372 (4.50; 4.54; 3.70; 3.59; 3.60)	1547–1575, 1602, 1632, 1662, 1683, 3230	72.52	6.76	72.57	6.66
XVb	170–171 (AcOEt)	224, 262, 308, 320, 372 (4.54; 4.66; 3.73; 3.62; 3.69)	1542–1586, 1625, 1661, 1685, 1712, 1742, 3230	72.88	6.87	72.90	6.86
XVIa	161–163 (EtOH)	245, 259, 384 (4.41; 4.47; 4.59)	1563, 1585, 1612, 3200	74.02	6.20	74.51	6.05
XVIb	193–195 (AcOEt)	248, 263, 382 (4.30; 4.34; 4.39)	1542–1576, 1622, 3330	74.42	6.68	74.83	6.28
XVIII	amorphous	266, 340 (3.78; 4.06)	1380, 1568, 1596, 1753, 3470	64.82	5.58	64.85	5.65

Compound	M.p., °C (solvent for crystallization)	λ_{max}^{EtOH}, mμ (lg ε)	ν_{max}^{nujol}, cm^{-1}	Found, % C	Found, % H	Calculated, % C	Calculated, % H
XIX	amorphous	269, 297, 308, 322, 407 (4.54; 3.72; 3.68; 3.56; 3.90)	1380, 1562–1580, 1620, 1755, 3400–3600	66.72	5.68	67.37	5.44

* Crystallosolvate with 0.5 mol AcOEt.

···of the compounds are given in Table 1). 9-Keto-4,10-diol (IIIa)[2] was converted by the action of acetic anhydride in pyridine into 4,10-diacetoxy-9-ketone (IIIb), which was reduced with 0.3 mole of `LiAlH$_{4}$` in tetrahydrofuran at −60° to the 9α-hydroxy-4,10-diacetate (IV) (the configuration of the asymmetric center C_9 in this compound was assigned on the basis of Cram' s rule). The hydroxyl group was then protected by alkylation with benzyl bromide in the presence of silver oxide, and the resulting 5,9-dibenzyloxy-4,10-diacetate (Va) was saponified with aqueous methanolic KOH to the 4,10-diol (Vb), and the latter was oxidized to the 10-hydroxy-4-ketone (VIII).

(IIIa): $R = H$ (IIIb): $R = Ac$

(IV)

(Va): $R = Ac$ (Vb): $R = H$

(VI) (VII) (VIII)

(IX) (Xa): $R = H$ (Xb): $R = Me$ (XI)

Introduction of the carbon chain necessary for construction of the fourth ring into position 2 of ketols (VI) and (VIII) was accomplished by condensation of these compounds with sodium malonate according to Michael. In the case of ketol (VIII), addition of the malonic residue to the double bond was accompanied by dehydration of the β-hydroxy ketone grouping, leading to the 4a,10-unsaturated keto ester (XI); on heating the latter with alcoholic `H$_{2}$SO$_{4}$`, the tetrahydroanthracene keto ester (Xa) was obtained. The Michael condensation with ketodiol (VI), or its O_{10}-acetate, proceeded analogously; depending on the reaction conditions, the keto ester (VII) or

Reaction scheme showing compounds (XIIa) R = H, (XIIb) R = Me → (XIIIa) R = H, (XIIIb) R = Me → (XIVa) R = H, (XIVb) R = Me → (XVa) R = H, (XVb) R = Me → (XVIa) R = H, (XVIb) R = Me; the final tetracyclic products have rings labeled D, C, B, A.

Figure 1: Reaction scheme showing compounds (XIIa) R = H, (XIIb) R = Me → (XIIIa) R = H, (XIIIb) R = Me → (XIVa) R = H, (XIVb) R = Me → (XVa) R = H, (XVb) R = Me → (XVIa) R = H, (XVIb) R = Me; the final tetracyclic products have rings labeled D, C, B, A.

Reaction scheme showing compounds (XVII) → (XVIII) → (XIX).

Figure 2: Reaction scheme showing compounds (XVII) → (XVIII) → (XIX).

its C_2-epimer (IX) was formed predominantly. Both of these keto esters, on dehydration with `H$_{2}$SO$_{4}$`, were converted into compound (Xb).

Saponification of keto esters (X) to the corresponding dicarboxylic acids proceeded unsatisfactorily, since under the action of bases compounds (X) undergo retro-Michael cleavage with elimination of malonic ester and formation of 5-benzyloxyanthrols-1. Therefore, for conversion into keto acids (XIV), keto esters (X) were first reduced with `NaBH$_{4}$` in neutral solution and then saponified with alkali to the hydroxy acids (XII); the latter were decarboxylated by heating in pyridine, and the resulting hydroxy acids (XIII) were oxidized to the keto acids (XIV).

Further construction of ring A was carried out by a method which is basically analogous to that proposed earlier ([3]), but is more convenient experimentally. The keto acids (XIV), by the action of phosgene on their triethylammonium salts in tetrahydrofuran at -70°, were converted into mixed anhydrides; acylation of an ethoxymagnesium derivative of N-tert-butylmalonamic ester with these anhydrides led in high yield to diketo amido esters (XV). Attempts to close ring A in these compounds by intramolecular acylation of the 3,4-methyleneketone group with the ester residue on heating with freshly prepared sodium amide, triphenylmethylsodium, or finely dispersed sodium (average granule size 1 μ) in various solvents were unsuccessful. Cyclization of the diketo amido esters (XV) was accomplished with the aid of NaH in dimethyl sulfoxide ([4]), as a result of which tetracyclic triketo amides (XVI) were obtained in yields of up to 80%.

The synthesis described opens the possibility of obtaining by an analogous route not only various hydronaphthacene compounds of type (XVI), but also 5a,6-anhydrotetracyclines (I) and, consequently, the natural tetracyclines themselves (II). Thus, for example, condensation of the unsaturated oxydiketone (XVII) synthesized by us earlier ([5]) with nitroacetic ester in the presence of triethylamine gives the adduct (XVIII); dehydration of this adduct with mineral acids affords the tetrahydroanthracene nitrooxy keto ester (XIX), which is a key intermediate for the total synthesis of anhydrotetracycline.

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Note: Figure translations are in progress. See original paper for figures.