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A NEW REACTION OF BIS(o-AMINOPHENYL)DISULFIDE WITH KETO-COMPOUNDS.

PART II. REACTION WITH 17β-HYDROXY-5α-ANDROSTAN-3-ONE

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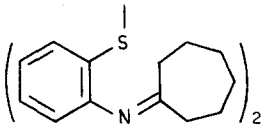
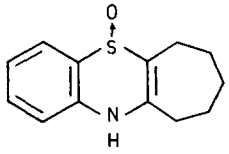
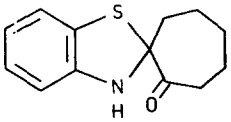
We have reported (1) the synthesis of spiro-compound (III) by reacting bis(o-aminophenyl)disulfide with cycloheptanone and we proved that (III) is formed via intermediates (I) and (II):



(I)



(II)



(III)

We wish now to discuss the application of this reaction and to suggest a mechanism explaining the rearrangement of sulfoxides of type (II) to spiro-compounds of type (III), on the basis of new evidence.

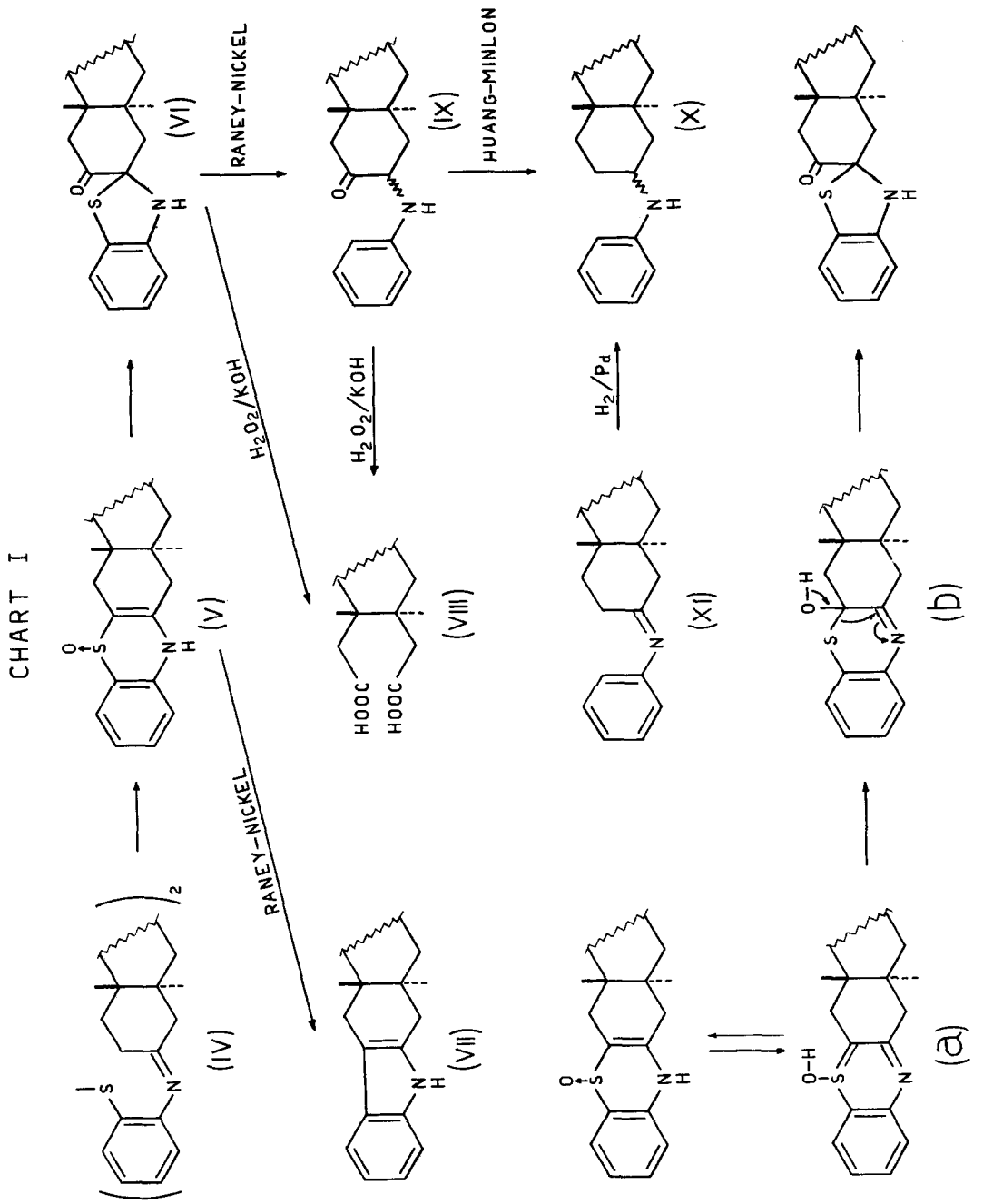
Thus, reacting bis(o-aminophenyl)disulfide with 17β-hydroxy-5α-androstan-3-one in benzene, in the presence of catalytic amounts of p-toluenesulfonic acid and under helium atmosphere, water was produced (1 mole per mole of ketone) and it was possible to isolate compound (IV) m.p. 202° (Found: C, 75.85 - H, 8.72 - N, 3.43 - S, 7.99 - Calcd. for $C_{50}H_{68}N_2O_2S_2$: C, 75.71 - H, 8.64 - N, 3.53 -

S, 8.08 - I.R. ν_{max}^{Nujol} = 3500 (OH), 1680 (C=N) cm^{-1}). To compound (IV) we have assigned the structure of bis(o-17β-hydroxy-5α-androstan-3-ylideneamino-phenyl)disulfide on the basis of the observed properties, and by the similarity of (IV) with the bis(o-cycloheptylideneaminophenyl)disulfide obtained in the cycloheptanone series (1). When (IV) in cyclohexane was stirred under air for several hours, it was converted into a mixture of two compounds: respectively (V) and (VI). These were separated from the oxidation mixture by dilution with ether: the insoluble portion was compound (V); by chromatography on silica gel of the soluble mixture it was possible to obtain pure compound (VI).

To compound (V), m.p. 233° dec. (Found: C, 73.17 - H, 7.94 - N, 3.58 - S, 7.99 - Calcd. for $C_{25}H_{33}NO_2S$: C, 72.95 - H, 8.08 - N, 3.40 - S, 7.79 - I.R. ν_{max}^{Nujol} = 3450 (OH), 3250-3200 (weak, NH), 1640 (C=C) and 960 (S→O) cm^{-1}), we have assigned the structure of 17β-hydroxy-5α-androstano-[2,3-b]-4'H-[1',4']-benzothiazine-1'-oxide. Chemical proof to the above structure was given by desulfurization with Raney-Nickel of sulfoxide (V) into indole-derivative (VII), which was identical with an authentic sample prepared by Fisher's synthesis starting from 17β-hydroxy-5α-androstan-3-one. The sulfoxide (V) was readly transformed into compound (VI) by refluxing with polar solvents.

To compound (VI), m.p. 214° (Found: C, 72.90 - H, 8.15 - N, 3.41 - S, 7.72 - Calcd. for $C_{25}H_{33}NO_2S$: C, 72.95 - H, 8.08 - N, 3.40 - S, 7.79 - I.R. ν_{max}^{Nujol} = 3500 (OH), 3300 (NH), 1700 (C=O) cm^{-1}), we assigned the structure of spiro[17β-hydroxy-5α-androstan-2-one-3,2'-benzothiazoline]. This structure was supported by the following chemical evidence: by oxidation with H_2O_2 in KOH solution, (VI) was converted into 2,3-seco-17β-hydroxy-5α-androstane-2,3-dicarboxylic acid (VIII), which was identical with an authentic sample, prepared according to Minssen et al. (2). Furthermore the Raney-Nickel desulfurization of (VI) yielded 17β-hydroxy-3-anilino-5α-androstan-2-one (IX) m.p. 211° (Found:

CHART I


RANEY-NICKEL
HUANG-MINLON
H_2O_2/KOH
H_2O_2/KOH
H_2/Pd
RANEY-NICKEL
HOOC
HOOC
(IV)
(V)
(VI)
(VII)
(VIII)
(IX)
(X)
(XI)
(a)
(b)

C, 78.45 - H, 9.26 - N, 3.74 - Calcd. for: $C_{25}H_{35}NO_2$: C, 78.68 - H, 9.25 - N, 3.67 - I.R. ν_{max}^{Nujol} = 3500 (OH), 3450 (NH), 1700 (C=O) cm^{-1}). The structure of (IX) was proved by oxidation to the dioic-acid (VIII) with H_2O_2 in KOH solution and by Huang-Minlon reduction to 17β-hydroxy-3-anilino-5α-androstane (X), m.p. 164° (Found: C, 81.80 - H, 10.47 - N, 3.71 - Calcd. for $C_{25}H_{37}NO$: C, 81.69 - H, 10.15 - N, 3.81 - I.R. ν_{max}^{Nujol} = 3500 (NH), 3300 (OH) cm^{-1}). Compound (X) was identical with an authentic sample obtained by catalytic reduction of N-(17β-hydroxy-5α-androstan-3-ylidene)aniline (XI) (°). (Chart I)

The observed sulfur migration, from C_2 to C_3 of steroidic system, in the rearrangement of (IV) to (VI), allow us to suggest the mechanism depicted in Chart I. This conversion, as already mentioned, is catalysed by polar solvents; it is possible therefore in analogy with what has been postulated before for the rearrangement of some sulfoxides (3) that the first step could be the formation of the enol (a), which could then rearrange to the hemithioketal (b) and this could lead, by sulfur migration, to the spiroketone (VI).

(°) We have not established the configuration of this anilino-derivative, which was the only product isolated from the catalytic reduction.

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