INVESTIGATION OF 2,3-POLYMETHYLENEQUINOLINES

XX.* REACTION OF N-CYCLOHEXYLIDENEANTHRANILIC ACID BENZYLAMIDES WITH PHOSPHORUS OXYCHLORIDE

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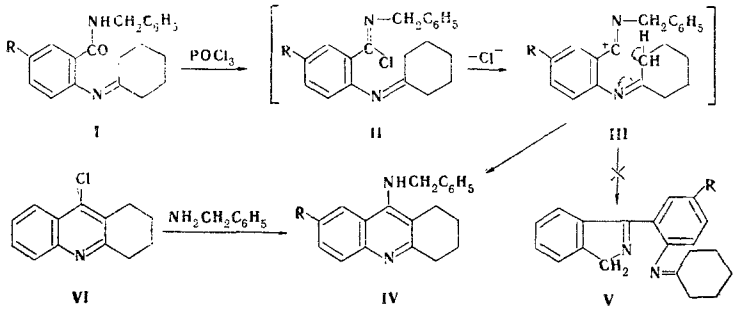
The reaction of N-cyclohexylideneanthranilic acid benzylamides with phosphorus oxychloride is accompanied by cyclization at the α-methylene group of the cyclohexylidene ring to give 9-benzylamino-1,2,3,4-tetrahydroacridines.

9-Alkylamino- [2] and 9-arylamino-1,2,3,4-tetrahydroacridines [3] are formed by intramolecular cyclization of N-cyclohexylideneanthranilic acid alkyl(aryl)amides by means of phosphorus oxychloride. This reaction has been extended to benzylamides I in order to evaluate the reactivity of the benzene ring and the α-methylene group in cyclohexylideneimines.



a R = H; b R = Cl; c R = Br

Under the influence of phosphorus oxychloride, benzylamides I are apparently converted to chloroimides II [4], which dissociate to ions III [5]. Ions III contain an electrophilic reaction center – the nitrilium – and two nucleophilic reation centers – the benzyl group and the cyclohexylidene ring. Although cyclization may, as a consequence of this, lead to two products – 9-benzylamino-1,2,3,4-tetrahydroacridines IV and substituted isoindoles V – the formation of only tetrahydroacridines IV was observed. The higher reactivity of the α-methylene group as compared with the benzene ring can be explained by hyperconjugation – $\overset{\curvearrowright}{N}{=}C-\overset{\curvearrowright}{C}H-H$.

The structure of IVa was confirmed by alternative synthesis from 9-chloro-1,2,3,4-tetrahydroacridine (VI) and by the IR spectrum, which contained an NH band at 3435-3445 cm^{-1}.

*See [1] for communication XIX.

Perm Pharmaceutical Institute. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 7, pp. 966-967, July, 1974. Original article submitted July 10, 1973.

EXPERIMENTAL

N-Cyclohexylideneanthranilic Acid Benzylamides (I). A solution of 0.01 mole of the benzylamide of the appropriate anthranilic acid and 0.01 mole of cyclohexanone in 10 ml of benzene was refluxed for 0.5-4 h, after which it was cooled, and the resulting crystalline precipitate was removed by filtration and crystallized. In the case of Ia, the heating time was 0.5 h, and the yield of product with mp 185-187° (from benzene) was 80%. Found: N 9.3%. $C_{20}H_{22}N_2O$. Calculated: N 9.2%. In the case of Ib, the heating time was 4 h, and the yield of product with mp 215-217° (from benzene) was 70%. Found: N 8.5%. $C_{20}H_{21}ClN_2O$. Calculated: N 8.2%. In the case of Ic, the heating time was 4 h, and the yield of product with mp 214° (from benzene) was 75%. Found: N 7.4%. $C_{20}H_{21}BrN_2O$. Calculated: N 7.3%.

9-Benzylamino-1,2,3,4-tetrahydroacridine (IVa). A 0.01-mole sample of benzylamine was added to a solution of 0.01 mole of VI [6] in 10 g of fused phenol, and the mixture was heated at 160-170° for 20 h. It was then treated with 10% NaOH solution, and the residue was crystallized to give IVa with mp 114° (from hexane) in 50% yield. Found: C 83.1; H 6.6; N 9.5%. $C_{20}H_{20}N_2$. Calculated: C 83.3; H 7.0; N 9.7%. The hydrochloride had mp 252° (from alcohol).

9-Benzylamino-1,2,3,4-tetrahydroacridines (IV). A solution of 0.05 mole of I in 3 ml of phosphorus oxychloride was refluxed for 30 min, after which it was poured into water and neutralized with 10% alkali solution (after decomposition of the phosphorus oxychloride). The precipitated IV was removed by filtration and crystallized. Compound IVa with mp 114° (from hexane) was obtained in 52% yield. No melting-point depression was observed for a mixture of this product with a sample of IVa obtained in the preceding experiment. Compound IVb with mp 124° (from alcohol) was obtained in 50% yield. Found: C 74.1; H 5.6; N 8.2%. $C_{20}H_{19}ClN_2$. Calculated: C 74.5; H 5.9; N 8.3%. Compound IVc with mp 112° (from alcohol) was obtained in 60% yield. Found: C 65.1; H 5.0; N 7.7%. $C_{20}H_{19}BrN_2$. Calculated: C 65.4; H 5.2; N 7.9%.

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