INVESTIGATIONS IN THE CHEMISTRY OF HETEROCYCLES

XLV. Synthesis and Properties of 9-Phenylacridine-2-carboxylic Acid*

P. A. Petyunin, A. F. Soldatova, and A. K. Sukhomlinov

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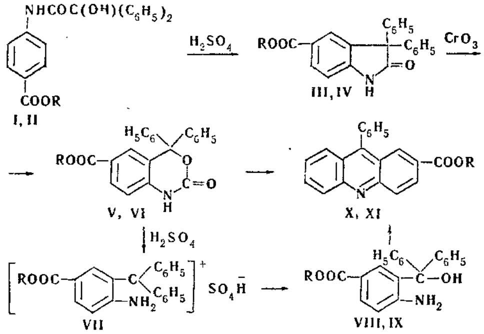
A method for obtaining 9-phenylacridine-2-carboxylic acid and its ethyl ester from derivatives of 2-aminophenyl(diphenyl)methanol and of 2-oxo-4,4-diphenyl-1,2-dihydro-3,1,4-benzoxazine has been developed.

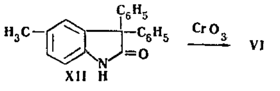
Methods have been developed for obtaining 9-phenylacridine and its halogen-substituted derivatives from 2-aminophenyl(diphenyl)methanols [2–5] and diphenylisatoic acid [6]. It appeared of interest to extend these investigations also to derivatives of 9-phenylacridine containing carboxyl groups.

On saponification, the starting material for the syntheses—the p-ethoxycarbonylanilide of benzilic acid (I) [7]—was converted into the p-carboxyanilide of benzilic acid (II). The acidochromic condensation of I and II yielded 5-ethoxycarbonyl-3,3-diphenyloxindole (III) and 5-carboxy-3,3-diphenyloxindole (IV), respectively. The latter was also obtained by the saponification of III. The conversion of III and IV into the corresponding derivatives of 2-oxo-4,4-diphenyl-1,2-dihydro-4H-3,1-benzoxazine (V, VI) was performed with a yield of 53–70% by oxidation with chromic anhydride in acetic acid.



I R=C_2H_5, II R=H; III R=C_2H_5, IV R=H; V R=C_2H_5, VI R=H; VIII R=C_2H_5, IX R=H; X R=C_2H_5, XI R=H

The synthesis of VI can also be carried out by a more practicable method—the oxidation of 5-methyl-3,3-diphenyloxindole (XII); in this process the pyrrolidone ring and the methyl group are oxidized simultaneously.



Under the action of conc H_2SO_4, the oxazine compounds V and VI are readily converted into the 2-aminophenyl(diphenyl)methanol derivatives VIII and IX. The reaction is accompanied by the evolution of CO_2 and takes place via the stage of the formation of the halochromic salt VII.

On being heated in nitrobenzene, the benzoxazines V and VI and 2-amino-5-ethyoxycarbonylphenyl(diphenyl)methanol (VIII) give ethyl 9-phenylacridine-2-carboxylate (X) and 9-phenylacridine-2-carboxylic acid (XI), as the case may be. The latter was also obtained by the saponification of X. Attempts to convert 2-amino-5-carboxyphenyl(diphenyl)methanol (IX) into XI were unsuccessful because of pronounced resinification.

The structures of V, VIII, X, and XI were confirmed by IR spectroscopy. The IR spectra were recorded on an IKS-14 instrument with LiF and NaCl prisms in tablets with KBr (concentration of the substance 0.5%). Both with respect to the availability of the starting materials with respect to the yield of the final reaction products, preference must be given to the syntheses of X and XI from the benzoxazine derivatives V and VI.

EXPERIMENTAL

p-Carboxyanilide of benzilic acid (II). A mixture of 2.5 g (6.6 mole) of I and 20 ml of 10% caustic soda solution was heated until dissolution was complete and was then acidified with HCl and the precipitate that deposited was filtered off and crystallized from ethanol, forming needles with mp 220° C. Yield 0.96 g (40%). Found, %: N 3.79; equiv. 343. Calculated for $C_{21}H_{17}NO_4$, %: N 4.03; equiv. 347.

Ethyl 3,3-diphenyloxindole-5-carboxylate (III). This was obtained with a yield of 71% by the acidochromic condensation of I. Prisms (from glacial CH_3COOH) with mp 258° C. Found, %: N 3.98. Calculated for $C_{23}H_{19}NO_3$, %: N 3.92.

3,3-Diphenyloxindole-5-carboxylic acid (IV). A) A mixture of 3 g (8.4 mM) of III and 40 ml of 10% caustic soda solution was heated until dissolution was complete and it was then acidified with hydrochloric acid and the precipitate that deposited was crystallized from aqueous acetic acid. Prisms with mp 297–298° C. Yield 1.64 g (59.7%).

B) A solution of 0.4 g of II in 5 ml of glacial CH_3COOH was treated with conc H_2SO_4 until the cherry-red coloration had disappeared and was then poured into 30 ml of water, and the precipitate that deposited was treated as described above. Yield 0.26 g (76.5%); mp 297° C. A mixture of the two samples gave no depression of the melting point. Found, %: N 4.27; equiv. 325.6. Calculated for $C_{21}H_{15}NO_3$, %: N 4.25; equiv. 329.

2-Oxo-4,4-diphenyl-1,2-dihydro-4H-3,1-benzoxazine-6-carboxylic acid (V). A solution of 10.92 g (0.03 mole) of III in 40 ml of glacial CH_3COOH was treated with 9 ml (0.044 mole) of 50% aqueous chromic anhydride, and the mixture was heated in the water bath until the yellow color had changed to green (1 hr) and was then poured into 120 ml of water. The precipitate was filtered off and crystallized from aqueous acetic acid. Yield 8 g (70.1%). Prisms with mp 218° C. Soluble in concentrated H_2SO_4 with the formation of an orange coloration and the evolution of CO_2. Found, %: N 3.63. Calculated for $C_{23}H_{19}NO_4$, %: N 3.74. IR spectrum, cm^{-1}: 3240 (NH), 1706 (ester C=O), 1674 (amide C=O), 1315 ($COOC_2H_5$).

2-Oxo-4,4-diphenyl-1,2-dihydro-4H-3,1-benzoxazine-6-carboxylic acid (VI). A) To a solution of 1.7 g (0.005 mole) of IV in 12 ml of glacial CH_3COOH was added 1.5 ml (0.007 mole) of a 50% solution of chromic anhydride, and the mixture was heated in the water bath for

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*For part XLIV, see [1].

1 hr and was then treated as in the preceding experiment. Yield 0.9 g (53%). Prisms (from aqueous CH_3COOH) with mp 308° C (decomp.).

B) To a solution of 2.14 g (0.071 mole) of **XII** in 15 ml of glacial CH_3COOH was added 7.6 ml of a 50% solution of chromic anhydride and the mixture was then treated as described above. Yield 1.05 g (43.8%), mp 308° C (decomp.). The substance is soluble in aqueous alkali and ammonia and with concentrated H_2SO_4 it gives an orange coloration accompanied by the evolution of CO_2. Found, %: N 4.08; equiv. 343.7. Calculated for $C_{21}H_{15}NO_4$, %: N 4.05; equiv. 345.4.

2-Amino-5-ethoxycarbonylphenyl(diphenyl)methanol (VIII). Compound **V** (8 g; 0.021 mole) was treated with concentrated H_2SO_4 (40 ml). After dissolution and the evolution of CO_2, the orange-yellow solution was poured into 100 ml of water. The precipitate was filtered off and was washed successively with sodium carbonate solution and water and was crystallized from ethanol. Needles with mp 160° C. Yield 4.9 g (66.2%). Found, %: N 4.30. Calculated for $C_{22}H_{21}NO_3$, %: N 4.03. IR spectrum, cm^{-1}: 3470 (OH), 3410 (NH_2), 1310 ($COOC_2H_5$).

2-Amino-5-carboxyphenyl(diphenyl)methanol (IX). This was obtained from **VI** in a similar manner with a yield of 55%. Prisms (from dioxane) with mp 315° C. Found, %: N 4.53. Calculated for $C_{20}H_{17}NO_3$, %: N 4.38.

Ethyl 9-phenylacridine-2-carboxylate (X). A mixture of 2.05 g of **V** and 6 ml of nitrobenzene was heated for 2 hr. The nitrobenzene was distilled off with steam and the residue was crystallized from dioxane. The yield was 1.5 g (86%) of orange prisms with mp 175° C. The solutions in concentrated H_2SO_4 possess a yellow-green fluorescence. Found, %: N 4.49. Calculated for $C_{22}H_{17}NO_2$, %: N 4.28. IR spectrum, cm^{-1}: 1705 (ester C=O), 1604 (C=N), 1310 ($COOC_2H_5$). **Picrate**, bright yellow needles with mp 219–220° C; **hydrochloride**, bright yellow prisms with mp 205° C (decomp.).

Compound **VIII** was obtained from **X** under similar conditions with a yield of 38%.

9-Phenylacridine-2-carboxylic acid (XI). A) A mixture of 0.33 g (0.0013 mole) of **VI** in 1 ml of nitrobenzene was boiled for 25 min and was then treated as described above. Yellow needles with mp 297° C. Yield 0.14 g (40%).

B) A mixture of 1 g of **X** and 15 ml of 15% NaOH solution was heated for 2.5 hr and was acidified with acetic acid, and the precipitate was crystallized from dioxane. Mp 297° C; yield 0.53 g (58.8%). A mixed melting point showed no depression. Found, %: N 4.68; equiv. 295.9. Calculated for $C_{20}H_{13}NO_2$, %: N 4.87; equiv. 299.3. IR spectrum, cm^{-1}: 1690 (COOH), 1606 (C=N), 1555 (weak, zwitterion) [8]. Readily soluble in ammonia, sparingly soluble in aqueous alkalies and mineral acids; solutions in conc. H_2SO_4 possess a yellow-green fluorescence. **Hydrochloride**, bright yellow plates with mp 301° C (decomp.).

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Khar'kov Pharmaceutical
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