

Acyl Indoles. II (1). Indolo[2,1-*b*]quinazolones
from 1-(2-Aminobenzoyl)indoles (2)

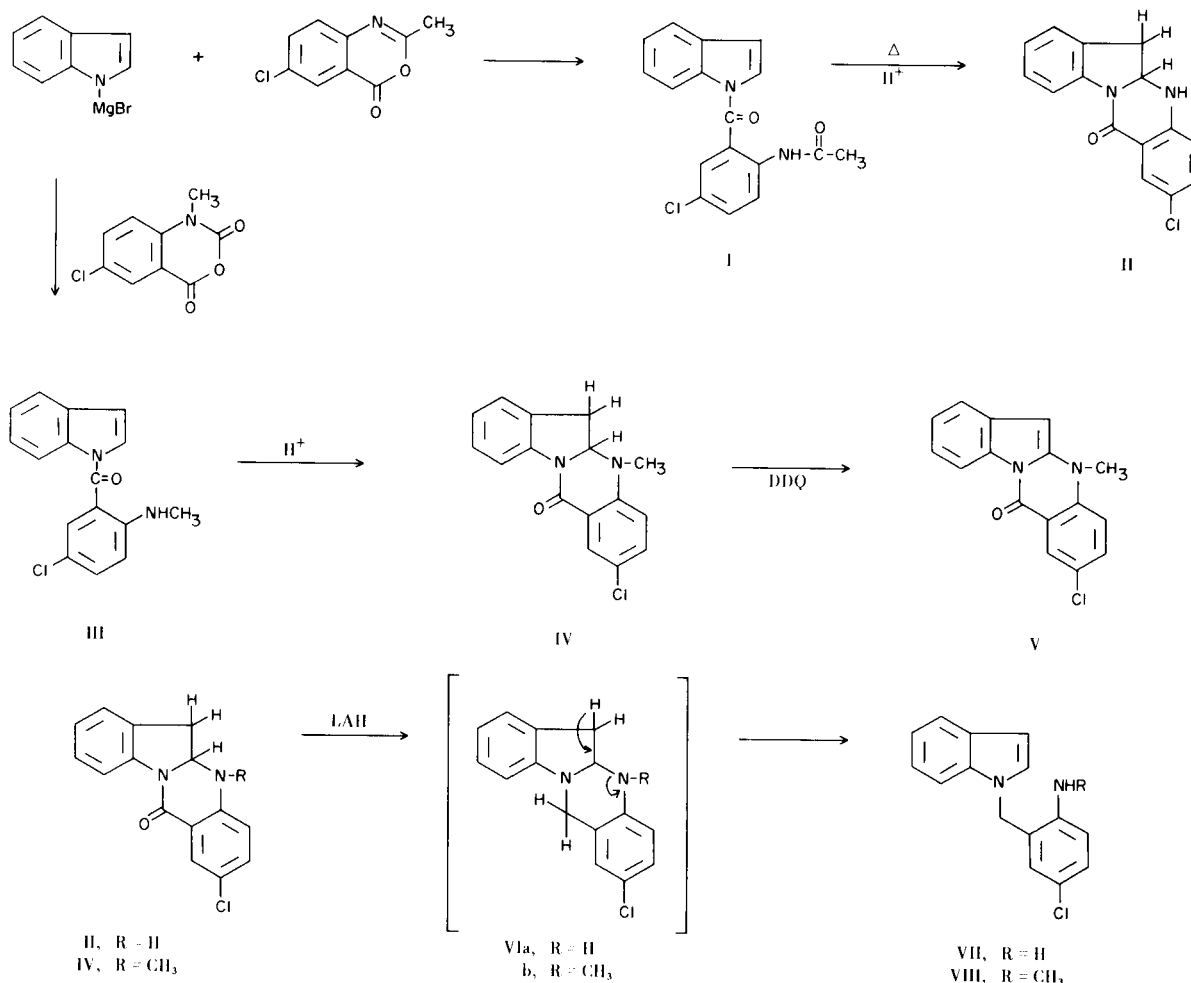
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As a continuation of our studies of acyl indoles (1), we have investigated the synthesis and reaction of 1-(2-aminobenzoyl) indoles. 1-(2-Acetamido-5-chlorobenzoyl)indole (I) was prepared in 60% yield by treating 6-chloro-2-methyl-4*H*-3,1-benzoxazin-4-one with indolylmagnesium bromide. The position of acylation was ascertained by its facile alkaline hydrolysis to give indole and the corresponding anthranilic acid moiety. When compound I was subjected to the action of refluxing ethanol-6*N* hydrochloric acid, the indolo[2,1-*b*]quinazolone II was produced. The NMR spectrum (see Experimental Section)

with its ABX pattern for the $-\text{CH}_2-\text{CH}<$ moiety was in perfect agreement with the structure assigned. Compound II was found to be sensitive to a variety of reagents. For example, it became a deep lavender color when treated with base or acylating agents and also during unsuccessful attempts at oxidation of the $-\text{CH}_2-\text{CH}<$ linkage.

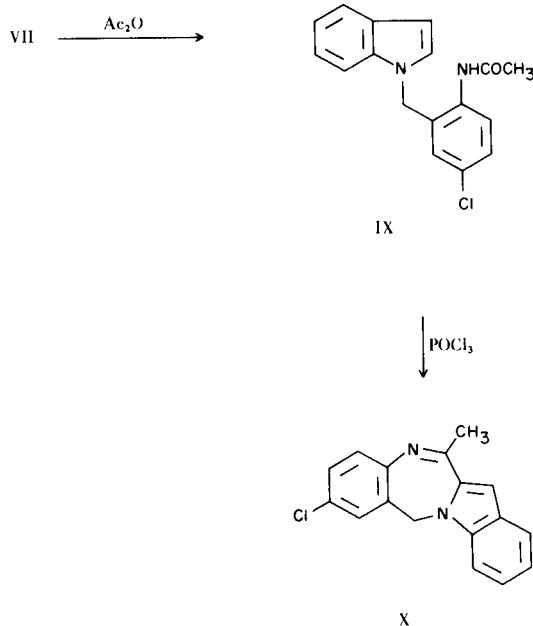
To test the generality of the ring closure of I to II, an additional 1-(2-aminobenzoyl)indole was prepared. Treatment of indolylmagnesium bromide with 5-chloro-*N*-methylisatoic anhydride gave the desired 1-substituted indole III. Exposure of III to aqueous acid resulted in



cyclization to the indoloquinazolone IV in good yield. In contrast to compound II, IV was easily oxidized with dichlorodicyanoquinone to yield compound V.

When II was reduced with lithium aluminum hydride, the 1-(2-aminobenzyl)indole (VII) was obtained and not the anticipated tetracyclic substance VIa. Structure VII was established by its nmr spectrum, which showed the loss of the ABX pattern of the starting material and the presence of two additional aromatic protons not present in the starting material. Compound VII as expected, gave a positive test for a primary aromatic amine when diazotized and coupled with β -naphthol. Analogously, lithium aluminum hydride reduction of IV gave the methylaminobenzyl indole VIII and not VIb. It appears likely that in these examples the anticipated reduced tetracyclics VIa and VIb are first formed, but, that under the reduction conditions these diamines then undergo a hydrogen shift to form the more stable indole structures (3).

Compound VII with acetic anhydride gave the acetyl derivative IX which was cyclized with phosphorus oxychloride to the indolo[2,1-c][1,4]benzodiazepine X in low yield.



EXPERIMENTAL (4)

1-(2-Acetamido-5-chlorobenzyl)indole (I).

To phenylmagnesium bromide prepared from 4.9 g. (0.2 g.-atom) of magnesium and 31.4 g. (0.2 mole) of bromobenzene in 125 ml. of ether, was added dropwise with stirring, 23.4 g. (0.2 mole) of indole in 75 ml. of benzene. The resultant solution

was heated under gentle reflux for 1 hour, cooled to room temperature and was then added dropwise with stirring to an ice cooled suspension of 39.1 g. (0.2 mole) of 6-chloro-2-methyl-4H-3,1-benzoxazin-4-one (5) in 480 ml. of ether. After stirring in ice for 1 hour and at room temperature for 1.5 hour, the mixture was hydrolyzed by the addition of 200 ml. of 2 N hydrochloric acid. The suspension was filtered and the precipitate washed with ether. The solid was dissolved in a large volume of chloroform, washed with dilute sodium hydroxide, then water, dried over sodium sulfate and evaporated to dryness. The resultant oil on standing solidified to give 32.5 g. of off-white crystals, m.p. 173-175°.

The ether filtrates were combined, washed with 1 N sodium hydroxide and water and evaporated to give an additional 4.4 g. of product, m.p. 171-172°, yield, 36.9 g. (54%). A small sample was recrystallized from ethanol to give white prisms, m.p. 173-175°.

Anal. Calcd. for $\text{C}_{15}\text{H}_{11}\text{ClN}_2\text{O}$: C, 66.55; H, 4.09; N, 10.34; Found: C, 66.38; H, 4.19; N, 10.62.

2-Chloro-5a,6-dihydroindolo[2,1-b]quinazolin-12(5H)-one (II).

A solution of 1.5 g. (0.0048 mole) of I dissolved in a mixture of 50 ml. of ethanol and 50 ml. of 6 N hydrochloric acid was heated under reflux, with stirring for 3 hours. The resultant suspension was cooled to room temperature, filtered, washed with water and vacuum dried to give 0.9 g. (60%) of a cream colored solid, m.p. 258-260°. Recrystallization from methylene chloride-heptane gave off-white micro needles, m.p. 261-263° (darkens prior to melting); IR (KBr) cm^{-1} 3280 (NH), 1640 (C=O); NMR (DMSO) δ 3.43, 3.09, 5.39 (3 protons, ABX, $-\text{CH}_\text{A}\text{H}_\text{B}-\text{CH}_\text{X}$, $J_{\text{AB}} = 16$, $J_{\text{AX}} = 8$, $J_{\text{BX}} = 9$ Hz); UV λ max, 225 (infl) (ϵ 30.5), 230 (31.5), 259 (18.4), 282 (7.6), 301 (9.5), 315 (infl) (7.5), 358 $m\mu$ (4.9).

Anal. Calcd. for $\text{C}_{15}\text{H}_{11}\text{ClN}_2\text{O}$: C, 66.55; H, 4.09; N, 10.34. Found: C, 66.38; H, 4.19; N, 10.62.

1-(5-Chloro-2-methylaminobenzyl)indole (III).

To phenylmagnesium bromide prepared from 2.43 g. (0.1 g.-atom) of magnesium and 17.7 g. (0.11 mole) of bromobenzene in 50 ml. of ether was added, 11.7 g. (0.1 mole) of indole in 100 ml. of benzene. After heating under gentle reflux for 45 minutes, the resultant solution was cooled to room temperature and was added dropwise to an ice-cooled solution of 21.1 g. (0.1 mole) of 5-chloro-N-methylisatoic anhydride in 250 ml. of THF (dried over alumina). After stirring in ice for 2.5 hours, the mixture was hydrolyzed by the addition of 100 ml. of 2 N sulfuric acid and filtered to remove a small amount of solid (discarded). The organic layer was separated, washed with water and concentrated. The residual oil was dissolved in ether, scratched until a solid separated and filtered to remove 2.5 g. of starting material. The filtrate was concentrated to small volume and refrigerated. Filtration gave 17.1 g. (60%) of yellow crystals, m.p. 86-100°. Recrystallization from 2-propanol yielded yellow rods, m.p. 101.5-104.5°; IR (chloroform) cm^{-1} 3420 (NH), 1670 (C=O).

Anal. Calcd. for $\text{C}_{16}\text{H}_{13}\text{ClN}_2\text{O}$: C, 67.49; H, 4.60; N, 9.84. Found: C, 67.44; H, 4.51; N, 9.76.

2-Chloro-5a,6-dihydro-5-methylindolo[2,1-b]quinazolin-12(5H)-one (IV).

A solution of 15 g. (0.053 mole) of III dissolved in a mixture of 150 ml. of 4 N hydrochloric acid and 150 ml. of ethanol was heated under reflux with stirring for 3 hours. The resultant mixture was filtered while hot and the precipitate washed thoroughly with water. Recrystallization from methanol yielded

11.8 g. (79%) of yellow plates, m.p. 179-180°; IR (KBr) cm^{-1} 1665 (C=O); NMR (DMSO) δ 3.35, 5.19 (3 protons, ABX or AA'X, $-\text{CH}_2-\text{CH}_X$, $J_{AX} = 7.5$, J_{BX} (or $A'X$) = 10 Hz); UV λ max, 225 (infl) (ϵ 29.7), 231 (31.5), 259 (19.5), 283 (6.4), 301 (8.85), 314 (infl) (6.8), 355 $\text{m}\mu$ (4.3).

Anal. Calcd. for $\text{C}_{16}\text{H}_{13}\text{ClN}_2\text{O}$: C, 67.49; H, 4.60; N, 9.84; Found: C, 67.78; H, 4.73; N, 9.67.

2-Chloro-5-methylindolo[2,1-b]quinazolin-12(5H)-one (V).

A solution of 28.4 g. (0.1 mole) of IV in 420 ml. of hot xylene was treated with 22.7 g. (0.1 mole) of 2,3-dichloro-5,6-dicyanoquinone and the resultant mixture was heated under reflux with stirring for 2.5 hours. The suspension was filtered while hot to remove the hydroquinone and the filtrate evaporated to dryness. The residue was recrystallized twice from acetonitrile-dichloromethane to yield 14.8 g. (52%) of yellow needles, m.p. 206-208°; NMR (DMSO) δ 6.27 (1 proton, singlet, $\text{CH}=\overset{\text{N}}{\underset{\text{N}}{\text{C}}}$).

Anal. Calcd. for $\text{C}_{16}\text{H}_{11}\text{ClN}_2\text{O}$: C, 67.97; H, 3.92; N, 9.91; Found: C, 68.13; H, 3.68; N, 9.69.

1-(2-Amino-5-chlorobenzyl)indole (VII).

To an ice-cooled, stirred suspension of 13.5 g. (0.32 mole) of lithium aluminum hydride in 150 ml. of dry THF was added dropwise a solution of 45 g. (0.166 mole) of II in 950 ml. of dry THF. The resultant mixture was heated under gentle reflux for 3 hours and then cooled in ice and hydrolyzed by the cautious addition of 20 ml. of water followed by 10 ml. of 1 N sodium hydroxide. After filtering the mixture over Celite and washing the solid with THF the filtrate was concentrated to dryness. The residue was dissolved in hot dichloromethane and refrigerated. Filtration and repeated concentration of the filtrates yielded 32.9 g. (79%) of pink-tinged crystals, m.p. 90-95°. The analytical sample was recrystallized from dichloromethane to give white needles, m.p. 90-95°; IR (chloroform), cm^{-1} 3480, 3400 (NH₂); NMR (DMSO) δ 3.30 (2 protons, singlet, NH₂), 4.97 (2 protons, singlet, CH₂), δ 6.54 (1 proton doublet, $J = 4$ Hz, $-\overset{\text{H}}{\text{C}}=\text{C}-\text{N}$),

6.96 (1 proton, doublet, $J = 4$ Hz, $-\overset{\text{H}}{\text{C}}=\text{N}$); UV λ max 249 (ϵ , 17.9), 287 (4.6), 293 (4.9) and 305 $\text{m}\mu$ (infl) (3.62).

Anal. Calcd. for $\text{C}_{15}\text{H}_{13}\text{ClN}_2$: C, 70.18; H, 5.10; N, 10.91. Found: C, 70.10; H, 5.23; N, 10.94.

1-(5-Chloro-2-methylaminobenzyl)indole (VIII).

To an ice-cooled stirred suspension of 3.15 g. (0.084 mole) of lithium aluminum hydride in 70 ml. of dry THF was added a solution of 11.5 g. (0.04 mole) of IV. The resultant mixture was heated under reflux for 3 hours and then cooled in ice. The mixture was hydrolyzed by the cautious addition of 8 ml. of water and 3 ml. of 1 N sodium hydroxide. After filtering over Celite and washing the filter cake with THF, the filtrate was concentrated to dryness. The resultant oil was crystallized with ether to give 6.2 g. (59%) of white crystals, m.p. 105-110°. A small sample was recrystallized from ether to give white plates, m.p. 106-109°; IR (chloroform) cm^{-1} 3480 (NH); NMR (DMSO), δ 2.62 (1 proton, singlet, CH₃), 3.23 (1 proton, broad singlet, NH), 4.84 (2 protons, singlet, CH₂), δ 6.47 (1 proton, doublet, $J = 4$ Hz, $-\overset{\text{H}}{\text{C}}=\text{C}-\text{N}$), 6.87 (1 proton, doublet, $J = 4$ Hz, $-\overset{\text{H}}{\text{C}}=\text{N}$), UV λ max 216 (43.5), 254 (18.0), 280 (6.9), 286 (6.78), 292 (6.35) and 205 $\text{m}\mu$ (sh) (3.2).

Anal. Calcd. for $\text{C}_{16}\text{H}_{15}\text{ClN}_2$: C, 70.97; H, 5.58; N, 10.34. Found: C, 71.09; H, 5.54; N, 10.36.

1-(2-Acetamido-5-chlorobenzyl)indole (IX).

To a mixture of 80 ml. of acetic anhydride and 250 ml. of

glacial acetic acid was added 13 g. (0.05 mole) of VII. The resultant solution was allowed to stand at room temperature for 1 hour and was then poured into ice and filtered. After washing with water the precipitate was dissolved in dichloromethane, dried over sodium sulfate, concentrated to a small volume and refrigerated. Filtration gave 12.8 g. (85%) of white crystals, m.p. 169-173°. Recrystallization from dichloromethane gave white needles, m.p. 171-173°; IR (chloroform) cm^{-1} 3450 (NH), 1700 (C=O).

Anal. Calcd. for $\text{C}_{17}\text{H}_{15}\text{ClN}_2\text{O}$: C, 68.34; H, 5.06; N, 9.38. Found: C, 68.10; H, 4.89; N, 9.41.

10-Chloro-6-methyl-12H-indolo[2,1-c][1,4]benzodiazepine (X).

A solution of 17.2 g. (0.057 mole) of IX in 90 ml. of freshly distilled phosphorus oxychloride was heated under reflux for 1 hour and then distilled at reduced pressure to remove the excess solvent.

The residue was treated with ice-water and basified with 4 N sodium hydroxide. The resultant mixture was filtered and the precipitate washed with water and then dissolved in dichloromethane. After washing with water and drying over sodium sulfate, the dichloromethane was concentrated to dryness and the residue placed on neutral alumina with the aid of benzene. After eluting with ca. 2 l. of benzene, the solvent was removed and the residue recrystallized from dichloromethane to give 3.8 g. (24%) of yellow crystals, m.p. 190-191° (6). The analytical sample was recrystallized from carbon tetrachloride to give yellow needles, m.p. 190-191°; NMR (DMSO) δ 2.65 (3 protons, singlet, CH₃), 3.27 (2 protons, singlet, CH₂), 6.97 (1 proton, singlet, $-\overset{\text{H}}{\text{C}}=\overset{\text{N}}{\text{C}}$); UV λ max 218 (33.9), 250 (sh) (13.5), 295 (infl) (7.2), 3.45 $\text{m}\mu$ (14.7).

Anal. Calcd. for $\text{C}_{17}\text{H}_{13}\text{ClN}_2$: C, 72.73; H, 4.67; N, 9.98; Found: C, 72.35; H, 4.65; N, 9.83.

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REFERENCES

- (1) E. E. Garcia, J. G. Riley and R. Ian Fryer, *J. Org. Chem.*, **33**, 2868 (1968).
- (2) Presented before the Northwest Regional ACS Meeting, Salt Lake City, Utah, June, 1969.
- (3) Any tautomeric shift prior to reduction of the carbonyl would have produced a 1-acyl indole which are known to undergo reductive cleavage at the N-C bond to produce indole itself (for example, see "Reduction with Complex Metal Hydrides," N. G. Gaylord, Interscience, Inc., N. Y. (1956).
- (4) All melting points were determined microscopically on a hot stage and are corrected. Infrared spectra were determined using a Beckman IR-9 spectrophotometer, NMR spectra with a Varian A-60 spectrometer and ultraviolet spectra in 2-propanol with a Cary Model 14 spectrophotometer. The ultraviolet ϵ values refer to $\epsilon \times 10^{-3}$.
- (5) A. J. Tomisek and B. E. Christensen, *J. Am. Chem. Soc.*, **70**, 2423 (1948).
- (6) Further elution of the alumina with chloroform gave a mixture of products which could not be separated.

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