Synthesis of Indolo- and Benzimidazoquinazolines and Benzodiazepines

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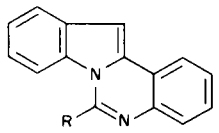
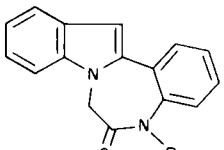
Indolo[1,2-*c*]quinazolines, indolo[1,2-*d*][1,4]benzodiazepines, indolo[1,2-*d*][1,4]benzodiazepin-6-ones and benzimidazo[1,2-*d*][1,4]benzodiazepin-6-ones were synthesized. In an acid medium, the indoloquinazolines were produced from 2-(*o*-aminophenyl)indole and acyl halides. However, in the presence of sodium acetate, the acylated amine was obtained and was cyclized to the indolobenzodiazepinones using sodium hydride. The syntheses are described in detail and characterization data are given.

An investigation of benzodiazepine type structures for possible biological activity produced some novel ring systems. The unique systems shown as A, B, C and D were synthesized by careful adjustment of the *p*H of the reaction medium.



A



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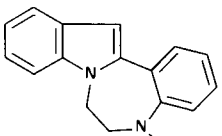

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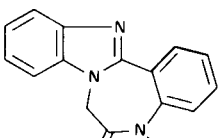

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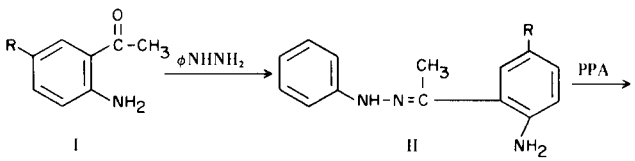
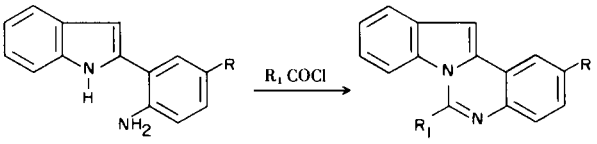


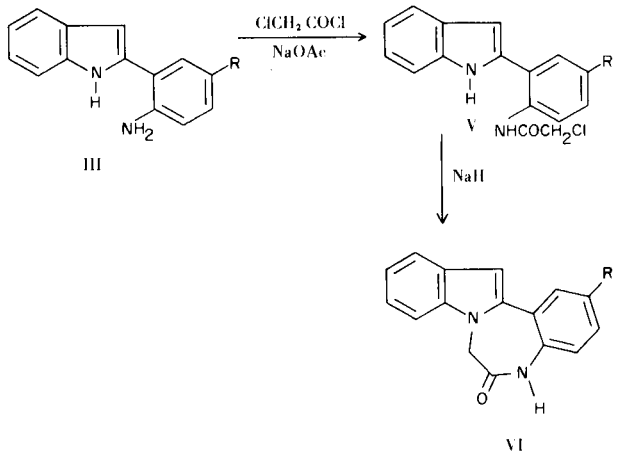
I II



III IV

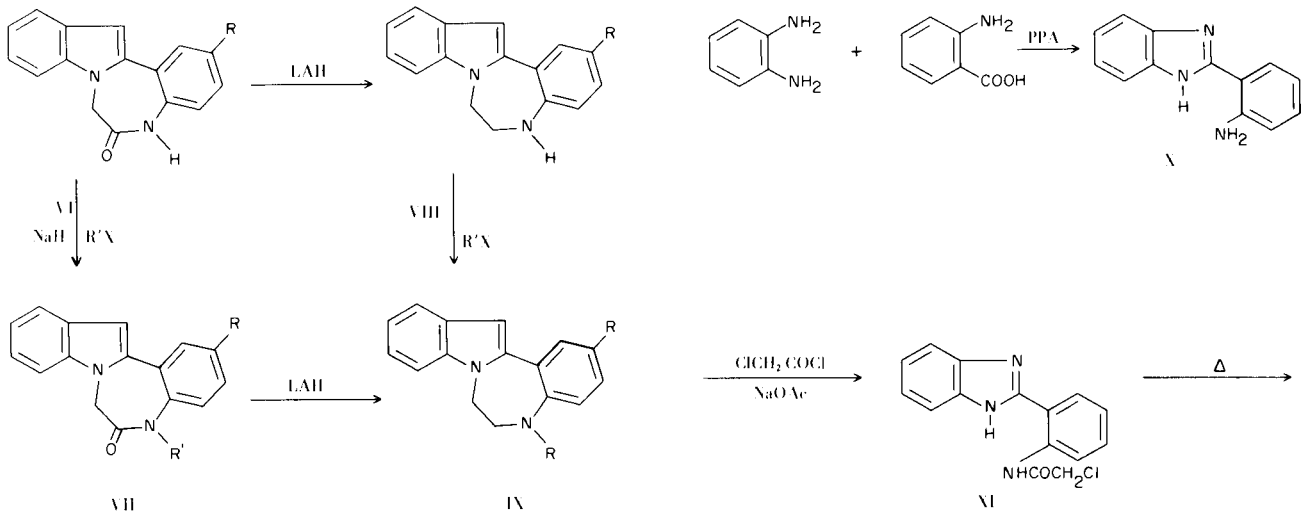
The synthesis of 6-substituted indolo[1,2-*c*]quinazolines (A) as indicated below began with the preparation of phenylhydrazones from phenylhydrazine and the appropriately substituted acetophenone. A Fisher-type cyclization (1) using polyphosphoric acid produced the expected aminophenylindole (III). Treatment of III under neutral or acidic conditions with an acid chloride afforded the cyclization to the indoloquinazoline (IV) (2).

When the aminophenylindoles (III) were treated with chloroacetyl chloride in the presence of an excess of sodium acetate, the corresponding amidophenylindole (V) was obtained. Cyclization of V to the indolo[1,2-*d*][1,4]-benzodiazepin-6-ones (VI) was effected using sodium hydride.



III V VI

The indolobenzodiazepinones (VI) were reduced to indolo[1,2-*d*][1,4]benzodiazepines (VIII) with lithium aluminum hydride. Alkylation of the amido nitrogen of VI followed by reduction was not as efficient, and as general as, reduction of VI to VIII followed by alkylation of the secondary amine.



The preparation of the benzimidazo[1,2-*d*][1,4]benzodiazepin-6-ones began by heating phenylenediamine and anthranilic acid in polyphosphoric acid. The *o*-aminophenylbenzimidazole (X) was treated with chloroacetyl chloride in the presence of sodium acetate. The amido compound (XI) was then cyclized by heating to reflux in diethylbenzene. Alkylation of XII to XIII was accomplished using sodium hydride and an alkyl halide.

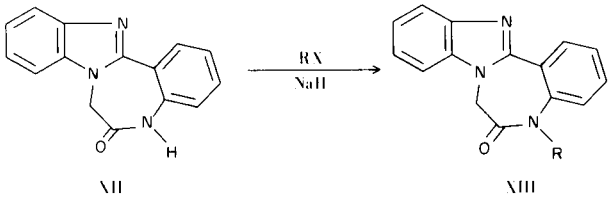
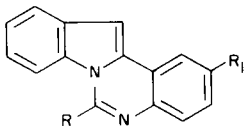


TABLE I



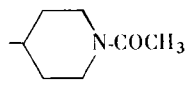
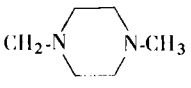
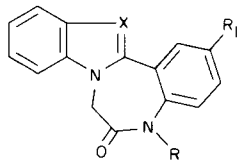
	R	R_1	% Yield	M.p. (°C)	Empirical Formula	%C Calcd.	%C Found	%H Calcd.	%H Found	%N Calcd.	%N Found
1	CH_2Cl	H	88	186-188	$C_{16}H_{11}ClN_2$	72.05	71.88	4.16	4.17	10.50	10.27
2	CH_2Cl	Cl	54	213-214	$C_{16}H_{10}Cl_2N_2$	63.80	63.71	3.35	3.29	9.30	9.19
3	$CH_2C_6H_4Cl$	H	33	193.5-196.5	$C_{21}H_{13}ClN_2$	76.71	76.85	3.99	4.07	8.52	8.49
4	CH_2CH_2COOH	H	90	210 dec.	$C_{18}H_{14}N_2O_2$	74.47	74.10	4.86	4.95	9.65	9.54
5	$CH_2CH_2CON(C_2H_5)_2$	H	17	151.5-154	$C_{22}H_{23}N_3O$	76.49	76.19	6.71	6.73	12.17	12.01
6		H	55	243-247	$C_{22}H_{21}N_3O$	76.94	76.47	6.16	6.11	12.24	12.15
7		H	51	144-145	$C_{21}H_{22}N_4$	76.33	76.58	6.72	6.92	16.95	-----

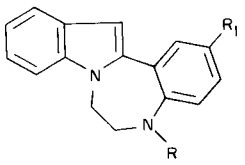
TABLE II



	R	R_1	X	% Yield	M.p. (°C)	Empirical formula	%C Calcd.	%C Found	%H Calcd.	%H Found	%N Calcd.	%N Found
8	H	H	C	86	278-281	$C_{16}H_{12}N_2O$	77.40	77.14	4.87	5.00	11.28	11.18
9	H	Cl	C	50	257-260	$C_{16}H_{11}ClN_2O$	67.97	68.47	3.92	3.94	9.91	9.73
10	H	Br	C	90	267-269	$C_{16}H_{11}BrN_2O$	58.73	58.81	3.39	3.49	8.56	8.47
11	H	H	N	27	261.5-263	$C_{15}H_{11}N_3O$	72.27	72.31	4.45	4.56	16.86	16.82
12	CH_3	H	C	34	129-131	$C_{17}H_{14}N_2O$	77.84	77.87	5.38	5.47	10.68	10.70
13	CH_3	Br	C	44.6	95-98	$C_{17}H_{13}BrN_2O$	59.84	60.23	3.84	4.09	8.21	7.95
14	$(CH_2)_3N(CH_3)_2$	H	C	40	Molecularly distilled	$C_{21}H_{23}N_3O$	75.64	75.36	6.95	6.89	12.60	12.47
15	$(CH_2)_3N(CH_3)_2$	H	N	34	277-280	$C_{19}H_{22}Cl_2N_4O$ (a)	58.02	57.83	5.64	5.62	14.25	14.23
16	$(CH_2)_3N(CH_3)_2$	Br	C	53	145-150	$C_{21}H_{25}BrClN_3O_2$ (b)	54.03	54.09	5.39	5.02	9.00	8.81
17	$(CH_2)_2N(CH_3)_2$	H	C	74	190-200	$C_{40}H_{46}Cl_2N_6O_3$ (c)	65.84	65.93	6.35	6.39	11.52	11.52
18	$(CH_2)_2N(CH_3)_2$	Br	C	59	145	$C_{20}H_{23}BrClN_3O_2$	53.05	53.34	5.12	4.76	9.28	9.19
19	$(CH_2)_2OH$	H	C	75	147-150	$C_{18}H_{16}N_2O_2$	73.95	73.85	5.52	5.51	9.59	9.58
20	$(CH_2)_2OH$	Br	C	72	135-138	$C_{18}H_{15}BrN_2O_2$	58.24	58.52	4.07	4.08	7.55	7.50
21	$(CH_2)_2O\overset{O}{\overset{\|}{C}}NH\text{-}C_6H_4pOCH_3$	Br	C	40	134-136	$C_{26}H_{22}BrN_3O_4$	60.01	59.84	4.26	4.33	8.08	7.81
22	$(CH_2)_2O\overset{O}{\overset{\|}{C}}NHC_6H_4m\text{-}Cl$	H	C	38	136-139	$C_{25}H_{20}ClN_3O_3$	67.34	67.07	4.52	4.46	9.42	9.30
23	$CH_2CHOHCH_2OH$	H	C	14.4	198-204	$C_{19}H_{18}N_2O_3$	70.79	70.44	5.63	5.56	8.69	8.71

(a) Di HCl salt. (b) HCl monohydrate. (c) HCl hemihydrate.

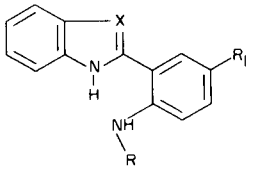
TABLE III



	R	R_1	% Yield	M.p. (°C)	Empirical Formula	%C Calcd.	%C Found	%H Calcd.	%H Found	%N Calcd.	%N Found
24	H	H	70	168.5-170	$C_{16}H_{14}N_2$	82.02	82.20	6.02	6.06	11.96	11.99
25	H	Br	45.5	161-163	$C_{16}H_{13}BrN_2$	61.36	61.47	4.18	4.26	8.94	8.87
26	$CONHC_6H_5$	H	66	167-169	$C_{23}H_{19}N_3O$	78.17	78.44	5.42	5.54	11.89	11.71
27	COC_6H_4pCl	H	59	194-197	$C_{23}H_{17}ClN_2O$	74.09	73.69	4.60	4.47	7.51	7.34
28	$(CH_2)_2N(CH_3)_2$	H	33	Molecularly distilled	$C_{20}H_{23}N_3$	78.65	78.26	7.59	7.58	13.76	13.71
29	$CONHC_6H_5$	Br	99	203.5-205.5	$C_{23}H_{18}BrN_3O$	63.90	64.22	4.20	4.31	9.72	9.60
30	$CONHC_6H_4mCF_3$	Br	53	211.5-213.5	$C_{24}H_{17}BrF_3N_3O$	57.62	58.15 (a)	3.43	3.58	8.40	8.54

(a) Six reanalyses after recrystallizing, drying, fusing, and chromatography give difference of 0.53% carbon. Nmr, ir, mass spectrum and tlc are good.

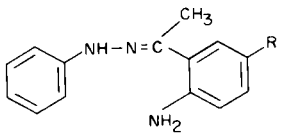
TABLE IV



	R	R_1	X	% Yield	M.p. (°C)	Empirical Formula	%C Calcd.	%C Found	%H Calcd.	%H Found	%N Calcd.	%N Found
31	$COCH_2Cl$	H	C	43	108.5-110	$C_{16}H_{13}ClN_2O$	67.49	67.67	4.60	4.66	9.84	9.70
32	$COCH_2Cl$	Br	C	87.5	158-162	$C_{16}H_{12}BrClN_2O$	52.85	53.09	3.33	3.37	7.70	7.59
33	$COCH_2Cl$	H	N	90	160 dec.	$C_{15}H_{12}ClN_3O$	63.04	62.81	4.23	4.34	14.71	14.52
34	$CONHCH_3$	H	C	94	157-159 (a)	$C_{16}H_{15}N_3O$	72.43	72.40	5.70	5.78	15.87	15.71
35	$CONHC_6H_5$	H	C	64	192.5-194	$C_{21}H_{17}N_3O$	77.04	76.76	5.24	5.33	12.84	13.03
36	H	H	C	54	153-154 (a)	$C_{14}H_{12}N_2$					13.45	13.32
37	H	Br	C	60	137-140	$C_{14}H_{11}BrN_2$	58.55	58.73	3.86	3.92	9.76	9.59
38	H	Cl	C	85	102-105	$C_{14}H_{11}ClN_2$	69.28	68.91	4.57	4.51	11.54	11.46

(a) Agrees with literature (2,3,4).

TABLE V



	R	% Yield	M.p. (°C)	Empirical formula	%C Calcd.	%C Found	%H Calcd.	%H Found	%N Calcd.	%N Found
39	H	72	104-106	$C_{14}H_{15}N_3$	74.64	74.58	6.71	6.72	18.65	18.94
40	Cl	61	149.5-152.5	$C_{14}H_{14}ClN_3$	64.74	64.50	5.43	5.37	16.18	16.16
41	Br	66	168-170	$C_{14}H_{14}BrN_3$	55.27	55.34	4.64	4.64	13.81	13.59

EXPERIMENTAL

The procedures given below are representative for the preparation of the compounds described in Tables I-V. Analyses, yields and physical properties are recorded in the tables. Microanalyses were done by the analytical research section of the A. H. Robins Co., Inc. The structure of each compound listed in Tables I-V has been verified by nmr and ir run by the instrumental section of the research division of A. H. Robins Co., Inc.

o-Aminoacetophenone Phenylhydrazone.

A mixture of 102.0 g. (0.95 mole) of phenylhydrazine and 128.0 g. (0.95 mole) of *o*-aminoacetophenone in 150 ml. of absolute ethanol and 50 ml. of glacial acetic acid was stirred at reflux for 15 to 20 minutes. The solution was cooled and an excess of water was added. The mixture was filtered and the solid residue was recrystallized from methanol, and 160 g. of the hydrazone melting at 104-106° was obtained.

2-(2-Amino-5-bromophenyl)indole.

A mixture of 6.5 g. (0.021 mole) of 2-amino-5-bromoacetophenone phenylhydrazone and 20 g. of polyphosphoric acid was heated to about 100° where an exothermic reaction raised the temperature to 130°. The temperature was maintained at 130° for 10 minutes. The mixture was cooled to about 90° and an excess of water was added. The mixture was filtered and the residue was dissolved in ethanol and the solution was made basic. The indoleamine which separated was extracted with chloroform and the collected extracts were dried and concentrated. The residue was recrystallized from ethanol and 3.5 g. of product was obtained which melted at 137-140°.

2-(*o*-Chloroacetamidophenyl)indole.

To a stirred solution of 4.2 g. (0.02 mole) of 2-(*o*-aminophenyl)-indole in 150 ml. of acetic acid was added a solution of 6.6 g. (0.08 mole) of sodium acetate in 20 ml. of water. The mixture was then cooled to *ca.* 20° and 4.5 g. (0.04 mole) of chloroacetyl chloride was added slowly. After the addition was completed, stirring was continued for 30 minutes and then 150 ml. of water was added to the reaction mixture. The crystalline product which formed was separated by filtration, dissolved in benzene and washed with water. The solvent was evaporated and the residue which crystallized on cooling was recrystallized from isopropyl ether. The white product weighed 2.5 g. and melted at 108.5-110°.

2-[*o*-(3-Methylureido)phenyl]indole.

A solution of 1.6 g. (0.024 mole) of methyl isocyanate in 25 ml. of chloroform was added to a solution of 5.0 g. (0.024 mole) of 2-(*o*-aminophenyl)indole in 100 ml. of chloroform and the mixture was stirred for one hour. The mixture was concentrated under vacuum and the residue was crystallized using methanol and water. Upon recrystallization from benzene 6.0 g. of the product melting at 157-159° was obtained.

6-Chloromethylindolo[1,2-*c*]quinazoline.

A solution of 1.1 g. (0.01 mole) of chloroacetyl chloride in 25 ml. of chloroform was added dropwise to a stirring solution of 2.1 g. (0.01 mole) of 2-(*o*-aminophenyl)indole in 25 ml. of chloroform. While stirring at room temperature an orange solid separated. The mixture was filtered and the residue was found to be 6-chloromethylindolo[1,2-*c*]quinazoline hydrochloride. Upon recrystallizing the solid from ethanol, 2.4 g. of the free amine was obtained as yellow needles melting at 186-188°.

6-(4-Methylpiperazinomethyl)indolo[1,2-*c*]quinazoline.

A stirred mixture of 5.5 g. (0.021 mole) of 6-chloromethylindolo[1,2-*c*]quinazoline, 2.5 g. (0.025 mole) of 4-methylpiperazine, 10 g. of anhydrous potassium carbonate and 75 ml. of toluene was heated at reflux for 6 hours, cooled and treated with 100 ml. of water. The organic layer was separated, washed with cold water, dried over anhydrous magnesium sulfate and the solvent evaporated. The light yellow crystalline residue was recrystallized from an isopropyl ether-isooctane mixture. The product weighed 3.5 g. and melted at 144-145°.

Indolo[1,2-*c*]quinazoline-6-propionic Acid.

An excess of ethereal hydrogen chloride was slowly added to a stirring solution of 12.0 g. (0.039 mole) of *N*-[*o*-(2-indolo)-phenyl]succinamic acid in 50 ml. of tetrahydrofuran. While stirring, the hydrochloride of the title compound precipitated from solution and was collected by filtration to give 11.4 g. of product. This 11.4 g. represented a 90% yield of the hydrochloride, and it was converted to the free quinazoline base. Recrystallization from methanol-water gave a melting point of 120° with decomposition.

Indolo[1,2-*d*][1,4]benzodiazepin-6-one.

A solution of 6.0 g. (0.021 mole) of 2-(*o*-chloroacetamidophenyl)indole in 50 ml. of dimethylformamide was added slowly to a mixture of 0.51 g. (0.021 mole) of sodium hydride in 150 ml. of dimethylformamide. The mixture was allowed to reflux for 4 hours. After cooling an excess of water was added. The mixture was filtered and air dried, and 4.5 g. of product was obtained. The solid was recrystallized from isobutyl methyl ketone and melted at 278-281°.

Benzimidazo[1,2-*d*][1,4]benzodiazepin-6-one.

A solution of 3.0 g. (0.011 mole) of 2-(*o*-chloroacetamidophenyl)benzimidazole in one liter of diethylbenzene (Matheson, Coleman and Bell, Technical Grade, *meta* and *para* Mixture) was heated at reflux (182°) for two hours, and the solvent was evaporated at reduced pressure. The residue was dissolved in hot 95% ethanol and made basic with 3*N* sodium hydroxide and finally filtered. The precipitate which formed when the filtrate was treated with cold water was separated by filtration and washed with cold water. After the white product was recrystallized from benzene it melted at 261.5-263° and weighed 0.7 g. The same product was prepared by fusing the amide at 170-200° (m.p. 260-262°).

5-Methylindolo[1,2-*d*][1,4]benzodiazepin-6-one.

A mixture of 0.77 g. (0.32 mole) of sodium hydride (1.4 g. of a 57% suspension in mineral oil) in 100 ml. of dry dimethylformamide was stirred and a solution of 8.0 g. (0.032 mole) of indolo[1,2-*d*][1,4]benzodiazepin-6-one in 25 ml. of dimethylformamide was added so as to give a moderate evolution of gas. The mixture was stirred until the evolution of gas ceased. A solution of 5.7 g. (0.04 mole) of methyl iodide in 10 ml. of dimethylformamide was added dropwise. The mixture was stirred for one hour and an excess of water was carefully added. The mixture was extracted with benzene and the collected extracts were dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under vacuum. The solid residue was recrystallized from chloroform-isopropyl ether and 3.0 g. of product melting at 129-131° was obtained.

5-[[2-[*N*-(*m*-Chlorophenyl)carbamoyloxy]ethyl]indolo[1,2-*d*]-[1,4]benzodiazepin-6-one.

To a stirring solution of 6.1 g. (0.021 mole) of 5-(2-hydroxy-

ethyl)indolo[1,2-*d*][1,4]benzodiazepin-6-one in 100 ml. of tetrahydrofuran was added 3.5 g. (0.023 mole) of *m*-chlorophenyl isocyanate. The mixture was allowed to stir for 20 hours and then concentrated under vacuum. The residue was triturated in methylene chloride and a white crystalline solid separated. This solid was confirmed by nmr to be di(*m*-chlorophenyl) urea. After filtering, the methylene chloride solution was concentrated under vacuum. The oily residue was triturated in ether and the solid which separated was collected by filtration. The white crystalline compound weighed 3.5 g. and was recrystallized from chloroform-ether and melted at 136-139°.

Indolo[1,2-*d*][1,4]benzodiazepine.

A slurry of 2.5 g. (0.01 mole) of indolo[1,2-*d*][1,4]benzodiazepine-6-one in 50 ml. of tetrahydrofuran was added slowly to a stirring mixture of 0.76 g. (0.02 mole) of lithium aluminum hydride in 100 ml. of tetrahydrofuran. The mixture was refluxed for one hour. After cooling, an excess of water was carefully added. The aqueous mixture was extracted with benzene and the collected benzene extracts were concentrated under vacuum. Recrystallization from chloroform or methanol gave 1.6 g. of product melting at 168.5-170°.

5-Phenylcarbamoylindolo[1,2-*d*][1,4]benzodiazepine.

A solution of 2.0 g. (0.0086 mole) of indolo[1,2-*d*][1,4]benzodiazepine in 50 ml. of dry benzene was stirred while 1.07 g. (0.009 mole) of phenyl isocyanate was slowly added. The mixture was stirred at room temperature for one hour and then heated to 50° for 2 hours. The mixture was concentrated under vacuum and the residue crystallized in isopropyl ether. Upon recrystallization from isopropyl ether, 2.0 g. of product melting at 167-169° was obtained.

5-(*p*-Chlorobenzoyl)indolo[1,2-*d*][1,4]benzodiazepine.

To a stirring solution of 5.0 g. (0.021 mole) of indolo[1,2-*d*]-[1,4]benzodiazepine in 50 ml. of chloroform was added dropwise 3.7 g. (0.021 mole) of *p*-chlorobenzoyl chloride. The mixture was allowed to stir for 3 hours at which time tlc indicated the reaction was complete. The mixture was concentrated under vacuum. The residue upon standing for a day became crystalline. Recrystallization from methanol gave 4.5 g. of the product, melting at 194-197°.

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