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Antitumor Activity of Some Derivatives of Daunorubicin at the Amino and Methyl Ketone Functions†

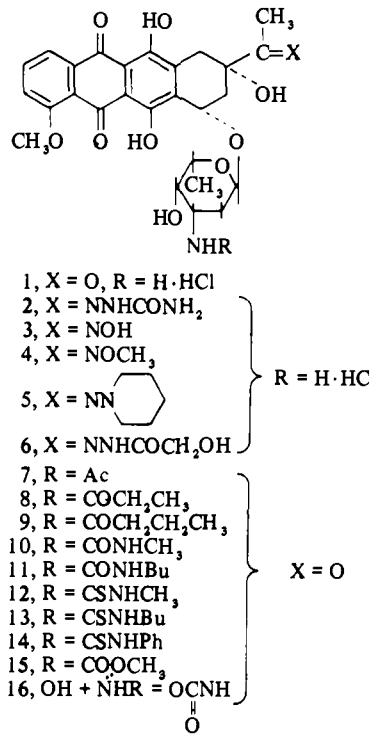
Kazuko Yamamoto, Edward M. Acton,* and David W. Henry

Life Sciences Division, Stanford Research Institute, Menlo Park, California 94025. *Received January 21, 1972*

The antitumor-antibiotic daunorubicin‡ (1) is a clinically effective agent for remission induction in acute leukemia and for treatment of other kinds of cancer.[1-3] Antitumor activity has also been reported for three derivatives of daunorubicin. The analogous hydroxymethyl ketone adriamycin (1, with $COCH_2OH$ in place of $COCH_3$) was reported to be superior to 1 in clinical trial[4] as well as in tests on experimental tumors in mice and rats.[5,6] In addition, the semicarbazone 2 and thiosemicarbazone have been reported in the patent literature[7] as antitumor agents. Since daunorubicin and adriamycin both show toxic side effects, additional analogs are of considerable interest for either greater activity or reduced toxicity.

Synthesis. Compds 2-16 were all prepared directly from daunorubicin by use of the standard reagents for derivatizing amines and ketones, in procedures modified to allow for the low solubility and limited stability of daunorubicin. It was often convenient to start from daunorubicin as the free base, which could be isolated from the HCl salt and stored in the cold for several weeks without deterioration. The ketone derivatives 2-6 were isolated as the mono-HCl salts, generally after extraction of the corresponding free bases and treatment with equivalent amounts of HCl. Physical properties of *N*-acetyldaunorubicin (7) have been described,[8] but without the details of its preparation.§ Some biological properties of the oxime 3 have been reported,[9] but with no mention of its synthesis or physical properties.

Biological Data. The compounds were evaluated for antitumor and/or cytotoxic properties by the Drug Research and Development Branch of the National Cancer Institute



(formerly the Cancer Chemotherapy National Service Center) according to its protocols.[10] Initial tests have employed leukemia L1210 in mice and, in some cases, KB cells in culture. All the ketone derivatives (2, 3, 5, 6), except the *O*-methyl oxime 4 and three (7, 13, 16) of the ten amine derivatives, gave positive results in one of these systems. Table I shows results against L1210 with a 3-injection schedule. The *N*-piperidinoimine 5 was active at doses comparable with those of daunorubicin 1. The semicarbazone 2 and oxime 3 were active at somewhat higher doses.

The most extensive tests with any single compound have been done with the acetamide 7. Results in Table II show the activity of 7 in varied regimens, and the importance of dose timing and dose level in these evaluations. Although 7 is less efficacious than 1, it displayed no acute toxicity under any of the regimens given in Table II. In contrast, the LD_{50} for daunorubicin in the mouse is 6-12 mg/kg (single ip injection).[2] These results are also of considerable interest because acetamide 7 is devoid of the deleterious effects on coronary vasculature (isolated dog heart) that are characteristic of daunorubicin and adriamycin.[11] This suggests that 7 or other derivatives of daunorubicin may be free of the cardiac toxicity that has been associated with clinical use of the parent antibiotic.[2,3] The homologous amides 8 and 9 were inactive against L1210, but the tests to date have been mostly at lower dosages than for 7 (see Table I for 8; 9 was inactive at doses up to 4 mg/kg in 9 daily injections). Because a limited quantity of *N*-carboxy δ-lactam 16 was available, it was tested with only a single-dose regimen. However, substantial activity was observed against L1210; at 200 mg/kg the *T/C* ratio was 148%, and at 400 mg/kg the *T/C* was 132%.

In addition to the L1210 results, activity against KB cells in culture was confirmed for the glycoloylhydrazone 6 ($ED_{50} < 0.63$ μg/ml) and for the *N*-butylthiourea 13 (ED_{50} 0.49 μg/ml).

These preliminary results demonstrate that significant levels of antitumor activity are retained among derivatives of daunorubicin. Further evaluation of these substances is

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‡Previously called daunomycin or rubidomycin.

§The authors are indebted to Dr. James E. Christensen for the initial preparation of *N*-acetyldaunorubicin in our laboratories.

Table I. Test Results[a] *vs.* L1210 in Mice.[b] Compounds in 3-Dose Regimens[c]

Compound	Dose, mg/kg									
	0.25	0.50	1.0	2.0	4.0	8.0	16	32	64	128
Daunorubicin (1)	112	122	139	155						
	122	127	144	144						
	105	133	144							
Semicarbazone (2)	107	108	107	110	120	135	137	139	133	
				110			144			
Oxime (3)			106	115	113	129	126	127		*d*
O-Methyloxime (4)	101	97	105	102	100	101	*d*			
				101						
N-Piperidinoimine (5)	110	118	116	128	131	127	86[e]			
	122	122	122	144						
				134						
Glycoloylhydrazone (6)			115	113	117	125				
Propionamide (8)	102	97	103	96	105	103	101	116	112	
				104			102			
N-Methylurea (10)	104	105	104	101	98	107	103	100	104	
				103			95			
N-Butylurea (11)			104	97	98	98	94	101		102
N-Methylthiourea (12)	103	102	103	98	106	107	108	116	110	
				107			111			
N-Phenylthiourea (14)	103	107	102	104	111	106	123	123	118	
				105			120			
N-Carboxy methyl ester (15)	107	106	103	106	106	112	111	110	110	
				105			109			

[a]The numerical results are ratios (*T/C*) of survival times of treated mice over control mice, expressed as per cent. A ratio ≥125 is a positive result denoting activity. [b]Six to 10 treated mice and an equal number of control mice at each dose level. [c]Three intraperitoneal injections were administered, on days 1, 5, and 9. [d]Toxic dose, less than half the treated mice survived. [e]Toxic dose, 5 out of 6 treated mice survived.

Table II. Test Results[a] *vs.* L1210 in Mice. *N*-Acetyldaunorubicin (7) in Varied Regimens[b,c]

No. of injections (ip)	Dose, mg/kg							
	2.5	5.0	10	20	40	80	160	320
1 (day 1)					121	121	121	115
2 (days 1, 8)					126	126	126	110
3 (days 1, 5, 9)					126	121	126	94
9 (daily)				126	115	126	105	
8 (day 1)[d]		126	121	136	121			
16 (days 1, 9)[d]		126	131	136				
24 (days 1, 5, 9)[d]	126	121	126	136				

[a]The numerical results are ratios (*T/C*) of survival times of treated mice over control mice, expressed as per cent. A ratio ≥125 is a positive result denoting activity. [b]Six to 10 treated mice and an equal number of control mice at each dose level. [c]No deaths due to toxicity were noted in any of these experiments. [d]Eight injections (every 3 hr) on the days cited.

under way. Additional modifications are being undertaken with the goal of further separating toxic and therapeutic properties within this important class of antitumor antibiotics.

Experimental Section

Reactions were carried out at room temp, except as noted for 10, 11, and 15. The pH 10 buffer was a commercially available phosphate buffer (W. H. Curtin and Co.). Extns were repeated until the aqueous layer was free of the strong red color of daunorubicin, and the exts became light in color; exts were dried over Na_2SO_4, filtered, and evapd under reduced pressure at room temp. The solids were dried *in vacuo* without heating, often for extended times. Melting points were observed in open capillaries and are uncorrected. Thin-layer chromatography (tlc) was done with silica gel HF (E. Merck) on 5 × 20 cm glass plates in $CHCl_3$–MeOH–H_2O systems (solvent ratios given in parentheses following the R_f's). Optical rotations were detd in 1-dm tubes with a Perkin-Elmer Model 141 automatic polarimeter.

Infrared spectra in Nujol mull all showed strong bands at μ 6.18 ± 0.02 (chelated quinone) and 6.32 ± 0.02 (always the more intense). Compds with the Me ketone underivatized all showed a medium intensity band at 5.82 μ. Other bands are listed where diagnostic for certain compds.

Nmr spectra were run at 60 or 100 MHz in $CDCl_3$, except where designated DMSO for dimethyl-d_6 sulfoxide, always using tetramethylsilane (δ 0.00) as internal reference. The spectra consistently showed a singlet for the aryl OMe (δ 3.93 ± 0.03 in $CDCl_3$, 3.90 ± 0.03 in DMSO), a singlet for the Me ketone (in 7-16; δ 2.37 ± 0.02 in $CDCl_3$, 2.28 ± 0.01 in DMSO), and a doublet (J = 6.5 Hz) for the sugar 5′-Me (δ 1.27 ± 0.01 in $CDCl_3$, 1.17 ± 0.01 in DMSO). These and other signals were as predicted from the lit. spectrum[8] of *N*-acetyldaunorubicin. Signals diagnostic for particular derivatives are also listed.

Daunorubicin Semicarbazone·HCl (2). A soln of 1.00 g (1.77 mmoles) of daunorubicin·HCl (1) in 15 ml of H_2O was treated with a soln of 2.00 g (17.9 mmoles) of semicarbazide·HCl and 2.45 g (18.0 mmoles) of $NaOAc \cdot 3H_2O$ in 10 ml of H_2O. The clear red soln was adjusted to pH 7.5 with 85 ml of 0.1 *M* aqueous Na_2CO_3, stirred at room temp for 21 hr, and treated with 25 ml of pH 10 buffer soln. The product was extd as the free base with 4 l. of $CHCl_3$–MeOH (3:1) in portions. The exts were evapd, and the residue dried *in vacuo* to give 1.0 g (92%) of free base, mp 222–227° dec (lit.[7,12] mp 264° mp 232–235° dec). A soln of free base in 50 ml of EtOH–$CHCl_3$–H_2O (60:30:10) was treated with 75 ml of 0.023 *M* ethanolic HCl (1.72 mmoles) to form the HCl salt, which was pptd by gradual addn of 900 ml of ether. The ppt was collected, washed with ether, and immediately dried *in vacuo*; if the wet ppt was exposed to the air for a short time, it began to darken and turn oily. Repptn from 85 ml of EtOH–MeOH (7:10) with ether yielded 0.69 g (63%), mp 183–189° dec, $[\alpha]^{24}D$ +313° (*c* 0.05, 95% EtOH), R_f 0.10 (80:30:3); ir 5.91 μ (C=O of semicarbazone); nmr (DMSO) δ 1.87 s (CH_3C=NN). *Anal.* ($C_{28}H_{32}N_4O_{10} \cdot HCl \cdot 2H_2O$) C, H, Cl, N.

Daunorubicin Oxime·HCl (3). Use of hydroxylamine·HCl in the procedure for 2 yielded 89% of crude oxime free base, mp 194–197°, and then 57% of HCl salt. Repptn of the salt, adding the ether slowly while stirring and allowing minimum exposure of the ppt to atmospheric moisture, was repeated a second time (25%

yield), mp 179–183° dec, $[\alpha]^{22}D$ + 314° (*c* 0.05, 95% EtOH), R_f 0.24 (80:30:3) with other trace spots at R_f 0.3 and R_f 0.4, nmr (DMSO) δ 1.80 s (CH_3C=NO). *Anal.* ($C_{27}H_{30}N_2O_{10}$·HCl·1.5H_2O) C, H, Cl, N.

Daunorubicin *N*-Piperidinoimine·HCl (5). A soln of 1.00 g (1.77 mmoles) of daunorubicin·HCl in 100 ml of MeOH–H_2O (9:1) was treated with 9.0 g (90 mmoles) of *N*-aminopiperidine, added in 3 equal portions, each followed by enough 1 *M* HCl to adjust the pH to 7.5–8.0. The mixt was stirred at room temp for 30 hr, 50 ml of pH 10 buffer soln was added, and the product was extd as the free base with $CHCl_3$ (200 ml total). Evapn gave a black, viscous residue, which was triturated with ether–petroleum ether to remove excess *N*-aminopiperidine. The insoluble residue (1.03 g) in 50 ml of $CHCl_3$ was converted with 0.046 *M* HCl–EtOH (1.8 mmoles) to the HCl salt, pptd with 500 ml of ether as for 2, to yield 0.64 g (55%), mp 160–164°, $[\alpha]^{18}D$ −380° (*c* 0.025, 95% EtOH), R_f 0.25 (120:20:1) with extraneous spots at R_f 0.18 (weak, same as daunorubicin) and R_f 0.38 (trace). In the nmr (DMSO, δ 1.96 s, CH_3C=NN) a few per cent of 1 (δ 2.30 s, CH_3C=O) could be detected; however, the activity of **5** cannot be attributed to the few per cent of 1 present as impurity at the levels tested. *Anal.* ($C_{32}H_{39}N_3O_9$·HCl·H_2O) C, H, Cl, N.

Daunorubicin from the HCl Salt. Daunorubicin hydrochloride (1) was stirred with an aqueous buffer soln at pH 10 (50 ml/g) at room temp until completely dissolved. The soln was extd with $CHCl_3$–MeOH (95:5). The exts (3 to 5 15-ml portions) were combined, dried, and concd (bath not over 25°). The residual free base (95–100%) was dried *in vacuo* and used without further purification. It could be stored at 5° for up to 2 months without decompn, according to tlc, R_f 0.1 (120:20:1).

Daunorubicin *O*-Methyloxime·HCl (4). Daunorubicin free base (from 1.20 g, 2.13 mmoles of HCl salt 1) was dissolved in 250 ml of MeOH–H_2O (4:1) and treated with a soln of 1.94 g (23.2 mmoles) of methoxyamine·HCl in 20 ml of MeOH. The pH was adjusted to 7.5 by adding 130 ml of 0.1 *M* aqueous Na_2CO_3, and the mixt was stirred at room temp for 24 hr. The ppt was collected and dissolved in $CHCl_3$, and the soln dried and evapd. The free base, mp 190–196° dec, was converted with an equimolar amt of HCl in EtOH, as described for 2, to the HCl salt (0.78 g), mp 170–177° dec; nmr (DMSO) δ 1.83 s (CH_3C=NO). A few per cent of unreacted 1 (δ 2.27 s, CH_3C=O) was removed by retreatment, as before, with 1.0 g of methoxyamine·HCl to yield 0.70 g (56%), mp 177–179° dec, $[\alpha]^{22}D$ + 220° (*c* 0.05, 95% EtOH), R_f 0.3 (40:15:1). *Anal.* ($C_{28}H_{32}N_2O_{10}$·HCl·1.5H_2O), C, H, N.

Daunorubicin Glycoloylhydrazone·HCl (6). A soln of daunorubicin (from 1.20 g, 2.13 mmoles of the HCl salt) in 220 ml of MeOH–H_2O (9:1) was treated with 1.50 g (16.7 mmoles) of glycoloylhydrazine[13] (mp 83–86° from EtOH), the pH (9.3) was adjusted to 7.5 with 12 ml of 0.1 *M* HCl, and the turbid red soln was stirred at room temp. Two addnl portions of glycoloylhydrazine were introduced after 7 days (1.0 g in 25 ml of MeOH) and 10 days (0.7 g). After 2 weeks, 50 ml of a pH 10 buffer was added, and the product was extd with $CHCl_3$. Evapn and repptn of the sticky residue from a $CHCl_3$–MeOH (1:1) soln (40 ml) with ether (120 ml) yielded the free base (1.07 g), mp 160–170° dec. It was redissolved in 100 ml of $CHCl_3$–MeOH (1:1) and converted to the HCl salt with 50 ml of 0.046 *M* HCl–EtOH (2.35 mmoles). Pptn with 150 ml of ether and vacuum drying without delay yielded 0.74 g. A repptn yielded 0.64 g (51%), mp 175–182° dec, $[\alpha]^{22}D$ + 260° (*c* 0.05, 95% EtOH); ir 5.9 μ (C=O), R_f 0.3 (40:15:1) with a trace spot at R_f 0.6. In the nmr (DMSO, δ 1.92 s, CH_3C=NN), a few per cent of 1 (δ 2.29 s, CH_3C=O) could be detected. *Anal.* ($C_{29}H_{33}N_3O_{11}$·HCl·H_2O) C, H, N; Cl: calcd, 5.42; found (ionic), 4.81.

N-Acetyldaunorubicin§ (7). Daunorubicin (from 5.00 g, 8.87 mmoles, of HCl salt 1) was partially dissolved in 250 ml of acetone and treated with two 1.50-ml (16.0 mmoles) portions of Ac_2O. The mixt was stirred at room temp for 2 hr, and the red ppt was collected, washed with acetone, and dried to give 4.04 g (78%), mp 166–177°, $[\alpha]^{22}D$ + 223° (*c* 0.1, $CHCl_3$), R_f 0.75 (80:30:3). The nmr spectrum was identical with that reported[8] (lit. mp 180°, $[\alpha]D$ + 228°). In some expts, trace amounts of daunorubicin (R_f 0.50) and daunomycinone# (R_f 0.90) were observed by tlc, and were removed by recrystn from *i*-PrOH or $CHCl_3$, followed by lyophilization of a fine aqueous suspension to remove the adhering solvent. *Anal.* ($C_{29}H_{31}NO_{11}$·1.25H_2O) C, H, N.

N-Propionyldaunorubicin (8) was obtained with propionic anhydride by the same procedure (78%), mp 153–159°, $[\alpha]^{23}D$ + 244° (*c* 0.1, $CHCl_3$), R_f 0.7 (80:30:3). *Anal.* ($C_{30}H_{33}NO_{11}$·1.5H_2O) C, H, N. An additional 10% was recovered from the mother liquor by recrystn from *i*-PrOH to remove a trace of daunomycinone,# R_f 0.85.

N-Butyryldaunorubicin (9) was similarly obtained (71%), mp 149–155°, $[\alpha]^{22}D$ + 216° (*c* 0.1, $CHCl_3$), R_f 0.55 (100:30:3). *Anal.* ($C_{31}H_{35}NO_{11}$·0.5H_2O) C, H, N.

N-(Methylcarbamoyl)daunorubicin (10). Daunorubicin (from 1.50 g, 2.66 mmoles, of HCl salt) was dissolved in 100 ml of H_2O and 70 ml of MeOH and treated with stirring at −10° with 0.25 ml (3.31 mmoles) of methyl isocyanate. After stirring at −5 to −10° for 45 min, extn with $CHCl_3$ (five 70-ml portions) afforded the crude product, 1.62 g, which upon trituration with 150 ml of boiling acetone afforded 1.33 g of insoluble red powder, mp 290–300° dec, R_f 0.73 (80:30:3). Traces of daunomycinone# (R_f 0.88) and daunorubicin (R_f 0.48) were removed by trituration with 200 ml of boiling MeOH to yield 0.76 g (49%), $[\alpha]^{24}D$ + 224° (*c* 0.1, 95% EtOH), nmr (DMSO) δ 2.08 s (NCH_3). Urea C=O absorption in the ir could be seen only as a slight broadening of the band at 6.18 μ (C=O, H-bonded quinone). *Anal.* ($C_{29}H_{32}N_2O_{11}$) C, H, N.

N-(Butylcarbamoyl)daunorubicin (11). Daunorubicin (1.2 g, 2.13 mmoles) in 80 ml of MeOH and 10 ml of H_2O was similarly treated with 0.3 ml (3.23 mmoles) of butyl isocyanate. The product was pptd by adding 120 ml of H_2O, collected, and recrystd from MeOH to yield 1.06 g (79%), mp 185–189° dec, $[\alpha]^{22}D$ + 275° (*c* 0.1, 95% EtOH), ir 6.09 μ (C=O, urea), R_f 0.61 (120:20:1). *Anal.* ($C_{32}H_{38}N_2O_{11}$) C, H, N.

N-(Methylthiocarbamoyl)daunomycin (12). Daunorubicin (1.20 g, 2.28 mmoles) in 100 ml of $CHCl_3$–MeOH (1:1) was treated with 1.82 g (25.0 mmoles) of methyl isothiocyanate and stirred for 18 hr. The soln was clarified by filtration and evapd. The crude product was dissolved in MeOH–$CHCl_3$ (1:1), repptd with 10 vols of ether, and recrystd from 125 ml of hot MeOH with addn of 125 ml of H_2O to yield 0.65 g in two crops (42%), mp 172–176° dec, $[\alpha]D$ + 269° (*c* 0.1, 95% EtOH), R_f 0.6 (120:20:1); nmr (DMSO) δ 2.78 d (NCH_3). *Anal.* ($C_{29}H_{32}N_2O_{10}S$·0.5H_2O) C, H, N, S.

N-(Butylthiocarbamoyl)daunorubicin (13). A 10-fold excess of butyl isothiocyanate was added to a daunorubicin soln (as for 12), followed by the same amt in 2 portions after 5 and 6 hr. After 7 hr, the reaction mixt was chilled to 0°, poured into 3 vols of H_2O, and extd with $CHCl_3$. Evapn of the combined exts afforded a solid residue which was sepd by filtration from an accompanying oil, washed with ether, and dried *in vacuo* (74% yield), mp 156–162° dec, $[\alpha]^{19}D$ + 140° (*c* 0.1, $CHCl_3$). R_f 0.65 (120:20:1). *Anal.* ($C_{32}H_{38}N_2O_{10}S$) C, H, N, S.

N-(Phenylthiocarbamoyl)daunorubicin (14). Addn of a 10-fold excess of phenyl isothiocyanate was followed after 1 hr by an addnl 5-fold excess. After 2 hr, an equal vol of water was added to the reaction mixt. Extn with $CHCl_3$ and evapn afforded a red gum (87%), R_f 0.75 (120:20:1), containing a trace of daunorubicin (R_f 0.20). Attempted recrystn from $CHCl_3$–MeOH gave an oil, which solidified on repeated trituration with ether (64% yield), mp 172–178° dec, $[\alpha]D$ −4.3° (*c* 0.1, $CHCl_3$). An addnl 9% was obtained from the combined filtrates by evapn and pptn from CH_3OH with ether. *Anal.* ($C_{34}H_{34}N_2O_{10}S$·H_2O) C, H, N.

N-Carboxydaunorubicin γ-Lactam (16). A soln of 0.40 g (0.76 mmole) of daunorubicin free base in 40 ml of anhyd pyridine was treated with a soln of 0.20 g (2.2 mmoles) of phosgene in 12.5 ml of anhyd toluene and stirred for 45 min at room temp. Water (50 ml) was added, and the product was extd with ether (eight 60-ml portions). Evapn of the exts and trituration of the dark red, oily residue with 25 ml of ether gave 0.15 g of red solid. An addnl 0.15 g of red solid was recovered from the H_2O layer by extn with $CHCl_3$ and trituration of the residual oil with MeOH. Both crops, according to tlc in $CHCl_3$–MeOH–H_2O (120:20:1) were mixts of two major components, one red (R_f 0.64) and one orange (R_f 0.50), plus 2 or 3 addnl weak red spots. Since sepn was not successful by MeOH recrystn, it was accomplished by preparative tlc, using five 20 × 20 cm plates (2-mm layer) for 300 mg of solid mixt. The major red zone afforded 0.116 g (homogeneous), mp 185–190° dec, $[\alpha]^{22}D$ −46° (*c* 0.1, $CHCl_3$), ir 5.68 μ (C=O; shoulder at 5.8). *Anal.* ($C_{28}H_{27}NO_{11}$·0.5H_2O) C, H; N: calcd, 2.49; found, 2.92. (The orange band afforded 20 mg, mp 225–226° after recrystn from $CHCl_3$–MeOH, which was not identified.)

N-Carboxydaunorubicin Methyl Ester (15). A soln of 1.00 g (1.77 mmoles) of daunorubicin·HCl (1) in 30 ml of MeOH was treated with 0.10 g (1.8 mmoles) of NaOMe, and the resulting soln of free base was dild with 20 ml of H_2O and 50 ml of 0.1 *M* $NaHCO_3$ and cooled to 15°. A fresh 0.26 *M* soln (8.0 ml, 2.1 mmoles) of methyl chloroformate in MeOH was added dropwise with stirring and cooling, with addnl $NaHCO_3$ (200 ml) to maintain a pH of 7.5.

#The aglycone from cleavage of 1; see ref 2.

After 20 min, an addnl 1.0 ml of the 0.26 *M* methyl chloroformate soln was added, and the mixt was stirred 40 min longer. The red ppt was collected, washed with water, triturated with ether, and dried *in vacuo* to yield 0.72 g (69%), mp 149–154°, $[\alpha]^{23}D + 251°$ (*c* 0.1, $CHCl_3$), R_f 0.7 (60:10:1), nmr δ 3.54 s (NCOOMe). *Anal.* ($C_{29}H_{31}NO_{12} \cdot 0.5H_2O$) C, H; N: calcd, 2.36; found, 2.71.

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New Compounds

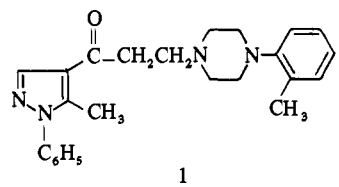
Mannich Bases of 2,3-Dihydro-4(1*H*)-carbazolones as Potential Psychotropic Agents

Ruddy Littell, E. N. Greenblatt, and George R. Allen, Jr.*

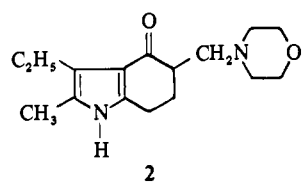
Lederle Laboratories, A Division of American Cyanamid Company, Pearl River, New York 10965. *Received January 12, 1972*

The potential utility of Mannich bases as pharmaceutical agents has been investigated frequently, and compounds **1** and **2** represent recent examples. The pharmacological profile of the former substance is similar to that of reserpine,[1] whereas the latter material is reported to be a potent antipsychotic agent in man.[2] Despite the availability of 2,3-dihydro-4(1*H*)-carbazolone (**3**)[3] and its 9-methyl derivative **4**,[4] the preparation of Mannich bases derived from these heterocycles has not been reported. Inasmuch as clinical studies with **2** suggest that it possesses utility in humans,[5] the preparation of similar compounds from **3** and **4** was undertaken. The synthesis of the Mannich bases **5** and **6** was accomplished by conventional procedures, the details of which may be found in the Experimental Section.

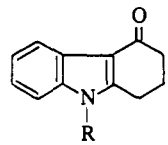
Pharmacology. Mannich bases **5** and **6** were tested for



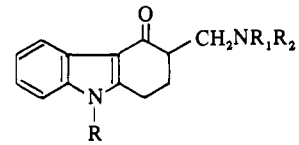
1



2



3, R = H
4, R = CH_3



5, R = H
6, R = CH_3

Table I. Biological Activities of Representative 3-(Substituted aminomethyl)-2,3-dihydro-4(1*H*)-carbazolones

Compound	Median effective dose, mg/kg ip				
	Ataxia[a]	Motor act. decrease[a]	Antielectro-shock[b]	Antistrych[c]	Lethality
1-(5-Methyl-1-phenyl-4-pyrazolyl)-3-(4-*o*-tolyl-1-piperazinyl)-1-propanone hydrochloride (1)	27	3			110
3-(1-Pyrrolidinomethyl)-2,3-dihydro-4(1*H*)-carbazolone		30			300
3-(4-Morpholinomethyl)-2,3-dihydro-4(1*H*)-carbazolone		4			40
3-(1-Piperidinomethyl)-2,3-dihydro-4(1*H*)-carbazolone	50	7			68
9-Methyl-3-(4-morpholinomethyl)-2,3-dihydro-4(1*H*)-carbazolone		30	29		300
9-Methyl-3-(1-piperidinomethyl)-2,3-dihydro-4(1*H*)-carbazolone		16			160
3-(3-Methyl-1-piperidinomethyl)-2,3-dihydro-4(1*H*)-carbazolone		8			80
9-Methyl-3-(3-methyl-1-piperidinomethyl)-2,3-dihydro-4(1*H*)-carbazolone	78	18	40		180
9-Methyl-3-(4-methyl-1-piperidinomethyl)-2,3-dihydro-4(1*H*)-carbazolone	32	10			128

[a]Determined as described by Wright, *et al.*,[6] the absence of a figure signifies no effect at 100 mg/kg. [b]Determined as described by Swinyard, *et al.*;[7] the lack of a figure indicates no effect at 50 mg/kg. [c]Determined by a modification of the method of Hanson and Stone;[8] the compounds were without effect at 50 mg/kg.