morphine in that it is analgesic without interfering markedly with intestinal motility.

Human Studies.—A 52-year-old female with metastatic carcinoma of the breast who was extremely tolerant to morphine was given 6-MDDM in doses of 0.5, 1.0, 2.0, and 3.0 mg., subcutaneously. After the 2.0- and 3.0-mg. doses, she was euphoric and less concerned with her pain. The effects occurred sooner (10–15 min.) than with morphine and were accompanied by a mild hypotensive effect (115/60 mm. from 130/75 mm.) and miosis (3.0-mm. pupil diameter from 3.4 mm.). In a single blind study the patient was given a placebo, 15 mg. of morphine, and 2 mg. of 6-MDDM in a 9-hr. period. The placebo was ineffective, and the morphine and 6-MDDM provided a similar degree of analgesia which was distinguishable to the observers by the hypotensive effect of the 6-MDDM. No depression of respiratory rate was noted.

Single 0.5-mg. doses of 6-MDDM were then administered intramuscularly to 3 healthy adult males. These subjects were supine and wore an anesthesia mask for administration of CO_2. All subjects were sedated within 15 min. and remained so for more than 2 hr.; recovery was nearly complete after 3 hr. End tidal CO_2 values were elevated in all subjects from 15–180 min. after drug administration, most markedly at 15 min. Intermittant breathing of 3 and 6% CO_2 produced a ventilatory response to a CO_2 curve which was shifted down and to the right as is typical for narcotic analgesics.[17] No hypotension was noted in the supine position and none of the subjects experienced euphoria, dysphoria, or nausea.

Thus, on the basis of limited trial in man, 6-MDDM appears to be an analgesic, sedative, and respiratory-depressant drug which exhibits partial cross tolerance with morphine and may produce orthostatic hypotension but not nausea or notable euphoria. Addiction liability studies will be done in monkeys and then in humans if the animal evidence is favorable.

(17) C. J. Lambertsen in "Handbook of Physiology," Vol. 1, W. O. Fenn and H. Rahn, Ed., American Physiological Society, Washington, D. C., 1961, p. 545.

Analgesic Antagonists. I. 4-Substituted 1-Acyl-2,3,4,5-tetrahydro-1H-1,4-benzodiazepines

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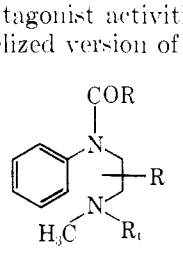
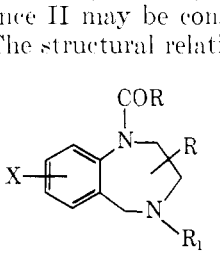
A series of 4-substituted 3H-1,4-benzodiazepine-2,5(1H,4H)-diones has been prepared by two methods. Reductive cyclization of an ethyl N-(*o*-nitrobenzoyl)glycinate gave the seven-membered cyclic diamide in very good yield. Heating an ethyl glycinate with an isatoic anhydride also gave the benzodiazepinedione, but in poor yield. Reduction of the diamides with lithium aluminum hydride followed by acylation gave the title compounds, which are analgesic antagonists.

Anilides of the structural type I have been shown[1] to be strong analgesics. In our search for analgesics and analgesic antagonists, we considered structures of the type II as likely to possess analgesic and/or analgesic antagonist activities, since II may be considered as a cyclized version of I. The structural relationship



I



II

between II and Librium[6] was a further spur to our interest in these compounds. The synthetic routes used for obtaining the benzodiazepines II are shown in Scheme I.

Miyatake and Kaga[2] reported the preparation of 3H-1,4-benzodiazepine-2,5(1H,4H)-dione (VI, $R_1 = R_2 = X = H$) by the reduction of *o*-nitrobenzoylglycine using Raney nickel catalyst. Uskokovic and co-workers[3a] have also prepared this compound by heating the piperidide of *o*-aminobenzoylglycine. They reported that heating ethyl *o*-aminobenzoylglycine gave a poor yield of VI ($R_1 = R_2 = X = H$).

We have repeated the preparation of VI ($R_1 = R_2 = X = H$) as described by Miyatake and Kaga[2] and have obtained the aforementioned product in 87% yield. The reduction of *o*-nitrobenzoylglycines[3b] or their ethyl esters was found to be a general method for the preparation of 3H-1,4-benzodiazepine-2,5(1H,4H)-diones. Either Raney nickel or iron–acetic acid was used as the reducing agent, depending on what functional groups were present in the *o*-nitrobenzoylglycine derivatives; the cyclic diamines (VI) were obtained in very good yields by evaporation of the filtered reaction mixture (see Table I).

Another method which was used to prepare compounds of the type VI was heating an isatoic anhydride (X) with a glycine ethyl ester (IX). The poor yields obtained made this method less desirable than the reduction method. However, VI ($R_2 = R_1 = X = H$) and VI ($R_1 = X = H$; $R_2 = CH_2CH{=}CH_2$) prepared by this method were found to be identical with the corresponding products prepared *via* the reduction

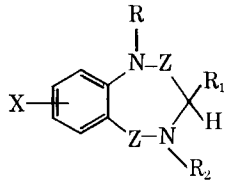
(1) W. B. Wright, H. A. Brabander, and R. A. Hardy, Jr., *J. Am. Chem. Soc.*, **81**, 1518 (1959).

(2) K. Miyatake and S. Kaga, *J. Pharm. Soc. Japan*, **72**, 1160 (1952).

(3) (a) M. Uskokovic, J. Iacobelli, and W. Wenner, *J. Org. Chem.*, **27**, 3606 (1962). (b) After this work had been completed, J. Krapcho, U. S. Patent 3,173,912 (March 16, 1965) was issued, describing a similar method for the preparation of 1,4-benzodiazepinediones.

TABLE I

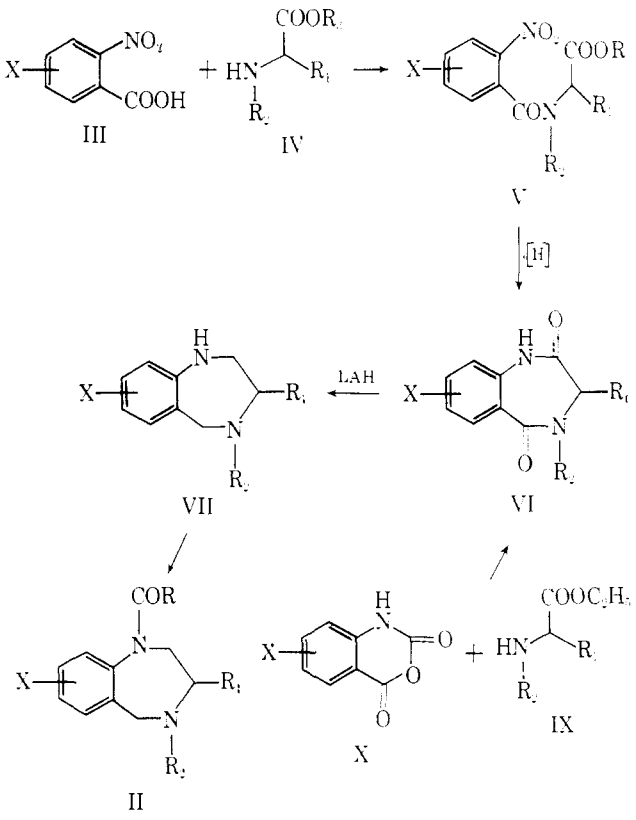
1,4-BENZODIAZEPINES



No.	R	R_1	R_2	X	Z	M.p., °C.	Yield, %	Formula	C, % Calcd.	C, % Found	H, % Calcd.	H, % Found	Cl or N, % Calcd.	Cl or N, % Found
1	H	H	H	H	C=O	322–325 dec.	86.9	$C_9H_8N_2O_2$	61.34	61.10	4.58	4.52	15.90[a]	15.77[a]
2	H	H	CH_3	H	C=O	246.2–247.0	73.0	$C_{10}H_{10}N_2O_2$	63.14	63.16	5.30	5.08	14.73[a]	14.78[a]
3	H	H	$CH_2CH=CH_2$	H	C=O	184.8–186.2	94.0	$C_{12}H_{12}N_2O_2$	66.64	66.34	5.60	5.81	12.96[a]	13.06[a]
4	H	H	CH_2-c-C_3H_5	H	C=O	175.0–176.8	87.5	$C_{13}H_{14}N_2O_2$	67.80	67.96	6.13	6.40	12.17[a]	11.95[a]
5	H	H	$CH_2CH_2C_6H_5$	H	C=O	188.0–189.2	36.0	$C_{17}H_{16}N_2O_2$	72.85	72.85	5.76	6.00	9.99[a]	10.09[a]
6	H	CH_3	$CH_2CH=CH_2$	H	C=O	137.4–139.2	63.7	$C_{13}H_{14}N_2O_2$	67.80	67.95	6.13	6.20	12.17[a]	11.84[a]
7	H	H	H	7-Cl	C=O	323–325 dec.	27.8	$C_9H_7ClN_2O_2$	51.33	51.50	3.55	3.46	16.84	16.77
8	H	H	$CH_2CH=CH_2$	7-Cl	C=O	189.0–191.0	12.3	$C_{12}H_{11}ClN_2O_2$	57.49	57.65	4.43	4.56	11.18[a]	11.26[a]
9	H	H	$CH_2CH=CH_2$	8-CH_3O	C=O	162.0–164.0	83.5	$C_{13}H_{14}N_2O_3$	63.40	63.50	5.73	5.44	11.38[a]	11.23[a]
10	H	H	$CH_2CH=CH_2$	7-NO_2	C=O	188.4–191.6	26.9	$C_{12}H_{11}N_3O_4$	55.21	55.19	4.15	4.46	16.10[a]	16.26[a]
11	H	H	$CH_2CH=CH_2$	7-$OCH_2C_6H_5$	C=O	185–187	75.7	$C_{19}H_{18}N_2O_3$	70.78	70.57	5.63	5.63	8.69[a]	8.67[a]
12	H	H	H	H	CH_2	246.2–248.0	97.0	$C_9H_{12}N_2 \cdot 2HCl$	48.89	48.56	6.38	6.28	32.08	32.43
13	H	H	CH_3	H	CH_2	210.2–214.8	92.1	$C_{10}H_{14}N_2 \cdot 2HCl$	51.05	50.86	6.86	6.70	11.91[a]	11.57[a]
14	H	H	$CH_2CH=CH_2$	H	CH_2	189.8–199 dec.	82.0	$C_{12}H_{16}N_2 \cdot 2HCl$	55.18	55.32	6.94	7.14	27.15	26.87
15	H	H	CH_2-c-C_3H_5	H	CH_2	210.0–215.0 dec.	99.1	$C_{13}H_{18}N_2 \cdot 2HCl$	56.74	56.91	7.32	7.42	25.77	25.88
16	H	H	$CH_2CH_2C_6H_5$	H	CH_2	80.0–83.0	71.5	$C_{17}H_{20}N_2$	80.89	80.77	7.98	8.12	11.10[a]	11.27[a]
17	H	H	$CH_2CH=CH_2$	8-CH_3O	CH_2	182.6–186.0	95.7	$C_{13}H_{18}N_2O \cdot 2HCl$	53.61	53.77	6.92	7.07	9.62[a]	9.67[a]
18	H	H	$CH_2CH=CH_2$	7-$OCH_2C_6H_5$	CH_2	77–79.2	65.3	$C_{19}H_{22}N_2O$	77.51	77.27	7.54	7.52	9.52[a]	9.60[a]
19	COC_2H_5	H	CH_3	H	CH_2	229.6–231.8	73.8	$C_{13}H_{18}N_2O \cdot HCl$	61.27	61.44	7.52	9.75	13.92	13.73
20	$COCH_3$	H	$CH_2CH=CH_2$	H	CH_2	230.6–231.4	84.2	$C_{14}H_{18}N_2O \cdot HCl$	63.03	63.31	7.18	7.28	13.29	13.37
21	COC_2H_5	H	$CH_2CH=CH_2$	H	CH_2	237.8–239.2	62.9	$C_{15}H_{20}N_2O \cdot HCl$	64.14	64.39	7.54	7.52	12.63	12.66
22	COC_3H_7	H	$CH_2CH=CH_2$	H	CH_2	184.8–186.8	61.0	$C_{16}H_{22}N_2O \cdot HCl$	65.20	65.08	7.86	7.92	12.03	12.21
23	COC_6H_5	H	$CH_2CH=CH_2$	H	CH_2	219.4–220.8	64.6	$C_{19}H_{20}N_2O \cdot HCl$	69.39	69.08	6.44	6.59	10.78	10.78
24	COC_2H_5	CH_3	$CH_2CH=CH_2$	H	CH_2	200.2–201.2	52.3	$C_{16}H_{22}N_2O \cdot HCl$	65.18	65.34	7.86	7.77	12.03	12.13
25	COC_2H_5	H	CH_2-c-C_3H_5	H	CH_2	226.0–227.0	72.0	$C_{16}H_{22}N_2O \cdot HCl$	65.18	65.36	7.86	7.97	12.03	12.24
26	$COCH_3$	H	$CH_2CH_2C_6H_5$	H	CH_2	239.8–240.6	75.0	$C_{19}H_{22}N_2O \cdot HCl$	68.90	68.81	6.95	6.83	10.72	10.67
27	COC_2H_5	H	$CH_2CH_2C_6H_5$	H	CH_2	214.6–216.4	77.5	$C_{20}H_{24}N_2O \cdot HCl$	69.64	69.82	7.30	7.56	10.28	10.47
28	$COCH_3$	H	$CH_2CH=CH_2$	7-Cl	CH_2	235.2–235.8	57.7	$C_{14}H_{17}ClN_2O \cdot HCl$	55.80	55.70	6.02	6.32	23.54	23.17
29	COC_2H_5	H	$CH_2CH=CH_2$	8-CH_3O	CH_2	210.0–212.0	41.6	$C_{16}H_{22}N_2O_2 \cdot HCl$	61.83	61.73	7.46	7.60	9.02[a]	9.01
30	COC_2H_5	H	$CH_2CH=CH_2$	7-OH	CH_2	245.0–246.0 dec.	43.5	$C_{15}H_{20}N_2O_2 \cdot HCl$	60.70	60.91	7.14	7.03	11.95	11.72

[a] Analyzed for nitrogen.

SCHEME I



procedure. 7-Nitro and 7-chloro derivatives of VI were also obtained by this method.

Reduction of the diamides (VI) with lithium aluminum hydride in boiling tetrahydrofuran produced the diamines (VII). Acylation of VII with either an acid chloride or anhydride gave the desired amides (II).

The phenolic amine (VII, R_1 = H; R_2 = $CH_2CH{=}CH_2$; X = 7-OH) was prepared by debenzylating VII (R_1 = H; R_2 = $CH_2CH{=}CH_2$; X = 7-$OCH_2C_6H_5$) with concentrated hydrochloric acid. The crude phenol was treated with excess propionic anhydride to give crude VII (R = C_2H_5CO; R_1 = H; R_2 = $CH_2OH{=}CH_2$; X = 7-C_2H_5COO) which was partially hydrolyzed with sodium hydroxide to yield VII (R = C_2H_5CO; R_2 = H; R_2 = $CH_2CH{=}CH_2$; X = 7-OH).

Pharmacology.—These compounds were tested for strong analgesic and analgesic-antagonist activity. The analgesic activity was assessed by the Bass and Vander Brook[4] modification of the rat tail-flick test of D'Amour and Smith.[5] Analgesic antagonism was determined by the method of Harris and Pierson.[6]

All of the compounds were inactive as strong, morphine-like analgesics in the tail-flick test. This was true even with the phenethyl compounds (**5**, **16**, **26**, and **27**) which, by analogy with other analgesic series,[7] might be expected to have high activity.

It was of interest, therefore, that certain of these compounds had the ability (Table II) to antagonize the analgesic effects of meperidine. Analgesic antagonism is usually associated with N-allylation in known series

(4) W. B. Bass and M. J. Vander Brook, *J. Am. Pharm. Assoc., Sci. Ed.*, **41**, 569 (1952).

(5) F. E. D'Amour and D. L. Smith, *J. Pharmacol. Exptl. Therap.*, **72**, 74 (1941).

(6) L. S. Harris and A. K. Pierson, *ibid.*, **143**, 141 (1964).

(7) N. B. Eddy, *Chem. Ind.* (London), 1462 (1959).

TABLE II

ANALGESIC ANTAGONIST ACTIVITY OF 1,4-BENZODIAZEPINES

Compd. no.	AI_{50} vs. meperidine, mg./kg. of base (95% confidence limits)[a]
1	Sl. active,[b,c] 100
2	47 (31–71)[d]
3	Sl. active,[c] 160
4	Inactive, 100[c]
5	Sl. Active,[c] 400
6	Inactive, 160[c]
7	Inactive, 100[d]
8	80 (42–152)[e]
9	Sl. active,[c] 100
10	Inactive, 40[c]
12	Inactive, 160[c]
13	140 (78–252)[d]
14	Sl. active,[d] 320
15	Sl. active,[d] 100
16	Inactive, 160[d]
17	34 (25–51)[d]
18	Sl. active,[d] 20
19	40 (27–60)[d]
20	95 (66–138)[d]
21	24 (15–38)[d]
22	70 (48–101)[d]
23	130 (72–234)[d]
24	22 (14–35)[d]
25	35 (24–51)[d]
26	58 (36–93)[d]
27	24 (15–38)[d]
28	48[d,e]
29	21 (15–28)[d]
30	Sl. active,[d] 80
Nalorphine	0.13 (0.10–0.18)[d]

[a] Determined by the method of J. T. Litchfield and F. Wilcoxon, *J. Pharmacol. Exptl. Therap.*, **96**, 99 (1949). [b] "Slightly active" indicates that some antagonism (<50%) was seen and the effect was not dose responsive. [c] Intraperitoneal administration. [d] Subcutaneous administration. [e] Dose–response curve too flat to permit calculation of confidence limits.

of strong analgesics. Thus, replacement of the N-methyl group of morphine (pentacyclic) by an allyl function results in an antagonist (nalorphine). Similar modification in the tetracyclic morphinan (levallorphan) and tricyclic benzomorphan series also leads to antagonists. Such modification in the bicyclic meperidine series, however, does not produce an antagonist.[8]

The present series has a fused bicyclic system, and groups such as N-allyl and N-cyclopropylmethyl, which are usually associated with potent antagonists, do impart properties which counteract the effects of meperidine. However, the N-methyl and N-phenethyl derivatives, which usually have analgesic activity, also shared this antagonistic property. Indeed, when one compares the effectiveness of N-allyl with N-methyl or N-phenethyl (*i.e.*, **2**, **3**; **13**, **14**; **19**, **21**; **20**, **26**; and **21**, **27**), the N-methyl and N-phenethyl compounds are as active or more so.

Other structure–activity relationships also emerge. The greatest and most consistent antagonistic activity was seen in the 1-acylated compounds (**19**–**30**), with the propionyl derivatives (**21** and **27**) seemingly the most potent. The 3-methyl compounds (**6** and **24**) are somewhat more active than their unsubstituted analogs (**3** and **21**). Substitution in the benzene ring also modifies potency. The 7-chloro compounds appear to

(8) S. Archer and L. S. Harris, "Fortschritte der Arzneimittel," Vol. 8, E. Jucker, Ed., Birkhäuser Verlag, Basel, 1965, p. 262.

be more active (**8**, **3** and **28**, **20**) as do the 8-methoxy derivatives (**9**, **3**; **7**, **14**; and **29**, **21**).

4-Allyl-3-methyl-1-propionyl-1,2,4,5-tetrahydro-3H-1,4-benzodiazepine (**24**) was also tested for its ability to reverse the analgesic effects of morphine and phenazocine. The subcutaneous ED_{50} values were 110 and 45 mg./kg., respectively. Although the compound was somewhat less active against these analgesics, it did produce a good dose–response relationship and was effective. This compound (**24**), like other analgesic antagonists,[9] was found to be effective in reversing the respiratory and cardiovascular depression produced by meperidine in the anesthetized dog.

Experimental Section[10]

Ethyl N-(*o*-Nitrobenzoyl)glycinate.—A suspension of ethyl glycinate hydrochloride (139.6 g., 1.0 mole) in 1 l. of $CHCl_3$ was stirred vigorously while *o*-nitrobenzoyl chloride (185.6 g., 1.0 mole) in 100 ml. of $CHCl_3$ and triethylamine (222 g., 2.2 moles) were added slowly through separate addition funnels at a rate causing steady reflux. Stirring was continued for 2 hr. after the additions were complete. The solution was stirred with 500 ml. of water for 5 min., the layers were separated, and the $CHCl_3$ layer was evaporated to a solid. Recrystallization from ethyl acetate gave 216 g. (86%) of product, m.p. 94–95°.

Anal. Calcd. for $C_{11}H_{12}N_2O_6$: N, 11.1. Found. N, 11.09.

Ethyl N-allyl-N-(*o*-nitrobenzoyl)glycinate was prepared similarly in 93% yield, b.p. 170–174° (0.2 mm.), $n^{29}D$ 1.5310.

Anal. Calcd. for $C_{14}H_{16}N_2O_5$: N, 9.69. Found: N, 9.69.

Ethyl N-allyl-N-(*o*-nitrobenzoyl)alaninate[11] (98.5% crude yield), **ethyl N-(*o*-nitrobenzoyl)-N-(2-phenethyl)glycinate**[12] (96.5% crude yield), and **ethyl N-cyclopropylmethyl-N-(*o*-nitrobenzoyl)glycinate** (97.2%) were prepared in like manner but were not purified before reduction and cyclization.

N-Methyl-(*o*-nitrobenzoyl)glycine.—Sarcosine (17.8 g., 0.2 mole) was dissolved in 50 ml. of water. Five milliliters of 35% NaOH was added, then *o*-nitrobenzoyl chloride (18.6 g., 0.1 mole) all at once. The mixture was stirred vigorously with cooling for 1 hr. while 35% NaOH was added as needed to keep the solution basic. The solution was filtered and acidified with concentrated HCl, to precipitate a red oil. The oil was dissolved in ethyl acetate, washed with water, and concentrated *in vacuo* to a pink solid which was recrystallized from ethanol to give 17.8 g. (74.9%) of product, m.p. 158–159°.

Anal. Calcd. for $C_{10}H_{10}N_2O_5$: N, 11.76. Found: N, 11.84.

Cyclopropylmethylamine.—Cyclopropyl cyanide (93.3 g., 1.4 moles) was added at a rate causing reflux, to a slurry of lithium aluminum hydride (52.5 g., 1.4 moles) in 1 l. of tetrahydrofuran. The mixture was stirred vigorously for 5.5 hr. and left overnight. After hydrolysis with water and 20% NaOH, the mixture was filtered and the filter cake was washed well with tetrahydrofuran. Distillation of the filtrate and washings gave 78.4 g. (79%) of product, b.p. 84–86° (760 mm.), $n^{29}D$ 1.4241. A small portion was converted to the hydrochloride which was recrystallized from ethanol–ether; m.p. 203–204°, lit.[13] m.p. 201.5–203.5°.

Ethyl N-cyclopropylmethylglycinate was prepared from cyclopropylmethylamine and ethyl bromoacetate in 74% yield by the method of Speziale and Jaworski[11]; b.p. 57–60° (11 mm.), $n^{28}D$ 1.4398.

Anal. Calcd. for $C_8H_{15}NO_2$: N, 8.91. Found: N, 8.83.

3H-1,4-Benzodiazepine-2,5(1H,4H)-dione (1). A. From N-*o*-Nitrobenzoylglycine.—*o*-Nitrobenzoylglycine[14] (107 g., 0.5 mole) in 1200 ml. of methanol was hydrogenated in an 1800-ml. Aminco autoclave at 2.8 atm. and 20–28° using 15 g. of Raney nickel catalyst. The theoretical amount of hydrogen was absorbed in 1 hr. The catalyst was filtered and washed with methanol. The filtrate and washings were evaporated *in vacuo* to a white solid which was boiled with methanol to remove colored impurities. The washings were evaporated to obtain a small second crop; total yield 73 g. (87%), m.p. 322–325° dec. (lit.[2] m.p. 327°).

Anal. Calcd. for $C_9H_8N_2O_2$: C, 61.34; H, 4.58. Found: C, 61.10; H, 4.52.

B. From Isatoic Anhydride and Glycine Ethyl Ester Hydrochloride.—Isatoic anhydride (16.3 g., 0.1 mole) and glycine ethyl ester hydrochloride (13.9 g., 0.1 mole) in 30 ml. of dimethylformamide was refluxed for 3 hr., cooled, and poured into 250 ml. of water. The resulting, tan solid was collected and washed with acetonitrile then methanol and recrystallized from dimethylformamide to give 3.5 g. (20%) of product, m.p. 326–329° dec. The infrared spectrum of this material was identical with that prepared from N-*o*-nitrobenzoylglycine.

C. From N-(*o*-Nitrobenzoyl)glycine Ethyl Ester.—*o*-Nitrobenzoylglycine ethyl ester (215.7 g, 0.9 mole) in 1400 ml. of methanol was hydrogenated as described in A. After removal of catalyst and evaporation of the filtrate *in vacuo*, a white solid, soluble in acetonitrile, probably N-(*o*-aminobenzoyl)glycine, was obtained. This was heated to 200–220° for 0.5 hr. The product melted, evolved ethanol, and resolidified. Washing with acetonitrile, then methanol gave 105 g. (69%) of product, m.p. 320–325° dec.

4-Allyl-3H-1,4-benzodiazepine-2,5(1H,4H)-dione (3). A. From Ethyl N-Allyl-N-(*o*-nitrobenzoyl)glycinate.—A vigorously stirred mixture of iron filings (117 g., 2.1 g.-atoms), 730 ml. of ethanol, 30 ml. of acetic acid, and 210 ml. of water was heated to reflux. The heat was removed and ethyl N-allyl-N-(*o*-nitrobenzoyl)glycinate (90.5 g., 0.3 mole) in 200 ml. of ethanol was added at a rate causing steady reflux. After the addition had been completed, the mixture was refluxed with stirring for 3 hr. Sodium carbonate (40 g.) was added cautiously. The mixture was stirred for 5 min. and filtered hot. The filter cake was washed with 1.5 l. of hot ethanol and the combined filtrate and washings evaporated *in vacuo* to a tan solid. This was washed with water and recrystallized from ethanol using decolorizing charcoal. There was obtained 63 g. (94%) of product, m.p. 184.8–186.2°. The 7-benzyloxy, 8-methoxy, 3-methyl, 4-(2-phenethyl), and 4-(cyclopropylmethyl) analogs were similarly prepared.

B. From Isatoic Anhydride and Ethyl N-Allylglycinate.—Isatoic anhydride (16.3 g., 0.1 mole) and ethyl N-allylglycinate (14.3 g., 0.1 mole) were combined and heated on the steam bath for 2 hr. Ethanol was added, the solution was chilled and scratched, and the resulting solid was collected. One recrystallization from ethanol gave 8.0 g. (36%) of product, m.p. 185–186°, undepressed on admixture with material from method A.

4-Methyl-3H-1,4-benzodiazepine-2,5(1H,4H)-dione (2).—N-Methyl-*o*-nitrobenzoylglycine (68.2 g., 0.286 mole) in 700 ml. of methanol was hydrogenated at 26–32° and 20 atm. in an 800-ml. Aminco rocking autoclave, using 11 g. of Raney nickel catalyst. The theoretical amount of hydrogen was absorbed in 1 hr. The catalyst was removed by filtration and the filtrate was concentrated to a pinkish solid. The solid was washed with a small amount of methanol and recrystallized from acetic acid–water. The product (33.6 g., 73%) had m.p. 246.2–247°.

4-Allyl-7-chloro-3H-1,4-benzodiazepine-2,5(1H,4H)-dione (8).—Ethyl N-allylglycinate (14.3 g., 0.1 mole) was added to 5-chloroisatoic anhydride (18.4 g., 0.1 mole) in a 250-ml. round-bottom flask. The flask was heated on the steam bath for 0.5 hr. The reaction mixture foamed vigorously while evolving CO_2 and eventually became a clear brown liquid. This was heated to 160–180° for 2.5 hr., while more gas was evolved. After standing for 2 days, the thick oil was dissolved in 100 ml. of boiling ethanol. The solution was chilled and scratched, and the resulting crystals were collected. After recrystallization from ethanol, 3.5 g. (12.3%) of product, m.p. 189–191°, was obtained.

The 7-nitro analog (**10**) was similarly obtained. In the preparation of this compound, careful control of the temperature is important, since an exothermic reaction occurs at about 190–200° giving a porous black solid.

7-Chloro-3H-1,4-benzodiazepine-2,5(1H,4H)-dione (7).—5-Chloroisatoic anhydride (36.7 g., 0.2 mole) and glycine ethyl ester hydrochloride (28 g., 0.2 mole) in 150 ml. of dimethylformamide was boiled 0.5 hr. in an open flask. A reflux condenser was attached and reflux continued for 2.5 hr. The solution was concentrated *in vacuo* to a solid which was washed with dilute

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HCl then water and recrystallized from dimethylformamide to yield 10.8 g. (27.8%) of product, m.p. 323–325° dec.

1H-2,3,4,5-Tetrahydro-1,4-benzodiazepine (12).—3H-1,4-Benzodiazepine-2,5(1H,4H)-dione (113 g., 0.64 mole) was added to a slurry of lithium aluminum hydride (66.6 g., 1.8 moles) in 1500 ml. of tetrahydrofuran at a rate causing reflux. The mixture was refluxed with stirring for 6 hr. and left for 2 days. Excess lithium aluminum hydride was decomposed by cautious addition of 70 ml. of water, followed by 270 ml. of a saturated sodium potassium tartrate solution. Stirring was continued for 1 hr., the white slurry was filtered, the filter cake was washed well with tetrahydrofuran, and the filtrate and washings were concentrated *in vacuo* to a red oil which crystallized on slight cooling. The crude solid weighed 91.8 g. (97%), m.p. 89–94°. The dihydrochloride was prepared (alcoholic HCl) and recrystallized from methanol; m.p. 246.2–249°, lit.[3] m.p. 243–244°. The other tetrahydro-1,4-benzodiazepines were similarly prepared.

4-Methyl-1H-2,3,4,5-tetrahydro-1,4-benzodiazepine (13), free base, b.p. 70–73° (0.2 mm.), m.p. 40–43°.

4-Allyl-1H-2,3,4,5-tetrahydro-1,4-benzodiazepine (14), free base, b.p. 84–85° (0.13 mm.), $n^{25}D$ 1.5723.

7-Chloro-4-allyl-1H-2,3,4,5-tetrahydro-1,4-benzodiazepine was obtained in 100% crude yield, but we were unable to purify it either as the free base or hydrochloride. It was converted directly to the acetyl derivative.

4-Allyl-1-propionyl-1H-2,3,4,5-tetrahydro-1,4-benzodiazepine Hydrochloride (21).—Propionyl chloride (4.6 g., 0.05 mole) was added to 4-allyl-1H-2,3,4,5-tetrahydro-1,4-benzodiazepine (9.2 g., 0.05 mole) in 50 ml of $CHCl_3$. The solution became very hot and was left overnight. The $CHCl_3$ was evaporated yielding a white, crystalline mush which was treated with ether. The resulting white solid was recrystallized twice from ethanol. There was obtained 8.8 g. (62.9%) of product, m.p. 237.8–239.2° dec. The other acyl derivatives were similarly prepared.

Ethyl N-Allyl-N-(5-benzyloxy-2-nitrobenzoyl)glycinate.—Dicyclohexylcarbodiimide (43.3 g., 0.21 mole) in 300 ml. of tetrahydrofuran was added to 5-benzyloxy-2-nitrobenzoic acid (55.0 g., 0.201 mole)[15,16] and ethyl N-allylglycinate (30.0 g., 0.21 mole) in 700 ml. of tetrahydrofuran, and the mixture was left for 20 hr. The precipitate of dicyclohexylurea was collected and washed well with tetrahydrofuran. The filtrate and washings were concentrated *in vacuo* to an oil which weighed 90 g.

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4-Allyl-7-benzyloxy-3H-1,4-benzodiazepine-2,5(1H,4H)-dione was prepared by iron–acetic acid reduction of the above glycinate.

4-Allyl-7-benzyloxy-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine (18).—Reduction and hydrolysis were carried out as described for other tetrahydro compounds in this series.

4-Allyl-7-hydroxy-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine.—Concentrated HCl (45 ml.) was added to **18** (13.1 g., 0.04 mole), and the resulting solution was immediately cooled in ice. After 1 hr., the solution was left at room temperature for 24 hr. The solution was diluted with 50 ml. of water and extracted three times with ether to remove benzyl chloride. The aqueous solution was evaporated *in vacuo* to a gum which was dissolved in 25 ml. of water and basified with 10% Na_2CO_3. Four extractions with CH_2Cl_2 and evaporation of the extracts gave 7.5 g. (82.5%) of an oil which crystallized after several days. The solid was triturated in a small amount of ethyl acetate to give a pink solid, m.p. 97–111°, which could not be recrystallized or converted to a crystalline salt.

4-Allyl-7-hydroxy-1-propionyl-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine Hydrochloride (30).—A mixture of the above compound (8.5 g., 0.04 mole), 20 ml. of propionic anhydride, and 1 drop of concentrated H_2SO_4 was heated on the steam bath until a clear solution resulted. This was left overnight. Methanol (25 ml.) was added and the solution was left for 5 hr. Evaporation *in vacuo* gave the oily N,O-dipropionyl derivative. The oil was heated in an open beaker for 2 hr. on the steam bath with 5 ml. of 35% NaOH, 20 ml. of water, and enough ethanol to give a clear solution. The solution was carefully neutralized by dropwise addition of acetic acid and extracted three times with ethyl acetate. Evaporation of the solvent gave a dark oil which was dissolved in 200 ml. of ether. A small amount of amorphous brown solid was removed by filtration. Ethereal HCl was added to the filtrate, and the resulting slightly gummy solid was collected. The product was recrystallized twice from absolute methanol. There was obtained 5.4 g. (43.5%) of product, m.p. 245.0–246.0°.

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Thyromimetics. V. The Synthesis and Biological Screening of α-Methylthyroxine

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α-Methylthyroxine was prepared by a combination of established synthetic procedures and was tested for thyroxine-inhibitory and thyromimetic activities. It was found to have weak thyroxine-like activity in antigoitrogenic, cholesterol-lowering, and heart-weight assays and no activity as a thyroxine antagonist.

Despite the enormous amounts of knowledge accumulated with regard to the synthesis, metabolism, excretion, and biochemical transformations of amino acids, relatively little is known of α-methyl-α-amino acids. Sankoff and Sourkes[1] demonstrated that intraperitoneal administration of α-methyl-DL-tryptophan depressed the body weight of rats by reducing their food intake. Lin and co-workers[2] showed, *in vitro*, that α-methyl analogs of α-aminobutyric acid, methionine, and tyrosine had a reduced intestinal transport rate when compared to several nonmethylated amino acids. Christensen, *et al.*,[3] examined the tissue concentration of three α-methyl-α-amino acids and found them to be chiefly concentrated in the liver. Recent studies with α-methyl analogs of phenylalanines[4] have shown that these substances act as decarboxylase inhibitors and prevent decarboxylation of their nonmethylated counterparts. In effect, this causes these

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