Synthesis of Some 7-α-Carboxyethyl-1,3-dihydro-(2*H*)-1,4-benzodiazepin-2-ones

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1,4-Benzodiazepin-2-ones possessing an α-carboxyethyl group in 7-position (**21-25**) were prepared from a key compound, 2-amino-5-α-carboxyethylbenzophenone (**8**) or from its *O*-benzyl derivative **14**, using methods developed previously. An optimized route to **8** starting from 2-nitro-5-chlorobenzophenone (**1**), as well as some unsuccessful attempts are described. Compound **8** was deaminated into racemic α-(3-benzoyl)-phenylpropionic acid (**9**), a well-known antiinflammatory agent.

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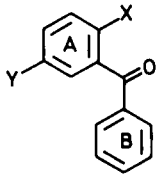
Introduction.

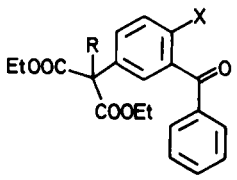
α-Aryl and α-heteroarylpropionic acid derivatives were reported as pharmacologically active reagents in several instances during the last few years. Most often they were found to possess antiinflammatory activity (1-4). Other biological effects observed include cholesterol lowering (5,6), influence on CNS functions (7), and stimulation of plant growth (8,9). On the other hand, 1,4-benzodiazepines in general (10) and C(3)-chiral-1,4-benzodiazepin-2-ones, in particular, as studied by us (11-13), are well known anxiolytic agents. Some of them definitely possessed analgetic and antiinflammatory activity (10).

Earlier structure-activity relationship studies in the 1,4-benzodiazepin-2-ones series included mainly 7-chloro-, bromo- and nitro-derivatives (15); recently, however, 7-trifluoromethoxy- (16), acetyl-, and α-hydroxyethyl derivatives were added to such studies (17). These new 1,4-benzodiazepine derivatives still had marked CNS activity. In this paper we describe the preparation of mixtures of diastereomeric pairs of 1,4-benozdiazepin-2-ones with an

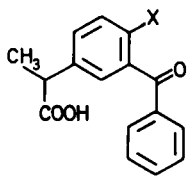
CHART 1



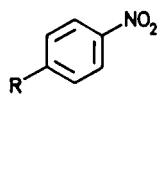
X	Y	
NO_2	Cl	1
Cl	NO_2	2
$CH(COOEt)_2$	NO_2	4



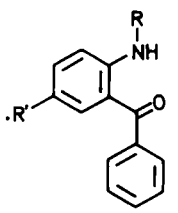
X	R	
NO_2	H	3
NO_2	CH_3	5
NH_2	CH_3	6



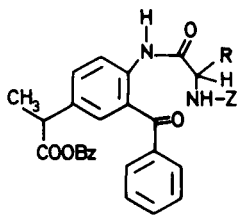
X		
NO_2	7	
NH_2	8	
H	9	



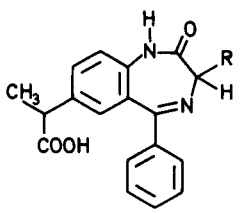
R	
$CH(COOEt)_2$	10
$C(CH_3)(COOEt)_2$	11
$CH(CH_3)(COOH)$	12
$C(CH_3)(p\text{-}NO_2\text{-}C_6H_4)COOEt$	13



R	R'	
H	$CH(CH_3)(COOBz)$	14
Bz	$CH(CH_3)(COOBz)$	15
CH_2BrCO	$CH(CH_3)(COOH)$	16



R	
CH_3	17
$CH(CH_3)_2$	18
Ph	19
3'-methylen-indolyl	20



R	
H	21
CH_3	22
$CH(CH_3)_2$	23
Ph	24
3'-methylen-indolyl	25

α-carboxyethyl pharmacophoric group in 7-position, having known configurations around the C(3) atom of the diazepine ring. The combination of two pharmacophores within the same structure seemed to us a worthwhile synthetic goal as such products might show interesting new pharmacological properties.

Results and Discussion.

Incorporation of the α-carboxyethyl group into the 7-position of the benzodiazepines **21-25** required early introduction of a suitable precursor substituent in the proper position on a starting compound (ring A). As suitable starting material we used the activated halobenzophenone **1**. Alkylation at (C)-5 with methyl-diethylmalonate anion, gave **5**, subsequent hydrolysis and decarboxylation converted the latter into 7. In a search for optimum conditions to alkylate at (C)-5, we prepared compound **2**. This product differs from **1** by "reversed" functionalities in the ring A, and was converted to **4** by alkylation with diethylmalonate anion. When the preparations of **3** and **4** were conducted in ethereal solution with HMPT as cosolvent, yields of about 80% in either product were obtained. Catalytic reduction of **7** gave compound **8**, subsequently used as the key intermediate, for further preparations. Three lines were followed. In the first route compound **8** was used to prepare the chiral derivatives **17-20**. Along this line it was necessary that the carboxylic group be protected, which was achieved by benzylation. Thus pure compound **14** was obtained by benzylating the potassium salt of **8** with benzylchloride in HMPT; when benzyl alcohol was used for esterification, in the presence of borontrifluoride-etherate (19), a mixture of **14** and **15** was obtained in all runs.

The second line was directed toward preparation of the benzodiazepine derivative **21**. The first step was acylation of **8** with α-bromoacetylchloride which yielded **16**, and this product was cyclised using our standard procedure (20,21) to give **21**.

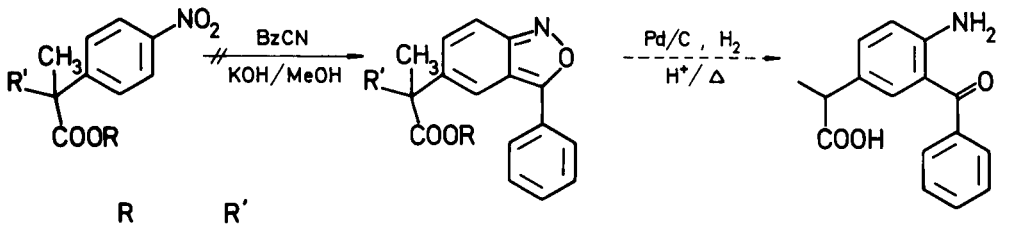
The third line, starting with diazotation and hydrogenolysis of **8** by procedures reported to work well with aminobenzophenone (22,23), led to racemic **9**, which is a well-known antiinflammatory agent under generic name of Ketoprofen (24,25). Even compound **8** might turn out as an antiinflammatory agent in view of the recently established activity of some related aminobenzophenone-acetic acid derivatives (26).

Two additional attempts to preparation of **8** are shown below.

Starting from *p*-chloronitrobenzene, compound **12** was obtained *via* **11** in 24% over-all yield. We tried to cyclize compounds **11** and **12** into corresponding anthranyls with benzylcyanide. Such products should be readily converted to **8** by reductive cleavage. All attempts at cyclization failed, however, which is in accordance with earlier failure to obtain an analogous reaction with *p*-nitrotoluene (27). Although a strong influence of substituents in *p*-substituted nitrobenzenes upon anthranyl cyclization was repeatedly observed (16,27), this influence could not be easily rationalized on the ground of the substituents electronic properties. Attempts to alkylate 5-chloro- and 5-bromo-3-phenyl-anthranyls, which were prepared as described earlier (27), failed when diehtylmalonate anion in HMPTA was used between 40-140°.

Diastereomeric 1,4-benzodiazepines (**22-25**) were obtained by acylation of **8** with appropriate *N*-protected amino acids. Intermediates **17-20** have been isolated and identified. In a subsequent step both protecting groups were eliminated concomitantly by catalytic hydrogenation. This step and the final cyclisation were performed following procedures described earlier (11). No attempt was made at this stage of investigation to separate the diastereomeric pairs **22-25**. Standard pharmacological antiinflammatory and CNS screening tests of products **22-25** as well as of some intermediates, are under way.

CHART 2



	R	R'
11	Et	COOEt
12	H	H

Table I

Yields, Analytical and Nmr Data for Compounds **17-20**

Compound No.	Yield %	Formula	Calcd./Found C%	H%	N%	Nmr (deuteriochloroform) δ in ppm
17	53	$C_{34}H_{32}N_2O_6$	72.30 72.46	5.72 5.94	4.96 4.78	1.48 (d, 3H), 1.52 (d, 3H), 3.75 (q, 1H), 4.51 (q, 1H), 5.09 (s, 2H), 5.13 (s, 2H), 5.52 (d, 1H), 7.5 (m, 17H), 8.58 (d, 1H), 11.1 (s, 1H)
18	55	$C_{36}H_{36}N_2O_6$	72.93 72.70	6.13 6.24	4.73 4.62	1.02 (m, 6H), 1.48 (d, 3H), 2.24 (m, 1H), 3.75 (q, 1H), 4.30 (m, 1H), 5.10 (s, 2H), 5.14 (s, 2H), 5.50 (d, 1H), 7.50 (m, 17H), 8.60 (d, 1H), 11.1 (s, 1H)
19	55	$C_{33}H_{34}N_2O_6$	74.73 74.60	5.47 5.68	4.47 4.27	1.48 (d, 3H), 3.62 (q, 1H), 5.08 (s, 2H), 5.11 (s, 2H), 5.37 (d, 1H), 6.16 (d, 1H), 7.4 (m, 22H), 8.5 (d, 1H), 11.1 (s, 1H)
20	51	$C_{42}H_{36}N_3O_6$	74.41 74.03	5.21 5.32	6.20 6.40	1.45 (d, 3H), 3.72 (q, 1H), 5.02 (s, 2H), 5.10 (s, 2H), 5.50 (d, 1H), 6.35 (d, 1H), 7.3 (m, 22H), 8.22 (d, 1H), 8.40 (d, (d, 1H), 11.0 (s, 1H)

Table II

Yields, Analytical and Nmr Data for Compounds **22-25**

Compound No.	Yield %	M.p.°	Formula	Calcd./Found C%	H%	N%	Nmr (deuteriochloroform) δ in ppm
22	86	135-137	$C_{19}H_{18}N_2O_3$	70.77 70.83	5.63 5.84	8.69 8.57	1.35 (d, 3H), 1.58 (d, 3H), 3.70 (m, 2H), 5.1-5.3 (broad s, 1H), 7.4 (m, 8H), 10.5 (s, 1H)
23	55	130-135	$C_{21}H_{22}N_2O_3$	71.96 71.81	6.33 6.56	8.00 8.15	1.16 (m, 6H), 1.48 (d, 3H), 2.80 (m, 1H), 3.18 (d, 1H), 3.72 (q, 1H), 7.4 (m, 8H), 7.93 (s, 1H), 9.95 (s, 1H)
24	64	151-155	$C_{24}H_{20}N_2O_3$	74.96 74.70	5.25 5.31	7.29 7.13	1.35 (d, 3H), 3.70 (q, 1H), 4.75 (s, 1H), 7.4 (m, 13H), 10.58 (s, 1H)
25	82	244-250	$C_{27}H_{23}N_3O_3$	74.10 74.25	5.30 5.47	9.61 9.91	1.28 (d, 3H), 3.55 (m, 4H), 7.3 (m, 13H), 10.6 (s, 1H), 10.85 (s, 1H)

EXPERIMENTAL

Melting points were determined on a Kofler microheating stage. Nmr spectra were recorded on a Varian T-60, and a Perkin Elmer R 12 A instruments with TMS as the internal standard. Ir spectra (potassium bromide pellets) were run on a Perkin Elmer M 720 instrument. Tlc was performed on "Fertigplatten F-254" (Merck), and column chromatography on silicagel of grain size 0.05-0.2 mm. Z-Protected amino acids used (L-Ala, L-Val, R-PheGly, L-Trypt) were puriss grade commercial products (Fluka). Light petroleum used refers to the fraction boiling between 40-60°.

Compound **1** was prepared in 70% yield from commercially available 2-amino-5-chlorobenzophenone, using 90% hydrogen peroxide, according to Emmons (28); compound **2** was prepared from 2-chloro-5-nitrobenzoic acid, using a described procedure (29); compound **10** was prepared from *p*-chloronitrobenzene (30).

Diethyl 3-Benzoyl-4-nitrophenylmalonate (**3**).

To HMPT (150 ml., freshly distilled from sodium, b.p. 85°/0.9 mm Hg) sodium hydride was added in the form of a 55-60% suspension in mineral oil (10.0 g., 0.24 mole). Diethyl malonate (39.4 ml., 0.24 mole) was added, dropwise, with water-cooling. The resulting solution was stirred for 15 minutes at ambient temperature, and warmed to 120-130° under an inert atmosphere (nitrogen, dried). Dropwise addition of compound **1** (37.0 g., 0.14 mole) dissolved in HMPT (100 ml.) was started, and the resulting deep-red solution was stirred for 3 hours. The solvent was evaporated (0.9 mm Hg, 85°). The oily residue was slurried into ice-water, and *p*H was adjusted to 4 adding dilute acetic acid. On extraction with ether (3 x 100 ml.), drying (sodium sulfate), and evaporation, a dark-coloured oil remained, which was purified on a column (300 g., silicagel, light-petroleum/ether 2:1 as the eluant). It was obtained 14.7 g. (27%) of pure **3**, m.p. 74-75° on recrystallization from light-petroluem/ether; nmr (deuteriochloroform) ppm: 1.26 (t, 6H), 4.25 (q, 4H), 4.76 (s, 1H), 7.56 (m, 7H), 8.23 (d, 1H); ir cm^{-1}: 1750, 1738, 1680, 1600-1628, 1530, 1350, 890, 860, 715, 689.

Anal. Calcd. for $C_{20}H_{19}NO_7$ (385.16): C, 62.31; H, 4.97; N, 3.64. Found: C, 62.46; H, 5.10; N, 3.70.

Diethyl 2-Benzoyl-4-nitrophenylmalonate (**4**).

Starting from **2** (8.0 g., 0.030 mole), diethyl malonate (10.6 ml., 0.064 mole), and sodium hydride, suspended in mineral oil (2.7 g., 0.064 mole), compound **4** was obtained (8.0 g., 68.3%), m.p. 148-150° on recrystallization from light-petroleum/ether; nmr (deuteriochloroform) ppm: 1.00 (t, 3H), 4.13 (q, 2H), 4.66 (q, 2H), 7.50 (m, 5H), 8.33 (m, 1H), 12.83 (s, 1H); ir cm^{-1}: 1740, 1650, 1503, 1340, 860, 840, 700.

Anal. Calcd. for $C_{20}H_{19}NO_7$ (385.16): C, 62.31; H, 4.97; N, 3.64. Found: C, 62.48; H, 4.78; N, 3.79.

Diethyl Methyl-(3-benzoyl-4-nitrophenyl)malonate (**5**).

A. Methylation of **3**.

Sodium (0.909 g., 39.5 mg. atoms) was dissolved in absolute ethanol (100 ml., L.B.). The resulting solution was cooled, then compound **3** (14.7 g., 38.2 mmoles) dissolved in 50 ml. of absolute ethanol, and methyl iodide (10.8 g., 76.26 mmoles) were added. After 6 hours stirring at room temperature, the solvent was evaporated *in vacuo*, the residual oil was emulsified with water (200 ml.) and extracted with ether (3 x 100 ml.). After drying the extract, and evaporation of the ether, the residual crude **5** was purified on a column (150 g. silicagel, light-petroleum/ether 1:1 as eluant), which gave 5.3 g. (35%) of pure material, m.p. 56.5-57.0° (from light-petroleum-ether); nmr (deuteriochloroform) ppm: 1.23 (t, 6H), 1.30 (s, 1H), 4.25 (q, 4H), 7.60 (m, 7H), 8.20 (d, 1H); ir cm^{-1}: 1733, 1680, 1600, 1590, 1530, 1350, 860, 715, 693.

Anal. Calcd. for $C_{21}H_{21}NO_7$ (399.18): C, 63.13; H, 5.30; N, 3.51. Found: C, 63.44; H, 5.40; N, 3.60.

B. Alkylation of **1**.

A suspension of sodium hydride in mineral oil (3.55 g., 81.5 mmoles) was added to dry ether (50 ml.) and the mixture was cooled in ice with stirring. Under contineud stirring diethyl methylmalonate (14.85 g., 81.5 mmoles) was added first, and followed with HMPT (5.0 ml.). Both liquids were added dropwise. After additional stirring for 1 hour at ambient temperature a clear solution resulted, to which a solution of **1** (15.0 g., 57.3 mmoles) in ether (100 ml.) was added dropwise. Stirring of the reaction mixture was continued under nitrogen atmosphere for 10 hours. Crude **5** was isolated as described under A, but the ethereal extracts were thoroughly washed with saturated aqueous sodium chloride solution before drying. Crude **5** (16.6 g., 72.5%) was used without purification in the next step. A recrystallized sample possessed the same m.p. and spectra as samples obtained by procedure A.

2-Nitro-5-α-carboxyethylbenzophenone (**7**).

Crude compound **5** (16.6 g.), dissolved in a mixture of 20% sulfuric acid and glacial acetic acid (140 ml., 1:1), was heated under reflux for 20 hours. Then the solvent mixture was partially evaporated *in vacuo*, and 2*N* potassium bicarbonate (470 ml.) added. The resulting slurry was extracted with ether to remove neutral side products, then acidified with concentrated sulfuric acid (15 ml.), and precipitated acid product **7**, was extracted with ether (3 x 100 ml.). On drying and evaporation crude **7** was collected (11.3 g., 56% calcd. with respect to compound **1** and recrystallized from light petroleum/ether, which gave the pure compound, m.p. 116-118°; nmr (deuteriochloroform) ppm: 1.55 (d, 3H), 3.87 (q, 1H), 7.55 (m, 7H), 8.16 (d, 1H), 10.05 (s, 1H); ir cm^{-1}: 1710, 1675, 1600, 1540, 1530, 1355, 860, 710, 698.

Anal. Calcd. for $C_{16}H_{13}NO_5$ (299.11): C, 64.13; H, 4.38; N, 4.68. Found: C, 64.25; H, 4.59; N, 5.00.

Diethyl Methyl-(3-benzoyl-4-aminophenyl)malonate (**6**).

The nitro compound **5** (3.9 g., 9.8 mmoles), dissolved in 96% ethanol (200 ml.), was hydrogenated at ambient temperature at a slight over-pressure, using 10% palladium/carbon (400 mg.) as a catalyst, until an equimolar quantity of hydrogen was absorbed. Filtration of the catalyst, and evaporation of the solvent gave crude **6** in a quantitative yield, in the form of an oily residue which crystallized on standing. On recrystallization from light petroleum/ether the product had m.p. 72-75°; nmr (deuteriochloroform) ppm: 1.18 (t, 6H), 1.71 (s, 3H), 4.13 (q, 4H), 6.10 (s, 1H), 6.70 (d, 1H), 7.45 (m, 7H); ir cm^{-1}: 3475, 3360, 1730, 1635, 1590, 1551, 1510, 860, 700.

Anal. Calcd. for $C_{21}H_{23}NO_5$ (369.19): C, 68.32; H, 6.28; N, 3.79. Found: C, 68.14; H, 6.41; N, 3.51.

2-Amino-5-α-carboxyethylbenzophenone (**8**).

Method A.

Compound **6** (3.6 g., 9.8 mmoles), dissolved in a mixture of 20% sulfuric acid and glacial acetic acid (25 ml., 1:1), was heated under reflux for 2 hours. The reaction mixture was diluted with water (80 ml.), and extracted with ether (3 x 50 ml.). The ethereal extracts were washed with saturated aqueous bicarbonate, dried and evaporated. The remaining oil was purified by column chromatography (50 g. silicagel, light-petroleum-ether, 1:1, as the eluant) to give 1.0 g. (63%) of pure, oily **8**. An analytically pure sample was obtained by repeated chromatography; nmr (deuteriochloroform) ppm: 1.40 (d, 3H), 3.53 (q, 1H), 5.36 (s, 2H), 6.70 (d, 1H), 7.45 (m, 7H); ir cm^{-1}: 3510, 3370, 1710, 1635, 1585, 1555.

Anal. Calcd. for $C_{16}H_{15}NO_3$ (269.13): C, 71.34; H, 5.62; N, 5.20. Found: C, 71.50; H, 5.89; N, 5.25.

Method B.

The carboxylic acid **7** (3.1 g., 10.3 mmoles), dissolved in 96% ethanol (100 ml.), was subjected to catalytic hydrogenation in the same manner as described for **6**. Usual work-up gave 2.0 g. (72%) of crude **8** which, after chromatographic purification, possessed the same tlc and spectroscopic properties as the sample described under A.

α-(3-Benzoyl)phenylpropionic Acid (**9**).

Compound **8** (5.4 g., 20.0 mmoles) was dissolved in ethanol (150 ml.) containing 50% aqueous tetrafluoroboric acid (10.6 g., 60 mmoles), and the resulting solution was stirred and cooled to 0°. Thereupon isoamyl nitrite (2.6 g., 22 mmoles) was added dropwise, keeping the temperature at 0°. The reaction mixture was stirred for 15-20 minutes, during which time crude diazonium tetrafluoroborate precipitated. Then ice-cold ether was added (500 ml.), and stirring at 0° was continued for another 30 minutes. The pale yellow to white precipitate was filtered, washed with ether (yield 85-90%), and immediately thereafter transferred to a vessel containing dioxane (1000 ml.) to which copper (I) oxide (1:1 g., 14.0 mmoles) was added. The resulting slurry was vigorously stirred for 6 hours at ambient temperature. The inorganic precipitate was filtered off, the solvent was evaporated and residual glassy oil was recrystallized from diisopropyl ether to give 3.8 g. (78%) of pure **9**, m.p. 92-94°, lit. (24) m.p. 93-95°; nmr and ir spectra were identical with an authentic specimen.

Diethyl Methyl-(4-nitrophenyl)malonate (**11**).

To compound **10** (1.7 g., 6.04 mmoles), dissolved in HMPT (4 ml.) and 0.247 g. (6.04 mmoles) of sodium hydride (previously added in the form of a 56% suspension in mineral oil), a solution of methyl iodide (0.859 g., 6.04 mmoles) in HMPT (2 ml.) was added dropwise. After 3 hours stirring at room temperature, ice-cold water (60 ml.) was added, and the mixture was extracted with ether (3 x 50 ml.). After drying and evaporation crude **11** (1.2 g.) was collected and purified by column chromatography (20 g. silicagel, light-petroleum-ether, 3:2, as the eluant) to obtain pure **11** (56.2%). An analytically pure sample was obtained after repeated chromatography; nmr (deuteriochloroform) ppm: 1.28 (t, 6H), 1.92 (s, 3H), 4.29 (q, 4H), 7.90 (*m*, *p*-disubst. benzene, J_{AX} 8.0 Hz, 4H).

Anal. Calcd. for $C_{14}H_{17}NO_6$ (295.14): C, 56.92; H, 5.80; N, 4.75. Found: C, 57.12; H, 6.01; N, 4.80.

Compound **11** was obtained in the maximal yield (37%), by alkylation of 4-chloronitrobenzene with diethyl methylmalonate anion at ambient temperature, according to method B as described for preparation of **5**. The main side product was a dimer, **13**, an oily material usually obtained in about 25% yield. This side

product was purified by repeated chromatography; nmr (deuteriochloroform) ppm: 1.20 (t, 3H), 2.00 (s, 3H), 4.25 (q, 2H), 7.80 (q, J_{AX} 8.0 Hz, 4H); ir cm^{-1}: 1735, 1610, 1520, 1355, 859, 700.

Anal. Calcd. for $C_{17}H_{16}N_2O_2$ (280.14): C, 59.27; H, 4.68; N, 10.00. Found: C, 59.58; H, 4.81; N, 9.79.

α-4-Nitrophenylpropionic Acid (**12**).

Compound **11** (0.9 g., 3.05 mmoles), dissolved in a mixture of 20% sulfuric acid and glacial acetic acid (4.3 ml., 1:1) was heated under reflux for 15 hours, after which the solvent mixture was partially evaporated *in vacuo*. The residue was partitioned between 35 ml. of 2*N* potassium bicarbonate solution and ether (3 x 30 ml.). Aqueous phase was acidified with concentrated sulfuric acid and extracted with ether. On drying and evaporation crude **12** (0.40 g., 67.2%) was obtained and was recrystallized from water-methanol, which gave the pure compound, m.p. 87-88°, lit. (31) m.p. 87.5-88.5°.

2-Amino-5-α-benzyloxycarbonylbenzophenone (**14**).

The sodium salt of **8** was prepared by mixing the solutions of **8** (1.3 g., 4.81 mmoles) in absolute ethanol (4.0 ml.), and sodium (0.27 g., 4.81 mmoles) in 3 ml. of absolute ethanol. After evaporation of the solvent, the remaining salt was dissolved in HMPT (10 ml.), and benzylchloride (1.5 ml.) was added. The mixture was stirred overnight, after which water (30 ml.) was added, and the crude ester, **14**, was extracted with ether (3 x 30 ml.). After drying and evaporation an oily product remained, and was distilled (b.p. 195-200°, 0.25 mm Hg) to give 1.21 g. (70%) of pure **14**; nmr (carbon tetrachloride) ppm: 1.35 (d, 3H), 3.48 (q, 1H), 4.99 (s, 2H), 5.98 (s, 2H), 6.52 (d, 1H), 7.2-7.8 (m, 12H); ir cm^{-1}: 3500, 3330, 1765, 1659, 1620, 820, 700.

Anal. Calcd. for $C_{23}H_{21}NO_3$ (359.18): C, 76.84; H, 5.89; N, 3.30. Found: C, 76.56; H, 6.18; N, 3.92.

In a typical experiment designed to obtain the ester **14** by reacting acid **8** with benzyl alcohol, 0.6 g. (2.25 mmoles) of **8** was heated, with 0.6 ml. (4.76 mmoles) of borotrifluoride etherate, in 3.5 ml. of benzyl alcohol for 18 hours at 40-50° in an oil-bath. Tlc control revealed a concomitant formation of two products with Rf's 0.82 and 0.69, respectively, (light petroleum/ether 2:1). After addition of dilute aqueous bicarbonate (70 ml.) to the reaction mixture, an extraction with ether was made, and the extract was dried and evaporated. The residue was applied to a silicagel column (30 g.) and eluted using the above solvent system. The faster moving zone (0.2 g.) revealed to contain a doubly-benzylated product, **15**; nmr (carbon tetrachloride) ppm: 1.36 (d, 3H), 3.46 (q, 1H), 4.43 (d, 2H), 4.96 (s, 2H), 6.56 (d, 1H), 7.2-7.8 (m, 17H), 8.9 (t, 1H); ir cm^{-1}: 3350, 1730, 1630, 1590, 1515, 820, 740.

Anal. Calcd. for $C_{30}H_{27}NO_3$ (449.22): C, 80.14; H, 6.06; N, 3.12. Found: C, 79.87; H, 6.45; N, 2.93.

The slower moving zone corresponded, according to Rf-value, to the ester **14**, but was always contaminated with benzyl alcohol. This alcohol was difficult to remove, either by chromatography or by distillation.

2-(*N*-α-Bromoacetyl)amino-5-α-carboxyethylbenzophenone (**16**).

Compound **8** (0.7 g., 2.6 mmoles) was dissolved in 13 ml. of benzene at 0-5°, then dropwise additions of α-bromoacetyl chloride (0.336 g., 3.04 mmoles), and 10% aqueous sodium hydroxide (1.04 ml.) were started simultaneously. After 0.5 hours stirring on ice, the aqueous layer was separated, the organic phase was thoroughly washed with water, dried, and evaporated. The crude product, **16**, was purified by column chromatography (25 g. silicagel, light petroleum/ether, 1:3, as eluant) to give 0.90 g. (89%) of pure **16**, m.p. 149-150° on recrystallization from light petroleum/ether; nmr (deuteriochloroform) ppm: 1.40 (d, 3H), 3.66 (q, 1H), 3.75 (s, 2H), 7.20 (s, 1H), 8.0-8.2 (m, 8H), 10.4 (s, 1H); ir cm^{-1}: 1713, 1685, 1640, 1590, 1520, 700.

Anal. Calcd. for $C_{18}H_{16}NO_4Br$ (390.05): C, 55.38; H, 4.13; N, 3.59. Found: C, 55.65; H, 4.35; N, 3.70.

5-Phenyl-7-(α-carboxyethyl)-1,3-dihydro-(2*H*)-1,4-benzodiazepin-2-one (**21**).

Compound **16** (0.9 g., 2.3 mmoles) was dissolved in 80 ml. of methanolic ammonia and left to stand at room temperature overnight. Methanol was evaporated *in vacuo*, the oily residue was slurried in water and *p*H adjusted to neutral. The amorphous precipitate was filtered off, dried, and recrystallized from light petroleum/ether to obtain 0.068 g., 9%, of **21**, m.p. 252-255°; nmr (DMSO-d_6) ppm: 1.33 (d, 3H), 3.70 (q, 1H), 4.16 (s, 2H), 5.43 (s, 5H), 7.2-7.8 (m, 8H), 11.5 (s, 1H); ir cm^{-1}: 3200, 3120, 1700, 1620, 1577, 1500, 700.

Anal. Calcd. for $C_{18}H_{16}N_2O_3$ (308.14): C, 70.10; H, 5.23; N, 9.09. Found: C, 70.21; H, 5.14; N, 9.27.

General Procedure for Preparation of Compounds **17-20**.

Compound **14** (0.72 g., 2.0 mmoles) and dicyclohexylcarbodiimide (0.44 g., 2.0 mmoles) were dissolved in 6.0 ml. of methylene chloride (for **17** and **18**) or THF (for **19** and **20**). The resulting solution was cooled to 0°, and 2.0 mmoles of the appropriate *N*-Z-amino-acid dissolved in a suitable solvent (2 ml.) was added dropwise. After stirring overnight, the precipitated dicyclohexylurea was filtered off, the filtrate was evaporated, and the residual oil was purified on a column (25 g. silicagel, light petroleum/ether, 1:1, as eluant). Analytical samples were obtained by repeated chromatography and these were subsequently dried (0.02 mm Hg, phosphorus pentoxide, overnight). Analytical and nmr data of these compounds are given in Table I.

General Procedure for Preparation of Compounds **22-25**.

Compounds **17-20** (2.0 mmoles) were dissolved in 96% ethanol (30 ml.), 10% palladium/carbon was added (120-150 mg.), and catalytic hydrogenation was performed at atmospheric pressure and room temperature. After about 10 hours the theoretical quantity of hydrogen was absorbed; the catalyst was filtered off, the filtrate was evaporated *in vacuo*, and the crude material was further purified by filtration through silicagel to obtain compounds **22-25**; analytical and nmr data are given in Table II.

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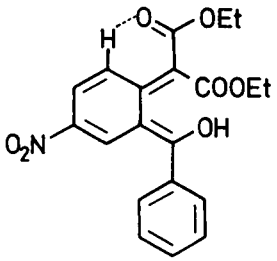
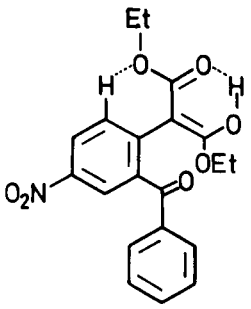
(18) Nmr spectra of **3** and **4** revealed their significant structural differences. While **4** exhibited entirely symmetrical structure for dicarboxymethyl group, the same group in **3** exhibited non-equivalent ethyl groups, and one largely downfield shifted proton (δ 12.83 ppm). These findings are in better accordance with structure B, rather than with *o*-quinodimethanic form A.



4A



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