[CONTRIBUTION FROM THE RESEARCH LABORATORIUM DR. C. JANSSEN]

Acylation and Tosylation of Substituted 3,3-Diphenyl-Δ^1-pyrrolines

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Acylation or tosylation of 2-alkyl-substituted 3,3-diphenyl-Δ^1-pyrrolines gives N-acylated or N-tosylated *exo*-unsaturated pyrrolidines. Acid hydrolysis of these pyrrolidines results in the formation of open-chain amidoketones. Benzoylation of 2,3,3-triphenyl-Δ^1-pyrroline in the presence of excess alkali immediately gives the corresponding amidoketone. The amidoketones can be considered as possible metabolites of normethadone and related basic ketones.

Introduction

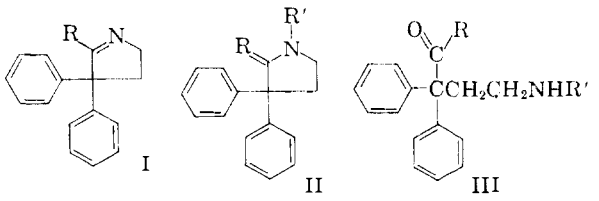
The literature dealing with the acylation of pyrrolines is rather restricted and, moreover, is not in agreement as to the exact structure of the products.

Kohler and Drake[1] reduced γ-nitro-β-phenylbutyrophenone catalytically and obtained oily products which could not be distilled. After treatment with benzoyl chloride in the presence of excess potassium hydroxide solution, a substance was formed with m.p. 179–180°, which was believed to be N-benzoyl-2,4-diphenyl-Δ^2-pyrroline.

Rupe and Gisiger[2] obtained the same product (m.p. 180°) from benzoyl chloride and the reduction product of β-cyano-β-phenylpropiophenone. Acetylation of the same reduction product gave the corresponding N-acetyl derivative, m.p. 105°.

Kloetzel, *et al.*,[3] showed that a Δ^1-pyrroline is formed by reduction of γ-nitro-β-phenylbutyrophenone over Raney nickel. Benzoylation of 2,4-diphenyl-Δ^1-pyrroline, as above, afforded the amidoketone γ-benzoylamino-β-phenylbutyrophenone, m.p. 182–183°. Acetylation of the same pyrroline gave the corresponding N-acetylaminoketone, m.p. 105°. From the similarity of the melting points, Kloetzel, *et al.*, concluded that the earlier investigators[1,2] also had isolated the amidoketones.

In the present paper, acylations and tosylation of 2-R-3,3-diphenyl-Δ^1-pyrrolines (I, R = methyl, ethyl and phenyl) are described. The Δ^1-pyrrolines were prepared by Grignard reaction on 2,2-diphenyl-4-bromobutyronitrile.[4]



Results and Discussion

2-Methyl- or 2-ethyl-3,3-diphenyl-Δ^1-pyrroline and 2,3,3-triphenyl-Δ^1-pyrroline were acylated at 100° with acetic anhydride, propionic anhydride, acetyl chloride, *p*-toluenesulfonyl chloride and benzoyl chloride in the presence of isopropyl alcohol or benzene or without a solvent.[3]

With benzoyl chloride, no pure reaction products could be isolated.

With the other reagents, the 2-alkyl-substituted Δ^1-pyrrolines (I, R = CH_3, C_2H_5) yielded crystalline products identified as *exo*-unsaturated, N-acylated or N-tosylated pyrrolidines (II) by infrared spectrophotometry.

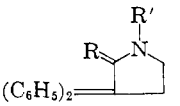
On the other hand, 2,3,3-triphenyl-Δ^1-pyrroline did not react.

The pyrrolines I also were treated with benzoyl chloride in the presence of excess sodium hydroxide solution, as described by Kloetzel, *et al.*,[3] for 2,4-diphenyl-Δ^1-pyrroline. Again, the 2-alkyl-substituted Δ^1-pyrrolines afforded the *exo*-unsaturated pyrrolidines II, whereas 2,3,3-triphenyl-Δ^1-pyrroline yielded a small amount of the amidoketone (III, R = C_6H_5, R′ = COC_6H_5), in addition to the hydrochloride of the starting material (I, R = C_6H_5).

The *exo*-unsaturated pyrrolidines (II) are not basic when titrated with perchloric acid in glacial acetic acid. Their infrared spectrum shows a sharp absorption peak at about 6.1 μ (amide C=O), and no NH– stretching frequency around 3 μ.

TABLE I

INFRARED SPECTRA[a] OF N-ACYLPYRROLIDINES (II)



Absorption maxima (μ) in the 5.5–7.0 μ region

R	R′	$R_1R_2C=CHR_3$ or $R_1R_2C=CH_2$	N-Amide carbonyl	Skeletal C=C vibrations in phenyl groups		
CH_2	$COCH_3$	5.99	6.13	6.27[b]	6.73	6.92
CH_3CH	$COCH_3$	5.96	6.06	6.30[b]	6.72	6.95
CH_3CH	COC_6H_5	5.99	6.13	6.31	6.75	6.97
CH_3CH	$SO_2C_6H_4$–*p*-CH_3	6.07	..	6.30	6.74	6.94

[a] One mg. in a 300-mg. KBr dis.; thickness about 0.9 mm. [b] Shoulder.

The terminal methylene group was identified in N-acetyl-2-methylene-3,3-diphenylpyrrolidine (II, R = CH_2, R′ = $COCH_3$) by near-infrared spectrophotometry: a 10% solution of the compound in carbon tetrachloride showed a sharp absorption peak at 1.72 μ (ϵ 0.40) and another one at 2.22 μ (ϵ 1.70). The starting material (I, R = CH_3), on the other hand, showed nearly rectilinear background absorption between 1.70 and 1.75 μ ($\epsilon_{1.72}$ 0.05), and an absorption peak at 2.23 μ (ϵ 1.50). The corrected molar absorption values for the pyrrolidine (II, R = CH_2, R′ = $COCH_3$) are therefore 0.35 at 1.72 μ and 0.20 at 2.22 μ.

These values are in good agreement with those found for acrylonitrile ($\epsilon_{1.73\ \mu}$ 0.24 and $\epsilon_{2.20\ \mu}$ 0.46)

(1) E. P. Kohler and N. L. Drake, THIS JOURNAL, **45**, 2144 (1923).
(2) H. Rupe and F. Gisiger, *Helv. Chim. Acta*, **8**, 338 (1925).
(3) M. C. Kloetzel, J. L. Pinkus and R. M. Washburn, THIS JOURNAL, **79**, 4222 (1957).
(4) P. J. A. Demoen and P. A. J. Janssen, *ibid.*, **81**, 6281 (1959).

TABLE II

INFRARED SPECTRA[a] OF AMIDOKETONES, III, $RC(=O)C(C_6H_5)_2CH_2CH_2NHR'$

Absorption maxima (μ) at about 3.1 μ and in the 5.5–7.0 μ-region

R	R′	NH stretch	Ketone carbonyl	Amide carbonyl	Amide II	Skeletal C=C vibrations in phenyl group		
CH_3	$COCH_3$	3.11	5.90	6.16	6.43	6.28[b]	6.72	6.98
CH_3	COC_6H_5	3.10	5.89	6.14	6.49	6.27	6.72	6.97
C_2H_5	$COCH_3$	3.11	5.90	6.14	6.43	6.30[b]	6.73	6.98
C_2H_5	COC_2H_5	3.09	5.89	6.16	6.46	6.26[b]	6.71	6.95
C_2H_5	COC_6H_5	3.08	5.87	6.15	6.43	6.27	6.72	6.97
C_2H_5	$SO_2C_6H_4p$-CH_3	3.09	5.90	..	..	6.28	6.72	6.97
C_6H_5	COC_6H_5	3.10	5.88	6.16	6.43	6.27	6.73	6.97

[a] One mg. in a 300-mg. KBr disk; thickness about 0.9 mm. [b] Shoulder.

and vinyl acetate ($\epsilon_{1.73\,\mu}$ 0.30 and $\epsilon_{2.21\,\mu}$ 0.40). They differ, however, by about +0.1 μ from the mean values as found R. Goddu[5] for 16 compounds containing a terminal methylene group (1.62 ± 0.02 μ, ϵ 0.20 to 0.45 or 2.10 ± 0.02 μ, ϵ 0.12 to 0.63).

All substances of structure II show the characteristic $R_1R_2C{=}CH_2$ or $R_1R_2C{=}CHR_3$ vibration between 5.95 and 6.00 μ[6,7] next to the tertiary amide carbonyl band around 6.1 μ. The characteristic absorption maxima between 5.5 and 7 μ of compounds II are given in Table I.

These data show that the intermediates II are *exo*-unsaturated N-acylated pyrrolidines. This conclusion is supported by the fact that 2,3,3-triphenyl-Δ^1-pyrroline (I, R = C_6H_5) cannot be converted to the corresponding pyrrolidine.

Hydrolysis of the *exo*-unsaturated pyrrolidines II in alcoholic acid solution yields the corresponding open-chain amidoketones[3] III which were identified by ultraviolet and infrared spectrophotometry.

The ultraviolet spectra of the amidoketones (III, R = CH_3 or C_2H_5; R′ = $COCH_3$ or COC_2H_5) show the characteristic α,α-diphenyl ketone spectrum[9-11] with three phenyl bands around 260 mμ (ϵ_{max} about 450), and a broader band with maximum between 295 and 300 mμ (ϵ_{max} about 400).

The infrared spectra of the amidoketones show NH- stretching vibration at 3.1 μ in a KBr disk, and at 2.95 μ in carbon tetrachloride solution (ϵ_{max} in carbon tetrachloride 55 to 75). In KBr disks, these various typical vibrations are found between 5.5 and 7 μ: ketone carbonyl around 5.9 μ; amide carbonyl between 6.10 and 6.15 μ; amide II band between 6.4 and 6.5 μ, and the less intense C=C skeletal vibrations in phenyl groups at about 6.25, 6.70 and 6.95 μ. The latter group of three vibrations is found in all compounds of structures I, II and III.

The important spectral bands of the amidoketones III in the infrared regions of interest are listed in Table II.

It should be noted that 1-acetylamino-3,3-diphenylhexan-4-one (III, R = C_2H_5, R′ = $COCH_3$) is the N-acetyl derivative of demethylated normethadone (4,4-diphenyl-6-dimethylaminohexan-3-one). Considering the evidence in favor of the metabolic breakdown of methadone and related analgesics by oxidative dialkylation and therefore the probable formation *in vivo* of secondary or primary amines related to methadone,[12] it is reasonable to consider 1-acetylamino-3,3-diphenylhexan-4-one as a possible metabolite of normethadone.

Experimental Part

N-Acetyl-2-methylene-3,3-diphenylpyrrolidine (II, R = CH_2, R′ = $COCH_3$).—2-Methyl-3,3-diphenyl-Δ^1-pyrroline (I, R = CH_3; m.p. 50.4–52.0°, 4.71 g., 20 mmoles) was warmed for one hour with 2.3 ml. (25 mmoles) of acetic anhydride in a boiling water-bath. After the addition of 30 ml. of warm water, the mixture was kept overnight at 2°. The precipitate was collected on a filter, washed with isopropyl alcohol and water (1:1) and dried at 45° *in vacuo*, yielding 5.16 g. (18.6 mmoles, 93%) of yellowish, crystalline powder, m.p. 104–106°; 4.65 g. was recrystallized from 10 ml. of isopropyl alcohol, giving 3.82 g. of N-acetyl-2-methylene-3,3-diphenylpyrrolidine (II, R = CH_2, R′ = $COCH_3$) as a white, microcrystalline powder, m.p. 105.5–107.0°; ultraviolet absorption: broad absorption band with maximum near 242 mμ (ϵ 6850); near-infrared absorption: no absorption band between 2.86 and 3.01 μ: no secondary amide (c = 0.2% in carbon tetrachloride); terminal methylene group: absorption maxima at 1.72 μ (ϵ 0.40) and 2.22 μ (ϵ 1.70)(c 10% in carbon tetrachloride).

Anal. Calcd. for $C_{19}H_{19}NO$ (277.37): C, 82.28; H, 6.91; N, 5.05. Found: C, 82.85; H, 6.94; N, 4.98.

1-Acetylamino-3,3-diphenylpentane-4-one (III, R = CH_3, R′ = $COCH_3$).—N-Acetyl-2-methylene-3,3-diphenylpyrrolidine (II, R = CH_2, R′ = $COCH_3$; 7 g., 25.2 mmoles) was dissolved in 40 ml. of isopropyl alcohol and refluxed for two hours with 5 ml. of hydrochloric acid. Although dilution of the reaction mixture showed only negligible α,α-diphenyl ketone absorption, 100 ml. of water was added and the solution was stored at 2° for 18 hours. A few crystals separated which were filtered and dried, yielding 0.93 g., (3.35 mmoles, 13.3%), m.p. 90.5.5°; 0.54 g. was recrystallized from 10 ml. of isopropyl alcohol and 10 ml. of water, yielding 0.38 g. of 1-acetylamino-3,3-diphenylpentan-4-one (III, R = CH_3, R′ = $COCH_3$) as a white, granular powder, m.p. 97.8–99.2°.

Anal. Calcd. for $C_{19}H_{21}NO_2$ (295.37): C, 77.26; H, 7.17; N, 4.74. Found: C, 77.05; H, 7.01; N, 4.67.

(5) R. F. Goddu, *Anal. Chem.*, **29**, 1790 (1957).

(6) N. Sheppard and G. B. Sutherland, *J. Chem. Soc.*, 1540 (1947).

(7) After this work was completed, Lukes, *et al.*,[8] showed that 1-methyl-2-alkyl-Δ^2-pyrrolines and 1-methyl-2,3-dialkyl-Δ^2-pyrrolines isomerize to the corresponding 1-methyl-2-alkylidenepyrrolidines or 1-methyl-2-alkylidene-3-alkylpyrrolidines. They found the absorption peak of the exocyclic double bond between 1677 and 1663 cm.$^{-1}$ (6.01 to 6.04 μ), whereas the endocyclic Δ^2-double bond showed an absorption maximum between 1640 and 1631 cm.$^{-1}$ (6.10 to 6.14 μ).

(8) R. Lukes, V. Dedek and L. Novotny, *Collection Czech. Chem. Commun.*, **24**, 1117 (1959).

(9) W. D. Kumler, L. A. Strait and E. L. Alpen, THIS JOURNAL, **72**, 1463 (1950).

(10) E. L. Alpen, W. D. Kumler and L. A. Strait, *ibid.*, **72**, 4558 (1950).

(11) J. Cymerman and W. S. Gilberg, *J. Chem. Soc.*, 3529 (1952).

(12) A. H. Beckett, A. F. Casy and N. J. Harper, *J. Pharm. Pharmacol.*, **8**, 874 (1956).

Ultraviolet absorption of α,α-diphenyl ketone: principal maxima at 262.3 mμ (ϵ 520) and 299.8 mμ (ϵ 445); near infrared spectrum: secondary amide, maximum at 2.95 μ, ϵ 73 (c 0.11% in carbon tetrachloride).

N-Acetyl-2-ethylidene-3,3-diphenylpyrrolidine (II, R = CH_3CH, R′ = $COCH_3$).—2-Ethyl-3,3-diphenyl-Δ^1-pyrroline (I, R = C_2H_5; m.p. 81.2–82.0°, 4 g., 16 mmoles) was heated in a boiling water-bath with 4 ml. (43 mmoles) of acetic anhydride for four hours. After cooling, 40 ml. of water was added and the oily product which separated was extracted with 100 ml. of ether. The ether was evaporated and the residue was dried at 60° *in vacuo*, yielding 4.0 g. of crude product, m.p. 82–86°; 3.8 g. was recrystallized from 10 ml. of ethyl acetate giving 1.45 g. (5.0 mmoles, 31%) of crystals, m.p. 139.8–141.0. A final recrystallization raised the melting point to 140.4–141.2°, yielding 1.1 g. of N-acetyl-2-ethylidene-3,3-diphenylpyrrolidine (II, R = CH_3CH, R′ = $COCH_3$); ultraviolet absorption: increasing absorption below 300 mμ, shoulder at about 272 mμ, ϵ about 700; near infrared spectrum: no absorption maximum between 2.86 and 3.01 μ: no secondary amide (c 0.2% in carbon tetrachloride).

Anal. Calcd. for $C_{20}H_{21}NO$ (291.38): C, 82.44; H, 7.26; N, 4.81. Found: C, 82.3; H, 7.21; N, 4.86.

The same pyrrolidine also was obtained from 5 g. (20 mmoles) of 2-ethyl-3,3-diphenyl-Δ^1-pyrroline (I, R = C_2H_5) and 3 ml. (42 mmoles) of acetyl chloride after heating in a water-bath for three hours. After cooling, the mixture was shaken with 30 ml. of ethyl acetate and 20 ml. of water. The organic layer was dried, concentrated to 15 g. and stored at −15° for 16 hours, yielding 2.11 g. of the above pyrrolidine, m.p. 135–137°. Crystallization raised the melting point to 140.1–140.8°.

1-Acetylamino-3,3-diphenylhexan-4-one (III, R = C_2H_5, R′ = $COCH_3$).—N-Acetyl-2-ethylidene-3,3-diphenylpyrrolidine (II, R = CH_3CH, R′ = $COCH_3$) (5 g. 17.2 mmoles) was refluxed for one hour in a boiling water-bath with 50 ml. of isopropyl alcohol and 5 ml. of hydrochloric acid. The solution was evaporated to 15 g., 10 ml. of water was added and the mixture was concentrated again to 15 g. The addition of water and concentration were repeated once.

After cooling, the precipitate was collected and dried at 60° *in vacuo*, yielding 4.4 g. (14.2 mmoles, 82.7%) of product, m.p. 135–137°. The product was recrystallized twice from 20 ml. of isopropyl alcohol and 20 ml. of water, giving 3.25 g. of 1-acetylamino-3,3-diphenylhexan-4-one (III, R = C_2H_5, R′ = $COCH_3$) as white, glistening plates, m.p. 136.5–137.5°; ultraviolet absorption of α,α-diphenyl ketone: maximum absorption at 257 mμ (ϵ 395), 262.5 mμ (ϵ 460), 268 mμ (ϵ 425), 298.5 mμ (ϵ 425); near infrared absorption: secondary amide absorption: maximum at 2.95 μ, ϵ 68 (c 0.14% in carbon tetrachloride).

Anal. Calcd. for $C_{20}H_{23}NO_2$ (309.39): C, 77.64; H, 7.49; N, 4.53. Found: C, 77.8; H, 7.42; N, 4.49.

The compound was prepared also in one step, without isolation of the N-acetylpyrrolidine: 5 g. (20 mmoles) of 2-ethyl-3,3-diphenyl-Δ^1-pyrroline (I, R = C_2H_5) was dissolved in 20 ml. of isopropyl alcohol and refluxed for one hour with 2.3 ml. (25 mmoles) of acetic anhydride. Hydrochloric acid (5 ml.) was added to the cooled mixture and refluxing was continued for one hour. The mixture was concentrated to 15 g., treated with 10 ml. of water and evaporated as above, yielding 4.32 g. (14 mmoles, 70%) of gray powder, m.p. 134.5–136.0°. Crystallization from 40 ml. of isopropyl alcohol–water (1:1) afforded 3.68 g. of 1-acetylamino-3,3-diphenylhexan-4-one, m.p. 135.7–137.2°.

Acetylation of 2,3,3-Triphenyl-Δ^1-pyrroline (I, R = C_6H_5).—A mixture of 5.95 g. (20 mmoles) of I (R = C_6H_5), m.p. 125.5–127.0° and 2.3 ml. (24 mmoles) of acetic anhydride was refluxed for one hour in 20 ml. of isopropyl alcohol. After the addition of 15 ml. of water, needle-like crystals separated. After drying at 60° *in vacuo*, 5.69 g. of yellowish needles were obtained, m.p. 125.0–127.0°; neut. equiv. calcd. for the starting material, 297.38; found 304.5 (acetous perchloric acid). The experiment was repeated omitting the solvent by refluxing 5 g. of the pyrroline (I, R = C_6H_5) with 5 ml. of acetic anhydride for three hours; yield 3.72 g. of brownish precipitate, m.p. 120.5–127.0°. After crystallization from 30 ml. of isopropyl alcohol–water (1:1), 2.9 g. of the starting material was obtained, m.p. 125.5–127.0°; neut. equivalent 300.4.

N-Benzoyl-2-methylene-3,3-diphenylpyrrolidine (II, R = CH_2, R′ = COC_6H_5).—2-Methyl-3,3-diphenyl-Δ^1-pyrroline (I, R = CH_3; 2.82 g., 12 mmoles) was shaken with 4 ml. (35 mmoles) of benzoyl chloride and 40 ml. of 10% sodium hydroxide solution until the benzoyl chloride was hydrolyzed (about 15 minutes). A waxy yellow mass separated. It was washed three times with cold water and twice with a few ml. of isopropyl alcohol. The product was dissolved by warming in 20 ml. of isopropyl alcohol, 20 ml. of diethyl ether was added and the solution was stored at −15° for 16 hours: a yellowish semisolid separated. The solvents were decanted and the precipitate was washed with ether and dried *in vacuo* at 40°, yielding 2.79 g. (8.2 mmoles, 68.4%) of impure N-benzoyl-2-methylene-3,3-diphenylpyrrolidine (II, R = CH_2, R′ = COC_6H_5). The product was not basic when titrated with acetous perchloric acid; near infrared absorption: $\epsilon_{2.95}$ μ 12, indicating the presence of 20 to 25% secondary amide (c 0.21% in carbon tetrachloride). No attempt was made to crystallize the product: it was transformed completely to the amidoketone.

1-Benzoylamino-3,3-diphenyl-pentan-4-one (III, R = CH_3, R′ = COC_6H_5).—Impure N-benzoyl-2-methylene-3,3-diphenylpyrrolidine (II, R = CH_2, R′ = COC_6H_5) (2.41 g., 7.1 mmoles) was refluxed for one hour in a boiling water-bath with 25 ml. of isopropyl alcohol and 2.5 ml. of hydrochloric acid. The solution was placed in a refrigerator overnight, giving 1.64 g. (4.6 mmoles, 64.8%) of yellowish powder, m.p. 119.8–121°. Recrystallization from 20 ml. of isopropyl alcohol–water (1:1) yielded 0.95 g. of 1-benzoylamino-3,3-diphenylpentan-4-one (III, R = CH_3, R′ = COC_6H_5) as white needle-like crystals, m.p. 122.0–123.0°; near infrared absorption: secondary amide, maximum absorption at 2.95 μ, ϵ 53 (c 0.21% in carbon tetrachloride).

Anal. Calcd. for $C_{24}H_{23}NO_2$ (357.43): C, 80.64; H, 6.49; N, 3.92. Found: C, 80.8; H, 6.49; N, 3.77.

N-Benzoyl-2-ethylidene-3,3-diphenylpyrrolidine (II, R = CH_3CH, R′ = COC_6H_5) was prepared from 6 g. (24 mmoles) of 2-ethyl-3,3-diphenyl-Δ^1-pyrroline (I, R = C_2H_5), 8 ml., (70 mmoles) of benzoyl chloride and 80 ml. of 10% sodium hydroxide solution as described above for the methylene pyrrolidine; yield 3.63 g. (10.3 mmoles, 42.7%), m.p. 152.0–152.8° A second crop of crystals was obtained from the filtrate, 1.62 g. (4.6 mmoles, 19.1%), m.p. 150.2–151.2°.

The product (4.90 g.) was recrystallized from 70 ml. of isopropyl alcohol at −15°, giving 3.65 g. of oblong, heavy crystals of N-benzoyl-2-ethylidene-3,3-diphenylpyrrolidine (II, R = CH_3CH, R′ = COC_6H_5), m.p. 152.8–153.2°; near infrared absorption: no maximum between 2.86 and 3.01 μ; no secondary amide (c 0.22 % in carbon tetrachloride).

Anal. Calcd. for $C_{25}H_{23}NO$ (353.44): C, 84.95; H, 6.56; N, 3.96. Found: C, 84.7; H, 6.49; N, 3.80.

1-Benzoylamino-3,3-diphenyl-hexan-4-one (III, R = C_2H_5, R′ = COC_6H_5) was prepared from 2.5 g. (7.1 mmoles) of N-benzoylamino-2-ethylidene-3,3-diphenylpyrrolidine (II, R = CH_3CH, R′ = COC_6H_5) as described above; yield 1.88 g. (5.1 mmoles, 71.7%) of 1-benzoylamino-3,3-diphenylhexan-4-one (III, R = C_2H_5, R′ = COC_6H_5), m.p. 155.2–156.2°. A second crop of crystals was obtained from the filtrate, 0.55 g. (1.5 mmoles, 20.9%), m.p. 152.0–153.6°. Recrystallization of the first fraction from isopropyl alcohol–water (1:1) gave 1.23 g. of fine needles, m.p. 155.4–156.2°; near infrared absorption: secondary amide maximum at 2.95 μ, ϵ 57 (c 0.20% in carbon tetrachloride).

Anal. Calcd. for $C_{25}H_{25}NO_2$ (371.46): C, 80.83; H, 6.78; N, 3.77. Found: C, 81.05; H, 6.96; N, 3.65.

γ-Benzoylamino-α,α-diphenylbutyrophenone (III, R = C_6H_5, R′ = COC_6H_5).—2-Phenyl-3,3-diphenyl-Δ^1-pyrroline (I, R = C_6H_5, 3.57 g., 12 mmoles) was shaken with 4 ml. (35 mmoles) of benzoyl chloride and 40 ml. of 10% sodium hydroxide solution for 20 minutes; a grayish paste separated. The mass was washed with water and isopropyl alcohol as above, and dissolved in 50 ml. of isopropyl alcohol. A cubical crystalline precipitate was obtained at −15°, 0.64 g. (1.52 mmoles, 12.7%), m.p. 148.2–149.0°.

A second precipitate was obtained after two days at −15° as an amorphous powder, 0.715 g. (1.70 mmoles, 14.2%), m.p. 150.0–151.0°. After evaporation of 25 ml. of the solvent, 1.21 g. of white powder was obtained by crystallization, m.p. 227–232°. It was identified (neut. equivalent,

chloride content and mixed melting point) as the hydrochloride of the starting pyrroline.

A portion (1.2 g.) of the material melting at about 150° was recrystallized from isopropyl alcohol, giving 0.86 g. of γ-benzoylamino-α,α-diphenylbutyrophenone (III, R = C_6H_5, R′ = COC_6H_5), m.p. 150.7–151.4°; near infrared absorption: secondary amide maximum absorption at 2.95 μ, ε 57 (*c* 0.21% in carbon tetrachloride).

Anal. Calcd. for $C_{29}H_{25}NO_2$ (419.50): C, 83.03; H, 6.01; N, 3.34. Found: C, 82.85; H, 6.19; N, 3.27.

1-Propionylamino-3,3-diphenylhexan-4-one (III, R = C_2H_5, R′ = COC_2H_5).—2-Ethyl-3,3-diphenyl-Δ¹-pyrroline (I, R = C_2H_5) (5 g., 20 mmoles) and 5 ml. (38 mmoles) of propionic anhydride were refluxed for three hours in a boiling water-bath; 40 ml. of water was added, and the mixture was extracted with a total of 120 ml. of diethyl ether. The organic layer was washed, dried over potassium carbonate and evaporated. The remaining oil (4.64 g.) was dissolved in 15 ml. of ethyl acetate. No crystallization occurred after 24 hours at −15°. A suitable dilution of the mixture showed an increasing ultraviolet absorption toward shorter wave lengths. The ethyl acetate was evaporated, and the remaining oil (4.61 g.) was refluxed for 30 minutes with 2.5 ml. of hydrochloric acid and 20 ml. of isopropyl alcohol. The solution was concentrated to 15 g., treated with 10 ml. of water and evaporated to 15 g. as above. The precipitate, weighing 1.30 g. (4.0 mmoles, 20.0%) melted at 125.0–127.0° and showed α,α-diphenyl ketone absorption.

A portion (1.25 g.) was recrystallized from 15 ml. of isopropyl alcohol and 15 ml. of water, yielding 0.75 g. of 1-propionylamino-3,3-diphenylhexan-4-one (III, R = C_2H_5, R′ = COC_2H_5), m.p. 134.5–135.5°; ultraviolet absorption: α,α-diphenyl ketone, principal maxima at 268.3 mμ (ε 465) and 299.7 mμ (ε 470); near infrared absorption: secondary amide maximum at 2.95 μ, ε 76 (*c* 0.13% in carbon tetrachloride).

Anal. Calcd. for $C_{21}H_{25}NO_2$ (323.42): C, 77.98; H, 7.79; N, 4.33. Found: C, 77.9; H, 7.83; N, 4.56.

N-*p*-Toluenesulfonyl-2-ethylidene-3,3-diphenylpyrrolidine (II, R = CH_3CH, R′ = $SO_2C_6H_4pCH_3$).—2-Ethyl-3,3-diphenyl-Δ¹-pyrroline (I, R = C_2H_5) (10 g., 40 mmoles) was refluxed with 8 g. (42 mmoles) of *p*-toluenesulfonyl chloride in 20 ml. of benzene for two hours. The solvent was evaporated and the residue was crystallized from 25 ml. of isopropyl alcohol at −15°; yield 4.5 g. (11.2 mmoles, 28%) of brownish powder, m.p. 139.5–142.0°. The product was recrystallized four times from isopropyl alcohol, yielding 3.10 g. of white, glistening crystals of N-*p*-toluenesulfonyl-2-ethylidene-3,3-diphenylpyrrolidine (II, R = CH_3CH, R′ = $SO_2C_6H_4CH_3$-*p*), m.p. 141.5–142.5°; near infrared absorption: no absorption maximum between 2.85 and 3.02 μ; no secondary amide (*c* 0.19% in carbon tetrachloride).

Anal. Calcd. for $C_{25}H_{24}NO_2S$ (403.53): C, 74.41; H, 6.24; N, 3.47; S, 7.95. Found: C, 74.5; H, 6.36; N, 3.37; S, 8.06.

1-*p*-Toluenesulfonamido-3,3-diphenylhexan-4-one (III, R = C_2H_5, R′ = $SO_2C_6H_4CH_3$-*p*).—N-*p*-Toluenesulfonyl-2-ethylidene-3,3-diphenylpyrrolidine (II, R = CH_3CH, R′ = $SO_2C_6H_4CH_3$-*p*)(7 g., 17.4 mmoles) was refluxed for two hours with 100 ml. of isopropyl alcohol and 10 ml. of hydrochloric acid. After standing for 30 hours at −15°, the precipitate was collected and dried; yield 2.52 g. (6.0 mmoles, 34.5%), m.p. 147.0–149.4°.

A portion (1.98 g.) was recrystallized from 45 ml. of isopropyl alcohol and dried at 60° *in vacuo*, giving 1.65 g. of 1-*p*-toluenesulfonamide-3,3-diphenylhexan-4-one (III, R = C_2H_5, R′ = $SO_2C_6H_4CH_3$-*p*), m.p. 151.2–153.0°; ultraviolet absorption: secondary sulfonamide maximum absorption at 2.99 μ, ε 66 (*c* 0.17% in carbon tetrachloride).

Anal. Calcd. for $C_{25}H_{27}NO_3S$ (421.27): C, 71.27; H, 6.46; N, 3.32; S, 7.62. Found: C, 71.6; H, 6.49; N, 3.32; S, 7.58.

Micro-analyses are by Mr. A. Sels, Analytical Department. Melting points are uncorrected and were determined on a Hershberg–Tottoli apparatus (Büchi). Titrations were performed in glacial acetic acid, using 0.02 *N* perchloric acid in the same solvent as a titrant. The titrations were followed potentiometrically (glass–calomel electrodes). All substances of structure II and III are devoid of basic properties.

Ultraviolet and near-infrared spectra were measured with a Beckman DK2-ratio recording spectrophotometer in 1-cm. silica cells; 0.01 *N* hydrochloric acid in 90% isopropyl alcohol was used as a solvent for ultraviolet spectra. Near-infrared spectra were measured in carbon tetrachloride solution. Infrared spectra were measured with a Perkin–Elmer sodium chloride "Infracord" in potassium bromide disks (300 mg.) containing about 1.0 mg. of the substance.

Sulfur was determined after burning the substance in an oxygen atmosphere as described by Schöniger,[13] and titrated with barium perchlorate and thorin as an indicator, as described by Wagner.[14]

(13) W. Schöniger, *Mikrochim. Acta*, 123 (1955).

(14) H. Wagner, *ibid.*, 19 (1957).

BEERSE, BELGIUM

[CONTRIBUTION FROM THE STERLING-WINTHROP RESEARCH INSTITUTE]

Some *s*-Triazolo[b]pyridazines

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A series of *s*-triazolo[b]pyridazines has been prepared for testing of biological activity. The greater number of compounds of interest were those having a basic chain attached to position 8 of the heterocyclic ring system.

The structural features present in the *s*-triazolo-[*b*]pyridazine[2] moiety I related it to the purine ring system and led to interest in the preparation of certain basic derivatives for testing as antiprotozoan and pharmacodynamic agents. At the inception of this work, relatively little attention had been given to derivatives of this heterocyclic moiety since it was first investigated[3–5]; however, since that time there has been considerably more interest.[6–10] The original designation for *s*-triazolo[b]pyridazine was 2,3-triazo-7.0-pyridazine; the ring system also has been called 2,3,7-triazaindolizine. It appears that the basically-substituted triazolo-pyrimidine types of Cook, *et al.*,[11] repre-

(1) McNeil Laboratories, Philadelphia 32, Penna.

(2) Ring Index No. 706, in A. M. Patterson and L. T. Capell, "The Ring Index," Reinhold Publishing Corp., New York, N. Y., 1940 (A.C.S. Monograph 84).

(3) C. Bülow, *Ber.*, **42**, 2208, 2555 (1909).

(4) C. Bülow, *ibid.*, **42**, 2594 (1909).

(5) C. Bülow and K. Haas, *ibid.*, **43**, 1975 (1910).

(6) N. Heimbach, U. S. Patents 2,390,707; 2,432,419.

(7) Y. Kuwabara and K. Aoki, *Konishiroku Rev.*, **6**, 1 (1955); *C. A.*, **49**, 11473 (1955).

(8) K. Murobushi, Y. Kuwabara, S. Baba and K. Aoki, *J. Chem. Soc. Japan, Ind. Chem. Sect.*, **58**, 440 (1955); *C. A.*, **49**, 14544i (1955).

(9) N. Takahayashi, *J. Pharm. Soc. Japan*, **75**, 1242 (1955); **76** 765, 1296 (1956).

(10) J. Sallé, N. Pesson and H. Kornowski, *Thérapie*, **13**, 1122 (1958).

(11) J. W. Cook, R. P. Gentles and S. H. Tucker, *Rec. trav. chim.*, **69**, 343 (1950).