Potential Psychotropic Agents. 7-Chloro-9-phenyl-3,3-diethyl-3*H*-pyrazolo-[5,1-*b*]quinazolin-10-ium-2-olate and 9-Chloro-2,3,4,5-tetrahydro-1-methyl-3,3-diethyl-7-phenyl-1*H*-benzo-1,5,6-triazonine-2,4-dione

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2-Amino-5-chloro-α-phenylbenzylidene hydrazone (**1**) or its methyl derivative **2** or acetyl derivative **10** react with diethylmalonic esters to give the corresponding malonyl derivatives **3, 4** and **8**. These esters were hydrolyzed to the acids **5** and **6**. Treating **5** with dehydrating agents the mesoionic compound 7-chloro-9-phenyl-3,3-diethyl-3*H*-pyrazolo[5,1-*b*]quinazolin-10-ium-2-olate (**14**) was obtained, while the methyl derivative **6** afforded the desired 9-chloro-2,3,4,5-tetrahydro-1-methyl-3,3-diethyl-7-phenyl-1*H*-benzo-1,5,6-triazonine-2,4-dione (**17**). Some derivatives of these compounds were also described. The structures of the new compounds were confirmed by an alternative synthesis and by mass and pmr spectral data.

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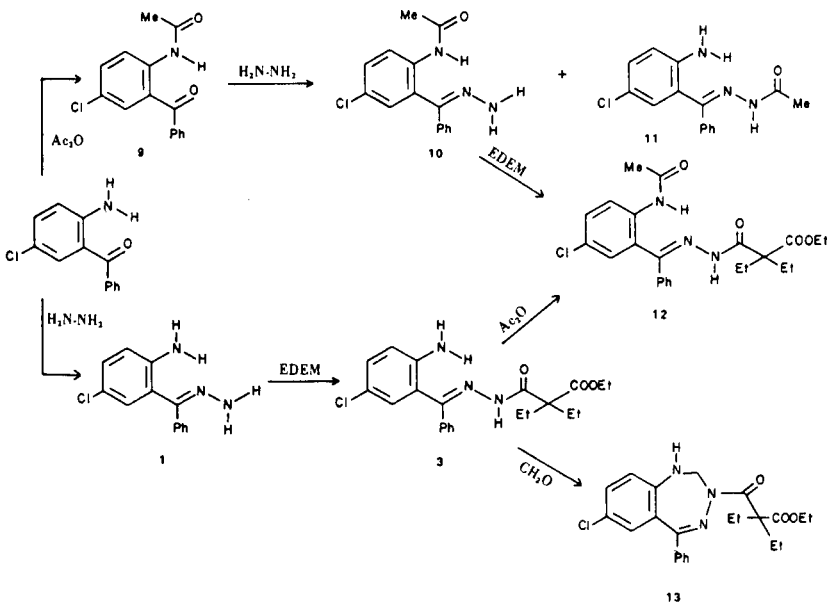
Many authors have pointed out in recent years the interesting pharmacological properties of quinazolines (1) and of benzodiazepines (2). On the other hand, the compounds whose heterocyclic ring is enlarged to benzodiazocines (3-6) and to benzotriazocines (7-9) have not been widely studied. Particularly, the enlargement of the ring from seven to eight atoms did not cause in the benzodiazocines a decrease of the pharmacological activity (5, 10).

Compounds with nine atoms, containing three atoms of nitrogen, as benzotriazonines, have not been studied as yet. Therefore, it appeared of interest to us, also on the basis of our preceding researches (6 and references cited), to synthesize compounds of such structure in order to test their pharmacological activity as tranquillizing agents. In the new molecules, both the chlorine atom and the phenyl group are in the characteristic positions on the benzodiazepine ring as those which are used in therapy.

By reaction of 2-amino-5-chlorobenzophenone with hydrazine hydrate the two isomeric forms of hydrazone **1**, *i.e. syn* and *anti* forms (11) were obtained. These have been separated and characterized with the aim only of a spectroscopic survey, as the use of both isomers made no difference to the subsequent synthesis.

Scheme I



The mixture of the two isomeric hydrazones **1**, treated with ethyldiethylmalonate (EDEM), in the presence of sodium hydride, yielded the ethyl ester of the malonyl derivative **3**, also in the two isomeric *syn* and *anti* forms, which have been separated and characterized. In order to confirm the structure of these intermediate esters, the 2-acetylamino-5-chlorobenzophenone (**9**) was treated with hydrazine hydrate affording **10** (12), which was made to react with EDEM. The isolated *N*-(1-ethoxy-2-diethylmalonyl)-*N'*-(acetamido-5-chloro-α-phenylbenzylidene)-hydrazine (**12**) appeared to be identical to the product obtained by direct acetylation of the ester **3**. Moreover this ester, treated with formaldehyde, gave the 7-chloro-2,3-dihydro-3-(1-ethoxy-2-diethylmalonyl)-5-phenyl-1*H*-benzo[*e*]-1,3,4-triazepine (**13**). These transformations are shown in Scheme 1.

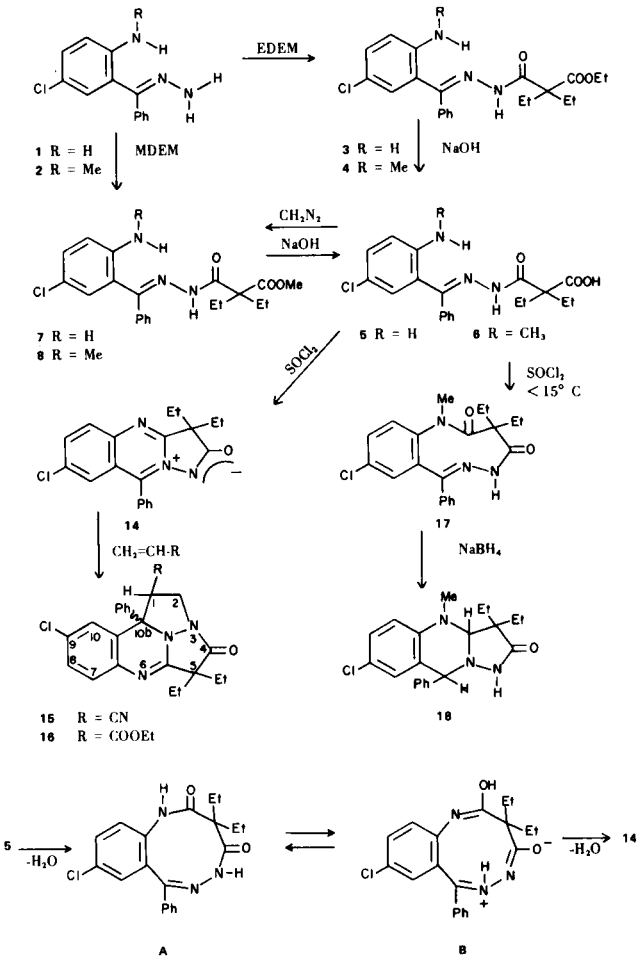
By heating **3**, both alone and with dehydrating agents (PPA, CCD, and so on), cyclization did not take place, only displacement of the equilibrium of the two *syn* and *anti* forms was observed. Therefore, we thought to hydrolyze the ester **3** and to carry out the cyclization on the resulting acid (Scheme 2). By boiling **3** with a diluted solution of sodium hydroxide, the expected acid **5** was obtained. This acid was characterized by transforming it into the corresponding methyl ester **7**, which was also directly prepared by treating the hydrazone **1** with methyldiethylmalonate (MDEM).

The acid **5**, treated whether with thionyl chloride or with PPA, or by the method of mixed anhydrides, *i.e.* with ethyl chloroformate and triethylamine (13), yielded a compound whose empirical formula was $C_{20}H_{18}ClN_3O$, due to **5** by the loss of two molecules of water. The mass spectrum (M^+ 351) confirmed such formula, while the pmr spectrum showed only the signals for 8 aromatic protons and 2 ethylic groups. This compound revealed a remarkable aromatic structure, being soluble in alkaline hydroxides and showing a marked fluorescence at λ = 254 nm and absorption bands at 224, 236, 269, 300, 345 and 382 nm in the uv spectrum.

On the basis of all these elements we presumed that the compound **14** had the mesoionic structure of a mesomeric betaine with aromatic character (14-16). The 1,3-dipolar structure of this 7-chloro-9-phenyl-3,3-diethyl-3*H*-pyrazolo[5,1-*b*]quinazolin-10-ium-2-olate (**14**) was also confirmed by the fact that, with the acrylates, it gave some addition products (17,18), as 1-cyano-**15** and 1-carbethoxy-2,4,5,10b-tetrahydro-5,5-diethyl-9-chloro-10b-phenyl-1*H*-*bis*-pyrazolo[3,2-*b*][2,3-c]quinazolin-4(3*H*)one (**16**), whose pmr spectra were in agreement with the proposed structure.

The formation of the mesoionic compound **14** from **5** probably occurs in two steps: firstly the formation of a nine atoms cycle A takes place; this cycle exists in tautomeric equilibrium with the B form, which is appropriately disposed to cyclodehydrate to **14**.

Scheme 2

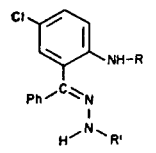


This mechanism may be confirmed by the fact that the compound **14** does not form from the ester **3** when this is treated under the same conditions as the acid **5**. In order to obtain the desired nine membered cyclic compounds, taking into consideration the formation mechanism of **14**, we used as the starting product the methylamine derivative **6**, obtained from **2** through compound **4** (see Scheme 2). In this case, as the existence of a tautomeric B form is impossible, the end product was the 9-chloro-2,3,4,5-tetrahydro-1-methyl-3,3-diethyl-7-phenyl-1*H*-benzo-1,5,6-triazonine-2,4-dione (**17**).

The reduction of **17** with sodium borohydride in methanol gave a tricyclic derivative in good yields, namely, the 7-chloro-2,3a,4,9-tetrahydro-3,3-diethyl-4-methyl-9-phenyl-1*H*-pyrazolo[5,1-*b*]quinazolin-2(3*H*)one (**18**), whose structure was confirmed by mass and pmr spectra. The latter showed the proton at C_{3a} as a singlet (δ 4.20) and the proton at C_9 (δ 4.70) also as a singlet, but broadened because the long-range coupling with the proton at C_8, which was confirmed by double resonance experiments.

The most significant data of the pmr spectra of the products described in this work are reported in the experimental part. Owing to the paucity of the data available in the literature (22) on the subject of the spectra of *syn* and *anti* stereoisomers of hydrazine derivatives of asymmetric benzophenones, we felt it was of interest to collect some additional experimental data whose relevant aspects are discussed below.

As it can be realized from inspection of the molecular models; in the case of the *anti*-Ph (II) isomer, the molecule is sterically hindered in assuming a planar configuration, whereas a relatively planar structure may be expected for the *syn*-Ph (I) form.



(I) syn-Ph

(II) anti-Ph

Consequently, as far as the products of the **3**, **4**, **5**, **6**, **7**, **8** type are concerned, in the *syn* isomers the signals of methyl and ethyl groups are more resolved than those of the corresponding *anti* isomers. Moreover, the =N-N*H*- proton in the *syn* isomers is exposed to a larger extent, than the corresponding proton of the *anti* form, to the effect from the ring current of the phenyl ring and it is hence more deshielded. Accordingly, the chemical shift value of such proton of the *syn* form (I) is found at lower fields than the corresponding value of the *anti* form (II). In these structures, still owing to their configuration, it is particualrly significant the signal pertaining to the aromatic amino group, which in the *syn* structures shows chemical shift values of about 6 ppm, while in the *anti* structures it is at higher fields, that is about 3.7 ppm. This effect is probably due to the coplanarity of the C=N bond and the benzene ring bearing the amino group. Such an anisotropic effect is not possible in the *anti* isomers.

Compounds **14**, **16**, **17** and **18** were screened using Swiss mice and were found to possess depressant activity at subtoxic doses. These compounds, when compared with clothiapine showed little inhibiting effect on central stimulants and/or the effects caused by barbiturates. Thus, none of the compounds possessed an appreciable pharmacological activity in these experimental systems.

EXPERIMENTAL

The melting points were determined by a Kofler apparatus and are uncorrected. The pmr spectra were recorded on a Varian HA-100 spectrometer, using TMS as an internal standard; the chemical shift values are expressed in ppm (δ), coupling constants in Hz. The mass spectra were determined by a LKB 9000-S apparatus at 20-70 eV and at 50-70°., by direct insertion into the ion source. The chromatographic separations have been carried out on silica gel Merck (Kieselgel 60, 70-230 mesh) column.

2-Amino-5-chloro-α-phenylbenzylidenhydrazone (**1**).

2-Amino-5-chlorobenzophenone (23.15 g., 0.1 mole) and 17.85 g. (0.35 mole) of 98% hydrazine hydrate in 30 ml. of diethylene glycol were heated at 100° for 48 hours. After cooling, the mixture was poured into water. The resulting precipitate was collected, washed with water and then with small amounts of cold ethanol. Two crystallizations from ethanol yielded 9.83 g. (40%) of **1** *anti* as pale yellow prisms, m.p. 133-134°; pmr (deuteriochloroform): 5.53 (2H, broad s, N-NH_2), 3.75 (2H, broad s, NH_2), 6.50-7.60 (8H, m, aromatic).

Anal. Calcd. for $C_{13}H_{12}ClN_3$: C, 63.58; H, 4.89; N, 17.10. Found: C, 63.54; H, 4.99; N, 17.22.

The mother liquors of the first crystallization were evaporated to dryness *in vacuo* and the resulting residue was chromatographed with benzene-ethyl acetate (9:1) as eluent. The first fractions gave 4.9 g. (20%) of the isomer **1** *syn*, which was recrystallized from hexane, m.p. 69-70°; pmr (deuteriochloroform): 5.21 (2H, broad s, N-NH_2), 5.96 (2H, broad s, NH_2), 6.40-7.70 (8H, m, aromatic).

Anal. Calcd. for $C_{13}H_{12}ClN_3$: C, 63.58; H, 4.89; N, 17.10. Found: C, 63.48; H, 4.95; N, 17.15.

2-Methylamino-5-chloro-α-phenylbenzylidenhydrazone (**2**).

This compound was prepared from 2-methylamino-5-chlorobenzophenone by the above procedure. In this case only the *anti* form was isolated. After chromatographic purification, the product was crystallized twice from 2-propanol to give a light yellow crystalline solid in 58% yield, m.p. 109-110°; pmr (deuteriochloroform): 2.72 (3H, d, J = 6, CH_3), 3.80 (1H, broad q, NH coupled with CH_3 protons), 5.52 (2H, s, N-NH_2), 6.50-7.60 (8H, m, aromatic). By adding deuterium oxide, the doublet at 2.72 collapses into a singlet.

Anal. Calcd. for $C_{14}H_{14}ClN_3$: C, 64.74; H, 5.39; N, 16.10. Found: C, 64.81; H, 5.43; N, 16.21.

General Procedure for the Preparation of *N,N'*-Disubstituted Hydrazines.

Sodium hydride (50% oil dispersion) (0.12 mole) was added under continuous stirring to a solution of the hydrazone **1** or **2** or **10** (0.1 mole) and of ethyldiethylmalonate (EDEM) or methyldiethylmalonate (MDEM) (0.12 mole) in anhydrous ether (150 ml.). The reaction mixture was stirred at room temperature for 48 hours, then poured into water and extracted with ether (3 x 50 ml.). The extracts were combined, dried over anhydrous sodium sulfate, and the solvent removed *in vacuo*. In the case of **3**, **4** and **12** the resulting residue was crystallized twice to give the *anti* form. The mother liquors of the first crystallization, evaporated *in vacuo*, gave a residue which was purified by chromatography with benzene-ethyl acetate (9:1) and recrystallized to yield the *syn* isomer. In the case of **7** and **8**, the residue was directly chromatographed with benzene-ethyl acetate (9:1). The first fractions gave starting material followed by the *syn* isomer. Further elution afforded the *anti* isomer.

In any case, by heating the *anti* isomer at 180-190° the equilibrium tends towards a greater formation of the *syn* isomer.

N-(1-Ethoxy-2-diethylmalonyl)-*N'*-(2-amino-5-chloro-α-phenylbenzylidene)hydrazine (**3**).

The *anti* isomer crystallized from ethanol was obtained in 40% yield, m.p. 138-139°; pmr (deuteriochloroform): 0.90 [6H, t, J = 7, =C(CH_2-CH_3)$_2$], 1.15 (3H, t, J = 7, $COOCH_2CH_3$), 2.10 [4H, m, =C(CH_2-CH_3)$_2$], 3.70 (2H, s, NH_2), 4.04 (2H, q, J = 7, $COOCH_2$-CH_3), 6.60-7.80 (8H, m, aromatic), 8.30 (1H, broad s, NH).

Anal. Calcd. for $C_{22}H_{26}ClN_3O_3$: C, 63.56; H, 6.25; N, 10.10. Found: C, 63.45; H, 6.27; N, 10.06.

The *syn* isomer crystallized from cyclohexane was obtained in 25% yield, m.p. 125-126°; pmr (deuteriochloroform): 0.79 [6H, t, J = 7, =C(CH_2-CH_3)$_2$], 1.18 (3H, t, J = 7, $COOCH_2$-CH_3), 1.90 [4H, well resolved m, =C(CH_2-CH_3)$_2$], 3.98 (2H, q, J = 7, $COOCH_2$-CH_3), 6.60 (2H, broad s, NH_2), 6.50-7.70 (8H, m, aromatic), 10.58 (1H, broad s, NH).

Anal. Calcd. for $C_{22}H_{26}ClN_3O_3$: C, 63.56; H, 6.25; N, 10.10. Found: C, 63.40; H, 6.28; N, 10.12.

N-(1-Ethoxy-2-diethylmalonyl)-*N'*-(2-methylamino-5-chloro-α-phenylbenzylidene)hydrazine (**4**).

The *anti* isomer crystallized from 2-propanol was obtained in 35% yield, m.p. 134-135°; pmr (deuteriochloroform): 0.93 [6H, t, J = 7, =C(CH_2-CH_3)$_2$], 1.22 (3H, t, J = 7, $COOCH_2$-CH_3), 2.10 [4H, broad m, =C(CH_2-CH_3)$_2$], 2.78 (3H, d, J = 5.5, N-CH_3), 3.60 (1H, broad q, N*H*-CH_3), 4.08 (2H, q, J = 7, $COOCH_2$-CH_3), 6.40-7.80 (8H, m, aromatic), 8.30 (1H, s, NH-CO). By adding of deuterium oxide the doublet at 2.78 collapses into a singlet.

Anal. Calcd. for $C_{23}H_{28}ClN_3O_3$: C, 64.25; H, 6.50; N, 9.77. Found: C, 64.18; H, 6.61; N, 9.73.

The *syn* isomer was obtained in 18% yield, m.p. 94-95° from isopropyl ether.

Anal. Calcd. for $C_{23}H_{28}ClN_3O_3$: C, 64.25; H, 6.50; N, 9.77. Found: C, 64.21; H, 6.48; N, 9.67.

N-(1-Methoxy-2-diethylmalonyl)-*N'*-(2-amino-5-chloro-α-phenylbenzylidene)hydrazine (**7**).

The *anti* isomer crystallized from methanol was obtained in 42% yield, m.p. 155-156°; pmr (deuteriochloroform): 0.82 [6H, t, J = 7, =C(CH_2-CH_3)$_2$], *ca.* 2.0 [4H, broad m, =C(CH_2-CH_3)$_2$], 3.56 (3H, s, $COOCH_3$), 3.70 (2H, broad s, NH_2), 6.50-7.80 (8H, m, aromatic), 8.25 (1H, s, NH-CO).

Anal. Calcd. for $C_{21}H_{24}ClN_3O_3$: C, 62.76; H, 6.02; N, 10.45. Found: C, 62.68; H, 6.07; N, 10.28.

The *syn* isomer was purified by crystallization from cyclohexane, m.p. 134-135°, yield 24%; pmr (deuteriochloroform): 0.75 [6H, t, J = 7, =C(CH_2-CH_3)$_2$], 1.90 [4H, m, =C(CH_2-CH_3)$_2$], 3.52 (3H, s, $COOCH_3$), 6.35 (2H, broad s, NH_2), 6.50-7.70 (8H, m, aromatic), 10.45 (1H, s, NH).

Anal. Calcd. for $C_{21}H_{24}ClN_3O_3$: C, 62.76; H, 6.02; N, 10.45. Found: C, 62.78; H, 6.15; N, 10.32.

N-(1-Methoxy-2-diethylmalonyl)-*N'*-(2-methylamino-5-chloro-α-phenylbenzylidene)hydrazine (**8**).

The *anti* isomer crystallized from methanol was obtained in 46% yield, m.p. 115-116°; pmr (deuteriochloroform): 0.82 [6H, t, J = 7, =C(CH_2-CH_3)$_2$], *ca.* 2.02 [4H, broad m, =C(CH_2-CH_3)$_2$], 2.72 (3H, d, NH-CH_3), 3.56 (3H, s, $COOCH_3$), 6.45-7.90 (9H, m, 8H aromatic and N*H*-CH_3), 8.22 (1H, broad s, NH-CO). The signal at 2.72 changes into a singlet by adding deuterium oxide.

Anal. Calcd. for $C_{22}H_{26}ClN_3O_3$: C, 68.98; H, 6.84; N, 10.90. Found: C, 69.02; H, 6.94; N, 10.82.

The *syn* isomer was obtained in 28% yield, m.p. 107-109° from cyclohexane; pmr (deuteriochloroform): 0.70 [6H, t, J = 7, =C(CH_2-CH_3)$_2$], 1.90 [4H, m, =C(CH_2-CH_3)$_2$], 3.00 (3H, d, NH-CH_3), 3.50 (3H, s, $COOCH_3$), 6.40-7.70 (8H, m, aromatic), 9.10 ? (1H, broad s, N*H*-CH_3), 10.35 (1H, broad s, NH-CO).

Anal. Calcd. for $C_{22}H_{26}ClN_3O_3$: C, 68.98; H, 6.84; N, 10.90. Found: C, 68.92; H, 6.80; N, 10.76.

N-(1-Ethoxy-2-diethylmalonyl)-*N'*-(2-acetamido-5-chloro-α-phenylbenzylidene)hydrazine (**12**).

The *anti* isomer crystallized from ethanol was obtained in 22% yield, m.p. 164-165°; pmr (deuteriochloroform): 0.90 [6H, t, J = 7, =C(CH_2-CH_3)$_2$], 1.20 (3H, t, J = 7, $COOCH_2$-CH_3), *ca.* 2.0 [4H, broad m, =C(CH_2-CH_3)$_2$], 2.02 (3H, s, CO-CH_3 superimposed on the preceding group signal), 3.98 (2H, broad q, $COOCH_2$-CH_3), 6.80-8.50 (10 H, 8H aromatic and two NH-CO groups).

Anal. Calcd. for $C_{24}H_{28}ClN_3O_4$: C, 62.94; H, 6.16; N, 9.17. Found: C, 62.99; H, 6.11; N, 9.23.

The *syn* isomer crystallized from cyclohexane was obtained in 20% yield, m.p. 144-145°; pmr (deuteriochloroform): 0.80 [6H, t, J = 7, =C(CH_2-CH_3)$_2$], 1.20 (3H, t, J = 7, $COOCH_2$-CH_3), 1.95 [4H, well resolved m, =C(CH_2-CH_3)$_2$], 2.43 (3H, s, CO-CH_3), 4.05 (2H, q, J = 7, $COOCH_2$-CH_3), 6.70-7.80 (7H, m, 7 aromatic and NH-CO), 8.76 (1H, d, J = 8.5, C_3 proton), 10.88 (1H, s, NH-CO).

Anal. Calcd. for $C_{24}H_{28}ClN_3O_4$: C, 62.94; H, 6.16; N, 9.17. Found: C, 63.15; H, 6.10; N, 9.24.

Compound **12** was also obtained from **3**. Acetic anhydride (8 ml.) was added dropwise to a stirred solution of **3** (4 g.) in dry benzene (30 ml.). The mixture was refluxed for 24 hours and then the solvent removed *in vacuo*. The resulting residue (*syn* and *anti* mixture) was worked up as for the above general procedure affording 1.5 g. (34%) of *anti* isomer, m.p. 164-165° and 2.1 g. (48%) of *syn* isomer, m.p. 144-145°. These isomers were identical in all respects to those obtained from **10**.

2-Acetamido-5-chloro-α-phenylbenzylidene Hydrazone (**10**).

A mixture of 2-acetamido-5-chlorobenzophenone (**9**) (23) (27.37 g., 0.1 mole) and 98% hydrazine hydrate (17.85 g., 0.35 mole) in 60 ml. of ethanol was refluxed for 24 hours, then cooled and poured into water. The precipitate was collected and recrystallized from ethanol to yield 17.8 g. (62%) of mixture of the *syn* and *anti* isomers as white crystals, m.p. 114-120°.

Anal. Calcd. for $C_{15}H_{14}ClN_3O$: C, 62.21; H, 4.90; N, 14.60. Found: C, 62.50; H, 4.88; N, 14.65.

By the chromatography (hexane-ethyl acetate 1:2) of the mother liquor, a small amount of a compound (m.p. 167-168° from ethanol) identical with the *N*-acetyl-*N'*-(2-amino-5-chloro-α-phenylbenzylidene)hydrazine (**11**) described below was obtained. When the reaction was performed without solvent and at room temperature, the 3-amino-6-chloro-3,4-dihydro-4-hydroxy-2-methyl-4-phenylquinazoline, m.p. 218-219°, was obtained (24).

N-Acetyl-*N'*-(2-amino-5-chloro-α-phenylbenzylidene)hydrazine (**11**).

A mixture of 2-amino-5-chlorobenzophenone (2.32 g., 0.01 mole) and acetylhydrazine (1.48 g., 0.02 mole) in ethylene glycol (10 ml.) was heated at 120° for 24 hours. After cooling, the mixture was poured into water and extracted with chloroform. The solvent was removed *in vacuo* to yield a solid, which was crystallized from ethanol to give 1.3 g. (45%) of *anti* isomer as white prisms, m.p. 167-168°; pmr (deuteriochloroform): 2.42 (3H, s, CO-CH_3), 3.72 (2H, broad s, Ph-NH_2), 6.60-7.70 (8H, m, aromatic), 8.40 (1H, broad s, NH-CO).

Anal. Calcd. for $C_{15}H_{14}ClN_3O$: C, 62.21; H, 4.90; N, 14.60. Found: C, 62.01; H, 4.95; N, 14.56.

7-Chloro-2,3-dihydro-3-(1-ethoxy-2-diethylmalonyl)-5-phenyl-1*H*-benzo[*e*]-1,3,4-triazepine (**13**).

A suspension of **3** (4.16 g., 0.01 mole) and paraformaldehyde (0.3 g., 0.01 mole) in xilol (100 ml.) was refluxed for 6 hours. The mixture was concentrated *in vacuo*, washed with water and then extracted with chloroform. The product was purified by chromatography, eluting with benzene-ethyl acetate (9:1) and recrystallized from cyclohexane to give 1.3 g. (30%) of white prisms, m.p. 179-180°; pmr (deuteriochloroform): 0.85 (9H, m, 3 CH_3), 2.04 [4H, dq, =C(CH_2-CH_3)$_2$], 3.72 (2H, q, $COOCH_2$-CH_3), 5.02 (2H, d, J = 6, NH-CH_2-N), 6.05 (1H, broad t, N*H*-CH_2), 6.60-7.60 (8H, m, aromatic). By irradiation of the NH signal (or by equilibration with deuterium oxide) the N-CH_2 protons gave rise to a singlet.

Anal. Calcd. for $C_{23}H_{26}ClN_3O_3$: C, 64.55; H, 6.12; N, 9.82. Found: C, 64.76; H, 6.22; N, 9.67.

N-(1-Hydroxy-2-diethylmalonyl)-*N'*-(2-amino-5-chloro-α-phenylbenzylidene)hydrazine (**5**).

To a solution of the ester **3** (10 g.) in ethanol (75 ml.) a solution of 4% sodium hydroxide (250 ml.) was added. The mixture was refluxed until solution and then allowed to stand for 12 hours. The alcohol was removed *in vacuo* and the residual solution was washed with ether, treated with acetic acid until *p*H 5, and then extracted with chloroform. The chloroform solution was washed, dried (sodium sulphate) and evaporated *in vacuo*. The crude product was recrystallized from ethanol to give 6.15 g. (65%) of ivory-white crystals, m.p. 153-154°.

Anal. Calcd. for $C_{20}H_{22}ClN_3O_3$: C, 61.93; H, 10.83; N, 5.72. Found: C, 61.79; H, 10.78; N, 5.71.

This compound was treated at 2-3° with a slight excess of freshly prepared ethereal diazomethane solution until the evolution of nitrogen ceased and then allowed to stand for 12 hours. The solution was evaporated to dryness and the solid residue gave **7** as a mixture of *syn* and *anti* isomers, which were separated as above. These isomers were identical in all respects to those obtained from **1**.

N-(1-Hydroxy-2-diethylmalonyl)-*N'*-(2-methylamino-5-chloro-α-phenylbenzylidene)hydrazine (**6**).

Following the procedure above described for preparing **5**, compound **4** gave **6** (6.3 g., 60%), m.p. 166-167° from ethanol.

Anal. Calcd. for $C_{21}H_{24}ClN_3O_3$: C, 62.76; H, 5.97; N, 10.45. Found: C, 62.57; H, 5.92; N, 10.36.

This compound, treated with diazomethane as above, afforded the ester **8** (*syn* and *anti* isomers).

7-Chloro-9-phenyl-3,3-diethyl-3*H*-pyrazolo[5,1-*b*]quinazolin-10-ium-2-olate (**14**)(2-Oxo-2,3-dihydro-3,3-diethyl-7-chloro-9-phenyl-1*H*-pyrazolo[5,1-*b*]quinazolin-10-ium Hydroxide Inner Salt).

Method A.

Thionyl chloride (2 ml.) dissolved in anhydrous chloroform (20 ml.) was added slowly and with stirring to a solution of 1 g. of the acid **5** in anhydrous chloroform (20 ml.). The solution was stirred for 8 hours at room temperature. Then the exceeding thionyl chloride was eliminated *in vacuo*, the residue was alkalinized with a sodium bicarbonate solution and then the mixture extracted with chloroform. Evaporation of the solvent left a white residue, which was recrystallized from cyclohexane to give 0.4 g. (45%) of white prisms, m.p. 231-232°; pmr (DMSO-d_6): 0.74 [6H, t, J = 6.5, $=C(CH_2\text{-}CH_3)_2$], 1.97 [4H, doublet of q, $=C(CH_2\text{-}CH_3)_2$], 7.60 (1H, d, J_{BX} = 2, C_8 proton), 7.68 (5H, s, phenyl group), 7.96 (1H, dd, J_{AB} = 9, C_6 proton), 8.16 (1H, d, Apart of an ABX system, C_5 proton). Mass spectrum: molecular ion at m/e 351.

Anal. Calcd. for $C_{20}H_{18}ClN_3O$: C, 68.28; H, 5.12; N, 11.94. Found: C, 68.25; H, 5.16; N, 11.87.

Method B.

A mixture of the acid **5** (1 g.) and 84% polyphosphoric acid (10 g.) was heated for 3 hours at 100° with stirring. After cooling, the mixture was poured on ice, alkalinized with diluted ammonium hydroxide solution, and extracted with chloroform, working up as above, yield 0.38 g., 42%.

Method C.

The acid **5** (1 g.) and triethylamine (3 ml.) were dissolved in 30 ml. of anhydrous dioxane. To this solution was added, dropwise and with stirring, ethylchloroformate (2.5 ml.). The mixture was allowed to stand for 1 hour, concentrated *in vacuo*, added of water and then extracted with chloroform. By this method the yield was 0.45 g. (50%).

Compound **14**, dissolved in ethanol and treated with 70% perchloric acid, gave the perchlorate m.p. 171-173° from methanol.

9-Chloro-1-cyano-2,4,5,10b-tetrahydro-5,5-diethyl-10b-phenyl-1*H*-bis-pyrazolo[3,2-*b*][2,3-*c*]quinazolin-4(3*H*)one (**15**).

A mixture of **14** (0.5 g.), acrylonitrile (5 ml.) and hydroquinone monomethylether (0.1 g.) in benzene (15 ml.) was refluxed for 48 hours. The solvent was evaporated and the residue, after addition of water, was extracted with chloroform. The crude product was purified by chromatography, eluting first with benzene, in order to separate traces of **14**, and then with benzene-ethyl acetate (9:1). Recrystallization from methanol gave 0.38 g. (66%) of white prisms, m.p. 199-200°; pmr (deuteriochloroform): 1.12 [6H, dt, J = 7, $=C(CH_2\text{-}CH_3)_2$], 2.06 [4H, doublet of q, $=C(CH_2\text{-}CH_3)_2$], 3.12 (1H, dd, X part of an ABX system, J_{AX} = 12 and J_{BX} = 5.5, C_1 proton), 4.25 (2H, dd, C_2 protons), 7.00-7.65 (8H, m, aromatic).

Anal. Calcd. for $C_{23}H_{21}ClN_4O$: C, 68.25; H, 5.19; N, 13.84. Found: C, 68.18; H, 5.27; N, 13.92.

9-Chloro-1-carbethoxy-2,4,5,10b-tetrahydro-5,5-diethyl-10b-phenyl-1*H*-bis-pyrazolo[3,2-*b*][2,3-*c*]quinazolin-4(3*H*)one (**16**).

This compound was synthesized in an analogous way as described above, using ethyl acrylate, and gave 0.39 g. (60%) of white crystals from isopropil ether, m.p. 144-145°.

Anal. Calcd. for $C_{25}H_{26}ClN_3O_3$: C, 66.47; H, 5.75; N, 9.30. Found: C, 66.29; H, 5.72; N, 9.30.

9-Chloro-2,3,4,5-tetrahydro-1-methyl-3,3-diethyl-7-phenyl-1*H*-benzo-1,5,6-triazonine-2,4-dione (**17**).

It was prepared from the acid **6** (1 g.) in a way similar to that described at Method A. for the above-mentioned product **14**, but keeping the temperature of reaction below 15°. Heating over this temperature, compound **14** is also formed. Crystallization of the crude product from cyclohexane gave 0.29 g. (30%) of ivory-white crystals, m.p. 172-173°; pmr (deuteriochloroform): 0.65 [6H, t, J = 7, $=C(CH_2\text{-}CH_3)_2$], 1.61 [4H, m, $=C(CH_2\text{-}CH_3)_2$], 3.24 (3H, s, N-CH_3), 7.10-8.0 (8H, m, aromatic), 8.15 (1H, broad s, NH-CO exchangeable with deuterium oxide); mass spectrum: molecular ion at m/e 383.

Anal. Calcd. for $C_{21}H_{22}ClN_3O_2$: C, 65.70; H, 5.77; N, 10.94. Found: C, 65.65; H, 5.75; N, 10.83.

7-Chloro-2,3a,4,9-tetrahydro-3,3-diethyl-4-methyl-9-phenyl-1*H*-pyrazolo[5,1-*b*]quinazoline-2(3*H*)one (**18**).

Sodium borohydride (0.76 g., 0.02 mole) was added in small portions at 2° under continuous stirring to a solution of **17** (3.84 g., 0.01 mole) in methanol (50 ml.). The mixture was allowed to stand for 12 hours, the solvent was removed *in vacuo*, water was added and the solution was extracted with chloroform. The product, purified by column chromatography, eluting with benzene-ethyl acetate (9:1), was recrystallized from ethanol to yield 1.47 g. (40%) of white prisms, m.p. 209-211°; pmr (DMSO-d_6): 0.96 [6H, pseudo q, $=C(CH_2\text{-}CH_3)_2$], 1.56 and 2.02 [4H, two q, $=C(CH_2\text{-}CH_3)_2$], 2.87 (3H, s, N-CH_3), 4.12 (1H, s, C_{3a} proton), 4.73 [1H, pseudo s, C_9 proton, which is broadened by coupling with the C_8 proton (NMDR)], 6.25 (1H, dd, C_8 proton, X part of an ABX system), 6.86 d and 7.12 dd (2H, C_5 and C_6 protons, AB part of an ABX system, J_{AB} = 9, J_{AX} = 2.5), 7.34 (5H, s, phenyl group), *ca.* 9.1 (1H, very broad s, NH-CO); mass spectrum: molecular ion at m/e 369.

Anal. Calcd. for $C_{21}H_{24}ClN_3O$: C, 68.19; H, 6.57; N, 11.36. Found: C, 68.42; H, 6.54; N, 11.28.

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