showed significant change in rotation after 3 hr.; $\nu_{\max}^{CH_2Cl_2}$ 1730, 1646, 1370, 1040, and 1032 cm.$^{-1}$.

Anal. Calcd. for $C_{25}H_{39}NO_2$: C, 77.87; H, 10.19; N, 3.63. Found: C, 77.85; H, 10.26; N, 3.68.

In a 100-ml., three-neck flask equipped with a condensor, dropping funnel, gas-inlet tube, and stirrer were placed 785 mg. (2.03 mmoles) of enamine IV, 235 mg. (2.32 mmoles) of triethylamine, and 10 ml. of chloroform, the latter two being freshly distilled and dried. To the stirred solution warmed to 40° and under nitrogen was added dropwise over a 20-min. period a solution of 167 mg. (2.13 mmoles) of acetyl chloride in 10 ml. of chloroform. The reaction temperature was raised to 55° for 4 hr., then lowered to 40° overnight.

The resulting orange-red solution was hydrolyzed with 30 ml. of 4 *N* hydrochloric acid and 20 ml. of chloroform by refluxing with vigorous stirring for 4 hr. The cooled mixture was extracted with methylene chloride; the organic layer was washed with water, dried, and evaporated to dryness, giving 620 mg. of orange-brown oil. A major portion of this, 580 mg., was chromatographed on 35 g. of silica gel (80–200 mesh). Following benzene, the eluate with 0.5% ethyl acetate–benzene yielded 152 mg. of III, identified after crystallization by melting point, mixture melting point, and infrared spectra. Further elution with 2% ethyl acetate–benzene gave 190 mg. of starting material (I).

The acylation of enamine IV in benzene followed a similar procedure with the difference that a white precipitate formed upon addition of acetyl chloride and persisted throughout the reaction. After hydrolysis with hydrochloric acid, 600 mg. of crude product was chromatographed on silica gel, yielding 135 mg. of III.

Methylation of 2-Acetyl-17β-acetoxy-5α-androstan-3-one (III).—To a solution of 2.0 g. of III in 75 ml. of acetone was added 4.0 g. of pulverized potassium carbonate and 7.0 ml. of freshly distilled methyl iodide. The mixture was refluxed with stirring for 20 hr., after which an additional 3 ml. of methyl iodide was added and the stirring with reflux was continued for 20 hr. more. After approximately half of the solvent was removed by distilling, the mixture was cooled and ether was added. The organic phase was washed with water, dried with magnesium sulfate, and evaporated to dryness. The 2.0-g. yield of crude product was chromatographed on 150 g. of silica gel (80–200 mesh). Elution with benzene was followed by several liters of 3% (v./v.) of ethyl acetate-benzene from which was obtained 1.64 g. of 2-methyl-2-acetyl-17β-acetoxy-5α-androstan-3-one (V). Homogeneity throughout the fraction was established by the identity of the melting points and spectra of samples from several aliquots. Repeated crystallizations from diisopropyl ether gave an analytical sample with m.p. 194–195°; $[\alpha]^{25}D$ +83.2° (*c* 1.01); $\nu_{\max}^{CCl_4}$ 1738, 1710, 1235, 1124, and 1034 cm.$^{-1}$. There was no major absorption peak in the ultraviolet.

Anal. Calcd. for $C_{24}H_{36}O_4$: C, 74.20; H, 9.34. Found: C, 74.17; H, 9.16.

A solution of 383 mg. of V in 40 ml. of methanol containing 4.0 g. of potassium carbonate and 17 ml. of water was refluxed for 4 hr. under nitrogen. Most of the solvent was removed by evaporation under reduced pressure. To the remainder was added methylene chloride and the organic phase was extracted with aqueous potassium carbonate, washed with water, and dried with magnesium sulfate. Evaporation of the solvent gave 289 mg. (96%) of a white solid which, without purification, had melting point and spectral properties close to those of VI. Recrystallization from diisopropyl ether gave crystals with a melting point and mixture melting point (with an authentic sample) of 148–149°. Identity of infrared spectra was established in both chloroform and carbon disulfide.

Hydrolysis of 2-Acetyl-17β-acetoxy-5α-androstan-3-one (III).—A solution of 600 mg. of III in 50 ml. of 95% ethanol and 20 ml. of 6 *N* hydrochloric acid was refluxed 6.5 hr. Approximately half the ethanol was distilled and the remaining solution was cooled, treated with 70 ml. of water, and refrigerated overnight. The solid was filtered, washed well with water, and dried, yielding 504 mg. of a glassy solid. Crystallization from hexane gave an amorphous solid of broad melting range. Recrystallizations successively from aqueous methanol and ether–hexane gave well-formed platelets, m.p. 153–154°; $[\alpha]^{24}D$ +62.4°; $\nu_{\max}^{CCl_4}$ 3620, 1640–1540 (broad), 1360, 1310, 1293, 1276, 1230, 1200, 1128, 1113, 1080, 1058, 1024, and 944 cm.$^{-1}$; ultraviolet absorption, $\lambda_{\max}$ 291 mμ (ε 8970).

Anal. Calcd. for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70. Found: C, 75.85; H, 9.51.

The same transformation was effected under mild conditions: a solution of 200 mg. of III in 30 ml. of methanol, 15 ml. of acetone, 5 ml. of water, and 2 ml. of concentrated hydrochloric acid was allowed to stand 64 hr. at room temperature. After addition of water, the mixture was extracted with methylene chloride and the latter phase was washed with dilute bicarbonate and water. Drying with magnesium sulfate followed by evaporation of solvent gave 177 mg. of crude material, which could be crystallized from petroleum ether to give semicrystalline material, m.p. 150–152°.

Bromine Titration of III.—The procedure followed was essentially that of Smith and Shriner.[14] To a solution of 0.463 mmole of III in 60 ml. of hot methanol was added an excess of bromine–methanol solution (*ca.* 0.1 *N*, freshly prepared) and followed immediately with 3 ml. of cyclohexene. An excess of potassium iodide solution was added; the mixture was warmed to 30–35°, and allowed to stand at room temprature for 10 min. After most of the iodine was titrated with 0.100 *N* sodium thiosulfate. there was added 2 ml. of acetic acid, 250 ml. of water, and 4 ml, of starch solution, and the titration was completed. A total of 8.15 ml. of thiosulfate solution was required, indicating an enol content of 88%. A repeat run gave a value of 86.6%.

Copper Chelate of III.—A solution of 500 mg. of III in 25 ml. of hot methanol was treated with cupric acetate solution [1 g. of $Cu(OAc)_2 \cdot H_2O$ in 10 ml. of hot water, filtered]. Dilution with water caused the precipitation of the green complex which was filtered and dried. Crystallization from acetone gave 427 mg. of green needles. From repeated crystallizations from acetone there was obtained an analytical sample, m.p. *ca.* 290° (began softening and darkening at *ca.* 270°); $\lambda_{\max}$ 243 mμ (ε 4100) and 311 (11,200); $\nu_{\max}^{CHCl_3}$ 1738, 1578, 1530, 1467, 1378, 1290, 1023, and 948 cm.$^{-1}$.

Anal. Calcd. for $C_{46}H_{66}CuO_8$: C, 68.11; H, 8.21; Cu, 7.84. Found: C, 67.75; H, 8.18; Cu, 8.13.

Isoxazole Formation from III.—A solution of 900 mg. of III and 10 g. of hydroxylamine hydrochloride in 50 ml. of pyridine and 50 ml. of ethanol was refluxed for 2 hr. After cooling, dilution with water gave a precipitate which was filtered, washed, and dried. Crystallization from acetone gave 886 mg. of isoxazole, m.p. 201–203°. Recrystallization from acetone and hexane successively gave an analytical sample, m.p. 202–203°; $[\alpha]^{24}D$ +33.6° (*c* 0.708); $\lambda_{\max}$ 227 mμ (ε 6950); $\nu_{\max}^{CCl_4}$ 1745, 1643, 1233, 1186, 1042, 1032, and 1021 cm.$^{-1}$.

Anal. Calcd. for $C_{23}H_{33}NO_3$: C, 74.36; H, 8.95; N, 3.77. Found: C, 74.19; H, 8.97; N, 4.08.

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(14) W. T. Smith and R. L. Shriner, "The Examination of New Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1956, p. 101.

The Reaction of Schiff Bases with Dicyandiamide. A New Synthesis of 4,6-Diamino-1,2-dihydro-*sym*-triazines

HOWARD NEWMAN[1] AND EDWARD L. MOON

Chemical Research and Development Laboratories,
Agricultural Division, American Cyanamid Company
Princeton, New Jersey

4,6-Diamino-1-aryl-1,2-dihydro-*sym*-triazine hydrochlorides[2] (I, R = aryl) have previously been prepared by either the condensation of an arylamine hydrochloride, ketone or aldehyde and dicyandiamide, or by allowing the ketone or aldehyde to react with an arylbiguanide hydrochloride.[3] The latter method was ex-

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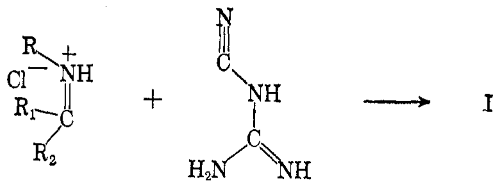
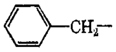
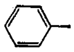
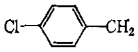
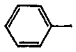
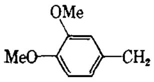
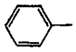
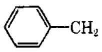
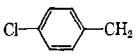
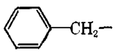
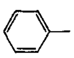
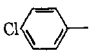
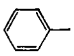
(1) Lederle Laboratories Division, American Cyanamid Co., Pearl River, N. Y.

(2) The tautomeric form indicated is done so arbitrarily: There is no evidence to date which favors this one over the other alternatives.

(3) (a) H. C. Carrington, A. F. Crowther, D. G. Davey, A. A. Levi, and F. L. Rose, *Nature*, **168**, 1080 (1951); (b) H. C. Carrington, A. F. Crowther, and G. J. Stacey, *J. Chem. Soc.*, 1017 (1954); (c) E. J. Modest, G. E. Foley, M. M. Pechet, and S. Farber, *J. Am. Chem. Soc.*, **74**, 855 (1952); (d) E. J. Modest, *J. Org. Chem.*, **21**, 1 (1956); (e) E. J. Modest and P. Levine, *ibid.*, **21**, 14 (1956).

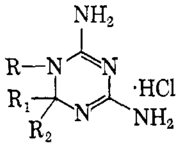
TABLE I



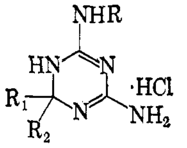
No.	R	R₁	R₂	M.p., °C.	Time, hr.	Yield, %	Calcd. Found C	H	N	Cl	F
1			H	228–230	16	91	60.91 60.93	5.75 5.84	22.12 22.85	11.22 11.06	
2			H	185–187	19	78^a	54.86 54.82	4.89 4.90	19.99 19.87	20.24 20.15	
3			H	183–185	27	48^a	57.51 56.95	5.90 6.10	18.63 18.55	9.43 9.65	
4		CF_3	H	290 dec.	0.5	73	42.93 43.10	4.25 3.87	22.76 22.71	11.52 11.54	18.52 18.86
5		CF_3	H	276–278	0.5	88	38.61 38.60	3.53 3.95	20.46 20.46	20.72 20.73	16.65 16.69
6		$(CH_3)_3C$—	H	245–247	20	88	56.83 56.79	7.49 7.62	23.67 23.73	11.98 11.97	
7			H	$232–235^b$	2.5	94	59.69 59.92	5.34 5.13	23.20 23.12	11.74 11.80	
8			H	245–247	72^c	65	53.58 53.81	4.49 4.44	20.83 20.81	21.09 21.03	
9		CH_3	CH_3	204–206	2.0	83	*d*				

[a] Based on unrecovered starting material. [b] Lit.[2b] m.p. 232–233°. [c] Week end. [d] Identical melting point and infrared spectrum with that of the compound prepared *via* the three-component synthesis.[2d]

tended by Lombardino[4] to the preparation of 4,6-diamino-1-alkyl-1,2-dihydro-2,2-dimethyl-*sym*-triazine hydrochlorides (I, R = alkyl; $R_1 = R_2 = CH_3$) from alkylbiguanide hydrochlorides and acetone.[5]

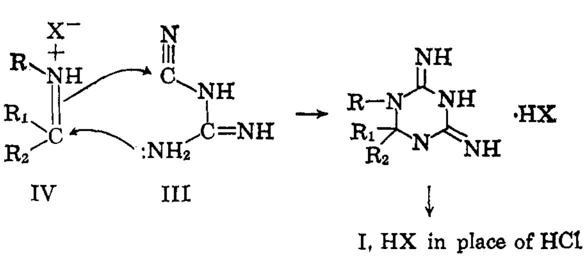


I



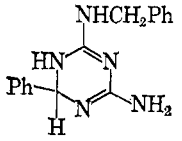
II

An alternate route to compounds of type I which suggested itself to us, was the reaction of dicyandiamide (III) and a protonated Schiff base of general structure IV.



The reaction proved quite satisfactory for Schiff bases in which R = aralkyl (Schiff bases in which R = alkyl was not tried), R_1 represents substituents which do not contain α-hydrogens, and R_2 = H. Thus, the 2,4-diaminodihydrotriazines listed in Table I were prepared by allowing the protonated Schiff base IV and dicyandiamide to react in dimethylformamide at room temperature.[6] The free Schiff base did not react. Earlier attempts to effect the reaction by fusing the Schiff base hydrochloride and dicyandiamide in the absence of solvent gave considerably inferior results except in the case of benzylidenebenzylamine hydrochloride (IV, R = benzyl; R_1 = phenyl; R_2 = H) and its *p*-chloro analog (IV, R = *p*-chlorobenzyl; R_1 = phenyl; R_2 = H). Here, too, no reaction was observed with the free Schiff base.

In accord with previous observations,[2d] I (R =



V

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(4) J. Lombardino, *J. Med. Chem.*, **6**, 213 (1963).

(5) Unfortunately, Lombardino did not offer any evidence in support of his structural assignments, apparently assuming that the reaction course in the alkyl series parallels that observed in the aryl series, where dihydrotriazines of type I are formed exclusively. Our unpublished findings on the reaction of benzylbiguanide hydrochloride and acetone from which I (R = benzyl; $R_1 = R_2 = CH_3$) and II (R = benzyl; $R_1 = R_2 = CH_3$) was isolated in roughly equal amounts would seem to invalidate this assumption.

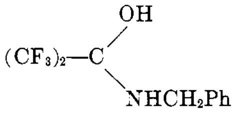
(6) Ingold and Piggott have demonstrated that benzylamine Schiff bases with a nitro substituent in either the benzylidene or benzylamine portion of the molecule are hydrolyzed back by acid to the aldehyde and amine from which they were formed [*J. Chem. Soc.*, 2381 (1922)], and we have found this to apply as well to the hydrochloride salt of the Schiff base obtained from 3,4-dimethoxybenzylamine and benzaldehyde. Cordes and Jencks [*J. Am. Chem. Soc.*, **85**, 2843 (1963)] also found no evidence for the isomerization of Schiff bases formed from ethylamine and a number of *meta*- and *para*-substituted benzaldehydes.

benzyl; R_1 = phenyl; R_2 = H) readily rearranged in base to V.

The reaction did not take place with the benzylamine Schiff bases of acetone, acetaldehyde, and acetophenone. The failure of the reaction with these α-hydrogen-containing Schiff bases is perhaps related to the previously reported difficulties encountered in the addition of nucleophiles to α-hydrogen-containing imines,[7] apparently owing to the faster attack at the α-hydrogen by the nucleophile compared to its addition across the carbon–nitrogen double bond.

As exemplified by no. 9 in the table, when R = aryl, the desired reaction does take place, in good yield, with α-hydrogen-containing R_1 and R_2 substituents.

An attempt to prepare hexafluoroisopropylidenebenzylamine (IV-HCl, R = benzyl; $R_1 = R_2 = CF_3$) under conditions (*p*-toluenesulfonic acid and benzene) satisfactorily employed for the preparation of the other Schiff bases was unsuccessful. The structure VI for the compound obtained was assigned on the basis of its infrared [sharp peak at 2.9 μ (NH), broad band at *ca.* 3.9 μ (hydrogen-bonded OH)] and n.m.r.[8] spectra [a five-proton singlet at τ 2.72 (aromatic protons), broad singlet at 5.65 (N–H), singlet at 6.00 (OH), and singlet at 6.36 (benzylic protons); the total area of the latter three peaks corresponded to four protons].[9]



$(CF_3)_2C(OH)NHCH_2Ph$

VI

Experimental[10]

Reaction of Schiff Base Hydrochloride IV (X = Cl) with Dicyandiamide in Dimethylformamide.—The general method is illustrated with a description of the procedure used to prepare 4,6-diamino-1-benzyl-1,2-dihydro-2-trifluoromethyl-*sym*-triazine. A slow stream of gaseous hydrogen chloride was passed through a solution of 5.6 g. (0.03 mole) of 2,2,2-trifluoroethylidenebenzylamine in 60 ml. of anhydrous ether contained in a well-dried three-necked flask under nitrogen until it was no longer consumed. The ether and excess hydrogen chloride were removed in a stream of nitrogen and the semisolid residue dissolved in 60 ml. of dimethylformamide (dried over molecular sieves). Dicyandiamide (2.52 g., 0.03 mole) was added in one portion, with stirring, the addition being accompanied by a 30° exotherm. After being stirred for an additional 20 min., the reaction mixture, which by this time had cooled to room temperature, was poured into a fairly large amount of ether–acetone (9:1) and the resulting suspension was stirred until the suspended material solidified (in this case, 10 min.). The liquid phase was decanted and the solid was washed with a fresh portion of ether and collected to yield 6.7 g. (73%) of V (R = benzyl; $R_1 = CF_3$; R_2 = H), m.p. 290° dec., after recrystallization from ethanol–acetone (5:1).

With IV (R = *p*-chlorobenzyl or 3,4-dimethoxybenzyl; R_1 = phenyl; R_2 = H), the work-up was modified as follows. The reaction mixture containing suspended solid (unreacted Schiff base) was separated by filtration and the filtrate was poured into a large excess of ether. After being stirred for a few hours and allowed to stand for 3 days, the ether was decanted from the gummy solid, and the latter crystallized from water. Presumably a longer reaction time was necessary in these cases.

Alternatively, a solution of the Schiff base and dicyandiamide in dimethylformamide was treated with a molar equivalent of 1 *N* hydrogen chloride in dimethylformamide and the resulting reaction mixture was processed as described.

Schiff base hydrochlorides which are not very sensitive to atmospheric moisture (*e.g.*, benzylidenebenzylamine, benzylidine-*p*-chlorobenzylamine, and 2,2,2-trimethylethylidenebenzylamine) do not necessarily have to be prepared *in situ*.

4,6-Diamino-1-benzyl-1,2-dihydro-2-phenyl-*sym*-triazine Hydrochloride (V, R = Benzyl; R_1 = Phenyl; R_2 = H) by Fusion of Benzylidenebenzylamine Hydrochloride and Dicyandiamide.—An intimate mixture of 2.3 g. (0.01 mole) of benzylidenebenzylamine hydrochloride (IV, R = benzyl; R_1 = phenyl; R_2 = H) and dicyandiamide was heated at 130–135° for 2 hr. (after 45 min. the solid mixture collapsed to a yellow melt) and cooled to room temperature. The yellow solid was broken up and crystallized from ethanol to give 1.7 g. (57%) of the crystalline 4,6-diamino-1,2-dihydrotriazine hydrochloride, m.p. 227–228°.

Anal. Calcd. for $C_{16}H_{18}ClN_5$: C, 60.91; H, 5.75; N, 22.12. Found: C, 60.95; H, 5.84; N, 22.05.

4,6-Diamino-1-*p*-chlorobenzyl-1,2-dihydro-2-phenyl-*sym*-triazine hydrochloride was similarly prepared in 55% yield by fusing dicyandiamide and benzylidene-*p*-chlorobenzylamine hydrochloride.

Base-Catalyzed Isomerization of 4,6-Diamino-1-benzyl-1,2-dihydro-2-phenyl-*sym*-triazine to 4-Amino-6-benzylamino-1,2-dihydro-2-phenyl-*sym*-triazine (VI).—A solution of 1 g. (0.0032 mole) of 4,6-diamino-1-benzyl-1,2-dihydro-2-phenyl-*sym*-triazine (V, R = benzyl; R_1 = phenyl; R_2 = H) in 40 ml. of aqueous methanolic sodium hydroxide (1:2, pH of reaction mixture, *ca.* 11) was heated on a steam bath for 1 hr. and cooled. The oil which separated was dissolved in a small amount of aqueous ethanol (1:1) and the pH of the solution was adjusted to 6–7 (alkacid test paper) with 1 *N* hydrochloric acid. After 1 week in the refrigerator, 0.48 g. (48%) of crystalline 4-amino-6-benzylamino-1,2-dihydro-*sym*-triazine hydrochloride (VI + HCl) separated, m.p. 174–176°. The infrared spectra of V (R = benzyl; R_1 = phenyl; R_2 = H), and VI + HCl were clearly different.

Anal. Calcd. for $C_{16}H_{18}ClN_5$: C, 60.91; H, 5.75; Cl, 11.22; N, 22.12. Found: C, 60.95; H, 5.84; Cl, 11.16; N, 22.05.

Preparation of Schiff Bases.—The Schiff bases employed were prepared as described by Overberger, *et al.*,[11] with the exception of isopropylidenebenzylamine. The latter was prepared as described by Kuhn and Schretzmann.[12]

2,2,2-Trifluoroethylidenebenzylamine.— Commercially available (Aldrich Chemical) ethyl trifluoroacetaldehyde hemiacetal was used for Schiff base formation in the Overberger procedure. The Schiff base boiled at 49° (2 mm.).

Anal. Calcd. for $C_9H_8F_3N$: C, 57.75; H, 4.30; F, 30.45; N, 7.48. Found: C, 57.78; H, 4.34; F, 30.4; N, 7.45.

Reaction of Hexafluoroacetone with Benzylamine.—A stream of hexafluoroacetone (Allied Chemical) was slowly bubbled through a cooled solution of 21.4 g. (0.2 mole) of benzylamine in benzene (reaction was exothermic) until the ketone was no longer consumed. A catalytic amount of *p*-toluenesulfonic acid was added and the solution was heated under reflux for 17 hr., a Dean–Stark trap containing Dri-Na (Baker) providing for water separation. The liquid residue obtained by evaporating the benzene was distilled *in vacuo* to yield 37 g. of a colorless liquid, b.p. 76–78° (0.5 mm.). The compound could be stored in a dry flask under nitrogen; however, it solidified (bicarbonate?, hydrate?) on short exposure to the atmosphere.

Acknowledgment.—We thank Dr. G. Berkelhammer for his continued interest and Mr. R. Wayne for the n.m.r. spectrum.

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(7) R. W. Layer, *Chem. Rev.*, **63**, 489 (1963).

(8) Taken in carbon tetrachloride with tetramethylsilane as an internal standard on a Varian A-60 spectrometer.

(9) While this investigation was in progress, we became aware of the work of Carrington, *et al.*,[2b] in which they prepared V (R = R_1 = phenyl; R_2 = H) in "small" yield, by the reaction of benzylideneaniline and dicyandiamide in aqueous acid. However, as they point out, the Schiff base is hydrolyzed under the reaction conditions and what is probably being observed is a three-component synthesis.[2d]

(10) Melting points are corrected. Microanalyses are by Galbraith Laboratories, Inc., Knoxville, Tenn. Infrared spectra were taken as mulls in Nujol with a Perkin-Elmer infracord spectrophotometer.

(11) C. G. Overberger, N. P. Marullo, and R. G. Hiskey, *J. Am. Chem. Soc.*, **83**, 1374 (1961).

(12) R. Kuhn and H. Schretzmann, *Chem. Ber.*, **90**, 557 (1957).